Zahid Hussain Khan *Editor*

Challenging Topics in Neuroanesthesia and Neurocritical Care

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Foreword

While training as a young intensive care consultant, I was always amazed at how little emphasis was placed on the well-being of the lump of gray matter sitting in our heads called the brain. Numerous ICU conferences elaborated on the exciting topics of ARDS and ventilation, diagnosis and mechanisms of sepsis, oscillators and jet ventilation, and ECMO. We discussed heart disease and physiology, pulmonary mechanics, dialysis, sepsis, and various other thought-provoking areas. But there existed a general lack of awareness that the point of all this was to ensure that the brain was maintained in an adequately working state. The impact of diseases and treatments on the brain were largely ignored. When the brain was directly impacted by disease such as following traumatic brain injury (TBI), stroke, or SAH, most clinicians took a relatively nihilistic view that as outcomes could not be significantly impacted by hospital management and as most patients survived who made it to hospital (although the level of functioning was largely ignored), there was little interest in pursuing research to improve outcomes for these patients. In many instances, this was because the brain was largely a closed book to most of us. While cardiac imaging was advancing in leaps and bounds, there was little insight into the working of the brain and even less into how to investigate and monitor cerebral activity.

Very few intensive care centers had taken any interest in neurocritical care at this time, and patients were often managed in general ICUs or neurosurgical HDUs and not necessarily by intensivists. A few specialized centers were emerging, however, notably Massachusetts General Hospital and Addenbrooke's Hospital in Cambridge, and these would eventually become the leaders in the push for a more brain-focused approach to the critically ill. Their efforts were pivotal in initiating the long process of undertaking and collating research in order to determine what did and, as importantly, what therapies didn't improve outcomes post ABI. Furthermore, a closer look at outcome measures would be necessary, as mortality alone in the setting of major neurological deficits was recognized as insufficient and issues of quality of life would have to be looked into.

Over the past 25 years, momentum has steadily grown, and a number of important papers have been produced demonstrating positive outcomes from a range of interventions including improving cerebral hemodynamics, cerebral vasospasm, and intracranial hypertension, to name a few. Furthermore, the Brain Trauma Foundation published their guidelines on the management of TBI and, although light on evidence, was able to provide a baseline from

which further research could be undertaken. As such, a PubMed search today will reveal a plethora of papers in the field of neurocritical care reflecting a massive increase in interest and funding in this field and setting the stage for new and exciting developments in the future.

With this newfound interest in all things brain, the number of books published on the topic has increased exponentially. Many seem to follow the time-honored tradition of approaching the topic broadly with a reference to basic physiology, general cerebral monitoring and management, and a few chapters on specific topics. As such, most books provide an overview of management for the ABI population as a whole but may be a little short on specifics when it comes to managing the individual patients or when specific problems develop which may be a little out of the ordinary.

In *Challenging Topics in Neuroanesthesia and Neurocritical Care*, Zahid Khan has attempted to delve into specific issues that are faced by the practicing clinician on a daily but also occasional basis. With many years of experience in neuroanesthesia and neurocritical care, Khan has chosen topics that may not readily be found in the average neuroICU textbook. And while many of the chapters cover topics broadly reviewed by other titles, Khan attempts to deal with specific issues confronting the neuroanesthetist and neurointensivist. For example, the chapters on airway and pain management, common but often overlooked issues, are reviewed in detail. A number of chapters are reserved for discussing anesthetic techniques in a variety of complex situations including posterior fossa surgery, pituitary surgery, and awake craniotomies. And newer therapies such as the use of inhalatory sedation in neurointensive care are also reviewed. And the final chapter on neuroprotection, a rapidly expanding and very promising area of research, concludes the reviews.

It is hoped that by dealing with specific topics, this book will provide an alternative source of information filling the gap in knowledge and improving clinicians' ability to manage patients with complex neurocritical issues. Many topics covered may be controversial and lacking in widespread evidence to guide management. As such, the title *Challenging Topics in Neuroanesthesia and Neurocritical Care* seems an apt choice.

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Preface

An overwhelming interest did exist with me when I started as a young anesthesiologist catering for neuro-cases more than two decades back. This interest could hardly have arisen but for a conflux of circumstances and an influx of patients, some of them exceedingly rare which I had the opportunity to report later.

Iran has the highest number of road accidents in the world, and as such, we have a large number of head injury and spinal cord injury patients landing in our emergency departments with compromised cardiovascular status requiring urgent resuscitative and airway management strategies. I thought of it and the fate of these patients by day and nursed it by night. It became an overpowering, absorbing passion with me, and I resolved to take up the task of writing a book with the aim of addressing the most challenging issues in neuroanesthesia and neurocritical care which I thought would be of help in the overall management of these cases. I had been thinking over it most deeply and most intently. Head injury has been a continual and ephemeral problem commonly felt but less acknowledged. For such a book, I needed to muster all my resources and get the help of celebrities in the field. A search provided me an egress to some of my old friends and scholars in the field.

Head injuries take a massive toll of our younger generation, and some of these cases are wheeled into the neurointensive care units with diffuse axonal injuries and with a Glasgow Coma Scale score of 6 or 7 or even below that. Ischemic injuries have been observed in more than 90% of patients dying as a result of head injury. Systemic insults, such as hypotension and hypoxia, are frequent in the early posttraumatic period as well as in the intensive care setting. Thus, these patients not only need an intensive care but in fact an extravigilant care; otherwise, they would pass away without pain or suffering like a clock someone had forgotten to wind.

Prognostic values of traumatic brain injury (TBI), brain tissue oxygenation in TBI, intracranial compliance, TBI and management, and biomarkers in TBI have been dealt with exquisite detail. Likewise, blood glucose concentration management, paroxysmal autonomic instability with dystonia, perioperative stroke, subarachnoid hemorrhage, postoperative hematoma, deep brain stimulation, and diagnosis of brain death have all be dealt with in sufficient detail. Apart from these, there are some highly important chapters on airway and pain management and anesthesia in different clinical and challenging scenarios, related to the central and peripheral nervous system.

The book covers areas about brain monitoring in severe head trauma. These chapters would provide the clinician an insight whether jugular bulb oxyhemoglobin saturation (SjO_2)-guided therapy provides better outcomes than intracranial pressure (ICP)- and cerebral perfusion pressure (CPP)-guided therapy in clinical practice based on expert opinion or based on randomized, clinical trials. SjO_2 monitoring is considered to be appropriate for detecting global cerebral ischemia. Low SjO_2 values indicate a higher extraction of oxygen and thus are indicative of ischemia. But as there are different types of tissue hypoxia, SjO_2 monitoring will not be able to detect all causes of tissue hypoxia, and furthermore, tissue hypoxia may be present despite normal or increased venous saturation values. The use of invasive monitoring system should be justified by a hierarchy of evidence. Jugular desaturation implies that cerebral blood flow (CBF) is inadequate for the metabolic needs of the brain, and SjO_2 values below 50% are a medical emergency. However, SjO_2 cannot always be relied upon if it is one sided, and bilateral SjO_2 monitoring should be applied if the SjO_2 data are inconsistent with other physiological variables. Currently, ICP- and CPP-guided therapies are the main therapeutic modalities in the treatment of severe head injuries. The underlying aim is to ensure that cerebral blood flow (CBF) and oxygenation are adequate to meet the metabolic demands.

Continuous monitoring of partial pressure of brain tissue oxygen ($PbrO_2$) that provides an additional information on the local oxygen status of the injured brain has also been described as a safe method of brain monitoring. Low $PbrO_2$ recordings reflect hypoxia of the relatively undamaged tissue in the first 24 h after head injury and thus could serve as a useful tool of monitoring in expert hands. In some studies, a correlation between low $PbrO_2$ and normal or even high SjO_2 has not been found. In intensive care management, it is imperative that a focus is made not only on increasing CPP but, more specifically, on attempts to increase brain tissue oxygen levels.

Early detection of impending cerebral ischemia in comatose patients is the cornerstone in obviating secondary insults to the brain that has received a trauma or injury. Several researchers have upheld the notion that the brain tissue PO_2 ($PtiO_2$) would be adequate if the CPP is maintained at 60 mmHg. Increasing the CPP above 60 mmHg would not further improve $PtiO_2$. Hyperventilation should preferably be carefully monitored by SjO_2 and $PtiO_2$ monitoring to prevent hypocapnic-induced cerebrovascular constriction and cerebral ischemia. The modifications in $PaCO_2$ have served to be of prognostic value in treating head injury patients and help as therapeutic strategies in controlling ICP and adjusting CBF to meet metabolic needs. The transcranial Doppler (TCD) measures the change in CBF during $PaCO_2$ variations and to test CO_2 cerebrovascular reactivity. This aspect has been adequately covered in one of the chapters.

Since head injury patients or those undergoing neurosurgical operations or monitoring present a plethora of problems, it is recommended that the different indices are monitored and optimized. These aspects are fully covered and dilated upon in the different chapters of the book. Some recommend continuous infusion of norepinephrine if the CPP is lower than 80 mmHg and ICP higher than 20 mmHg and/or jugular venous oxygen saturation ($SvjO_2$) is

equal to or less than 55%. Of course, under such circumstances, it is mandatory that the blood volume is optimized first. This treatment modality is used with the explicit purpose to stabilize CPP between 80 and 100 mmHg so as to optimize ICP and CPP. However, when CPP is compromised between 65 and 80 mmHg but ICP remains lower than 20 mmHg and $SvjO_2$ higher than 55%, no therapeutic intervention is needed. The first chapter of the book tackles in sufficient detail the intracranial compliance which is defined as the change in cerebrospinal fluid volume per unit change in pressure, which is not constant but increases as pressure rises. The lower limit of autoregulation represents the CPP level (about 40 mmHg in normal subjects) below which cerebral vasodilation and reduction in cerebrovascular resistance (CVR) can no longer compensate adequately for the decreasing CPP.

The lower limit of autoregulation is best defined by serial TCD monitoring, such as measurements of SjO_2. The authors fully highlight these domains in their respective chapters.

In the chapters on anesthetic management, controversial issues have been brought to the limelight and adequately addressed which would serve as a useful reference book for the practicing anesthesiologists and neurointensivists.

Each author has fortified his/her discourse with all the arguments and evidence that human art and wit would devise, and this is clearly evident in all the three parts of the book. I am grateful to all the authors who most willingly opted to serve as contributors and presented their scholastic works for this book. By writing these exemplary chapters, the neuro-patients would be debtor to you so long as they live and would be paying you their gratitude so long as they are breathing, and until that moment, they take the last sigh of their life. If anything would increase my happiness and delight, it would be perceiving that the baby would have outgrown its set of caps or in other words the book would have received a general applause from its readers.

All the reviews presented herein would help the neurointensivists, neuroanesthesiologists, emergency medicine specialists, pulmonologists, and airway care specialists in taking the required and appropriate steps when such challenging cases are encountered.

I also avail of this opportunity in extending my profound gratitude to the Springer publications and the team involved in the publication of this book who helped me at every step through their suggestions and advices. It was indeed very rewarding working with the Springer publishers and its highly diligent team.

I owe a great deal to my father who has always been the driving force for all my academic pursuits, to my spouse who has always been a source of help and encouragement, and to my patients who taught me a lot the intricacies of this discipline through their illnesses and eventual outcomes.

I am also grateful to Professor Hayden White for having spared the time in writing a foreword for my book.

Tehran, Iran Zahid Hussain Khan, MD, FCCM

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Part III Neuroanesthesia and Neurocritical Care

Part I

Traumatic and Spinal Cord Injury

Intracranial Compliance, Traumatic Brain Injury and Management

1

Zahid Hussain Khan and Pooya Kalani

1.1 Introduction

Traumatic brain injury (TBI) has been reported to be 50,000 annually in the mean age group of 35 year in the United States alone [1]. Survivors live with the TBI related disabilities. In the contemporary literature, a 20% reduction in mortality has been reported, and this could be attributed to an improvement of our knowledge of pathophysiology of TBI and an advancement in our management strategies. The last decade has witnessed giant strides in monitoring, critical care techniques, indications and timing of surgery, which had an overall favorable impact on the mortality.

The brain is an organ that is exquisitely sensitive to hypoxemia, episodes of hypotension and alterations in the blood pH. TBI ushers in a cascade of events that bring in a change in the body hemostasis which if not corrected urgently can end up in more profound damage to the brain that would be difficult to treat.

The major causes of head injury include road vehicle accidents, falls from heights and sports, etc. Traditionally, head injury has been divided into the primary injury and the secondary injury. The initial assault or impact damage once inflicted is hard to reverse, that, it causes inevitable destruction depending upon the severity of the injury but is preventable if safety measures are adopted and rules of driving and other sports abided.

The impact damage can appear in the form of contusions or lacerations, or else appear as epidural, subdural or intracerebral hematomas when bleeding occurs in the contusions or else several contusions coalesce together because of bleeding occurring within them. The secondary brain damage occurs within minutes to days after the initial insult in the form of hypoxia, hypercarbia, brain edema, brain shift, ischemia and infection which are preventable to some extent, and this aspect is the cornerstone in the management of TBI.

1.2 Intracranial Compliance/ Elastance

The brain is besieged by the rigid skull and an increase in intracranial pressure (ICP) may reduce cerebral perfusion pressure (CPP), and demolish cerebral blood flow (CBF) leading to cerebral ischemia.

The craniospinal axis is essentially a partially closed box containing both viscous and elastic elements. The elastic or its inverse the compliant properties of the container will ascertain as to how much volume can be added to it before the ICP shows a rise.

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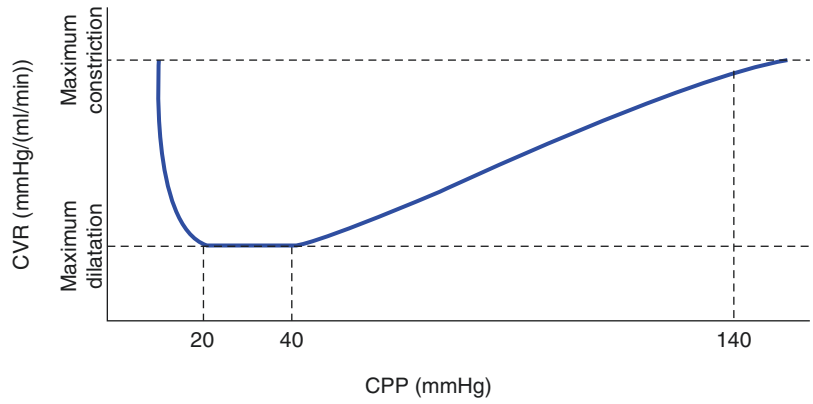

Fig. 1.1 Auto-regulatory relationship between vascular resistance (CVR) and CPP. *CVR* main cerebrovascular resistance, *CPP* cerebral perfusion pressure

Intracranial compliance (dP/dV) is the inverse of compliance. Elastance is sometimes referred to as the volume-pressure response (VPR).

$$\text{Compliance} = \frac{1}{Elastance} = \frac{1}{VPR}$$

Cerebral compliance literally expresses the capability to buffer an intracranial volume increase while buffering a rise in ICP. The auto-regulatory response to any variation in CPP influences the cerebral blood volume (CBV) which is an important determinant of intracranial compliance [2]. The ability of the intracranial compartment to compensate to added volume is an important factor in the development of raised ICP after TBI [3]. Intracranial compliance or its inverse elastance is considered to be index of the volume buffering capability of the brain, and a reduced compliance will eventually lead to increased ICP [4]. Variations in CPP have significant influence upon cerebrovascular resistance (CVR) and on CBV which regulate a constant cerebral blood flow (CBF) (Fig. 1.1).

$$CVR = \frac{MAP - ICP}{CBF}$$

Different methods have been developed to measure cerebral compliance.

Marmarou [2] provided a full mathematical description of the craniospinal volume-pressure correlation and also found a mathematical model of the CSF system for general solution of the CSF pressure. He described nonlinear volume–pressure relationship as a straight line segment relating the logarithm of pressure to volume.

It can be determined as a monoexponential relationship between volume and pressure.

Relationship has been described quantitatively by a pressure-volume index (PVI) which is the notional volume required to raise ICP tenfold. In fact, the slope of pressure-volume relationship determines this index (Fig. 1.2).

PVI can be calculated by the underlying formula:

$$PVI = \frac{dV}{\log \frac{P_0}{P_m}}$$

dV = Volume = milliliters
P_0 = initial pressure
P_m = final pressure

Ordinarily, the PVI measures are obtained by repeated withdrawal and injections of 2 ml and the average PVI is calculated from multiple injections. In ICP rising, fluid injection is not performed and PVI is obtained only from withdrawal of fluid.

Miller and colleagues [5, 6] introduced another craniospinal volume pressure relationship parameter, the volume pressure response (VPR). It is calculated from the ICP response resulting from a rapid bolus injection of saline into the CSF space, as a direct measure, not of compliance, but of its inverse elastance.

The fundamental principles of raised ICP were developed by Monro [7] and Kellie [8]. But

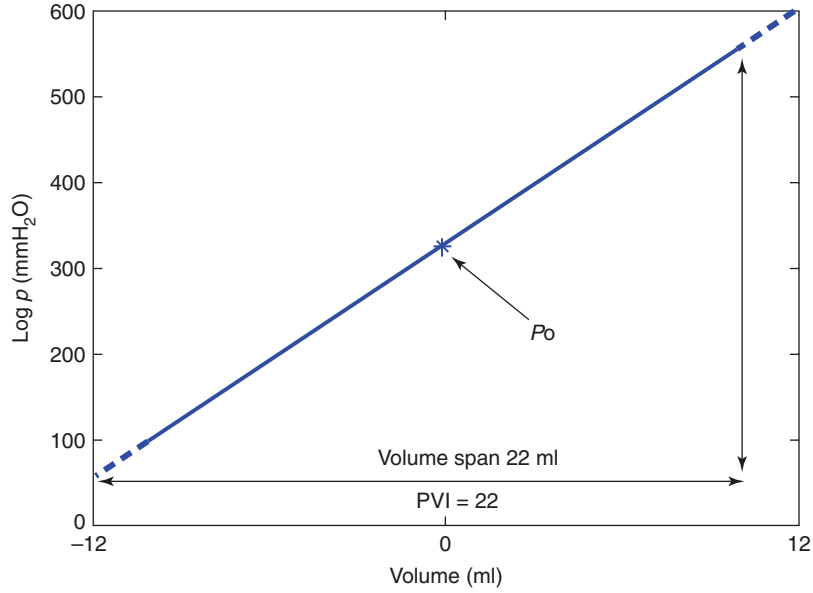

Fig. 1.2 These methods are based upon the manual injection from the CSF space of the patient while measuring the ICP before and after the volume change. PVI is defined as the volume of CSF that would have to be infused to raise the ICP ten-fold. Normal PVI is 26 ml. Less than 13 ml is considered to indicate reduced volume buffering capacity. VPR is defined as the change in ICP with the infusion of 1 ml of CSF. Normal VPR is less than 2 mmHg and greater than 5 ml is considered to indicate reduced volume buffering capacity

this doctrine did not take into account the CSF as a component of the cranial component. The concept of reciprocal volume changes between blood and CSF was introduced by Burrows and was later extended in the early twentieth century [9, 10] to allow for reciprocal changes in all the craniospinal constituents.

The brain floats in the CSF which has an important role. Pascal's principle describes that the transmission of fluid pressure exerted anywhere in a confined incompressible fluid is transmitted equally in all directions throughout so that the pressure variations remain the same. According to this law, all gradients of the ICP within the CNS are equilibrated. Marmarou's mathematical model introduced interrelationship of the static and dynamic process of formation, storage and absorption mechanisms of CSF. Also, Davson [11] has shown the relationship between CSF pressure and cerebral venous pressure. As a result, the steady-state ICP equation developed:

ICP = CSF formation rate × [CSF outflow resistance + venous pressure (pressure in sagittal sinus)].

The production of CSF is balanced by its storage and reabsorption via the sagittal sinus.

Marmarou has extended this hypothesis with mathematical model:

$$R_0 = t_2 * \frac{P_0}{(PVI)\log\left(\left(\frac{P_2}{P_1}\right) * \frac{(P_p - P_0)}{(P_2 - P_0)}\right)}$$

V_0 = Single volume injection
P_0 = Starting pressure
Pp = the peak pressure resulting from bonus volume injection
P_2 = the pressure point on the return trajectory at time T_2 (T_2 = 2 min post injection)
R_0 = out flow resistance

The formula is derivation of an equation for CSF out flow resistance based on a bolus injection technique.

After traumatic brain injury, CSF out flow resistance is one possible parameter of raised ICP.

Mamarou's study has shown that the role of CSF in ICP raising was only about 30%. Therefore, jugular bulb pressure was measured by Marmarou in 1993 [12] and it determines that ICP elevation relates to venous outflow pressure.

Gray and Rosner [13] determined the role of vascular factors in craniospinal compliance.

It revealed that the PVI could be regarded complex function of CPP, reinforcing the idea that the direction of the CPP-PVI relationship

depends on whether CPP stands above or below the autoregulatory range for CBF.

Further studies by Anile, Portnoy and Branch [14] showed that compliance is also time dependent. They described two components based on the rate of injection of volume bolus:

1. Physical compliance
2. Physiological compliance

Heifetz and Weiss [15] described physical compliance with expansion of spinal dura matter and of any minute amount of brain compression and skull expansion that may occur.

Physiological compliance of intracranial system is related to cerebrovascular alternations, specifically venous outflow resistance [16].

All data show that craniospinal pressure–volume relationships depend on the dynamic and viscoelastic properties of CSF, nervous tissue and vascular factors.

Zee and Shapiro [17] demonstrated the role of brain tissue elasticity on lumped craniospinal elastance. But their investigations were rejected by Walsh and Schettini [18].

Avezaat and Van Eijndhoven [19] introduced first exponential craniospinal volume–pressure relationship with ICP waveform pulse amplitude (ICPplse) for the elastance (dV/dP) and pulsatile blood volume for the volume injection. Their data revealed that there was a linear rise in the ICP pulse with ICP up to a pressure of 60 mmHg following which occurred a break point. Above 60 mmHg, the ICP pulse showed a rapid rise with rising ICP. With an Improvement in both hardware and software computer technology, it is becoming more probable to develop complex mathematical models of craniospinal system. Czosnyka et al. [20] introduced a novel mathematical pertaining to the cerebrovascular bed and craniospinal compartment, and they introduced electrical equivalent circuit of a CBF and CSF circulation model.

Finally, cerebrospinal complex was derived into three compliances as follows:

1. CSF space
2. Arterial bed compliance
3. Venous compliance

Arterial compliance has the lowest role of the three components. The venous compartment has far greater compliance, and cerebral venous blood volume is an important component of cerebral buffering capacity as cerebral venous pressure is low and approximates ICP.

After exhaustion of all CSF buffering capacity (150–170 ml), venous blood volume is the next buffer that comes into play.

1.3 The Circulating Blood Volume

It has been confirmed that the volume of intracranial blood is largely dependent upon the vascular bed, and the volume of the vascular bed in turn is predominantly maintained by chemical agents and vasomotor impulses. Elevated levels of partial pressure of carbondioxide in arterial blood ($PaCO_2$) bring about marked vasodilation which increases the intracranial blood volume, and as a consequence increases intracranial volume as a whole. This cerebral vasodilation initiated by CO_2 is again a compensatory phenomenon because the vasodilation so produced prevents a fall in extracellular pH which would be inevitable if cerebral blood flow (CBF) had not increased.

At times, slowing of the circulation or stasis, which is frequently apparent and found in acute vasomotor paralysis, would cause an increase in intracranial blood volume. Therefore, it should be understood that vasomotor paralysis produces an increase in intracranial blood volume by a mechanism altogether different from that cited for hypercarbia.

The principal role of CBF is to provide oxygen and glucose to the brain in order to maintain normal brain function. When CBF is decreased below a critical level to maintain normal metabolism, dysfunction occurs in the form of increased glycolysis and a reduction in the process of oxidative phosphorylation which produces adenosine triphosphate (ATP). Brain activity soon ceases or stops for lack of oxygen. Thus, insufficient oxygen not only stops the function of this exquisitely sensitive organ, the brain, but it wrecks the entire functions of the body.

It is important to grasp that the two pathological mechanisms that are involved in limiting oxygen availability are hypoxemia and ischemia. Hypoxemia signifies a reduction in the partial pressure of the oxygen in the arterial blood (PaO_2), while ischemia indicates a reduction in CBF. Tissue hypoxia sufficient to disrupt metabolism can occur as a result of reduction in the volume of blood flowing through the tissue which is termed ischemic hypoxia or insufficient oxygen per unit volume which is termed hypoxic hypoxia.

1.4 Cerebrospinal Fluid Volume

CSF is a specialized extracellular fluid in the ventricles and subarachnoid space which is produced at a rate of 0.3–0.4 ml/min (500 ml/day). It provides mechanical protection by buoyancy. The low specific activity of CSF (1.007) reduces the effective weight of the brain from 1.4 kg to 47 g (Archimede's principle). This reduction in mass reduces brain inertia and thereby protects it against deformation caused by acceleration or deceleration forces.

The CSF acts as a blessing in disguise. When the intracranial volume shows a dramatic increase, CSF is the first that tries to neutralize this increase. In gross or severe cerebral edema, the CSF may be squeezed off the brain during the phase of compensation. The CSF otorrhea or rhinorhea at times seen in patients with acute head injuries may in fact act as a life-saving safety valve for some time at least. It shows that nature also comes into play to counteract evolving hematoma following head injury and any intervention in nature by packing the CSF's efflux would be detrimental for the patient.

1.5 Extravascular Fluid

The volume of intracellular and extracellular fluid (ECF) is invariably altered in cerebral edema. There exists a fine relationship between the capillary loop and the tissue fluid. This fine relationship gets disturbed by an increase in the osmotic pressure of blood or the tissue fluid. The normal ECF accounts for just 4% of the brain bulk. The fluid gets accumulated in response to the same vascular and osmotic forces that govern the extracellular dynamics elsewhere, but in the brain, the blood brain barrier (BBB) prevents the passage of proteins out of the capillary bed and thus causing a sharp reduction in the osmotic power component. Following TBI and cerebral trauma, the integrity of the BBB no longer remains intact and thus protein leaks out into the extracellular compartment. With no lymphatic system to remove them, increased osmotic pressure attracts water and edema results. In the initial stages, the cellular membranes remain intact, but in the late stages there is rupture of the cell membranes. Therefore, hypertonic fluids are of no benefit in the late stages of cerebral trauma because the intracellular compartment of the glial cells is severely damaged by this time.

The expansion of brain or to be more exact edema is normally accommodated by a reduction in one or more of the above-mentioned intracranial compartments, but it is usually the CSF, and it is because of this reason that the ICP does not at all manifest initially. But at a later stage when displacement of the CSF is no longer possible or else the edema is of such a large extent that the CSF displacement fails to accommodate it, a small increase in intracranial volume would cause a sharp rise in the ICP. At this stage, hypoxia and hypercapnia can further deteriorate the condition. At this particular stage, hypertonic fluids and reduction of cerebral blood volume by means of hyperventilation can bring about a reduction in ICP. But at an advanced stage, the pressure rapidly rises again. This is because of the fact that there is increase in the intracranial blood volume following the reduction of ICP. The mechanism is not fully understood, but it could be due to vasomotor paralysis with resultant loss of resting tone of the cerebral vessels. An added factor may be the rapid passage of fluid from the intravascular space to the extravascular space.

1.6 Pathophysiology

TBI is a major cause of morbidity and mortality in young adults [21]. The primary brain injury results when the initial traumatic force applied to the head exceeds the ability of the brain to sustain the insult.

A host of events can follow in the form of skull fractures, brain contusions and/or hemorrhages depending upon the severity of the contact force. Likewise focal or diffuse brain injuries can occur as a consequence of acceleration and deceleration forces. The consequence of initial injury includes physical disruption, distortion of cell membranes and the infrastructure and an overwhelming disturbance of ionic hemostasis [22] secondary to an increased membrane permeability. Research has been targeted mostly to secondary injuries as primary injuries are irreversible.

The secondary injury occurs as a consequence of further physiological insults such as ischemia [23–25], reperfusion and hypoxia to areas of at risk brain in the period after initial injury and is an interplay of biochemical mediators that in fact expand the injury beyond the primary insult. The mediators that have been implicated in secondary brain injury include excitatory amines, that is, glutamate and aspartate, [26] oxygen free radicals, cytokines and inflammatory substances. This in turn may lead to astrocytic and neuronal swelling, relative hypoperfusion [23, 25] and a cascade of neurotoxic events because of increased intracellular calcium [26, 27].

The common denominator of secondary injury is ischemia which in fact triggers the release of such mediators. These mediators disturb the cellular metabolism and function. Factors that can contribute to or else exacerbate the overall situation include hypoxia, hypercarbia, hypotension, intracranial hypertension, transtentorial and cerebral herniation. Hypotension worsens neurological deficits, disrupts cerebral high energy phosphate stores and triggers intracerebral lactic acidosis [28, 29]. Early management of TBI is thus principally directed towards minimizing progression of injury in the at risk brain [23].

1.7 Cerebral Circulatory Responses

The TBI imparts an enormous adverse impact on the cerebral circulatory hemodynamics in the form of reduced CBF, impaired cerebral pressure autoregulation and increased ICP. In one-third of head-injured patients having sustained injury <6 h previously, CBF was <18 ml/100G/min, that is, exactly at the threshold for cerebral ischemia [23].

The oxygen extraction enhances as the oxygen delivery to the brain declines, resulting in a decrease in jugular bulb oxygen saturation (SJO_2) and an increase in anterior-jugular venous oxygen content difference ($AJDO_2$). The brain oxygenation is further reduced if CBF is reduced following hyperventilation [30]. Further reduction in oxygen supply will lead to a fall in cerebral metabolic rate of oxygen ($CMRO_2$) heralding anaerobic metabolism with an increased production of lactic acid, a cascade which if not corrected will end up in infarction. Within the initial few hours after injury, the cerebral arteriovenous oxygen content difference (systematic arterial oxygen content – jugular venous bulb oxygen content) was abnormally high but then gradually decreased [23]. Hyperventilation may bring in an added insult in the form of reducing CBF and thus curtailing cerebral oxygenation [30]. In severely head injured patients, both the cerebral oxygen consumption ($CMRO_2$) and CBF may be depressed. In some, the reduction in CBF and $CMRO_2$ occurs in tandem, that is, following a reduction in $CMRO_2$, secondarily there is a decline in CBF, but such a coupling is not seen in other patients, and the CBF may be less depressed than $CMRO_2$ [31].

In one third of patients, the CBF passively changed as the CPP changed [25]. Patients with reduced CBF are susceptible to an exaggerated vasoconstriction during the process of acute hyperventilation. Almost 20% of patients are liable to develop a wide cerebral arteriovenous oxygen content difference ($A\text{-}VDO_2$) secondary to hyperventilation [32]. The CBF has been found to be poorly maintained in response to hemorrhagic hypotension in experimental animals after TBI [33]. Thus, in order to achieve a promising cerebral circulatory profile, it is incumbent to control intracranial hypertension, maintain an adequate level of CPP and preserve the CBF in its physiological limits as far as possible.

The plasma norepinephrine levels inversely correlate with the initial Glasgow Coma Score

(GCS) [34]. This could perhaps account for the tachycardia, hypertension and elevated cardiac output seen in patients following head injury and it could also account for the raised intracranial hypertension. Respiratory depression also follows immediately after severe head injury leading to ventilation-perfusion mismatch if there has been aspiration of vomitus or concomitant neurogenic pulmonary edema [35].

1.8 Pressure–Volume Curve

As pointed out earlier, the cranium is a semi-closed and non-yielding box. The contents inside the cranium are incompressible and the only way open to avoid a rise in the ICP is for the CSF to shift from within the skull to the spinal subarachnoid space or else its absorption is hastened or enhanced. Thus, an increase in volume of one of the compartments, for example, brain the form of a hematoma ushers in the compensatory mechanisms to help maintain a normal ICP. There is a flat curve depicted as 1 and 2 and a steep curve represented as 3 and 4 (Fig. 1.3). Initially as the mass inside the cranium enlarges or in other words, as the volume increases, such as a hematoma developing after head injury, the compensatory mechanisms come in to play and prevent any rise in the ICP and maintain it within the normal limits (0–10 mmHg). Eventually the compensatory mechanisms get exhausted and give way, and it is at this particular stage that even very small increases in volume results in marked rises in pressure. If appropriate steps are not speedily taken to reduce the ICP, the CPP falls drastically reaching its critical level. Such a scenario is associated with a significant reduction in the CBF. The CBF ceases altogether once the ICP equals mean arterial pressure (MAP).

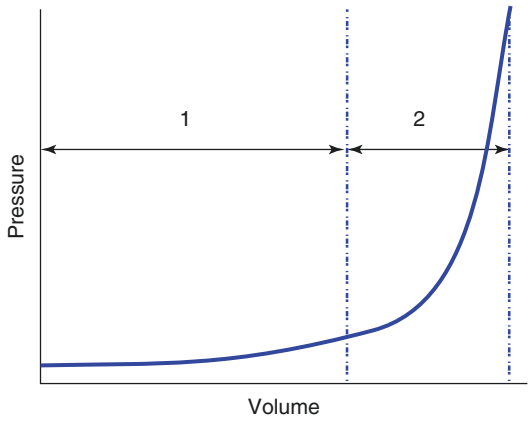

Fig. 1.3 Compensatory mechanisms help maintain the pressure within the intracranial vault stable as the volume of a space occupying lesion shows a rise [1]. But the intracranial pressure shows a marked rise as these compensatory mechanisms get exhausted [2]

Thus, all those agents that cause a slight increase in CBF and CBV should be strictly avoided as they would cause a steep rise in ICP. Treatment should be instituted when the ICP exceeds 20 mmHg [36].

1.9 Autoregulation

The autoregulatory response of the brain commonly referred to as autoregulation is a compensatory response which helps maintain a constant and stable CBF over a wide range of CPP ranging from 50–150 mmHg. To put it in simplified words, the cerebral vasculature dilates when there is a decline in CPP and constricts when there is a rise in CPP (Fig. 1.4). The caliber of intracranial vessels alters automatically, that is, vessels dilate if perfusion pressure is low or if metabolic activity in one of the region is high thus maintaining a stable CBF in the face of changing MAP/CPP. This sterling property exhibited by the cerebral vasculture is mediated by the myogenic phenomenon inherent in the vasculature to maintain a constant flow of the CPP and thus prevent an overspill of blood flow causing cerebral edema or else allowing the CPP to reach its critical threshold leading to cerebral ischemia together with its adverse effects. The neurogenic influences on the contrary exhibit very slight or negligible effects on the cerebral vasculature and ranges from 5% to 10%. When the CPP falls below 50 mmHg or else exceeds its upper limit of 150 mmHg, the flow becomes entirely dependent on the perfusion pressure or becomes passive. In situations, in which the autoregulation is maintained as in normal persons, an

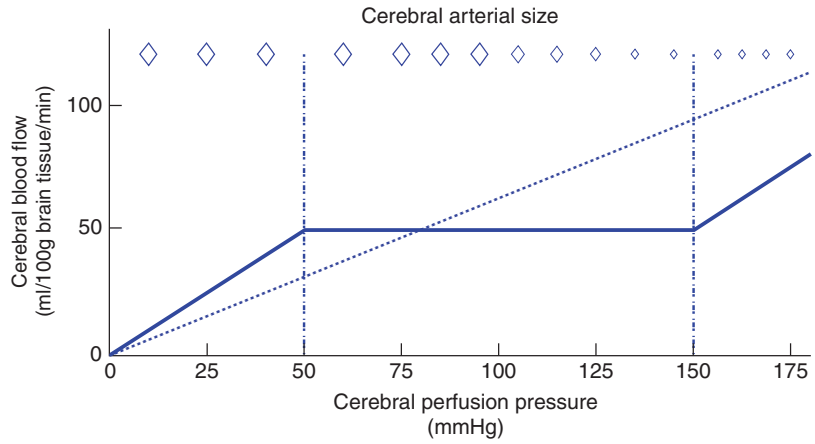

Fig. 1.4 Impact of cerebral Arterial size on Cerebral Blood Flow (CBF) and Cerebral Perfusion Pressure (CPP)

increase in mean arterial pressure(MAP) is beneficial as it brings about a reduction in ICP owing to the compensatory vasoconstriction mediated by the autoregulatory response [37]. However, the problem sets in when the autoregulatory response is impaired as seen in patients following TBI. In such a clinical scenario, those in whom the lower limit of autoregulation has been shifted to the right would perhaps derive some benefit if the MAP is kept at level above the normal range [38]. The autoregulation is not only not impaired but preserved and shifted to the right necessitating a higher CPP to help maintain CBF. It is argued that a higher CPP would curtail ICP by causing a reduction in the CBV and brain edema through autoregulatory vasoconstriction. Following head injury, the autoregulatory gets impaired and as a result a decline in CPP most likely causes a drop in CBF thus setting in a stage for cerebral ischemia – one of the most dreaded complications encountered in patients with TBI.

The lower limit of autoregulatory curve of 50 mmHg has been challenged of late, and it is being postulated that the lower limit maybe closer to 70 mmHg [39]. However, it is to be grasped that the lower limit of autoregulation indicates that this is the point at which CBF starts to decrease rather than the point at which ischemia ensues. Head injured patients have little reserve in intracranial elastance so that small increases in intracranial volume may cause significant increases in ICP. As the physiological basis for cerebral autoregulation lies in vasodilation and a consequent increase in CBV, ICP may actually rise as the blood pressure falls in the patient with intact autoregulation but decreased reserve. This may be the basis for increases in ICP with drugs that lower MABP such as sufentanil and is the basis for considering maintenance of CPP above 70 mmHg when ICP is elevated as in head injured patients [38].

Intracellular acidosis ensues once the CBF falls below 18 ml/100G /min, and electrical activity ceases at 12 ml/100G/min. A total of 50% of the oxygen delivery is normally utilized to maintain electrical activity of the brain and the rest of the 50% is channeled to maintain cellular integrity. When the CBF falls to a critical level of 12 ml100G/min, electrical activity ceases in the form of silent EEG as the CBF is diverted to maintain the much need cellular integrity. However, if CBF shows a further decline to values as low as 8 ml/100G/min., cellular death ensues.

Autoregulation is undoubtedly impaired following TBI and a CBF is maintained at higher values of CPP from 60 to 70 mmHg to prevent adverse sequelae.

1.10 Diagnosis

Clinical assessment is of value and may help in averting an impending danger in these patients. Head injured patients may have marked hypertension, and bradycardia or tachycardia which are attributed to actual or impending medullary

ischemia. This Cushing response is perhaps natures's endowment in helping the brain to preserve its perfusion. The hypertension occurring in patients with TBI requires treatment, but there is no consensus as to which level it should be adjusted. Although hypertension is hazardous, but some patients may tolerate blood pressures as high as 160 or 170 mmHg [40].

A neurological examination comprising Glasgow Coma Score (GCS) to test overall brain function, and pupillary light responses, and occulocephalic or vestibulocochlear reflexes to be tested in all comatose patients. However, computed tomographic (CT) scan is regarded as the gold standard imaging technology in the diagnosis of acutely head injured patients. Magnetic resonance imaging (MRI) is of value in detecting lesions not detectable by CT scan and it entails time and thus is of limited value in TBI patients when time is of utmost value. A CT scan is required in all TBI patients except the ones who are asymptomatic. It is to be emphasized that patients with GCS score 14 or 15 with loss of unconsciousness documented, amnesia, seizure attacks, focal neurological deficits and evidence of skull fractures should all have a CT scan [41].

Traditionally head injured patients are classified depending upon the severity of injury and the GCS obtained upon evaluation into mild head injury (GCS = 14–15), moderate head injury (GCS = 9–13), and severe head injury (GCS $\leq$ 8) and management strategies and protocols initiated depending upon the severity of the case.

1.11 Classification

Head injury for simplicity can be classified as mild, moderate or severe depending upon the impact of injury and its effects on the cardiovascular and neurological systems. In mild traumatic head injury, a CT scan is recommended except for those cases that are truly asymptomatic. If for any reason a CT scan cannot be obtained, the patient should preferably be hospitalized for surveillance. Although the majority of these cases recover fully, a small percentage can deteriorate rapidly because of having sustained a serious insult. In one series of patients, in 30% of the patients except for a mild headache, other signs and symptoms such as loss of consciousness, amnesia or vomiting were not reported; however, about 40% had either a skull fracture, focal neurological deficit or an extra cranial lesion (42). Although these cases are termed mild as far as head injury is concerned, extra cranial injuries if present can significantly affect mortality. Likewise age, use of anticoagulants, use or better say abuse of alcohol, and the presence of a nonoperable small hematoma on CT scan can again be of high import in influencing the overall mortality. It has been recommended that these patients should report for a follow-up visit with in 1 month. Moderate head injury patient require hospital admission as the risk of neurological deterioration is almost 20%. A second CT scan should be normal. Upon discharge, they should report for a follow-up check up with in 1 week.

Patients with severe head injury need emergency care and management. The airway, breathing and circulation should receive our top most attention because both hypoxia and hypotension are highly detrimental and can aggravate the precarious situation of the patient. Endotracheal intubation should be performed in all patients with a GCS of $\leq$8. Care should be exercised during intubation in patients with cervical injuries and a neurological assessment performed before sedating the patient or paralyzing the patient with neuromuscular blocking drugs. Electrolyte imbalance should be corrected and hemodynamic stability ascertained. Both hyponatremia and hypomagnesemia should be corrected as both lower the seizure threshold. Control CT scans should be obtained if there is worsening of the neurological status such as a decline in the level of consciousness, progressive pupillary asymmetry or hemiparesis.

Since head injury is an evolving pathology, aggressive management and intensive care is of pivotal importance.

The GCS (Table 1.1) is invaluable to evaluate the deteriorating neurological status of patients with head injury. Patients who have sustained head injury can be categorized into four grades according to the level of consciousness as under:

Table 1.1 GCS score in head-injured patients

Parameter	Response	Score
Eye opening	Spontaneous	4
	To sound	3
	To pain	2
	No response	1
Verbal response	Oriented	5
	Confused	4
	Inappropriate word	3
	Incomprehensive sound	2
	None	1
Motor response	Obeys commands	6
	Localizes pain	5
	Normal withdrawal	4
	Abnormal flexion	3
	Extension	2
	Nil	1

Grade I: It comprises those patients who have had transient loss of consciousness but are alert now and have no neurological deficit.

Grade II: It refers to those patients who are exhibiting impaired level of consciousness but retaining the ability to follow commands. The patients may be alert but a focal neurological deficit may be present.

Grade III: It encompasses patients with a distorted level of consciousness who are unable to follow commands.

Grade IV: It includes those patients who display no evidence of brain function and the brain appears biologically dead.

This grading helps the physician in determining the severity of brain damage and thus predicting the ultimate outcome. However, the GCS is more accurate in evaluating the level of consciousness. The score made by a patient depends upon the patient's response to certain parameters such as eye opening, verbal response and motor response as appears in the table (Table 1.1).

The GCS is undoubtedly of value but falls short of an ideal parameter or assessment tool because it fails to include the lower brain stem reflexes such as the corneal and the calorics and does not take other valuable indices into consideration such as the pulse, blood pressure and the respiratory patterns of the patients with head injuries. The GCS helps in evaluating the level of consciousness but should preferably be combined with other parameters. The level of consciousness, the degree of amnesia or retrograde amnesia must be correctly sought while examining these patients. If a patient can recall the incident or the events immediately preceding it, one can be almost 99% sure that the patient has not sustained a severe head injury.

Bedsides the GCS, focal signs and symptoms also help in assessing the gravity of the head injury. Increased reflexes noteworthy on one side suggest irritability in that particular area. Initially only a limp may be noticed in a limb, but frank paralysis signifies a contralateral hematoma.

Localized brain injury or a hematoma may present in the form of focal fits. Widely fixed dilated pupils with or without a concomitant nystagmus is suggestive of a widespread cerebral injury and carries bad prognosis. Dilation of the pupil usually on the ipsilateral side is frequently seen in transtentorial herniation and occurs as a result of compression of the third cranial nerve. Again, it should be noted that cranial nerve palsies are also a frequent accompaniment of cerebral injury.

1.12 Intracranial Hypertension

A strong association between elevated ICP and poor outcome after a severe head injury has been well established. Again it has been stated that the reduction of elevated ICP improves outcome after TBI. Thus, it is essential to understand the pathophysiology of intracranial hypertension so that remedial measures can be adopted to curtail the intracranial hypertension in itself and to prevent any sequelae secondary to a raised intracranial hypertension. There is a convincing and compelling argument to control ICP because a strong association between an ICP >20 mmHg and poor outcome has been well documented [42]. The pathophysiology of intracranial hypertension is complex. Under normal physiological conditions, the blood brain barrier (BBB) serves as a semipermeable membrane, thus preventing the influx of fluid from the cerebral capillaries into the brain parenchyma. The actual flow of fluid into the brain parenchyma however is determined by the transcapillary hydrostatic pressure gradient and the osmotic pressure gradi-

ent. When the BBB is intact, serum osmolarity rather than oncotic pressure controls water movement in and out of the brain. However, when the BBB is seriously disrupted, oncotic pressure may become more important in the determination of ICP as small molecules such as sodium and simple sugars are no longer anatomically excluded from the brain [43]. This scenario is clinically evident and seen in head trauma. The BBB as the name implies serves as a barrier in that it is relatively impermeable to small salutes and proteins. Having said that following head injury or trauma, the BBB no longer serves as a barrier to proteins and electrolytes and thus their flow is facilitated across the disrupted BBB. Hydrostatic pressure thus becomes the driving force for fluid to move from the intravascular space into the brain parenchyma [44]. The influx of fluid into the brain parenchyma or tissue initiates a cascade of events such as an increase in ICP colloquially termed as intracranial hypertension, a decrease in CPP, cerebral hypoxia and an onslaught of secondary brain injury and its attendant devastating sequelae, and in such a complex scenario, our role as clinicians is to interrupt this ongoing vicious cycle and restore a physiological melieu in the intracranial compartment. Mannitol recommended as an osmotic agent of choice by both the brain trauma foundation, and the European Brain Injury Consortium [45, 46] improves CPP and cerebral oxygenation owing to its effects on blood rheology and cardiac output.

An improvement in cerebral oxygenation induces cerebral artery vasoconstriction and subsequent reduction in CBV and ICP. Furthermore, it also brings about a substantial reduction in CSF production, which has a prolonged effect in reducing ICP via the Monro-Kellie doctrine [47].

1.13 Intracranial Pressure Monitoring and Treatment Strategies for Intracranial Hypertension

Head-injured patients have little reserve in intracranial elastance so that small increases in intracranial volume may cause significant increase in ICP. As the physiological basis for cerebral autoregulation lies in vasodilation and a consequent increase in CBV, ICP may actually rise as the blood pressure falls in the patient with intact autoregulation but decreased reserve. This may be the basis for increases in ICP with drugs that lower mean arterial blood pressure (MABP) such as sufentanil and is the basis for considering maintenance of CPP above 70 mmHg when ICP is elevated as in head-injured patients [38].

As ICP monitoring entails its own risks such as parenchymal injury, infection, hemorrhage, malfunction or malposition, it is solely recommended in patients with GCS ≤ 8 with moderate head injury coupled with repeated CT scans in the first 12 h [41]. The gold standard technique for ICP monitoring is a catheter inserted into the lateral ventricle, usually via a small right frontal burr hole. This is connected to a standard pressure transducer via a fluid-filled catheter. After TBI, treatment is instituted when the ICP exceeds 20 mmHg [36]. When the ICP exceeds 20 mmHg, prompt measures have to be adapted because a raised ICP adversely affects the CPP (MAP-ICP) and its attendant sequelae. It has been stated that an ICP >20 mmHg entails poor neurological outcome and thus emergent measures for its reduction should be instituted. In patients with head injury, a CPP below 60 mmHg is associated with a poor outcome and grim prognosis, but a CPP above 60 mmHg has little influence on patients with intracranial lesions [48]. Again hypotension episodes and hypoxemia are highly dreaded complications in the face of raised ICP as both are associated with a poor outcome in patients with severe traumatic brain injuries [49].

Regarding treatment for raised ICP, the fundamental principle is to remove any space occupying lesion and restore the arterial blood gases to their normal values. Some patients may still exhibit signs and symptoms of raised ICP, although the expanding mass has been removed. Under such circumstances, the following treatment strategies should be employed.

1. Mannitol: 100 ml of 20% mannitol infused over 15 min establishes a sufficient osmotic gradient to quench the brain of its added water. The method of infusion is effective and buys time before a planned craniotomy.

Since 6 hourly infusion of mannitol can cause acute tubular necrosis and causes high blood pressures, it is seldom used unless highly indicated.

2. Hyperventilation: The aim of hyperventilation is to promote mild hypocapnia ($PaCO_2$ of 30–35 mmHg) which causes vasoconstriction thus lowering CBV and hence ICP. In some patients, the intracranial complex adapts itself to the new $PaCO_2$ levels after some hours and the ICP again shoots to its previous levels. Hyperventilation below the values mentioned above can be used temporarily before the initiation of further medical or surgical therapies as part of a treatment plan for excessive rises in ICP. Levels of $PaCO_2$ below 25 mmHg are not to be targeted but in fact should be strictly avoided as it brings drastic reductions in CBF which would be halved if the $PaCO_2$ level reaches 20 mmHg. Moreover, extreme hyperventilation can cause arterial hypoxemia and this is seen specially in those patients whose cerebral circulation is already on the brink of inadequacy. Repeated blood gas analysis should be performed and $PaCO_2$ levels checked because lower values can usher in intracerebral steal syndrome as blood gets shunted from the normal brain to the ischemia brain and thus make things all the more complicated and worse by causing hyperemia, cerebral vasodilation and diffuse brain swelling. If correctly and timely applied, hyperventilation not only ensures adequate oxygenation but at the same time guarantees CO_2 removal and both these effects provide hyperventilation its special esteem and place in the realms of critical care management of patients with head injury.
3. CSF drainage: CSF drainage either intermittent or continual is an appealing option for the treatment of elevated ICP because it is devoid of causing adverse systemic effects. This method of treating raised ICP if applied once would fail to achieve its purpose because the CSF production is a continuous process and remains unaltered. On the other hand if withdrawn in excess would cause collapse of the lateral ventricles. Thus, a continuous drainage has been advocated by some, but it should be kept in mind that lumbar drainage of CSF can promote uncal herniation in patients with supratentorial mass lesions and should be avoided in patients with effacement of the ambient cisterns [42].
4. Barbiturate therapy: High-dose barbiturate therapy is considered in traumatic brain-injured patients with high ICP refractory to other treatments [50]. It reduces the metabolic rate and oxygen consumption by causing cerebral vasoconstriction thus decreasing CBV and ICP. Acceptable guidelines to institute high-dose pentobarbital therapy include 30 min of ICP over 30 mmHg despite a CPP of 70 mmHg. Loss of pupillary reactivity commonly seen with high-dose pentobarbital therapy should not be considered as a treatment failure. Barbiturates induce burst suppression [51] which is considered as the goal of sedation. The barbiturate was guided by the bispectral index (BSI) with the infusion rate decreased if the BIS was <6 and increased if the BIS was >15 [52].

Pentobarbital is started in a loading dose of 10 mg/kg over 1 h, followed by 5–10 mg/kg/h. for 3 h. Maintenance of the drug is adjusted at 1 mg/kg/h. It should produce burst suppression in the electroencephalogram (EEG) with maintenance of MABP over 60 mmHg (with dopamine infusion of 10–20 μ/kg/min if needed). The dose should not be increased if ICP reduction is not noticed during burst suppression. Except for a few studies that have shown encouraging results, the clinical results have failed to come up with convincing and unflinching benefit.

5. Steroids: They have been found to be of benefit in the treatment of ischemia or traumatic damage. They are however useful in reducing peritumoral edema and for this reason, dexamethasone is used extensively in neurosurgery. High-dose methylprednisolone with in 8 h from trauma is highly indicated if head injury is associated with acute spinal cord injury.
6. Anticonvulsants: Although widely used, their role in prophylaxis in patients with head injury

remains controversial. Prophylactic antiepileptic drugs are said to be effective in controlling early seizures, but no evidence exists that they would reduce the occurrence of late seizures. Posttraumatic epilepsy occurs in about 15–30% of severely head injured patients and in 5% of closed head injuries or minor head injuries. The incidence is high when the focal damage is near the Rolandic fissure. In the presence of cortical contusion around the epileptogenic area, in the acute phase of subdural hematoma, open skull fractures with dural or cortical lacerations and patients with severe head injury, anticonvulsant therapy is recommended. Following that if the CT scan is normal and there are no seizures, treatment is discontinued otherwise it is continued for a period of 1 year. Phenytoin is the commonly used drug. It is started in a loading dose of 15 and 1 mg/kg as a maintenance drug.

7. Sedative drugs: A struggling and gagging patient can make matters worse, therefore sedation is required. Diazepam is a valuable drug because of its skeletal muscle relaxant property and because it causes a reduction in CBF and cerebral metabolic oxygen consumption. Midazolam and propofol have also been effective when used in sedative doses. When an unconscious patient becomes restless, think of two things. Either he has a full head or a full bladder. Thus, a full bladder should not be forgotten as the cause of restlessness and an indwelling catheter placed in all unconscious patients.

It is to be remembered that pain and anxiety may produce a marked rise in oxygen uptake and CBF because they initiate arousal type of responses. Therefore, some advocate narcotic analgesics such as morphine and fentanyl even in nonresponding patients coupled of course with controlled mechanical ventilation.

8. Diuretic therapy: Among the diuretics, mannitol enjoys widespread popularity based on its effect on volume expansion causing an increase in CPP and in improving CBF because of causing a reduction in the blood viscosity. Lower doses initially are recommended because of the risk of renal failure however, if the targeted effect is not achieved, larger doses can be tried but the serum osmolarity should preferably be kept <320 mOSm/L. Mannitol remains as the osmotic agent of choice [45]. It induces a change in blood rheology and increases cardiac output leading to improved CPP and cerebral oxygenation. It also causes a 50% reduction in the production of CSF, which can lead to a reduction in ICP [47]. A serum osmolarity exceeding 320 mOSmol/L is associated with adverse effects renal and central nervous system effects [53]. Hourly infusion of mannitol can cause acute tubular necrosis and cause high blood pressures, and based on these unwanted effects are seldom employed.

Furosemide in doses ranging from 0.3–0.5 mg/kg potentiates the diuretic effects of mannitol and helps enormously in causing shrinkage of the brain tissue.

9. Hypothermia: There is no convincing report from clinical data as to whether hypothermia employed after TBI improves outcome or not [54]; however, there is an agreement that hyperthermia is potentially dangerous and should be avoided at all costs [55]

1.14 ICU Management of TBI

1.14.1 Mechanical Ventilation

Hyperventilation to the desired value is useful, but if the limits are exceeded, it can act like a dagger with two sharp edges. If correctly employed, it not only ensures adequate oxygenation but at the same time guarantees CO_2 removal, and both these achievements give hyperventilation its special esteem in the management of TBI patients. The arterial PCO_2 should preferably be kept between 25–35 mmHg. Levels below 25 mmHg are not in the interest of the patient because it can cause drastic reductions in CBF and thus initiate cerebral ischemia in a patient

whose cerebral circulation is already on the brink of inadequacy. Levels of $PaCO_2$ should be closely monitored because excessive reductions in $PaCO_2$ can usher in the intracerebral steal syndrome as blood gets shunted from the normal brain to the ischemia brain and thus make the scenario all the more complicated, worse and nonmanageable. Nevertheless, mechanical ventilation is mandatory to control PaO_2 and $PaCO_2$, but those patients with TBI with added trauma to the lungs or in a state of shock needed additional ventilatory strategies such as positive end expiratory pressure (PEEP) and inverse ratio ventilation to circumvent atelectasis [56]. Employing PEEP levels of 10–15 cmH_2O should not be feared as these levels are regarded safe in patients with intracranial hypertension and severe chest trauma and incur no adverse effects on ICP and CPP [57]. The reduction in the functional residual capacity (FRC) and venous admixture due to atelectasis or pulmonary neurogenic edema can be restored to normal by employing PEEP, but these advantages according to some should be weighed against its disadvantages that include a rise in mean intrathoracic pressure reflected by a fall in MABP. The reduction in MABP and the rise in jugular venous pressure can further comprise the CPP and worsen the brain edema. PEEP may improve shunting by restoring the FRC to normal and by reducing hypoxic pulmonary vasoconstriction, but at the same time paradoxically may increase shunting by diverting pulmonary blood flow to nonventilated regions of the lung. Thus, it should be adjusted depending upon the cardiovascular status and according to the other variable.

Similarly, inverse ratio ventilation did not bring significant changes in ICP, MAP and CPP when employed in a clinical study [58], but in rabbit model of raised ICP, it further increased intracranial hypertension [59].

A reduction in $PaCO_2$ causes constriction of the cerebral vessels, decreasing CBF and CBV and thus decreases ICP. However, a reduction in CBF should be gauged with extreme caution as an increased ICP in these patients might already have decreased the CBF to its critical threshold of 18–20 ml/100 g of brain tissue per minute and any further reduction in it would lead to cerebral ischemia and an irreversible brain damage. $PaCO_2$ has a profound influence on the cerebrovascular tone so much so that the CBF gets doubled if the $PaCO_2$ is raised to 80 mmHg and almost gets halved if $PaCO_2$ drops down to 20 mmHg.

Hyperventilation, however, is of value in life threatening situations such as acute elevations in ICP and should not be routinely employed because the extracellular space of the brain accommodates itself to any hyperventilation induced PH change [60].

1.14.2 Hypotension and Hypoxia

Both of these secondary insults adversely affect the outcome of TBI patients and should be avoided under all circumstances. Hypoxia is a natural sequela in seriously head injured unconscious patients. As we all know the brain is highly dependent upon oxygen to perform its skilled functions because anaerobic glycolysis to lactic acid is far from being sufficient to meet cerebral energy demands. Thus, any reduction in the oxygen supply to the brain can be hazardous and often lethal. Hypoxemia and ischemia limit the oxygen availability as dilated upon in the aforementioned paragraphs. Insufficient oxygen as a result of curtailment in the CBF is extremely hazardous to the brain. When hypoxia ensues in patients with head injuries, the cerebral vessels undergo marked vasodilation. This dilatation could be a compensatory phenomenon and perhaps a blessing in disguise to promote a rise in CBF to circumvent the adverse effects secondary to a hypoxic insult. To compensate for less oxygen per unit of blood, vasodilation helps in promoting an increased blood supply to the brain and hence forth more oxygen is made available to the brain in such critical situations. However, it should not erroneously deducted that hypoxia is beneficial as it helps in providing the needed oxygen by causing an increase in CBF. If the PaO_2 falls to 20 mmHg, the stimulus for vasodilation becomes maximum, and a further reduction in PaO_2 leads to anaerobic glycolysis.

Hypoxia by inflicting serious lethal blows finally affects the cellular Na^+-K^+ pump and inactivates it. Subsequent to this inactivation, K^+ leaks out of the damaged cells, and as the pump remains out of order, K^+ cannot be pumped in. Ischemia, which is always accompanied with hypoxia, brings about an increase in brain osmolarity and a reduction in serum osmolarity, thus favoring shift of fluid inside the brain parenchyma. Thus, hypoxia whether hypoxic hypoxia or anemic hypoxia can exacerbate the existing edema by causing release of substances, ionic shifts as well as the production of lactate. The energy stores of the brain are marginal and do not tolerate these hypoxic episodes. In the same context, a rise in $PaCO_2$ brings about marked cerebrovascular dilation which further worsens the prevailing edema and eventually causes a marked rise in ICP [61].

It has been stated in several studies that there is a direct correlation between systemic hypotension and poor outcome and a single episode of hypotension could well double the mortality [45, 62]. Similarly intraoperative hypotension has grave consequences and results in a three-fold increase in mortality [63]. Although an association between early hypoxia ($SPO_2 < 90\%$) and poor outcome does exist [64, 65]; however, the association is not as strong as for hypotension.

1.14.3 Hyper or Hypoglycemia

Hyperglycemia may occur if the glucose load is too much. It would not occur if the glucose administration is slowly or gradually increased, thus allowing the body ample time to produce endogenous insulin to meet the needs and tackle the load. However, if it does occur, it can be adequately controlled by curtailing the glucose administration or else administering insulin. Stress, trauma, infection and the use of drugs such as corticosteroids and glucagon can precipitate hyperglycemia. The onset of hyperglycemia is taken as a bad omen because it is deemed as the conclusive sign of developing sepsis in a previously euglycemic patient.

Hyperglycemia is predictive of an unfavorable outcome and is related to impaired pupillary reaction and intracranial hypertension [66]. Many clinical trials have correlated neurological outcomes and concluded that hyperglycemia worsens the severity of traumatic brain injury [67, 68].

Hypoglycemia on the other hand may occur in patients on glucose infusions if their infusions are suddenly halted.

1.14.4 Hypothermia

Hypothermia has generally being regarded as neuroprotective, but there is no convincing report from the clinical data as to whether hypothermia improves outcome or not [54]. However, there is an agreement that hyperthermia is deleterious and is to be avoided at all costs [55].

1.14.5 Hyponatremia and Hypernatremia

Dilutional hyponatremia is characterized by signs of nausea, emesis, apathy, coarse muscular fibrillation, generalized muscle irritability, disorientation and frank convulsions. These signs would ensue once the serum sodium level falls to 115–125 mEq/L. Hyponatremia hastens the shift of water and ions inside the brain, thus aggravating the edema that exists already or else is in the process of evolution. Hypotonic solutions under these circumstances would be harmful, and therefore, water restriction and salt solution should be considered. While treating hyponatremia, some resort to give normal or even hypertonic saline right at the start. However, if hyponatremia is mild, all that is required is to withhold fluids. If serum sodium level falls below 115 mEq/L, sodium replacement becomes a compulsion and must be carried out to raise the level of sodium to 135 mEq/L. Balanced salt solutions can be employed to maintain the sodium levels in the range of 140–150 mEq/L. But their continued or chronic administration should be timed and adjusted with the serum sodium levels. The patient with head injury has absolutely

no incentive or urge to drink water attributed to confusion and disorientation that commonly accompanies such injuries. Water loss may also ensue as a result of osmotherapy or diabetes insipidus. Hypernatremia is further enhanced by administering sodium penicillin or sodium administration. Signs include delirium, hyperreactive reflexes, muscle twitching and brain damage especially in children. The sodium input varies from as little as 30–40 mmol/24 h to as high as 400–600 mmol/24 h if there is excessive obligatory loss. The usual input however is 120 mmol/24 h.

1.14.6 Fluids, Blood and Blood Products

Both mannitol and furosemide cause massive diuresis. A total of 65–75% of the urine output is to be relapsed with half normal saline and potassium supplements. Losses that are in excess are to be replaced with Ringer lactate so as to keep the serum sodium level within the range of 140–150 meq/L. Packed red cells should be started immediately if the hematocrit level falls below 30% because low levels of hematocrit would cause anemic hypoxia and play havoc with the already traumatized and injured brain [61].

1.14.7 Surgical Options

Surgical exploration is required to remove an epidural, subdural or intracerebral hematoma. An epidural surgical drain at the end of craniotomy and its attachment to a vacuum drainage system and the application of negative pressure to the epidural space led to bradycardia which improved after release of vacuum [69]. Others are of the opinion that the intracranial suction drainage is hazardous and of questionable value and innumerate other causes that can lead to a bradycardic response such as vagal response, closure of craniotomy around a tense brain and cardiac decompensation [70].

If ICP remains elevated despite utilizing the standard and prevailing protocols, and when a CT scan demonstrates diffuse and generalized edema without a mass lesion, a bifrontal craniotomy is indicated [71]. Decompressive craniotomy if performed early may reduce the mortality rate and increase the conscious recovery rate [72]. Similarly, it has been reported that decompression craniotomy could attain social rehabilitation in 25% of severely head injured patients with a high risk of brain death [73].

A 40-year-old male who met a road accident was brought to our centre with severe head injury, acute subdural hematoma and severe brain edema (Fig. 1.5a). Decompression craniotomy performed upon arrival which resulted in resolution of edema and normal lateral ventricles (Fig. 1.5b). Subsequently the patient developed trephine syndrome (Fig. 1.5c). A cranioplasty was performed (Fig. 1.5d) and the patient rehabilitated fully and returned to his work. This case demonstrates the role of decompressive craniotomy at its earliest stage in tackling intractable massive brain edema and a concomitant epidural hematoma evolving within hours of sustaining head injury [74].

1.15 The CPP: What Is Our Target?

In our management of patients with TBI, a plethora of cerebral hemodynamics should be taken into consideration as there exists an extremely complex interplay between the CBF, CBV, ICP and a host of other factors that affect these variables leading to a worsened outcome and a proportionally high morbidity and mortality [75]. Thus, it is imperative to maintain the CBF, arterial oxygen content and cerebral metabolic rate of oxygen consumption in these critical patients. Although among all the variables the CPP has been addressed the most; nevertheless, it has always remained as a bone of contention and there is hardly any consensus about the exact figure of CPP to be maintained in TBI patients. CBF is determined by both the CPP and cerebrovascular resistance (CVR) and is expressed as CBF = CPP/CVR [76]. However, it has to be mentioned that a host of other physiological factors such as PaO_2, $PaCO_2$, PH,$CMRO_2$ and glucose affect both the CBF and the CVR. The basic

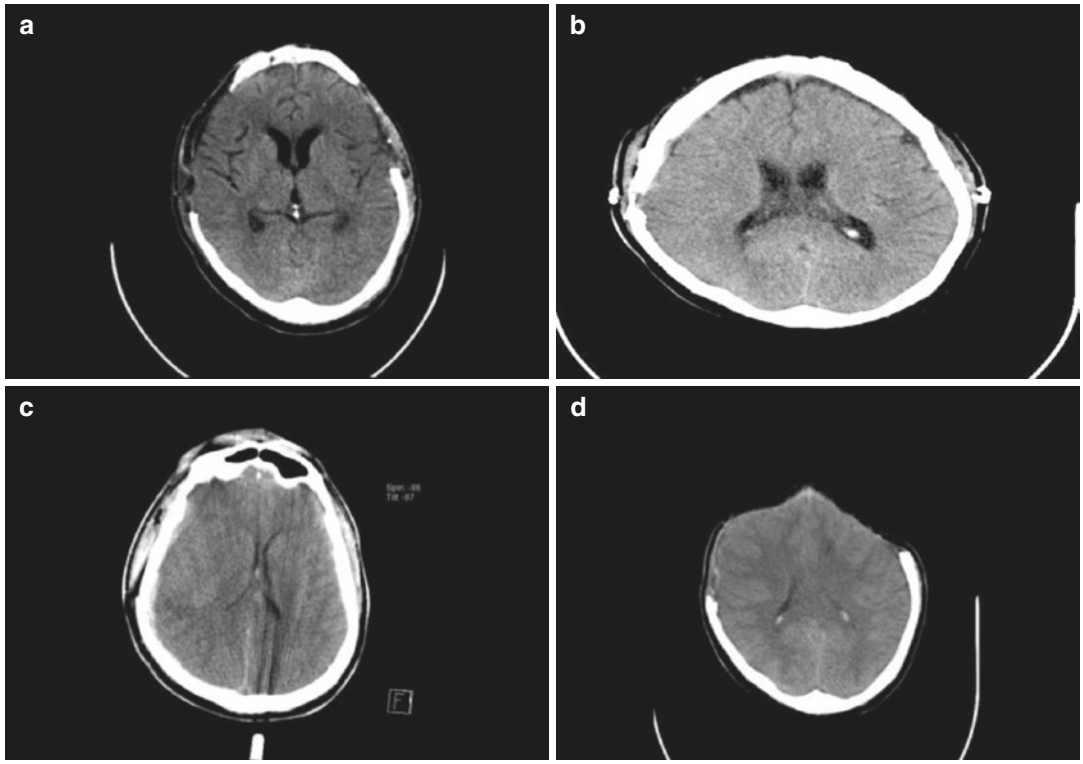

Fig. 1.5 40-year-old man with road accident: Brain CT scan on admission. (**a**) Acute sub-dural hematoma(Rt. Side) (**b**) Post-op CT scan 10 days after operation, bone flaps from frontal and parietal lobes are removed (decompressive craniectomy performed) (**c**) Post-op CT scan 20 days after operation, Trephine syndrome is seen, that is, bilateral hemispheres are compressed because of atmospheric pressure (A known side effect of decompressive craniectomy) (**d**) Post-cranial reconstruction, collapsed brain, is recovered with bone flap replacement

tenet of our understanding is that autoregulation helps in maintaining a stable and a constant CBF over a CPP ranging from 60–150 mmHg. Above and below these figures, the myogenic phenomenon governing the arteriolar diameter gives way and the flow becomes pressure dependent. In normal persons with normal autoregulatory response, an increase in MAP is beneficial as it brings about a reduction in ICP owing to the compensatory vasoconstriction mediated by the autoregulatory response. On the contrary in TBI patients, when the autoregulatory response is impaired, the lower limit of autoregulation has been shifted to the right and thus perhaps would derive some benefit if the MAP is engineered and kept at a level above the normal range [37]. Thus seemingly, the autoregulation is not only not impaired but in fact preserved and shifted to the right thus necessitating a higher CPP to help maintain the CBF. It is also argued that a higher CPP would curtail ICP by causing a reduction in the CBV and brain edema through autoregulatory vasoconstriction. Rosner and Johnson [38] maintained CPP above 70 mmHg and at times raised it to 80–90 mmHg on the valid assumption that the traumatized brain shows a greater hunger for a higher CPP compared to the normal brain.

In sharp contrast to this theory, others claim that TBI patients exhibited cerebral hyper fusion and thus suggested hyperventilation to improve CBF/Oxygen extraction coupling which helps in curtailing ICP [76]. Again, the Lund concept states that when the autoregulation is impaired as is seen in TBI patients, there is an increase in CBF and capillary hydrostatic pressure subsequent to a spike in blood pressure precipitating intracranial hypertension and aggravating the already present or existing cerebral edema.

Under such a tenuous pathological state of intracranial compliance and impaired autoregulatory scenario, a logical approach would include a reduction of the capillary hydrostatic pressure, establishing normovolemia and a normal colloid oncotic pressure apart from preventing cerebral vasoconstriction by maintaining optimal cerebral oxygenation and hyperventilation [77]. Clinical evidence suggests that the CPP is lower after TBI and is deleterious as it worsens the neurological outcome. However, there is little evidence from randomized clinical trials to support a specific CPP target.

The lower limit of the autoregulatory curve may be closer to 70 mmHg rather than 50 mmHg [39]. However, it is to grasped that the lower limit of autoregulation indicates that this is the point at which the CBF starts to decrease rather than the point at which ischemia ensues. The universal strategy has been to bring about a reduction in brain edema or brain bulk and at the same time maintain arterial blood pressure, thus preserving an optimal CPP. However, the dilemma about an optimal CPP remains unresolved, but most agree in maintaining CPP above 60 mmHg [78]. In the same vein, the controversy widens further and it is being held that not only deliberate hypertension entails a risk for TBI patients [79], but there is hardly an evidence that controlled CPP affects the overall outcome [80]. This has been well documented by Cremer et al. [81] in their study that an increase in CPP was of value in those patients who had an ICP >20 mmHg and not in patients with an ICP <20 mmHg. An augmentation of CPP in the former group improved brain tissue oxygen partial pressure ($PtiO_2$) and autoregulatory capacity and at the same time brought a reduction in ICP, but in the latter group failed to bring any improvement in the aforesaid variables.

Some have advocated CPP-directed management and have emphasized in maintaining a CPP of 70 mmHg or higher [38]. This approach obviously prevents secondary ischemic insults, thus controlling ICP by preventing vasodilation secondary to hypotensive episodes. Others, however, have failed to notice a reduction in intracranial hypertension by instituting a CPP targeted management [82]. Fluid loading or vasopressor also entails the risk of cardio-respiratory complications if a target CPP is aimed at [79, 80].

In the same context, some are of the opinion that a rise in MAP in patients with impaired BBB and vasomotor tone can be transmitted to the capillaries, resulting in a sudden rise in capillary hydrostatic pressure and subsequent brain edema. These authors in sharp contrast to others recommend MAP reduction, thus facilitating CPP to values less than 50 mmHg [82].

Both SBP $\leq$ 90 mmHg and hypoxemia $\leq$60 mmHg on admission substantially increase the risk of unfavorable outcomes [83]. Similarly in another study, hypotension proved to be a powerful predictor of adverse outcome [64]. The problem is further aggravated as the compensatory cerebral vasodilation in response to hypotension, hypoxemia and acute anemia is impaired after experimental TBI [84, 85], and such a state is seen in clinical scenarios as well. Severe traumatic brain injury may result in permanent neurological injury if compounded with uncontrolled bleeding [86]. The commonly associated approaches in tackling hemorrhagic hypotension include resuscitation with intravenous fluids and the use of vasoactive drugs. In one study conducted on rats, the authors concluded that both saline in large amounts and phenylephrine produced an increase in blood loss and worsened neurological status or else decreased the overall survival, thus negating the strongly held notion that large amounts of saline or administering phenylephrine to maintain MAP >70 mmHg would improve outcome during the initial hours of hemorrhage following head trauma [87]. Possible explanations forwarded by these authors for the worsened outcome include a sudden increase in the ICP, dislodgement of thrombus, dilution of coagulation factors, cardiovascular compromise and a decreased CPP secondary to a rise in ICP. Their findings however do not deny the indispensable role of supporting the blood pressure in patients with head injury compounded with shock.

Adequate volume management is pivotal in critically ill patients, especially in those with cranio-cerebral trauma. An aggressive fluid resuscitation strategy is needed to maintain an

appropriate CPP counteracting the increased ICP typically seen in these patients. A variety of infusion solutions are available, among them blood products (e.g., packed red blood cells and plasma products), crystalloids, for example, lactated ringer's solution or normal saline and colloids, for example, gelatin, dextran , or hydroxyethylstarch (HES). HES 130/0.4 (6% voluven R) even in large doses is as safe as gelatin preparations [88] and interferes less with blood coagulation and hemostasis [89]. In their study, Neff et al. [90] found that HES 130/0.4 improved microcirculation and provided better rheological properties compared to conventional 200/0.5. It is to be appreciated that in areas with normal autoregulation, a decrease in blood viscosity and hence a decrease in resistance to flow as a result of decreased blood viscosity is balanced by compensatory vasoconstriction. Thus, the net CBF remains unchanged. However, in areas with impaired autoregulation as in TBI, a decrease in viscosity is not accompanied by vasoconstriction with the result that the CBF would increase providing enough oxygen to the highly dependent traumatic brain tissue.

Although most clinical investigations would avoid hypotension, only a few argue based on experimental and clinical observations that arterial blood pressure should be aggressively increased in patients with at TBI [38]. After TBI, cerebral vascular dilation is impaired at previously "normal" blood pressure , which leads to a decrease in CBF. Ischemia is the basis of secondary brain injury after trauma [23] and systemic hypotension is associated with significant morbidity and mortality after TBI [64]. Basically all agree on the basic tenet that hypotension should be avoided at all costs (SBP $\leq$ 90 mmHg) and a CPP maintained above 70 mmHg [90]. Based on this tenet, according to some, the clinical outcome is improved in head injured patients if the CPP is kept above 70 mmHg [38], but others have not supported this so-called aggressive strategy based on lack of agreement with this management paradigm. The Lund method or concept [91] not fully explored maintains CPP at levels as low as 50 mmHg. Talmor et al. [92], however, failed to show any improvement during induced hypertension.

Different solutions have been employed in an attempt to bring an overall improvement in indices such as MAP, CPP and thus an improved neurological outcome. While using hypertonic saline (HTS), it has been claimed that it causes shrinkage of the brain tissue and thus a reduction in ICP. These beneficial effects are observed because it causes an osmotic gradient between the intravascular compartment and the intracellular or interstitial compartments. Based on these properties, HTS is alleged to increase the circulating blood volume, the MAP and the CPP [93]. However, others could not demonstrate an improved outcome in TBI patients given HTS [94]. This latter study makes physicians more cautious in selecting HTS for augmenting volume resuscitation. Nevertheless, animal studies suggest that small volume resuscitation with HTS helps in maintaining hemodynamic stability and thus increase CPP and CBF and decreasing ICP [95]. We all agree that hypertonic fluid improves intracranial compliance and CBF by dehydrating the injured brain. An intact BBB is needed for osmotherapy to be effective. HTS has been found to be more effective than mannitol in reducing ICP because of its longer duration of action of up to 500 min in contrast to 120 min for that of mannitol [96], but regarding improved outcome, none is superior. HTS however is of value in patients with refractory intracranial hypertension as confirmed in many studies [97–99]. HTS (2 ml/kg, 7.5%) has been found to be both helpful and safe for intracranial hypertension episodes [100]. As for other cases, HTS has been reported to be associated with a poor outcome and increased in hospital mortality [101, 102]. Thus, a consensus is lacking regarding its dosage, timing and frequency of administration . As reported, hypertonic-hyperoncotic solutions (HHS) may minimize tissue damage in the brain and heart and improve neurological outcome patients after resuscitation from cardiac arrest and may be useful in restoring both macro and microcirculation after shock and reperfusion [103]. The underlying mechanism involved is a shift of fluid from the endothelial cells into the intravascular space which improves conductance of the microcirculation.

The rationale for hemodilution therapy is based on an observed correlation between reductions in blood viscosity and CBF. Hemodilution has a favorable effect on cerebral ischemia by augmenting CBF via one of the two mechanisms. The first mechanism is by decreasing viscosity of which hematocrit is the major determinant [104], while the second is a direct myogenic vasodilatory response to a reduction in oxygen content [105].

Presently, it is assumed that oncotic pressure has a negligible effect on brain edema formation [106], but others state that brain injury was greater in animals hemodiluted with lactated ringer's solution than in animals hemodiluted with hetastarch [107].

It appears that TBI is a highly diabolical entity and no steadfast rules and guidelines exist in managing these patients as the pathogenesis and the primary insult differs from case to case and likewise the secondary insults also differ. However, most agree that hypotensive and hypoxic episodes should be strictly avoided and all physiological variables such as MAP, CBF, CPP, ICP and arterial jugular venous oxygen saturations monitored as indicated and appropriate measures adopted if there are any alternations from the normal figures.

Conclusion

Traumatic brain injury is an established cause of major morbidity and mortality. Osmotherapy is usually employed to promote an egress of water from the brain tissue thus decreasing intracranial pressure. The cerebral hemodynamics and intracranial compliance should be optimized to ensure adequate cerebral blood flow. In cases of intractable brain edema, decompressive craniectomy can be the only plausible solution in salvaging the brain from additional insults of raised intracranial pressure and its highly deleterious aftermath.

References

1. Corrigan JD, Selassie AW, Orman JA. The epidemiology of traumatic brain injury. J Head Trauma Rehabil. 2010;25(2):72–80.
2. Marmarou A, Shulman K, Rosende RM. A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics. J Neurosurg. 1978;48(3):332–44.
3. Raabe A, Czosnyka M, Piper I, Seifert V. Monitoring of intracranial compliance: correction for a change in body position. Acta Neurochir. 1999;141(1):31–6.
4. Marmarou A, Maset AL, Ward JD, Choi S, Brooks D, Lutz HA, Moulton RJ, Muizelaar JP, Desalles A, Young HF. Contribution of CSF and vascular factors to elevation of ICP in severely head-injured patients. J Neurosurg. 1987;66(6):883–90.
5. Miller JD, Garibi J. Intracranial volume/pressure relationships during continuous monitoring of ventricular fluid pressure. In: Intracranial pressure. Berlin/Heidelberg: Springer; 1972. p. 270–4.
6. Miller JD, Garibi J, Pickard JD. Induced changes of cerebrospinal fluid volume: effects during continuous monitoring of ventricular fluid pressure. Arch Neurol. 1973;28(4):265–9.
7. Monro A. Observations on the structure and function of the nervous system. Edinburgh: Creech & Johnston; 1783.
8. Kellie G. An account of the appearances observed in the dissection of two of three individuals presumed to have perished in the storm of the third and whose bodies were discovered in the vicinity of Leith on the morning of the 4th, November 1821, with some reflections on the pathology of the brain. Trans Med Chir Soc (Edinburgh). 1824;1:84–169.
9. Weed LH, McKibben PS. Pressure changes in the cerebro-spinal fluid following intravenous injection of solutions of various concentrations. Am J Physiol. 1919;48(4):512–30.
10. Weed LH. Some limitations of the Monro-Kellie hypothesis. Arch Surg. 1929;18(4):1049–68.
11. Davson H. Physiology of the cerebrospinal fluid. London: Churchill; 1967.
12. Marmarou A, Foda MA, Bandoh K, Stocchetti N, Yoshihara M, Young HF. Elevated venous outflow pressure in head injured patients. In: Intracranial pressure VIII, vol. 1. Berlin/Heidelberg: Springer; 1993. p. 712–5.
13. Gray WJ, Rosner MJ. Pressure-volume index as a function of cerebral perfusion pressure: part 1: the effects of cerebral perfusion pressure changes and anesthesia. J Neurosurg. 1987;67(3):369–76.
14. Portnoy HD, Branch C, Chopp M. The CSF pulse wave in hydrocephalus. Childs Nerv Syst. 1985;1(5):248–54.
15. Heifetz MD, Weiss M. Detection of skull expansion with increased intracranial pressure. J Neurosurg. 1981;55(5):811–2.
16. Chopp M, Portnoy HD, Branch C. Hydraulic model of the cerebrovascular bed: an aid to understanding the volume-pressure test. Neurosurgery. 1983;13(1):5–11.
17. Zee CM, Shapiro K. The viscoelasticity of normal and hydrocephalic brain tissue. In: Intracranial pressure VII. Berlin/Heidelberg: Springer; 1989. p. 263–6.
18. Walsh EK, Schettini A. Brain tissue elasticity and CSF elastance. In: Intracranial pressure VII. Berlin/Heidelberg: Springer; 1989. p. 271–4.

19. Avezaat C, van Eijndhoven JH. Cerebrospinal fluid pulse pressure and craniospinal dynamics: a theoretical, clinical and experimental study. Erasmus: University Medical Center Rotterdam; 1984.
20. Czosnyka M, Piechnik S, Koszewski W, Laniewski P, Maksymowicz W, Paluszek K, Smielewski P, Zabolotny W, Zaworski W. The dynamics of cerebral blood flow, perfusion pressure and CSF circulation—a modelling study. In: Intracranial pressure VIII. Berlin/Heidelberg: Springer; 1993. p. 699–706.
21. Binder S, Corrigan JD, Langlois JA. The public health approach to traumatic brain injury: an overview of CDC's research and programs. J Head Trauma Rehabil. 2005;20(3):189–95.
22. Stiefel MF, Tomita Y, Marmarou A. Secondary ischemia impairing the restoration of ion homeostasis following traumatic brain injury. J Neurosurg. 2005;103(4):707–14.
23. Bouma GJ, Muizelaar JP, Choi SC, Newlon PG, Young HF. Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. J Neurosurg. 1991;75(5):685–93.
24. Marion DW, Darby J, Yonas H. Acute regional cerebral blood flow changes caused by severe head injuries. J Neurosurg. 1991;74(3):407–14.
25. Bouma GJ, Muizelaar JP, Stringer WA, Choi SC, Fatouros P, Young HF. Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. J Neurosurg. 1992;77(3):360–8.
26. Reilly PL. Brain injury: the pathophysiology of the first hours.'Talk and Die revisited'. J Clin Neurosci. 2001;8(5):398–403.
27. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. Br J Anaesth. 2007;99(1):4–9.
28. Ishige N, Pitts LH, Hashimoto T, Nishimura MC, Bartkowski HM. Effect of hypoxia on traumatic brain injury in rats: part 1: changes in neurological function, electroencephalograms, and histopathology. Neurosurgery. 1987;20(6):848–53.
29. Ishige N, Pitts LH, Pogliani L, Hashimoto T, Nishimura MC, Bartkowski HM, James TL. Effect of hypoxia on traumatic brain injury in rats: part 2: changes in high energy phosphate metabolism. Neurosurgery. 1987;20(6):854–8.
30. Thiagarajan A, Goverdhan PD, Chari P, Somasunderam K. The effect of hyperventilation and hyperoxia on cerebral venous oxygen saturation in patients with traumatic brain injury. Anesth Analg. 1998;87(4):850–3.
31. Obrist WD, Langfitt TW, Jaggi JL, Cruz J, Gennarelli TA. Cerebral blood flow and metabolism in comatose patients with acute head injury: relationship to intracranial hypertension. J Neurosurg. 1984;61(2):241–53.
32. Muizelaar JP, Lutz III HA, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. J Neurosurg. 1984;61(4):700–6.
33. DeWitt DS, Prough DS, Taylor CL, Whitley JM. Reduced cerebral blood flow, oxygen delivery, and electroencephalographic activity after traumatic brain injury and mild hemorrhage in cats. J Neurosurg. 1992;76(5):812–21.
34. Clifton GL, Ziegler MG, Grossman RG. Circulating catecholamines and sympathetic activity after head injury. Neurosurgery. 1981;8(1):10–4.
35. Malik AB. Mechanisms of neurogenic pulmonary edema. Circ Res. 1985;57(1):1–8.
36. The brain trauma Foundation. The American Association of Neurological Surgeons. The joint section on neurotrauma and critical care. Intracranial pressure threshold. J Neurotrauma. 2007;24:S55–8.
37. Baguley IJ, Nicholls JL, Felmingham KL, Crooks J, Gurka JA, Wade LD. Dysautonomia after traumatic brain injury: a forgotten syndrome? J Neurol Neurosurg Psychiatry. 1999;67(1):39–43.
38. Rosner MJ, Rosner SD, Johnson AH. Cerebral perfusion pressure: management protocol and clinical results. J Neurosurg. 1995;83(6):949.
39. Drummond JC. The lower limit of autoregulation time to revise our thinking? Anesthesiology. 1997;86(6):1431–3.
40. Simard JM, Bellefleur M. Systemic arterial hypertension in head trauma. Am J Cardiol. 1989;63(6):C32–5.
41. Iacoangeli M, Roselli R, Pompucci A, Scerrati M. Acute management of head injury: part I: medical management. Contemp Neurosurg. 2000;22(11):1–8.
42. Marion DW, Letarte PB. Management of intracranial hypertension. Contemp Neurosurg. 1997;19(3):1–6.
43. Zornow MH, Todd MM, Moore SS. The acute cerebral effects of changes in plasma osmolality and oncotic pressure. Anesthesiology. 1987;67(6):936–41.
44. Harukuni I, Kirsch JR, Bhardwaj A. Cerebral resuscitation: role of osmotherapy. J Anesth. 2002;16(3):229–37.
45. The brain trauma Foundation. Management and prognosis of severe traumatic brain injury. New York: Brain Trauma Foundation; 2000.
46. Maas AI, Dearden M, Teasdale GM, Braakman R, Cohadon F, Iannotti F, Karimi A, Lapierre F, Murray G, Ohman J, Persson L. EBIC-guidelines for management of severe head injury in adults. Acta Neurochir. 1997;139(4):286–94.
47. Paczynski RP. Osmotherapy: basic concepts and controversies. Crit Care Clin. 1997;13(1):105–29.
48. Juul N, Morris GF, Marshall SB, Marshall LF. Intracranial hypertension and cerebral perfusion pressure: influence on neurological deterioration and outcome in severe head injury. J Neurosurg. 2000;92(1):1–6.
49. Chesnut RM. Avoidance of hypotension: conditio sine qua non of successful severe head-injury management. J Trauma Acute Care Surg. 1997;42(5S):4S–9S.
50. The brain trauma Foundation.The American Association of Neurological Surgeons. The joint section on neurotrauma and critical care. Initial magement. J Neurotrauma. 2000;17:463–9.
51. Kiersey DK, Bickford RG, Faulconer A. Electroencephalographic patterns produced by thiopental sodium during surgical operations: description and classification. Br J Anaesth. 1951;23(3):141–52.

52. White H, Cook D, Venkatesh B. The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury. Anesth Analg. 2006;102(6):1836–46.
53. Roberts I, Schierhout G, Wakai A. Mannitol for acute traumatic brain injury. Cochrane Database Syst Rev:CD001049.
54. Clifton GL. Is keeping cool still hot? An update on hypothermia in brain injury. Curr Opin Crit Care. 2004;10(2):116–9.
55. Grocott HP, Mackensen GB, Grigore AM, Mathew J, Reves JG, Phillips-Bute B, Smith PK, Newman MF. Neurologic Outcome Research Group, Cardiothoracic Anesthesiology Research Endeavors (CARE) Investigators of the Duke Heart Center. Postoperative hyperthermia is associated with cognitive dysfunction after coronary artery bypass graft surgery. Stroke. 2002;33(2):537–41.
56. Schreiter D, Reske A, Stichert B, Seiwerts M, Bohm SH, Kloeppel R, Josten C. Alveolar recruitment in combination with sufficient positive end-expiratory pressure increases oxygenation and lung aeration in patients with severe chest trauma. Crit Care Med. 2004;32(4):968–75.
57. Huynh T, Messer M, Sing RF, Miles W, Jacobs DG, Thomason MH. Positive end-expiratory pressure alters intracranial and cerebral perfusion pressure in severe traumatic brain injury. J Trauma Acute Care Surg. 2002;53(3):488–93.
58. Clarke JP. The effects of inverse ratio ventilation on intracranial pressure: a preliminary report. Intensive Care Med. 1997;23(1):106–9.
59. Taplu A, Gökmen N, Erbayraktar S, Sade B, Erkan N, Karadibak K, Arkan A. Effects of pressure-and volume-controlled inverse ratio ventilation on haemodynamic variables, intracranial pressure and cerebral perfusion pressure in rabbits: a model of subarachnoid haemorrhage under isoflurane anaesthesia. Eur J Anaesthesiol. 2003;20(09):690–6.
60. Robertson C. Every breath you take: hyperventilation and intracranial pressure. Cleve Clin J Med. 2004;71:S14–5.
61. Khan ZH, Tabatabai S. Head injuries, pathophysiology and management. Jahad Daneshgahi: Tehran University of Medical Sciences; 1992. p. 30–42.
62. Chesnut RM, Marshall SB, Piek J, Blunt BA, Klauber MR, Marshall LF. Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in the Traumatic Coma Data Bank. Acta Neurochir. 1993;59:121–5.
63. Pietropaoli JA, Rogers FB, Shackford SR, Wald SL, Schmoker JD, Zhuang J. The deleterious effects of intraoperative hypotension on outcome in patients with severe head injuries. J Trauma Acute Care Surg. 1992;33(3):403–7.
64. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, Jane JA, Marmarou A, Foulkes MA. The role of secondary brain injury in determining outcome from severe head injury. J Trauma. 1993;34(2):216–22.
65. Jeremitsky E, Omert L, Dunham CM, Protetch J, Rodriguez A. Harbingers of poor outcome the day after severe brain injury: hypothermia, hypoxia, and hypoperfusion. J Trauma Acute Care Surg. 2003;54(2):312–9.
66. Rovlias A, Kotsou S. The influence of hyperglycemia on neurological outcome in patients with severe head injury. Neurosurgery. 2000;46(2):335.
67. Longstreth WT, Inui TS. High blood glucose level on hospital admission and poor neurological recovery after cardiac arrest. Ann Neurol. 1984;15(1):59–63.
68. Pulsinelli WA, Levy DE, Sigsbee B, Scherer P, Plum F. Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. Am J Med. 1983;74(4):540–4.
69. Wasnick JD, Lien CA, Rubin LA, Fraser RA. Unexplained bradycardia during craniotomy closure: the role of intracranial hypotension. Anesth Analg. 1993;76(2):432–3.
70. Khan ZH, Tabatabai SA. Unexplained bradycardia during craniotomy closure: the role of intracranial hypotension. Anesth Analg. 1994;79(5):1024.
71. Polin RS, Shaffrey ME, Bogaev CA, Tisdale N, Germanson T, Bocchicchio B, Jane JA. Decompressive bifrontal craniectomy in the treatment of severe refractory posttraumatic cerebral edema. Neurosurgery. 1997;41(1):84–94.
72. Cho DY, Chen TC, Lee HC. Ultra-early decompressive craniectomy for malignant middle cerebral artery infarction. Surg Neurol. 2003;60(3):227–32.
73. Albanèse J, Leone M, Alliez JR, Kaya JM, Antonini F, Alliez B, Martin C. Decompressive craniectomy for severe traumatic brain injury: Evaluation of the effects at one year. Crit Care Med. 2003;31(10):2535–8.
74. Khan ZH, Zeinalizadeh M. Successful outcome following decompressive craniectomy in a patient with severe traumatic brain injury. 2015. [Unpublished data].
75. Lassen NA. Control of cerebral circulation in health and disease. Circ Res. 1974;34(6):749–60.
76. Cruz J. The first decade of continuous monitoring of jugular bulb oxyhemoglobin saturation: management strategies and clinical outcome. Crit Care Med. 1998;26(2):344–51.
77. White H, Venkatesh B. Cerebral perfusion pressure in neurotrauma: a review. Anesth Analg. 2008;107(3):979–88.
78. The brain Trauma Foundation. Update notice: guide lines for the management of severe traumatic brain injury. Cerebral perfusion pressure. New York: The brain trauma Foundation ; 2003.Available from http://www2.braintrauma.org/guidelines/
79. Contant CF, Valadka AB, Gopinath SP, Hannay HJ, Robertson CS. Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. J Neurosurg. 2001;95(4):560–8.
80. Robertson CS, Valadka AB, Hannay HJ, Contant CF, Gopinath SP, Cormio M, Uzura M, Grossman RG. Prevention of secondary ischemic insults after severe head injury. Crit Care Med. 1999;27(10):2086–95.

81. Cremer OL, van Dijk GW, Amelink GJ, de Smet AM, Moons KG, Kalkman CJ. Cerebral hemodynamic responses to blood pressure manipulation in severely head-injured patients in the presence or absence of intracranial hypertension. Anesth Analg. 2004;99(4):1211–7.
82. Kongstad L, Grände PO. Arterial hypertension increases intracranial pressure in cat after opening of the blood-brain barrier. J Trauma Acute Care Surg. 2001;51(3):490–6.
83. Miller JD, Butterworth JF, Gudeman SK, Faulkner JE, Choi SC, Selhorst JB, Harbison JW, Lutz HA, Young HF, Becker DP. Further experience in the management of severe head injury. J Neurosurg. 1981;54(3):289–99.
84. Lewelt W, Jenkins LW, Miller JD. Effects of experimental fluid-percussion injury of the brain on cerebrovascular reactivity to hypoxia and to hypercapnia. J Neurosurg. 1982;56(3):332–8.
85. DeWitt DS, Prough DS, Taylor CL, Whitley JM, Deal DD, Vines SM. Regional cerebrovascular responses to progressive hypotension after traumatic brain injury in cats. Am J Physiol Heart Circ Physiol. 1992;263(4):H1276–84.
86. Avellino AM, Lam AM, Winn HR. Management of acute head injury. Textbook of Neuroanesthesia. New York: McGraw Hill; 1997. p. 1137–75.
87. Talmor D, Merkind V, Artru AA, Shapiro O, Geva D, Roytblat L, Shapira Y. Treatments to support blood pressure increases bleeding and/or decreases survival in a rat model of closed head trauma combined with uncontrolled hemorrhage. Anesth Analg. 1999;89(4):950.
88. Haisch G, Boldt J, Krebs C, Suttner S, Lehmann A, Isgro F. Influence of a new hydroxyethylstarch preparation (HES 130/0.4) on coagulation in cardiac surgical patients. J Cardiothorac Vasc Anesth. 2001;15(3):316–21.
89. Neff TA, Doelberg M, Jungheinrich C, Sauerland A, Spahn DR, Stocker R. Repetitive large-dose infusion of the novel hydroxyethyl starch 130/0.4 in patients with severe head injury. Anesth Analg. 2003;96(5):1453–9.
90. The Brain Trauma Foundation. Resuscitation of blood pressure and oxygenation. J Neurotrauma. 1996;13:661–6.
91. Grande PO, Asgeirsson B, Nordstrom CH. Physiologic principles for volume regulation of a tissue enclosed in a rigid shell with application to the injured brain. J Trauma Acute Care Surg. 1997;42(5S):23S–31S.
92. Talmor D, Roytblat L, Artru AA, Yuri O, Koyfman L, Katchko L, Shapira Y. Phenylephrine-induced hypertension does not improve outcome after closed head trauma in rats. Anesth Analg. 1998;87(3):574–8.
93. Schmoker JD, Shackford SR, Wald SL, Pietropaoli JA. An analysis of the relationship between fluid and sodium administration and intracranial pressure after head injury. J Trauma Acute Care Surg. 1992;33(3):476–81.
94. Cooper DJ, Myles PS, McDermott FT, Murray LJ, Laidlaw J, Cooper G, Tremayne AB, Bernard SS, Ponsford J. HTS Study Investigators. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. JAMA. 2004;291(11):1350–7.
95. Shackford SR. Effect of small-volume resuscitation on intracranial pressure and related cerebral variables. J Trauma Acute Care Surg. 1997;42(5S):48S–53S.
96. Mirski AM, Dencher ID, Schnitzer SM, Hanley FD. Comparison between hypertonic saline and manitol in the reduction of elevated intracranial pressure in a rodent model of acute cerebral injury. J Neurosurg Anesthesiol. 2000;12:334–44.
97. Worthley LI, Cooper DJ, Jones N. Treatment of resistant intracranial hypertension with hypertonic saline: report of two cases. J Neurosurg. 1988;68(3):478–81.
98. Einhaus SL, Croce MA, Watridge CB, Lowery R, Fabian TC. The use of hypertonic saline for the treatment of increased intracranial pressure. J Tenn Med Assoc. 1996;89(3):81.
99. Härtl R, Ghajar J, Hochleuthner H, Mauritz W. Treatment of refractory intracranial hypertension in severe traumatic brain injury with repetitive hypertonic/hyperoncotic infusions. Zentralbl Chir. 1996;122(3):181–5.
100. Vialet R, Albanèse J, Thomachot L, Antonini F, Bourgouin A, Alliez B, Martin C. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. Crit Care Med. 2003;31(6):1683–7.
101. Qureshi AI, Suarez JI, Bhardwaj A. Malignant cerebral edema in patients with hypertensive intracerebral hemorrhage associated with hypertonic saline infusion a rebound phenomenon? J Neurosurg Anesthesiol. 1998;10(3):188–92.
102. Qureshi AI, Suarez JI, Castro A, Bhardwaj A. Use of hypertonic saline/acetate infusion in treatment of cerebral edema in patients with head trauma: experience at a single center. J Trauma Acute Care Surg. 1999;47(4):659.
103. Christ F, Niklas M, Kreimeier U, Lauterjung L, Peter K, Messmer K. Hyperosmotic-hyperoncotic solutions during abdominal aortic aneurysm (AAA) resection. Acta Anaesthesiol Scand. 1997;41(1):62–70.
104. Harrison MJ. Influence of haematocrit in the cerebral circulation. Cerebrovasc Brain Metab Rev. 1988;1(1):55–67.
105. Brown MM, Wade JP, Marshal J. Fundamental importance of arterial oxygen content in the regulation of cerebral blood flow in man. Brain. 1985;108(1):81–93.
106. Zornow MH, Prough DS. Fluid management in patients with traumatic brain injury. New Horiz. 1995;3(3):488–98.
107. Korosue K, Heros RC, Ogilvy CS, Hyodo A, Tu YK, Graichen R. Comparison of crystalloids and colloids for hemodilution in a model of focal cerebral ischemia. J Neurosurg. 1990;73(4):576–84.

2 Advanced Monitoring in Neurocritical Care: Brain Tissue Oxygen Pressure

Rafael Badenes and Armando Maruenda

2.1 Introduction

Our brain represents only 2–3% of the total body weight, but its activity comprises 25% of the total energy expended, and 20% of cardiac output goes toward it. Its high metabolic demands—the brain consumes between 25% and 45% of the oxygen that reaches it—as well as its incapacity to store glucose (its main energy substrate), oxygen itself, or high-energy phosphated molecules explain its total dependence on a continuous supply of substrates through the bloodstream that make it possible to meet this demand.

The main objective of neuromonitoring is early detection, attempting through therapeutic measures to avoid or reduce secondary brain injury. Achieving this objective involves ensuring an adequate supply of oxygen to the brain.

The failure to maintain adequate cerebral oxygenation aggravates secondary injury. There is a direct correlation between episodes of cerebral hypoxia and the poor functional status of patients, as proved through the Glasgow Outcome Scale. This affects all types of neurocritical pathologies: subarachnoid hemorrhage (SAH), cranioencephalic trauma (CET), cerebrovascular accident (CVA), anoxic coma [1–3].

Hypoxia is defined as the decrease of tissue oxygenation—in this case, of brain tissue—to levels insufficient to maintain its function and metabolism. According to Siggaard–Andersen's classification, there are seven types of tissue hypoxia [4]. The most frequent causes of cerebral hypoxia are ischemic hypoxia, due to a cerebral blood flow (CBF) lower than what the brain requires, generally due to increased intracranial pressure (ICP) and/or low cerebral perfusion pressure (CPP), without neglecting systemic causes such as hypocapnia or hypothermia from low oxygen extraction conditions (P_{50} low blood pressure) or from anemia. As a matter of fact, hyperoxia can also be harmful sometimes.

To detect hypoxia and/or tissue ischemia, we have a considerable diagnostic–therapeutic arsenal [5]. On the one hand, we have the variables that provide us with indirect information about the global cerebral blood flow (cerebral perfusion pressure, jugular bulb oximetry techniques, transcranial Doppler, near-infrared spectroscopy (NIRS), and on the other hand, we have metabolic (cerebral microdialysis) and blood parameters (hemoglobin content, arterial oxygen saturation, partial pressure of oxygen, etc.) as well as the hemodynamic variables that are increasingly crucial to the survival of these patients [6]. The joint analysis of all these variables provides us with extremely valuable

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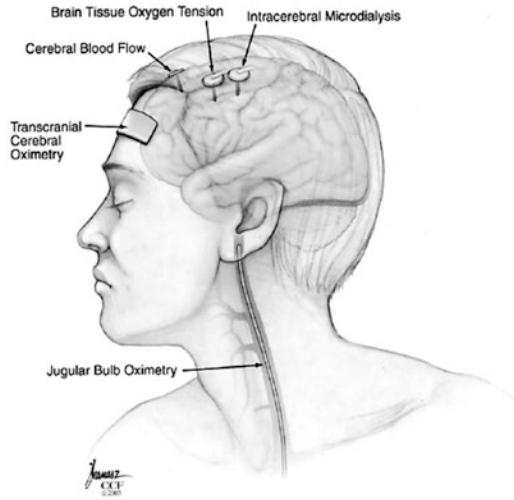

Fig. 2.1 Multimodal neuromonitoring available at the patient's bedside (Reproduced with permission from Fleckenstein [8], Deogaonkar [73])

information regarding tissue oxygen availability. However, none of these means offers direct information about the degree of brain tissue oxygenation.

At the clinic, we currently offer the possibility of measuring O_2 pressure directly from the encephalic parenchyma [7]. The measurement of $PtiO_2$ (partial pressure of brain tissue oxygen, measured in mmHg) is continuous, objective, direct, and in real time. The aim of this review is to provide a simple yet comprehensive view of the role that $PtiO_2$ plays as a clinical monitoring method to locally quantify the degree of cerebral ischemia in neurocritical patients as well as its clinical application (Fig. 2.1).

2.2 Fundamentals

It is worth mentioning that tissue oximetry sensors were originally designed to be used in transplants, as they were considered a very useful tool to quantify the viability of the transplanted organ. In the brain, their initial directions were for the measurement of oxygen pressure in the cerebrospinal fluid in the field of animal testing [8] and then subsequently in humans [9].

Quantification of $PtiO_2$ in the brain is done by inserting a small oxygen-sensitive microcatheter into the encephalic parenchyma. After the Kett–White studies [10] it is assumed that the $PtiO_2$ value obtained corresponds to the partial pressure of oxygen at the end of the capillary network, this being an average value of the vascular, intracellular, and extracellular compartments.

We currently have two types of invasive devices whose purpose is to measure tissue oxygen pressure: one is Licox® (PMO Integra LifeSciences, Plainsboro, NJ) and the other is Neurovent® (PTO-Raudomedic Lifeline to Health, G). The main differences between them lie in the manner of detection, the depth of insertion, and in the diameter of the area measured.

A third device, *Neurotrend* ® (Multiparameter Intravascular Sensor, Biomedical Sensors, Malvern, PA) determines, aside from $PtiO_2$, CO_2 tissue pressure ($PtiCO_2$) and tissue pH (pHti). Measurement of $PtiO_2$ is done using optical luminescence. The oxygen molecules disperse from the brain tissue in a silicone matrix and they change the color of a ruthenium coloring. This change of color affects the frequency of the halo of light emitted by a fiber optic filament, and this change in frequency then turns into a partial pressure of oxygen. At present, this device is no longer commercially available.

We make use of the *LICOX*® system. We perform its implantation in conjunction with the neurosurgical service, both in the intensive care unit and in the operating room. It is inserted by means of a threaded bolt (Fig. 2.2) which may be single or double lumen (one for $PtiO_2$ and the other for ICP).

The catheter is inserted approximately 25 mm below the dura mater and finally placed in the infracortical white matter. Measurement of tissue oxygen pressure is done using a Clark-type polarographic electrode mounted on a catheter. It does not determine $PtiCO_2$ or pHti. The part sensitive to PO_2, called revoxode (Fig. 2.3), is found 5 mm from the intracranial tip of the catheter. It determines a mean tissue oxygen pressure within an area measuring 22 mm. In the sensitive area of the electrode, oxygen dissolves in an aqueous electrolyte solution at a pH of 7.4. The membrane has to be only permeable to oxygen. Oxygen

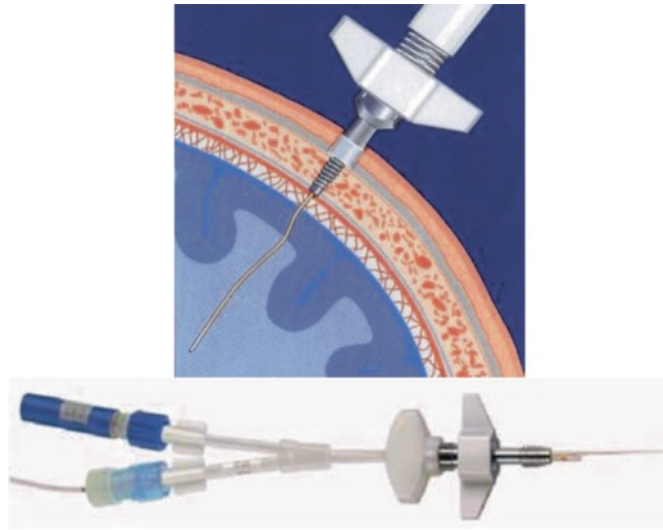

Fig. 2.2 Double lumen threaded bolt (one for $PtiO_2$ and the other for ICP). Intraparenchymal location in which the $PtiO_2$ sensor is placed

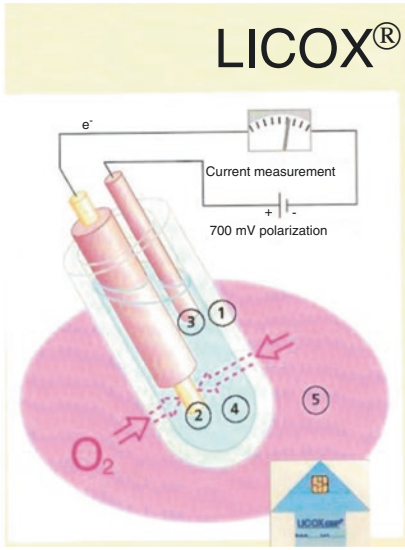

Fig. 2.3 The revoxode is found at the distal tip, where the oxidation–reduction reactions that generate the electrical current that will determine the $PtiO_2$ value will take place (ceded by GMS). (*1*) Oxygen diffusion membrane. (*2*) Polarographic cathode. (*3*) Cathode insulation. (*4*) Anode. (*5*) Electrolytic solution

from the tissue disperses to the inside of the electrode and is transformed into OH^- ions in the cathode according to the reaction:

$$O_2 + 2H_2O + 4e^- \longrightarrow 4\,OH^-$$

This reaction takes place in the (gold-coated) cathode of a polarographic circuit. The anode contains silver. The diffusion membrane has to be only permeable to O_2 and it separates the electrolyte chamber from the tissue. The electrodes are calibrated during manufacture, in terms of sensitivity, the zero point (in the absence of oxygen), and the thermal coefficient (sensitivity % with regard to degrees centigrade). The determination of $PtiO_2$ depends on tissue temperature, with a variance of approximately 4.4% for each degree of change in temperature [10]. The Licox system® makes it possible to continuously monitor brain temperature. The reduction of oxygen generates an electrical current, detected by a voltmeter that digitalizes the electrical signal, which appears as a numerical value on the front panel monitor (Integra Licox® monitor).

Although the INTEGRA® monitor was recently introduced at the clinic, numerous studies have proven that the $PtiO_2$ monitoring method, thanks to the Clark-type polarographic electrode, is safe, reliable, and technically simple to assess cerebral oxygenation until 7–10 days after its placement. When brain T exceeds 39 °C, results may vary.

Neurovent® (PTO-Raudomedic Lifeline to Health, G), a new device for the measurement of $PtiO_2$, was recently launched in the market. It is a

fiber optic catheter which is thicker than the Licox device, and is also meant for intraparenchymal use. The catheter itself has an ICP, temperature, and $PtiO_2$sensor. It has a transducer (NPS 2, Raumedic) which enables connection to the ICU bedside monitors, such as those of Datex Omeda.

Neurovent® measures $PtiO_2$ in the same way as Paratrend using the method of luminescence. Using in vitro comparison with the Licox system, both offer similar results in terms of accuracy and stability [11]. In animal testing, it has been observed that increases in ICP with CPP <30 mmHg match increases in the lactate/pyruvate ratio obtained through microdialysis and $PtiO_2$ <10 mmHg, which would indicate cerebral ischemia [12]. Although some publications can be found at the clinic [13], there is still not enough evidence to interpret the meaning of the low $PtiO_2$ values obtained by this device.

2.3 Method of Implantation

In accordance with the guidelines of our intensive care unit, when we have a patient with instructions to monitor the ICP, we also monitor the $PtiO_2$ and the temperature of the encephalic parenchyma. We do this by drilling a single burr hole and placing a double lumen (ICP and $PtiO_2$) intracranial bolt.

As we have already mentioned previously, the Licox® sensors do not require calibration. Each sensor comes with a smart card containing a microchip, which will be inserted into the relevant slot on the monitor when required (Fig. 2.4).

Fig. 2.4 Integra monitor used on a patient with severe CET, which shows the $PtiO_2$ and brain T values, as well as the smart card for individual calibration of the Licox® (PMO) sensor on the right side of the image

The sensor is systematically placed by a doctor from the neurosurgical service in the intensive care unit. With a minimal, single burr hole craniostomy, the threaded bolt is attached to the cranial vault. The bolt serves as a guide for the sensor's introducer, by making a trajectory in the encephalic parenchyma. We insert the oximetry sensor through the introducer and then we attach it to the introducer. The microtrauma that results from sensor insertion into the encephalic parenchyma [14] makes the initial $PtiO_2$ readings not have high levels of reliability until 40–120 min have passed according to the studies by Van den Brink [15] and Dings [16].

As regards the systematic assessment of variables such as sensitivity and the deviation from 0 of the sensor, we do not do this routinely, based on the results published by Dings [17] and Poca [18].

With regard to the most suitable place to insert the $PtiO_2$ sensors, opinions vary. On the one hand, there are those who advocate the implantation of the sensor on the healthy hemisphere, taking into account that this hemisphere can be extrapolated to all of the healthy tissue, with the purpose of "protecting" this healthy tissue from the appearance of the much-feared secondary injuries. On the contrary, it is worth mentioning that the most valuable information comes from the ischemic penumbra, considering as such the tissue surrounding the focal lesions [19]. The Consensus Conference on Neuromonitoring [20] suggests that the site of sensor placement should be chosen individually, depending on the diagnosis, type, and location of the brain injury and the ease of insertion technique (strongly recommended, low level of evidence). After assessing the different opinions thereon, and in line with the published literature, at our intensive care unit, in case of diffuse injuries, we place the sensor on the right hemisphere in conjunction with the ICP. In the case of a focal lesion, we try to place the sensor in the more injured hemisphere near the ischemic penumbra. In any case, in accordance with the current clinical guidelines for neuromonitoring, we perform a computed tomography (CT) scan to check its placement. We know for certain that in some centers, in the cases of focal lesions, whenever possible, they place two sensors—one in each hemisphere [18, 21].

Another much-debated issue is whether the sensor should be placed in white matter or gray matter.

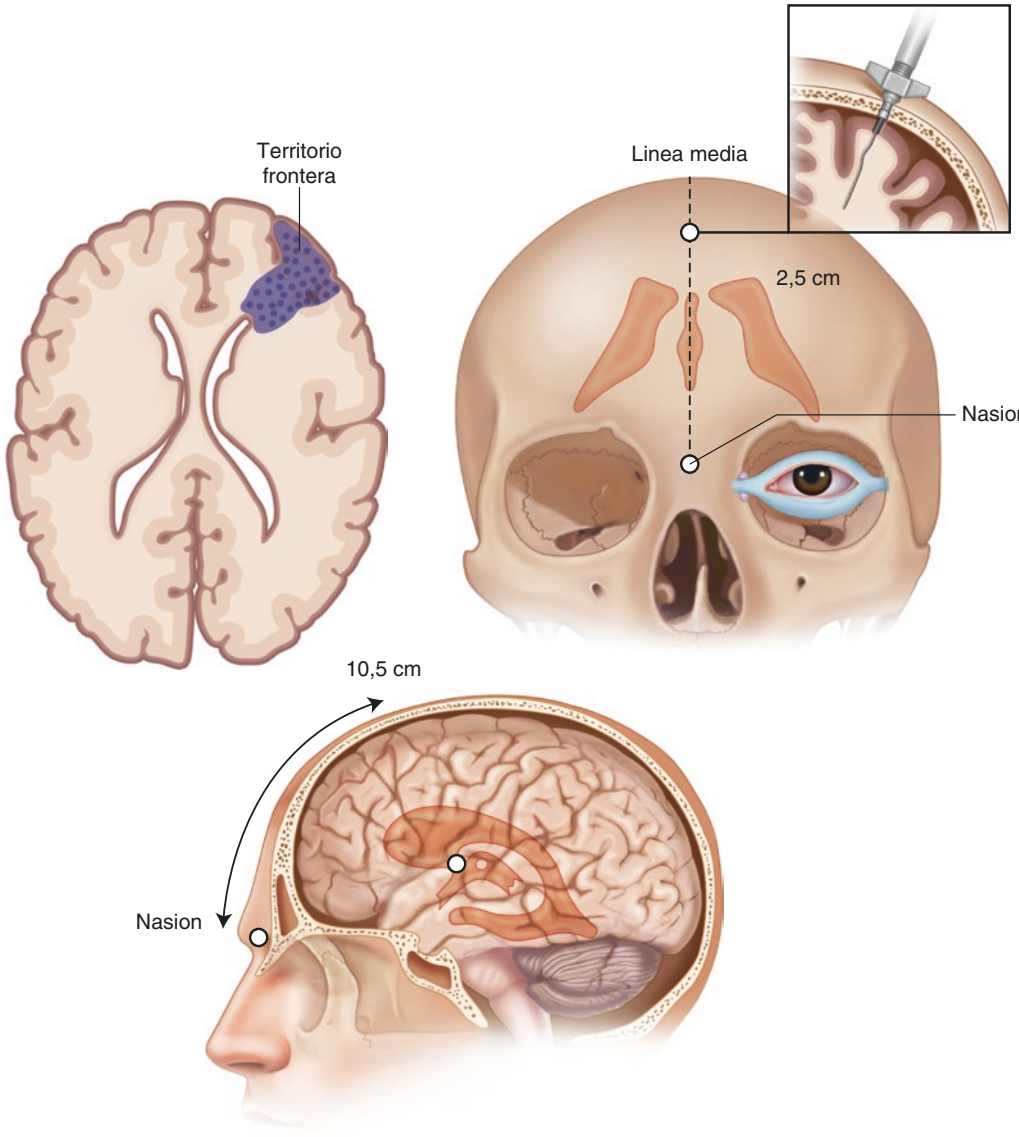

Fig. 2.5 $PtiO_2$ sensor implantation area. The catheter is implanted in the frontal region, in the border zone between the middle cerebral artery and the anterior cerebral artery. The anatomical references are 10.5 cm from the nasion and 2.5 cm from the midline (Reproduced with permission from Poca et al. [18])

For some time now, the concept that gray matter is much more sensitive than white matter to ischemic events of an equal magnitude has prevailed. Recently, the idea that white matter may possibly be much more sensitive in episodes of tissue hypoxia, supported by anatomical and physiological knowledge of encephalic vascularization, has begun to take root. At the cortical level, an extensive cortical vascularization can be found, which enables irrigation to be initially replaced by means of the adjacent capillaries in the face of an ischemic event. By contrast, irrigation of the white matter is terminal and much less dense as far as capillaries are concerned, which makes it more vulnerable in the face of ischemic episodes. As a result, we currently opt for the optimal situation of placing the sensor in infracortical white matter. Moreover, sensors placed in white matter provide more stable $PtiO_2$ values [21].

Lastly, as regards sensor implantation, we must consider the optimal territory to monitor. Our center follows the guidelines established by Poca et al. [18]. In the case of diffuse injuries, the catheter is implanted in the frontal region, in the border zone between the middle cerebral artery and the anterior cerebral artery (border zone between two arteries, an area more susceptible to tissue hypoxia) (Fig. 2.5).

2.4 Complications in Catheter Insertion

As catheter insertion is an invasive process, which involves cranial perforation, puncture of the dura mater and cerebral cortex, it is logical to consider the complications that—despite infrequent—have been described. There are four main complications for this type of monitoring: parenchymal hematoma resulting from the cerebral puncture, infection, catheter rupture, and thrombosis. If an incision in the dura mater is not made prior to the entry of the stylet, it could tear away from the cranium and possibly result in a hemorrhage. In the review by Dings et al. [16] in which 118 monitored patients were studied, only two (1.7%) developed a small intracerebral hematoma at the point of insertion which did not require surgical evacuation. No case of infection related to catheter insertion was reported. As far as mechanical complications were concerned, there were 8 cases (6.8%) in which the catheters slipped out and 4 cases (3.4%) in which a sudden interruption in recording with an abrupt drop to "0" occurred, which was attributed to electrode rupture. These series concur with the results of other series such as the works of Van den Brink [15] and Van Santbrink [13].

With regard to sensor malfunction, it is closely related with improper handling, mainly during the transfer of these patients from the resuscitation unit to the CT or operating room. As these transfers are unavoidable, it is absolutely necessary to take all precautions during the transfer, with the doctor accompanying the patient responsible for ensuring the sensor's proper operation.

When sensor gives a "0" reading, we follow the procedure below: first, we review the integrity of the system, catheter, etc; then, we rule out the possibility of a local problem (hematoma at the catheter tip, clots, areas of necrosis, etc.); and lastly, we temporarily increase the inspiratory oxygen fraction, by increasing the values if the sensor is working properly. The case would be different for patients diagnosed as cerebrally dead. It is evident—we have verified this at our center—that the $PtiO_2$ values drop to "0" in patients already diagnosed with the preceding clinical examination for cerebral death.

2.5 Clinical Application

The normal $PtiO_2$ values that we have used as described are 23–35 mmHg in healthy brain tissue [23]. Values less than 20 mmHg signify compromised brain tissue oxygenation, and is the limit that requires treatment—as it is associated with other markers of cerebral ischemia or cell dysfunction—although this value may slightly vary according to the type of catheter used and should be interpreted based on its location as verified by a CT scan [24, 25].

Maintaining cerebral oxygenation in neurocritical patients has become one of the main references of the doctors involved in the management of this type of patients. This is because the brain and the spinal cord have poor tolerance to ischemia—although greater than that of other tissues—and moreover, ischemia and hypoxia are the main mechanisms of brain damage in several types of acute neurological pathologies such as cranioencephalic trauma (CET), subarachnoid hemorrhage (SAH), cerebral infarction, and global anoxia.

The Brain Trauma Foundation (BTF), in its clinical guidelines for the management of CET [25], specifies that patients should be monitored using a means that reflects cerebral oxygenation. The first 12 h after cranioencephalic trauma have been defined as the most critical for the development of cerebral ischemia, and several studies on monitoring of cerebral oxygenation have shown that 30% of the episodes of cerebral ischemia arise during this period [23], and 50% during the first 24 h [27]. For this reason, prompt assistance at specialized centers coupled with early monitoring of these patients is absolutely vital. It is

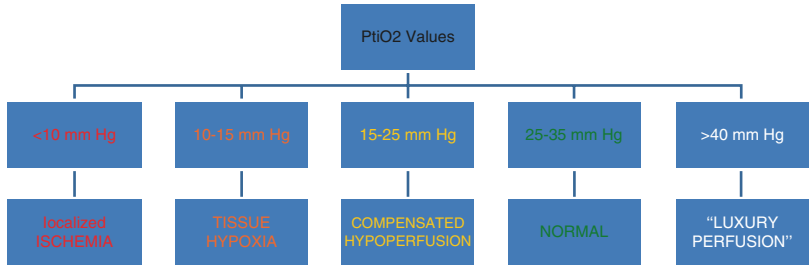

Fig. 2.6 Diagram for the assessment of severity levels according to the $PtiO_2$ values obtained in relation to their duration

worth mentioning that there is a unanimous opinion that values below 15 mmHg are indicative of tissue hypoxia [9, 27, 28]. Many efforts have been made to quantify the severity of tissue hypoxia, so values ranging between 15 and 10 mmHg are considered moderate [28, 29], while values below 10 mmHg are considered severe or serious [20, 30–32]. $PtiO_2$ <5 mmHg has been associated with death [33]. Values >40 mmHg are considered indicative of tissue hypoxia, which we would interpret as "luxury perfusion" in this territory [26]. It is for this reason that for neurotrauma patients, one of the therapeutic goals is to maintain $PtiO_2$ levels greater than 20 mmHg.

Not only the magnitude of the decline in $PtiO_2$ levels but also the duration of the event [34] has an impact on secondary injury. Thus, $PtiO_2$ values <15 mmHg maintained during more than 4 h are associated with a 50% mortality, while values below 10 mmHg during more than 30 min are associated with a 56% mortality. Figure 2.6 is a diagram that our unit follows for the assessment of severity levels according to the $PtiO_2$ values.

The next question that comes to mind is: does $PtiO_2$ replace jugular bulb oxygen saturation? SjO_2 was introduced at the clinic for adequate management of CET patients at the end of the 1980s by Cruz et al. [35]. It consists of the continuous monitoring of oxygen saturation of the blood in the jugular bulb by means of a fiber optic catheter placed in a retrograde direction. It is comparable to mixed venous saturation and is a reflection of the global cerebral oxygen consumption.

Nevertheless, SjO_2 has a series of limitations as regards clinical use:

(a) Technical issues: Defects in calibration, defects in light intensity, incorrect catheter placement, and occlusion. All of these defects can be minimized if we use an adequate screening protocol for false desaturations.
(b) Extracerebral blood contamination. Despite having the catheter tip inserted more than 2 cm deep into the jugular bulb, in some patients, especially those with low CBF, extracerebral blood contamination may occur [36]. This may lead to false rises in SjO_2.
(c) Anatomical anomalies in cerebral venous drainage. Discussions on whether the SjO_2 catheter should be placed on the same side of injury or on the side with greater drainage have been plenty. It seems that to detect episodes of global cerebral ischemia, it is better to monitor the dominant side [37].

Despite these limitations, SjO_2 monitoring has proven to be useful as a measurement of global cerebral oxygenation at the clinic.

The greatest limitation of $PtiO_2$ monitoring is the localized nature of this measure. Nevertheless, experiments measuring different areas of normal brains have proven that the differences are minimal [38]. It is currently accepted that in diffuse brain injuries, the $PtiO_2$ measurement from either side of the frontal white matter can be extrapolated as a global measurement of the degree of cerebral oxygen availability.

It is due to this localized nature that it is possible for $PtiO_2$ to detect episodes of regional ischemia—especially if the catheter is located in the affected area (ischemic penumbra)—whereas

SjO_2—a method that assesses global cerebral oxygenation—does not. When the pathology is diffuse, $PtiO_2$ is a good indicator of cerebral oxygenation, insofar as the hemisphere where the catheter has been placed [38–40].

In principle, both techniques can be considered complementary—SjO_2 would provide us with a reflection of oxygen consumption while $PtiO_2$ of the supply of oxygen [41]—although some authors, due to the aforementioned issues, consider $PtiO_2$ more effective than SjO_2 in monitoring cerebral hypoxia at the foot of the bed [42, 43]. Moreover, $PtiO_2$ responds more quickly to changes in cerebral oxygenation than other cerebral oxygenation monitoring methods (SJO_2, NIRS).

Additionally, as $PtiO_2$ is the measurement of oxygen in brain extracellular space, it reflects the balance between cerebral perfusion, oxygen diffusion in brain tissue, and cellular oxygen consumption. As a result, $PtiO_2$ may present low values (cerebral hypoxia) despite normal ICP and CPP values.

2.5.1 Prognostic Value

After analyzing the $PtiO_2$ scale, the first impression that emerges is that it is a tool with considerable prognostic value. Twenty-eight studies describe a relationship between low $PtiO_2$ values and therapeutic outcomes, the majority for CET (28) compared to SAH (3). Thus, the low $PtiO_2$ values in CET have been related to an increase in mortality (OR 4.0, 1.9–8.2) [2], worse recovery at 6 months (OR 0.6, 2.2–9.6) [2], and increased neurologic deficits [44]. In this regard, in 2005, our group [44] reported the importance of $PtiO_2$ as a prognostic value in a study conducted at our center. It was a prospective observational nonrandomized study conducted in the resuscitation unit of a tertiary university hospital. Eighteen patients (mean age of 32 ± 14 years) were consecutively included in the study from February 2004 until November 2004. In relation to demographic characteristics, 14 were men while 4 were women. The median Glasgow Coma Scale (GCS) upon admission to the hospital was 5 (range from 3 to 14), including patients who were initially admitted to the hospital with a GCS greater than 8 but who later showed neurological deterioration, leading to a drop in GCS to ≤ 8. As regards the tomographic classification of the Traumatic Coma Data Bank, four patients showed focal lesions requiring evacuation, whereas the rest were classified as having diffuse brain injuries. Evidently, in terms of the general management of these patients, the Brain Trauma Foundation's clinical guidelines were followed, with particular emphasis on the prevention of secondary injuries as well as the prompt evacuation of lesions with a lesion volume greater than 25 cc. $PtiO_2$ was continuously monitored using a Clark-type polarographic catheter connected to a Licox® monitor. The catheter was placed in the healthy area of the right frontal lobe in the cases of diffuse injuries and in the frontal lobe of the hemisphere with more damage in the rest. After catheter placement, we waited 120 min for the brain tissue to stabilize to ensure the validity of the values. We established a cut-off point for the obtained values—$PtiO_2$ <15 mmHg during more than 30 min in the first 48 h of CET—despite treatment optimization. Assessment of the patients at 3 months was done using the Glasgow Outcome Scale Extended (GOSE). As regards the results, it is worth mentioning that out of the 18 patients, 12 showed $PtiO_2$ levels below 15 mmHg during more than 30 min, between 2 and 48 h after trauma (Group I), and it is this group that had a poorer evolution [GOS 1 (5 patients, 27.7%), GOS 2 (2 patients, 11%), GOS 3 (5 patients, 27.7%)]. By contrast, the six patients that did not show $PtiO_2$ values below 15 mmHg (Group II) under the conditions described above had a favorable evolution [GOS 4 (2 patients, 11%), GOS 5 (4 patients, 22.22%)]. This difference was statistically significant ($p < 0.002$ Mann-Whitney U). Other series such as the study by Van den Brink [15] with 101 patients, as well as the studies by Valadka [28], Doppenberg [45], and Bardt [46] support this thesis.

In other pathologies in which it is important to monitor cerebral oxygenation due to the risk of cerebral ischemia, such as subarachnoid hemorrhage (SAH) or cerebral infarction, $PtiO_2$ has

been suggested as a way to monitor cerebral oxygenation [4]. However, there is not enough scientific evidence for this and the majority of oxygenation-guided therapy studies are based on SjO_2 and no relationship has been proven with the results. However, in Kett–White's [47] study of 30 patients with SAH monitored with Neurotrend inserted in the area irrigated by the aneurysmal artery, 13 patients suffering from severe hypoxia—defined as five or more episodes of $PtiO_2$ <10 mmHg during 30 min—were found to have a GOS lower than those not suffering from hypoxia at 3 and 6 months. Having a normal ICP and/or a normal CPP does not preclude the existence of hypoxia and the consequent metabolic distress in SAH. The sensitivities of ICP, CPP, and $PtiO_2$ have been calculated to detect this metabolic distress as measured by the cerebral lactate/pyruvate ratio found using microdialysis. The $PtiO_2$ shows a higher sensitivity of 53.4% (false negatives of 46.6) vs. 10% of ICP, and 12.7% of CPP [1].

The use of $PtiO_2$ has likewise been suggested for major neurological interventions—both intraoperative and post-operative—especially for vascular surgery [48]. Mortality in aneurysmal SAH is related to the development of secondary ischemia to vasospasm with secondary hemodynamic alterations upon the increase of ICP and the loss of autoregulation. However, surgical manipulation of cerebral blood vessels or the necessity to perform transient artery occlusions contributes to significantly increasing the risks of developing ischemic changes. To diagnose and eventually treat cerebral hypoxia early, it is necessary to determine cerebral oxygenation and, if possible, the accompanying metabolic changes. The intraoperative Doppler, which has a small probe, makes it possible to find out after placement of the aneurysmal occlusion whether there is any disorder or deficit in artery blood flow after manipulation. However, this technique only provides us with information about larger arteries and does not provide data about cerebral microcirculation or the supply of oxygen to the cells. As an alternative to the Doppler system, blood flow has been determined using the laser-Doppler, which performs cortical measurements and jugular oximetry. However, it only provides generalized information. There are two other options for intraoperative monitoring of oxygenation of the affected territory: the determination of $PtiO_2$ in the territory vascularized by the artery and cerebral microdialysis. We know that many patients who suffer an SAH tend to have low $PtiO_2$ in the territory where the aneurysm is located. This is why during the clipping surgery, we should obtain a basal value of $PtiO_2$ from the affected territory, which will drop during clipping and will only recover after proper clip placement [49].

Recently, the $PtiO_2/PaO_2$ ratio has been related to GOS in CET. Thus, Figaji [50] after studying 28 children with severe CET and 48 $PtiO_2$ measurements from pericontusional or healthy areas with low basal $PtiO_2$, observed that the increase in the $PtiO_2/PaO_2$ ratio was inversely proportional to GOS (r = 0.54 p = 0.02, confidence interval 0.03–0.78). This could be explained by the effect of cerebral vasoconstriction that hyperoxia caused by hyperoxia. However, our group found results to the contrary. For 3 years, we studied 32 patients with a mean age of 37 ± 17.4 years, with an ISS (Injury Severity Score) of 27.7 ± 10.7 and GCS 5.2 ± 3.4. At 6 months, 7 patients (21.8%) had died and 20 patients had a favorable neurological outcome (patients with no, little, or moderate neurologic dysfunction). This favorable neurological outcome is correlated to a high level of the $PtiO_2/PaO_2$ ratio in the first 24 h in contrast to the nonsurviving group, to the extent that a $PtiO_2/PaO_2$ ratio <0.2 during the first 24 h predicts mortality or poor neurological outcomes [51]. There is no clear mechanism that explains the lack of response of $PtiO_2$ to normobaric hyperoxia, which would probably indicate that the supplementary supply of oxygen is not being used, possibly because of hypoxia from dispersion due to cerebral edema, which would diminish the diffusion of oxygen to the cellular compartment.

It is important to improve PaO_2 in neurocritical patients; in this way, in acute respiratory distress syndrome (ARDS), the $PtiO_2$ is low in correlation to poor systemic oxygenation or PaO_2, but is equally related to a worse neurological outcome.

Hence the importance of maneuvers for optimization such as prone positioning [52] or alveolar recruitment maneuvers [53].

It is more difficult to prove that $PtiO_2$-guided therapy for neurocritical patients is associated with better therapeutic outcomes. First, the determination of $PtiO_2$ is a nontherapeutic monitoring method and just like all monitoring methods, it is difficult to prove its therapeutic effect. Therapy in CET based on the control of intracranial pressure (ICP) was started in the 60s with good outcomes and was even related to a decrease in mortality; [54] in the 80s, therapy based on maintaining cerebral perfusion pressure (CPP). When this therapy was compared with a group in which systemic hypotension had been removed, no differences were found [55]. Inasmuch as it is possible to have a normal ICP and CPP in CET while experiencing episodes of hypoxia both in pericontusional areas and in apparently healthy areas [56], in the twenty-first century, Stieffel started $PtiO_2$-guided therapy [57]. In this study with 25 patients, the therapy, aside from maintaining an ICP <20 mmHg and a CPP >60 mmHg, had the additional objective of maintaining $PtiO_2$ >25 mmHg compared to a historical control group with ICP-guided therapy. They achieved this objective by optimizing treatment at different levels and increasing the inspiratory oxygen fraction to 100% if the objective could not be achieved with the previous measures taken. The authors reported a decrease in mortality by 25% ($p < 0.05$) in those patients in which particular effort was made to obtain $PtiO_2$ values greater than 25 mmHg.

A review by Maloney–Wilensky has shown that $PtiO_2$-guided therapy in severe CET is associated with better neurological recovery compared to ICP/CPP-guided therapy (OR = 2.1; 95% CI = 1.4–3.1) [2]. In this regard, Oddo [3] shows that $PtiO_2$ is a factor independent of poor neurological outcome in severe CET. Nangunoori et al. [58], after carrying out a review of 491 patients, concluded that in patients with severe CET, therapy based on ICP/CPP + PTiO2 monitoring was associated with a better prognosis as compared to one based on ICP/CPP alone. However, Martini [59] reports that in 123 patients with severe CET, ICP/CPP + $PtiO_2$ vs. ICP/CPP does not lead to a decrease in mortality or better neurological recovery. That said, the author himself states that the groups are not homogeneous, with the ICP/CPP + $PtiO_2$ group with the more severe cases.

There are other studies that compare ICP/CPP + $PtiO_2$-guided therapy vs. ICP/CPP-guided therapy alone with no conclusive results, among other things, due to the fact that the therapy to improve $PtiO_2$ is not homogeneous. At present, there is an ongoing prospective randomized study [60] whose therapeutic aims are: (1) Precisely determine how ICP or $PtiO_2$ should be treated. (2) Monitor the protocol. (3) Prove that the addition of $PtiO_2$ decreases the magnitude of cerebral hypoxia more than the maintenance of CPP and the decrease of ICP before examining its significance on the neurological outcome.

2.5.2 Therapeutic Measures to Maintain Adequate $PtiO_2$

We have already seen that a low $PtiO_2$ is a prognostic factor independent of poor neurological outcome in severe CET [3] and generally speaking, the failure to maintain adequate cerebral oxygenation aggravates secondary injury in neurocritical patients. It is for this reason that we will attempt to enumerate a series of therapeutic measures to correct a $PtiO_2$ <20 mmHg.

The easiest way would be to simply raise FiO_2 to increase the systemic supply of oxygen to the brain. But we have already seen that the significance of this maneuver on cerebral oxygenation, as well as its beneficial mechanism, is unclear. Generally speaking, the lower the $PtiO_2$, the more difficult it is to raise it by increasing the PaO_2, which is the opposite of what occurs when the $PtiO_2$ is high [61]. One explanation would be that the increase in $PtiO_2$ produces a decrease in the CBF due to vasoconstriction and another would be that the so-called tissue oxygen response has been altered to reflect the loss of oxygen autoregulatory mechanisms (ORx) [62] which on many occasions is associated with a loss of cerebrovascular autoregulation, worsening neurological outcome.

Hyperbaric hypoxia has been used, while maintaining FiO_2 1 and observing that the obtained lactate/pyruvate ratio values decreased, which suggested that rather than improving cerebral metabolism, what actually occurred was that it slowed it down [63]. Moreover, because of its adverse effects both on a systemic level and a cerebral level, hyperoxia is currently not recommended, so we should try to maintain a PaO_2 >100 mmHg, and if this is not possible, maintain a $PtiO_2$ >20 mmHg after having treated the causes of cerebral hypoxia, and as a last resort, raise the FiO_2.

The leading cause of cerebral hypoxia is cerebral ischemia arising from intracranial hypertension (IH), which compromises CPP and decreases CBF, both at a global and regional level, resulting in a decrease in tissue oxygenation. Usually, the more severe IH is, the more pronounced tissue hypoxia is. $PtiO_2$ gives us the opportunity to assess the effects of this IH at a regional level, aside from being a quicker way than jugular bulb oxygen saturation [42] and NIRS [43]. Moreover, it can help us regulate the intensity with which we should perform therapeutic maneuvers such as osmotherapy, muscular relaxation, or second-level measures, among which is hyperventilation [64]. The adequate level of hyperventilation would be that which leads to a level of arterial CO_2, which by means of vasoconstriction in cerebral circulation will result in a decrease in ICP with an increase in CBF, and the limit would be that which results in excessive vasoconstriction, which gives rise to cerebral ischemia and a decrease in $PtiO_2$.

It is well known that a decline in CPP to below-cerebral autoregulation induces tissue hypoxia [65]. Decreases in CPP tend to go hand in hand with declines in $PtiO_2$. Stocchetti [49] confirmed that increasing CPP in patients with low $PtiO_2$ levels was beneficial and in many cases succeeded in bringing the $PtiO_2$ values to normal, in ischemic areas due to different pathologies (CET, SAH, meningioma, etc.). We have learned from similar studies that we can manipulate CPP to see its effectiveness on $PtiO_2$ by establishing the optimal CPP margins. Nevertheless, this is not always the case, as Kiening [29] established that in patients with low CPP and low $PtiO_2$, increasing CPP did not lead to improvements with regard to $PtiO_2$ values. The explanation would be that for these cases, cerebral autoregulation is preserved. In addition, Sahuquillo [66] showed us how supranormal PPC values could coexist with tissue hypoxia and that a parallelism between an increase in CPP and that of $PtiO_2$ did not always exist, as increasing CPP does not always mean an increase in oxygen availability.

The consensus reached by different neuromonitoring studies [20, 22] highlights the need to assess the status of cerebral autoregulation. The decline in MAP, and therefore in CPP, results in a decrease in $PtiO_2$. This has been observed in patients with severe cranioencephalic trauma with increases in ICP; the CPP thresholds must be maintained between 60–70 mmHg [25]. Therefore, it is absolutely vital to ensure that this value remains in this range for the maintenance of appropriate cerebral perfusion. A CPP >70 mmHg can be allowed if cerebral autoregulation is intact. However, when autoregulation has been abolished, the CPP target can be individualized. Thus, if the curve is shifted to the right (Rosner's theory), the CPP required will be greater, whereas if the curve is shifted to the left, lower CPPs would be needed (Lund concept).

The capacity for cerebral autoregulation has traditionally been measured using the Prx coefficient which establishes the relationship between the ICP and systemic arterial pressure curves (Software ICM+, Cambridge, +UK). Thus, positive Prx values or those near 1 indicate abolished autoregulation, whereas negative Prx values or near 0 signify that autoregulation is present [67].

Another way to assess cerebral autoregulation is by using the oxygen reactivity index (ORx) [68], which represents the relationship between the change in $PtiO_2$ (which reflects CBF) and the change in CPP. When autoregulation is preserved, the $PtiO_2$ hardly changes with changes in CPP and the ORx is negative or near 0. However, when autoregulation is altered, the $PtiO_2$ follows the changes in CPP and the ORx is negative, as is the case with Prx. Both the Prx and the ORx have been related to poor neurological outcome in neurocritical patients [69, 70].

Another reason why $PtiO_2$ is low is due to anemia. Smith et al. discovered in 35 neurocritical patients, that with low $PtiO_2$, red blood cell transfusions increased $PtiO_2$ by 3.2 ± 8.8 mmHg or 15% of the basal value, independently of CPP, SaO_2, and FiO_2 [71]. However, transfusions are not free from risks. In critical patients, they have been related to an increase in mortality, and additionally, it is not quite clear what the transfusion threshold is for neurocritical patients; some set it at 9 g/dl while others at 10 g/dl. It seems that the $PtiO_2$ level can help us make the decision on whether to transfuse or not.

Other therapeutic measures such as mannitol infusions or even decompressive craniectomy have been taken according to the $PtiO_2$ value. The latter may seem particularly daring, but this is what we have gleaned from Reithmeier's studies [72]. The authors observed a statistically significant increase in $PtiO_2$ to normal levels in patients with IH as well as $PtiO_2$ values below 10 mmHg after they were subjected to decompressive craniectomy. It is also worth mentioning that the ICP values decreased to normal.

Conclusions

$PtiO_2$ is a very crucial part of the diagnostic–therapeutic arsenal for the adequate management of neurocritical patients. It is true that this field still has no gold standard as regards monitoring, with gold standard defined as a well-established and standardized monitoring method against which the effectiveness of new devices is compared.

At present, it is possible to measure cerebral oxygenation continuously and instantly using an intraparenchymal sensor as part of our multimodal neuromonitoring system. This is a technique that is readily available, clinically applicable, and safe. Brain $PtiO_2$ monitoring provides us with a great opportunity to delve deeper into the physiopathology of neurocritical patients, with implications for the prognosis and even more so, serving as guidelines for action for us doctors who have the opportunity to treat these patients. We are of the opinion that intensive care units that care for neurocritical patients should seriously consider the possibility of having useful tools for the early detection of the much-feared secondary injury, and this device most certainly fits the bill.

References

1. Chen HI, Stiefel MF, Oddo M, et al. Detection of cerebral compromise with multimodality monitoring in patients with subarachnoid hemorrhage. Neurosurgery. 2011;69(1):53–63.
2. Maloney-Wilensky E, Gracias V, Itkin A, et al. Brain tissue oxygen and outcome after severe traumatic brain injury: a systematic review. Crit Care Med. 2009;37:2057–63.
3. Oddo M, Levine JM, Mackenzie L, et al. Brain hypoxia isassociated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. Neurosurgery. 2011;69:1037–45.
4. Sigaard-Andersen O, Fogh-Andersen N, Gothgen I, Larsen VH. Oxygen status of arterial and mixed venous blood. Crit Care Med. 1995;23:1284–93.
5. Oddo M, Bosel J. and the Participants in the International Multidisciplinary Consensus Conference on Multimodality Monitoring. Monotoring of brain and systemic Oxygenation in NeuroCritical Care Pateints. Neurocrit Care. 2014;21(2):S103–20.
6. Mulvey JM, Dorsch NW, Mudaliar Y, Lang EW. Multimodality monitoring in severe traumatic brain injury: the role of brain tissue oxygenation monitoring. Neurocrit Care. 2004;1:391–402.
7. Nicholls TP, Shoemaker WC, Wo CCJ, Gruen JP, Amar A, Dang ABC. Survival, hemodynamics, and tissue oxygenatio after head trauma. J Am Coll Surg. 2006;202:120–30.
8. Fleckenstein W, Maas AIR. Continuos recordings of oxygen pressure in cerebrospinal fluid of cat, dog and man. Funktionsanalyse Biologisher Systeme. 1989;19:211–22.
9. Ai M, Fleckenstein W, de Jong DA, van Santbrink H. Monitoring cerebral oxygenation:experimental studies and preliminary clinical results of continuos monitoring of cerebrospinal fluid and brain tissue oxygen tension. Acta Neurochir Suppl. 1993;59:50–7.
10. Kett-White R, Hutchinson PJ, Czosnyka M, Boniface S, Pickard JD, Kirkpatrick PJ. Multi-modal monitoring of acute brain injury. Adv Tech Stand Neurosurg. 2002;27:87–134.
11. Purins K, Enblad P, Sandhagen B. Brain tissue oxygen monitoring: a study in vitro accuracy and stability of Neurovent-PTO and Lycox senss. Acta Neurochir. 2010;152:681–8.
12. Purins K, Enblad P, Sandhagen B, Lewén A. Brain tissue oxygenation and cerebral perfussion pressure

thresolds of ischemia in a standarized Pib brain death model. Neurocrit Care. 2012;16:462–9.
13. Purins K, Lewén A, Hillerd L, Howell T, Enblad P. Brain tissue oxygenation and cerebral metabolic patterns in focal and diffuse traumatic brain injury. Front Neurol. 2014;5:1–10.
14. Van den Brink WA, Haitsma IK, Avezaat CJ, Houstmuller AB, Kros JM, Maas AI. Brain parenchyma/pO_2 catheter interface: a histopathological study in the rat. J Neurotrauma. 1998;15:813–24.
15. Van den Brink WA, Van Santbrink H, Steyerberg EW, et al. Brain oxygen tension in severe head injury. Neurosurgery. 2000;46:868–76.
16. Dings J, Meixensberger J, Jager A, Roosen K. Clinical experience with 118 brain tissue oxygen partial pressure catheter probes. Neurosurgery. 1998;43:1082–95.
17. Dings J, Meixensberger J, Roosen K. Brain tissue pO_2 monitoring: catheter stability and complications. Neurol Res. 1997;19:241–5.
18. Poca MA, Sahuquillo J, Mena MP, Vilalta A, Riveiro M. Actualizaciones en los métodos de monitorización cerebral regional en los pacientes neurocríticos: presión tisular de oxígeno, microdiálisis cerebral y técnicas de espectroscopia por infrarrojos. Neurocirugía. 2005;16:385–410.
19. Coles JP, Fryer TD, Smielewski P, Chatfield DA, Steiner LA, Johnston AJ, Downey SP, Williams GB, Aigbirhio F, Hutchinson PJ, Rice K, Carpenter TA, Clark JC, Pickard JD, Menon DK. Incidence and mechanisms of cerebral ischemia in early clinical head injury. J Cereb Blood Flow Metab. 2004;24:2002–120.
20. Le Roux P, Menon DK, Citerio G, Vespa P, cols. Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care. A statement for healthcare professionals from the Neurocritical Care Society and the European Societyof Intensive Care Medicine. Intensive Care Med. 2014;40:1189–209.
21. Lubillo S, Blanco J, López P, Domínguez J, Ruiz C, Molina I, Morera J. Role of decompressive craniectomy in brain injury patient. Med Intensiva. 2009;33:74–83.
22. Andrews PJD, Citerio G, Longhi L, Polderman K, Sahuquillo J, Vajkoczy P. Neuro-Intensive Emergency Medicine (NICEM) Section of the European Society of Intensive Care Medicine. Intensive Care Med. 2008;34:1362–70.
23. Pennings FA, Schuurman PR, van den Munckhof P, Bouma GJ. Brain tissue oxygen pressure monitoring in awake patients during functional neurosurgery: the assessment of normal values. J Neurotrauma. 2008;25:1173–7.
24. Ponce LL, Pillai S, Cruz J, Li X, Julia H, Gopinath S, Robertson CS. Position of probe determines prognostic information of brain tissue PO in severe traumatic brain injury. Neurosurgery. 2012;70:1492–502.
25. Brain Trauma Foundation, American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care. Guidelines for the management of severe traumatic brain injury. J Neurotrauma. 2000;17:451–5.
26. Bouma GJ, Muizelaar JP, Stringer WA, Choi SC, Fatouros P, Young HF. Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. J Neurosurg. 1992;77:360–8.
27. Haitsma IK, Maas AIR. Advanced monitoring in the intensive care unit: brain tissue oxygen tension. Curr Opin Crit Care. 2002;18:115–20.
28. Valadka AB, Gopinath SP, Contant CF, Uzura M, Robertson CS. Relationship of brain tissue pO_2 to outcome after severe head injury. Crit Care Med. 1998;26:1576–81.
29. Kiening KL, Hartl R, Untenberg AW, Schneider GH, Bardt T, Lanksch WR. Brain tissue pO_2-monitoring in comatose patients: implications for therapy. Neurol Res. 1997;19:233–40.
30. Sarrafzadeh AS, Kiening KL, Bardt TF, et al. Cerebral oxygenation in contusional vs nonlosioned brain tissue: monitoring of $PtIO_2$ with Lycox and Paratrend. Acta Neurochir Suppl. 1998;71:186–9.
31. Kett-White R, Hutchinson PJ, Al Rawi PG, et al. Cerebral oxygen and microdyalisis monitoring during aneurysm surgery: efects of blood pressure, ceebrospinal fluid drainage, and temporary clipping on infarction. J Neurosurg. 2002;96:1013–9.
32. Kiening KL, Untenberg AW, Bardt T, Schneider GH, Lanksch WR. Monitoring of cerebral oxygenation in patients with severe head injuries: brain tissue pO_2 versus jugular vein oxygen saturation. J Neurosurg. 1996;85:751–7.
33. Scheufler KM, Lehnert A, Nadstawek J, Thees C. Individual value of brain tissue oxygen ppressure, microvascular oxygen saturation, citocrome redox level and energy metobolites in detectec critically reduced energy state during changes in global cerebral perfusión. J Neurosurg Anesthesiol. 2004; 16:210–9.
34. Ghajar J. Traumatic brain injury. Lancet. 2000;356:923–9.
35. Cruz J. Continous versus serial global cerebral hemometabolic monitoring.Applicactions in acute brain trauma. Acta Neurochir Suppl. 1988;42:35–9.
36. Jakobsen M, Enevolldsen E. Retrograde catheterization of the right internal jugular vein serial measurements cerebral venous oxygen content. J Cereb Blood Flow Metab. 1989;9:717–20.
37. Lam JM, Chan MS, Poon WS. Cerebral venous oxygen saturation monitoring: Is dominant yugular bulb cannulation good enough? Br J Neurosurg. 1996;10:357–64.
38. Gupta AK, Hutchinson PJ, Fryer T, Al-Rawi PG, Parry DA, Kett-White R, Kirkpatric PJ, Mathews JC, Downey S, Aigbirhio F, Clark J, Pickard JD, Menon DK. Measurement of brain tissue oxygenation performed using positrón emission tomography scanning to valited a novel monitoring method. J Neurosurg. 2002;96:263–8.

39. Sauquillo J. Hipoxia tisular cerebral asociado a hiperemia evaluada por parámetros hemometabolicos globales ¿Mito o realidad?. Libro de Ponencias PIC 2000. Barcelona. p. 155.
40. Van Stanbrunk H, Maas A, Avesta CJJ. Continuos monitoring of partial pressure of brain tissue oxygen in patients with severe head injury. Neurosurgery. 1996;38:21–31.
41. Rosenthal G, Hemphill JC, Sorani M, Martin C, Morabito D, Obritst WD, Manley GF. Brain tissue tension is more indicative of oxygen diffusion than oxygen delivery and metabolism in patients with traumatic brain injury. Crit Care Med. 2008;36:1917–24.
42. Batha A, Gupta AK. Neuromonitoringin the intensive care unit II. Cerebral oxynation monitoring and microdyalisis. Intensive Care Med. 2007;33:1322–8.
43. Leal-Noval SR, Cayuela A, Arellano-Orden V, Marin-Caballos A, Padilla V. Invasive and noinvasive assesment of cerebral oxygenation in patients with severe traumatic brain injury. Intensive Care Med. 2010;36:309–17.
44. Badenes R, Maruenda A, García-Pérez ML, Chisbert V, Talamantes F, Belda FJ. Valor pronóstico de la presión tisular de oxígeno cerebral en los traumatismos craneoencefálicos graves. Rev Esp Anestesiol Reanim. 2005;52:A-753.
45. Bardt TF, Unterberg AW, Hartl R, Kiening KL, Schneider GH, Lanksch WR. Monitoring of brain tissue pO_2 in traumatic brain injury: effect of cerebral hypoxia on outcome. Acta Neurochir Suppl. 1998;71:153–6.
46. Doppenberg EM, Zauner A, Bullock R, Ward JD, Fatouros PP, Young HF. Correlations between brain tissue oxygen tension, carbon dioxide tension, ph, and cerebral blood flow. A better way of monitoring the severely injured brain? Surg Neurol. 1998;49:650–4.
47. Kett-White R, Hutchinson PJ, Al-Rawi PG, Gupta AK, Pickard JD, Kirkpatrick PJ. Adverse cerebral events detected after subarachnoid hemorrhage using brain oxygen and microdialysis probes. Neurosurgery. 2002;50:1213–21.
48. Cerejo A, Silva PA, Dias C, Vaz R. Monotoring of brain oxygenation in surgery of ruptured middle artery aneurysms. Surg Neurol Int. 2011;7:70.
49. Stocchetti N, Chieregato A, De Marchi M, Croci M, Benti R, Grimoldi N. High cerebral perfusion pressure improves low values of local brain tissue O_2 tension ($PtiO_2$) in focal lesions. Acta Neurochir Suppl. 1998;71:162–5.
50. Figaji A, Zwane AG, Fieggen AG, Argent AC, Le Roux PD, Peter JC. The effect of increased inspired fraction of oxygen on brain. Neurocrit Care. 2010;12:430–7.
51. Badenes R, Lozano A, Bilota F, Cuev A, Ortolá B, Maruenda A, Belda J. A novel prognostic marker in sever traumatic brain injury. Intensive Care Med Exp. 2015;3(Suppl 1):A487.
52. Reinprecht A, Greher M, Wolfberger S, Dietrich W, Illeievich UM, Gruber A. Prone position in subarachnoid hemorrhage patients with acute distress syndrome. Crit Care Med. 2003;3:338–44.
53. Maruenda A, Duca A, Lozano A, Gracia E, Ferrando C, Belda J. Ventilatory strategie in SDRA associeted a sever traumatic brain injury. XXXII Congreso de la Sociedad Española de anestesiología, reanimación y terapéutica del dolor – SEDAR 2015. Santander Octubre 2015. P 0–0453.
54. Farahvar A, et al. Response to intracranial hypertension treatment as a predictor of death in patients with severe traumatic brain injury. J Neurosurg. 2011;114:1471–8.
55. Chesnut RM. Avoidance of hypotension: the condition sine qua non of successful severe head injury management. J Trauma. 1996;42:S45–52.
56. Longhi L, Pagan F, Valeriani V, Magnoni S, Zanier ER, Conte V, Branca V, Stocchetti N. Monitoring brain tissue oxygen tension in brain-injured patients reveals hypoxicepisodes in normal-appearing and in peri-focal tissue. Intensive Care Med. 2007;33:2136–42.
57. Stieffel MF, Spiotta A, Gracias VH, Garuffe AM, Guillamondegui O, Maloney-Wilensky E, Bloom S, Grady MS, LeRoux PD. Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. J Neurosurg. 2005;103:805–11.
58. Nangunoori R, Maloney-Wilensky E, Stiefel M, Park S, Kofke A, Levine JM, et al. Brain tissue oxygen-based therapy and outcome after severe traumatic brain injury: a systematic literature review. Neurocrit Care. 2012;17:131–8.
59. Martini RP, Deem S, Yanez D, Chestnut RM, Weiss NS, Daniel S, et al. Management guided by brain tissue oxygen monitoring andoutcome following severe traumatic brain injury. J Neurosurg. 2009;111:644–9.
60. Brain tissue oxygen monitoring in traumatic brain injury, BOOST 2. Identifier NCT00974259. www.ClinicalTrials.gov.
61. Hlatky R, Valadka AB, Gopinath SP, Robertson CS. Brain tissue oxygen tension response to induced hyperoxia reduced in hypoperfusedbrain. J Neurosurg. 2008;108:53–8.
62. Van Santbrink H, vd Brink WA, Steyerberg EW, Carmona Suazo JA, Avezaat CJ, Maas AI. Brain tissue oxygen response in severe traumatic brain injury. Acta Neurochir. 2003;145:429–38.
63. Magnoni S, Ghisoni L, Locatelli M, et al. Lack of improvement in cerebral metabolism after hyperoxia in severe head injury: a microdialysis study. J Neurosurg. 2003;98:952–8.
64. Dings J, Meixensberger J, Amschler J, Roosen K. Continous monitoring of brain tissue pO2: a new tool to minimize the risk of ischemia caused by hyperventilation therapy. Zentralbl Neurochir. 1996;57:177–83.

65. Hemphill JC, Knudson MM, Derugin N, Morabito D, Manley GT. Carbon dioxide reactivity and pressure autoregulation of brain tissue oxygen. Neurosurgery. 2001;48:377–83.
66. Sahuquillo J, Amoros S, Santos A, Poca MA, Panzardo H, Dominguez L, et al. Does an increase in cerebral perfusion pressure always mean a better oxygenated brain? A study in head injured patients. Acta Neurochir Suppl. 2000;76:457–62.
67. Czosnyka M, Smielewski P, Kirkpatrick P, Piechnik S, Laing R, Pickard JD. Continuos monitoring of cerebrovascular pressure-reactivity in head injury. Acta Neurochir Suppl. 1998;71:74–7.
68. Jaeger M, Schuhmann MU, Soehle M, Meixensberger J. Continuous assessment of cerebrovascular autoregulation after traumatic brain injury using brain tissue oxygen pressure reactivity. Crit Care Med. 2006;34:1783–8.
69. Czosnyka M, Balestreri M, Steiner L, et al. Age, intracranial pressure, autoregulation, and outcome after brain trauma. J Neurosurg. 2005;102:450–4.
70. Jaeger M, Soehle M, Schuhmann MU, Meixensberger J. Clinical significance of impaired cerebrovascular autoregulation after severe aneurysmal subarachnoid hemorrhage. Stroke. 2012;43:2097–101.
71. Smith MJ, Stiefel MF, Magge S, et al. Packed red blood cell transfusion increases local cerebral oxygenation. Crit Care Med. 2005;33:1104–8.
72. Reithmeier T, Lohr M, Pakos P, Ketter G, Ernestus RI. Relevance of ICP and ptiO(2) for indication and timing of decompressive craniectomy in patients with malignant brain edema. Acta Neurochir. 2005; 147:947–52.
73. Deogaonkar A. Multimodal monitoring in the neurological intensive care unit. Neurologist. 2005; 11:45–54.

Predictors of Outcome in Traumatic Brain Injury

3

Angels Lozano and Rafael Badenes

3.1 Introduction

Estimates of prognosis are often considered to be one of the most debated and challenging questions that specialist physicians working with severe traumatic brain injury (TBI) must respond to. Estimates of prognosis are an important component in clinical decision making, since an improved estimation of prognosis for a given patient permits more accurate information about family and more consistent clinical and ethical decisions. Considering that poor prognosis may result in a decision to withdraw life-sustaining therapy, it is important to fully appreciate the aspects involved in the process of prognostication.

However, it has always been considered difficult to predict the likely outcome in patients with TBI.

In this chapter, our aim is to describe and review the current knowledge about traditional and newly recognized predictors of outcome. We will focus on the prediction of outcome in terms of mortality and functional outcome in adult patients with moderate and severe TBI.

To simplify their study, predictors of outcome can be divided in different ways. Prognostic factors present at the admission phase are really important in the prediction of a poor outcome, and partly explain the very high level of early mortality in this patients; and prognostic factors during the acute admission phase are neurologic or nonneurologic events that influence patients outcome, and maybe they have more importance as knowledge of their consequences than as predictive model.

A. *Prognostic Factors at Admission*

- Age
- Glasgow Coma Scale (GCS)
- TC-scan abnormalities
- Hypotension during admission

B. *Prognostic Factors During Admission*

- Intracranial pressure (ICP)
- Hypotension
- Cerebral perfusion pressure (CPP)

We can divide TBI predictors of outcome by the type of factor we are talking about too, for example:

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A. *Laboratories*

- Plasma/urine S100B and S100BB
- GFAP
- Pentraxin
- Interleukin-2
- Coagulation profile (prothrombin time, activated partial thromboplastin time, INR)
- Ubiquitin C-terminal hydrolase
- C-reactive protein
- Creatine kinase brain isoenzyme
- Plasma deoxyribonucleic acid
- Brain-derived neurotropic factor
- Secretagogin
- Interleukin-10
- Heat shock protein 70

B. *Neuroimaging*

- Brain-stem injuries on MRI
- DTI and low axial diffusivity values
- CBF on xenon CT
- Quantitative CT (midline shift, cisternal effacement, volume of SDH)

C. *Electrophysiology*

- Isoelectric cortical spreading depolarization

D. *Extracranial Injuries*

- Increased number of extracranial/nonneurological injuries

Actually, "novel and emerging" biomarkers are appearing, they can be used for a better characterization of TBI and tracking of disease processes, and they can also add prognostic information. So for a better understanding of the different predictors of outcome, we have decided to divide them into "traditional" and "novel and emerging" predictors.

A. *Traditional Predictors of Outcome*

- Demographic factors
- Type of injury
- Clinical severity: Extracranial and intracranial injuries
- Second insults (hypotension and hypoxia)
- Imaging abnormalities
- Pupillary reactivity

B. Novel and Emerging Predictors of Outcome

- Extended neuromonitoring
- Genetic constitution
- Laboratory values and biomarkers
- Advanced MR imaging techniques

3.2 Traditional Predictors of Outcome

3.2.1 Demographic Factors

3.2.1.1 Age

The association between increasing age and poorer outcome has been widely demonstrated in many publications [1–7]. Age is one of the strongest predictors of outcome after TBI.

There is a continuous association between age and outcome that has been demonstrated in multiple studies with a continuous relation across ages [2–6, 8] (Fig. 3.1).

Older age is associated with worse outcome and increased mortality [4]; mortality increases especially after 60 years, and unfavorable evolution increases after 29 years [8].

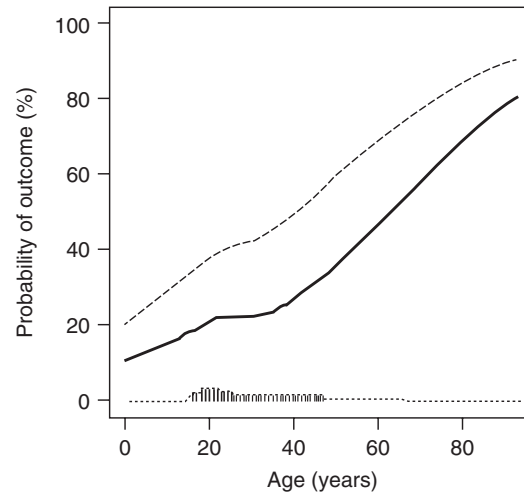

Fig. 3.1 Continuous association between age and outcome as demonstrated in the IMPACT studies. The upper line denotes probability of unfavorable outcome. The lower line denotes the probability of mortality (Reproduced with permission from Mushkundiani et al. 2007)

3.2.1.2 Gender

A clear association between gender and outcome has not been shown for TBI. Most studies have not found differences between male or female gender as a prognostic factor [4].Otherwise, some recent studies have found increased mortality [9], poorer quality of life, and worse functional outcome [10] in females who survived severe TBI compared to males. Otherwise, this association needs to be studied extensively to support these findings.

Many studies have demonstrated that an association between race and outcome after TBI exists, but this association is not clearly understood. It could imply differences in genetic constitution, but it could also be caused by differences in access to clinical care.

The IMPACT study group confirmed this association in a meta-analysis; they reported that black patients have a poorer outcome than white or Asian patients, and this has been shown in many other studies [11–13]. After all, this association should be widely studied in future researches.

3.2.2 Type of Injury

The type of injury (closed, penetrating, crush, blast, etc.) shown in the CT-scan is an important prognostic factor that will determine the initial evolution of a severe TBI [14]. There are some early injuries in the CT-scan of patients with severe TBI that are associated with greater mortality and worse neurologic outcome.

Penetrating injuries result in a significantly higher mortality and poorer outcome [15, 16], but the data available for the rest of different types of injury are too less to allow comparisons between different prognostic effects.

The evidence for this is very indirect, and more studies should be conducted to assess a prognostic analysis between the different types of injuries in detail.

3.2.3 Clinical Severity

3.2.3.1 Extracranial Injuries

Extracranial injury is frequently present in patients with TBI. The severity of this injury is commonly assessed with the Injury Severity Score (ISS) [17] or the Abbreviated Injury Score (AIS) [18, 19].

Trauma patients with concurrent injuries to the brain or skull seem to have increased mortality [20], and multiple organ trauma (MOT) associated to a TBI has been shown to increase rates of infection, length of hospital stay, and ventilator use. Extracranial injuries in TBI patients are also associated with slower physical recovery and increased return-to-work times [21].

The estimated prevalence of major extracranial injury (MEI) in TBI populations varies between 23% [5] and 41% [22], depending on the study population and the definition used.

How extracranial injury affects prognosis has been much debated. Some studies have demonstrated that outcome mainly depends on the severity of the primary cerebral damage and is not worsened by the presence of extracranial injuries [22, 23]. Other studies, however, suggest that the presence of MEI carries a poorer outcome in TBI patients [5, 24–26]. Recent investigations have shown that the prognostic effect of MEI varies by the population studied [27]; in patients with mild TBI the effect of the interaction with brain injury severity seems to be greater. In severe TBI the outcome is mostly determined by the brain injury.

However, the impact of multiple concomitant injuries outside of the brain during initial trauma in TBI patients has not been well defined [28–31].

3.2.3.2 Intracranial Injuries

Intracranial injuries appearing in the CT-scan have a prognostic value as shown in multiple studies.

The level of consciousness assessed by the GCS reflects the clinical severity of intracranial injuries. The association between lower scores on the GCS and poorer outcome is well documented [5]; there is an inverse correlation between GCS and outcome, and lower scores on the GCS are associated with poorer outcome.

Using the GCS could overestimate the severity of a severe TBI (GCS <8) [32] but also underestimate the severity of moderate TBI with severe

injuries in the CT-scan [33]. Many authors only use the motor component of the GCS; it has the greatest predictive value in severe TBI, as the eye and verbal component could be affected by sedation and intubation [32].

The IMPACT study [34] analyzed GCS values obtained before admission, on admission to hospital, and when patients enrolled in the study (GCS following primary respiratory and hemodynamic stabilization) and found significant differences between the GCS value at different time periods. The GCS obtained at the moment of joining the study (poststabilization) showed the greatest association with prognosis at 6 months. Even so, the other GCS values showed a great association with prognostic too. This demonstrated that GCS scores may fluctuate and prognostic effects of the GCS are different between clinical time periods [34].

In general, poststabilization GCS is considered the best suitable for predictive purposes, and the motor component showed the greatest predictive value.

So, it should be taken into account that the GCS value could be affected by sedation, intubation, hemodynamic destabilization, hypotension or hypoxia; and its value fluctuates under different clinical situations. In addition, when the motor component raises its value, better situations cannot be evaluated.

However, despite its limitations, the GCS is still used and highly recommended to classify and predict the outcome of patients with TBI [34].

3.2.4 Second Insults (Hypotension and Hypoxia)

Hypotension is recognized as one of the most important systemic secondary insults following traumatic brain injury (TBI) [35]. Hypotension at the hospital setting (defined as any episode with a systolic blood pressure <90 mmHg) is associated with poorer outcome [36] with a 67% of positive predictive value (PPV) and if there is hypoxia (defined as PaO_2 <60 mmHg) too, the PPV increases to 79% [35]. Various studies have shown that the combination of hypoxia and hypotension has a greater adverse effect on outcome than either insult in isolation [37]. Furthermore, the depth and duration of hypoxia and hypotension are related to poorer outcome [38–40].

The incidence of hypotension at admission is 23–42% [41]. It has been shown that low blood pressures from the moment of traumatism and prehospital setting since resuscitation and stabilization are an independent prognostic factor of worse outcome together with age, GCS, CT-scan injuries, and pupillary reactivity [42]. On the other hand, some studies have shown that both low and high blood pressures are associated with poorer outcome [43]. However, following adjustment for age, motor score, and pupillary reactivity, the effects of higher blood pressure on outcome largely disappear, suggesting that these are merely indicative of more severe injuries and could possibly be caused by raised intracranial pressure (Cushing response). Hypoxic events are associated with worse outcome too, but with less effect [44].

3.2.5 Imaging Abnormalities

Injuries visualized in CT-scanning or magnetic resonance (MR) imaging are highly associated with prognosis.

In this way, computerized tomography (CT) scan is found to be very useful for prognosis. In the acute phase after TBI, CT is considered the technique of choice to identify and classify structural abnormalities.

CT-scan variables including midline shift, effacement of basal cisterns, traumatic subarachnoid hemorrhage, subdural hematoma volume or presence and type of any abnormality [45] may also be useful predictors of outcome at 6 months in patients with TBI [46]. These individual imaging features have been found to have class I and II evidence for >70% positive predictability in TBI [47].

Besides these individual intracranial injuries, the Marshall CT-scan classification system is also found to have good predictability [48, 49] and is widely used as a predictor of outcome [50].

The Marshall classification [51] consists in a descriptive classification of head injury, based on CT characteristics which focuses on the presence of a mass lesion and differentiates diffuse injuries by signs of increased intracranial pressure such as compression of the basal cistern and midline shift (Table 3.1).

Though the Marshall system is widely used, it has important limitations:

- The classification of traumatic intracranial mass lesion as "evacuated" or "nonevacuated" depends on the knowledge of what subsequently happened to the patient; hence, it can be applied only retrospectively.
- The basis of cut-off of 25 cc as volume of mass lesion is not clear. The guidelines for the surgical management of traumatic brain injury mention different cut-offs for specific traumatic lesions [52].
- The Marshall system does not classify the types of hematoma. The outcome of surgery is dependent on the type of hematoma. Mortality of EDH is 7–12.5%, SDH 40–60%, and contusions 16–72%.
- The system does not further categorize the extent of basal cisterns compression. Various studies have found that as the extent of basal cistern compression increases from normal to partially effaced to totally effaced, mortality increases [47].
- Traumatic subarachnoid hemorrhage (tSAH) is not included as a predictor. The presence of tSAH has been found to have a significant impact on outcome [47]. After adjustment for age, GCS, motor scores, and admission CT findings, tSAH had a strong, highly statistically significant association with poor outcomes (OR, 2.49) (1.74–3.55; $p < 0.001$) [53].
- The Marshall classification cannot be used as a grading system. The mortality or unfavorable outcome is less for evacuated mass lesion than for nonevacuated mass lesion, though the former is mentioned as class 5, and the latter as class 6.

Thus, this classification may not fully use the prognostic information contained in individual CT characteristics.

To overcome these limitations, various CT-scan classification systems have been proposed [47, 48, 52, 54].

The Rotterdam CT score (Table 3.2) is one of them. It combines individual CT characteristics [54] with the addition of tSAH and EDH and further categorization of cisternal compression. This system has been shown to provide better prediction of outcome [49] by better discrimination

Table 3.1 Marshall computed tomographic classification

Structural damage CT	
Diffuse injury I	No visible pathology
Diffuse injury II	Cisterns present, midline shift 0–5 mm and/or lesion densities present or no mass lesion >25 mL
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift 0–5 mm or no mass lesion >25 mL
Diffuse injury IV (shift)	Midline shift >5 mm, no mass lesion >25 mL
Evacuated mass lesion	Any lesion surgically evacuated
Nonevacuated mass lesion	High or mixed density lesion >25 mL, not surgically evacuated

Table 3.2 Rotterdam scoring system

CT-scan feature	Score
Basal cisterns	
Normal	0
Compressed	1
Absent	2
Midline shift	
No shift or shift ≤ 5 mm	0
Shift >5 mm	1
Epidural mass lesion	
Present	0
Absent	1
IVH or SAH	
Absent	0
Present	1
Sum score	+1

CT computed tomography, *IVH* intraventricular hemorrhage, *SAH* subarachnoid hemorrhage

between better and poorer outcome than the Marshall classification [55].

3.2.6 Pupillary Reactivity

Assessment of pupillary reactivity is a standard procedure of neurological evaluation. Pupillary reactivity has demonstrated to have a good ability to predict outcome in patients with TBI [34] and has been widely used in TBI prognostic models. Acute pupillary dilatation in head-injured patients indicates a neurological emergency [56, 57].

3.3 Novel and Emerging Predictors of Outcome

3.3.1 Extended Neuromonitoring

Basic neuromonitoring includes neurologic examination, computerized tomography, and ICP. On the other hand, extended neuromonitoring comprises $SjvO_2$, $ptiO_2$, microdialysis, TCD, and electrophysiologic recordings including CSD.

Basic neuromonitoring alone cannot assess changes in cerebral perfusion, oxygenation, metabolism, and electrophysiological function. This implies that we will miss important signs of deterioration and so we will also fail to adapt and reduce therapeutic interventions once the previous impairment has been corrected. There is increasing evidence that extended neuromonitoring is an important therapeutic tool, and the $ptiO_2$ value or the TCD (as we will see later) are emerging as new prognostic factors showing a good association with the patient outcome in recent studies [58–62].

When only relying on changes in ICP and CPP, we may not only miss important signs of deterioration, but also fail to adequately reduce therapeutic interventions [63, 64].

Based on current evidence, extended neuromonitoring in daily clinical practice could help us to identify optimal CPP, guide ventilator support (O_2 and ventilation), define adequate hemoglobin level and guide transfusion, determine optimal blood and brain glucose, and guide decompressive craniectomy [65, 66]. All this information can improve our treatment options by characterizing functional influences, defining threshold values, and adapting therapeutic interventions in type, extent, and duration. In addition, extended neuromonitoring helps us to prevent induction of additional brain damage due to excessive therapeutic corrections.

3.3.2 Genetic Constitution

Different genes and polymorphisms have been studied in patients with TBI. The majority of the studies use an approach based on a priori understanding of the pathophysiology of TBI coupled with genetics. Maybe genetic variability could be the clue to explain why the clinical course and outcome are so different between patients with similar injury severity and CT-scan injuries at admission.

The most extensively studied gene in the field of TBI is undoubtedly Apolipoprotein E. APOE-e4 has been widely studied and many studies have shown its association with poorer functional recovery [67–69].

On the other hand, there are studies that show no clear association between APOE-e4 and outcome in TBI [70, 71]. A recent systematic review [72] concluded that the effect size might only be significant in severe TBI. One large study [73] found an altered trajectory of recovery in APOE-e 4 carriers, but ultimately the same outcome over a 2-year period.

Teasdale et al. [74] performed an observational study with 1094 patients with TBI and could not confirm an association between APOE-e4 and poorer outcome.

However, while the risk of late neurodegenerative disease scales with the severity of TBI, the possession of an APOE-e4 allele may modulate this response [75]. Mayeux et al. [76] found that APOE-e4 increased the risk of dementia twofold, but the combination of APOE-e4 and a TBI increased the risk tenfold. This suggests that the effect of APOE-e4 genotype on outcome after head injury may be expressed through the processes of repair and recovery. Otherwise,

despite extensive research, the relationship of APOE genotype to outcome from TBI remains unclear.

A variety of polymorphisms (ABCB1, ABCC1 and ABCC2) exist which impact the bioavailability of both drugs and endogenous substrates in the brain [77]. Patients homozygous for the T allele of ABCB1 or the G allele of ABCC1 appear to have better outcomes after severe TBI [78]. Further work is required to move this outside the experiment.

Regarding prognosis, there are currently no genes for which the effect size is sufficiently well determined that they could be incorporated into existing prognostic models. Genetic association studies require large numbers, and none of the existing studies in TBI have been sufficiently powered to quantify prognostic effects adequately. Potential roles of genetic information may include better characterization, more accurate prognostication and therapy stratification, and identification of molecular targets for future drug development.

3.3.3 Laboratory Values and Biomarkers

Proteomic approaches and clinical studies have identified novel biomarker candidates considered more specific for neuronal or glial cell damage and help elucidate their time course and changes associated with pathophysiological processes in TBI.

These biomarkers may provide rapid biofluid-based biomarker tests to optimize diagnosis, track disease progression, and facilitate prognosis in TBI patients. Blood molecular biomarkers might also provide insights into pathogenic mechanisms underlying TBI, refine patient characterization, and allow specific molecular classifications. Such knowledge might be a target for novel therapeutic interventions, drug development, and clinical trials. If used in the appropriate setting, prognostic markers in TBI may be able to aid decisions to either avoid prolonged and unnecessary treatment or to intensify therapy.

A large number of biomarkers have been proposed as potentially prognostic. Different markers are relevant in different stages after injury (Table 3.3). In the acute phase, markers of innate inflammatory responses and brain-specific molecules released into the CSF and blood upon cell death and/or damage may reflect the magnitude of injury [79]. In the subacute phase, innate inflammatory responses decrease, while adaptive immune responses may be initiated [80]. In the chronic stages, markers of neurodegeneration are being explored for long-term sequelae including degenerative disorders linked to TBI, such as chronic traumatic encephalopathy (CTE) and Alzheimer's disease (AD). We are not going to study all the biomarkers in this chapter; in Table 3.3 you can find the most promising biomarkers for TBI that are being studied nowadays.

On the other hand, there are some laboratory variables routinely measured on admission that are associated with outcome following TBI. The

Table 3.3 Overview of promising biomarkers for TBI

Biomarker	Phase	Type	Major confounder
S100-B	Acute	Glial/BBB change	Not CNS specific
NSE	Acute	Neuronal	Red blood cells
GFAP	Acute	Glial	
UCH-L1	Acute	Neuronal	Intestinal tumors
αII-Spectrin BDPs	Acute	Axonal	Mainly in CSF
Neurofilament proteins	Acute/Subacute	Axonal	Under investigation
Cytokines	Subacute/chronic	Inflammatory response	Systemic injuries/complications
Auto-antibodies	Chronic	Autoimmune	Under investigation
Tau protein, Phospho-protein and amyloid β peptides	Acute/Chronic	Neurodegenerative	Under investigation

greatest prognostic effects exist for high glucose concentrations, low hemoglobin, low platelets, and coagulation disturbances [81–85].

Glucose management remains of big relevance. Hyperglycemia is associated with poor outcomes [81, 86–88] and tight glycemic control offers little benefit [89, 90]. Hypoglycemia with intensive insulin therapy has been corroborated as a risk for TBI by microdialysis studies [91, 92]. A brain:serum glucose ratio less than 0.12 predicts cerebral metabolic distress and mortality after severe TBI [93].

3.3.4 Advanced MR Imaging Techniques

Neuroimaging techniques increase the specificity of pathoanatomical diagnosis and facilitate therapy stratification and application of precision medicine approaches. Advanced multiparametric MR imaging techniques with potential prognostic relevance in TBI encompass diffusion tensor imaging (DTI) with fractional anisotropy (FA) mapping, diffusion kurtosis imaging (DKI), susceptibility-weighted imaging (SWI), functional MRI (fMRI), perfusion weighted imaging (PWI), and magnetic resonance spectroscopy (MRS).

DTI is an MRI sequence that can identify and quantify white matter damage and which offers a method of assessing axonal damage in vivo [94, 95].

DTI has emerged as a useful tool for assessing TBI, since focal injuries are usually easily identified using conventional computed tomography and MRI but do not completely explain observed long-term clinical outcome. Traumatic and axonal injury appears to be a key determinant of clinical outcome, which can be missed by conventional MRI. Studies on DTI have demonstrated its accurate visualization of traumatic axonal injury [96, 97].

In this way, quantitative DTI has been shown to improve the accuracy of long-term outcome prediction [98–100].

MR spectroscopy permits semiquantitative detection of metabolites in regions of the brain. Many studies have been carried out with MR spectroscopy in TBI, for example with N-acetylaspartate (NAA), choline (Cho), and their ratio to creatinine and lactate [101] showing that their extracellular levels are higher in non-TBI survivors. Despite this, MR spectroscopy has not gained acceptance as a routine clinical diagnostic tool in acute TBI, and it has been widely used as a research tool to examine changes in tissue biochemistry.

All these MRI studies, which represent a progress in the comprehension of pathophysiology of severe TBI, need confirmations with new series of patients before being used routinely. Neuroimagery will probably help us to test treatments to limit secondary damage or enhance spontaneous anatomic recuperation, but modifications in cell metabolism evaluated by MRI were disappointing. Furthermore, logistic considerations limit the use of MR imaging. There is a need to check for contraindications to MRI that can be difficult to ascertain in the acute setting or even in routine in many specialized hospitals and may be dangerous, notably in cases of intracranial hypertension.

Conclusion

Estimates of prognosis are a key point for the adequate management of patients with TBI. An improved estimation of prognosis in these patients permits a more accurate clinical and ethical decision making.

Nowadays, the availability of large databases and an exponential increase in prognostic research in TBI has facilitated prognostic analysis and the development of validated prognostic models with good generalizability. The exhaustive knowledge of prognostic factors offers new opportunities and should be considered an important instrument in clinical decision making and research.

Relevant prognostic factors, as the ones studied in this chapter, have been identified by multivariable analysis. However, the development of prognostic models in TBI must be an ongoing process and further studies and investigations are needed to truly validate the use of these prognostic factors.

References

1. Signorini DF, Andrews PJ, Jones PA, Wardlaw JM, Miller JD. Predicting survival using simple clinical variables: a case study in traumatic brain injury. J Neurol Neurosurg Psychiatry. 1999;66:20–5.
2. Gomez PA, Lobato RD, Boto GR, De la Lama A, González PJ, de la Cruz J. Age and outcomeafter severe head injury. Acta Neurochir. 2000;142:373–80; discussion 380–1.
3. Ono J, Yamaura A, Kubota M. Outcome prediction insevere head injury: analyses of clinical prognostic factors. J Clin Neurosci. 2001;8:120–3.
4. Mushkudiani NA, Engel DC, Steyerberg EW, Butcher I, Lu J, Marmarou A, et al. Prognostic value of demographic characteristics in traumatic brain injury: results from the IMPACT study. J Neurotrauma. 2007;24:259–69.
5. Trial Collaborators MRCCRASH, Perel P, Arango M, Clayton T, Edwards P, Komolafe E, et al. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. BMJ. 2008;336:425–9.
6. Tokutomi T, Miyagi T, Ogawa T, Ono J, Kawamata T, Sakamoto T, et al. Age-associated increases in poor outcomes after traumatic brain injury: a report from the Japan Neurotrauma Data Bank. J Neurotrauma. 2008;25:1407–14.
7. Demetriades D, Murray J, Martin M, Velmahos G, Salim A, Alo K, et al. Pedestrians injured by automobiles: relationship of age to injury type and severity. J Am Coll Surg. 2004;199:382–7.
8. Hukkelhoven CW, Steyerberg EW, Rampen AJ, Farace E, Habbema JD, Marshall LF, et al. Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. J Neurosurg. 2003;99:666–73.
9. Kraus JF, Peek-Asa C, McArthur D. The independent effect of gender on outcomes following traumatic brain injury: a preliminary investigation. Neurosurg Focus. 2000;8:1–7.
10. Farace E, Alves WM. Do women fare worse? A metaanalysis of gender differences in outcome after traumatic brain injury. Neurosurg Focus. 2000;8:e6.
11. Sorani MD, Lee M, Kim H, Meeker M, Manley GT. Race\ethnicity and outcome after traumatic brain injury at a single, diverse center. J Trauma. 2009;67:75–80.
12. Shafi S, Marquez de la Plata C, Diaz-Arrastia R, Shipman K, Carlile M, Frankel H, et al. Racial disparities in long-term functional outcome after traumatic brain injury. J Trauma. 2007;63:1263–70.
13. Arango-Lasprilla JC, Rosenthal M, Deluca J, Komaroff E, Sherer M, Cifu D, et al. Traumatic brain injury and functional outcomes: does minority status matter? Brain Inj. 2007;21:701–8.
14. Boto GR, Gómez PA, De la Cruz J, Lobato RD. Severe head injury and the risk of early death. J Neurol Neurosurg Psychiatry. 2006;77:1054–9.
15. Aarabi B, Alden TD, Chestnut RM, et al. Management and prognosis of penetrating brain injury. J Trauma. 2001;51(Suppl):S1–S86.
16. Brenneman FD, Boulanger BR, McLellan BA, Culhane JP, Redelmeier DA. Acute and long-term outcomes of extremely injured blunt trauma victims. J Trauma. 1995;39:320–4.
17. Baker SP, O'Neill B, Haddon Jr W, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma. 1974;14:187–96.
18. AAAM. The Abbreviated Injury Scale, 1990 revision. Association for the Advancement of Automotive Medicine, 15–24, Des Plaines. 1990.
19. Greenspan L, McLellan B, Greig H. Abbreviated injury scale and injury severity Score: a scoring chart. J Trauma. 1985;25:60–4.
20. Gennarelli TA, Champion HR, Sacco WJ, Copes WS, Alves WM. Mortality of patients with head injury and extracranial injury treated in trauma centers. J Trauma. 1989;29:1193–201; discussion 1201–192.
21. Stulemeijer M, van der Werf SP, Jacobs B, Biert J, van Vugt AB, Brauer JM, et al. Impact of additional extracranial injuries on outcome after mild traumatic brain injury. J Neurotrauma. 2006;23:1561–9.
22. Heinzelmann M, Platz A, Imhof HG. Outcome after acute extradural haematoma, influence of additional injuries and neurological complications in the ICU. Injury. 1996;27:345–9.
23. Sarrafzadeh AS, Peltonen EE, Kaisers U, Küchler I, Lanksch WR, Unterberg AW. Secondary insults in severe head injury – do multiply injured patients do worse? Crit Care Med. 2001;29:1116–23.
24. Lefering R, Paffrath T, Linker R, Bouillon B, Neugebauer EA, Deutsche Gesellschaft für Unfallchirurgie/German Society for Trauma Surgery. Head injury and outcome – what influence do concomitant injuries have? J Trauma. 2008;65:1036–43.
25. Ho KM, Burrell M, Rao S. Extracranial injuries are important in determining mortality of neurotrauma. Crit Care Med. 2010;38:1562–8.
26. Jacobs B, Beems T, Stulemeijer M, van Vugt AB, van der Vliet TM, Borm GF, et al. Outcome prediction in mild traumatic brain injury: age and clinical variables are stronger predictors than CT abnormalities. J Neurotrauma. 2010;27:655–68.
27. Van Leeuwen N, Lingsma HF, Perel P, Lecky F, Roozenbeek B, Lu J, Shakur H et al.. Prognostic value of major extracranial injury in traumatic brain injury: an individual patient data meta-analysis in 39,274 patients. Neurosurgery. 2012;70:811–8; discussion 818.
28. Zygun DA, Doig CJ, Gupta AK, Whiting G, Nicholas C, Shepherd E, et al. Non-neurological organ dysfunction in neurocritical care. J Crit Care. 2003;18:238–44.
29. Leitgeb J, Mauritz W, Brazinova A, Majdan M, Wilbacher I. Impact of concomitant injuries on outcomes after traumatic brain injury. Arch Orthop Trauma Surg. 2013;133:659–68.

30. Lefering R, Paffrath T, Linker R, Bouillon B, Neugebauer EA. Deutsche Gesellschaft fur Unfallchirurgie/German Society for Trauma, S. Head injury and outcome—what influence do concomitant injuries have? J Trauma. 2008;65: 1036–43.
31. Andruszkow H, Probst C, Grun O, Krettek C, Hildebrand F. Does additional head trauma affect the long-term outcome after upper extremity trauma in multiple traumatized patients: is there an additional effect of traumatic brain injury? Clin Orthop Relat Res. 2013;471:2899–905.
32. Stocchetti N, Pagan F, Calappi E, Canavesi K, Beretta L, Citerio G, et al. Inaccurate early assessment of neurological severity in head injury. J Neurotrauma. 2004;21:1131–40.
33. Balestreri M, Czosnyka M, Chatfield DA, Steiner LA, Schmidt EA, Smielewski P, et al. Predictive value of Glasgow coma scale after brain trauma: change in trend over the past ten years. J Neurol Neurosurg Psychiatry. 2004;75:161–2.
34. Marmarou A, Lu J, Butcher I, McHugh GS, Mushkudiani NA, Murray GD, et al. IMPACT Database of traumatic brain injury: design and description. J Neurotrauma. 2007;24:239–50.
35. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma. 1993;34:216–22.
36. Marshall LF, Becker DP, Bowers AS, Cayard C, Eisenberg H, Gross CR, et al. The National Traumatic Coma Data Bank. Part I: design, purpose, goals and results. J Neurosug. 1983;59:276–84.
37. Mchugh GS, Butcher I, Steyerberg EW, Lu J, Mushkudiani N, Marmarou A, et al. Statistical approaches to the univariate prognostic analysis of the IMPACT database on traumatic brain injury. J Neurotrauma. 2007;24:251–8.
38. Chesnut RM. Secondary brain insults after head injury: clinical perspectives. New Horiz. 1995;3:366–75.
39. Manley G, Knudson MM, Morabito D, Damron S, Erickson V, Pitts L. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. Arch Surg. 2001;136:1118–23.
40. McHugh GS, Engel DC, Butcher I, Steyerberg EW, Lu J, Mushkudiani N, et al. Prognostic value of secondary insults in traumatic brain injury: results from the IMPACT study. J Neurotrauma. 2007;24:287–93.
41. Hukkelhoven C, Steyerberg EW, Habbema JD, Farace E, Marmarou A, Murray GD, et al. Predicting outcome after traumatic brain Injury: development and validation of a prognostic score based on admission characteristics. J Neurotrauma. 2005;22:1025–39.
42. Marmarou A, Anderson RL, Ward JD, Choi SC, Young HF, Eisenberg HM, et al. Impact of ICP inestability and hypotension on outcome in patients with severe head trauma. J Neurosurg. 1991;75: S59–66.
43. Butcher I, Maas AI, Lu J, Marmarou A, Murray GD, Mushkudiani NA, et al. Prognostic value of admission blood pressure in traumatic brain injury; results from the IMPACT study. J Neurotrauma. 2007;24:294–302.
44. Murray GD, Butcher I, McHugh GS, Lu J, Mushkudiani NA, Maas AIR, et al. Multivariable prognostic analysis in traumatic brain injury: results from the IMPACT study. J Neurotrauma. 2007;24:329–37.
45. Foundation BT. Guidelines for the management and prognosis of severe traumatic brain injury. J Neurotrauma. 2001;51(Suppl. 2):S1–S86.
46. Yuh EL, Cooper SR, Ferguson AR, Manley GT. Quantitative CT improves outcome prediction in acute traumatic brain injury. J Neurotrauma. 2012;29:735–46.
47. Foundation BT. Early indicators of prognosis in severe traumatic brain injury. J Neurotrauma. 2000;17(6–7):555–627.
48. Bobinski L, Olivecrona M, Koskinen L-OD. Dynamics of brain tissue changes induced by traumatic brain injury assessed with the Marshall, Morris-Marshall, and the Rotterdam classifications and its impact on outcome in a prostacyclin placebo-controlled study. Acta Neurochir. 2012;154:1069–79.
49. Mata-Mbemba D, Mugikura S, Nakagawa A, Murata T, Ishii K, Li L, et al. Early CT findings to predict early death in patients with traumatic brain injury: marshall and Rotterdam CTscoring systems compared in the major academic tertiary care hospital in northeastern Japan. Acad Radiol. 2014;21(5):605–11.
50. Deepika P, Saikia S. Comparison of predictability of Marshall and Rotterdam CT scan scoring system in determining early mortality after traumatic brain injury. Acta Neurochir. 2015 Nov;157(11):2033–8.
51. Marshall LF, Marshall SB, Klauber MR, Clark MV. A new classification of head injury based on computerized tomography. J Neurosurg. 1991;75(1s):S14–20.
52. Bullock MR, Chesnut R, Ghajar J, Gordon D, Hartl R, Newell DW, et al. Guidelines for the surgical management of traumatic brain injury. Neurosurgery. 2006;58(Supplement):S2–S62.
53. Servadei F, Murray GD, Teasdale GM, Dearden M, Iannotti F, Lapierre F et al.. Traumatic subarachnoid hemorrhage: demographic and clinical study of 750 patients from the European brain injury consortium survey of head injuries. Neurosurgery. 2002;50(2):261–7; discussion 267–9
54. Maas AI, Hukkelhoven CW, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. Neurosurgery. 2005;57:1173–82.
55. Chun KA, Manley GT, Stiver SI, Aiken AH, Phan N, Wang V, et al. Interobserver variability in the assessment of CT imaging features of traumatic brain injury. J Neurotrauma. 2010;27:325–30.

56. Ritter AM, Muizelaar JP, Barnes T, Choi S, Fatouros P, Ward J, et al. Brain stem blood flow, pupillary response, and outcome in patients with severe head injuries. Neurosurgery. 1999;44:941–8.
57. Mauritz W, Leitgeb J, Wilbacher I, Majdan M, Janciak I, Brazinova A, et al. Outcome of brain trauma patients who have a Glasgow Coma Scale score of 3 and bilateral fixed and dilated pupils in the field. Eur J Emerg Med. 2009;16:153–8.
58. Badenes R, Maruenda A, García-Pérez ML, Chisbert V, Talamantes F, Belda FJ. Valor pronóstico de la presión tisular de oxígeno cerebral en los traumatismos craneoencefálicos graves. Rev Esp Anest Rea. 2005;52:A-75.
59. Valadka AB, Gopinath SP, Contant CF, Uzura M, Robertson CS. Relationship of brain tissue PO2 to outcome after severe head injury. Crit Care Med. 1998;26:1576–81.
60. Van den Brink WA, van Santbrink H, Steyerberg EW, Avezaat CJ, Suazo JA, Hogesteeger C, et al. Brain oxygen tension in severe head injury. Neurosurgery. 2000;46:868–78.
61. Dings J, Jäger A, Meixensberger J, Roosen K. Brain tissue pO2 and outcome after severe head injury. Neurol Res. 1998;20:71–5.
62. Bardt TF, Unterberg AW, Härtl R, Kiening KL, Schneider G-H, Lanksch WR. Monitoring of brain tissue pO2 in traumatic brain injury: effect of cerebral hypoxia on outcome. Acta Neurochir. 1998;71:153–6.
63. Jaeger M, Soehle M, Schuhmann MU, Winkler D, Meixensberger J. Correlation of continuously monitored regional cerebral blood flow and brain tissue oxygen. Acta Neurochir. 2005;147(1):51–6.
64. Jull N, Morris GF, Marshall SB. The executive commitee of the international Selfotel trial, Marshall LF. Intracranial hypertension and cerebral perfusion pressure: influence on neurological deterioration and outcome in severe head injury. J Neurosurg. 2000;92:1–6.
65. Stover JF. Actual evidence for neuromonitoring-guided intensive care following severe traumatic brain injury. Swiss Med Wkly. 2011;141:w13245.
66. Marini CP, Stoller C, Shah O, Policastro A, Lombardo G, Asensio JA, et al. The impact of early flow and brain oxygen crisis on the outcome of patients with severe traumatic brain injury. Am J Surg. 2014;208:1071–7.
67. Teasdale GM, Nicoll JA, Murray G, Fiddes M. Association of apolipoprotein E polymorphism with outcome after head injury. Lancet. 1997;350:1069–71.
68. Friedman G, Froom P, Sazbon L, Grinblatt I, Shochina M, Tsenter J, et al. Apolipoprotein E-epsilon4 genotype predicts a poor outcome in survivors of traumatic brain injury. Neurology. 1999;52:244–8.
69. Ost M, Nyle'n K, Csajbok L, Blennow K, Rosengren L, Nellgård B. Apolipoprotein E polymorphism and gender difference in outcome after severe traumatic brain injury. Acta Anaesthesiol Scand. 2008;52:1364–9.
70. Olivecrona M, Wildemyr Z, Koskinen LO. The apolipoprotein E epsilon4 allele and outcome in severe traumatic brain injury treated by an intracranial pressuretargeted therapy. J Neurosurg. 2010;112:1113–9.
71. Pruthi N, Chandramouli BA, Kuttappa TB, Rao SL, Subbakrishna DK, Abraham MP, et al. Apolipoprotein E polymorphism and outcome after mild to moderate traumatic brain injury: a study of patient population in India. Neurol India. 2010;58:264–9.
72. Bulstrode H, Nicoll JAR, Hudson G, Chinnery PF, Di Pietro V, Belli A. Mitochondrial DNA and traumatic brain injury. Ann Neurol. 2014;75:186–95.
73. Ponsford J, McLaren A, Schönberger M, Burke R, Rudzki D, Olver J, et al. The association between apolipoprotein E and traumatic brain injury severity and functional outcome in a rehabilitation sample. J Neurotrauma. 2011;28:1683–92.
74. Teasdale GM, Murray GD, Nicoll JA. The association between APOE epsilon4, age and outcome after head injury: a prospective cohort study. Brain. 2005;128:2556–61.
75. Shively S, Scher AI, Perl DP, Diaz-Arrastia R. Dementia Resulting From Traumatic Brain Injury. Arch Neurol. 2012;69:1245–51.
76. Mayeux R, Ottman R, Maestre G, Ngai C, Tang MX, Ginsberg H, et al. Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. Neurology. 1995;45:555–7.
77. Conseil G, Deeley RG, Cole SPC. Polymorphisms of MRP1 (ABCC1) and related ATP-dependent drug transporters. Pharmacogenet Genomics. 2005;15:523–33.
78. Cousar JL, Conley YP, Willyerd FA, Sarnaik AA, Puccio AM, Empey PE, et al. Influence of ATP-binding cassette polymorphisms on neurological outcome after traumatic brain injury. Neurocrit Care. 2013;19:192–8.
79. Dash PK, Zhao J, Hergenroeder G, Moore AN. Biomarkers for the diagnosis, prognosis, and evaluation of treatment efficacy for traumatic brain injury. Neurotherapeutics. 2010;7:100–14.
80. Cox AL, Colesa J, Nortje J, Bradley PG, Chatfield DA, Thompson SJ, et al. An investigation of autoreactivity after head injury. J Neuroimmunol. 2006;174:180–6.
81. Lannoo E, Van Rietvelde F, Colardyn F, Lemmerling M, Vandekerckhove T, Jannes C, et al. Early predictors of mortality and morbidity after severe closed head injury. J Neurotrauma. 2000;17:403–14.
82. Rovlias A, Kotsou S. The blood leukocyte count and its prognostic significance in severe head injury. Surg Neurol. 2001;55:190–6.
83. Van Beek JG, Mushkudiani NA, Steyerberg EW, Butcher I, McHugh GS, Lu J, et al. Prognostic value of admission laboratory parameters in traumatic brain injury: results from the IMPACT study. J Neurotrauma. 2007;24:315–28.
84. Saggar V, Mittal RS, Vyas MC. Hemostatic abnormalities in patients with closed head injuries and their role in predicting early mortality. J Neurotrauma. 2009;26:1665–8.

85. Helmy A, Timofeev I, Palmer CR, Gore A, Menon DK, Hutchinson PJ. Hierarchical log linear analysis of admission blood parameters and clinical outcome following traumatic brain injury. Acta Neurochir. 2010;152:953–7.
86. Rovlias A, Kotsou S. The influence of hyperglycemia on neurological outcome in patients with severe head injury. Neurosurgery. 2000;46:335–43.
87. Andrews PJ, Sleeman DH, Statham PF, McQuatt A, Corruble V, Jones PA, et al. Predicting recovery in patients suffering from traumatic brain injury by using admission variables and physiological data: a comparison between decision tree analysis and logistic regression. J Neurosurg. 2002;97:326–36.
88. Salim A, Hadjizacharia P, Dubose J, Brown C, Inaba K, Chan LS, et al. Persistent hyperglycemia in severe traumatic brain injury: an independent predictor of outcome. Am Surg. 2009;75:25–9.
89. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology. 2005;64:1348–53.
90. Bilotta F, Caramia R, Cernak I, Paoloni FP, Doronzio A, Cuzzone V, et al. Intensive insulin therapy after severe traumatic brain injury: a randomized clinical trial. Neurocrit Care. 2008;9:159–66.
91. Vespa P, Boonyaputthikul R, McArthur DL, Miller C, Etchepare M, Bergsneider M, et al. Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury. Crit Care Med. 2006;34:850–6.
92. Oddo M, Schmidt JM, Carrera E, Badjatia N, Connolly ES, Presciutti M, et al. Impact of tight glycemic control on cerebral glucose metabolism after severe brain injury: a microdialysis study. Crit Care Med. 2008;36:3233–8.
93. Kurtz P, Claassen J, Schmidt JM, Helbok R, Hanafy KA, Presciutti M, et al. Reduced brain/serum glucose ratios predict cerebral metabolic distress and mortality after severe brain injury. Neurocrit Care. 2013;19:311–9.
94. Hellyer PJ, Leech R, Ham TE, Bonnelle V, Sharp DJ. Individual prediction of white matter injury following traumatic brain injury. Ann Neurol. 2013;73:489–99.
95. Galanaud D, Perlbarg V, Gupta R, Stevens RD, Sanchez P, Tollard E, et al. Assessment of white matter injury and outcome in severe brain trauma: a prospective multicenter cohort. Anesthesiology. 2012;117(6):1300–10.
96. Paliotta C, Bakhadirov K, Marquez de la Plata C, Krishnan K, Bakhadirov K, Paliotta C, et al. Analyzing diffusion tensor imaging data in traumatic axonal injury: what is the best approach? J Neurotrauma. 2009;26:A36.
97. Mac Donald CL, Johnson AM, Cooper D, Nelson EC, Werner NJ, Shimony JS, et al. Detection of blast-related traumatic brain injury in U.S. military personnel. N Engl J Med. 2011;364:2091–100.
98. Perlbarg V, Puybasset L, Tollard E, Lehéricy S, Benali H, Galanaud D. Relation between brain lesion location and clinical outcome in patients with severe traumatic brain injury: a diffusion tensor imaging study using voxel-based approaches. Hum Brain Mapp. 2009;30:3924–33.
99. Tollard E, Galanaud D, Perlbarg V, Sanchez-Pena P, Le Fur Y, Abdennour L, et al. Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: preliminary results. Crit Care Med. 2009;37:1448–55.
100. Kis D, Mencser Z, Czigner A, Sanchez-Pena P, Le Fur Y, Abdennour L, et al. Prediction of long term outcome in severe traumatic brain injury using diffusion tensor imaging and probabilistic tractography. Acta Neurochir. 2011;153:1883.
101. Belli A, Sen J, Petzold A, Russo S, Kitchen N, Smith M, et al. Extracellular N-acetylaspartate depletion in traumatic brain injury. J Neurochem. 2006;96:861–9.

4 Brain Death: Understanding the Process of Brain Death Declaration Through Real-Life Case Scenarios

Abhijit Lele and Michael Souter

4.1 Introduction

Under the Uniform Declaration of Death Act (UDDA) [1] in the United States, death is legally determined by demonstrating either (a) irreversible cessation of circulatory and respiratory functions defining death from cardiovascular causes, or (b)irreversible cessation of all functions of the entire brain including the brain stem to define death from neurological causes i.e., brain death. In some sense, all death can be considered as brain death in that the sustained cessation of cardiovascular activity will eventually give rise to irreversible cessation of brain function. This concept of a dual etiology of death has subsequently spread throughout most of the world.

However, an accurate and comprehensive understanding of the diagnosis of death from neurological causes remains a persistent challenge for medical practitioners everywhere.

This book chapter is written to guide that understanding, which in turn demands consideration of principles of brain death declaration within the special contexts of hypothermia, family refusal to accept the declaration based on religious grounds, appropriate use of ancillary testing, and understanding post-declaration events.

The principles of the process of declaring brain death will be discussed in the context of case scenarios where on analysis of a clinical problem, the readers will be presented with our rationale for management, given the current evidence.

In essence, this chapter is intended to provide the reader with a practical approach to the declaration of brain death.

4.2 Historical Milestones in Brain Death Declaration

The exact incidence of patients progressing to brain death around the world is largely unknown. In a study by Kramer et al., in a cohort of 2788 intensive care patients in Southern Alberta, Canada, neurologic death constituted about 3–8% of all deaths over a 10-year period [8]. It is estimated that brain death declaration occurs in approximately 5% of patients with acute brain injury [9]. Leading causes of brain injury progressing to brain death include traumatic brain injury, intracranial hemorrhage, and hypoxic/anoxic-ischemic encephalopathy [10, 11].

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Year	Details
1968	Definition of irreversible coma, JAMA, Ad Hoc Committee of the Harvard Medical School [2]
1971	Minnesota clinical pathological study [3]
1971	Finland becomes first European country to accept brain death
1971	Kansas is first state in the US to legally recognize brain death
1981	NINCDS Collaborative Study of Brain Death on autopsy correlate in 503 patients with brain death validating Harvard criteria [4]
1981	Uniform Death Declaration Act (http://www.law.upenn.edu/bll/archives/ulc/fnact99/1980s/udda80.htm.)
1987	New York Department of Health regulates hospitals to accommodate religious and moral objections
1991	New Jersey Declaration of Death Act permits religious exemption [5]
1996	United Kingdom Royal College of Physicians included brain stem death (Journal of Royal College of Physicians)
1995	American Academy of Neurology (AAN) practice parameters for determining brain death [6]
2009	California statue requires hospitals to accommodate objections
2010	Evidence-based practice update by Quality Standards of the AAN [7]

NINCDS National Institute of Neurological and Communicative Disorders and Stroke

It is generally accepted that while legally any licensed physician can determine brain death, all physicians who participate in this process should be intimately familiar with the concept of brain death, and have conformed to existing local, institutional, state, and national accepted standards in making that diagnosis. In a recent survey of 50 neurological institutions across the United States, 42% of all declarations were carried out by neurologists/neurosurgeons, while a majority (65%) of these declarations were performed by resident physicians as opposed to attendings [12].

Around the world, most countries require at least two physicians to declare patient brain death (ostensibly to avoid error), while only in a few can a single physician pronounce patient brain dead (Canada, Sweden, Columbia, Chile, Mexico, Panama, and the Russian Federation) [10].

Recently, simulation-based courses have shown to improve educational efficiency and consequently reduce opportunity for error [13–16].

At the core of declaration is the presence of coma, supported by an adequate history of complaint with radiological findings. Physical findings include the absence of response to noxious stimulation, absence of cranial nerve reflexes, and absence of respiratory drive on a PCO_2 (pH) challenge. Neurological examinations are confounded by hypoxia, hypotension, abnormal biochemistry, and reasonable suspicion for toxins (either iatrogenic or accidental) (Tables 4.1, 4.2, and 4.3). We will show how these criteria can be included in diagnostic decision making, through consideration of the following examples.

Case Scenarios

An 18-year-old male is involved in a high-speed motor vehicle accident, and suffers severe traumatic brain injury, with severe facial injuries. He is intubated in the field and is placed in a cervical collar, but without cervical spine fracture on x-ray. Initial neurological examination reveals no cough, gag, or response to noxious stimuli. He has bilateral eyelid edema (rendering pupils difficult to examine), and blood coming out of his ears.

Comprehensive clinical evaluation and neurological assessment form the basis of any brain death examination [7]. Patients must lack all evidence of responsiveness, with absent eye opening or eye movement to noxious stimuli. There must be absence of brainstem reflexes, such as absence of pupillary response to a bright light documented in both eyes. Pinpoint pupils raise concern for pontine lesions or opiates. Usually the pupils are fixed in midsize or dilated (4–9 mm),

Table 4.1 Testing for brain function, including the brain stem

Coma/Unresponsiveness
Apply painful stimulus in central location (such as supraorbital or earlobe pinch) and peripheral stimuli such as nailbed pressure. Brain motor response excludes brain death. Other motor responses that are not clear due to spinal reflexes will require an ancillary study.
Pupillary reflex
Shine light into each eye to observe change in pupil size. Any change excludes brain death.
Oculovestibular reflex
Elevate head of bed to 30°. Open eyes by pulling up on eyelids. Irrigate external auditory canal with 50 ml iced water. No eye movements should be seen in the 60 s following completion of the irrigation. Both sides should be tested with at least 5 min between testing each side.
Oculocephalic reflex (test only when no fractures or instability of cervical spine is apparent)
Briskly rotate head 90° lateral from midline (horizontal) and briskly flexion (vertical) head. Any eye movement excludes brain death.
Corneal reflex
Touch cornea with end of cotton-tipped swab. Blinking movement excludes brain death.
Cough reflex
Stimulate tracheobronchial tree by passing cannula or irrigating endotracheal tube. Movement, coughing or bradyarrhythmia excludes brain death.
Gag reflex
Stimulate back of pharynx with tongue depressor or suction catheter. Movement of uvula or gagging excludes brain death.

Table 4.2 Apnea trial procedure and flowchart

1. Criteria for an apnea trial:
1. Absent brain motor responses.
2. Absent brainstem reflexes.
3. 24 h of temperature greater than or equal to 35 °C.
4. Hemodynamically stable without cardiac arrhythmias (Systolic blood pressure >100 mm Hg either with or without vasopressors).
5. Adequate oxygenation (PaO_2 greater than or equal to 200 mm Hg on an FiO_2 of 1.0).
6. Serum pH greater than 7.30 (severe metabolic acidosis is a contraindication to an apnea trial).
7. Absence of a known cervical spinal cord injury.
8. The apnea test should be completed as part of the first examination in which no other brain function is demonstrated. The apnea test should be completed after the motor response and brainstem reflex testing.
2. Normalize patient's $PaCO_2$ on the ventilator ($PaCO_2$ 35–45 mm Hg or the patient's known baseline $PaCO_2$). This is necessary if patient has been hyperventilated to decrease ICP. A low $PaCO_2$ may increase the amount of time needed for the $PaCO_2$ to reach the level needed to confirm apnea.
3. Hyperoxygenate with 100% oxygen before the trial for 10 min.
4. Estimate with the pretrial ABG the time required to reach an apneic $PaCO_2$ of approximately 60 mm Hg or 20 mm Hg greater than normal baseline, whichever is greater, considering the $PaCO_2$ will rise approximately 4–5 mm Hg in the first minute and approximately 3–4 mm Hg for each consecutive minute.
5. Place patient on 100% oxygen source (Ambu bag) for the calculated period of time.
6. Observe the patient for spontaneous respirations. If they do not occur after the calculated period of time, an ABG is drawn.
7. If spontaneous respirations occur, return the patient to the ventilator. Measure tidal volume and rate before the underlying ventilator rate is used.
8. If hypotension, cardiac arrhythmias, or desaturation (SpO_2 < 88%) occur during the trial, obtain an ABG if it can be done safely and return the patient to the ventilator immediately.
9. Results of trial should be documented in medical record, including length of apneic period, blood gas results, and rate and measurable volume of breaths, if any occurred.

Table 4.3 Common pharmacologic agents that can affect clinical brain death assessment

Drug	Half-life (T1/2)	Distribution	Suggested time to brain death exam
Barbiturates			
Pentobarbital	~4–50 h	~35–45% bound to plasma proteins	Pentobarbital level ≤10mcg/ml
Phenobarbital	~2–6 days	~20–45% bound to plasma proteins	Phenobarbital level ≤10mcg/ml
Benzodiazepines			
Lorazepam	10–20 h	Widely distributed in most body tissues	Variable, if expect toxicity, wait 1.5–2 times the half-life
Midazolam	1–12.5 h	Widely distributed, 95% protein bound	Variable, if expect toxicity, wait 1.5–2 times the half-life
Diazepam	20–50 h, active metabolite 40–100 h	Widely distributed, 94–99% protein bound	Variable, if expect toxicity, wait 1.5–2 times the half-life
Chlordiazepoxide	10–48 h, active metabolite 14–95 h	Widely distributed	Variable, if expect toxicity, wait 1.5–2 times the half-life
Neuromuscular blocking agents			
Atracurium	Biphasic T1/2 (2–3.4 min and 20 min respectively)	Low body distribution	Train of four via peripheral nerve stimulation should result in four thumb twitches
Pancuronium	Triphasic T1/2, terminal T1/2 ~2 h	87% protein bound	Train of four via peripheral nerve stimulation should result in four thumb twitches
Rocuronium			Train of four via peripheral nerve stimulation should result in four thumb twitches
Succinylcholine	Metabolized rapidly, with effect lasting ~10 min	Widely distributed	Train of four via peripheral nerve stimulation should result in four thumb twitches
Vecuronium	Biphasic T1/2 (3–9 min and 30–80 min respectively)	Not fully characterized	Train of four via peripheral nerve stimulation should result in four thumb twitches
Narcotics			
Morphine	1.5–4.5 h	Widely distributed, 30–35% protein bound	Variable, if suspect toxicity evaluate after 1.5–2 times the half-life
Fentanyl	3–7 h, duration 30–60 min	Widely distributed, 80–86% protein bound	Variable, if suspect toxicity evaluate after 1.5–2 times the half-life
Hydromorphone	2.5 h, duration 4–5 h	Two distributive T1/2's, 1.27 and 14.7 h respectively	Variable, if suspect toxicity evaluate after 1.5–2 times the half-life
Meperidine	3.2–3.7 h, active metabolite 24–48 h	Widely distributed, 65–80% protein bound	Variable, if suspect toxicity evaluate after 1.5–2 times the half-life

(continued)

Table 4.3 (continued)

Drug	Half-life (T1/2)	Distribution	Suggested time to brain death exam
Miscellaneous drugs			
Propofol	Biphasic:Alpha T1/2 = 1–8 minBeta T1/2 = 1.5–12.4 h	Moderately distributed throughout the body	Neurologic exams can generally be performed after drip has been off for 5–10 min, brain death exam can performed after 2–3 times the half-life
Dopamine	~2 min, duration~10 min		Extremely high doses have been reported to fix/dilate pupil
Atropine	Duration of cardiac effects ~5 min		Pupil effects after IV administration are transient
Ketamine	2–3 h	50% protein bound	Recovery time 2–3 h

Common Electrolyte Disturbances Confounding Brain Death

Hypoglycemia	Serum glucose <40 mg/dl
Hyperglycemia	Serum glucose >800 mg/dl
Hyponatremia	Serum sodium <120 mEq/L
Hypernatremia	Hypernatremia as a result of therapy for cerebral edema, or as a consequence of diabetes insipidus due to cerebral herniation should not confound brain death

and there is absence of oculocephalic and oculovestibular reflexes. In the above case scenario, since the cervical spine is not cleared, the oculocephalic reflex cannot be tested. Also, oculovestibular reflex pre-testing requires demonstration of patency of the external auditory canal, which may be difficult in our case. Periorbital edema may confound assessment of eye movements as well as pupillary reflex. In addition, documentation of absence of corneal reflex, absence of facial muscle movements to noxious stimuli at level of temporomandibular joints or supraorbital and supratrochlear ridges, absence of pharyngeal (gag) reflex and absence of tracheal (cough) reflex are all required.

For complete description of testing for coma and brainstem reflexes, refer to Table 4.1.

A 43-year-old male sustains motor vehicle accident with severe traumatic brain injury, and pulmonary contusions. On admission he is noted to have a Glasgow Coma Scale (GCS) score of 5. Assessment of vital signs reveals blood pressure of 108/46 mm Hg, heart rate of 92 beats/min, while pulse oximetry shows 97% saturation on 60% FIO_2. Six hours later he is noted to be unresponsive, with dilated pupils, and no cough or gag reflex. At this time blood pressure is 78/34, heart rate is 126/min, and pulse oximetry reveals 89% saturation on 100% FIO_2.

This would be an error. Details of performing the apnea trial are provided in Table 4.2. During performance of an apnea test, close attention must be paid to the baseline starting PCO_2 and PCO_2 achieved after a period of apnea. Generally, one should calculate the period of apnea needed to increase PCO_2 20 mm Hg above baseline, and an absolute PCO_2 of greater than 60 mm Hg (based on normal body temperature). A low starting PCO_2 may indicate respiratory alkalosis, and a 20 mm Hg change may be insufficient to lower the cerebrospinal fluid pH enough to stimulate

ventilation. If the baseline PCO_2 is high, it may indicate either respiratory acidosis or chronic respiratory dysfunction with CO_2 retention. Consideration of the pre-apnea arterial blood pH can help distinguish between these causes. If close to 7.40, then it is likely that the patient is a CO_2 retainer and the CSF pH is adjusted to that baseline level of PCO_2. A lower pH would indicate respiratory acidosis, and ventilation should be adjusted to first produce normocapnia and the test then performed. It is not uncommon for patients to experience desaturations during apnea, despite pre-oxygenation with 100% FIO_2, as well as some hemodynamic instability. Thus, close attention must be paid to P/F ratio and systolic blood pressure prior to the initiation of apnea test. In patients with severe hypoxia, including those on ECMO, the apnea test has been safely conducted by adding positive end-expiratory pressure with pulmonary recruitment [17].

A 38-year-old female is undergoing apnea testing during the process of brain death testing. Her baseline ABG reveals pH 7.41, PCO_2 36, PO_2 156 on 100% FIO_2. The respiratory therapist places the patient on a T-piece circuit with reservoir bag, and the patient undergoes 6 min of apnea. Her repeat ABG is pH 7.21, PCO_2 56, PO_2 78. The resident physician concludes that since there is rise in PCO_2 of greater than 20 mm Hg, she meets criteria.

One of the fundamental principles of assessment of patients with catastrophic brain injury is to pay close attention to the stability of vital signs. Evaluation of patients using the GCS is invalid in the presence of hypoxia and hypotension. It is prudent not to prognosticate such patients until all possible secondary confounders are ruled out. The documented absence of shock during clinical testing occurs in only 71% of all brain death declarations [14]. Per revised AAN guidelines published in 2010, maintenance of systemic perfusion pressure, i.e. systolic blood pressure of greater than or equal to 100 mm Hg, is required during assessment of patients for brain death. Consequently, in this clinical scenario, his hypotension would confound neurologic assessment, while PaO_2/FiO_2 ratio under 200 would rule out safe performance of an apnea test.

A 58-year-old gentleman underwent induced hypothermia treatment to 33 °C for treatment of hypoxic neurological injury following a cardiac arrest. He was sedated with midazolam and fentanyl infusions for control of shivering. Clinical examination demonstrated the absence of eye opening, verbal response, and motor response, as well as absence of all brain stem reflexes, with apnea on the ventilator. Twelve hours later, the patient is rewarmed to 36 °C, with midazolam and fentanyl infusion now off for 2 h. The treating physician is concerned for the possibility of brain death and proceeds with a formal declaration based on clinical criteria. His family gives authorization for organ donation. While the patient is awaiting organ procurement, some spontaneous respirations are observed. ICU staff and the family are significantly concerned.

The current plan for donation should be discontinued, pending further time or an ancillary investigation. A reasonable period of observation must be given to a patient in order to demonstrate irreversible cessation of brain function. Since there are no gold standards for minimal observation periods [7], it is left to the treating physician to decide an optimal period of observation, determined in each individual case.

The above scenario highlights two important elements that require consideration prior to brain death declaration; (1) time elapsed since correction of hypothermia and (2) effect of hypothermia on metabolism of sedative agents.

In patients who have spontaneous or induced hypothermia, it is recommended to maintain core body temperature greater than 36 °C at the time of brain death examination. Many centers now

also advocate maintenance of normothermia (defined as core body temperature >36 °C) for at least 24 h prior to proceeding with brain death testing.

In the circumstances of the hypothermia experienced by this patient there would be concern for delayed drug metabolism during hypothermia and upon rewarming.

Propofol, midazolam, fentanyl, morphine, and neuromuscular blocking agents are commonly prescribed agents for patients undergoing sedation to treat shivering.

Zhou and Poloyac [18] undertook a comprehensive review of drugs commonly used during hypothermia and rewarming, and provide detailed explanations regarding how those drugs may confound brain death declaration.

Flow-limited drugs such as propofol and fentanyl are significantly affected during hypothermic conditions. In patients cooled to 34 °C, propofol clearance has shown to be reduced by 25% compared to that during normothermia. It is also shown in animal models that fentanyl plasma concentrations are elevated by about 25% at 31.6 °C compared to normothermic group.

Capacity-limited binding drugs are also affected during therapeutic hypothermia. Phenytoin is metabolized through CYP2C9 and CYPXC19 isoforms. At 34 °C for 72 h, phenytoin area under the curve was increased by 180%. Midazolam, a CYP3A4/5 substrate, is reported to show a fivefold increase in plasma concentration in hypothermic patients, with 84% increase in volume of distribution under hypothermic conditions. It is estimated that systemic clearance of midazolam is reduced 11.1% per °C reduction in body temperature.

Vecuronium, also a CYP3A-metabolized agent, was estimated to have reduced clearance 11.3% per °C in healthy volunteers. Thus, it is clear that metabolism of drugs depending on CYP3A activity would be inhibited during hypothermic conditions.

CYP2C9 and CYP2C19 are important isoforms for drugs such as carbamazepine, neostigmine, phenytoin, and pentobarbitone. Pentobarbitone (CYP2C19 and CYP2B6) levels are also increased during hypothermic conditions, as excretion was delayed along with increased volume of distribution. Rocuronium is metabolized through CYP2D6 and CYP2C19. Under hypothermic conditions, there is reduction in plasma clearance due to reduction in metabolic rate.

While drug metabolism and clearance are decreased under these conditions, they remain decreased after rewarming. Even at 6 h after rewarming, fentanyl concentrations were increased when compared to baseline normothermic conditions.

Longer periods of observation may be additionally required after rewarming for agents with a longer half-life. Assuming normal hepatic and renal function, it is recommended to use five times the drug half-life to gauge adequate clearance as a prerequisite before formal brain death declaration [7].

Consequently, during hypothermic conditions, reduced metabolism and drug clearance are seen for opiates, benzodiazepines, and neuromuscular blockers, and extra caution must be exercised in these patients prior to declaration of brain death [19].

Details of pharmacokinetics affecting brain death testing are provided in Table 4.3.

Proposed observation periods for observation before declaration include

(a) Four hours for apneic coma after major neurosurgery, confirmed aneurysm, or aneurysmal re-bleed; head injury with no secondary brain damage from hematoma, shock, or brain hypoxia; spontaneous intracranial hemorrhage without secondary hypoxic brain damage
(b) 24 hours after brain hypoxia after drowning and cardiac arrest
(c) More than 50–100 h for any of the above conditions with suspicion of drug intoxication, without any screening facilities [20]

In situations where therapeutic hypothermia is used after return of spontaneous circulation, neuro-prognostication should be delayed for at least 72 h after return of normothermia [21]

according to American Academy of Neurology, and 2015 updated ACLS guidelines. Even in normothermic circumstances, it is now advised to wait until after 72 h after cardiac arrest to simply prognosticate [21].

The waiting period before declaration may be abbreviated by performing an ancillary test of cerebral blood flow to substantiate the clinical examination, as hypothermia cannot protect against the sustained cessation of blood flow.

Variability exists across the world with respect to observation times between clinical examinations. It is our institutional policy to perform a confirmatory clinical examination 6 h from the first formal brain death examination. In Europe, similar to Asia, the range of observation period between examinations is quite wide (2–12 h) [22, 23]. Greece, Lithuania, Sri Lanka have the longest periods of 12 h between examinations, Indonesia allows only 25 min [23], while Denmark stipulates 1 h between examinations [22].

One of the drawbacks of prolonged periods of observation between two examinations is a high rate of cardiac arrest (12%), and is associated with intensive care unit costs and loss of viable organs [24].

A 36-year-old woman is admitted with anoxic brain injury. She undergoes a 24-h period of observation and the medical team proceeds with evaluation and declaration of brain death, as immediate family is making efforts to arrive at the bedside. Upon arrival, but after declaration, the family notice she is "moving her toes" and subsequently refuse to believe in the examination and subsequent discontinuation of mechanical ventilation.

One of the most consistent motor responses observed in patients undergoing brain death testing are spinal reflexes [25–27]. Neuronal interconnections present in the spinal cord are thought to be involved in the generation of spinal reflex movements—"central generators". The corticospinal and rubrospinal tracts in the spinal lateral funiculus are control pathways for distal motor control of the extremities. The vestibulospinal and reticulospinal tracts ventrally in the spinal white matter are the media of control over muscle tone, posture, and "synergistic" whole limb movement. These and the central generators are inhibited by supraspinal glycinergic neurotransmitters. Disconnection from inhibition after spinal cord injury or brain death increases excitability at the spinal level-inciting spinal reflex movements to varying stimuli. 40–50% of patients exhibit reflex movements after declaration of brain death [25, 26, 28]. Some of the spontaneous and reflex movements (SRMs) that have been described include flexor extensor plantar responses, triple flexion response, abdominal reflex, cremasteric reflex, tonic neck reflexes, isolated jerks of the upper extremities, asymmetric opthistotonic posturing of trunk, undulating toe flexion sign, myoclonus, Lazarus sign, respiratory-like movements, quadriceps contraction, eye opening response, leg movements mimicking periodic leg movement, thumbs up sign [29], and facial myokymia [30].

Majority of the Intra- hospital deaths are declared by cardio-respiratory definitions. When faced with a relative who is brain dead, families are often unaware of the clinical criteria used for brain death declaration. It is not uncommon for families to be startled, or shocked by these findings and in some cases refuse to accept the diagnosis. Those unfortunate situations may be accentuated by the appearance of spinal reflexes without warning or preparation.

In questionnaire-based studies by Omrod et al. [31], and Pugh et al. [32], families were receptive to the idea of participating in brain death examination, which in turn would have helped them in understanding brain death. In fact, in a subsequent randomized control study, Tawil et al. [33] demonstrated that allowing families to participate in the examination was safe, feasible, and improved the understanding of brain death without apparent adverse impact on their psychological well-being. Just as family presence during rounds and during cardio-pulmonary resuscitation, and open family visiting has been shown to improve communication and understanding of information, this likely also holds true with family presence during brain death evaluation [34].

Around brain death declaration, some commonly observed comments from families include the lack of opportunity to participate during brain death examination, and lack of formal educational and support tools to better understand brain death in general [35–37].

Participation in the brain death examination [38] provides opportunities for physicians to demonstrate clinical criteria used in the declaration of brain death as well as providing education regarding confusing motor signs described in brain-dead patients such as Babinski's, Lazarus, and thumbs up signs. It also provides opportunity to educate the family about post-declaration events, and alleviates anxiety and fears surrounding this emotionally distressing clinical exercise [39–41].

It is important to note that declaration of brain death is a process, and opportunities to provide educational and coping support tools not only to families, but also to fellow physicians, nurses, and other allied health personnel should not be missed.

A multi-step approach has been advocated for communication with families of patients suffering devastating brain injury. These include (i) initial communication with the relatives about the patient's severe condition, (ii) subsequent communication of the adverse prognosis, including the high probability of brain death (iv) confirmation of the diagnosis and declaration of death, (v) allow time to be with the patient, and finally (vi) depending upon patient's organ donation eligibility [42], allow for local organ procurement agency to approach the family to discuss donation. In the United States and many other countries, the pathways of brain death declaration and organ donation are kept separate (Fig. 4.1).

A 23-year-old Native American male with severe traumatic brain injury is admitted to the neurocritical care unit. Physician declares patient brain dead by clinical criteria. Family requests continuation of mechanical ventilation due to religious reasons, and until additional family members arrive from out-of-town.

In a not-so-uncommonly encountered clinical scenario, families may request continuation of organ support due to either nonacceptance of death, distrust of treating physicians, religious beliefs, or simply out of wishes to await arrival of other family members.

Each of these situations is unique and there is need for detailed understanding of the exact reason for continuation of organ support before making a final clinical decision. Often, the physician is left to his or her clinical judgment to continue organ support, as there is lack of specific protocols in many countries to clearly address these issues.

There are pros and cons for delaying the discontinuation of organ support. The advantages include providing families additional time to come to terms with patient's death, which may allow more family members to be present at time of discontinuation of life support. However, confusion about patient's clinical status, potential violation of bodily integrity and dignity, and the institutional financial implications of maintaining a dead patient in the intensive care unit (especially where resources are limited) may inhibit this practice.

In some circumstances, families can deny acceptance of brain death due to religious reasons (conscience clause). There are only select few states in the United States, such as New Jersey [5], New York and California, which allow for accommodation of religious and moral objections [43]. All other states within the US mandate prompt discontinuation of mechanical ventilation. The majority of major world religions recognize the diagnosis of brain death [44].

A 45-year-old lady with high-grade subarachnoid hemorrhage has undergone aggressive medical and endovascular management of severe diffuse vasospasm. The resident physician orders a Technetium-99 scan to evaluate for cerebral circulatory arrest. In his opinion, there is no need to do an exam, as simply demonstrating lack of cerebral blood flow is confirmatory of brain death.

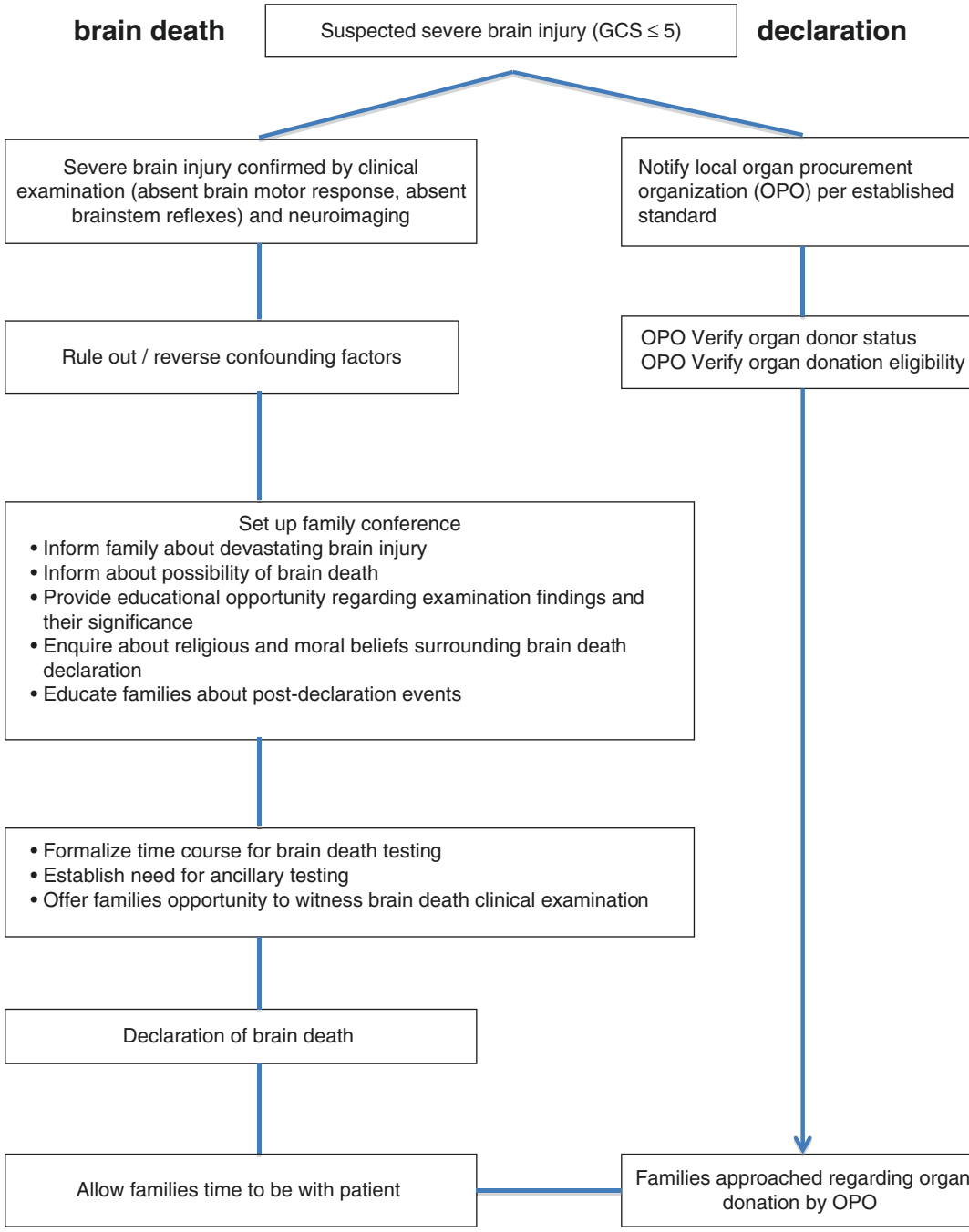

Fig. 4.1 Process of brain death declaration

First and foremost, brain death is a clinical diagnosis of an absence of neurological function. The clinical diagnosis of brain death at its core demonstrates the absence of cerebral and brain stem function.

Multiple scenarios exist where ancillary testing may be appropriately performed and offer resolution of uncertainty [45]. These include the presence of conditions that depress apparent level of consciousness (recent use of sedatives, opi-

ates, neuromuscular blockers [12]), conditions that may prevent full assessment of cranial nerves (acute or pre-existing ophthalmological conditions, facial and skull-base trauma, severe neuromuscular conditions or pre-existing cranial neuropathies), conditions that may interfere with reliable apnea testing (physiological instability with severe hypoxia, hypotension or metabolic acidosis, high cervical spinal cord injuries, chronic respiratory acidosis), and conditions where physical examination may not prove whole-brain death (posterior fossa mass effect, brainstem hemorrhage or infarction, and in diagnosis within the initial 24 h following return of spontaneous circulation after cardiac arrest).

Less widely accepted indications for ancillary testing include unclear etiology of brain death, patient's family refusal of the clinical diagnosis of brain death, and abnormal movements inducing uncertainty on the diagnosis [45].

In any of these circumstances where a comprehensive clinical examination cannot be performed with confidence, ancillary testing can be carried out for demonstration of cerebral circulatory arrest. Following as much clinical examination as possible, the clinician can then declare the patient brain dead using available clinical criteria and ancillary test findings. It is important to consider the possible errors associated with ancillary testing, and reiterating to all involved in clinical care that the most appropriate examination is still a clinical one, supplemented by ancillary investigations as appropriate.

Ancillary testing is not mandatory in the United States and United Kingdom [46], but may be so in other countries, such as China, Japan, and South Korea [23]. Within Europe, EEG is mandatory for defining brain death in five of the 28 EU countries [22]. In countries such as Estonia, the Netherlands, and Spain, an ancillary test can be used to confirm brain death or shorten observation between tests [22]. Ancillary testing is also required in Pan-American region (Argentina, Brazil, Ecuador, Honduras, Mexico), Southeast Asian region (India, Indonesia, Sri Lanka), Western Pacific region (Australia, South Korea, Vietnam), and Eastern Mediterranean region (Jordan, Lebanon, Qatar, Saudi Arabia) [10].

Of the many ancillary tests available, the most commonly performed tests include EEG (84%), conventional angiography (74%), radionuclide scintigraphy (66%), transcranial Doppler (TCD) (42%), somatosensory evoked potentials (18%), and MR angiography (9%) [12].

While ancillary testing is not mandatory in the USA, in a survey of 600 hospitals across the country, nine hospitals mandated them, with the majority accepting EEG and cerebral blood flow and angiographic studies [47].

While newer ancillary testing is being increasingly reported in brain death declarations [48–52] according to 2010 AAN practice parameters, due to high risk of bias and inadequate statistical precision [53], there is insufficient evidence to support use of new ancillary testing such as CT angiography, MRI or MR angiography, and bispectral index [7]. The preferred ancillary tests include EEG (minimum eight scalp electrodes), nuclear scan (technetium Tc 99 m hexametazime (HMPAO)) [54], cerebral angiogram [54] (inject contrast medium in the aortic arch), and transcranial Doppler [55, 56, 57] (TCD, used only if reliable signal found with demonstration of reverberating flow or small systolic spikes in early systole on bilateral insonation or both anterior and posterior circulation) [7].

Conclusion

Thorough understanding of accepted institutional, national, and international standards, along with a well-mapped practical algorithm provides a solid framework for determination of brain death across various clinical scenarios.

References

1. Uniform Delaration of Death Act http://www.healthcare.findlaw.com1980 [cited 2015 October 22]. Available from: http://pntb.org/wordpress/wp-content/uploads/Uniform-Determination-of-Death-1980_5c.pdf.
2. A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death. JAMA. 1968;205(6):337–40.

3. Mohandas A, Chou SN. Brain death. A clinical and pathological study. J Neurosurg. 1971;35(2):211–8.
4. Molinari GF. Collaborative Study of Brain Death, The National Institutes of Health, National Institute of Neurological and Communicative Disorders and Stroke 1981.
5. Olick RS. Brain death, religious freedom, and public policy: New Jersey's landmark legislative initiative. Kennedy Inst Ethics J. 1991;1(4):275–92.
6. Practice parameters for determining brain death in adults (summary statement). The quality standards subcommittee of the American Academy of Neurology. Neurology. 1995;45(5):1012–4.
7. Wijdicks EF, Varelas PN, Gronseth GS, Greer DM. American academy of N. Evidence-based guideline update: determining brain death in adults: report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2010;74(23): 1911–8.
8. Kramer AH, Zygun DA, Doig CJ, Zuege DJ. Incidence of neurologic death among patients with brain injury: a cohort study in a Canadian health region. CMAJ. 2013;185(18):E838–45.
9. Wijdicks EF. Brain death guidelines explained. Semin Neurol. 2015;35(2):105–15.
10. Wahlster S, Wijdicks EF, Patel PV, Greer DM, Hemphill 3rd JC, Carone M, et al. Brain death declaration: practices and perceptions worldwide. Neurology. 2015;84(18):1870–9.
11. An appraisal of the criteria of cerebral death. A summary statement. A collaborative study. JAMA. 1977;237(10):982–6.
12. Greer DM, Varelas PN, Haque S, Wijdicks EF. Variability of brain death determination guidelines in leading US neurologic institutions. Neurology. 2008;70(4):284–9.
13. Araki T, Yokota H, Ichikawa K, Osamura T, Satomi A, Tsuru T, et al. Simulation-based training for determination of brain death by pediatric healthcare providers. Springerplus. 2015;4:412.
14. Hocker S, Schumacher D, Mandrekar J, Wijdicks EF. Testing confounders in brain death determination: a new simulation model. Neurocrit Care. 2015;23(3):401–8.
15. Hocker S, Wijdicks EF. Simulation training in brain death determination. Semin Neurol. 2015;35(2):180–7.
16. MacDougall BJ, Robinson JD, Kappus L, Sudikoff SN, Greer DM. Simulation-based training in brain death determination. Neurocrit Care. 2014;21(3):383–91.
17. Giani M, Scaravilli V, Colombo SM, Confalonieri A, Leo R, Maggioni E, et al. Apnea test during brain death assessment in mechanically ventilated and ECMO patients. Intensive Care Med. 2016;42(1):72–81.
18. Zhou J, Poloyac SM. The effect of therapeutic hypothermia on drug metabolism and response: cellular mechanisms to organ function. Expert Opin Drug Metab Toxicol. 2011;7(7):803–16.
19. Webb AC, Samuels OB. Reversible brain death after cardiopulmonary arrest and induced hypothermia. Crit Care Med. 2011;39(6):1538–42.
20. The ANZICS Statement on Death and Organ Donation (Edition 3.2). 2013.
21. Ludikhuize J, Brunsveld-Reinders AH, Dijkgraaf MG, Smorenburg SM, de Rooij SE, Adams R, et al. Outcomes associated with the nationwide introduction of rapid response systems in the Netherlands. Crit Care Med. 2015;43(12):2544–51.
22. Citerio G, Murphy PG. Brain death: the European perspective. Semin Neurol. 2015;35(2):139–44.
23. Chua HC, Kwek TK, Morihara H, Gao D. Brain death: the Asian perspective. Semin Neurol. 2015;35(2):152–61.
24. Lustbader D, O'Hara D, Wijdicks EF, MacLean L, Tajik W, Ying A, et al. Second brain death examination may negatively affect organ donation. Neurology. 2011;76(2):119–24.
25. Dosemeci L, Cengiz M, Yilmaz M, Ramazanoglu A. Frequency of spinal reflex movements in brain-dead patients. Transplant Proc. 2004;36(1):17–9.
26. Han SG, Kim GM, Lee KH, Chung CS, Jung KY. Reflex movements in patients with brain death: a prospective study in a tertiary medical center. J Korean Med Sci. 2006;21(3):588–90.
27. Jain S, DeGeorgia M. Brain death-associated reflexes and automatisms. Neurocrit Care. 2005;3(2):122–6.
28. Saposnik G, Basile VS, Young GB. Movements in brain death: a systematic review. Can J Neurol Sci. 2009;36(2):154–60.
29. Mittal MK, Arteaga GM, Wijdicks EF. Thumbs up sign in brain death. Neurocrit Care. 2012;17(2):265–7.
30. Beckmann Y, Ciftci Y, Incesu TK, Secil Y, Akhan G. Spinal reflexes in brain death. Acta Neurol Belg. 2014;114(4):303–6.
31. Ormrod JA, Ryder T, Chadwick RJ, Bonner SM. Experiences of families when a relative is diagnosed brain stem dead: understanding of death, observation of brain stem death testing and attitudes to organ donation. Anaesthesia. 2005;60(10):1002–8.
32. Pugh J, Clarke L, Gray J, Haveman J, Lawler P, Bonner S. Presence of relatives during testing for brain stem death: questionnaire study. Br Med J. 2000;321(7275):1505–6.
33. Tawil I, Brown LH, Comfort D, Crandall CS, West SD, Rollstin AD, et al. Family presence during brain death evaluation: a randomized controlled trial*. Crit Care Med. 2014;42(4):934–42.
34. Davidson JE. Improving the family experience through presence at brain death evaluation*. Crit Care Med. 2014;42(4):1002–3.
35. Burkle CM, Sharp RR, Wijdicks EF. Why brain death is considered death and why there should be no confusion. Neurology. 2014;83(16):1464–9.

36. Doran M. The presence of family during brain stem death testing. Intensive Crit Care Nurs. 2004;20(1):32–7.
37. Long T, Sque M, Addington-Hall J. Conflict rationalisation: how family members cope with a diagnosis of brain stem death. Soc Sci Med. 2008;67(2):253–61.
38. Kompanje EJ, de Groot YJ, Bakker J, Ijzermans JN. A national multicenter trial on family presence during brain death determination: the FABRA study. Neurocrit Care. 2012;17(2):301–8.
39. Long T, Sque M, Addington-Hall J. What does a diagnosis of brain death mean to family members approached about organ donation? A review of the literature. Prog Transplant. 2008;18(2):118–25. quiz 26
40. McAdam JL, Dracup KA, White DB, Fontaine DK, Puntillo KA. Symptom experiences of family members of intensive care unit patients at high risk for dying. Crit Care Med. 2010;38(4):1078–85.
41. McAdam JL, Puntillo K. Symptoms experienced by family members of patients in intensive care units. Am J Crit Care. 2009;18(3):200–9. quiz 10
42. Kompanje EJ. Families and brain death. Semin Neurol. 2015;35(2):169–73.
43. Olick RS, Braun EA, Potash J. Accommodating religious and moral objections to neurological death. J Clin Ethics. 2009;20(2):183–91.
44. Bernat JL. The concept and practice of brain death. Prog Brain Res. 2005;150:369–79.
45. Kramer AH. Ancillary testing in brain death. Semin Neurol. 2015;35(2):125–38.
46. Smith M. Brain death: the United kingdom perspective. Semin Neurol. 2015;35(2):145–51.
47. Powner DJ, Hernandez M, Rives TE. Variability among hospital policies for determining brain death in adults. Crit Care Med. 2004;32(6):1284–8.
48. Brasil S, Bor-Seng-Shu E, de-Lima-Oliveira M, M KA, M JT, Bernardo L, et al. Role of computed tomography angiography and perfusion tomography in diagnosing brain death: a systematic review. J Neurobiologia. 2015;43(2):133–140.
49. Sahin H, Pekcevik Y. CT angiography as a confirmatory test in diagnosis of brain death: comparison between three scoring systems. Diagn Interv Radiol. 2015;21(2):177–83.
50. Sawicki M, Bohatyrewicz R, Safranow K, Walecka A, Walecki J, Rowinski O, et al. Computed tomographic angiography criteria in the diagnosis of brain death-comparison of sensitivity and interobserver reliability of different evaluation scales. Neuroradiology. 2014;56(8):609–20.
51. Taylor T, Dineen RA, Gardiner DC, Buss CH, Howatson A, Pace NL. Computed tomography (CT) angiography for confirmation of the clinical diagnosis of brain death. Cochrane Database Syst Rev. 2014;3:CD009694.
52. Venkatram S, Bughio S, Diaz-Fuentes G. Clinical brain death with false positive radionuclide cerebral perfusion scans. Case Rep Crit Care. 2015;2015:630430.
53. Greer DM, Strozyk D, Schwamm LH. False positive CT angiography in brain death. Neurocrit Care. 2009;11(2):272–5.
54. Young GB, Shemie SD, Doig CJ, Teitelbaum J. Brief review: the role of ancillary tests in the neurological determination of death. Can J Anaesth. 2006;53(6):620–7.
55. Chang JJ, Tsivgoulis G, Katsanos AH, Malkoff MD, Alexandrov AV. Diagnostic accuracy of transcranial doppler for brain death confirmation: systematic review and meta-analysis. AJNR Am J Neuroradiol. 2016;37(3):408–14.
56. Sharma D, Souter MJ, Moore AE, Lam AM. Clinical experience with transcranial Doppler ultrasonography as a confirmatory test for brain death: a retrospective analysis. Neurocrit Care. 2011;14(3):370–6.
57. Hadani M, Bruk B, Ram Z, Knoller N, Spiegelmann R, Segal E. Application of transcranial doppler ultrasonography for the diagnosis of brain death. Intensive Care Med. 1999;25(8):822–8.

5 Paroxysmal Sympathetic Hyperactivity Following Acute Acquired Brain Injury

Parmod Kumar Bithal and Keshav Goyal

5.1 Introduction

Elevated physiological parameters from increased sympathetic surge are common following severe acute brain insult from many pathological conditions, most commonly following traumatic brain injury (TBI). In TBI patients admitted to intensive care unit (ICU), the incidence of elevated physiological parameters is seen in 62–92% [1, 2]. However, a subset of these patients develops exaggerated sympathetic response that has the potential to produce additional significant morbidity.

Paroxysmal sympathetic hyperactivity (PSH) is a syndrome of episodic physiological sympathetic hyperactivation associated with acute brain insult [3, 4]. The conceptual definition of PSH has been given recently by a group of international multidisciplinary experts as "A syndrome, recognized in a subset of survivors of severe acquired brain injury, of simultaneous, paroxysmal transient increase in sympathetic and motor (posturing) activity" [5]. The paroxysms of the condition generally develop abruptly and episodically and last for a brief period of time, but they can also last longer and result in secondary brain damage and even death [3, 6, 7]. Lack of awareness about this entity often leads to unnecessary work-up, administration of costly investigations and medications, which, in turn leads to prolonged hospitalization and potentially harmful outcome of the patients [8, 9].

This syndrome was first described by Penfield in 1929, wherein, he described a female patient with a tumor near the third ventricle who experienced episodes of diaphoresis, pupillary dilation, hypertension, and shivering, and he coined the term "diencephalic autonomic seizures" [10]. Since then many different terms and clinical criteria have been used in the literature for this disorder: episodic autonomic instability, dysautonomia, autonomic dysregulation, central autonomic dysfunction, paroxysmal autonomic instability with dystonia (PAID), sympathetic storming, autonomic storming, dysautonomic crisis, diencephalic fits, diencephalic autonomic seizures, and paroxysmal sympathetic hyperactivity [4]. One feature that remains common is the episodic dysregulation of the sympathetic nervous system. The term paroxysmal sympathetic hyperactivity, first given by Rabinstein [(11)], has been recently accepted by consensus among the international expert group [5, 12–14]. However, there is no

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consensus regarding risk factors, pathophysiology and treatment approaches.

This chapter will provide an overview of the epidemiology, etiology, pathophysiology, risk factors, clinical features, differential diagnosis, management, outcome and prognostication, and future directions of PSH after acute brain injury.

5.2 Epidemiology

A large chunk of the data is representative of patients with TBI. Estimated prevalence of PSH ranges from 7.7% to 41% in patients admitted to the ICU [1, 11–19]. Such wide range reflects differences in the patient population under study, diagnostic criteria being considered, and time of examination. Baguley et al. [1] in their study in TBI patients showed that 92% patients had evidence of autonomic hyperactivation within the first week; at the end of first week it reduced to 25% of patients and at 2 weeks only 8% met the criteria for dysautonomia.

5.3 Etiology

PSH can result from any acute brain insult, but majority of the cases are reported after TBI (79.4%), hypoxic brain insult (9.7%), and stroke (5.4%) [4]. Most of the studies are skewed in favor of TBI population, because brain trauma constitutes the most common cause of acquired acute brain injury. High proportion of patients with encephalitis (70–80%) too shows symptoms similar to PSH, but since encephalitis is not as common as TBI, it has not received due attention in the literature [1]. Patients with N-Methyl D-Aspartate (NMDA) receptor-associated encephalitis have a rather aggressive and difficult to treat PSH-like syndrome [18, 20, 21]. Recently, PSH associated with meningoencephalitis has also been reported in children [19]. PSH has been reported after tubercular meningitis, intracranial hemorrhage (ICH), and subarachnoid hemorrhage (SAH), tumors and hydrocephalus [22–24]. However, the clinical manifestations of the syndrome remain similar irrespective of etiology [4].

5.4 Pathophysiology

There is lack of extensive investigation in the field of the pathophysiology of PSH. Initially, epileptic discharges arising from diencephalon were considered responsible for this entity. However, failure to identify epileptic discharges during the episode led to this theory being discarded. Although seizure can accompany PSH, it is not caused by epileptic discharge [25–30]. Moreover, antiepileptic agents do not control this disorder. The commonly proposed mechanism causing PSH is an imbalance of adrenergic outflow.

Instead of epileptic seizure as a cause, now there is greater support for disconnection theory. According to this theory, dysautonomia follows the release of one or more excitatory centers from the higher control. Thus the functional disconnection results in heightened activity of diencephalon and its connections due to either direct activation or disinhibition, that is, a release phenomenon [11, 26, 27]. The precise anatomic location of the dysfunction remains elusive, and the proposed sites vary from the medulla, brainstem, diencephalon, and hypothalamus to cortical and subcortical centers and the connections in between [29–33]. Regardless of the location of the lesions, the final common pathway is excessive sympathetic discharge.

Recently, the excitatory–inhibitory ratio (EIR) model has been postulated to explain the pathophysiology of PSH. This model readily explains pathophysiology compared with the disconnection model. It hypothesizes the over-reactive nature of responses of these patients to even non-noxious stimuli. A balance of sympathetic and parasympathetic input modulates autonomic efferents centrally at the level of the spinal cord .Additionally, afferents from the spinal cord can modulate this balance with input, such as noxious stimuli, from the environment [3, 34–36]. This model suggests that the afferent stimulus from the spinal cord has an allodynic tendency,

normally controlled by tonic inhibition from higher centers (diencephalic/brainstem). Any damage to these inhibitory centers releases excitatory spinal cord process. Once the tonic inhibitory cycle is broken, there is positive-feedback loop that produces sympathetic over-activity to any afferent stimuli [3, 36]. This model is able to explain how a normally nonnoxious stimulus can become a noxious stimulus and is accompanied with an uncontrolled sympathetic response. One advantage of the EIR theory over conventional disconnection theory is the ability of the former to explain the constellation of symptoms related to the sympathetic over reactivity associated with stimuli [37].

5.5 Risk Factors

Though PSH is more often associated with severe brain injury, in a prospective study it was observed that characteristics of PSH and non-PSH groups at admission were similar in terms of severity of TBI and extraneurological injury severity [12]. Younger age is associated with higher risk of PSH because the response of the autonomic nervous system to external stimuli is stronger in this age group [8, 38, 39]. Hypoxic brain injury is another risk factor to develop this syndrome [40]. Stroke patients too, are prone to develop this syndrome, with hemorrhagic stroke more commonly associated with PSH than ischemic stroke (ratio of 4:1) [4]. PSH is often associated with large (volume >60 ml), right-sided intracranial hemorrhage (right:left = 7:2), mostly involving subcortical structures [11, 22, 41–45]. Injuries along the pathway from the insular cortex to downstream sympathetic centers may abolish tonic inhibition originating from that insular cortex, leading to unopposed sympathetic outflow. Literature suggests that both insular cortices affect the sympathetic tone but right-sided insular cortex plays a greater role in controlling the sympathetic surge [22]. Although studies have observed male gender to be associated with increased incidence of PSH, but it may be a confounding factor as most studies have been conducted in TBI patients which have male preponderance [4, 12, 17]. Many studies have reported that patients with diffuse axonal injury (DAI) are prone to higher risk of developing PSH [8, 26, 34, 46, 47]. Almost all TBI patients have some degree of DAI irrespective of focal lesions [48]. Emergence from coma and liberation from high-dose opiates and sedatives are usually the precursors of PSH. Raised intracranial pressure (ICP) was thought to be associated with PSH episodes and it was considered both as a driver as well as a feature of it [43, 49–51]. But Fernandez-Ortega et al. [12] failed to show any alterations in measured ICP during and in between episodes of PSH.

5.6 PSH and Children

Children present with different clinico-epidemiological features. According to Moeller et al., most of the data analysis done on children with encephalitis and meningoencephalitis have observed PSH in 41% of children [19]. These authors also observed PSH to be more frequent in female children, and these children present with fever and/or seizure. Seizures at presentation are reported in 88% of patients with PSH while only in 50% patients without PSH. Similarly, fever is present in 94% of PSH patients and only 63% patients of non-PSH group [19].

5.7 Imaging Studies for Detection of Risk Factors

Various imaging modalities may predict the risk of PSH. Computerized scan (CT scan) studies have suggested that focal intracranial lesions (extradural hematoma, subdural hematoma, and space-occupying lesions) may be common in patients with PSH [12]. While there are other studies which have reported a significant presence of diffuse or very heterogeneous lesions in both intracerebral and extracerebral structures in patients who develop PSH [1, 34].

Sensitivity of MRI is more than that of CT scan for detecting lesions in the corpus callosum, insula, diencephalon, deep nuclei, and brainstem,

which appear to be associated with the occurrence of PSH. Recently, MRI studies have shown injury to various other brain structures, emphasizing the importance of DAI as a causative factor [7, 52]. Patients with PSH have more number of lesions in the dorsolateral aspect of the midbrain and upper pons compared to the number of lesions in the cortex, sub-cortex, corpus callosum, and diencephalon [38]. PSH has also been attributed to bilateral diencephalon lesions in hypoxic ischemic encephalopathy, and multiple micro-bleeds on the susceptibility-weighted imaging are associated with PSH [53, 54]. Mesencepahalic injury too, has been associated with higher risk. However, contrary to above findings, brainstem and diencephalic abnormalities were comparable in critically ill children in PSH and non-PSH group [19]. More advanced tools such as diffusion tensor imaging, functional MRI, or PET scan may have role in providing better anatomical localization of PSH [12].

5.8 Association Between Plasma Catecholamine Levels and PSH

Increase in dopamine, adrenaline, and noradrenaline levels during the episode has been reported in PSH [55]. Levels are elevated in proportion to the severity of injury and neurologic outcome of PSH [55, 56]. Given the brief elevations in plasma catecholamines, variability between patients and complex factors that influence serum catecholamine levels, an absolute threshold level of catecholamines to diagnose PSH is unrealistic [3].

5.9 Clinical Features and Diagnosis

A high index of suspicion and clinical examination is the mainstay of detecting this entity. Furthermore, PSH is a diagnosis of exclusion, and one should rule out opioid and/or sedation withdrawal resulting in agitation, and infection, before labeling it as PSH. However, PSH may co-exist with these confounders, thereby making distinction between reactive sympathetic activation and PSH difficult. Characteristically, PSH tends to be triggered by minimal and/or nonnoxious external stimuli, such as touch, passive movement (turning, moving limbs, and bathing), tracheal tube suctioning, bladder distension or manipulation of the indwelling urinary catheter, and environmental stimuli such as loud noise.

Rabenstein and Benarroch [14] proposed to define PSH by the transient presence of four of the following six criteria in the absence of other causes of sympathetic activation:

1. Fever (body temperature more than 38.3°C)
2. Tachycardia (heart rate more than 120 beats per min or more than 100 in presence of beta-blocker)
3. Hypertension (systolic blood pressure more than 160 mmHg or pulse pressure more than 80 mmHg)
4. Tachypnea (respiratory rate more than 30 per min)
5. Excessive diaphoresis
6. Extensor posturing or severe dystonia

Since these features may occur transiently, there should be at least one episode per day for at least 3 consecutive days in a patient with acquired brain injury. In addition, the concept of "triggering" of paroxysm following minor and/or nonnoxious stimuli has been proposed as a clinical sign that may help to differentiate individuals with and without this syndrome [35]. This feature of over-reactivity to nonnoxious stimuli or the allodynic response is a characteristic feature for making the diagnosis [36]. As many as 72% of patients with PSH develop symptoms with these nonnoxious external stimuli [9, 12]. Several authors have used only four or five of the most specific symptoms for identifying the syndrome [11, 17, 57]. In a retrospective analysis, tachycardia was almost uniformly present. Diaphoresis, fever, hypertension, and tachypnea were also present in most cases. Dystonia and posturing were present in less than half of the patients [57]. Occasionally, patients may have pupillary dilation and depressed level of consciousness.

Horripilation, agitation, and teeth grinding have also been considered part of the syndrome but occur less frequently [4, 11, 13, 57].

Recently, a multidisciplinary international committee [5], while preparing PSH diagnostic likelihood tool, has also considered six core sympathetic and motor clinical features (tachycardia, tachypnea, hypertension, hyperthermia, sweating, and posturing during episodes). The important clinical items to diagnose PSH according to this committee are:

1. Simultaneity of clinical features
2. Clinical features are paroxysmal in nature
3. Sympathetic over-reactivity to normally nonpainful stimuli
4. Absence of parasympathetic features during episodes
5. Features persist for more than 3 consecutive days
6. Features persist for more than 2 weeks post brain injury
7. Features persist despite treatment of alternative differential diagnoses
8. More than two episodes per day
9. Medications are required to decrease sympathetic features
10. Lack of alternative explanation
11. Antecedent acquired brain injury

Based on various clinical features and diagnostic likelihood tool, the consensus committee has designed a numerical scale. This tool consisted of two components; the diagnosis likelihood tool (DLT) and clinical feature scale (CFS). The added numerical values of these two components would give PSH assessment measure (PSH-AM), which tells the diagnostic likelihood of PSH at that time point in the particular patient. The DLT is derived from the aforementioned 11 diagnostic items, with the presence of an item being scored as one and its absence as zero, giving DLT score range from 0 to 11. The CFS assigns a value (from 0 to 3 depending on the severity of clinical features) in a graded manner for the severity of PSH-like clinical features (six core sympathetic and motor features). The combined total score of DLT and CFS will give PSH-AM. If the total score of PSH-AM is less than 8, PSH is unlikely, it is possible if the numerical score is between 8 and 16 and, PSH is probable if the score is more than 16.

Various studies have failed to predict the duration and time course of the episode. The onset of paroxysms of PSH is usually in 5–7 days post brain injury or may even occur earlier. Mean time to diagnose the syndrome may be as late as 3 weeks, though more often than not the syndrome is identified within the first week following brain insult. Each episode of PSH lasts from 3–5 min to 1–2 h and recurs at a frequency of 2–3 to 8 times per day, with an average of 5.6 [12, 40, 50, 58]. It may continue into rehabilitation phase and may last for weeks to months post injury and in severe cases, it may persist even for more than 1 year [12, 36]. Symptoms of PSH may present either in an acute form or chronic, occurring over weeks to months. Acute PSH is more common, occurring in 25–33% patients with brain injury, while chronic is seen only in 8% and both presentations influence outcome differently [8, 9, 11]. PSH lasting for a longer period is associated with poor outcome.

5.10 Differential Diagnosis

Owing to overlapping of symptoms of PSH with other common neurological sequelae of the acute brain injury, seizures, opioids withdrawal, airway obstruction, sepsis, etc., makes the diagnosis difficult, and often it is only the diagnosis of exclusion. Rule out any infection and sepsis before making a diagnosis of PSH. Severe inflammatory response syndrome (SIRS) is one of the differential diagnoses [34]. Presence of hypotension and high or below normal total leucocyte count points to sepsis. However, physiological changes in SIRS are unrelated to any stimuli. Other causes of tachycardia and hypertension should be sought. The high incidence of seizures in the critically ill population supports the need for continuous EEG to rule out seizures in patients with abnormal repetitive movements and encephalopathy [59].

Other possible causes and differential diagnosis (Table 5.1) should be considered before diagnosing PSH [4, 24].

Table 5.1 Differential diagnosis of hypertension, tachycardia, and dystonia following acquired acute brain injury

1. Neurological diseases
Increased intracranial pressure
Non-convulsive status epilepticus
Central fever
Autonomic dysreflexia
Cushing response
Agitation
Dystonia
Malignant catatonia
Stiff man syndrome
Paroxysmal sympathetic hyperactivity
Mixed autonomic hyperactivity syndrome (MAHS)
2. Infectious diseases
Meningitis
Encephalitis
Sepsis
Ventilator-associated pneumonia
Systemic inflammatory response syndrome (SIRS)
3. Drugs/toxins
Delirium
Serotonin syndrome
Acute drug withdrawal (intrathecal baclofen, dopamine agents)
Narcotic withdrawal
Neuroleptic syndrome
Malignant hyperthermia
Scorpion envenomation
Gamma hydroxybutyrate intoxication
Fenfluramine-phentirmine overdose
4. Endocrine diseases
Pheochromocytoma
Thyroid storm
5. Other diseases
Carotid sinus injury
Baroreceptor failure
Renal artery stenosis
Irukandji syndrome

5.11 Effects of PSH on Various Organ Systems

Table 5.2 depicts the multisystem sequelae of PSH [60].The dysautoregulated autonomic nervous system may have a role in causing unopposed inflammation resulting in secondary brain injury .Extremely high metabolism and prolonged irregularities of gastrointestinal function

Table 5.2 Multisystem dysfunctions associated with sympathetic surge [60]

Organ system	Sign/symptom
Cardiovascular	Tachycardia
	Increased cardiac contractility
	Increased cardiac output
	Hypertension
Pulmonary	Tachypnea
	Bronchial dilation
	Pulmonary edema
Eyes	Pupillary dilation
Gastrointestinal (GI)	Decreased GI motility
	Increased tube feed residual
	Ileus
Musculoskeletal	Dystonia
	Posturing
	Contractures
	Spasticity
Adrenal	Increased release of epinephrine and norepinephrine

can lead to decreased body weight by 25% in acute period alone [9, 61, 62]. Subsequent malnourishment may predispose the patient to critical illness neuropathy. The risk of myocardial infarction is also a concern. Spastic quadriparesis and dystonic posturing during paroxysms are common, and in combination with weight loss lead to increased incidence of pain, pressure areas, and contractures. Dysautonomic episodes make splinting of extremities very difficult, with potential complications of ruptured tendons. Lack of voluntary movement and the potential for locked in syndrome to occur can result in undermanaged pain or a misdiagnosis of persistent vegetative state [63]. There is also increased incidence of heterotrophic ossification [18], cardiac ischemic injury [64], immune suppression [65], secondary brain injury, dehydration, and muscle wasting.

5.12 Natural History of PSH

The hospital course of brain-injured patients with dysautonomia may be studied under three phases:

The first phase, from admission to ICU to the cessation of paralysis and/or sedation, shows

little variability among the dysautonomic and nondysautonomic patients in terms of physiological variables [8].

The onset of second phase heralds with the discontinuation of sedation/paralyzing agent. They show characteristic alterations in the vitals with higher regional muscle tone. In the early second phase, episodes are frequent, prolonged, and intense. Over a period, gradually the episodes decrease in duration, frequency, and intensity; with resting blood pressure, heart rate, respiratory rate, and temperature returning to normal. During this phase any underlying neurological deficits become overt. Sweating patterns often vary in their occurrence from whole body to upper trunk to head and neck before ceasing entirely [27]. Most of these patients develop increased muscle tone with variable flexor, extensor responses, or muscle dystonias in the extremities, neck, trunk, and facial muscles. Resolution of episodes is accompanied with improvement of neurological status, although many of them are left with variable degree of residual spasticity and dystonia.

In the third and final phase, regular paroxysms cease to occur. However, by this time, severe dystonia will have resulted in major deformities of joints with markedly restricted range of movements. According to Baguley et al. [25], noxious stimuli may still provoke an episode for at least 14 months post injury, despite normal autonomic nervous system. Patients who are able to communicate by some means, often complain of persistent abnormal painful response to normally nonnoxious stimuli.

5.13 Current Controversies

The estimated incidence of the condition varies widely in various studies [66]. The matter is complicated further due to large number of synonyms used for the condition in literature (approximately 33 in total), most of which have been used for once or twice only. Another difficulty with research into the condition is the many (at least five) current sets of overlapping diagnostic criteria [8]. Furthermore, it has been suggested that the concept of "triggering" of episode following even minor stimuli should be taken as clinical sign that may help differentiate patients with or without this syndrome [35]. Now, since the consensus regarding the diagnostic criteria has been reached, the PSH diagnostic likelihood tool will tell better about the likelihood of presence/absence of PSH at that time point in a particular patient.

5.14 Treatment

Management of PSH is challenging. There is wide variability in the management of this condition due to scarcity of data from randomized controlled trials or historically controlled patients. It is difficult to interpret treatment outcome due to simultaneous administration of many medications and, lack of comparison group. Moreover, most studies do not detail the drug dosage used in the management of this condition.

Treatment is symptomatic (restoration of normovolemia and normothermia) and pharmacological. Management of PSH hinges on the optimum use of pharmacological agents to prevent and abort the episodes.

5.14.1 Morphine

Morphine administered in adequate dose is most effective to abort episodes of severe PSH [26, 46]. Its therapeutic effect is quick and reliable but dose dependent. The possible mechanism of action of morphine is modulation of central pathways. The benefit from this drug probably results from stimulating medullary vagal nuclei, thereby producing cholinergic effects, such as bradycardia, and inducing the release of histamine, causing peripheral vessel dilation [26, 29]. Some authors recommend starting with intravenous (IV) administration and then switching to a scheduled oral route. Individual patient's response determines appropriate dose.

Standard dose: 2–8 mg IV at the onset of PSH episode. However, requirement may be as high as 20 mg.

5.14.2 Propranolol

Nonselective beta-blockers decrease the frequency as well as intensity of episodes. Propranolol is the most commonly used drug of this group because it inhibits peripheral catecholamine activity, and being highly lipophilic has the ability to cross blood brain barrier [14, 49]. It may also exert central effects through membrane stabilization or receptor blockade. Moreover, propranolol may reduce sustained muscle contraction [67]. Other nonselective beta-blocker, such as labetalol was used successfully in a case report but cardio-selective agents are ineffective [67]. Beta-blockers also attenuate the effects of circulating catecholamines and decrease the resting metabolic rate which is increased in patients with severe acute brain injury [68, 69]. Most manifestations of PSH such as hypertension, tachycardia, fever, diaphoresis, and even dystonic posturing respond to beta blockade. It mainly ameliorates the consequences of the disorder.

Dose: Oral dose: 20–60 mg every 4–6 h. Dose should be titrated to avoid compromising cerebral perfusion pressure.

5.14.3 Clonidine

It is a presynaptic alpha 2 agonist with both central and peripheral action. It decreases central sympathetic outflow from the hypothalamus and ventrolateral medulla and may enhance sympathetic inhibition in the brainstem. Part of the therapeutic action of clonidine may also result from binding to imidazoline receptors [70]. Clonidine also reduces circulating plasma catecholamine levels [71]. It is most effective in treatment of hypertension and tachycardia, but it is relatively ineffective in controlling the other manifestations of PSH. Therefore, it has limited usefulness.

Dose: 0.1–0.3 mg three times a day orally. Maximum dose 1.2 mg/day.

Use it cautiously when cerebral perfusion pressure is borderline between the episodes of PSH.

5.14.4 Bromocriptine

This synthetic dopamine agonist stimulates dopamine D2 receptors and acts on hypothalamus and the corpus striatum. It has been reported to control PSH in a few published cases [27, 72, 73]. However, its effect is modest and delayed. The use of bromocriptine PSH is based on the similarities between this entity and neurolept malignant syndrome, which results from dopamine blockade. Its effectiveness is probably enhanced when given along with other agents, especially morphine. It is a useful drug to control fever in mixed autonomic hyperactivity following neurosurgery [72]. A drawback of this drug is its propensity to lower the seizure threshold.

Dose: Starting dose is 1.25 mg orally, twice daily, then titrate up to 10–40 mg/day.

5.14.5 Dexmedetomidine

It is a sedative and the only currently approved IV alpha 2 agonist. It has favorable effects on HR, BP, and agitation. It was used successfully in a case report of refractory PSH [50].

Dose 0.2–0.7 mcg/kg/hr infusion.

The main drawback of this agent is that it can be used only as IV infusion.

Caution should be exercised in presence of heart block, hypovolemia, diabetes mellitus, and in elderly patients.

5.14.6 Baclofen

It is a GABA-B agonist, used to treat muscle spasms. Oral and intrathecal baclofen have been used successfully in few refractory cases of PSH [40]. Intrathecal baclofen is invasive, costly, and has a complication rate of 20–50% [74]. According to these authors, the rationale for using this drug derives from the observation that acute baclofen withdrawal may produce manifestations similar to those seen with episodes of PSH after acute brain injury.

Dose: Oral dose 5 mg thrice daily, titrated up to 80 mg/day. Intrathecal administration requires

a test dose and titration according to established protocols.

5.14.7 Benzodiazepines

Various benzodiazepines have been tried to treat PSH with variable success rate. They reduce HR and BP and control agitation. Midazolam, lorazepam, and diazepam all have been used [49]. They may be particularly beneficial because of their properties of muscle relaxation, sedation, and anxiolysis. The precise mechanism in patients with PSH remains speculative and there is concern for possibility of worsening of neurological function in newly injured brain [75].They are not as effective as morphine, especially for severe spells with dystonia. Combination of morphine and short-acting benzodiazepines is the most effective method of treating this syndrome. The goal should be to control the symptoms without producing deep sedation. Diazepam has the advantage because of its longer duration of action. However, benzodiazepines are the most suitable agents to manage anxiety during the recovery phase.

Dose: Midazolam 1–2 mg IV; lorazepam 2–4 mg IV; diazepam 5–10 mg IV.

5.14.8 Gabapentin

It binds alpha-2 delta subunit of presynaptic voltage-gated calcium channels. It is thought to act primarily by inhibiting neurotransmitter release in the dorsal horn of the spinal cord and throughout the central nervous system [9] .It may be useful during the recovery phase in patients with sub-acute brain injury and milder dysautonomic symptoms. It can be beneficial in the acute phase when other agents have failed to control the manifestations of PSH [9]. Its mechanism of action too, is speculative. It derives its popularity because of its long-term effectiveness. In addition, it also reduces the dosage of concomitant medications.

Dose: Starting oral dose 300–900 mg, titrated up to 3600–4800 mg/day.

5.14.9 Dantrolene

Dantrolene produces muscle excitation–contraction dissociation by interfering with calcium release from the sarcoplasmic reticulum. It is particularly effective for the amelioration of severe dystonic posturing [49]. Hepatic toxicity is its main side effect [76].

Doses: 0.25–2 mg/kg IV every 6–12 h. The maximum recommended dose is 10 mg/kg/day.

5.14.10 Hyperbaric oxygen

According to LQ and colleagues hyperbaric oxygen therapy may present an option for PSH in addition to pharmacological methods [77]. The authors speculate it to stimulate restoration of normal function in inactive neurons.

While no single medicine is successful, a combination of morphine and propranolol seems to be most effective. The challenge is controlling the symptoms with minimal sedative and other side effects of medications. Data on efficacy of treatment has come only from case reports and small series [4]. Treatment is initiated as soon as episode of PSH is recognized. Typically, beta-blockers are used to minimize the frequency of the spells, whereas IV morphine is useful to abort the episodes. When the dysautonomic manifestations are under control for several days (or even sometimes weeks, if the dysautonomia was severe), the medications may be tapered. Treatment is continued even for many months. Dopamine antagonists, such as chlorpromazine and haloperidol, have the potential to worsen the condition and therefore, should be avoided [46]. Antiepileptic agents are useless in true cases of PSH but should be tried if the question about a possible epileptic nature of the spells remains unresolved.

5.15 Outcome/Prognosis

PSH patients, regardless of age group, have been found to suffer from higher morbidity. More numbers of mechanical ventilation days, more infections, more inflammation, increased

tracheostomy rate, longer ICU and hospital stay, and higher health care costs, accompany this disorder [6, 8, 12, 15, 17, 19, 28, 61]. PSH has direct impact on the fever burden, which may be due to dysregulated autonomic nervous system leading to unopposed inflammation [78]. In dysautonomic patients mean daily maximum temperature can remain more than 38°C for more than 2 weeks [8].

Patients of PSH have worse Glasgow Outcome Score (GOS) and worse functional independent measures than their non-PSH counterparts [1, 12, 17, 56] though, Fernandez-Ortega et al. [12], from their prospective study in the two groups observed no difference in terms of GOS at discharge from ICU or 12-month GOS status of PSH patients as compared to the non-PSH group. The former group of patients have slower neurological recovery and take considerably longer to reach a similar degree of functional recovery [8].

5.16 Future Directions

Since various studies have reported varied incidence, a large observational multicenter study with standardized diagnostic criteria is required in unravelling incidence, pathophysiology, and protocolized and evidence-based pharmacological management. There is requirement for robust tools to establish the diagnosis and measure treatment efficacy. Identification of biomarkers in plasma/cerebrospinal fluid may go a long way to predict the onset of PSH with high precision. Further advancements in imaging technologies such as MRI and PET might help to study PSH more completely. Treatment algorithms need to be designed and tested against each other for their relative efficacy. It is imperative to establish management guidelines. Future studies should also aim at its prophylaxis in susceptible patients.

Conclusion

PSH results following diverse neurological injuries. Its exact etiology is unclear. There is an ever-expanding list of the predisposing factors. Its diagnosis is based on exclusion of other conditions commonly encountered in neurointensive care unit. The most common clinical feature is persistent tachycardia, though other signs of sympathetic hyperactivity too may be seen. There is no single diagnostic feature suggestive of this condition on MRI of brain. Owing to lack of understanding of etiology, many drugs have been used to manage this condition. Patients with PSH fare poorly compared to their non-PSH counterparts.

References

1. Baguley IJ, Slewa-Younan S, Heriseanu RE, Nott MT, Mudaliar Y, Nayyar V. The incidence of dysautonomia and its relationship with autonomic arousal following traumatic brain injury. Brain Inj. 2007;21(11):1175–81.
2. Jennett B, Teasdale G, Galbraith S, Pickard J, Grant H, Braakman R, et al. Severe head injuries in three countries. J Neurol Neurosurg Psychiatry. 1977;40(3):291–8.
3. Choi HA, Jeon SB, Samuel S, Allison T, Lee K. Paroxysmal sympathetic hyperactivity after acute brain injury. Curr Neurol Neurosci Rep. 2013;13(8):370.
4. Perkes I, Baguley IJ, Nott MT, Menon DK. A review of paroxysmal sympathetic hyperactivity after acquired brain injury. Ann Neurol. 2010;68(2):126–35.
5. Baguley IJ, Perkes IE, Fernandez-Ortega JF, Rabinstein AA, Dolce G, Hendricks HT. Paroxysmal sympathetic hyperactivity after acquired brain injury: Consensus on conceptual definition, nomenclature, and diagnostic criteria. J Neurotrauma. 2014;31:1515–20.
6. Hinson HE, Sheth KN. Manifestations of the hyperadrenergic state after acute brain injury. Curr Opin Crit Care. 2012;18(2):139–45.
7. Lv LQ, Hou LJ, Yu M, Qi XO, Chen JX, Hu GH, et al. Risk factors related to dysautonomia after severe traumatic brain injury. J Trauma. 2011;71(3):538–42.
8. Baguley IJ, Nicholls JL, Felmingham KL, Crooks J, Gurka JA, Wade LD. Dysautonomia after traumatic brain injury: a forgotten syndrome? J Neurol Neurosurg Psychiatry. 1999;67(1):39–43.
9. Baguley IJ, Heriseanu RE, Gurka JA, Nordenbo A, Cameron ID. Gabapentin in the management of dysautonomia following severe traumatic brain injury: a case series. J Neurol Neurosurg Psychiatry. 2007;78(5):539–41.
10. Penfield W. Diencephalic autonomic epilepsy. Arch Neurol Psychiatry. 1929;22:358–74.
11. Rabinstein AA. Paroxysmal sympathetic hyperactivity in the neurological intensive care unit. Neurol Res. 2007;29(7):680–2.
12. Fernandez-Ortega JF, Prieto-Palomino MA, Garcia-Caballero M, Galeas-Lopez JL, Quesada-Garcia G, Baguley IJ. Paroxysmal sympathetic hyperactivity after

traumatic brain injury: clinical and prognostic implications. J Neurotrauma. 2012;29(7):1364–70.
13. Perkes IE, Menon DK, Nott MT, Baguley IJ. Paroxysmal sympathetic hyperactivity after acquired brain injury: a review of diagnostic criteria. Brain Inj. 2011;25(10):925–32.
14. Rabinstein AA, Benarroch EE. Treatment of paroxysmal sympathetic hyperactivity. Curr Treat Options Neurol. 2008;10(2):151–7.
15. Dolce G, Quintieri M, Leto E, Milano M, Pileggi A, Lagani V, et al. Dysautonomia and clinical outcome in vegetative State. J Neurotrauma. 2008;50:502–4.
16. Fearnside MR, Cook RJ, McDougall P, McNeil RJ. The Westmead head injury project outcome in severe head injury. A comparative analysis of prehospital, clinical and CT variables. Br J Neurosurg. 1993;7(3):267–79.
17. Fernandez-Ortega JF, Prieto-Palomino MA, Munoz-Lopez A. Lebron- Gallardo M, Cabrera-Ortiz H, Quesada-Garcia G. Prognostic influence and computed tomography findings in dysautonomic crises after traumatic brain injury. J Trauma. 2006;61(5):1129–33.
18. Hendricks HT, Geurts AC, van Ginnken BC, Heeren AJ, Vos PE. Brain Injury severity and autonomic dysregulation accurately predict heterotopic ossification in patients with traumatic brain injury. Clin Rehabil. 2007;21(6):545–53.
19. Moeller RF, Carpenter JL, Dean N, Wells EM. Paroxysmal Sympathetic hyperactivity in critically ill Children with encephalitis and meningoencephalitis. Neurocrit Care. 2015;23(3):380–5.
20. Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007;61(1):25–36.
21. Nazif TM, Vázquez J, Honig LS, Dizon JM. Anti-N-methyl-D-aspartate receptor encephalitis: an emerging cause of centrally mediated sinus node dysfunction. Europace. 2012;14(8):1188–94.
22. Gao B, Jeffrey A, Holly P, Hinson E. Paroxysmal sympathetic hyperactivity in hemispheric intraparenchymal haemorrhage. Annals of Clinical and Translational Neurology. 2014;1(3):215–9.
23. Liu Y, Jolly S, Pokala K. Prolonged Paroxysmal Sympathetic Storming Associated withSpontaneous Subarachnoid Hemorrhage. Case Reports in Medicine. 2013;1-4
24. Ramdhani NA, Sikma MA, Witkamp TD, Slooter AJC, de Lange DW. Paroxysmal autonomic instability with dystonia in a patient with tuberculous meningitis: a case report. J Medical Case Reports. 2010;4:304.
25. Baguley IJ, Heriseanu RE, Felmingham KL, Cameron ID. Dysautonomia and heart rate variability following severe traumatic brain injury. Brain Inj. 2006;20(4):437–44.
26. Boeve BF, Wijdicks EF, Benarroch EE, Schmidt KD. Parxysmal sympathetic storms (diencephalic seizure) after severe diffuse axonal head injury. Mayo Clin Proc. 1998;73(2):148–52.
27. Bullard DE. Diencephalic seizures: responsiveness to bromocriptine and morphine. Ann Neurol. 1987;21(6):609–11.
28. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008;7(12):1091–8.
29. Pranzatelli MR, Pavlakis SG, Gould RJ, De Vivo DC. Hypothalamic-midbrain dysregulation syndrome: hypertension, hyperthermia, hyperventilation, and decerebration. J Child Neurol. 1991;6(2):115–22.
30. Thorley RR, Wertsch JJ, Klingbeil GE. Acute hypothalamic instability in traumatic brain injury: a case report. Arch Phys Med Rehabil. 2001;82(2):246–9.
31. Carmel PW. Vegetative dysfunctions of the hypothalamus. Acta Neurochir (Wien). 1985;75(1-4):113–21.
32. Doshi R, Neil-Dwyer G. Hypothalamic and myocardial lesions after subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry. 1977;40(8):821–6.
33. Reynolds RW. Pulmonary Edema as a consequence of hypothalamic lesions in rats. Science. 1963;141(3584):930–2.
34. Baguley IJ. The excitatory:inhibitory ratio model (EIR model): An integrative explanation of acute autonomic overactivity syndromes. Med Hypotheses. 2008;70(1):26–35.
35. Baguley IJ, Heriseanu RE, Nott MT, Chapman J, Sandanam J. Dysautonomia after severe traumatic brain injury: evidence of persisting overresponsiveness to afferent stimuli'. Am J Phys Med Rehabil. 2009;88(8):615–22.
36. Baguley IJ, Nott MT, Slewa-Younan S, Heriseanu RE, Perkes IE. Diagnosing dysautonomia after acute traumatic brain injury: evidence for overresponsiveness to afferent stimuli. Arch Phys Med Rehabil. 2009;90(4):580–6.
37. Baguley IJ, Heriseanu RE, Cameron ID, Nott MT. Slewa-Younan S.A critical review of the pathophysiology of dysautonomia following traumatic brain injury. Neurocrit Care. 2008;8(2):293–300.
38. Lv LQ, Hou LJ, Yu MK, Qi XQ, Chen HR, Chen JX, et al. 'Prognostic influence and magnetic resonance imaging findings in paroxysmal sympathetic hyperactivity after severe traumatic brain injury. J Neurotrauma. 2010;27(11):1945–50.
39. Cuny E, Richer E, Castel JP. Dysautonomia syndrome in the acute recovery phase after traiumatic brain injury: relief with intrathecal baclofen therapy. Brain Inj. 2001;15(10):917–25.
40. Krach LE, Kriel RL, Morris WF, Warhol BL, Luxenberg MG. Central autonomic dysfunction following acquired brain injury in children. Neuroreahabil Neural Repair. 1997;11:41–5.
41. Becker R, Benes L, Sure U, Hellwig D, Bertalaeffy H. Intrathecal baclofen alleviates autonomic dysfunction in severe brain injury. J ClinNeurosci. 2000;7(4):316–9.
42. Ko S-B, Kim CK, Lee S-H, et al. Morphine-sensitive paroxysmal sympathetic storm in pontine intracerebral hemorrhage. Neurologist. 2010;16(6):384–5.
43. Rossitch Jr E, Bullard DE. The autonomic dysfunction syndrome: aetiology and treatment. Br J Neurosurg. 1988;2(4):471–8.

44. Siu G, Marino M, Desai A, Nissley F. Sympathetic storming in a patient with intracranial basal ganglia hemorrhage. Am J Phys Med Rehabil. 2011;90(3):243–6.
45. Tong C, Konig MW, Roberts PR, Tatter SB, Li XH. Autonomic dysfunction secondary to intracerebral hemorrhage. Anesth Analg. 2000;91(6):1450–1.
46. Baguley IJ, Cameron ID, Green AM, Slewa-Younan S, Marosszeky JE, Gurka JA. Pharmacological management of Dysautonomia following traumatic brain injury. Brain Inj. 2004;18(5):409–17.
47. Hendricks HT, Heeren AH, Vos PE. Dysautonomia after severe traumatic brain injury. Eur J Neurol. 2010;17(9):1172–7.
48. Zhang J, Mitsis EM, Chu K, Newmark RE, Hazlett EA, Buchsbaum MS. Statistical parametric mapping and cluster counting analysis of [18F] FDG-PET imaging in traumatic brain injury. J Neurotrauma. 2010;27(1):35–49.
49. Blackman JA, Patrick PD, Buck ML, Rust Jr RS. Paroxysmal autonomic instability with dystonia after brain injury. Arch Neurol. 2004;61(3):321–8.
50. Goddeau Jr RP, Silverman SB, Sims JR. Dexmedetomidine for the treatment of paroxysmal autonomic instability with dystonia. Neurocrit Care. 2007;7(3):217–20.
51. Rabinstein AA. Paroxysmal autonomic instability after brain injury. Arch Neurol. 2004;61(10):1625.
52. Kelly AB, Zimmerman RD, Snow RB, Gandy SE, Heier LA, Deck MD. Head trauma: comparison of MR and CT--experience in 100 patients. AJNR. 1988;9(4):699–708.
53. Diesing TS, Wijdicks EF. Arc de cercle and dysautonomia from anoxic injury. Mov Disord. 2006;21(6):868–9.
54. Huang P, Lin WC, Huang PK, Khor GT. Susceptibility weighted imaging in a patient with paroxysmal sympathetic storms. J Neurol. 2009;256(2):276–8.
55. Wang VY, Manley G. Recognition of paroxysmal autonomic instability with dystonia (PAID) in a patient with traumatic brain injury. J Trauma. 2008;64(2):500–2.
56. Clifton GL, Ziegler MG, Grossman RG. Circulating catecholamines and sympathetic activity after head injury. Neurosurgery. 1981;8(1):10–4.
57. Hughes JD, Rabinstein AA. Early diagnosis of paroxysmal sympathetic hyperactivity in the ICU. Neurocrit Care. 2014;20:454–9.
58. Srinivasan S, Lim CC, Thirugnanam U. Paroxysmal autonomic instability with dystonia. ClinAuton Res. 2007;17(6):378–81.
59. Oddo M, Carrera E, Claassen J, Mayer SA, Hirsch LJ. Continuous electroencephalography in the medical intensive care unit. Crit Care Med. 2009;37(6):2051–6.
60. Meyer KS. Understanding paroxysmal sympathetic hyperactivity after traumatic brain injury. SurgNeurol Int. 2014;5(Suppl 13):S490–2.
61. Mehta NM, Bechard LJ, Leavitt K, Duggan C. Severe weight loss and hypermetabolic paroxysmal dysautonomia following hypoxic ischemic brain injury: the role of indirect calorimetry in the intensive care unit. JPEN J Parenter Enteral Nutr. 2008;32(3):281–4.
62. Ott L, Young B, Phillips R, McClain C, Adams L, Dempsey R, Tibbs P, Ryo UY. Altered gastric emptying in the head-injured patient: relationship to feeding intolerance. J Neurosurg. 1991;74(5):738–42.
63. Scott JS, Ockey RR, Holmes GE, Varghese G. Autonomic dysfunction associated with locked-in syndrome in a child. Am J Phys Med Rehabil. 1997;76(3):200–3.
64. Ryan JB, Hicks M, Cropper JR, Garlick SR, Kesteven SH, Wilson MK, et al. Functional evidence of reversible ischemic injury immediately after the sympathetic storm associated withexperimental brain death. J Heart Lung Transplant. 2003;22(8):922–8.
65. Woiciechowsky C, Asadullah K, Nestler D, Eberhardt B, Platzer C, Schöning B, et al. Sympathetic activation triggers systemic interleukin-10 release in immunodepression induced by brain injury. Nat Med. 1998;4(7):808–13.
66. Baguley IJ. Autonomic complications following central nervous system injury'. Semin Neurol. 2008;28(5):716–25.
67. Do D, Sheen VL, Bromfield E. Treatment of paroxysmal sympathetic storm with labetalol. J Neurol Neurosurg Psychiatry. 2000;69(6):832–3.
68. Chioléro RL, Breitenstein E, Thorin D, Christin L, de Tribolet N, Freeman J, et al. Effects of propranolol on resting metabolic rate after severe head injury. Crit Care Med. 1989;17(4):328–34.
69. Meythaler JM, Stinson 3rd AM. Fever of central origin in traumatic brain injury controlled with propranolol. Arch Phys Med Rehabil. 1994;75(7):816–8.
70. Head GA, Chan CK, Burke SL. Relationship between imidazoline and alpha2-adrenoceptors involved in the sympatho-inhibitory actions of centrally acting antihypertensive agents. J Auton Nerv Syst. 1998;72(2-3):163–9.
71. Payen D, Quintin L, Plaisance P, Chiron B, Lhoste F. Head injury: clonidine decreases plasma catecholamines. Crit Care Med. 1990;18(4):392–5.
72. Kang SH, Kim MJ, Shin IY, Park DW, Sohn JW, Yoon YK. Bromocriptine for control of hyperthermia in a patient with mixed autonomic hyperactivity after neurosurgery: a case report. J Korean Med Sci. 2012;27(8):965–8.
73. Russo RN, O'Flaherty S. Bromocriptine for the management of autonomic dysfunction after severe traumatic brain injury. J Paediatr Child Health. 2000;36(3):283–5.
74. Cunningham JA, Jelic S. Baclofen withdrawal: a cause of prolonged fever in the intensive care unit. Anaesth Intensive Care. 2005;33(4):534–7.
75. Lazar RM, Fitzsimmons BF, Marshall RS, Mohr JP, Berman MF. Midazolam challenge reinduces neurological deficits after transient ischemic attack. Stroke. 2003;34(3):794–6.
76. Chan CH. Dantrolene sodium and hepatic injury. Neurology. 1990;40(9):1427–32.

77. Lv LQ, Hou LJ, Yu MK, Ding XH, Qi XQ, Lu YC. Hyperbaric oxygen therapy in the management of paroxysmal sympathetic hyperactivity after severe traumatic brain injury: a report of 6 cases. Arch Phys Med Rehabil. 2011;92(9):1515–8.

78. Greer DM, Funk SE, Reaven NL, Ouzounelli M, Uman GC. Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. Stroke. 2008;39(11):3029–35.

Spinal Cord Injury

6

K.H. Kevin Luk and Michael J. Souter

6.1 Epidemiology

Most of the spinal cord injuries (SCI) sustained in this world are trauma related [1, 2]. Other non-traumatic causes of SCI include spinal stenosis, vascular insufficiency, demyelinating diseases, and tumor. The true incidence and prevalence of spinal cord injuries is not known due to the lack of a worldwide systematic database [1]. Several studies had attempted to estimate the global incidence and prevalence of SCI in the last decade [3, 4, 5]. Lee and colleagues estimate the global incidence rate of traumatic SCI to be 23 cases per million, or about 180,000 new cases per year [3]. An important aspect is that this is often a non-fatal condition, producing a persistent social morbidity in dealing with and caring for the survivors of SCI. An estimated 800–900 per million people in the United States live with SCI, as compared to 440 per million people in Iran, even though the incidence of spinal cord injury is comparable (about 40 in the US vs 44 in Iran) [2, 6]. Age of the victims with SCI follows a bimodal distribution with a first peak between the ages of 15–29 and then a second peak at age >65 [2–5]. Globally, motor vehicle accidents, falls, and violence are the leading causes of traumatic SCI [3–5]. In developed countries, falls are becoming a more common cause for SCI, likely due to an aging population [3–5]. On the other hand, in low- to middle-income countries (LMIC), road traffic accidents and violence account for the majority of the SCI [3–5].

The global economic impact of SCI is unclear. The costs incurred in LMICs are likely lower due to the poor survivability of the initial injury, lack of access to care, and absence of specialized rehabilitation therapies [1]. However, in developed countries, where survival rate is higher with a resultant higher prevalence, the economic impact of SCI is becoming an increasingly important topic. A recent Canadian study published by Krueger and colleagues estimated the lifetime economic burden of SCI to range from CAD$1.47 million for a patient with incomplete paraplegia to $3.03 million for a patient with complete tetraplegia. The annual economic burden associated with SCI in Canada is estimated to be $2.67 billion ($1.57 billion in direct costs and $1.10 billion in indirect costs). The majority of the cost is associated with equipment and home modifications ($310 million/11.6%) and

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attendant care ($870 million/32.7%). In contrast, hospitalizations and health care provider visits only make up of 13.2% of the total cost ($250 million) [7].

6.2 Functional Anatomy

One cannot understand the diagnosis and treatment of acute spinal cord injury without understanding spinal cord anatomy and function. The spinal cord has a total of 31 segments and can be anatomically divided into three sections (Fig. 6.1):

1. Cervical cord (C1–C8) – controls the diaphragm via the phrenic nerve (C3–C5), and the upper extremity musculature via the brachial plexus (C4–T1); provides sensory innervation to the neck and the upper extremities.
2. Thoracic cord (T1–T12) – controls the intercostal and abdominal musculature, which is required for forced exhalation/expectoration; provides sensory innervation to the trunk; also contains the sympathetic ganglia that innervate the heart and the abdominal viscera.
3. Lumbosacral cord (L1–S5) – controls the lower extremity musculature via the lumbosacral plexus (L1–S2); provides sensory innervation to the lower extremities and perineum; also provides parasympathetic innervation to the abdominal and pelvic viscera.

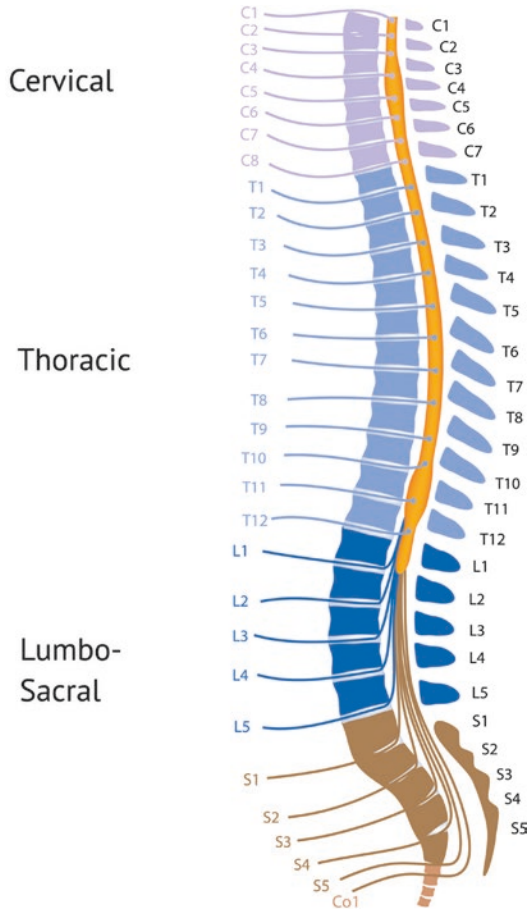

Fig. 6.1 Anatomic divisions of the spine with exiting nerve roots of the cord

The spinal cord is shorter than the intravertebral space, terminating at the level of L1–L3 in adults, and L2–L4 in children, with the conus medullaris. Below this, a collection of lumbosacral nerve roots (the cauda equina) traverses the remaining space down toward their respective point of exiting the spinal canal [8, 9].

Each spinal cord segment contains a pair of ventral and dorsal nerve roots, which are responsible for motor and sensory function, respectively. The ventral and dorsal nerve roots on each side join together to form the respective segmental spinal nerve as they form the vertebral column via the transverse foramen. The spinal cord is comprised of the outer white matter tracts, which contain the axons and dendrites, and the inner gray matter, which contains the neuronal cell bodies. The gray matter can be further divided into the dorsal (sensory) and ventral (motor) horns [8, 9]. Understanding of spinal cord anatomy is crucial for determining the level and degree of spinal cord injury.

The dorsal horn is divided into six laminae and is responsible for relay, processing, and modulation of sensory input. Large, myelinated nerve fibers mediating fine touch, proprioception, and vibration enter the ipsilateral dorsal column and cross midline at the level of the medulla (nuclei cuneatus and gracilis). Small, unmyelinated nerve fibers mediating pain and temperature cross the midline at or within several levels of entry into the spinal cord and then enter the contralateral anterior or lateral spinothalamic tract. It also contains the afferent limb from muscle spindles and completes the spinal reflex arc [8, 9].

The ventral horn is the signal-integration center for motor function, which contains neurons and

interneurons from the pyramidal (corticospinal) and extrapyramidal motor systems, which synapse with the alpha/gamma motor neurons to orchestrate complex movements. The lateral corticospinal tracts carry the majority (~80–85%) of the axons from the upper motor neurons in the motor cortex and synapse with the anterior horn cells at the level of the spinal cord, after decussating (crossing midline) at the cervicomedullary junction. The axons are topographically arranged with the lower extremity fibers in the more lateral/superficial part and the upper extremity fibers in the more medial/deep part of the tract. The anterior corticospinal tracts carry undecussated fibers from the motor cortex, some of which subsequently cross the midline via the anterior commissure at the level of the spinal cord, and are responsible for controlling the truncal musculature [8–11].

The sympathetic neurons originate in the thoracolumbar level (T1–L3), most of which synapse at the paravertebral ganglia, while a minority synapse at the celiac/mesenteric ganglia. These neurons are important in the maintenance of cardiovascular stability including blood pressure and heart rate. Injury to the system can result in neurogenic shock. Chronic dysregulation of the sympathetic nervous system at a level of T6 or above can also result in autonomic dysreflexia, presenting with facial/truncal flushing, hypertension, bradycardia, and profuse sweating. The parasympathetic nervous system originates in the lumbosacral level and its fibers synapse at the ganglia close to the end organ in the pelvis. Functionally, injury to the parasympathetic nervous system is evident by loss of bowel and urinary bladder control (neurogenic bowel/bladder) [8, 9].

The spinal cord is perfused by two posterior spinal arteries, which supply the dorsal columns, and a single anterior spinal artery, which supplies the anterior two-thirds of the cord. All three arteries originate from the vertebral arteries at the base of skull and travel caudally. In addition, radicular arteries originating from the thoracoabdominal aorta provide additional blood supply to the spinal cord – most notably the artery of Adamkiewicz, which supplies the anterior spinal artery and originates at the level between T5 to L1 (most commonly T9–12) [8, 9, 12].

6.3 Pathophysiology of Spinal Cord Injury

Most traumatic spinal cord injuries are associated with concomitant injury to the vertebral column, which can include fracture, dislocation, disruption/herniation of the intervertebral disc, tear of ligaments, and disruption of blood supply [13]. The primary injury is an immediate consequence of the trauma, which can be due to compression, contusion, shear, hyperextension, transection, and frank hemorrhage of the spinal cord [13, 14]. Minutes to hours after the initial insult, neurons in the penumbral region are exposed to the risk of secondary injury [14]. Histologically, this manifests as inflammation, additional petechial hemorrhage into the white matter, edema, and release of coagulation factors and vasoactive amines, all resulting in hypoperfusion and cellular hypoxia within the injured segment. At the cellular level, this subsequently promotes free radical formation, loss of membrane potential, lipid peroxidation, and glutaminergic excitotoxicity, resulting in cellular necrosis, apoptosis, demyelination, and axonal degeneration [15–20]. Cord swelling occurs as a result and tends to peak between days 3 and 6 post-injury.

6.4 Clinical Presentation and Classification of Spinal Cord Injury

Since the cervical cord is the least well-protected segment of the spinal cord, it is involved in around half of traumatic SCI cases, with a resulting quadriparesis or quadriplegia [2]. Most patients with isolated spinal cord trauma present with pain or tenderness to palpation overlying the fracture site. However, concomitant injuries (e.g., traumatic brain injury, intra-abdominal injuries, and pneumo- or hemothoraces) in a multisystem trauma patient can mask the presence of SCI. This can potentially delay diagnosis and adversely affect the patient's outcome.

The severity of SCI is graded based on the American Spinal Injury Association (ASIA)

Impairment Scale (Table 6.1) and a detailed assessment is performed based on the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI, Fig. 6.2) [21].

6.4.1 Complete Cord Injury (AIS A)

In a patient with complete cord injury, there may be a distinctly spared sensory level cephalad to the injury, but no sensation in the levels

Table 6.1 ASIA Impairment Scale (AIS) – International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)

A = Complete	No sensory or motor function is preserved in the sacral segments S4–5
B = Sensory incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4–5 (light touch or pin prick at S4–5 or deep anal pressure), and no motor function is preserved more than three levels below the motor level on either side of the body
C = Motor incomplete	Motor function is preserved at the most caudal sacral segments for voluntary anal contraction or the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments [S4–S5] by light touch, pinprick, or deep anal pressure) and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body (This includes key or non-key muscle functions to determine motor incomplete status.) For AIS C – less than half of key muscle functions below the single NLI have a muscle grade ≥3
D = Motor incomplete	Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single neurological level of injury having a muscle grade ≥3
E = Normal	If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade

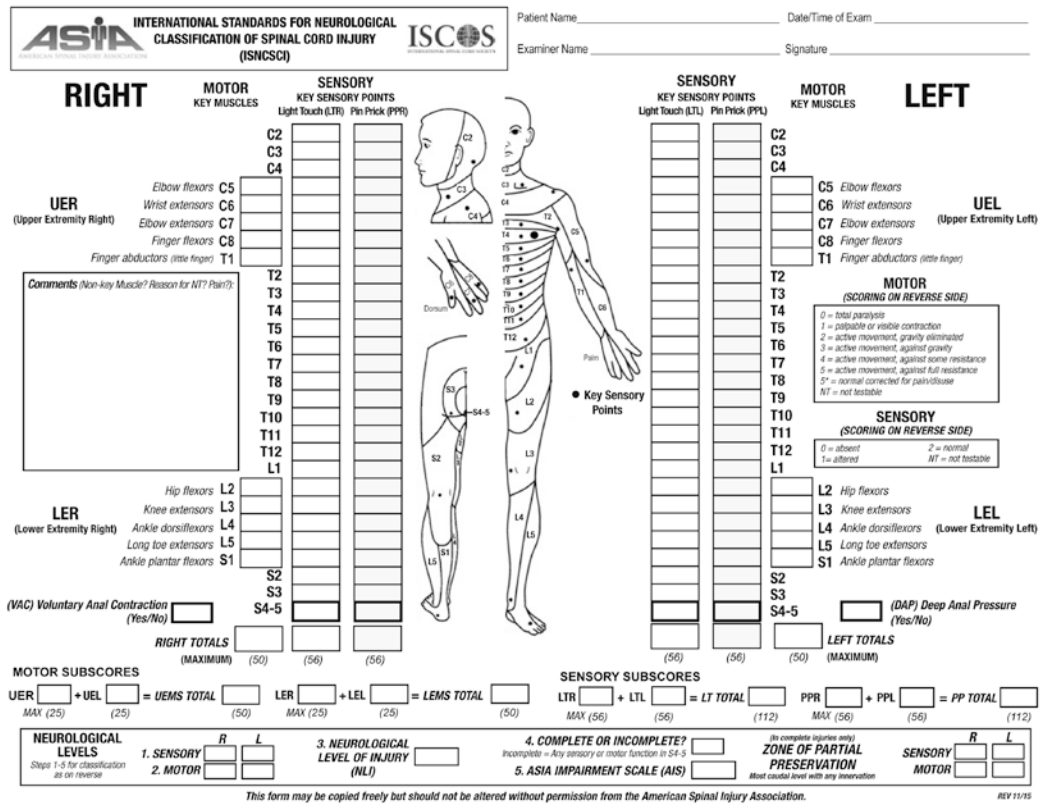

Fig. 6.2 Injury worksheet

caudal to the injury, including the sacral S4–S5 segments. In addition, muscle weakness may be evident immediately below the level of injury, transitioning to complete paralysis more caudally. Patients acutely present with areflexia and flaccid muscle tone. Rectal and bladder tone are lost, which can result in fecal incontinence and urinary retention with overflow incontinence, respectively.

6.4.2 Incomplete Cord Injury (AIS B to D)

In incomplete cord injury, sensation is usually preserved to a greater extent compared to motor function. In AIS B patients, sensation is preserved below the level of injury, but not motor function. In AIS C and D patients, some motor function is preserved below the level of the neurological level of injury. Often, the anal sphincter tone and sensation are preserved.

There are also specific cord syndromes that offer insights into lesion site, prognosis and the potential for early, targeted treatment interventions.

6.4.3 Central Cord Syndrome (CCS)

Patients with CCS present with significantly greater upper extremity weakness than that seen in the lower extremities, related to the topographic laminar arrangement within corticospinal and spinothalamic tracts, as mentioned previously. They can also present with a cape-like distribution of paresthesia and neuropathic pain, with a variable degree of sensory loss below the level of the injury. It is the most common of the incomplete spinal cord injuries. Pathophysiologically, the cervical cord suffers anterior (osteophytic) and posterior (buckled ligamentum flavum) impingement during hyperextension, but this such injury may also be a result of fracture dislocation or compression fracture mechanisms. CCS is seen in patients with relatively minor trauma in the setting of preexisting cervical spondylosis, but can present in a diverse range of injury mechanisms, including high-energy trauma in the young, or falls in the elderly, with such pathological consequences as axonal disruption of lateral columns, or hemorrhage into the central part of the cord (which carries a worse prognosis) [22].

6.4.4 Anterior Cord Syndrome

This usually occurs as a result of compromised blood flow in the anterior spinal artery, which supplies the anterior two-thirds of the spinal cord. Patients have preserved fine touch and proprioception but are paralyzed from the level of the injury. The syndrome often occurs as a consequence of direct compression by a herniated intervertebral disc or bone fragment. However, it can also occur as a complication of thoracoabdominal aortic surgery, if the artery of Adamkiewicz is compromised [12].

6.4.5 Brown-Sequard Syndrome

Brown-Sequard syndrome is a form of incomplete cord injury caused by hemisection of the spinal cord. It was first described by the French physician Charles-Edouard Brown-Sequard in 1850 [23]. Patients will present with ipsilateral loss of motor function and fine touch/proprioception, as well as loss of contralateral pain and temperature sensation several levels below the level of the injury. This is a result of the disruption of corticospinal, dorsal column, and spinothalamic tracts on one side of the spinal cord [24].

6.4.6 Spinal Shock/Transient Paralysis

The term “spinal shock” should be reserved for the description of complete loss of spinal cord function below the level of the injury [25]. It should not be used interchangeably with “neurogenic shock.” Spinal shock describes a state of flaccid paralysis, complete anesthesia, absent bowel/bladder control, areflexia, and possible

bradycardia and hypotension after an SCI [26]. Some patients, especially younger patients seen in athletic injuries can make complete recoveries. More often however, patients progress to some form of spastic paresis, reflecting the underlying spinal cord pathology [26]. It is believed that the state of spinal shock is caused by local release of potassium resulting in the hyperpolarization of the neuronal membranes [27].

6.5 Management of Acute Spinal Cord Injury

6.5.1 Prehospital

For field responders, the primary survey begins with C (circulation), A (airway), B (breathing), D (disability), and E (exposure). Once the integrity of airway, breathing, and circulation is established, the patient should be evaluated for any midline back pain, tenderness to palpation, focal weakness, or loss of sensation. These are characteristics of patients at high risk for traumatic SCI. In patients who have a concomitant head injury, or are confused or unconscious, a traumatic SCI should be assumed until proven otherwise. The spine should be stabilized and movement minimized by using the logrolling maneuver, placement of a rigid cervical collar, and immobilization using a backboard [28]. If placement of an advanced airway is indicated, care should be taken with in-line cervical stabilization (Fig. 6.3) to maintain cervical spinal neutrality during direct laryngoscopy and placement of the endotracheal tube [29].

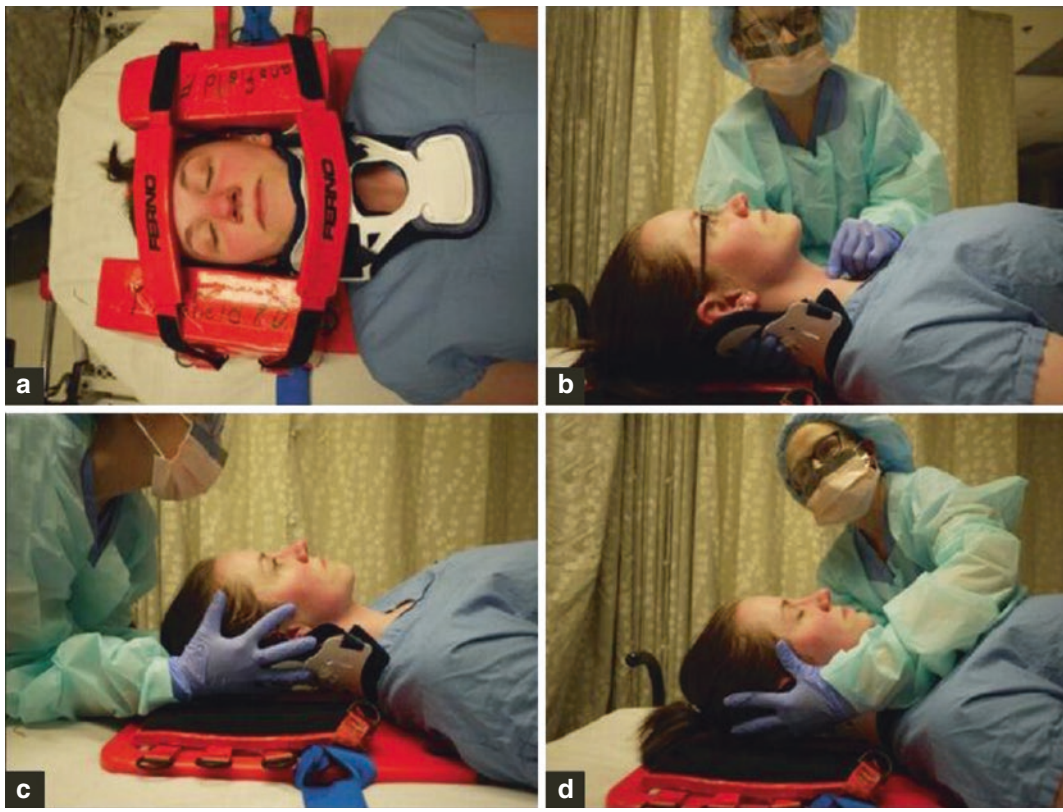

Fig. 6.3 Neck maneuvers during airway management. (**a**) Neck stabilization using sandbag-collar-tape on hardboard for prehospital care. (**b**) Cricoid pressure application with anterior half of hard cervical collar removed and other hand behind posterior cervical collar. (**c**) Manual in-line stabilization from the head of bed, with anterior cervical collar removed and hands cradling occiput and mastoid process. (**d**) Manual in-line stabilization from side of bed to facilitate airway intervention from head of bed (From Austin et al. [29])

6.5.2 Emergency Room

In the emergency department, primary survey continues using the same scheme of CABDE. Patient with multisystem trauma should be evaluated using the Advanced Trauma Life Support (ATLS) guidelines developed by the American College of Surgeons [30]. The management of life-threatening injuries including unstable airway, excessive bleeding, pneumothorax, or hemothorax, should take precedence over that of traumatic SCI. Vital signs should be monitored as recommended by the American Society of Anesthesiologists, to include heart rate, electrocardiogram, blood pressure, pulse oximetry, capnography, and temperature [31].

Monitoring of both capnography and pulse oximetry allows for continuous monitoring of respiratory status. Hypoxia is poorly tolerated by the brain and the spinal cord, and supplemental oxygen should be used to correct for hypoxemia. A patient with cervical SCI is at high risk for respiratory failure and may require endotracheal intubation and mechanical ventilation. Patients should be assumed to have full stomachs and rapid-sequence intubation with in-line cervical immobilization should be used [29, 32]. In our center, a combination technique of videolaryngoscopy and fiberoptic bronchoscopy is often employed for intubating patients with a rigid cervical collar in place [33], as maintenance of the collar adversely affects laryngeal views [34].

Hypovolemia due to blood loss, cardiac dysrhythmia, and sympathectomy (loss of adrenergic tone) can result in hypotension. Aggressive volume resuscitation and source control are essential for restoration of circulatory volume. If the patient continues to be hypotensive despite correction to euvolemia, neurogenic shock should be suspected, and vasoactive infusions used to restore vascular tone. A urinary catheter should be placed to assess for hematuria, monitor urine output, and to relieve bladder distention. A full neurological examination should be promptly performed to evaluate for the level and severity of the deficit.

6.5.3 Initial Imaging

Patients should remain immobilized using a rigid cervical collar and rigid backboard until the spine is cleared either clinically or radiographically. Clinical clearance is indicated in patients without focal neurological deficits and midline back pain/tenderness, who are fully alert, not confused or intoxicated, and without other distracting injuries. Based on the NEXUS [35] study, these clinical findings combined have a negative predictive value of 99.8% for cervical spine injury, enabling subsequent removal of the cervical collar. As mentioned previously, the presence of an SCI should be assumed in patients who are confused or obtunded, and precautions continued until adequately cleared. In a meta-analysis [36], the incidence of SCI in trauma patients with altered sensorium was 7.5% with 42% of cases associated with unstable spinal fractures.

Computed tomography (CT) of the spine has largely replaced plain radiography as the initial modality for evaluation of suspected spinal cord injury. Patients who are awake with pain and/or neurological deficits should undergo focused CT scan of the affected spinal segments. In patients who are unconscious or who are suspected to have other injuries, CT examinations of the head, neck, chest, abdomen, and pelvis with reformatting for coronal and sagittal cuts are indicated to evaluate for the presence of spinal injury. For patients with neurological deficits but no CT findings of SCI, magnetic resonance imaging (MRI) of the spine should be pursued. MRI allows for better assessment of the paraspinal soft tissue, spinal ligaments, and intervertebral discs [37].

Clearance of spine status to allow for mobilization for patient care and therapies (e.g., for performance of procedures, head of bed elevation for aspiration prevention, etc.) remains a challenge for patients with altered mental status. At our institution, negative CT scan or plain films of the thoracolumbar spine are considered sufficient for spine clearance at the respective levels. However, for cervical spine clearance, both CT imaging and clinical exam (i.e., equal strength in bilateral upper extremities without

midline cervical tenderness with palpation) are required for cervical spine clearance. For patients who are comatose or unable to cooperate with a clinical exam, an MRI is recommended to rule out potential ligamentous or soft tissue injuries [37].

6.5.4 Corticosteroids and Acute Spinal Cord Injury

For patients with acute traumatic spinal cord injury, two randomized controlled trials (NASCIS [38] and a Japanese study [39]) published in the 1990s demonstrated improvement in neurological outcome in patients treated with high-dose methylprednisolone infusion within 8 h of injury [40]. In contrast, a French study failed to replicate the results [41]. A large-scale, multinational, randomized controlled trial would likely be required to address this dichotomy. Currently, the Congress of Neurological Surgeons recommends against using MP for the treatment of acute spinal cord injury due to conflicting data on efficacy and potential serious effects [42].

6.5.5 Perioperative Management

In a large, international, multicenter prospective cohort study [43], early surgical decompression (within 24 h after injury) is associated with a 2.5–2.8-fold increased likelihood of demonstrating an improved neurological outcome, as defined as an enhancement of AIS by two grades or more. Consequently, urgent surgical consultation (Orthopedics or Neurosurgery) is recommended as soon as an SCI has been diagnosed. Once surgical intervention is decided, an anesthesiologist experienced in neurosurgery or spine surgery care should assess the patient by performing a focused, but thorough history and physical exam. Challenges to the airway should be meticulously evaluated, including assessment of facial trauma, presence of beard, mouth opening, loose dentition, blood or foreign body in the upper airway, thyromental distance, and anterior protrusion of the mandible.

As the population continues to age in developed countries with an increasing incidence of elderly patients presenting with SCI, cardiovascular risk stratification using the Revised Cardiac Risk Index is advisable in patients 55 years of age or older. However, surgical intervention should not ordinarily be delayed for additional testing and hemodynamics may need to be managed expectantly in the operating room. A serum B-type natriuretic peptide level may inform suspicions for cardiac failure and/or pulmonary edema. The anesthesiologist can also pursue a preoperative point-of-care cardiac [44] and lung ultrasound [45] to assess cardiac function and volume status to aid in planning of the anesthetic. If the patient is already intubated, ventilator settings should be reviewed with attention to the peak/plateau airway pressures, partial pressure of arterial oxygen to fractional inspired oxygen ratio (P/F ratio), and the presence of upsloping of the plateau phase in the capnogram (suggestive of bronchospasm or small airway obstruction).

Since spinal instrumentation and fusion is frequently associated with significant blood loss, adequate peripheral (two 16-gauge or large catheters) or central (an introducer sheath) venous access is required. In addition, arterial catheterization delivers continuous blood pressure monitoring, along with sampling of arterial blood for laboratory testing during surgery. The use of pulse pressure variation or stroke volume variation via the arterial pressure tracing can offer additional insight to the volume status of the patient, superior to use of CVP monitoring [46]. A PPV of >11–15% predicts fluid responsiveness with a resultant increase in cardiac output for patients in the supine and prone positions, respectively [46, 47]. The choice of anesthetic agents is dependent upon the procedure planned, patient's comorbid conditions, and whether neuromonitoring is used. Vasoactive infusions are often necessary to maintain adequate mean arterial pressure. For patients with injuries above the sympathetic cardioaccelerator fibers (T1–T4), vasopressors with inotropic, chronotropic, and vasoconstrictive properties, e.g., epinephrine, norepinephrine, and dopamine, are required to maintain heart rate, contractility,

and blood pressure. For patients with lower level SCI, vasoconstrictors such as norepinephrine and phenylephrine are often adequate for maintenance of blood pressure once euvolemia is achieved. The effect of sympathetic denervation and general anesthetics will result in temperature dysregulation and patients will often require active warming to maintain normothermia.

Given the fairly high prevalence of chronic pain in patients with SCI (approx. 45–50%) [48], a multimodal strategy is preferred for intraoperative and postoperative analgesia. In terms of emergence and extubation, patients with cervical and high thoracic cord injury are often left intubated and taken to the intensive care unit mechanically ventilated, due to the high risk of respiratory failure. Subsequent functional evaluation on the ICU will determine their capacity for liberation from the ventilator. For patients with lower level SCI, the decision to extubate at the end of the procedure should take into account the length of surgery, operative blood loss, intravenous fluid administered, and the degree of facial/laryngeal edema.

6.5.6 Intensive Care Unit

Most patients with spinal cord injury will require care and frequent monitoring in the intensive care unit initially. Vital signs, including electrocardiogram, heart rate, pulse oximetry, and blood pressure, as well as neurological function are monitored frequently in the ICU. There are several well-known neurological and systemic complications associated with SCI that are potentially avoidable or reversible if detected early.

6.5.6.1 Cardiovascular System

Most of the cardiovascular complications can be attributed to the effect of neurogenic shock as a result of sympathectomy or disruption of the sympathetic chain [49, 51, 52]. Patients often present with hypotension due to the decreased peripheral vascular resistance. Occasionally, patients can present with hypovolemic shock due to blood loss in addition to neurogenic shock. However, ECG abnormalities are often present in cervical and thoracic SCI [50]. Bradycardia can be seen if the lesion involves the higher thoracic cord (T1–T4) or cervical cord, above the innervation of the cardiac plexus [53].

Initial resuscitation should therefore focus on restoring circulatory volume using intravenous fluids and blood products. If the patient is persistently hypotensive, vasopressors should be added.

Hypotension is believed to be detrimental to the spinal cord, given the potential exacerbation of secondary ischemic insult in the penumbral region (as discussed previously). Therefore, an adequate mean arterial pressure is required to maintain critical perfusion to the injured spinal cord. There is no prospective data to define a targeted level of mean arterial pressure. The American Association of Neurological Surgeons recommendation (Level 3) is to maintain a mean arterial pressure of at least 80–90 mmHg for 5–7 days after injury [54]. Bradycardia may require pharmacological intervention such as atropine, or chronotropic infusions, e.g., epinephrine or dopamine, and in severe cases may even require external pacing.

6.5.6.2 Respiratory System

Pulmonary dysfunction is the most common complication after a traumatic SCI, and is a significant contributor to morbidity and mortality [55, 56]. It includes respiratory failure, pulmonary edema, pneumonia, and pulmonary thromboembolism [57, 59]. Patients with cervical and thoracic cord lesions are at particularly high risk of pulmonary complications because of weakness of the diaphragm, intercostal muscles, and abdominal muscles which result in ineffective cough, impaired secretion clearance, hypoventilation, and atelectasis [58–60]. Elderly patients [61] who received large volume resuscitation with marginal cardiac function are at significant risk of pulmonary edema 48–96 h postoperatively. For patients with cervical SCI, most of the respiratory failure occurs within the first 72 h of injury and pulmonary function tends to improve over the next 12 months [61, 62]. Signs of impending respiratory failure include

progressive hypercapnea, and/or hypoxemia, declining forced vital capacity or negative inspiratory pressure, and increased rapid shallow breathing index (low tidal volume and increased respiratory rate).

Patients who are mechanically ventilated should undergo trials of daily spontaneous awakening and spontaneous breathing to determine if the patient can be extubated and/or liberated from mechanical ventilation [63]. In addition, strength of the respiratory muscles should be assessed daily by measuring maximum negative inspiratory pressure and forced vital capacity [57]. Patients with high cervical spine injury are prone to a phenomenon known as "ping-pong" atelectasis, and appear to respond well to higher tidal volumes. Consequently, once the patient is no longer at risk for lung injury, our approach is to liberalize the tidal volume gradually to 12–15 ml/kg of ideal body weight [64].

Early tracheotomy may be indicated in patients with high cervical spine injury with no expectation of recovery of adequate spontaneous ventilation [65, 66]. This procedure can aid in secretion clearance and allow for decreased level of sedatives and analgesics, as a tracheotomy appears to be better tolerated than an endotracheal tube [65]. Alternatively, if the patient fails to wean from the mechanical ventilator for other reasons, a tracheotomy should be considered within 10–14 days from day of admission [67, 68].

In order to prevent atelectasis and pneumonia, a comprehensive bronchial hygiene protocol is recommended – this can include the use of specially trained respiratory therapists who follow the SCI patients during their hospitalization and tailor therapy for them. The interventions include breathing exercises, bronchodilator treatment, and mechanical cough assist. For secretion clearance, patients undergo cough assist via a mechanical insufflator–exsufflator several times a day, and chest physiotherapy if a focal consolidation is identified on chest radiograph [57]. They are often given scheduled ipratropium or tiotropium for bronchospasm prevention [69]. In addition, the use of abdominal binder has been shown to improve lung volumes in patients with cervical SCI [70].

6.5.6.3 Deep Venous Thrombosis/ Pulmonary Thromboembolism

SCI patients are at high risk for deep venous thrombosis (DVT) and pulmonary embolism (PE), due to the general inflammatory milieu after trauma and immobility with reduced venous return [71]. Therefore, all SCI patients should receive DVT prophylaxis unless contraindicated [72]. Low molecular weight heparin is the preferred anticoagulant of choice [72, 73] but a combination of unfractionated heparin with sequential compression device appears to be equally effective [74]. Patients in whom DVT prophylaxis is contraindicated, a retrievable inferior vena cava filter can be considered [75, 76]. Such filter can decrease the incidence of catastrophic pulmonary embolism [77] but can increase the propagation of DVT [78]. Therefore, filters should be removed as soon as anticoagulation is initiated.

6.5.6.4 Pressure Ulcers

Pressure ulcer is a frequent complication of SCI patients due to immobility [79]. The most commonly seen affected areas are the buttocks and heels. Frequent turning (every 2–3 h) and heel elevation using specialized foam boots are effective in preventing ulcer formation [80]. In patients with unstable spine injury who cannot be turned, a rotating bed with specialized pressure relieving mattress may be indicated.

6.5.6.5 Other Common Problems

SCI patients are exquisitely vulnerable to a wide range of complicating conditions presenting both acutely and chronically. Initially they are at high risk for stress ulceration due to increased parasympathetic tone. Stress ulcer prophylaxis with a proton pump inhibitor is recommended. Generally, trauma patients are hypermetabolic and require nutritional support for wound healing. In addition, early feeding can improve gastric mucosa blood flow and may prevent stress ulceration. Early enteral feeding is consequently recommended and a nutrition consult should be obtained to make sure that the patient's caloric intake is adequate. A urinary catheter should be maintained initially to monitor for fluid status. It should be switched to intermittent catheteriza-

tion as soon as possible to decrease the incidence of urinary tract infection. An aggressive bowel regimen including daily digital stimulation should be used to avoid stool impaction, which may in the quadriplegic induce a respiratory embarrassment that transcends "simple constipation." A rehabilitation medicine specialist well versed in SCI care should be consulted to assess the patients' need and potential for rehabilitation. Early mobility with occupational and physical therapy is crucial in limiting contracture formation. Patients and families may also benefit from additional counseling by a rehabilitation psychologist, as grief reactions can often be prolonged and severe.

Conclusions

In summary, SCI is a global health problem that has a bimodal age distribution affecting young adults and the elderly, with a male predominance. Motor vehicle accidents, falls, and violence remain the leading causes of SCI. As the safety of motor vehicles and the quality of prehospital improve, more people are surviving the initial trauma. With the advances in critical care and surgery, more people are living with the long-term sequelae of SCI and are becoming a significant economic burden to the society. Unfortunately, there is no cure for SCI at the moment, albeit promising therapies on the horizon. More resources are necessary to understand the global pattern of SCI and devise strategies to help prevent SCI.

References

1. Rubiano AM, Carney N, Chesnut R, Puyana JC. Global neurotrauma research challenges and opportunities. Nature. 2015;527:S193–7.
2. National Spinal Cord Injury Statistical Center. Spinal cord injury facts and figures at a glance. Birmingham: University of Alabama at Birmingham; 2013. https://www.nscisc.uab.edu/PublicDocuments/fact_figures_docs/Facts%202013.pdf. Accessed 18 Oct 2015.
3. Lee BB, Cripps RA, Fitzharris M, Wing PC. The global map for traumatic spinal cord injury epidemiology: update 2011, global incidence rate. Spinal Cord. 2014;52:110–6.
4. Devivo MJ. Epidemiology of traumatic spinal cord injury: trends and future implications. Spinal Cord. 2012;50(5):365–72.
5. Singh A, Tetreault L, Kalsi-Ryan S, Nouri A, Fehlings MG. Global prevalence and incidence of traumatic spinal cord injury. Clin Epidemiol. 2014;6:309–31.
6. Rahimi-Movaghar V, Saadat S, Rasouli MR, Ganji S, Ghahramani M, Zarei MR, Vaccaro AR. Prevalence of Spinal Cord Injury in Tehran Iran. J Spinal Cord Med. 2009;32(4):428–31.
7. Krueger H, Noonan VK, Trenaman LM, Joshi P, Rivers CS. The economic burden of traumatic spinal cord injury in Canada. Chronic Dis Inj Can. 2013;33(3):113–22.
8. Waxman SG. Chapter 5: The spinal cord. In: Waxman SG, editor. Clinical neuroanatomy. 27th ed. New York: McGraw-Hill; 2013. http://accessmedicine.mhmedical.com/content.aspx?bookid=673&Sectionid=45395963. Accessed 24 Oct 2015.
9. McCormick PC, Stein BM. Functional anatomy of the spinal cord and related structures. Neurosurg Clin N Am. 1990;1:469–89.
10. Goulding M, Bourane S, Garcia-Campmany L, Dalet A, Koch S. Inhibition downunder: an update from the spinal cord. Curr Opin Neurobiol. 2014;26:161–6.
11. Jessell TM, Surmeli G, Kelly JS. Motor neurons and the sense of place. Neuron. 2011;72(3):419–24.
12. Melissan G, Bertoglio L, Rinaldi E, Leopardi M, Chiesa R. An anatomical review of spinal cord blood supply. J Cardiovasc Surg (Torino). 2015;56(5):699–706.
13. Norenberg MD, Smith J, Marcillo A. The pathology of human spinal cord injury: defining the problems. J Neurotrauma. 2004;21(4):429–40.
14. Sharma HS. Pathophysiology of blood-spinal cord barrier in traumatic injury and repair. Curr Pharm Des. 2005;11(11):1353–89.
15. Tator CH, Fehlings MG. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. J Neurosurg. 1991;75(1):15–26.
16. Schwartz G, Fehlings MG. Secondary injury mechanisms of spinal cord trauma: a novel therapeutic approach for the management of secondary pathophysiology with the sodium channel blocker riluzole. Prog Brain Res. 2002;137:177–90.
17. Allan SM, Rothwell NJ. Cytokines and acute neurodegeneration. Nat Rev Neurosci. 2001;2(10):734–44.
18. Carlson SL, Parrish ME, Springer JE, Doty K, Dossett L. Acute inflammatory response in spinal cord following impact injury. Exp Neurol. 1998;151(1):77–88.
19. Park E, Velumian AA, Fehlings MG. The role of excitotoxicity in secondary mechanisms of spinal cord injury: a review with an emphasis on the implications for white matter degeneration. J Neurotrauma. 2004;21(6):754–74.
20. Tzekou A, Fehlings MG. Treatment of spinal cord injury with intravenous immunoglobulin G: preliminary evidence and future perspectives. J Clin Immunol. 2014;34(S1):S132–8.

21. American Spinal Injury Association. International standards for neurological classification of spinal cord injury. American Spinal Injury Association, Chicago; 2002. http://www.asia-spinalinjury.org/elearning/ASIA_ISCOS_high.pdf. Accessed 20 Oct 2015.
22. Molliqaj G, Payer M, Schaller K, Tessitore E. Acute traumatic central cord syndrome: a comprehensive review. Neurochirurgie. 2014;60(1-2):5–11.
23. Brown-Séquard C-É. De la transmission croisée des impressions sensitives par la moelle épinière. C R Soc Biol. 1851;2:33–44.
24. Leven D, Sadr A, Aibinder WR. Brown-Séquard syndrome after a gun shot wound to the cervical spine: a case report. Spine J. 2013;13(12):e1–5.
25. Nacimiento W, Noth J. What, if anything, is spinal shock? Arch Neurol. 1999;56:1033–5.
26. Atkinson PP, Atkinson JL. Spinal shock. Mayo Clin Proc. 1996;71:384–9.
27. Ditunno JF, Little JW, Tessler A, Burns AS. Spinal shock revisited: a four-phase model. Spinal Cord. 2004;42(7):383–95.
28. Sundstrøm T, Asbjørnsen H, Habiba S, Sunde GA, Wester K. Prehospital use of cervical collars in trauma patients: a critical review. J Neurotrauma. 2014;31(6):531–40.
29. Austin N, Krishnamoorthy V, Dagal A. Airway management in cervical spine injury. Int J Crit Illn Inj Sci. 2014;4(1):50–6.
30. American College of Surgeons. Advanced trauma life support. https://www.facs.org/quality-programs/trauma/atls. Accessed 1 Nov 2015.
31. Standard and Practice Parameters Committee. Standard for basic anesthetic monitoring. http://www.asahq.org/~/media/Sites/ASAHQ/Files/Public/Resources/standards-guidelines/standards-for-basic-anesthetic-monitoring.pdf. American Society of Anesthesiologists. Last amended 2010, reaffirmed 2015. Accessed 20 Dec 2015.
32. El-Orbany M, Connolly LA. Rapid sequence induction and intubation: current controversy. Anesth Analg. 2010;110(5):1318–25.
33. Doyle DJ. 2004 GlideScope-assisted fiberoptic intubation: a new airway teaching method. Anesthesiology. 2004;101(11):1252.
34. Heath KJ. The effect of laryngoscopy of different cervical spine immobilisation techniques. Anaesthesia. 1994;49(10):843–5.
35. Hoffman JR, Wolfson AB, Todd K, Mower WR. Selective cervical spine radiography in blunt trauma: methodology of the National Emergency X-Radiography Utilization Study (NEXUS). Ann Emerg Med. 1998;32(4):461.
36. Halpern CH, Milby AH, Guo W, Schuster JM, Gracias VH, Stein SC. Clearance of the cervical spine in clinically unevaluable trauma patients. Spine. 2010;35(18):1721.
37. Schuster R, Waxman K, Sanchez B, Becerra S, Chung R, Conner S, Jones T. Magnetic resonance imaging is not needed to clear cervical spines in blunt trauma patients with normal computed tomographic results and no motor deficits. Arch Surg. 2005;140(8):762.
38. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the third national acute spinal cord injury randomized controlled trial. National acute spinal cord injury study. JAMA. 1997;277:1597–604.
39. Otani K, Abe H, Kadoya S, Nakagawa H, Ikata T, Tominaga S. Beneficial effect of methylprednisolone sodium succinate in the treatment of acute spinal cord injury. Sekitsui Sekizui. 1994;7:633–47.
40. Bracken MB. Steroids for acute spinal cord injury. Cochrane Database Syst Rev. 2012;(1):CD001046.
41. Pointillart V, Petitjean ME, Wiart L, Vital JM, Lassié P, Thicoipé M, et al. Pharmacological therapy of spinal cord injury during the acute phase. Spinal Cord. 2000;38:71–6.
42. Cheung V, Hoshide R, Bansal V, Kasper E, Chen CC. Methylprednisolone in the management of spinal cord injuries: lessons from randomized, controlled trials. Surg Neurol Int. 2015;6:142.
43. Fehlings MG, Vaccaro A, Wilson JR, Singh AW, Cadotte D, Harrop JS, Aarabi B, Shaffrey C, Dvorak M, Fisher C, Arnold P, Massicotte EM, Lewis S, Rampersaud R. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). PLoS One. 2012;7(2):e32037.
44. Spencer KT, Kimura BJ, Korcarz CE, Pellikka PA, Rahko PS, Siegel RJ. Focused cardiac ultrasound: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr. 2013;26(6):567–81.
45. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. Chest. 2008;134(1):117–25.
46. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med. 2009;37(9):2642–7.
47. Biais M, Bernard O, Ha JC, Degryse C, Sztark F. Abilities of pulse pressure variations and stroke volume variations to predict fluid responsiveness in prone position during scoliosis surgery. Br J Anaesth. 2010;104(4):407–13.
48. Michalilidou C, Martson L, Sutherland I. A systematic review of the prevalence of musculoskeletal pain, back and low back pain in people with spinal cord injury. Disabil Rehabil. 2014;36(9):705–15.
49. Grigorean VT, Sandu AM, Popescu M, Iacobini MA, Stoian R, Neascu C, Strambu V, Popa F. Cardiac dysfunctions following spinal cord injury. J Med Life. 2009;2(2):133–45.
50. Furlan JC, Verocai F, Palmares X, Fehlings MG. Electrocardiographic abnormalities in the early stage following traumatic spinal cord injury. Spinal Cord. 2016;54(10):852–77. doi:10.1038/sc.2016.11.
51. Teasell RW, Arnold JM, Krassioukov A, Delaney GA. Cardiovascular consequences of loss of supraspinal control of the sympathetic nervous system

after spinal cord injury. Arch Phys Med Rehabil. 2000;81(4):506–16.
52. Hagen EM, Faerestrand S, Hoff JM, Rekand T, Gronning M. Cardiovascular and urological dysfunction in spinal cord injury. Acta Neurol Scand Suppl. 2011;191:71–8.
53. Rodrigues D, Tran Y, Guest R, Middleton J, Craig A. Influence of neurological lesion level on heart rate variability and fatigue in adults with spinal cord injury. Spinal Cord. 2016;54(4):292–7.
54. Ryken TC, Hurlbert RJ, Hadley MN, Aarabi B, Dhall SS, Gelb DE, Rozzelle CJ, Theodore N, Walters BC. The acute cardiopulmonary management of patients with cervical spinal cord injuries. Neurosurgery. 2013;72:84–92.
55. Jackson AB, Groomes TE. Incidence of respiratory complications following spinal cord injury. Arch Phys Med Rehabil. 1994;75(3):270–5.
56. Lidal IB, Snekkevik H, Aamodt G, Hjeltnes N, Biering-Sørensen F, Stanghelle JK. Mortality after spinal cord injury in Norway. J Rehabil Med. 2007;39(2):145–51.
57. Brown R, DiMarco AF, Hoit JD, Garshick E. Respiratory dysfunction and management in spinal cord injury. Respir Care. 2006;51(8):853–68.
58. Stepp EL, Brown R, Tun CG, Gagnon DR, Jain NB, Garshick E. Determinants of lung volumes in chronic spinal cord injury. Arch Phys Med Rehabil. 2008;89(8):1499–506.
59. Fishburn MJ, Marino RJ, Ditunno Jr JF. Atelectasis and pneumonia in acute spinal cord injury. Arch Phys Med Rehabil. 1990;71(3):197–200.
60. Schileroa GJ, Spungena AM, Baumana WA, Radulovica M, Lessera M. Pulmonary function and spinal cord injury. Respir Physiol Neurobiol. 2009;166(3):129–41.
61. Claxton AR, Wong DT, Chung F, Fehlings MG. Predictors of hospital mortality and mechanical ventilation in patients with cervical spinal cord injury. Can J Anaesth. 1998;45(2):144–9.
62. Mueller G, de Groot S, van der Woude L, Hopman MT. Time-courses of lung function and respiratory muscle pressure generating capacity after spinal cord injury: a prospective cohort study. J Rehabil Med. 2008;40(4):269–76.
63. Call MS, Kutcher ME, Izenberg RA, Singh T, Cohen MJ. Spinal Cord Injury: Outcomes of ventilatory weaning and extubation. J Trauma. 2011;71(6):1673–9.
64. Wong SL, Shem K, Crew J. Specialized respiratory management for acute cervical spinal cord injury: a retrospective analysis. Top Spinal Cord Inj Rehabil. 2012;18(4):283–90.
65. Romero J, Vari A, Gambarrutta C, Oliviero A. Tracheostomy timing in traumatic spinal cord injury. Eur Spine J. 2009;18(10):1452–7.
66. Choi HJ, Paeng SH, Kim ST, Lee KS, Kim MS, Jung YT. The effectiveness of early tracheostomy (within at least 10 Days) in cervical spinal cord injury patients. J Korean Neurosurg Soc. 2013;54(3):220–4.
67. Gomes Silva BN, Andriolo RB, Saconato H, Atallah AN, Valente O. Early versus late tracheostomy for critically ill patients. Cochrane Database Syst Rev. 2012;(3):CD007271.
68. Liu CC, Livingstone D, Dixon E, Dort JC. Early versus late tracheostomy: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2015;152(2):219–27.
69. Almenoff PL, Alexander LR, Spungen AM, Lesser MD, Bauman WA. Bronchodilatory effects of ipratropium bromide in patients with tetraplegia. Paraplegia. 1995;33(5):274–7.
70. Wadsworth BM, Haines TP, Cornwell PL, Rodwell LT, Paratz JD. Abdominal binder improves lung volumes and voice in people with tetraplegic spinal cord injury. Arch Phys Med Rehabil. 2012;93(12):2189–97.
71. Roussi J, Bentolila S, Boudaoud L, Casadevall N, Vallée C, Carlier R, Lortat-Jacob S, Dizien O, Bussel B. Contribution of D-Dimer determination in the exclusion of deep venous thrombosis in spinal cord injury patients. Spinal Cord. 1999;37(8):548–52.
72. Ploumis A, Ponnappan RK, Maltenfort MG, Patel RX, Bessey JT, Albert TJ, Harrop JS, Fisher CG, Bono CM, Vaccaro AR. Thromboprophylaxis in patients with acute spinal injuries: an evidence-based analysis. J Bone Joint Surg Am. 2009;91(11):2568–76.
73. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, Samama CM, American College of Chest Physicians. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S–77S.
74. Spinal Cord Injury Thromboprophylaxis Investigators. Prevention of venous thromboembolism in the acute treatment phase after spinal cord injury: a randomized, multicenter trial comparing low-dose heparin plus intermittent pneumatic compression with enoxaparin. J Trauma. 2003;54(6):1116–24.
75. Johns JS, Nguyen C, Sing RF. Vena cava filters in spinal cord injuries: evolving technology. J Spinal Cord Med. 2006;29(3):183–90.
76. Giannoudis PV, Pountos I, Pape HC, Patel JV. Safety and efficacy of vena cava filters in trauma patients. Injury. 2007;38(1):7–18.
77. Patel SH, Patel R. Inferior vena cava filters for recurrent thrombosis: current evidence. Tex Heart Inst J. 2007;34(2):187–94.
78. Blebea J, Wilson R, Waybill P, Neumyer MM, Blebea JS, Anderson KM, Atnip RG. Deep venous thrombosis after percutaneous insertion of vena caval filters. J Vasc Surg. 1999;30(5):821–8.
79. van der Wielen H, Post MW, Lay V, Gläsche K, Scheel-Sailer A. Hospital-acquired pressure ulcers in spinal cord injured patients: time to occur, time until closure and risk factors. Spinal Cord. doi:10.1038/sc.2015.239.
80. Groah SL, Schladen M, Pineda CG, Hsieh CH. Prevention of pressure ulcers among people with spinal cord injury: a systematic review. PM R. 2015;7(6):613–36.

Aneurysmal Subarachnoid Hemorrhage

7

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A 54-year-old woman presented with a history of severe headache, nausea, and vomiting. She is a smoker with a history of mild hypertension, but has no other known medical problems. She had presented to her family physician a week earlier with a similar headache, but the pain resolved within a few hours. Her older sister died of a brain hemorrhage 8 years ago. Today, she has neck stiffness, visual blurring, and is now feeling drowsy. She has no obvious weakness of her peripheries or cranial nerves excepting in that she cannot look upwards. Her heart rate is 108 bpm, with a blood pressure of 102/68 mm Hg, and respiratory rate of 28/min. Pulse oximetry reveals a saturation of 94%. A CT scan reveals blood in and around the right sylvian fissure, as well as some thin layering in the right lateral ventricle.

Neurosurgery plan to admit her to the intensive care unit for workup.

7.1 Overview and Epidemiology

Aneurysmal subarachnoid hemorrhage (aSAH) is an important type of hemorrhagic stroke with a disproportionate morbidity and mortality. The incidence of subarachnoid hemorrhage ranges from 2 to 22 patients per 100,000 population per year; the incidence is highest in Finland and Japan [1–3]. The overall case fatality report rates range from 26% to 50%, with the most comprehensive population-based study reporting a mortality rate of 21% within 24 h of aSAH, and 7- and 30-day mortalities of 37% and 44% [4], although a prehospital mortality of between 12% and 15% may elevate this [1]. aSAH accounts for 3% of all strokes, 4% of all stroke mortality, but accounts for 27% of all stroke-related years of potential life lost before the age of 65 [5].

Well-described risk factors for aSAH include longstanding hypertension, tobacco smoking, a family history of aSAH (especially in a first-degree relative), the use of cocaine (and other sympathomimetics), having a known aneurysm >7 mm in size, and presence of the aneurysm in the posterior communicating artery or in the posterior circulation [1].

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7.2 Pathophysiology

Excluding trauma, rupture of a cerebral aneurysm is the most common cause of subarachnoid hemorrhage. The presence of previously unknown cerebral aneurysms is likely quite common as 1–6% of subjects at autopsy will have at least one unruptured cerebral aneurysm identified.

There is evidence of genetic predisposition, with familial and regional clustering of aSAH. First-degree relatives of patients with aSAH are approximately three times more likely to have aSAH, and aneurysms are more prevalent in patients with well-described connective disorders such as Ehlers–Danlos syndrome, neurofibromatosis type I, Marfans syndrome, and autosomal dominant polycystic kidney disease [6]. However, aneurysms frequently develop in individuals without these diseases, and atherosclerosis is implicated in degenerative disease of the vessel wall, especially around areas of turbulent flow (e.g., branching vessels) or highly pulsatile oscillations of flow – both increasing wall shear stress [7]. The complex interactions of abnormal flow, atherosclerotic vessel wall changes, shear stresses, and genetic factors initiate aneurysmal formation and subsequent expansion, to a level that exceeds the tensile strength of what by now is a diseased and thinned vessel wall (consistent with the Law of Laplace). The result is rupture and hemorrhage.

Similarly, the pathologically high blood flow seen in arteriovenous malformation is also associated with aneurysmal formation [8].

Perimesencephalic subarachnoid hemorrhage is another important subtype of subarachnoid hemorrhage. In its classic form (thin layer of subarachnoid hemorrhage on initial imaging clustered around the upper brainstem), perimesencephalic subarachnoid hemorrhage accounts for approximately 10% of cases of nontraumatic subarachnoid hemorrhage. It accounts for approximately two-thirds of patients with nontraumatic subarachnoid hemorrhage who have had a negative angiogram. Intraventricular extension of the hemorrhage is rare and the patients typically present with less severe neurologic symptoms. Their course is significantly less likely to be complicated by cerebral vasospasm, and rebleeding is quite rare [9].

Table 7.1 Other causes of SAH

Intradural vertebral artery dissection
Rupture of a cerebral arteriovenous malformation
Dural arteriovenous fistula
Mycotic aneurysm
Pituitary apoplexy
Moya-Moya syndrome
Cocaine or sympathomimetic abuse
Vasculitis of the central nervous system
Reversible cerebral vasoconstriction syndrome (Call–Fleming Syndrome)
Hypertensive crisis

As already mentioned, trauma is the most common cause of subarachnoid hemorrhage, but often with a more peripheral distribution and less symptomatology than other variants. Other important causes to consider are listed in Table 7.1 – however, the focus here remains on aneurysmal SAH.

7.3 Clinical Features

Our case illustrates a classic presentation of a patient with aSAH – namely a patient that complains of a sudden severe headache, or "Worst Headache of Life (WHOL)." Unfortunately, this clinical history is not pathognomic for aSAH as only a minority of patients (6–17%) prospectively screened presenting with an acute severe headache will have aSAH [10, 11]. Other presenting symptoms can include seizure at onset (6%), transient loss of consciousness (26%), and vomiting prior to severe headache onset (69%) [10] (Table 7.2). Some patients may report a severe headache a few days prior to presentation

Table 7.2 Common presenting features

Sentinel leaks – 30–50%
Meningitis – 80%
Loss of consciousness – 45% at ictus, 10% for several days
Seizures – 10–25%
Focal neurology – 25% (hemiparesis, aphasia, hemineglect, cranial nerve palsies, and memory loss)
Motor deficits – 10–15%
Retinal hemorrhage (Terson's syndrome) – 20–30%
Hypertension – 50%

with aSAH – a phenomenon termed "Sentinel Headache" or "Herald Bleed." Many authors ascribe this cephalgia to a change in the aneurysm morphology or a small contained leak from the aneurysm that later ruptures to cause the presenting subarachnoid hemorrhage. Physical exam findings are typically nonspecific but can include depressed level of consciousness or confusion. A new third cranial nerve palsy (partial or complete) should raise the suspicion for an ipsilateral posterior communicating artery aneurysm causing compression on the third nerve.

7.4 Diagnosis

Noncontrast head CT remains the imaging modality of choice for screening for subarachnoid hemorrhage. Modern-day spiral acquisition multi-slice CT scanners are highly sensitive (almost 100%), but this sensitivity declines as time passes and based upon the expertise of the reviewer of the images [12]. False positive results are possible in patients with diffuse cerebral edema, retained IV CT contrast (especially in patients with renal failure), and subarachnoid injection of radiopaque contrast agents.

A lumbar puncture is recommended if the initial head CT does not reveal subarachnoid hemorrhage or other cause of presentation. Ideally, if a lumbar puncture is pursued it would be performed at least 6 h after the onset of symptoms to maximize the sensitivity in detection of xanthochromia. Spectrophotometry of the CSF supernatant is more sensitive than visual inspection of the CSF supernatant [13].

MRI of the brain is an alternative imaging modality that can be helpful in patients where a high clinical suspicion remains but the initial head CT is negative and the cephalgia onset was 3–4 days prior. Sequences that can be especially helpful are T2 hyperintense signal in the subarachnoid space (especially on FLAIR) and gradient-echo or susceptibility-weighted imaging demonstrating loss of adjacent cerebral parenchymal signal due to the presence of subarachnoid or intraventricular blood [14].

Computed tomography angiography (CTA) has become increasingly useful in avoiding the invasiveness of catheter angiography, while offering advantages of speed and aneurysmal volume assessment. 3D-CTA uses post-procedural reformatting with volume rendering techniques and maximum intensity projections to significantly enhance imaging perspectives of aneurysmal morphology – including complicating branch or perforating vessels. The ability to extract bone and facilitate 3D rotation allows visualization consistent with the actual surgical approach. The main drawbacks are a limited resolution of vessels less than 1 mm in size, as well as the reformatting itself, which, of necessity, consumes time and computing resources [15].

Conventional catheter angiography remains the gold standard for evaluation of the cerebral circulation. The conventional cerebral angiogram is critical in multiple ways: defining the cerebral vascular anatomy, precise localization and characteristics of the ruptured cerebral aneurysm, identification of unruptured cerebral aneurysm(s), and assisting the neurosurgeon and endovascular team in the decision of clipping vs coiling of the aneurysm. If the conventional catheter angiogram is negative on first imaging, and especially if the pattern of subarachnoid blood is not classic for perimesencephalic subarachnoid hemorrhage, most physicians will pursue a repeat cerebral angiogram at some point during the same hospital stay or within short-term follow-up.

7.5 Grading Scales

A number of important grading scales are published in the literature. The most commonly used are the Hunt and Hess [16], The World Federation of Neurological Surgeons (WFNS) [17], and Fisher grading scales [18]. The Hunt and Hess grading scale is a clinical scale and was first described in 1968 as a tool to gauge surgical risk and plan the timing of surgery; it is now used to assist in predicting clinical outcome (Table 7.3). It has been criticized for high degrees of

Table 7.3 Mortality according to admission Hunt–Hess grade [20]

Hunt–Hess grade	Mortality rate, %
1. Mild headache	3.5
2. Severe headache or cranial nerve deficit	3.2
3. Confusion, lethargy, or lateralized weakness	9.4
4. Stupor	23.6
5. Coma	70.5
Total	18.0

Table 7.4 Odds ratio of poor outcome for the WFNS scale [19]

WFNS category	%	Odds ratio (95% CI)
I	14.8	Reference
II	29.4	2.3 (1.3–4.1)
III	52.6	6.1 (2.9–12.8)
IV	58.3	7.7 (4.3–13.7)
V	92.7	69.2 (30.6–156.5)

Table 7.5 Fisher grade of cerebral vasospasm risk in subarachnoid hemorrhage

Group	Appearance of blood on head CT scan
1	No blood detected
2	Diffuse deposition or thin layer with all vertical layers (in interhemispheric fissure, insular cistern, ambient cistern) less than 1-mm thick
3	Localized clot and/or vertical layers 1 mm or more in thickness
4	Intracerebral or intraventricular clot with diffuse or no subarachnoid blood

inter-observer variability [17]. The WFNS Scale applies the Glasgow Coma Scale (GCS) Score to patients with SAH, in order to describe level of consciousness combined with the presence or absence of focal deficits, with the intent of both describing the severity of neurological injury and predicting patient outcomes (Table 7.4). The Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage (PAASH) scale is a relatively recent refinement of this concept and may offer greater discrimination of prognosis, but requires wider validation [19]. The Fisher grading scale is a radiographic scale originally developed to be a predictor for cerebral vasospasm (Table 7.5), but has been criticized on the basis of confused progression of risk from grades 3 to 4.

7.6 Treatment

Treatment for aSAH focuses on prevention of rebleeding, treatment of the aneurysm, and monitoring for cerebral vasospasm and delayed cerebral ischemia (DCI).

Rebleeding is a major cause of early mortality in patients with aSAH that survive to hospital admission. It occurs in 4–17% of patients within the first 72 h after presentation, and the mortality associated with rebleeding is significant with estimates up to 50–60% [9, 21, 22]. Antifibrinolytic therapy with aminocaproic acid was widely used in the 1980s and 1990s as it decreases the rate of rerupture, but it is no longer routinely used as it increases the risk of DCI [23], and some authors have reported increased rates of hydrocephalus [24]. There is renewed interest in the selective use of a short course of antifibrinolytics (<72 h) until the aneurysm is secured, especially in patients that are initially too ill to safely transport to the Interventional Neuroradiology suite or the operating room, but concerns on hydrocephalus remain [25]. Acute treatment of hypertension (SBP < 160) is also thought to decrease the rate of aneurysmal rerupture, but there is a dearth of data on the exact target and agents used. Antihypertensive control of blood pressure is driven predominantly by case series, but target levels of anywhere between 90 and 140 mm Hg are seen and there is no firm consensus [26]. Overly aggressive reductions risk ischemic stroke [27]. Our practice is to dichotomize treatment between less than 120 mm Hg in those younger than 70 years of age and less than 140 mm Hg in those older.

Obviously, early treatment of the source of bleeding reduces the need for and risk of antihypertensive therapy.

Treatment of the aneurysm is performed with open surgical clipping or endovascular coiling of the aneurysm. The modality chosen for treatment of ruptured cerebral aneurysms remains controversial (especially in the United States) and is beyond the scope of this discussion, but local institutional expertise, practice patterns, and patient characteristics are critical. Among the important factors to be considered in the decision of clipping vs coiling are patient age, aneurysm location, aneurysm morphology, presence of concomitant intraparenchymal hematoma, and the patient's medical comorbidities and condition after aneurysm rupture. However, the most recent follow-up of a comparison of endovascular and surgical interventions reported a significantly greater probability of disability-free survival after 10 years [28].

7.7 Hydrocephalus

Acute hydrocephalus is seen in approximately 20% of cases after aSAH [29]. Increasing age, female gender, poor admission Hunt and Hess grade, higher Fisher grade (especially grade 4), and aneurysmal location in the distal posterior circulation are some of the factors associated with hydrocephalus development [30]. The cause may be a simple obstruction (or noncommunicating cause) of the aqueduct, third or fourth ventricles from hemorrhagic clot, as opposed to the scarring of arachnoid villi and limited rCSF reabsorption (communicating type) seen in more chronic courses – although mixed patterns are not unusual. Severe headache, cognitive decline and loss of upward gaze are all associated features. Acute drainage may reduce pain and improve conscious level [31], and should be considered in any severely obtunded patient before decisions on limitations of care.

7.8 Delayed Cerebral Ischemia

The major causes of neurologic morbidity among survivors of aSAH arise from delayed cerebral ischemia (DCI) – thought to be a consequence of cerebral vasospasm. Cerebral vasospasm is defined as the reversible narrowing of cerebral arteries and arterioles and is most commonly reported after aneurysmal subarachnoid hemorrhage (occurring in approximately two-thirds of patients presenting with aSAH [32]), but narrowing of the cerebral vasculature has also been reported in association with a number of conditions including nonaneurysmal and traumatic subarachnoid hemorrhage, reversible cerebral vasoconstriction syndrome (Call–Fleming syndrome), and CNS infections including meningitis and encephalitis. DCI is defined as neurologic deterioration related to local cerebral ischemia and occurs in approximately one-third of patients presenting with aSAH [33]. Cerebral vasospasm can certainly induce DCI and there are considerable case series recording the benefit of angioplasty to improve flow. However, recent pharmaceutical interventions demonstrably reducing vasospasm have not had significant effect upon neurological outcomes, suggesting a more complex interaction between vasospasm and other etiologies of ischemia, such as microcirculatory thrombosis or spreading cortical depolarizations, in determining subsequent neuronal injury [34, 35].

This does not mean that vasospasm should be ignored, but rather that its treatment should be focused on and titrated toward measures of functional neurologic outcome, rather than the surrogate features of vasospasm [36].

Cerebral vasospasm and DCI typically occur between days 3–14 following aSAH with a peak incidence at 7–10 days. Patients with larger amounts of blood in the subarachnoid and intraventricular spaces are reported to be at the highest risk for cerebral vasospasm [37]. Clinically symptomatic vasospasm can manifest with a wide spectrum of symptoms and signs including newly progressive cephalgia, confusion, a change in the level of consciousness, or new focal neurologic deficit.

Monitoring for cerebral vasospasm integrates a multimodality approach. The fundamental basis for the testing of cerebral function is frequent neurologic examination, most commonly in a dedicated Neurointensive Care Unit at high volume

centers. Most centers will perform transcranial Doppler monitoring to assess the trends of flow velocity of the proximal cerebral vasculature on a daily or every-other-day basis. Promising and novel techniques include monitoring of regional cerebral blood and metabolic markers using regional cerebral blood flow monitors and cerebral microdialysis, and continuous EEG monitoring may detect subtle changes on EEG hours before clinical manifestations of cerebral vasospasm.

The treatment of cerebral vasospasm centers on improving cerebral blood flow to the territories affected. The concept of "triple-H therapy" (induced hypertension, induced hypervolemia, and hemodilution) was introduced in the 1970s and practiced through the early 2000s at many centers, but the medical treatment of cerebral vasospasm now centers around induced hypertension and aggressive euvolemia [1, 38–40]. The efficacy of "triple-H therapy" was and remains unclear; meta-analysis of individual components of this strategy has not demonstrated benefit and the complications of this approach are prominent [38, 41, 42]. There is no role for prophylactic hypervolemia. Since the last decade our ICU has abandoned hypervolemic therapy in favor of the maintenance of euvolemia with induced hypertension, as a treatment strategy for patients with vasospasm.

Currently all pharmaceutical interventions against vasospasm have proven ineffective when measured against neurologic outcome [34, 43].

Nimodipine has been shown to decrease the risk of poor outcome after aSAH and is the standard of care to be administered to all patients with aSAH, but it does not decrease the risk of vasospasm per se [44, 45]. Interestingly, it is fibrinolytic, suggesting some possible role in reducing microcirculatory thrombotic complications [46]. At many centers, conventional catheter angiography is performed in patients with suspected or documented vasospasm based upon clinical signs and noninvasive testing; a cerebral angiogram can also be a therapeutic maneuver in the treatment of cerebral vasospasm, with catheter-directed delivery of intra-arterial vasodilators and/or balloon angioplasty of vasospastic segments of proximal vasculature [47–50].

7.9 Secondary Insults

Aside from delayed cerebral ischemia, many other secondary insults may manifest within the ICU, with consequent effects upon neurologic outcome [51].

Cardiac abnormalities are common with frequent observation of ECG changes after SAH. These do not relate to outcome [52]. One-third of admitted SAH patients will have abnormal perfusion scans [53], while around the same number demonstrate increased troponins [54].

Eight percent of SAH patients demonstrate abnormal echocardiography, especially those with blood in the basal cistern [55]. This proportion is greatly increased in those with elevated troponins (≥0.3 ng/ml), with 44% having an ejection fraction (EF) of less than 50%, as compared to 5% of patients with no troponin rise. An almost identical ratio is seen with regional wall motion abnormalities (44% vs 4%). There are likely genetic predispositions to this entity of neurologic myocardial stunning, with evidence of differences in adrenoreceptor subtypes having an effect, and there are functional similarities to Tsakotsubo cardiomyopathy [56]. Treatment for coronary ischemia is not usually indicated, as significant recovery often occurs within several days, with no persistent sequelae. However, it is also prudent to consider that the risk factors and age groups experiencing coronary artery disease and subarachnoid hemorrhage may indeed overlap.

The ICU clinician should have a low threshold for suspecting cardiac involvement – especially when patients experiencing the severe pain of SAH fail to manifest a hypertensive response. QTc prolongation, symmetrical T inversion, and troponin elevation may all indicate acute need for echocardiography with subsequent inotropic and pressor treatment titrated to cardiac output [55]. This may limit surgical intervention and favor a decision for early endovascular treatment in unsecured aneurysms. Similarly, patients with secured aneurysms and new vasospasm may require angioplasty as opposed to aggressive pressor therapy [57].

Pulmonary injury to varying degrees is often observed in up to 44% of patients after SAH, but only a third of those experience severe dysfunction [58]. This may again be consequent to myocardial dysfunction, but there is also some element of systemic inflammatory response following SAH [59]. Care should be expectant, and although diuresis may occasionally be indicated, close attention should be paid to volemic status given previously identified risks of hypovolemia and stroke [60] – especially in the context of vasospasm.

Transfusion has been shown to increase risks of acute lung injury in SAH patients [61]. While anemia is associated with worse neurological outcome, corrective transfusion has not been associated with benefit – rather the converse [62]. There is no agreed consensus on appropriate transfusion thresholds, with observed variation between intensivists and surgeons [63].

Fever has been previously overlooked and underrated as a contribution to worse outcome but recent studies have demonstrated both prevalence and significant effect [51, 64, 65]. There have been no studies establishing benefits of hypothermia – rather, treatment is targeted toward maintenance of normothermia [66].

Hyponatremia is the most common electrolyte abnormality seen in patients after SAH, with up to 40% of patients requiring treatment [67]. The etiology is ascribed to either cerebral salt wasting syndrome – as a consequence of either cerebral or cardiac expression of "B" natriuretic peptide [68, 69] – or the syndrome of inappropriate antidiuretic hormone (SIADH) [70]. Treatment of either etiology is very different, and careful attention must be paid to volume status. The frequently observed polyuria tends to support the former mechanism. However, some confounding is introduced when considering that both volume and pressure elevation will themselves induce a compensatory natriuresis as a normal part of renal function [71].

Salt tablets may be combined with moderate free water restriction to limit derangements. The comparison of sodium and osmolality in both urine and serum may offer insights into whether large urine volumes are losing sodium, and may indicate the use of fludrocortisone. Severe cases may require intravenous hypertonic saline infusions.

Anorexia is common in SAH patients, and while understandable in the context of the cephalgia and nausea induced by SAH (as well as the effects of subsequent opiate analgesia), the negative catabolic effects may be profound. Energy requirements are elevated beyond those patients with ischemic stroke [72], with a consequent observed negative nitrogen balance. In turn this is associated with an increased risk of hospital-acquired infection and poor outcome [73]. Hypoalbuminemia may complicate the maintenance of intravascular volume status [74].

7.10 Critical Care Teams

Patients with SAH present with a life-threatening pathology matched by complex derangements of neurologic, cardiac, pulmonary, endocrine, and nutritional function. In the face of those problems and possible morbidities, it is not a surprise that the introduction of a dedicated neurocritical care team is associated with reduced in-hospital mortality and length of stay [75–77].

References

1. Connolly ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43(6):1711–37.
2. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8(4):355–69.
3. Ingall T, Asplund K, Mahonen M, Bonita R. A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. Stroke. 2000;31(5):1054–61.
4. Pobereskin LH. Incidence and outcome of subarachnoid haemorrhage: a retrospective population based study. J Neurol Neurosurg Psychiatry. 2001;70(3):340–3.
5. Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. Neurology. 1998;50(5):1413–8.
6. Schievink WI. Intracranial aneurysms. N Engl J Med. 1997;336(1):28–40.

7. Sforza DM, Putman CM, Cebral JR. Hemodynamics of cerebral aneurysms. Annu Rev Fluid Mech. 2009;41:91–107.
8. Stapf C, Mohr JP, Pile-Spellman J, Sciacca RR, Hartmann A, Schumacher HC, et al. Concurrent arterial aneurysms in brain arteriovenous malformations with haemorrhagic presentation. J Neurol Neurosurg Psychiatry. 2002;73(3):294–8.
9. van Gijn J, Rinkel GJ. Subarachnoid haemorrhage: diagnosis, causes and management. Brain. 2001;124(Pt 2):249–78.
10. Linn FH, Wijdicks EF, van der Graaf Y, Weerdesteyn-van Vliet FA, Bartelds AI, van Gijn J. Prospective study of sentinel headache in aneurysmal subarachnoid haemorrhage. Lancet. 1994;344(8922):590–3.
11. Morgenstern LB, Luna-Gonzales H, Huber Jr JC, Wong SS, Uthman MO, Gurian JH, et al. Worst headache and subarachnoid hemorrhage: prospective, modern computed tomography and spinal fluid analysis. Ann Emerg Med. 1998;32(3 Pt 1):297–304.
12. Edlow JA, Caplan LR. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. N Engl J Med. 2000;342(1):29–36.
13. Perry JJ, Sivilotti ML, Stiell IG, Wells GA, Raymond J, Mortensen M, et al. Should spectrophotometry be used to identify xanthochromia in the cerebrospinal fluid of alert patients suspected of having subarachnoid hemorrhage? Stroke. 2006;37(10):2467–72.
14. UK-I JM, Koo B, Trivedi RA, Higgins NJ, Tay KY, Cross JJ, et al. Current diagnostic approaches to subarachnoid haemorrhage. Eur Radiol. 2005;15(6):1135–47.
15. Kumar A, Kato Y, Hayakawa M, Junpei O, Watabe T, Imizu S, et al. Recent advances in diagnostic approaches for sub-arachnoid hemorrhage. Asian J Neurosurg. 2011;6(2):94–8.
16. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg. 1968;28(1):14–20.
17. Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid hemorrhage grading scale. J Neurosurg. 1988;68(6):985–6.
18. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery. 1980;6(1):1–9.
19. van Heuven AW, Dorhout Mees SM, Algra A, Rinkel GJ. Validation of a prognostic subarachnoid hemorrhage grading scale derived directly from the Glasgow Coma Scale. Stroke. 2008;39(4):1347–8.
20. Lantigua H, Ortega-Gutierrez S, Schmidt JM, Lee K, Badjatia N, Agarwal S, et al. Subarachnoid hemorrhage: who dies, and why? Crit Care. 2015;19:309.
21. Starke RM, Connolly Jr ES. Participants in the International Multi-Disciplinary Consensus Conference on the Critical Care Management of Subarachnoid H. Rebleeding after aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011;15(2):241–6.
22. Larsen CC, Astrup J. Rebleeding after aneurysmal subarachnoid hemorrhage: a literature review. World Neurosurg. 2013;79(2):307–12.
23. Fridriksson S, Saveland H, Jakobsson KE, Edner G, Zygmunt S, Brandt L, et al. Intraoperative complications in aneurysm surgery: a prospective national study. J Neurosurg. 2002;96(3):515–22.
24. Pinna G, Pasqualin A, Vivenza C, Da Pian R. Rebleeding, ischaemia and hydrocephalus following anti-fibrinolytic treatment for ruptured cerebral aneurysms: a retrospective clinical study. Acta Neurochir. 1988;93(3–4):77–87.
25. Harrigan MR, Rajneesh KF, Ardelt AA, Fisher WS 3rd. Short-term antifibrinolytic therapy before early aneurysm treatment in subarachnoid hemorrhage: effects on rehemorrhage, cerebral ischemia, and hydrocephalus. Neurosurgery. 2010;67(4):935–9; discussion 9–40.
26. Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. N Engl J Med. 2006;354(4):387–96.
27. Wijdicks EF, Vermeulen M, Murray GD, Hijdra A, van Gijn J. The effects of treating hypertension following aneurysmal subarachnoid hemorrhage. Clin Neurol Neurosurg. 1990;92(2):111–7.
28. Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RS. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). Lancet. 2015;385(9969):691–7.
29. van Gijn J, Hijdra A, Wijdicks EF, Vermeulen M, van Crevel H. Acute hydrocephalus after aneurysmal subarachnoid hemorrhage. J Neurosurg. 1985;63(3):355–62.
30. Dorai Z, Hynan LS, Kopitnik TA, Samson D. Factors related to hydrocephalus after aneurysmal subarachnoid hemorrhage. Neurosurgery. 2003;52(4):763–9; discussion 9–71.
31. Ochiai H, Yamakawa Y. Continuous lumbar drainage for the preoperative management of patients with aneurysmal subarachnoid hemorrhage. Neurol Med Chir (Tokyo). 2001;41(12):576–80; discussion 81.
32. Dorsch N. A clinical review of cerebral vasospasm and delayed ischaemia following aneurysm rupture. Acta Neurochir Suppl. 2011;110(Pt 1):5–6.
33. Dorsch NW, King MT. A review of cerebral vasospasm in aneurysmal subarachnoid haemorrhage Part I: incidence and effects. J Clin Neurosci. 1994;1(1):19–26.
34. Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A, et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). Lancet Neurol. 2011;10(7):618–25.
35. Etminan N, Vergouwen MD, Ilodigwe D, Macdonald RL. Effect of pharmaceutical treatment on vasospasm,

delayed cerebral ischemia, and clinical outcome in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. J Cereb Blood Flow Metab. 2011;31(6):1443–51.
36. Etminan N, Vergouwen MD, Macdonald RL. Angiographic vasospasm versus cerebral infarction as outcome measures after aneurysmal subarachnoid hemorrhage. Acta Neurochir Suppl. 2013;115:33–40.
37. Claassen J, Bernardini GL, Kreiter K, Bates J, Du YE, Copeland D, et al. Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: the Fisher scale revisited. Stroke. 2001;32(9):2012–20.
38. Lee KH, Lukovits T, Friedman JA. "Triple-H" therapy for cerebral vasospasm following subarachnoid hemorrhage. Neurocrit Care. 2006;4(1):68–76.
39. Diringer MN, Bleck TP, Claude Hemphill 3rd J, Menon D, Shutter L, Vespa P, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011;15(2):211–40.
40. Bederson JB, Connolly Jr ES, Batjer HH, Dacey RG, Dion JE, Diringer MN, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke. 2009;40(3):994–1025.
41. Treggiari MM, Walder B, Suter PM, Romand JA. Systematic review of the prevention of delayed ischemic neurological deficits with hypertension, hypervolemia, and hemodilution therapy following subarachnoid hemorrhage. J Neurosurg. 2003;98(5):978–84.
42. Feigin VL, Rinkel GJ, Algra A, van Gijn J. Circulatory volume expansion for aneurysmal subarachnoid hemorrhage. Cochrane Database Syst Rev. 2000;2:CD000483.
43. Sillberg VA, Wells GA, Perry JJ. Do statins improve outcomes and reduce the incidence of vasospasm after aneurysmal subarachnoid hemorrhage: a meta-analysis. Stroke. 2008;39(9):2622–6.
44. Rinkel GJ, Feigin VL, Algra A, van den Bergh WM, Vermeulen M, van Gijn J. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2005;(1):CD000277.
45. Dorhout Mees SM, Rinkel GJ, Feigin VL, Algra A, van den Bergh WM, Vermeulen M, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2007;(3):CD000277.
46. Roos YBWEM, Levi M, Carroll TA, Beenen LFM, Vermeulen M. Nimodipine increases fibrinolytic activity in patients with aneurysmal subarachnoid hemorrhage. Stroke. 2001;32(8):1860–2.
47. Jun P, Ko NU, English JD, Dowd CF, Halbach VV, Higashida RT, et al. Endovascular treatment of medically refractory cerebral vasospasm following aneurysmal subarachnoid hemorrhage. AJNR Am J Neuroradiol. 2010;31(10):1911–6.
48. Shankar JJ, dos Santos MP, Deus-Silva L, Lum C. Angiographic evaluation of the effect of intra-arterial milrinone therapy in patients with vasospasm from aneurysmal subarachnoid hemorrhage. Neuroradiology. 2011;53(2):123–8.
49. Smith WS, Dowd CF, Johnston SC, Ko NU, DeArmond SJ, Dillon WP, et al. Neurotoxicity of intra-arterial papaverine preserved with chlorobutanol used for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke. 2004;35(11):2518–22.
50. Terry A, Zipfel G, Milner E, Cross 3rd DT, Moran CJ, Diringer MN, et al. Safety and technical efficacy of over-the-wire balloons for the treatment of subarachnoid hemorrhage-induced cerebral vasospasm. Neurosurg Focus. 2006;21(3):E14.
51. Wartenberg KE, Schmidt JM, Claassen J, Temes RE, Frontera JA, Ostapkovich N, et al. Impact of medical complications on outcome after subarachnoid hemorrhage. Crit Care Med. 2006;34(3):617–23; quiz 24.
52. Manninen PH, Ayra B, Gelb AW, Pelz D. Association between electrocardiographic abnormalities and intracranial blood in patients following acute subarachnoid hemorrhage. J Neurosurg Anesthesiol. 1995;7(1):12–6.
53. Szabo MD, Crosby G, Hurford WE, Strauss HW. Myocardial perfusion following acute subarachnoid hemorrhage in patients with an abnormal electrocardiogram. Anesth Analg. 1993;76(2):253–8.
54. Hravnak M, Frangiskakis JM, Crago EA, Chang Y, Tanabe M, Gorcsan 3rd J, et al. Elevated cardiac troponin I and relationship to persistence of electrocardiographic and echocardiographic abnormalities after aneurysmal subarachnoid hemorrhage. Stroke. 2009;40(11):3478–84.
55. Mayer SA, LiMandri G, Sherman D, Lennihan L, Fink ME, Solomon RA, et al. Electrocardiographic markers of abnormal left ventricular wall motion in acute subarachnoid hemorrhage. J Neurosurg. 1995;83(5):889–96.
56. Deininger MH, Radicke D, Buttler J, Scheufler KM, Freiman T, Zentner JF. Tako-tsubo cardiomyopathy: reversible heart failure with favorable outcome in patients with intracerebral hemorrhage. Case Rep J Neurosurg. 2006;105(3):465–7.
57. Jain R, Deveikis J, Thompson BG. Management of patients with stunned myocardium associated with subarachnoid hemorrhage. AJNR Am J Neuroradiol. 2004;25(1):126–9.
58. Gruber A, Reinprecht A, Gorzer H, Fridrich P, Czech T, Illievich UM, et al. Pulmonary function and radiographic abnormalities related to neurological outcome after aneurysmal subarachnoid hemorrhage. J Neurosurg. 1998;88(1):28–37.
59. Gruber A, Reinprecht A, Illievich UM, Fitzgerald R, Dietrich W, Czech T, et al. Extracerebral organ dysfunction and neurologic outcome after aneurysmal

subarachnoid hemorrhage. Crit Care Med. 1999;27(3):505–14.
60. Kasuya H, Onda H, Yoneyama T, Sasaki T, Hori T. Bedside monitoring of circulating blood volume after subarachnoid hemorrhage. Stroke. 2003;34(4):956–60.
61. Kahn JM, Caldwell EC, Deem S, Newell DW, Heckbert SR, Rubenfeld GD. Acute lung injury in patients with subarachnoid hemorrhage: incidence, risk factors, and outcome. Crit Care Med. 2006;34(1):196–202.
62. Rosenberg NF, Koht A, Naidech AM. Anemia and transfusion after aneurysmal subarachnoid hemorrhage. J Neurosurg Anesthesiol. 2013;25(1):66–74.
63. Kramer AH, Diringer MN, Suarez JI, Naidech AM, Macdonald LR, Le Roux PD. Red blood cell transfusion in patients with subarachnoid hemorrhage: a multidisciplinary North American survey. Crit Care. 2011;15(1):R30.
64. Oliveira-Filho J, Ezzeddine MA, Segal AZ, Buonanno FS, Chang Y, Ogilvy CS, et al. Fever in subarachnoid hemorrhage: relationship to vasospasm and outcome. Neurology. 2001;56(10):1299–304.
65. Douds GL, Tadzong B, Agarwal AD, Krishnamurthy S, Lehman EB, Cockroft KM. Influence of fever and hospital-acquired infection on the incidence of delayed neurological deficit and poor outcome after aneurysmal subarachnoid hemorrhage. Neurol Res Int. 2012;2012:6.
66. Badjatia N, Fernandez L, Schmidt JM, Lee K, Claassen J, Connolly ES, et al. Impact of induced normothermia on outcome after subarachnoid hemorrhage: a case-control study. Neurosurgery. 2010;66(4):696–700; discussion −1.
67. Harrigan MR. Cerebral salt wasting syndrome: a review. Neurosurgery. 1996;38(1):152–60.
68. Qureshi AI, Suri MF, Sung GY, Straw RN, Yahia AM, Saad M, et al. Prognostic significance of hypernatremia and hyponatremia among patients with aneurysmal subarachnoid hemorrhage. Neurosurgery. 2002;50(4):749–55; discussion 55–6.
69. Berendes E, Walter M, Cullen P, Prien T, Van Aken H, Horsthemke J, et al. Secretion of brain natriuretic peptide in patients with aneurysmal subarachnoid haemorrhage. Lancet. 1997;349(9047):245–9.
70. Sherlock M, O'Sullivan E, Agha A, Behan LA, Rawluk D, Brennan P, et al. The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. Clin Endocrinol (Oxf). 2006;64(3):250–4.
71. Cowley Jr AW, Roman RJ. Control of blood and extracellular volume. Baillieres Clin Endocrinol Metab. 1989;3(2):331–69.
72. Nagano A, Yamada Y, Miyake H, Domen K, Koyama T. Increased resting energy expenditure after endovascular coiling for subarachnoid hemorrhage. J Stroke Cerebrovasc Dis. 2016;25(4):813–8.
73. Badjatia N, Monahan A, Carpenter A, Zimmerman J, Schmidt JM, Claassen J, et al. Inflammation, negative nitrogen balance, and outcome after aneurysmal subarachnoid hemorrhage. Neurology. 2015;84(7):680–7.
74. Kasuya H, Kawashima A, Namiki K, Shimizu T, Takakura K. Metabolic profiles of patients with subarachnoid hemorrhage treated by early surgery. Neurosurgery. 1998;42(6):1268–74; discussion 74–5.
75. Suarez JI, Zaidat OO, Suri MF, Feen ES, Lynch G, Hickman J, et al. Length of stay and mortality in neurocritically ill patients: impact of a specialized neurocritical care team. Crit Care Med. 2004;32(11):2311–7.
76. Varelas PN, Conti MM, Spanaki MV, Potts E, Bradford D, Sunstrom C, et al. The impact of a neurointensivist-led team on a semiclosed neurosciences intensive care unit. Crit Care Med. 2004;32(11):2191–8.
77. Samuels O, Webb A, Culler S, Martin K, Barrow D. Impact of a dedicated neurocritical care team in treating patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011;14(3):334–40.

Part II

Airway and Pain Management

8 Airway Management in Neurosurgical Procedures (Along with Ventilation Management)

Isabel Gracia, Anna M. López, and Ricard Valero

8.1 General Considerations for Airway Management in Neurosurgery

Airway management in neuroanaesthesia does not differ much from the standard airway management for general anaesthesia recommended by the international guidelines. However, there are some unique factors related to the nature of some neurosurgical procedures and to the clinical implications of certain neurological diseases that present specific challenges to maintain ventilation and airway patency along the entire perioperative process. Neuroanaesthesiologists need to be aware of the risks and be skilled in different techniques for managing the airway in a safe and efficient way.

The variety of non-conventional patient positions and the complexity of surgical instrumentations create ergonomic barriers that hinder the access to the patient's head and airway (Fig. 8.1). Therefore, it is mandatory to carefully plan the best strategy to manage the airway throughout the process, from the initial plan to secure the airway to extubation, including rescue plans in case of an unintentional tracheal extubation, or unexpected complications.

Furthermore, airway management and neurologic pathology are reciprocally related (Table 8.1). Neurologic conditions commonly seen in this patient population, such as a reduced level of consciousness, a certain degree of myopathy or neurological deficits, directly impair airway patency, protective reflexes or ventilation control, decreasing the safety margin for securing the airway. On the other hand, the response to aggressive airway manipulations and failure to deliver adequate oxygenation and ventilation may have a devastating impact on neurological outcomes in patients with cervical spine injuries or intracranial hypertension, for instance.

Finally, some specific neurological diseases, for example acromegaly or cervical spine lesions, are well-known causes of difficult airway, which require specific and well-planned approach.

All the above considerations emphasize the recommendation that anaesthetists taking care of neurosurgical patients need to master a wide range of airway management techniques (fibre-optic intubation, second-generation supraglottic devices, videolaryngoscopes, cricothyroidotomy, etc.), in order to address all the related events that may occur during induction of anaesthesia, patient positioning, surgery course, awakening extubation and postoperative care.

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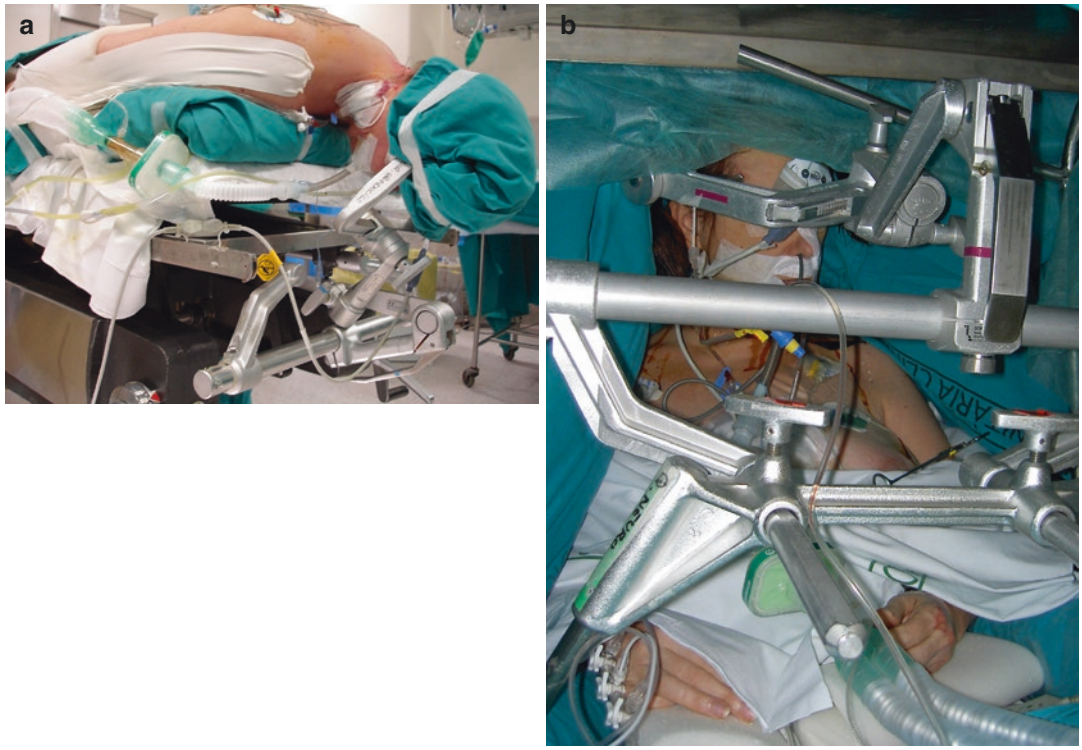

Fig 8.1 Difficult airway access during neurosurgery in prone (**a**) or sitting position (**b**)

Table 8.1 Implications of the neurological disease and neurosurgical procedures over the airway management

Reduced level of consciousness
Myopathy
Neurological deficits
Anatomical impairment: acromegaly, cervical stiffness
Potential neurological impairment during airway manipulation (spine trauma, ICP increase)
Positions for neurosurgical procedures: sitting, prone, extreme lateral neck, park bench

8.2 Airway Management in Craniotomies

Challenging positions during craniotomies include prone, lateral, park bench or sitting. Management of neurosurgical patients in prone position will be extensively discussed in Chap. 16. In a great number of surgeries, patient's head is fixed to the surgical table with a Mayfield-Kees skull-pin head frame, making neck manipulation or mouth opening extremely difficult. Even more, the head is covered with sterile surgical drapes, and the table containing the surgical instruments may be placed over the patient's chest. Additional bulky equipment may also obstruct the access to the airway.

8.2.1 Preoperative Evaluation

With a few exceptions, airway assessment for neurosurgical patients is similar to the general surgical population. A comprehensive evaluation of the airway is recommended, especially in those patients with a known disease associated to anticipated difficult airway, for example rheumatoid arthritis, cervical/spinal disease, acromegaly, etc.

Special consideration during preoperative assessment should be given to the potential increase of intracranial pressure (ICP) and its repercussion on patient's neurological situation. A reduced level of consciousness may be associated with a high risk of upper airway obstruction during the perioperative period and

should be taken into account. Low cranial nerves dysfunction might cause a decrease of airway protective reflexes leading to a higher risk of aspiration or hypoventilation. Neuroanaesthesiologists should discuss in advance the surgical details and the intended position of the patient's body, head and neck to plan the appropriate strategy for airway management.

8.2.2 Standard Management

Patients without criteria for difficult airway that require tracheal intubation are typically managed using direct laryngoscopy after induction of anaesthesia. In patients with predicted difficult airways, the use of videolaryngoscopes or flexible scopes is the best choice, according to the most recent and relevant guidelines. For patients at risk of regurgitation and pulmonary aspiration, a rapid sequence induction should be considered, if awake fibreoptic intubation is not indicated. The use of 1.2 mg/kg rocuronium would provide adequate muscle relaxation allowing tracheal intubation in 1 min. Supraglottic airway devices (SGDs) are feasible options for patients that do not necessarily need tracheal intubation, specifically in case of awake neurosurgery [1], as discussed below.

The airway must be carefully secured and the tracheal tube (or SGD device) tightly taped before positioning the patient, to decrease the risk of unintended extubation. For positions that do not maintain neutral position of head and neck, the use of reinforced tubes is preferred. A soft bite-block is recommended to prevent occlusion of the airway tube, and it is mandatory when motor evoked potentials (MEPs) monitoring is scheduled to assess the functional integrity of motor pathways.

Haemodynamic disturbances during laryngoscopy and tracheal intubation must be blunted to avoid an acute increase of ICP. Drugs such as lidocaine 1 mg/kg intravenously [2] or esmolol [3] before anaesthesia induction can minimize the haemodynamic and cerebral response to the laryngeal stimulation. Other effective measures include the administration of clonidine 2–4 μg/kg orally the night before and/or 1 h before arrival to the operating room [4, 5] and the α-2 agonist dexmedetomidine during induction and maintenance of anaesthesia to provide haemodynamic stability [6].

Guided tracheal intubation through an SGD, as the I-gel or Aura gain laryngeal mask airway, may also reduce the haemodynamic response to laryngoscopy [7].

Hypercapnia or hypocapnia during manual ventilation at induction should be avoided (see ventilation management).

8.2.3 Extubation and Awakening

Rapid recovery and extubation after intracranial tumour surgery are desirable in order to assess patient neurological status and to detect potential intracranial complications. Since residual pharmacological sedation may worsen a neurological deficit, short-acting anaesthetics are preferable intraoperatively. Extubation, however, may be associated with agitation, increased oxygen consumption, catecholamine secretion, hypercapnia and systemic hypertension. This may exacerbate the cerebral hyperaemia observed even during an uneventful recovery, leading to cerebral oedema or haemorrhage [8]. Moreover, unintended Valsalva manoeuvres, coughing or bucking during awakening impairs venous return and could increase ICP. The effect of coughing on the ICP has a variable duration, depending on brain compliance, but is usually less than 5 min [8].

Several studies have explored methods to reduce the effects of extubation on cerebral haemodynamics. Drugs such as lidocaine [9], esmolol [10, 11], diltiazem/nicardipine [12], fentanyl [13] and dexmedetomidine [14] have been effectively given for this purpose. Remifentanil infusion, which is widely used in neurosurgery, has also been suggested as a strategy for smoothing emergence [15], although no studies have demonstrated its efficacy in neurosurgical patients. The use of remifentanil during this period improves analgesia and could reduce haemodynamic impairment but must be carefully titrated

to avoid neurological depression (which could mask a neurological complication), as well as respiratory depression (which could cause hypercapnia and further hyperemia, thus abolishing the beneficial effect of haemodynamic control).

Non-pharmacologic methods to optimize emergence from anaesthesia and extubation have also been investigated, as replacing the endotracheal tube (ETT) by a SGD before awakening the patient. In a randomized trial in patients undergoing supratentorial craniotomy, the use of a SGD at the end of surgery, not only attenuated the haemodynamic disturbance and its effects on cerebral hyperemia, but also dramatically decreased the incidence of cough episodes compared to the ETT [16]. Replacement of the ETT by a SGD may be an effective alternative to provide haemodynamic stability in vulnerable neurosurgical patients, particularly in patients with a history of chronic hypertension [7, 16], reducing the risk of potential serious complications in the postoperative period.

8.2.4 Specific Procedures

8.2.4.1 Awake Craniotomy: Functional Neurosurgery

Indications for awake craniotomy include resection of tumours or vascular malformations located in eloquent areas and deep-brain stimulation in patients with Parkinson's disease or epilepsy.

The patient is positioned facing the anaesthesiologist or the neurophysiologist, allowing continuous communication and interaction with pictures/cartoons or a laptop during brain mapping. However, as these neurosurgical procedures typically last for several hours, immediate access to secure the airway in case of emergency should be planned [17]. Sleep apnoea syndrome must be considered as an exclusion criterion for awake craniotomy due to high risk of severe airway obstruction.

In the asleep-awake-asleep technique (see Chaps. 12 and 13), where anaesthetic approach consists of general anaesthesia before and after brain mapping, SGDs seem to be the most widely accepted technique [1, 17]. One of the most critical steps is the patient awakening right before brain mapping, while the patient's head is fixed to the surgical table with a Mayfield-Kees head frame or a stereotactic frame. It is crucial to avoid coughing, that may result in cervical spine lesion, and to blunt any hypertensive response, as haemodynamic fluctuations have more repercussion on the cerebral perfusion while the patient' dura mater is opened. Compared to tracheal intubation, SGDs offer some advantages such as avoiding neck extension for laryngoscopy, easier placement in challenging patient positions, and reduced incidence of coughing and hypertension during emergence. Second-generation SGDs with a gastric channel are recommended, as they provide a better airway seal and allow insertion of a gastric tube, reducing the risk of gastric insufflation and regurgitation. It is recommended to have a flexible scope at hand to check the position of the SGD or to guide tracheal intubation, if needed.

In case of monitored anaesthesia care approach (see Chap. 12), supplemental oxygen is given via nasal prongs or facial mask. A nasopharynx cannula may be used, which is usually well tolerated by the patient, although the risk of nose bleeding may be considered. Additional material to control airway, such as a SGD, must be available during the procedure in case of a respiratory depression.

8.2.4.2 Ventriculoperitoneal Shunts

For this procedure, the patient's head is laterally rotated, as much as possible, to one side to facilitate tunnelling the shunt (Fig. 8.2). Although tracheal intubation with a reinforced ETT seems to be the most extended airway management in these patients, some studies [18, 19] suggest that the use of SGD is a feasible alternative for short neurosurgical procedures. Compared to tracheal intubation, the use of SGD reduces haemodynamic changes and may speed anaesthesia recovery (lighter anaesthesia, no need for muscle relaxants). As a precaution, the position of the SGD should be checked and adjusted after the lateral rotation of the neck and during tunnelling at the level of the neck [20], as this manoeuvre may cause displacement of the device resulting in air leaks or airway obstruction. Second-generation or flexible SGDs are the best-suited options for

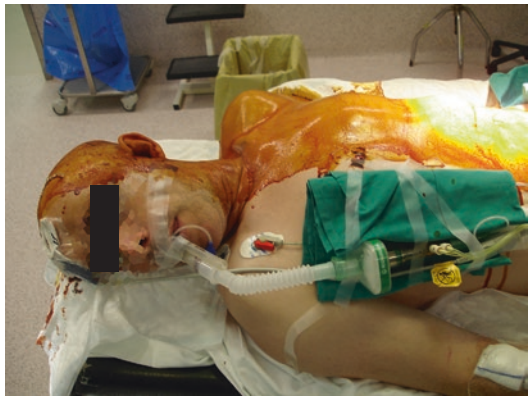

Fig. 8.2 Extreme lateral patient's head position for a ventriculoperitoneal shunt procedure, performed with supraglottic device

this purpose. In case of unsuccessful adjustments, tracheal intubation may be required.

8.3 Airway Management in Pituitary Surgery

8.3.1 Preoperative Evaluation

Patients with non-functioning tumours, Cushing disease or prolactinomas have an incidence of difficult intubation similar to general surgical population [21]. However, acromegaly, due to the overproduction of growth hormone (GH), is a well-recognized cause of difficult intubation and airway management. The unregulated secretion of GH results in hypertrophy of facial bones and tissues leading to typical alterations in the airway anatomy: prognathism, macroglossia and reduction of the glottic inlet. Such patients require a careful assessment of the airway prior to induction of anaesthesia, taking into account that clinical signs used to assess potential difficult intubation, such as the upper lip bite test and the Mallampati classification, have shown less sensitivity and accuracy compared with non-acromegalic controls [22]. A correlation between duration of symptoms and thyromental distance has been reported, but failed to show a relationship between difficulty of direct laryngoscopy and thyromental distance [23]. No correlation between GH levels and thyromental distance has been found [23]. Patient gender and tumour size have not been related to the incidence of unanticipated difficult airway [21].

Anatomic changes affect the management of the airway because an increased effort is required to displace the enlarged tongue into the restricted submental space, making it harder to align the laryngeal and pharyngeal axes, and therefore laryngoscopic visualization becomes more difficult. Limitations in head and neck mobility may also contribute to the difficulty of the procedures [21, 23]. The incidence of difficult laryngoscopy (Cormack-Lehane grades III–IV) has been reported between 9.1 and 26% in this patient population [21–24].

Presumably because of the changes in upper airway anatomy, acromegaly is associated with higher incidence (20–80%) of obstructive sleep apnoea (OSA), which is also related to difficult airway [25]. Patients with a combination of acromegaly and OSA have been described to have a higher risk of perioperative airway compromise [26, 27]. In these cases, difficult facemask ventilation and difficult laryngoscopy should be expected.

8.3.2 Standard Management

An extensive discussion about the anaesthesia for pituitary surgery may be seen in Chap. 18. At present, most surgical procedures are performed through trans-nasal trans-sphenoidal approach. Therefore, orotracheal intubation is a requisite.

Awake intubation is indicated in case of acromegaly with predicted difficult airway. Target-controlled sedation for awake fibreoptic intubation is useful to avoid apnoea and recall in these patients [28].

If the patient has no criteria for difficult ventilation or intubation, a standard induction of anaesthesia can be performed, having additional equipment immediately available as a safety measure.

8.3.3 Extubation and Awakening

The patient's nose is usually packed at the end of the surgery, causing extra discomfort during

awakening. This should be explained to the patient during the pre-anaesthesia assessment.

A well-planned strategy to avoid hypertension and coughing (Valsalva manoeuvres) during awakening is mandatory in order to avoid bleeding or cerebrospinal fluid leak. The same considerations discussed above are applicable in these patients.

8.4 Airway Management in Cervical Spine Surgery

Common indications for cervical or upper thoracic spine surgery are trauma, infection, malignancy and congenital or degenerative disease [29]. Acute spinal cord injury management will be discussed extensively in Chap. 6.

8.4.1 Preoperative Evaluation

The preoperative assessment should focus on the presence of radiculopathy, myelopathy or abnormal function of the ligaments and joints leading to instability of the spine. Rheumatoid arthritis, trisomy 21 or Klippel-Feil abnormality are some of the most common syndromes associated with asymptomatic instability of the cervical spine. However, other diseases such as diabetes may have neurological symptoms due to radiculopathy without associated anatomical changes. Preoperative assessment may also consider previous difficult intubation and neck movement restriction (Fig. 8.3).

Patients with cervical spine injury are at risk for airway obstruction, the management of

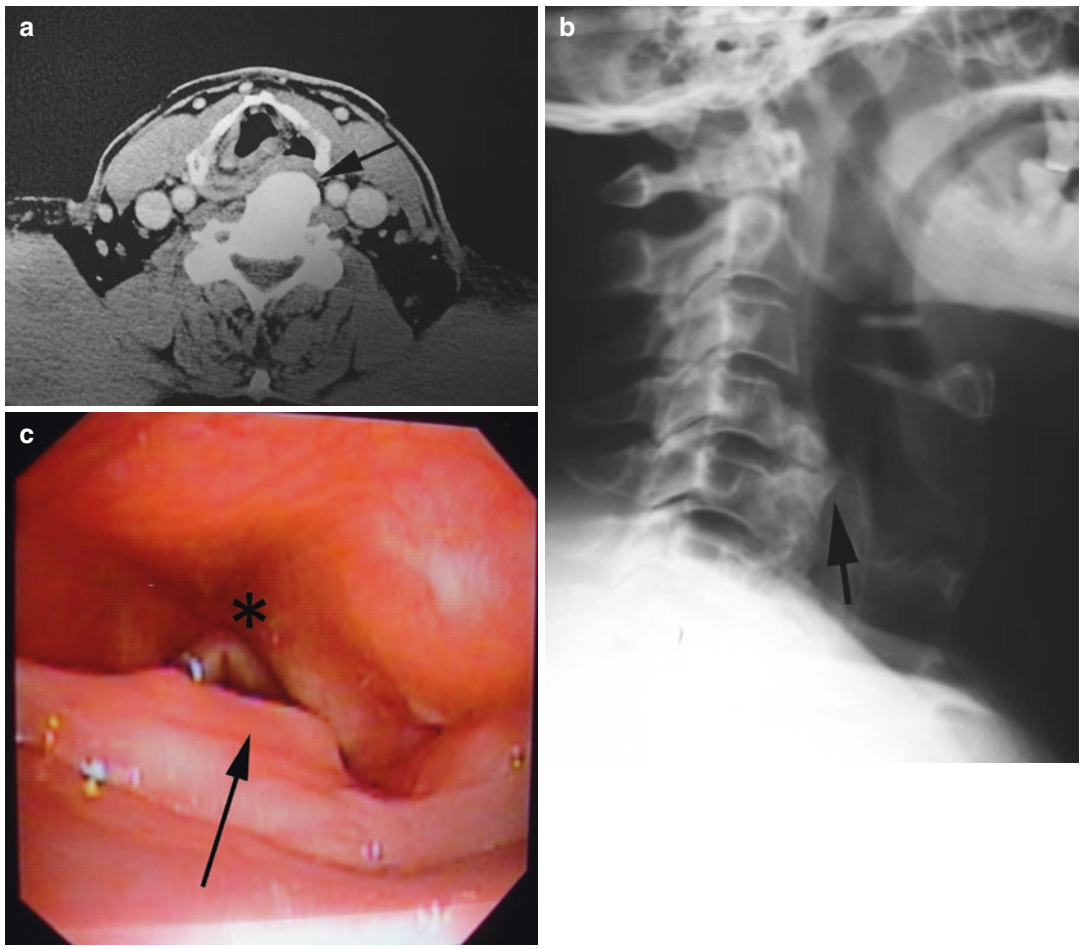

Fig. 8.3 Upper airway compression provoked by a cervical osteophyte (*arrow*: osteophyte; *asterisk*: anterior commissure of the vocal cords). (**a**) CT scan showing laryngeal distortion; (**b**) lateral neck X-ray showing the anterior protrusion; (**c**) fibreoptic view of the larynx during intubation

airway being the highest priority in the management of trauma [30]. In most cases, cervical trauma patients do not often require an immediate airway manipulation on arrival. The risk of upper airway obstruction in a cervical spine injury is due to prevertebral soft tissue swelling. It is crucial to closely monitor these patients in order to promptly act in case life-threatening complications appear [31]. Careful inspection of soft tissues in radiological imaging is relevant. A rare but potential cause of upper airway obstruction is retropharyngeal haematoma. Minor head and neck hyperextension injuries, especially in the elderly, can be associated with haematoma formation in the retropharyngeal space due to rupture of small anterior branches of the vertebral arteries.

Airway assessment may be difficult in this situation since patient's overall status may not allow for a detailed examination (unconscious or not cooperative). Moreover, a part of the assessment could be difficult because of the effects of injury or immobilization devices [32]. In addition, patients with cervical fractures may be at risk for secondary neurologic injury from fracture impingement or subluxation, resulting in serious neurological long-term damage.

8.4.2 Standard Management

Airway management priority in these patients is to avoid cervical spine displacement that could provoke a secondary spinal injury or aggravate an existing one.

Unstable Cervical Spine The conventional approach for airway management in patients with arthrosis or atlanto-axial instability presenting for elective cervical spine surgery is the flexible fibreoptic intubation. More recently, the widespread use of videolaryngoscopes has opened an alternative to successfully manage the difficult airway in these situations [32, 33].

Cervical Trauma Airway obstruction is a major cause of death following trauma, therefore quick establishment of a patent airway to ensure adequate ventilation without cervical displacement is the main priority. However, immobilization devices (cervical collar or halo) can make mask ventilation extremely difficult, and manoeuvres to open airway, as head tilt, chin lift and jaw thrust, have been reported to displace the spine in cadavers, to even higher extent than laryngoscopy, potentially causing secondary injury [34–36]. In the prehospital setting, oral or nasal pharyngeal airways can help in opening airway, but do not always work. The use of a SGD has been advocated to rescue ventilation in these patients. Caution should be taken though, to avoid overinflation of the cuff that may exert excessive pressure against the injured cervical spine [37, 38] and potentially cause secondary neurological injury.

Rapid sequence induction and direct laryngoscopy maintaining manual in-line immobilization (MILI) is the fastest way to intubate an unstable patient with cervical spine injury. Laryngoscopy induces movement of the cervical spine during blade elevation and ETT insertion, but probably these movements are not of so much impact as previously thought [34, 39–41]. MILI stabilizes the head and neck to offset any applied force to the spine during airway management, but its efficacy in reducing secondary spinal injury is unclear. The technique may be useful in reducing overall cervical spinal movements, but may have lesser effect if the injury is at midcervical level. MILI does impair visualization and may make tracheal intubation more difficult. Given the evidence, a prudent approach in case of emergency is to apply MILI during laryngoscopy with the anterior part of the cervical collar removed and avoiding axial traction [32].

Flexible scopes are the best choice for tracheal intubation as they cause minimal cervical displacement and do not necessarily require removal of neck-stabilizing devices. However, since it is more time consuming, requires patient cooperation, and is often impaired by blood or secretions, this technique is indicated in stable patients or elective surgery. The use of videolaryngoscopes for cervical spine injury continues growing, and clinical studies show it is a reliable technique in this patient population [32]. Indications for awake intubation include the risk of delayed gastric emptying and the need to assess neurology deficit after intubation [29].

8.4.3 Extubation, Awakening and Postoperative Follow-Up

8.4.3.1 Awakening

Difficult airway management and surgical airway equipment should be available during extubation. Most of the patients could be successfully extubated in the operating room without complications.

For high-risk patients (Table 8.2), it is recommended to take additional safety measures, as performing extubation over an airway exchange bougie to facilitate reintubation [42–45] or examining the airway with fibreoptic visualization [42, 43, 45, 46] or lateral X-ray/CT [43, 46] in order to detect neck swelling.

Since the average time to reintubation is 24 h [47, 48], some authors recommend to maintain a postoperative overnight monitored care admission for at least 24 h in high-risk surgery (lasting 5 or more hours on surgery, exposure of four or more vertebral bodies including C4 or higher). Even a conservative management may be considered, including overnight intubation, in order to avoid emergency reintubation or tracheostomy in selected patients [42, 43, 45, 47].

8.4.3.2 Postoperative Follow-Up

Upper airway obstruction is a well-known complication after neck surgery (carotid endarterectomy or thyroidectomy), although it is uncommon after cervical spine surgery. Few cases requiring reintubation [46] or even death [48] have been reported in few extensive reviews analyzing its aetiology. Potential causes are pharyngeal oedema, haematoma, cerebrospinal fluid leak, angioedema, and graft or plate dislodgement. Several risk factors for postoperative airway and respiratory complications have been identified (Table 8.2). Duration of surgery and total blood loss (indicating the extent and complexity of the surgery) are factors closely related to the incidence of airway complication in all case series. A long procedure would be accompanied by a longer period of retraction, increase in local tissue trauma and swelling. The type and site of surgery also have important implications. Manipulation above C4 often lies underneath the mandible and requires forceful retraction adding more trauma to the tissues. During anterior approach, the cervical spine is accessed between the carotid sheath and the trachea and oesophagus that are retracted laterally, which could lead to recurrent laryngeal nerve palsy, dysphonia, oesophageal perforation, hoarseness and sore throat [47]. An overflexion during cervical fixation, mainly if the C0-C2 (occipito-atlanto-axial) joint is involved [44, 49, 50], may cause the C2 vertebral body to protrude the posterior pharynx wall, leading to pharyngeal stenosis and upper airway obstruction immediately after extubation. The presence of myelopathy is related to an increased risk of respiratory distress [47] and should be considered a risk factor for reintubation in the postoperative period.

Table 8.2 Risk factors for postoperative airway and respiratory complications

Prolonged operative time (>5 h)
More than three vertebral bodies exposed
Manipulation above C4
Blood loss >300 mL
Combined anterior-posterior approach
Myelopathy
Second surgery [42]

Upper airway obstruction is a life-threatening complication that requires early recognition and aggressive management [43]. The patient usually starts complaining of difficult breathing, dysphonia and changes in voice quality that may be exacerbated in supine position. As the obstruction progresses, the patient becomes agitated, due to hypercapnia and/or hypoxia, and shows dyspnoea, stridor, desaturation and cyanose is that may quickly progress to a respiratory arrest [45]. If an airway complication appears, direct laryngoscopy and tracheal intubation might be difficult due to unstructured anatomy and have the potential of worsening the reactive changes of soft tissue [50]. The first choice is flexible scope guided intubation under spontaneous ventilation. If desaturation progresses, insertion of an SGD should be attempted to establish a patent airway and rescue oxygenation. Fibreoptic intubation through the SGD should be tried. In case of no-ventilation no-intubation scenario, a surgical emergent subglottic access must be performed.

8.5 Airway Management in Spine Surgery

8.5.1 Preoperative Evaluation

In addition to standard airway assessment, it is important to consider whether the pathology that brings the patient to the operating room affects the spine globally or is a local problem (ankylosing spondylitis vs discal herniation).

8.5.2 Standard Management

Spine surgery could be achieved either in flat prone position or in knee-chest prone position (Fig. 8.4). The standard approach to manage the airway for surgical procedures in these positions is to perform tracheal intubation in supine position, and then, turn the patient onto the final position. The use of a reinforced ETT is recommended to avoid airway obstruction. Mobilizing an anaesthetized patient not only requires time and manpower, but also encompasses several risks during the process, such as unintended extubation, loss of IV lines or injury to the patient or assistants. Care should be taken during positioning so that ventilation is not impaired, venous return is not compromised and all pressure points are protected. Special attention should be paid to ocular protection and limb positioning in order to avoid nerve injuries. Head and neck can be in neutral position on top of a dedicated support or laterally rotated to one side. If that is the case, excessive rotation should be avoided to ensure normal blood flow in carotid and vertebral arteries [51].

Despite the ongoing controversy, the use of SGD for spine surgery is gaining popularity. Placement of SGD following the patient's self-positioning in the prone position overcomes some of the above-mentioned risks of turning an unconscious patient and saves time [52]. Several studies have shown that the success rate of insertion and ventilation with an SGD in the prone position is similar to that achieved in supine position by an experienced anaesthesiologist [53–56], even in obese patients [57]. Despite the safety of this method has been called into question, it has

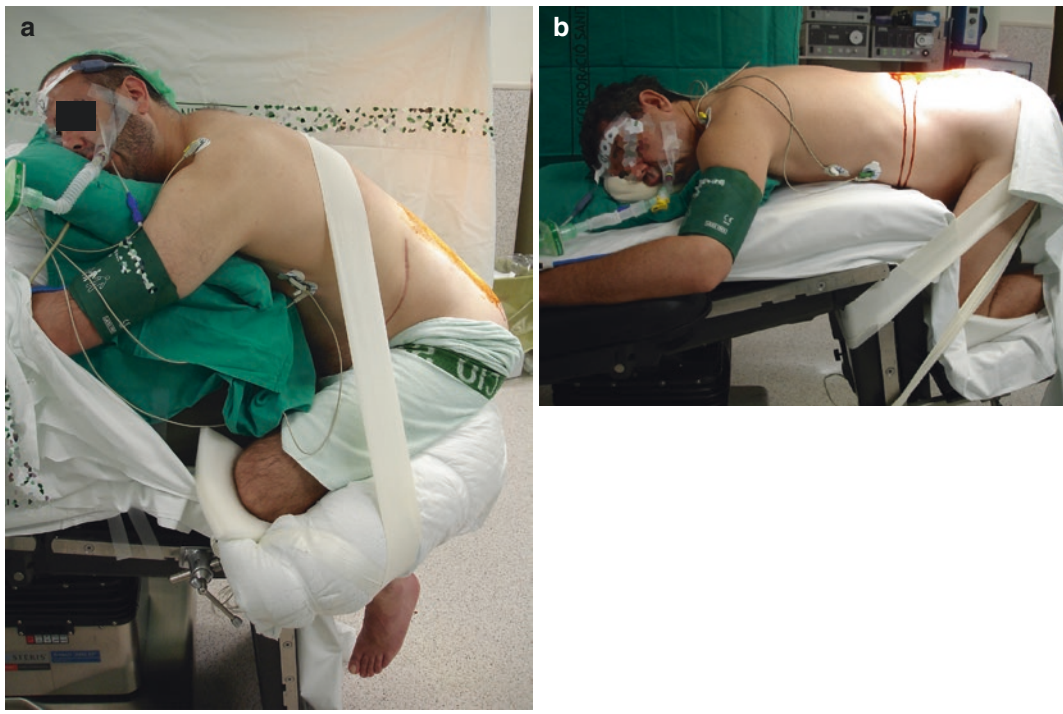

Fig. 8.4 Diverse positions for spine surgery that may provoke airway access difficult (**a**) modified Andrews frame; (**b**) knee-chest position

been successfully used as a rescue technique after unintended extubation in prone position [58, 59].

The methodology for SGD placement in prone patients has been described elsewhere [53, 54, 57]. As the use of SGD in prone position is an advanced indication, some relevant considerations should be emphasized for safe clinical use. First, the anaesthetist should have wide experience with SGD use and be able to quickly identify and manage any complication that might arise. Second, as previously discussed, second-generation devices are strongly recommended for this particular use, as they provide better ventilation conditions and airway protection. Third, additional material needed to manage a difficult airway should be at hand. And finally, careful selection of patients suitable for this approach is essential [56].

8.5.3 Extubation and Awakening

The same considerations for awakening a patient after a craniotomy apply for spine surgery patients. Increase in blood pressure after extubation has been shown to be a risk factor for the appearance of spinal epidural haematoma [60].

Awakening the patient in the prone position, allowing self-positioning into supine position is an additional advantage of using an SGD in this setting.

8.6 Airway Management in Interventional Neuroradiology

General precautions about working in an area with ionizing radiations must be always taken into account. The respiratory circuit as well as the monitoring wires and the IV lines must be placed in such a way that does not interfere with the X-ray equipment, especially with the 3-D devices, which need to rotate all around (360°) the patient's head. ETT must be carefully taped and fixed in order to avoid accidental extubation during 3-D image acquisition. The access to patient's head is hampered by the presence of cumbersome imaging equipment. If access to the airway is necessary during the procedure, the process must be stopped.

8.6.1 Cerebral Aneurysms

Coiling of cerebral aneurysms can be performed under general anaesthesia and tracheal intubation [61] or under light sedation to allow intraprocedural evaluation of neurological status [62]. Induction of anaesthesia should be smooth to prevent rebleeding at this time, as an increase or decrease in the transmural pressure can lead to rupture of the aneurysm sac. Invasive blood pressure monitoring before anaesthesia induction is useful to control any sudden change.

A supraglottic device may be used to control the airway in case of unruptured aneurysm coiling. The SGD reduces the haemodynamic impact, both at the moment of induction and emergence of anaesthesia, attenuating the variation on arterial pressure, and its effect on the wall of the aneurysm.

Maintaining normoventilation throughout the process is a priority, avoiding prolonged periods of apnoea or hyperventilation.

The need for postoperative controlled ventilation and sedation must be individually discussed in each patient. Labetalol boluses may be useful to control hypertensive peaks during anaesthesia emergence [63].

8.6.2 Acute Ischaemic Stroke

Intracranial intra-arterial revascularization is usually performed with the patient awake, in order to continuously assess the neurological function. A light sedation might be administered in case of agitation, but always checking the level of consciousness.

In case of neurological impairment, agitation or decreased level of consciousness, airway management may be necessary. Rapid sequence induction of anaesthesia and tracheal intubation is indicated, avoiding facemask ventilation as far as possible. Special care should be considered to

maintain arterial blood pressure stable (above 140 mmHg systolic pressure) during anaesthesia induction. The decision to awaken the patient needs to be taken individually in each case [64].

For carotid stenting, the most widespread approach is a monitored anaesthesia care, although general anaesthesia could be needed in the event of neurological impairment. In the rare event of carotid bleeding and neck haematoma causing airway obstruction, tracheal intubation must be performed immediately.

8.7 Ventilation Management in Neurosurgical Patients

Spontaneous ventilation was used as a monitor of brainstem function during brainstem surgery in the past. However, the widespread use of sophisticated electrophysiological monitoring makes this approach no longer relevant to neurosurgical anaesthesia.

There is no data supporting one mode of ventilation over another, provided there is adherence to reasonable pO_2 and pCO_2 targets, particularly in patients without pulmonary disease.

Hypercapnia and hypoxemia will induce increase in cerebral blood flow (CBF) and cerebral blood volume (CBV), leading to an increase of intracranial pressure (ICP) and potential decrease of cerebral perfusion pressure (CPP). Recognition and prompt treatment of these changes is of crucial relevance in the management of neurosurgical patients, making capnography and oxymetry mandatory in every neurosurgical procedure. Normocapnia is the routine target in brain-injured patients, and that should be in all neurosurgical procedures. Mild to moderate hypocapnia can be used to improve brain conditions by reducing CBF and CBV. Monitoring of brain oxygenation (SrO_2, SjO_2 or PtO_2) is advisable in these cases.

The use of PEEP only has a minimal effect on ICP, which is not considered clinically relevant, particularly when PEEP is set at levels that are lower than ICP [65]. Moreover, in a normovolaemic patient, an increase in mean airway pressure is not detrimental [66, 67]. The haemodynamic effects of PEEP (reduction of mean arterial pressure and CPP) can usually be solved by the administration of fluids or vasoactive drugs.

Conclusion

Airway management for neurosurgery procedures poses unique challenges to anaesthetists. Difficult airways are often associated with common neurosurgical pathology. Careful preoperative assessment of the airway and neurologic status of the patient, as well as discussion of the planned surgical position and details, are essential to plan the best-suited strategy to establish and maintain airway patency and optimal oxygenation throughout the procedure. Neuroanaesthesiologists need to be aware of the risks and to master a wide range of airway management techniques in order to address all the related events that may occur during induction of anaesthesia, patient positioning, surgery course, awakening, extubation and postoperative care.

References

1. Bilotta F, Rosa G. "Anesthesia" for awake neurosurgery. Curr Opin Anaesthesiol. 2009;22(5):560–5.
2. Qi DY, Wang K, Zhang H, Du BX, Xu FY, Wang L, et al. Efficacy of intravenous lidocaine versus placebo on attenuating cardiovascular response to laryngoscopy and tracheal intubation: a systematic review of randomized controlled trials. Minerva Anestesiol. 2013;79(12):1423–35.
3. Samaha T, Ravussin P, Claquin C, Ecoffey C. Prevention of increase of blood pressure and intracranial pressure during endotracheal intubation in neurosurgery: esmolol versus lidocaine. Ann Fr Anesth Reanim. 1996;15(1):36–40.
4. Chadha R, Padmanabhan V, Joseph A, Mohandas K. Oral clonidine pretreatment for haemodynamic stability during craniotomy. Anaesth Intensive Care. 1992;20(3):341–4.
5. Traill R, Gillies R. Clonidine premedication for craniotomy: effects on blood pressure and thiopentone dosage. J Neurosurg Anesthesiol. 1993;5(3):171–7.
6. Tanskanen PE, Kyttä JV, Randell TT, Aantaa RE. Dexmedetomidine as an anaesthetic adjuvant in patients undergoing intracranial tumour surgery: a double-blind, randomized and placebo-controlled study. Br J Anaesth. 2006;97(5):658–65.
7. Tang C, Chai X, Kang F, Huang X, Hou T, Tang F, et al. I-gel laryngeal mask airway combined with

tracheal intubation attenuate systemic stress response in patients undergoing posterior fossa surgery. Mediators Inflamm. 2015;2015:965925.
8. Bruder NJ. Awakening management after neurosurgery for intracranial tumours. Curr Opin Anaesthesiol. 2002;15(5):477–82.
9. Andrzejowski J, Francis G. The efficacy of lidocaine administered via the LITA tracheal tube in attenuating the extubation response in beta-blocked patients following craniotomy. Anaesthesia. 2002;57(4):399–401.
10. Bilotta F, Lam AM, Doronzio A, Cuzzone V, Delfini R, Rosa G. Esmolol blunts postoperative hemodynamic changes after propofol-remifentanil total intravenous fast-track neuroanesthesia for intracranial surgery. J Clin Anesth. 2008;20(6):426–30.
11. Grillo P, Bruder N, Auquier P, Pellissier D, Gouin F. Esmolol blunts the cerebral blood flow velocity increase during emergence from anesthesia in neurosurgical patients. Anesth Analg. 2003;96(4):1145–9.
12. Tsutsui T. Combined administration of diltiazem and nicardipine attenuates hypertensive responses to emergence and extubation. J Neurosurg Anesthesiol. 2002;14(2):89–95.
13. Bhagat H, Dash HH, Bithal PK, Chouhan RS, Pandia MP. Planning for early emergence in neurosurgical patients: a randomized prospective trial of low-dose anesthetics. Anesth Analg. 2008;107(4):1348–55.
14. Soliman RN, Hassan AR, Rashwan AM, Omar AM. Prospective, randomized study to assess the role of dexmedetomidine in patients with supratentorial tumors undergoing craniotomy under general anaesthesia. Middle East J Anaesthesiol. 2011;21(3):325–34.
15. Popat M, Mitchell V, Dravid R, Patel A, Swampillai C, Higgs A. Difficult Airway Society Guidelines for the management of tracheal extubation. Anaesthesia. 2012;67(3):318–40.
16. Perello-Cerda L, Fàbregas N, López AM, et al. Proseal laryngeal mask airway attenuates systemic and cerebral hemodynamic response during awakening of neurosurgical patients. A randomized controlled trial. Eur J Anaesthesiol. 2013;30:115.
17. Piccioni F, Fanzio M. Management of anesthesia in awake craniotomy. Minerva Anestesiol. 2008;74(7–8):393–408.
18. Agarwal A, Shobhana N. LMA in neurosurgery. Can J Anaesth. 1995;42(8):750.
19. Hurtado P, Valero R, Tercero J, Carrero E, de Riva N, López AM, et al. Experience with the proseal laryngeal mask in ventriculoperitoneal shunting. Rev Esp Anestesiol Reanim. 2011;58(6):362–4.
20. Kumar SS, Chaterjee N, Kamath S. LMA and ventriculo-peritoneal shunt surgery: is it the ideal airway? J Neurosurg Anesthesiol. 2009;21(1):66.
21. Nemergut EC, Zuo Z. Airway management in patients with pituitary disease. J Neurosurg Anesthesiol. 2006;18(1):73–7.
22. Sharma D, Prabhakar H, Bithal PK, Ali Z, Singh GP, Rath GP, et al. Predicting difficult laryngoscopy in acromegaly: a comparison of upper lip bite test with modified Mallampati classification. J Neurosurg Anesthesiol. 2010;22(2):138–43.
23. Ali Z, Bithal PK, Prabhakar H, Rath GP, Dash HH. An assessment of the predictors of difficult intubation in patients with acromegaly. J Clin Neurosci. 2009;16(8):1043–5.
24. Schmitt H, Buchfelder M, Radespiel-Troger M, Fahlbusch R. Difficult intubation in acromegalic patients: incidence and predictability. Anesthesiology. 2000;93(1):110–4.
25. Scacchi M, Cavagnini F. Acromegaly. Pituitary. 2006;9(4):297–303.
26. Piper JG, Dirks BA, Traynelis VC, VanGilder JC. Perioperative management and surgical outcome of the acromegalic patient with sleep apnea. Neurosurgery. 1995;36(1):70–4.
27. García AIP. Comment on “an assessment of the predictors of difficult intubation in patients with acromegaly”. J Clin Neurosci. 2010;17(2):279.
28. Cafiero T, Esposito F, Fraioli G, Gargiulo G, Frangiosa A, Cavallo LM, et al. Remifentanil-TCI and propofol-TCI for conscious sedation during fibreoptic intubation in the acromegalic patient. Eur J Anaesthesiol. 2008;25(8):670–4.
29. Raw DA, Beattie JK, Hunter JM. Anaesthesia for spinal surgery in adults. Br J Anaesth. 2003;91(6):886–904.
30. Link M, Berkow L, Kudenchuk P. Part 7 : adult advanced cardiovascular life support. Circulation. 2015;132(Suppl 2):444–64.
31. Cleiman P, Nemeth J, Vetere P. A significant cervical spine fracture: think of the airway. J Emerg Med. 2012;42(2):e23–5.
32. Diedrich DA, Rose PS, Brown DR. Airway management in cervical spine injury. Curr Anesthesiol Rep. 2013;3(3):197–204.
33. Barbeito A, Guerri-Guttenberg RA. Cervical spine instability in the surgical patient. Rev Esp Anestesiol Reanim. 2014;61(3):140–9.
34. Donaldson WF, Towers JD, Doctor A, Brand A, Donaldson VP. A methodology to evaluate motion of the unstable spine during intubation techniques. Spine (Phila Pa 1976). 1993;18(14):2020–3.
35. Hauswald M, Sklar DP, Tandberg D, Garcia JF. Cervical spine movement during airway management: cinefluoroscopic appraisal in human cadavers. Am J Emerg Med. 1991;9(6):535–8.
36. Brimacombe J, Keller C, Künzel KH, Gaber O, Boehler M, Pühringer F. Cervical spine motion during airway management: a cinefluoroscopic study of the posteriorly destabilized third cervical vertebrae in human cadavers. Anesth Analg. 2000;91(5):1274–8.
37. Keller C, Brimacombe J, Keller K. Pressures exerted against the cervical vertebrae by the standard and intubating laryngeal mask airways: a randomized, controlled, cross-over study in fresh cadavers. Anesth Analg. 1999;89(5):1296–300.
38. Kihara S, Watanabe S, Brimacombe J, Taguchi N, Yaguchi Y, Yamasaki Y. Segmental cervical spine movement with the intubating laryngeal mask during

manual in-line stabilization in patients with cervical pathology undergoing cervical spine surgery. Anesth Analg. 2000;91(1):195–200.
39. McLeod AD, Calder I. Spinal cord injury and direct laryngoscopy–the legend lives on. Br J Anaesth. 2000;84(6):705–9.
40. Sawin PD, Todd MM, Traynelis VC, Farrell SB, Nader A, Sato Y, et al. Cervical spine motion with direct laryngoscopy and orotracheal intubation. An in vivo cinefluoroscopic study of subjects without cervical abnormality. Anesthesiology. 1996;85(1):26–36.
41. Horton WA, Fahy L, Charters P. Disposition of cervical vertebrae, atlanto-axial joint, hyoid and mandible during x-ray laryngoscopy. Br J Anaesth. 1989;63(4):435–8.
42. Epstein NE, Hollingsworth R, Nardi D, Singer J. Can airway complications following multilevel anterior cervical surgery be avoided? J Neurosurg. 2001;94(Suppl 2):185–8.
43. Stefanutto TB, Gatt S. Cervical decompression and unexpected soft tissue oedema: case report. Anesth Pain Med. 2012;2(2):97–100.
44. Tagawa T, Akeda K, Asanuma Y, Miyabe M, Arisaka H, Furuya M, et al. Upper airway obstruction associated with flexed cervical position after posterior occipitocervical fusion. J Anesth. 2011;25(1):120–2.
45. Palumbo MA, Aidlen JP, Daniels AH, Bianco A, Caiati JM. Airway compromise due to laryngopharyngeal edema after anterior cervical spine surgery. J Clin Anesth. 2013;25(1):66–72.
46. Terao Y, Matsumoto S, Yamashita K, Takada M, Inadomi C, Fukusaki M, et al. Increased incidence of emergency airway management after combined anterior-posterior cervical spine surgery. J Neurosurg Anesthesiol. 2004;16(4):282–6.
47. Sagi HC, Beutler W, Carroll E, Connolly PJ. Airway complications associated with surgery on the anterior cervical spine. Spine (Phila Pa 1976). 2002;27(9):949–53.
48. Emery SE, Smith MD, Bohlman HH. Upper-airway obstruction after multilevel cervical corpectomy for myelopathy. J Bone Joint Surg Am. 1991;73(4):544–51.
49. Yoshida M, Neo M, Fujibayashi S, Nakamura T. Upper-airway obstruction after short posterior occipitocervical fusion in a flexed position. Spine (Phila Pa 1976). 2007;32(8):E267–70.
50. Lee Y-H, Hsieh P-F, Huang H-H, Chan K-C. Upper airway obstruction after cervical spine fusion surgery: role of cervical fixation angle. Acta Anaesthesiol Taiwan. 2008;46(3):134–7.
51. Edgcombe H, Carter K, Yarrow S. Anaesthesia in the prone position. Br J Anaesth. 2008;100(2):165–83.
52. Olsen KS, Petersen JT, Pedersen NA, Rovsing L. Self-positioning followed by induction of anaesthesia and insertion of a laryngeal mask airway versus endotracheal intubation and subsequent positioning for spinal surgery in the prone position: a randomised clinical trial. Eur J Anaesthesiol. 2014;31(5):259–65.
53. Brimacombe JR, Wenzel V, Keller C. The proseal laryngeal mask airway in prone patients: a retrospective audit of 245 patients. Anaesth Intensive Care. 2007;35(2):222–5.
54. López AM, Valero R, Brimacombe J. Insertion and use of the LMA Supreme in the prone position. Anaesthesia. 2010;65(2):154–7.
55. López AM, Valero R. Use of supraglottic airway devices in patients positioned other than supine. Trends Anaesth Crit Care. 2012;2(2):65–70.
56. Hurtado P, Fàbregas N, Forero C, Tercero J, Carrero E, de Riva N, et al. Laryngeal mask ventilation during lumbar spine neurosurgery in knee-chest position is feasible. J Neurosurg Anesthesiol. 2016. [Epub ahead of print].
57. Sharma V, Verghese C, McKenna PJ. Prospective audit on the use of the LMA-Supreme for airway management of adult patients undergoing elective orthopaedic surgery in prone position. Br J Anaesth. 2010;105(2):228–32.
58. Hinkelbein J. PRO: laryngeal masks can be used for surgery in the prone position. Eur J Anaesthesiol. 2014;31(5):253–5.
59. Abrishami A, Zilberman P, Chung F. Brief review: airway rescue with insertion of laryngeal mask airway devices with patients in the prone position. Can J Anaesth. 2010;57(11):1014–20.
60. Yamada K, Abe Y, Satoh S, Yanagibashi Y, Hyakumachi T, Masuda T. Large increase in blood pressure after extubation and high body mass index elevate the risk of spinal epidural hematoma after spinal surgery. Spine (Phila Pa 1976). 2015;40(13):1046–52.
61. Connolly ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43(6):1711–37.
62. Qureshi AI, Suri MF, Khan J, Kim SH, Fessler RD, Ringer AJ, et al. Endovascular treatment of intracranial aneurysms by using Guglielmi detachable coils in awake patients: safety and feasibility. J Neurosurg. 2001;94(6):880–5.
63. Randell T, Niemelä M, Kyttä J, Tanskanen P, Määttänen M, Karatas A, et al. Principles of neuroanesthesia in aneurysmal subarachnoid hemorrhage: the Helsinki experience. Surg Neurol. 2006;66(4):382–8.
64. Talke PO, Sharma D, Heyer EJ, Bergese SD, Blackham KA, Stevens RD. Society for Neuroscience in Anesthesiology and Critical Care Expert consensus statement: anesthetic management of endovascular treatment for acute ischemic stroke*: endorsed by the Society of NeuroInterventional Surgery and the Neurocritical Care Society. J Neurosurg Anesthesiol. 2014;26(2):95–108.
65. Andrews PJD. Pressure, flow and Occam's Razor: a matter of "steal"? Intensive Care Med. 2005;31(3):323–4.
66. Caricato A, Conti G, Della Corte F, Mancino A, Santilli F, Sandroni C, et al. Effects of PEEP on the intracranial system of patients with head injury and subarachnoid hemorrhage: the role of respiratory system compliance. J Trauma. 2005;58(3):571–6.
67. Mascia L, Grasso S, Fiore T, Bruno F, Berardino M, Ducati A. Cerebro-pulmonary interactions during the application of low levels of positive end-expiratory pressure. Intensive Care Med. 2005;31(3):373–9.

9 A New Airway Assessment Classification for Edentulous Patients and Its Potential Role in Neurocritical Care

Zahid Hussain Khan and Ramooz Hussain Khan

9.1 Airway Patency and Its Significance

To prevent the frequently occurring episodes of hypoventilation, hypoxia and imminent death, anesthesiologists take it as their primary responsibility to ensure an effective patent airway to maintain unimpaired and optimal oxygenation. Failure to maintain oxygenation in an apneic or paralyzed patient entails catastrophic events including death. It has been reported that the incidence of difficult intubation (DI) ranges between 1% and 18% [1–4].

9.2 Edentulous Patients and Airway Assessment

The available preoperative airway assessment tests [1, 4–8] provide us a powerful and lucid account of the subject, but unfortunately these tests fail to encompass the edentulous patients who form a large proportion of our population and as such these patients are usually excluded from studies pertaining to airway assessment. This arena has either not been touched or perhaps left neglected on the grounds of nonavailability of a diagnostic test for airway assessment in edentulous patients.

Dentition seemingly imparts a protection in maintaining a patent airway besides being an important factor in airway management. The teeth obviously serve to be of mechanical advantage of leverage while using the traditionally employed laryngoscopic blades. They provide a monumental help in supporting a static weight that is transferred during laryngoscopy and their absence as in edentulous patients would perhaps make some problems during laryngoscopy.

Lack of dentition would make axis alignment easier during laryngoscopy but the tongue would be an obvious impediment in visualizing the hypopharyngeal structures, thus making an intubation difficult. As senility ensues, all the structures of the body undergo atrophic changes except for the tongue, which for some unknown reasons enlarges or perhaps undergoes hypertrophic changes. Likewise, it has been held that as the age advances, the laryngeal structures tend to descend caudally [9, 10]. Thus, the edentulous patients who commonly fall in the old-age group would have their larynx positioned low and caudally, and this coupled with the tongue occupying most of the oral cavity would make laryngoscopy exceedingly difficult. Edentulous patients, according to many, do not pose much of a problem as far as their intubation is concerned but no clinical trials have been conducted to

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ascertain the validity of this commonly held belief.

As there is no study in the literature about airway assessment in edentulous patients, we sought to assess the potential value of the upper lip catch test (ULCT) as our primary goal in this category of patients based on the observations in our pilot study [11].

9.3 The Upper Lip Catch Test

As most of the edentulous patients are in their old age, an assessment of their airway class prior to induction would facilitate a smooth induction of anesthesia and a subsequent quick intubation will guarantee no insult to their precarious cardiovascular system, being more vulnerable to acute hemodynamic stress or heart rate fluctuations. Moreover, the blood supply to many organs because of related atherosclerotic changes may put these patients at higher risk of hypoxic–ischemic and even hemorrhagic events, and such a scenario is bound to occur if the intubation takes a little longer time.

Since no airway assessment has been conducted before induction because of nonavailability of an airway assessment test targeted at this population, unanticipated events are likely to occur during the process of intubation.

In edentulous patients having sustained head injuries and their life's blood sprouting in a stream, a quick assessment of the ULCT in a conscious patient can be of significant help if an endotracheal intubation is to be considered later during the course of surveillance or when the level of consciousness shows a decline. Flawless information about the nervous system is as much necessary as is a subtle observation of the airway class and its difficulty. This would prevent the foreboding of an unanticipated difficult intubation in a rapidly deteriorating neurosurgical patient.

The ULCT classification was initially introduced by Khan et al. [11] to assess airway class in edentulous patients. In performing the test, the patient is asked to roll over the lower lip over the upper lip as far as feasible and tolerable for the patient, and then the airway class is determined according to the criteria proposed by Khan et al. (Figs. 9.1 and 9.2). Based on the observations obtained from their pilot study, Khan et al. [12] assessed the diagnostic value of the ULCT in their prospective study and compared the results with Cormack–Lehane Grading (CLG) [13] as a gold standard for laryngoscopic view. Although their primary intent was to test the predictive value of ULCT in edentulous patients and compare it with the gold standard of CLG, they also evaluated the modified Mallampati test (MMT) and its role in detecting difficult intubation in edentulous patients never tested before as their secondary goal. CLG of III and IV were found in 12 (2%) out of the total of 588 patients. The sensitivity (Se) and specificity (Sp) of the ULCT were 15% and 89.4% respectively, in contrast to 66.7% and 81.3% respectively for the MMT. The positive predictive value (PPV) was found to be low for both the tests, suggesting a high false positive (FP) rate. The negative predictive value (NPV) on the contrary was high for both the tests. Although a higher FP rate of a test pushes us toward more cautious handling of the situation thereby helping us in preventing a poor outcome, nevertheless, a higher rate of NPV gives us a margin of safety, or in other words, provides us reassurance of an easy intubation and thus helps us in eliminating cases of difficult intubation. Interpreting the significance of the results, a high FP rate impels us to take the needed steps before laryngoscopy in terms of adequate provision of all the paraphernalia that are needed to facilitate a difficult intubation drill. This in itself is without any harm except that it entails an extra burden on the OR personnel.

However, the ULCT had a high NPV of 99.4% imparting a useful information that the chances of a DI would be exceedingly low and in the range of 0.6%. Again a high Sp of ULCT as found out in the results could document that the ULCT had the potential to easily demarcate those

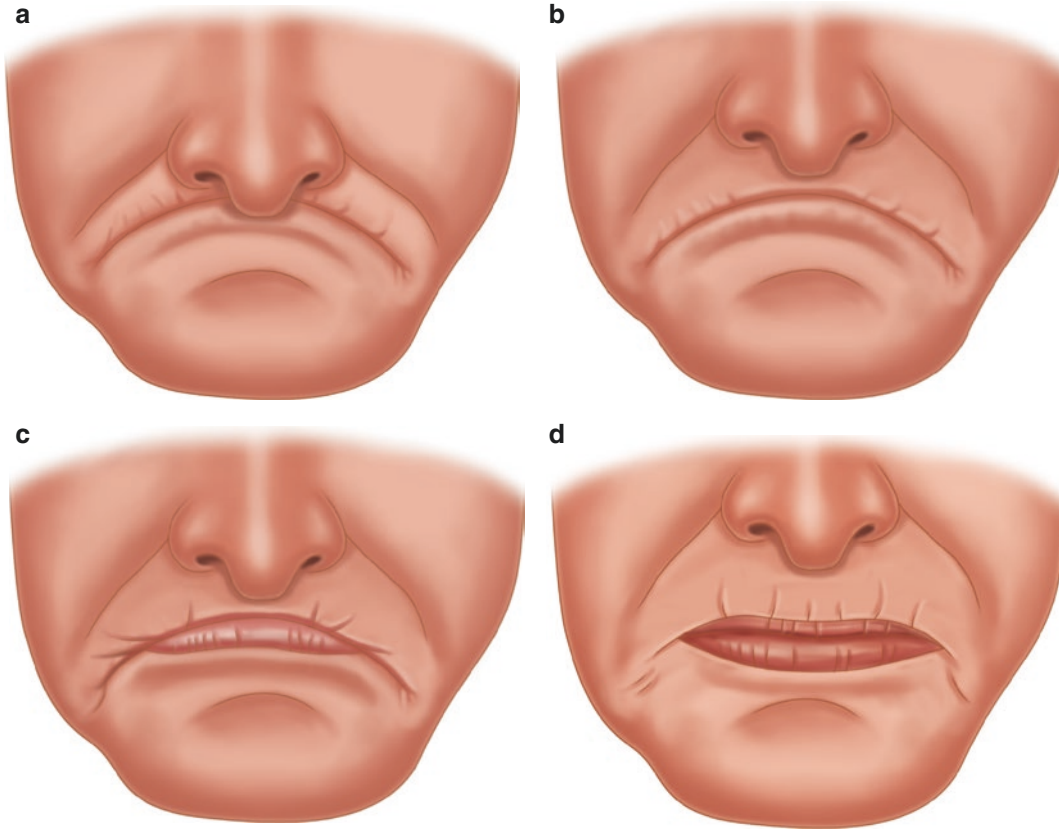

Fig. 9.1 Schematic frontal view of the upper lip catch test. (**a**) Class 0; the lower lip rolling over the upper lip advancing as high as the rhinion or else positioning itself at any point above midway between the vermilion line and the rhinion. Note that the lower lip rolling over the upper lip exhibiting wrinkles and folds of senility, and the area above the chin contracted giving a goose pimple appearance. (**b**) Class I; the lower lip catching the upper lip, between a point 2 mm above the vermilion line and the point midway between the vermilion line and the rhinion. (**c**) Class II; the lower lip catching the upper lip at the level of the vermilion line or positioning itself just above it (2 mm). (**d**) Class III; the lower lip just caresses the upper lip unable to make further advancement and falls short of vanishing the vermilion line. (Reproduced with permission from Khan et al. [11]. Copyright 2003 Lippincott Williams & Wilkins)

edentulous patients who were subsequently found to have an easy intubation.

Difficult laryngoscopy is a dreaded outcome following loss of consciousness and entails a host of complications, thus the NPV becomes an important index in the evaluation of a test. It helps the anesthesiologist to know with reasonable certainty to safely anesthetize the patient without the need for special airway equipment in the operating room. Bag mask ventilation had been difficult in some cases and it corroborates with other studies which state a difficult mask ventilation in edentulous patients. Since it was not our study outcome, we cannot offer statistical figures to unequivocally state the degree or the percentage of difficulty of bag mask ventilation in this class of population.

The brain is ingenious enough to invent an arrangement for itself, but in the face of an obstructed airway, things weigh against you as an attending intensivist.

This test needs to be assessed in different ethnic and racial groups to get a clear role of its efficacy in such groups and also in patients with craniofacial malformations.

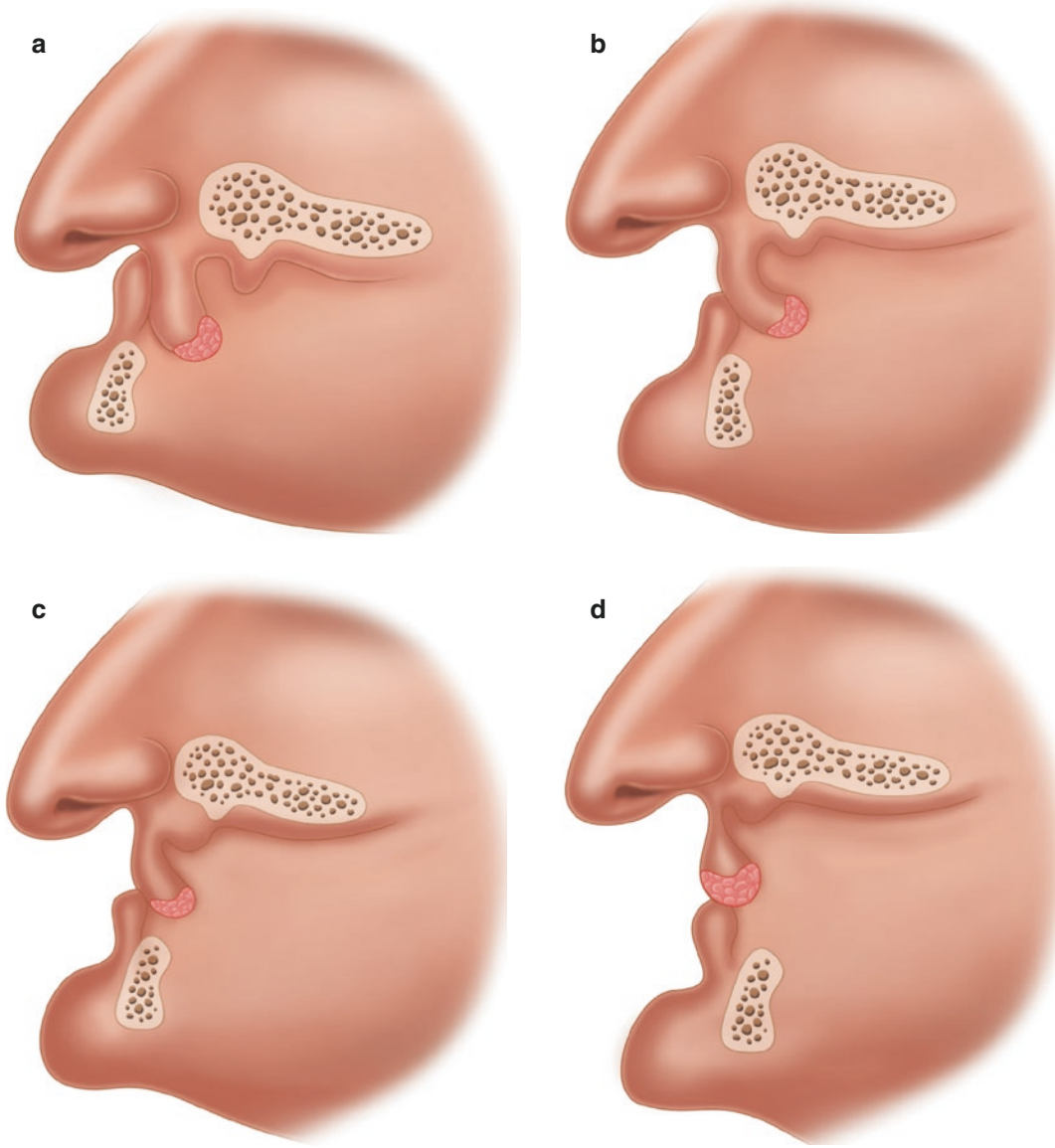

Fig. 9.2 Schematic lateral view of the upper lip catch test. Dotted area depicts the mucosa of the upper lip. (**a**) Class 0; the lower lip rolling over the upper lip advancing as high as the rhinion or else stationing itself at any point above midway between the vermilion line and the rhinion. (**b**) Class I; the lower lip catching the upper lip, between a point 2 mm above the vermilion line and the point midway between the vermilion line and the rhinion. (**c**) Class II; the lower lip catching the upper lip at the level of the vermilion line or positioning itself just above it (2 mm). (**d**) Class III; the lower lip just caressing the upper lip but fails to obliterate the vermilion line. (Reproduced with permission from Khan et al. [11]. Copyright 2003, Philadelphia, Lippincott Williams & Wilkins)

Conclusion

Airway assessment and timely endotracheal intubation in a rapidly deteriorating head injury patient is of immense importance. Its implementation becomes all the more important in edentulous patients who are vulnerable to become hypercapnic because the leverage of the teeth is missing promoting the tongue to fall backwards, thus impeding ventilation. The ULCT helps us in assessing the airway in

this class of patients, especially so when there lurks an impending danger of apnea.

Of all the complications in anesthesia and intensive care unit, the one I most fear and consider horrid is a failed intubation in an apneic patient. Thus airway assessment is of paramount importance. The ULCT is of high import in edentulous patients and should be evaluated in this class of patients to prevent encountering a difficult airway after the induction agent is administered.

References

1. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. Br J Anaesth. 1988;61(2):211–6.
2. Shiga T, Wajima ZI, Inoue T, Sakamoto A. Predicting difficult intubation in apparently normal patients: a meta-analysis of bedside screening test performance. J Am Soc Anesthesiology. 2005;103(2):429–37.
3. Biebuyck JF, Benumof JL. Management of the difficult adult airway with special emphasis on awake tracheal intubation. J Am Soc Anesthesiology. 1991;75(6):1087–110.
4. Jimson CT, Rimm EB, Hussain A. Predicting difficult endotracheal intubation in surgical patients scheduled for general anesthesia: a prospective blind study. Anesth Analg. 1995;81(2):254–8.
5. Karkouti K, Rose DK, Wigglesworth D, Cohen MM. Predicting difficult intubation: a multivariable analysis. Can J Anaesth. 2000;47(8):730–9.
6. Khan ZH, Kashfi A, Ebrahimkhani E. A comparison of the upper lip bite test (a simple new technique) with modified Mallampati classification in predicting difficulty in endotracheal intubation: a prospective blinded study. Anesth Analg. 2003;96(2):595–9.
7. Krobbuaban B, Diregpoke S, Kumkeaw S, Tanomsat M. The predictive value of the height ratio and thyromental distance: four predictive tests for difficult laryngoscopy. Anesth Analg. 2005;101(5):1542–5.
8. Merah NA, Wong DT, Ffoulkes-Crabbe DJ, Kushimo OT, Bode CO. Modified Mallampati test, thyromental distance and inter-incisor gap are the best predictors of difficult laryngoscopy in West Africans. Can J Anaesth. 2005;52(3):291–6.
9. Chou HC, Wu TL. Large hypopharyngeal tongue: a shared anatomic abnormality for difficult mask ventilation, difficult intubation, and obstructive sleep apnea? Anesthesiology. 2001;94(5):936–7.
10. Schwartz DS, Keller MS. Maturational descent of the epiglottis. Arch Otolaryngol Head Neck Surg. 1997;123(6):627–8.
11. Khan ZH, Kashfi A. Evaluating a patient's airway: in response. Anesth Analg. 2003;97(3):915–6.
12. Khan ZH, Arbabi S, Yekaninejad MS, Khan RH. Application of the upper lip catch test for airway evaluation in edentulous patients: an observational study. Saudi J Anaesth. 2014;8(1):73.
13. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. Anaesthesia. 1984;39(11):1105–11.

Airway Management in Neurocritical Care

10

Mohammad Jalili

10.1 Introduction

Airway compromise may occur in a multitude of neurological conditions mainly as a result of muscle weakness or significant decline in mental function [1]. In fact, in patients with severe neurological disorder, the need for airway protection is one of the main indications for admission to neurological intensive care units. Therefore, physicians who care for patients with neurological/neurosurgical disorders must possess the required skills for managing this type of emergency.

Airway management in the setting of neurocritical care may pose a particular challenge. Unlike the elective nature of airway management in the operating room, the complication rate of airway management in this setting is higher, partly due to the limited physiologic reserve and the existence of co-morbidities [2]. Moreover, there is little time for preparation, and a thorough evaluation of the patient's airway is rarely feasible prior to the airway intervention.

While knowledge of the basic principles of airway management is necessary, these patients merit some specific considerations. In this chapter, we overview the general principles of airway management and then briefly discuss the specific considerations in neurocritically ill patients.

10.2 The General Principles of Airway Management

10.2.1 Indications for Intubation

Patients with neurological problems may require intubation on the basis of three general criteria [1]:

(a) Failure to maintain or protect the airway: decreased level of consciousness, absence of gag reflex, and inability to handle oral secretions are clinical indicators suggesting inability of the patient to protect his/her airway. Failure to maintain a patent airway even for a brief period of time is life threatening and may lead to untoward consequences. So, a timely recognition of the need for intubation is of paramount importance.

(b) Failure to ventilate or oxygenate: decreased oxygen saturation, hypercarbia, and respiratory distress are clues to respiratory insufficiency. Ventilation failure is defined as the inability of the respiratory system to oxygenate arterial blood and eliminate carbon dioxide from the body, resulting in $PaO_2 < 60$ mm Hg and $PaCO_2 > 50$ mm Hg. Oxygenation failure is characterized by the presence of a PaO_2 less than 60 mmHg and a normal or low $PaCO_2$ level [3].

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(c) Anticipated course of clinical deterioration: Condition may worsen and cause progressive airway compromise in a neurological patient not already in obvious jeopardy. Decreasing level of consciousness in a trauma victim leaving the emergency room for a CT scan is a typical example of anticipated course of clinical deterioration which requires prophylactic intubation.

The decision to intubate is not always straightforward, especially when the patient is not in extremis but is approaching it. Most experts recommend intubating a patient "as soon as one considers this option."

10.2.2 Modalities of Airway Management

An overwhelming multitude of techniques and devices are available for establishing an airway; the most commonly practiced one being endotracheal intubation through direct laryngoscopy [2]. However, noninvasive airway management (manual airway maneuvers and bag-mask ventilation [BVM]) and the use of extraglottic devices (such as cuffed, orally inserted hypopharyngeal airways [LMAs], or cuffed orally inserted esophageal airways [Combitubes]) are other available choices. While these basic airway techniques are important temporizing and at times lifesaving methods and hence should not be overlooked, we will not discuss these techniques in this chapter and refer the reader to more comprehensive textbooks for a detailed description of these topics. Intubation itself may be accomplished using different methods including fiberoptic intubation, awake intubation, blind nasal intubation, or retrograde techniques.

Many factors including the severity of the situation, the setting, and the skills of the healthcare provider as well as the factors related to the patient [2, 4] may affect the choice of the airway management modality.

10.2.3 Airway Assessment

When evaluating a patient for airway management, one essential step is to determine whether the patient bears attributes that will make his/her airway difficult to manage. While in elective anesthesia practice the incidence of airway management failure is very low (unpredictably difficult to intubate 0.1–0.4% and unpredictably difficult to oxygenate and ventilate 0.01%) [5], it is probably much more common in the emergency setting. The incidence of rescue cricothyrotomy was reported to be 1% in a cohort of 1288 emergency patients [6]. In a study of 3423 emergency nonoperating room intubations, difficult intubation (Cormack and Lehane grade >3 or >3 intubation attempts) was encountered in about 10% of the cases, almost twice as often as in patients with apparently normal airways scheduled for operation [7, 8]. Several other studies in critically ill patients have corroborated this finding (e.g., 8% [9], 10% [10], and 12% [11]).

While often difficult and sometimes even virtually impossible, assessment of the patient's airway prior to the intervention is necessary and influences the strategy for airway management and the success of the procedure. Anticipating the degree of difficulty will enable the physician to select a potentially successful technique rather than a method which is destined to fail. The goal of this assessment is to determine the risk for difficult mask ventilation (DMV) as well as the risk for difficult intubation (DI).

A number of clinical indicators for DI and DMV have been proposed. Factors pointing to the possibility of DMV include, but is not limited to, age of 55 years, body mass index of >26 kg/m^2, lack of teeth, male gender, and presence of a beard [2].

Mallampati score describes the degree to which visualization of the base of the tongue, faucial pillars, uvula, and posterior pharynx is possible. A Mallampati class III or IV points to a disproportionately large size of the base of the tongue and can predict airway management difficulty. The maneuver is performed with the patient seated, the neck extended, and the tongue protruded. While this is seldom possible or practical in an unresponsive or critical patient, the maneuver can be done with the patient supine using a tongue blade.

The so-called 3-3-2 rule states that a difficult airway can be expected if an adult patient is

unable to open his/her mouth at least three fingerbreadths (about 6 cm), or if the distance from tip of the chin to the hyoid bone is less than three fingerbreadths, or if the distance from the floor of the mouth to the top of the thyroid cartilage is less than three fingerbreadths [12].

Upper airway obstruction or distortion also makes intubation difficult and so does reduced cervical mobility (extension of the atlanto-occipital joint less than 35°), which may be caused by diseases such as rheumatoid arthritis or C-spine immobilization in a trauma victim.

A systematic approach to stratify the risk of DI is the "LEMON law." It has not yet been vigorously validated but is simple and sensible. According to this law, for difficult airway assessment, one should *L*ook externally for risk factors of DI and DMV, *E*valuate the 3-3-2 rule, determine the *M*allampati score, and look for *O*bstruction and *N*eck mobility [13]. Furthermore, difficulty in intubation can be anticipated based on the view obtained during direct laryngoscopy, the so-called Cormack and Lehane classification [14].

While none of these tools has a high positive predictive value, one can expect a straightforward intubation if all the results are negative [2]. Moreover, many of these tests suffer from very poor interobserver reliability [15]. It has been suggested that a combination of multiple tests is a better predictor of difficult intubation than any single test. The predictive value of the risk factors for DI and DMV has commonly been derived from elective situations and their values in the setting of neurocritical patients is unknown.

10.2.4 Organized Approach to Airway Management

Rapid-sequence intubation (RSI) is a logical approach for the majority of ICU patients requiring endotracheal intubation, because they commonly have a full stomach. This procedure requires an organized and orderly approach which allows the physician to be prepared for unforeseen complications.

The discrete steps of RSI can be memorized as seven Ps: *P*reparation, *P*reoxygenation, *P*retreatment, *P*aralysis with induction, *P*rotection and positioning, *P*lacement with proof, and *P*ostintubation management. Every step should be planned and carefully taken.

10.2.4.1 Preparation

Before embarking on the procedure, one should ensure the presence of adequate personnel, optimal patient positioning (proper height of the bed with the wheels locked), sufficient lighting, and availability of the necessary equipment including 100% oxygen, a well-fitting mask with attached bag-valve device, suctioning equipment, a Magill forceps, a laryngoscope with straight and curved blades of various sizes, and oral and nasal airways [2]. In this initial phase of RSI, the details of intubation are planned, the patient is placed on cardiac monitoring and pulse oximetry, and good-quality IV lines are established.

10.2.4.2 Preoxygenation

RSI requires several minutes of apnea before significant oxygen desaturation to less than 90% occurs. This can be achieved by the essential step of preoxygenation, which causes the functional residual capacity of the lungs to be replaced with oxygen and creates an oxygen surplus in both blood and tissues. It should be remembered that a commonly used non-re-breather oxygen mask can deliver concentration in the range of 70–75%. A concentration of 100% can be provided using a ventilation bag and mask placed over the face and nose and the patient taking normal tidal volume breaths for 3–5 min. In cases when this is not feasible, eight rapid, deep breaths from a 100% oxygen source will achieve the goal of preoxygenation.

10.2.4.3 Pretreatment

Several drugs are administered before intubation to mitigate its adverse effects. The most commonly used drugs include *L*idocaine, to blunt the bronchospastic reactivity of the airways or intracranial pressure (ICP) response, *O*piods (mainly fentanyl) to mitigate the sympathetic responses, *A*tropine, for children 10 years old or younger, and a small *D*efasiculating dose of a competitive neuromuscular blocker. The mnemonic *LOAD* can be used to remember the drugs. A 3-min interval is desirable between pretreatment and induction.

10.2.4.4 Paralysis with Induction

In this step, prompt loss of consciousness is produced by intravenous (IV) administration of a potent, rapidly acting sedative (induction) agent. Immediately following this, a neuromuscular blocking agent (NMBA), usually succinylcholine, is given via IV push. It should be noted that in critically ill patients there might be contraindications to the use of succinylcholine. In these cases, the physician should be aware of the alternatives and use them judiciously.

10.2.4.5 Protection and Positioning

Twenty to thirty seconds after the receipt of the sedative agent and the neuromuscular blocker, apnea will ensue and consciousness will be lost. The patient should then be positioned for intubation. Head extension with neck flexion is often recommended, but simple head extension or extension of both head and neck may be as effective [16, 17].

Backward application of firm pressure over cricoids cartilage, referred to as Sellick's maneuver, has traditionally been recommended; its alleged benefit of minimizing the risk of regurgitation, however, has been challenged recently by two systematic reviews. There are even claims that it may make laryngoscopy or intubation difficult [18]. Therefore, the maneuver is optional and should be applied selectively.

10.2.4.6 Placement with Proof

Approximately 45 s after the administration of the NMBA, intubation should be attempted. Many physicians test the patient for flaccidity by moving the patient's mandible to ensure sufficient relaxation of the musculature, which is important for allowing better access to the airway.

The intubator visualizes the glottis aperture and places the tube under direct visualization. The stylet is then removed and the cuff inflated. Confirmation of the correct position of the tube should be undertaken employing one of the methods described below.

The choice of blade shape depends on the operator's preference, but direct laryngoscopy using a straight blade probably requires less force and head extension [19]. Plastic single-use blades, in comparison to metal reusable blades, are inexpensive and carry a lower risk of infection, but they are less efficient in critical care settings and have been shown to result in a significantly higher rate of failed intubation on the first attempt [20]. Several other laryngoscope blades have been introduced, but there are no data on their utility in the ICU. Some data, however, suggest that video-assisted or fiberoptic devices can lead to better glottic visualization than conventional blades [21, 22].

Confirmation of Proper Tube Positioning

Once the endotracheal tube (ETT) is inserted, the physician should ascertain the position of the tube within the trachea. Common methods to obtain this goal include bilateral auscultation of the lungs and measurement (or detection) of end-tidal carbon dioxide (CO_2). None of these methods is flawless, and fiberoptic bronchoscopy is the only way to document correct position of the tube with absolute certainty [2]. Esophageal intubation can lead to serious consequences, and hence auscultation of the chest should not be the only way to confirm tube position.

Capnography, the noninvasive measurement of the partial pressure of CO_2 in exhaled breath, is the most reliable indicator of proper endotracheal tube placement and is an emerging standard of care in intensive care units. In patients with adequate tissue perfusion, end-tidal CO_2 detector can be used to confirm endotracheal tube position. But in patients with markedly decreased perfusion such as those in cardiac arrest it may be less accurate. Use of capnography at the time of intubation is widely accepted as an appropriate standard. The Intensive Care Society has strongly recommended the use of capnography during tracheal intubation in the critically ill patients [23]. Despite this recommendation, a survey demonstrated that in only one-third of ICUs in the United Kingdom, capnography was invariably used for confirmation of the tube placement [24]. This infrequent use of capnography in the ICUs has also been echoed in other studies [25]. In a study on ICU patients, Cook et al. showed that failure to use capnography contributed to 17 outcomes of death or brain injury [26].

10.2.4.7 Postintubation Management

After ETT has been inserted and secured in place, a chest radiograph needs to be obtained to rule out main stem intubation. In addition, opioid analgesics and benzodiazepines should be administered to improve patient comfort and facilitate mechanical ventilation.

10.2.5 Complications

According to a prospective study in England and Wales, over 1000 airway incidents in the ICU were reported between 2005 and 2007, 18% of which occurred at intubation [25]. When facing a difficult airway, the physician can expect complications at a rate of between 5% and 40% [6]. Emergent airway management in the critical care setting also frequently becomes complicated [2]. The risk of intubation-associated serious complications in critically ill patients is higher than patients undergoing elective intubation [4], but the exact incidence of RSI-related complications in the ICU is unknown and thought to be underreported. Complications are reported at rates ranging from 4% to 39% [27, 28]. The rate of complications increases in cases where more than two intubation attempts are required [29].

Adverse consequences of endotracheal intubation can be generally categorized into traumatic complications, hemodynamic alterations, and other complications.

Some of the most common traumatic complications comprise dental damage, vocal cord injury, laceration of pharynx, larynx, trachea, or esophagus, and even dislocation of arytenoids cartilage.

Occurrence of an episode of hypotension or at least a drop in blood pressure almost always follows intubation. Depending on the definition of severe hypotension, its incidence following intubation is 6–25% [27, 30, 31]. In patients with CNS disorders in whom cerebral autoregulation is impaired, even a small systemic hypotension can decrease cerebral perfusion pressure and hence be detrimental. This complication is seen more frequently in patients with a baseline mean arterial pressure <70 mmHg, age >50 years, more severe underlying disease, and when propofol or high doses of fentanyl are used for induction [32]. Etomidate is less vascular active and so more suitable for induction of cerebrovascular patients, but it leads to adrenocortical suppression [33] and may increase mortality in patients with septic shock [34]. Ketamine is another alternative induction agent and has no depressing circulatory effects but is thought to be associated with increases in ICP, although this was not confirmed in several studies. Both ketamine and etomidate reduce the incidence of severe hypotension compared to thiopental or propofol [35].

The depolarizing agent succinylcholine induces small increases in ICP. This is especially true in patients with traumatic brain injury (TBI). However, in a recent Cochrane analysis of 50 good-quality studies on the subject the authors concluded that succinylcholine created superior intubation conditions to nondepolarizing muscular blocker rocuronium in achieving excellent and clinically acceptable intubating conditions [36].

Other complications of intubation include, but are not limited to, severe hypoxemia, arrhythmias, esophageal intubation, aspiration, cardiac arrest (at a rate of 2–3% [37, 38]), and even death.

10.3 Specific Considerations in Neurocritically Ill Patients

Respiratory failure in neurologic patients may result from conditions not directly related to their neurological disease. Examples include chest contusions in the major trauma patient with TBI, pneumothorax after central line placement in a stroke patient, respiratory depression by sedatives and analgetics, and so on. On the other hand, respiratory compromise in this group of patients may be due to disease-related causes, which in turn may be central or peripheral.

Central respiratory failure may be caused by impaired respiratory coordination or reduced airway protection due to loss of pharyngeal muscle tone or loss of protective reflexes. On the other hand, lung mechanics may be severely impaired in peripheral nervous system diseases such as

Guillain-Barré syndrome, amyotrophic lateral sclerosis, or myasthenia gravis crisis.

Basically, the general criteria for intubation also apply to these patients as well. While the details of intubation in this group of patients have not been systematically studied, some specific considerations deserve mention.

10.3.1 Specific Situations

10.3.1.1 Prehospital Airway Management

In the austere environment of the field, where limited resources are available, several options exist for creating a definitive airway. While orotracheal intubation is the most common method of intubation in the prehospital setting [39–41], digital intubation, nasotracheal intubation, use of LMAs, lighted stylet, and Combitube are also some other available options. Emergency medical service (EMS) personnel should be trained to master these techniques. Conditions which preclude direct laryngoscopy are frequently encountered in the field, and digital intubation is a useful alternative in these situations [42]. Nasotracheal intubation has the advantage of not requiring pharmacological assistance, but it results in more agitation and cannot be used in patients with mid-facial fractures or apnea [1].

In children, prehospital intubation does not improve survival or neurological outcome as compared to BVM ventilation [43, 44]. Although prehospital intubation using RSI has proved to be highly successful [45], some studies have pointed to a negative effect on patient outcome when it is used by EMS personnel [46, 47]. This finding may be justified by the extra time spent in the field to intubate or the unintentional hyperventilation with subsequent cerebral vasoconstriction and reduction in brain perfusion [48]. A definite conclusion is yet to be made.

10.3.1.2 Trauma Patients

Many trauma patients benefit from maintenance of a patent and secured airway to provide adequate oxygenation and prevent aspiration. Major trauma patients comprise a sizable proportion of intubations. In the National Emergency Airway Registry (NEAR), 31% of the patients were trauma cases [6]. However, in this setting, many trauma-related factors make definitive airway management technically more difficult and pose unique challenges; these include a combative head injury patient, a facial trauma patient, extraluminal compression of the airway due to hematoma, a potential cervical spine injury, and finally a full stomach [49]. Inadequate airway management is the primary cause of preventable death in trauma patients [50].

While many conditions such as shock, disrupted airway anatomy, and chest trauma in trauma may impact the airway management, we will focus on two important aspects, namely, spinal cord injury and traumatic brain injury.

Spinal Cord Injury

Quite often, the results of initial radiographic studies are unknown when a critically ill patient with potential cervical spine injury requires emergent airway management. Under these circumstances, cervical spine precautions should be maintained throughout the procedure. This requires careful planning and significant experience. However, neurologic deterioration is not common in patients with cervical spine injuries who undergo endotracheal intubation [51–55].

During airway instrumentation in patient with suspected cervical spine injury, it is recommended that an assistant helps with the manual in-line immobilization of the neck. This technique has proved to be safe and effective for the prevention of morbidity. If the victim is wearing a cervical collar, the anterior portion should be removed as manual in-line immobilization is maintained [21, 56]. This method is associated with less spinal movement than cervical collar immobilization.

No conclusive evidence exists in the literature to allow favoring one endotracheal intubation technique over the other, some authors strongly suggest that awake fiberoptic intubation, if feasible, should be considered in the setting of limited neck mobility and cervical spine injury [2].

Traumatic Brain Injury

In patients with severe head injury, maintenance of cerebral perfusion is of paramount importance. Hypoxemia and hypotension increase the mortality in patients with TBI and should be avoided at all costs. It has been proved in several studies that patients with TBI benefit from intubation in the prehospital or early emergency department phase. Therefore, intubation has been included in the American Association of Neurologic Surgery guideline and the guideline of the Brain Trauma Foundation for TBI patients with a Glasgow Coma Scale (GCS) ≤ 8 [57, 58]. In patients with head injury whose GCS score is above 8, the threshold for intubation should be lowered if concomitant severe injury exists, the patient must leave the controlled environment of ED, or the patient is clinically deteriorating.

However, intubating head trauma patients can be very challenging. Laryngoscopy, both directly and through a sympathetically mediated response, may raise ICP. Pretreatment with lidocaine and fentanyl attenuates the potential increase in ICP. The choice of the medications is also affected by the patient's condition. Etomidate is the preferred drug for induction since it maintains stable hemodynamics and protects the brain. Thiopental bears cerebroprotective properties but is a myocardial depressant and vasodilator and, hence, may not be an appropriate choice in trauma patients. Although controversial, ketamine is believed to increases ICP and is better avoided in patients with TBI.

In cases of major facial or airway trauma, one should soon proceed to surgical airway techniques such as cricothyroidotomy.

10.3.1.3 Stroke

Patients with ischemic stroke, especially those with large vessel involvement, may undergo intubation. This occurs increasingly often in those receiving endovascular revascularization. Ischemic stroke may be complicated by respiratory impairment due to the disturbances in brainstem control of respiration, diminished consciousness, or aspiration or systemic complications such as pneumonia, pulmonary embolism, or pulmonary edema. Inadequate ventilation due to a reduced level of consciousness and failure to maintain a patent airway are the most common reasons for endotracheal intubation and mechanical ventilation in these patients [59, 60].

The need for intubation worsens the prognosis of the patients with acute stroke, about 50% of them survive 30 days and 30% survive 1 year [61]. Low GCS score at intubation and absence of pupillary light reflexes predict a poorer prognosis and mortality. More than two-thirds of the survivors, however, regain normal activities of daily living with mild to moderate impairment [62]. After hemispheric ischemic stroke, the need for mechanical ventilation is associated with an increased rate of mortality [63, 64].

RSI is the preferred method of airway management in stroke patients [65]. Depolarizing agents, fentanyl, lidocaine, and propofol have not been shown to be deleterious to the stroke patient. According to AHA/ASA scientific statement guideline [66], the $PaCO_2$ should be corrected to normocarbia (Class IIa; Level of Evidence C).

10.3.1.4 Raised Intracranial Pressure

ICP may increase as a result of injury or medical problems. Raised ICP leads to diminished cerebral perfusion pressure, which is detrimental to the viability and function of the brain. During intubation, a significant afferent discharge due to the stimulation of the supraglottic larynx results in sympathetic activity and catecholamine surge. Administration of a single 3 μg/kg dose of fentanyl over 30–60 s as a pretreatment drug in patients with elevated ICP can blunt this reflex sympathetic response to laryngoscopy (RSRL). Even when RSRL is blunted, laryngoscopy or insertion of ETT may directly increase the ICP. This reflex ICP response to laryngoscopy can be blunted by IV administration of lidocaine during pretreatment phase.

Rapacuronium and rocuronium are competitive (nondepolarizing) NMBAs and are preferred to succinylcholine because they do not cause ICP elevation. In cases where competitive NMBAs are used, no "defasciculating" dose will be required. Both drugs have a rapid onset of action and result in a limited duration of paralysis.

10.3.1.5 Status Epilepticus

Patients with status epilepticus need to be intubated if the seizures cannot be stopped during the first steps of treatment. Otherwise, nasopharyngeal airway placement would suffice. Furthermore, respiratory depression in patients receiving excessive doses of benzodiazepines can lead to early need for intubation [67]. If rapid sequence induction is planned, short-acting paralytic agents should be employed to ensure that ongoing seizure activity is not masked. Continuous EEG monitoring may become necessary especially if long-acting paralytics are used.

Conclusion

Airway management in the neurological/neurosurgical patients relies mainly on basic principles of airway intervention, but several specific recommendations need to be borne in mind. These include careful attention to indications and contraindications for intervention, selection of the optimal technique, and appropriate choice of medications. Physicians responsible for taking care of the neurocritically ill patients should be well equipped with this knowledge and expertise.

References

1. Roppolo LP, Walters K. Airway management in neurological emergencies. Neurocrit Care. 2004;1(4):405–14.
2. Walz JM, Zayaruzny M, Heard SO. Airway management in critical illness. Chest. 2007;131(2):608–20. Review
3. Chakrabarti B, Calverley PM. Management of acute ventilatory failure. Postgrad Med J. 2006; 82(969):438–45.
4. Nolan JP, Kelly FE. Airway challenges in critical care. Anaesthesia. 2011;66(2):81–92.
5. Murphy MF, Doyle DJ. Evaluation of the airway. In: Hung O, Murphy MF, editors. Management of the difficult and failed airway. 2nd ed. New York: McGraw Hill Professional; 2011.
6. Brown CA 3rd, Bair AE, Pallin DJ, Walls RM; NEAR III Investigators. Techniques, success, and adverse events of emergency department adult intubations. Ann Emerg Med. 2015;65(4):363–70.
7. Jaber S, Jung B, Corne P, Sebbane M, Muller L, Chanques G, Verzilli D, Jonquet O, Eledjam JJ, Lefrant JY. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. Intensive Care Med. 2010;36(2):248–55.
8. Rabinstein AA, Wijdicks EF. Outcome of survivors of acute stroke who require prolonged ventilatory assistance and tracheostomy. Cerebrovasc Dis. 2004; 18(4):325–31.
9. Berrouschot J, Rössler A, Köster J, Schneider D. Mechanical ventilation in patients with hemispheric ischemic stroke. Crit Care Med. 2000;28(8):2956–61.
10. Wijdicks EF, Scott JP. Causes and outcome of mechanical ventilation in patients with hemispheric ischemic stroke. Mayo Clin Proc. 1997;72(3):210–3.
11. Mayer SA, Copeland D, Bernardini GL, Boden-Albala B, Lennihan L, Kossoff S, Sacco RL. Cost and outcome of mechanical ventilation for life-threatening stroke. Stroke. 2000;31(10):2346–53.
12. Reed MJ, Dunn MJ, McKeown DW. Can an airway assessment score predict difficulty at intubation in the emergency department? Emerg Med J. 2005; 22(2):99–102.
13. Walls RM, Murphy M. Identification of difficult and failed airway. In: Walls RM, Murphy M, editors. Manual of emergency airway management. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2012.
14. Gupta S, Rajesh Sharma KR, Jain D. Airway assessment : predictors of difficult airway. Indian J Anaesth. 2005;49(4):257–62.
15. Finucane BT, Tsui BCH, Santora AH. Evaluation of the airway. In: Finucane BT, Tsui BCH, Santora AH, editors. Principles of airway management. 4th ed. New York: Springer New York; 2011.
16. Lee L, Weightman WM. Laryngoscopy force in the sniffing position compared to the extension-extension position. Anaesthesia. 2008;63(4):375–8.
17. Adnet F, Baillard C, Borron SW, Denantes C, Lefebvre L, Galinski M, Martinez C, Cupa M, Lapostolle F. Randomized study comparing the "sniffing position" with simple head extension for laryngoscopic view in elective surgery patients. Anesthesiology. 2001;95(4):836–41.
18. El-Orbany M, Woehlck H, Salem MR. Head and neck position for direct laryngoscopy. Anesth Analg. 2011;113(1):103–9.
19. Hastings RH, Hon ED, Nghiem C, Wahrenbrock EA. Force, torque, and stress relaxation with direct laryngoscopy. Anesth Analg. 1996;82(3):456–61.
20. Amour J, Marmion F, Birenbaum A, Nicolas-Robin A, Coriat P, Riou B, Langeron O. Comparison of plastic single-use and metal reusable laryngoscope blades for orotracheal intubation during rapid sequence induction of anesthesia. Anesthesiology. 2006; 104(1):60–4.
21. Watts AD, Gelb AW, Bach DB, Pelz DM. Comparison of the Bullard and Macintosh laryngoscopes for endo-

tracheal intubation of patients with a potential cervical spine injury. Anesthesiology. 1997;87(6):1335–42.
22. Sun DA, Warriner CB, Parsons DG, Klein R, Umedaly HS, Moult M. The GlideScope Video Laryngoscope: randomized clinical trial in 200 patients. Br J Anaesth. 2005;94(3):381–4.
23. Intensive Care Society. Standards for capnography in critical care. London: Intensive Care Society. 2009. Available online at: http://members.ics.ac.uk/ICS/guidelines-and-standards.aspx.
24. Georgiou AP, Gouldson S, Amphlett AM. The use of capnography and the availability of airway equipment on Intensive Care Units in the UK and the Republic of Ireland. Anaesthesia. 2010;65(5):462–7.
25. Thomas AN, McGrath BA. Patient safety incidents associated with airway devices in critical care: a review of reports to the UK National Patient Safety Agency. Anaesthesia. 2009;64(4):358–65.
26. Cook TM, Woodall N, Harper J, Benger J; Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. Br J Anaesth. 2011;106(5):632–42.
27. Griesdale DE, Bosma TL, Kurth T, Isac G, Chittock DR. Complications of endotracheal intubation in the critically ill. Intensive Care Med. 2008; 34(10):1835–42.
28. Martin LD, Mhyre JM, Shanks AM, Tremper KK, Kheterpal S. 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. Anesthesiology. 2011;114(1):42–8.
29. Mort TC. Emergency tracheal intubation: complications associated with repeated laryngoscopic attempts. Anesth Analg. 2004;99(2):607–13.
30. Jaber S, Amraoui J, Lefrant JY, Arich C, Cohendy R, Landreau L, Calvet Y, Capdevila X, Mahamat A, Eledjam JJ. Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. Crit Care Med. 2006;34(9):2355–61.
31. Mayo PH, Hegde A, Eisen LA, Kory P, Doelken P. A program to improve the quality of emergency endotracheal intubation. J Intensive Care Med. 2011; 26(1):50–6.
32. Gaba DM, Howard SK, Small SD. Situation awareness in anesthesiology. Hum Factors. 1995; 37(1):20–31.
33. Jabre P, Combes X, Lapostolle F, Dhaouadi M, Ricard-Hibon A, Vivien B, Bertrand L, Beltramini A, Gamand P, Albizzati S, Perdrizet D, Lebail G, Chollet-Xemard C, Maxime V, Brun-Buisson C, Lefrant JY, Bollaert PE, Megarbane B, Ricard JD, Anguel N, Vicaut E, Adnet F; KETASED Collaborative Study Group. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. Lancet. 2009; 374(9686):293–300.
34. Cuthbertson BH, Sprung CL, Annane D, Chevret S, Garfield M, Goodman S, Laterre PF, Vincent JL, Freivogel K, Reinhart K, Singer M, Payen D, Weiss YG. The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock. Intensive Care Med. 2009;35(11):1868–76.
35. Jabre P, Avenel A, Combes X, Kulstad E, Mazariegos I, Bertrand L, Lapostolle F, Adnet F. Morbidity related to emergency endotracheal intubation–a substudy of the KETAmine SEDation trial. Resuscitation. 2011;82(5):517–22.
36. Tran DT, Newton EK, Mount VA, Lee JS, Wells GA, Perry JJ. Rocuronium versus succinylcholine for rapid sequence induction intubation. Cochrane Database Syst Rev. 2015;(10):CD002788.
37. Schwartz DE, Matthay MA, Cohen NH. Death and other complications of emergency airway management in critically ill adults. A prospective investigation of 297 tracheal intubations. Anesthesiology. 1995;82(2):367–76.
38. Mort TC. The incidence and risk factors for cardiac arrest during emergency tracheal intubation: a justification for incorporating the ASA Guidelines in the remote location. J Clin Anesth. 2004;16(7):508–16.
39. Atherton GL, Johnson JC. Ability of paramedics to use the Combitube in prehospital cardiac arrest. Ann Emerg Med. 1993;22(8):1263–8.
40. Rumball CJ, MacDonald D. The PTL, Combitube, laryngeal mask, and oral airway: a randomized prehospital comparative study of ventilatory device effectiveness and cost-effectiveness in 470 cases of cardiorespiratory arrest. Prehosp Emerg Care. 1997;1(1):1–10.
41. Vollmer TP, Stewart RD, Paris PM, Ellis D, Berkebile PE. Use of a lighted stylet for guided orotracheal intubation in the prehospital setting. Ann Emerg Med. 1985;14(4):324–8.
42. Butler KH, Clyne B. Management of the difficult airway: alternative airway techniques and adjuncts. Emerg Med Clin North Am. 2003;21(2):259–89.
43. Cooper A, DiScala C, Foltin G, Tunik M, Markenson D, Welborn C. Prehospital endotracheal intubation for severe head injury in children: a reappraisal. Semin Pediatr Surg. 2001;10(1):3–6.
44. Gausche M, Lewis RJ, Stratton SJ, Haynes BE, Gunter CS, Goodrich SM, Poore PD, McCollough MD, Henderson DP, Pratt FD, Seidel JS. Effect of out-of-hospital pediatric endotracheal intubation on survival and neurological outcome: a controlled clinical trial. JAMA. 2000;283(6):783–90. Erratum in: JAMA 2000:283(24):3204.
45. Bulger EM, Copass MK, Maier RV, Larsen J, Knowles J, Jurkovich GJ. An analysis of advanced prehospital airway management. J Emerg Med. 2002;23(2):183–9. PubMed PMID: 12359289
46. Davis DP, Hoyt DB, Ochs M, Fortlage D, Holbrook T, Marshall LK, Rosen P. The effect of paramedic rapid sequence intubation on outcome in patients with severe traumatic brain injury. J Trauma. 2003; 54(3):444–53.

47. Bochicchio GV, Ilahi O, Joshi M, Bochicchio K, Scalea TM. Endotracheal intubation in the field does not improve outcome in trauma patients who present without an acutely lethal traumatic brain injury. J Trauma. 2003;54(2):307–11.
48. Bochicchio GV, Scalea TM. Is field intubation useful? Curr Opin Crit Care. 2003;9(6):524–9.
49. Langeron O, Birenbaum A, Amour J. Airway management in trauma. Minerva Anestesiol. 2009; 75(5):307–11.
50. Khan RM, Sharma PK, Kaul N. Airway management in trauma. Indian J Anaesth. 2011;55(5):463–9.
51. Lord SA, Boswell WC, Williams JS, Odom JW, Boyd CR. Airway control in trauma patients with cervical spine fractures. Prehosp Disaster Med. 1994;9(1):44–9.
52. Norwood S, Myers MB, Butler TJ. The safety of emergency neuromuscular blockade and orotracheal intubation in the acutely injured trauma patient. J Am Coll Surg. 1994;179(6):646–52.
53. Suderman VS, Crosby ET, Lui A. Elective oral tracheal intubation in cervical spine-injured adults. Can J Anaesth. 1991;38(6):785–9.
54. Talucci RC, Shaikh KA, Schwab CW. Rapid sequence induction with oral endotracheal intubation in the multiply injured patient. Am Surg. 1988;54(4):185–7.
55. Wright SW, Robinson 2nd GG, Wright MB. Cervical spine injuries in blunt trauma patients requiring emergent endotracheal intubation. Am J Emerg Med. 1992;10(2):104–9.
56. Majernick TG, Bieniek R, Houston JB, Hughes HG. Cervical spine movement during orotracheal intubation. Ann Emerg Med. 1986;15(4):417–20.
57. Badjatia N, Carney N, Crocco TJ, Fallat ME, Hennes HM, Jagoda AS, Jernigan S, Letarte PB, Lerner EB, Moriarty TM, Pons PT, Sasser S, Scalea T, Schleien CL, Wright DW; Brain Trauma Foundation; BTF Center for Guidelines Management. Guidelines for prehospital management of traumatic brain injury 2nd edition. Prehosp Emerg Care. 2008;12:S1–52.
58. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS, Carney NA, Ghajar J. Guidelines for the management of severe traumatic brain injury. Introduction. J Neurotrauma. 2007;24 Suppl 1:S1–2. Erratum in: J Neurotrauma. 2008;25(3):276–8.
59. Berrouschot J, Sterker M, Bettin S, Köster J, Schneider D. Mortality of space-occupying ('malignant') middle cerebral artery infarction under conservative intensive care. Intensive Care Med. 1998;24(6):620–3.
60. Malm J, Bergenheim AT, Enblad P, Hårdemark HG, Koskinen LO, Naredi S, Nordström CH, Norrving B, Uhlin J, Lindgren A. The Swedish Malignant Middle cerebral artery Infarction Study: long-term results from a prospective study of hemicraniectomy combined with standardized neurointensive care. Acta Neurol Scand. 2006;113(1):25–30.
61. Milhaud D, Popp J, Thouvenot E, Heroum C, Bonafé A. Mechanical ventilation in ischemic stroke. J Stroke Cerebrovasc Dis. 2004;13(4):183–8.
62. Santoli F, De Jonghe B, Hayon J, Tran B, Piperaud M, Merrer J, Outin H. Mechanical ventilation in patients with acute ischemic stroke: survival and outcome at one year. Intensive Care Med. 2001;27(7):1141–6.
63. Steiner T, Mendoza G, De Georgia M, Schellinger P, Holle R, Hacke W. Prognosis of stroke patients requiring mechanical ventilation in a neurological critical care unit. Stroke. 1997;28(4):711–5.
64. Golestanian E, Liou JI, Smith MA. Long-term survival in older critically ill patients with acute ischemic stroke. Crit Care Med. 2009;37(12):3107–13.
65. Seder DB, Jagoda A, Riggs B. Emergency neurological life support: airway, ventilation, and sedation. Neurocrit Care. 2015;23:S5–22.
66. Wijdicks EF, Sheth KN, Carter BS, Greer DM, Kasner SE, Kimberly WT, Schwab S, Smith EE, Tamargo RJ, Wintermark M; American Heart Association Stroke Council. Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(4):1222–38.
67. Spatola M, Alvarez V, Rossetti AO. Benzodiazepine overtreatment in status epilepticus is related to higher need of intubation and longer hospitalization. Epilepsia. 2013;54(8):e99–e102.

Postoperative Pain Management After Craniotomy

11

Ramani Vijayan and Loh Pui San

11.1 Introduction

It had been a common belief in the past that patients undergoing craniotomy experience minimal pain in the postoperative period. This probably goes back to a study conducted in the 1970s [1]. However, several surveys in the last two decades have shown that many patients suffer from moderate to severe pain following craniotomy. Pain following craniotomy is common. De Benedittis et al. from the Institute of Neurosurgery in Milan assessed important pain variables in 37 consecutive patients who underwent various brain neurosurgical procedures [2]. Pain intensity was recorded regularly over 48 h following surgery. Postoperative pain was more common than generally assumed (60%), and the intensity was moderate to severe. Pain was predominantly superficial (86%) suggesting that it was somatic rather than visceral in origin. Subtemporal and suboccipital surgical routes yielded the highest incidence of postoperative pain. That site of surgery as an important variable was shown by Thibault et al. in a retrospective study of 299 patients, designed to assess the intensity of postoperative pain in relation to the location of craniotomy [3]. Frontal craniotomy was associated with the lower pain scores than those who underwent posterior fossa craniotomy and required significantly less opioid analgesics.

Post-operative pain management following intracranial surgery has not been well studied and there is a lack of good evidence-based guidelines to provide appropriate postoperative analgesia protocols for these neurosurgical patients. The study of post-craniotomy pain can be challenging because of several variables such as intraoperative opioids, subjectivity of pain assessment techniques and primarily the patient's neurological status. Opioid administration after major intracranial surgery is limited by both a presumed lack of need and a concern that opioids will adversely affect the postoperative neurological status. This attitude can be seen in the surveys of post-craniotomy analgesic practices in neurosurgical centres. In a 1996 survey, Stoneham and Walters sent a postal questionnaire to 183 consultant members of Neuroanaesthesia Society of Great Britain [4]. They received responses from 110 neuroanaesthetists from 37 different centres. Intramuscular (IM) codeine phosphate or dihydrocodeine was the mainstay of postoperative analgesia for 97% of neuroanaesthetists despite the fact that over half of them thought that analgesia was inadequate. Only four of them would consider using stronger opioids because of fears of respiratory depression and sedation, yet all except one used opioids intraoperatively. Postoperative analgesia was perceived to be

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inadequate, yet traditional prejudice against opioids prevented its use.

Ten years later, another survey of current practices in British neurosurgical centres showed not much difference in the way pain was addressed following craniotomy [5]. A postal questionnaire was sent to every neurosurgical unit within the UK enquiring about the current, standard analgesic practices following craniotomy. The response rate was 70%. Intramuscular codeine phosphate, a weak opioid, was found to be the principal first-line analgesic post-craniotomy. Only three centres used morphine as the first-line analgesic and only one centre used patient-controlled analgesia (PCA). This survey demonstrates that codeine phosphate continues to be the first-line analgesic of choice, at least in the UK. Codeine is a weak opioid and only 5–15% is converted to morphine. The enzyme that catalyses the demethylation of codeine to morphine exhibits genetic polymorphism resulting in about 15% of Caucasians experiencing no analgesic effect with it [6]. In addition, analgesics were prescribed regularly in only half the units surveyed.

In a more recent survey of Canadian neurosurgeons, with regard to pain management in post-craniotomy patients, codeine was also the most prescribed first-line analgesic (59%) followed by morphine (38%) [7]. The use of a second-line opioid was significantly higher among codeine prescribers compared to morphine. The majority of respondents reported a high level of satisfaction with their current choice of analgesia; they predominantly described their practice as personal preference or protocol driven rather than evidence based.

11.2 Treatment of Acute Postoperative Pain After Intracranial Surgery

11.2.1 Opioids and Patient-Controlled Analgesia

With the increasing realization that patients were suffering from inadequate analgesia following craniotomy, there have been several studies in the last two decades to improve it, by including opioids as first line in pain management. In an early study, nearly 20 years ago, Stoneham et al. compared patient-controlled analgesia (PCA) with morphine with the traditional intramuscular (IM) codeine phosphate [8]. In a prospective randomized trial of 30 patients, they compared PCA morphine, 1 mg bolus with 10 min lockout and no background infusion with IM codeine. There was a wide variation in the amounts of morphine requested in the PCA group with some reduction in pain scores. There were no significant differences between the two groups with respect to nausea and vomiting, sedation scores and respiratory rate and no major adverse effects in either group. They concluded that PCA morphine can be an alternative to IM codeine. Tanskanen and group in Finland evaluated the feasibility and safety of PCA with oxycodone in neurosurgical patients and compared the efficacy of paracetamol with ketoprofen [9]. In a group of 45 patients who were randomized to receive either paracetamol 1000 mg or ketoprofen 100 mg three times, all patients were allowed to use PCA oxycodone boluses of 0.03 mg/kg with a maximum of three times an hour with a lockout time of 10 min. The ketoprofen group required less oxycodone with comparable pain scores and both groups were satisfied with pain relief. There was no progressive hypoventilation, desaturation or excessive sedation with the use of oxycodone.

The above two studies showed that PCA morphine/oxycodone did not produce any adverse effects. However, the effect on arterial CO_2 levels was not known. Hence, Sudheer and colleagues compared the analgesic efficacy and respiratory effects of morphine, tramadol and codeine after craniotomy [10]. Sixty patients were randomly allocated to receive morphine PCA, tramadol PCA or codeine phosphate 60 mg intramuscularly following craniotomy. Baseline values of pain and sedation scores and arterial CO_2 tension were recorded at the time of first analgesic administration and at 30 min, 1, 4, 8, 12, 18 and 24 h. Patient satisfaction was assessed at 24 h. There were no differences in $PaCO_2$ or sedation scores between groups at any time, but in all

three groups, some patients had increased $PaCO_2$ levels greater than 1 kPa. Morphine produced significantly better analgesia than tramadol at all time points ($p < 0.005$) and better analgesia than codeine at 4, 12 and 18 h. Patients were more satisfied with morphine than codeine and tramadol ($p < 0.001$). In addition, vomiting and retching was noted in 50% of patients on tramadol. Tramadol has been advocated by some due to its dual mechanism of action and less incidence of sedation, but it showed that it had a higher incidence of vomiting, which is not suitable for patients following craniotomy.

Despite this, tramadol continued to be evaluated for postoperative pain management. Rahimi et al. conducted a randomized, blinded prospective study to evaluate the efficacy of tramadol as an alternative strategy for post-craniotomy pain management [11]. They found the group of patients assigned to tramadol and opioids had better pain control, reduced length of hospital stay than the group assigned to paracetamol and opioids. Besides morphine, the shorter-acting fentanyl has been used recently to evaluate its efficacy for neurosurgical patients who have undergone intracranial surgery. Morad et al. hypothesized that intravenous PCA would safely and more effectively treat postoperative craniotomy pain than conventional as needed (PRN) therapy [12]. Following a standardized course of general anaesthesia, adult patients who underwent elective supratentorial intracranial surgery were randomized to receive either PRN intravenous fentanyl 5–50 μg every 30 min or PCA fentanyl 0.5 μg/kg every 15 min (maximum 50 μg fentanyl/dose; four doses per hour). The authors measured pain (self-reported pain scores), sedation (Ramsay Sedation Scale scores), Glasgow Coma Scale scores, fentanyl use and major adverse events (excessive sedation, respiratory rate, nausea, vomiting hourly). Sixty-four patients with a mean age of 48 years were randomized to receive PCA or PRN fentanyl. Patients receiving PCA had significantly lower pain scores than those receiving IV, PRN fentanyl. They also received significantly more fentanyl than the PRN group. There were no differences between the two groups regarding the number of patients with adverse events. They concluded that IV PCA with fentanyl was an effective method of pain relief.

Following their success, this same group studied patients who underwent posterior fossa surgery, which often produces more intense postoperative pain [13]. They therefore designed a prospective, randomized controlled trial, with a 1:1 allocation ratio to evaluate whether IV PCA would lead to reductions in postoperative pain when compared to nurse-administered PRN therapy. Eighty patients were randomized to two arms. One group to receive PCA fentanyl 0.5 μg/kg/dose with a maximal dose limit of 50 μg and a 15-min lockout interval, while the other group received fentanyl 25–50 μg every 30 min, PRN. Patients in the PCA group reported less pain at rest ($p = 0.003$) and received more fentanyl than the PRN group ($p = 0.002$). There were no differences in side effects and no adverse effects related to analgesic therapy. All patients were also treated with paracetamol, local anaesthetic nerve blockade and anti-inflammatory steroids as well as opioids. The limitation of this study is that it was done at a single centre with a dedicated critical care unit, and it was not specifically designed to access the safety of IV PCA.

11.2.2 Paracetamol

Paracetamol is used regularly as part of multimodal analgesia following craniotomy to reduce opioid requirements. Paracetamol alone is not adequate to control postoperative pain in these patients. Verchere et al. randomized patients into three groups: one group was given paracetamol, nalbuphine was added to the second group and tramadol was added to the third group [14]. Inclusions into the paracetamol group were stopped after eight patients, as pain relief was insufficient with paracetamol alone. Addition of either nalbuphine or tramadol was deemed to be necessary to achieve adequate analgesia. Paracetamol continues to be part of multimodal analgesia and one needs to be careful not to exceed 4 g/day.

11.2.3 Coxibs/Non-selective NSAIDs

The addition of ketoprofen was shown to be more effective than paracetamol in reducing PCA opioids following surgery [9]. Diclofenac sodium has also been used to improve pain relief and improve patient comfort after major intracranial surgery [15]. There is, however, a concern about using non-selective NSAIDs following neurosurgery as the cyclooxygenase enzyme-1 (COX-1) inhibitor component of the drug can lead to intracranial bleeding. In a large, single-centre, retrospective cohort study of 6668 cases over 5 years, there was an association between the development of postoperative haematoma and the use of aspirin or non-selective NSAIDs, which the authors concluded was an avoidable risk factor in 75% of the cases [16].

With the availability of the COX-2 selective drugs (coxibs), there was renewed enthusiasm to use them to reduce pain following surgery. However, a single dose of parecoxib did not show any benefit over placebo in the first 24 h regarding pain scores, morphine consumption or analgesia-related adverse effects in one study [17], when scalp infiltration, paracetamol and morphine was used in both groups. In an earlier study, Jones and colleagues from Melbourne administered a single dose of parecoxib 40 mg at dural closure and only found some pain reduction at 6 and 12 h with a only a modest impact on overall postoperative analgesia [18]. Perhaps a single dose is not adequate, and it may need to be repeated at 12 h for better efficacy.

11.2.4 Scalp Infiltration with Local Anaesthetics (Regional Scalp Blocks)

In efforts to reduce the need for opioids in the postoperative period, regional scalp blocks have been tried to improve pain relief. Most neurosurgeons routinely infiltrate the scalp prior to incision. Scalp blocks have been used extensively as it is intuitive that they will be found to be useful. Guilfoyle et al. recently published a systematic review and meta-analysis on regional scalp block (RSB) for post-craniotomy analgesia [19]. They identified seven high-quality RCTs which met their criteria with a total recruitment of 320 patients. All studies used standard local anaesthetic drugs (lignocaine, bupivacaine, ropivacaine), with three studies combining LA with adrenaline. RSB was done preoperatively in three studies and after wound closure in four studies. Meta-analysis found a pooled reduction on pain scores at 1 h. Both pre-and post-groups showed significant reductions in pain scores at 2, 4, 6, 8 and 12 h with an overall reduction in opioid requirements in the first 24 h. There were no complications attributable to RSB. This meta-analysis has confirmed the standard protocols in most neurosurgical units to include RSB as part of multimodal analgesia.

In a more recent study, Hwang et al. showed that inclusion of scalp blocks with levobupivacaine improved the recovery profile of patients undergoing aneurysm clipping [20]. In this study, 52 patients scheduled for elective frontoparietal craniotomy for unruptured aneurysm clipping were randomized to receive scalp blocks with either normal saline or levobupivacaine 0.75%. Postoperative pain scores and PCA consumption were recorded for 72 h. The time from patient recovery to first use of PCA, requirements for vasoactive drugs and adverse effects of PCA and LA were recorded. Scalp blocks lowered postoperative pain and PCA consumption without severe adverse events and reduced the requirements for antihypertensive agents. Besides RSB, superficial cervical plexus blocks have been successfully used as transitional analgesia for infratentorial and occipital craniotomy [21].

11.3 Post-craniotomy Pain in Children

Children from infancy to adolescents need intracranial surgery for a variety of causes which include tumours, epilepsy, vascular malformations and craniofacial reconstruction. To evaluate the incidence of pain after craniotomy in children, a multicentre observational study was conducted in nine Italian hospitals [22]. After IRB

approval, 213 infants and children <10 years old undergoing major craniotomy were enrolled. Pain intensity, analgesic therapy and adverse effects were evaluated for the first 2 days. Moderate to severe pain was defined as a median FLACC or NRS score ≥4; severe pain was defined as a median FLACC or NRS score of ≥7. The overall postoperative median FLACC/NRS score was 1. Twenty-one children (16%) presented with moderate to severe pain in the recovery room and 14(6%) on the first and second days after surgery. Rectal codeine was the weak opioid used, while remifentanil and morphine were widely used in the paediatric ICU. They concluded that children receiving multimodal analgesia experienced minimum pain, while longer surgical procedures correlated with increased risk of having postoperative pain.

In another prospective observational cohort study, 200 children undergoing intracranial surgery in three academic children's hospitals were evaluated to determine the incidence of pain, prescribed analgesics, method of analgesic delivery and patient/parent satisfaction [23]. Neither intraoperative anaesthetic management nor postoperative pain management was standardized. The age of the children ranged from 2 months to 18.5 years with an average of 7.8 ± 5.8 years. Despite considerable variation in mode and route of administration, there were no differences in average pain score, length of hospital stay and parental satisfaction with care. Parenteral opioids were used along with paracetamol and this was changed to oral oxycodone and/or paracetamol once oral intake was allowed. The most common opioid-induced side effect was vomiting, and it did not relate to the total daily opioid consumption.

The safety and efficacy of continuous morphine infusions following paediatric cranial surgery was reported from a hospital in British Columbia, Canada [24]. The medical records of 71 children were retrospectively reviewed. The outcome measures included pain control and adverse events. Thirty-seven children received continuous morphine infusion and 34 received paracetamol and codeine. There was no statistical difference in pain control between the two groups, but there was a significant increase in nausea in the morphine group. They recommend the use of continuous morphine infusion if pain is poorly controlled with non-opioid analgesics.

In the absence of trials comparing different analgesic regimes in children, these observational cohort studies indicate that multimodal analgesia including potent opioids can be safely used in the setting of high dependency units, in which these children will be nursed in the postoperative period.

11.4 Chronic Pain Following Craniotomy

Following intracranial surgery, patients not only have acute pain lasting several days but can develop chronic post-craniotomy headaches. One of the risk factors for the development of chronic pain is unrelieved acute pain [25]. Diagnostic criteria according to the International Headache Society is that it is of variable intensity, maximum in the area of the craniotomy performed for other than head trauma, occurs within 7 days and persists >3 months after craniotomy [26]. Batoz et al. conducted a prospective single-blinded study to evaluate if scalp infiltration with local anaesthetic will reduce postoperative pain [27]. Fifty-two patients were enrolled and half of them received infiltration of the surgical site with 20 mL of 0.75% ropivacaine at the end of surgery. The VAS pain scores were significantly higher in the control group with a trend towards lower consumption of nalbuphine in the infiltration group. In addition, 2 months post-surgery, persistent pain was significantly lower than in the control group ($p = 0.0003$). Scalp infiltration may be relevant for the rehabilitation of neurosurgical patients and their quality of life by limiting the development of persistent pain.

Conclusions

Postoperative pain following intracranial surgery is an area of clinical concern that is receiving increasing attention in the last decade. Studies show that craniotomy leads to significant pain in the early postoperative period. There have been no large-scale stud-

ies to definitively draw up guidelines and protocols for pain management in this group of patients. However, the judicious use of opioids (morphine/fentanyl), along with non-opioid analgesics such as paracetamol/coxibs and regional scalp blocks, have all provided effective pain relief after craniotomy. Unrelieved acute pain after intracranial surgery can lead to chronic persistent headaches, which can diminish the quality of life.

References

1. Geevarghese K. Postoperative care of the patient undergoing neurological surgery. Int Anaesthesiol Clin. 1977;15:309–20.
2. De Benedittis G, Lorenzetti A, Migliore M, Spagnoli D, Tiberio F, Villani R. Postoperative pain in neurosurgery: a pilot study in brain surgery. Neurosurgery. 1996;38(3):466–70.
3. Thibault M, Girard F, Moumdjian R, Chouinard P, Boudreault D, Ruel M. Craniotomy site influences postoperative pain following neurosurgical procedures: a retrospective study. Can J Anaesth. 2007;54(7):544–8.
4. Stoneham MD, Walters FJ. Post-operative analgesia for craniotomy patients: current attitudes among neuroanaesthetists. Eur J Anaesthesiol. 1996;12(6):571–5.
5. Roberts GC. Post-craniotomy analgesia: current practices in British neurosurgical centres – a survey of post-craniotomy analgesic practices. Eur J Anaesthesiol. 2005;22:328–32.
6. Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, et al. Clinical pharmacogenetics implementation consortium (CPIC) guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014;95(4):376–82.
7. Hassouneh B, Centofanti JE, Reddy K. Pain management in post-craniotomy patients: a survey of Canadian neurosurgeons. Can J Neurol Sci. 2011;38(3):456–60.
8. Stoneham MD, Cooper R, Quiney NF, Walters FJM. Pain following craniotomy: a preliminary study comparing PCA morphine with intramuscular codeine phosphate. Anaesthesia. 1996;51:1176–8.
9. Transkanen P, Kytta J, Randell T. Patient-controlled analgesia with oxycodone in the treatment of post craniotomy pain. Acta Anaesthesiol Scand. 1999; 43(1):42–5.
10. Sudheer PS, Logan SW, Terblanche C, Ateleanu B, Hall JE. Comparison of the analgesic efficacy and respiratory effects of morphine, tramadol and codeine after craniotomy. Anaesthesia. 2007;62(6):555–60.
11. Rahimi SY, Alleyne CH, Vernier E, Witcher MR, Vender JR. Postoperative pain management with tramadol after craniotomy: evaluation and cost analysis. J Neurosurg. 2010;112(2):268–72.
12. Morad AH, Winters BD, Yaster M, Stevens RD, White ED, Thompson RE, Weingart JD, Gottschalk A. Efficacy of intravenous patient-controlled analgesia after supratentorial intracranial surgery: a prospective randomized controlled trial. J Neurosurg. 2009;111(2):343–50.
13. Morad A, Winters B, Stevens R, White E, Weingart J, Yaster M, Gottschalk A. The efficacy of intravenous patient-controlled analgesia after intracranial surgery of the posterior fossa: a prospective, randomized controlled trial. Anesth Analg. 2012; 114:416–23.
14. Verchere E, Grenier B, Mesli A, Siao D, Sesay M, Maurette P. Postoperative pain management after supratentorial craniotomy. J Neurosurg Anesthesiol. 2002;14(2):96–101.
15. Gunes Y, Unlugenc H, Yilmaz D, Ozcengiz D. Management of acute craniotomy pain; the analgesic effect of diclofenac sodium-tramadol or paracetamol-tramadol. Neurosurg Quarterly. 2011;21(4):236–9.
16. Palmer JD, Sparrow OC, Iannotti F. Postoperative hematoma: a 5-year survey and identification of avoidable risk factors. Neurosurgery. 1994;35(6):1061–4.
17. Williams DL, Pemberton E, Leslie K. Effect of intravenous parecoxib on post-craniotomy pain. Br J Anaesth. 2011;107(3):398–403.
18. Jones SJ, Cormack J, Murphy MA, Scott DA. Parecoxib for analgesia after craniotomy. Br J Anaesth. 2009;102(1):76–9.
19. Guilfoyle MR, Helmy A, Duane D, Hutchinson PJ. Regional scalp block for postcraniotomy analgesia: a systematic review and meta-analysis. Anesth Analg. 2013;116(5):1093–102.
20. Hwang JY, Bang JS, Oh CW, Joo JD, Park SJ, Do SH, Yoo YJ, Ryu JH. Effect of scalp blocks with levobupivacaine on recovery profiles after craniotomy for aneurysm clipping: a randomized, double-blind, and controlled study. World Neurosurg. 2015;83(1):108–13.
21. Girard F, Quentin C, Charbonneau S, Ayoub C, Boudreault D, Chouinard P, Ruel M, Moumdijian R. Superficial cervical plexus block for transitional analgesia in infratentorial and occipital craniotomy: a randomized trial. Can J Anaesth. 2010;57(12):1065–70.
22. Bronco A, Pietrini D, Lamperti M, et al. Incidence of pain after craniotomy in children. Paediatr Anaesth. 2014;24(7):781–7.
23. Maxwell LG, Buckley GM, Kudchadkar SR, Ely E, Stebbins EL, Dube C, Morad A, et al. Pain management following major intracranial surgery in pediatric patients: a prospective cohort study in three academic children's hospitals. Paediatr Anaesth. 2014;24(11):1132–40.

24. Warren DT, Bowen-Roberts T, Ou C, Purdy R, Steinbok P. Safety and efficacy of continuous morphine infusions following pediatric cranial surgery in a surgical ward setting. Childs Nerv Syst. 2010;26(11):1535–41.
25. De Gray LC, Matta BF. Acute and chronic pain following craniotomy. A review. Anaesthesia. 2005; 60(7):693–704.
26. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache disorders. 2nd ed. Cephalalgia. 2004;24(Suppl 1):9–160.
27. Batoz H, Verdonck O, Roux G, Maurette P. The analgesic properties of scalp infiltrations with ropivacaine after intracranial tumoral resection. Anesth Analg. 2009;109(7):240–4.

Part III

Neuroanesthesia and Neurocritical Care

Anesthesia for Awake Craniotomy

12

Luca Titi, Shaun E. Gruenbaum,
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12.1 Introduction

Providing anesthesia for patients undergoing awake craniotomy presents unique clinical challenges that require frequently changing states of consciousness and analgesia [1, 2]. The goals in managing patients undergoing awake craniotomy are to ensure optimal patient comfort without interfering with electrophysiological monitoring and patient cooperation, to optimize cerebral and systemic hemodynamics, and to maintain adequate oxygenation [3, 4]. Awake craniotomy is the preferred approach for functional neurosurgery including deep-brain stimulation for the treatment of Parkinson's disease, epilepsy surgery [5–9]. Moreover, awake craniotomy has become the gold standard for patients who require intraoperative monitoring of speech and motor functions to localize an area of surgical interest, such as resection or biopsy of brain tumors in eloquent areas, and has been shown to allow for a wider tumor excision and lower perioperative morbidity [10–13]. More recently, awake craniotomy has been successfully performed in patients with other conditions including obesity and severe obsessive compulsive disorders [14–16]. Many approaches have been used to provide anesthesia for the patient undergoing awake craniotomy, which are often institutional dependent or tailored to meet the patient's specific individual needs. These techniques range from local anesthesia, with or without conscious sedation, to general anesthesia with an asleep–awake–asleep sequence, with or without airway instrumentation [17, 18]. In this chapter, we review some of the approaches that have been described in the literature with regard to airway management, local anesthesia, sedation, and hemodynamic management in the patient undergoing awake craniotomy.

12.2 Airway Management

A prerequisite for providing anesthesia for the patient undergoing awake craniotomy is to have expertise in advanced airway management. In managing the airway of an awake, spontaneously breathing patient, it is essential that adequate oxygen is provided and carbon dioxide is removed. Awake craniotomy is often complicated by inadequate ventilation, and to this end, studies have demonstrated that 9.5% of patients experience

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hypercarbia (end-tidal CO_2 > 50 mmHg), 7.1% experience respiratory depression (respiratory rate <8 breaths/min), and 4.8% experience oxygen desaturation (SpO_2 < 95%) at some point during the procedure [19]. Airway instrumentation might therefore be necessary at any point during the procedure and is often needed emergently. Hence, a thorough preoperative airway assessment and intraoperative accessibility of endotracheal and supraglottic airway devices is of paramount importance [20]. Although various techniques can be used for placing a laryngeal mask airway (LMA) during awake craniotomy, proper positioning (even when the surgical approach requires that the patient is in the lateral or semi-sitting position) is extremely important to allow the anesthesiologist to easily maneuver the airway and maintain optimal patient comfort [20, 21]. Although nasopharyngeal cannulas have been advocated by some experts to improve intraoperative ventilation [22], their use is not without risk. Placement of nasopharyngeal cannulas carries a risk of intranasal bleeding, is often difficult to position, and the device can interfere with the surgical field [17].

In most spontaneously breathing patients, providing 50% FiO_2 via a facial mask maintains adequate oxygenation without suppressing the ventilatory drive. The real-time $EtCO_2$ concentration, sampled in the upper airways, provides useful information on ventilatory mechanics, and can prompt gentle facial mask ventilatory support if hypercarbia develops. Inadequate ventilation, a complication that might arise during seizures or intractable cough, should be treated with the administration of appropriate sedation and placement of an LMA or endotracheal tube [18].

12.3 Local Anesthesia

The sensory innervation is summarized in Fig. 12.1. The anterior scalp and forehead is innervated by the trigeminal nerve, the largest cranial nerve and principal source of sensory innervation to the head and face. The trigeminal nerve has three branches, the ophthalmic, maxillary, mandibular nerves, which innervate part of the forehead and scalp.

The ophthalmic branch is further split into the frontal, supraorbital, and supratrochlear nerves. The maxillary branch is further divided into the infraorbital, zygomatic temporal, and zygomati-

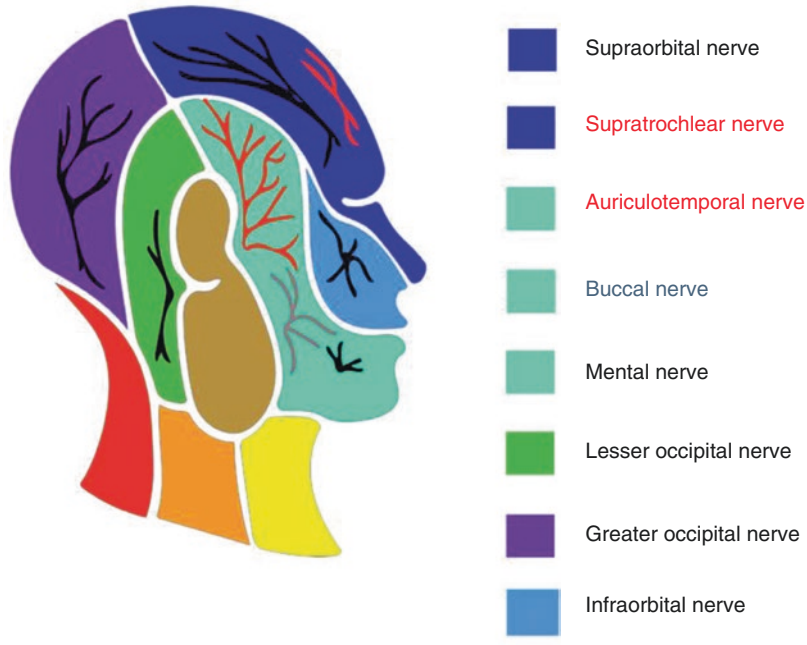

Fig. 12.1 Anatomy of nerves required for performing a scalp block during awake craniotomy

cofacial nerves. The mandibular branch is further divided into the auriculotemporal, mental, and buccal nerves. The innervation of the posterior scalp is provided by the greater occipital nerve, which arises from the second cervical nerve, C2 root, and the lesser occipital nerve, which is derived from ventral rami of the C2 and C3 spinal nerves [19]. The posterior scalp is principally innervated by the greater occipital nerve, whereas the lesser occipital nerve supplies the scalp skin behind the ear [19].

Providing adequate local anesthesia, which aims to block the sensory branches of the trigeminal nerve, is essential in managing patients undergoing awake craniotomy. A scalp block with local anesthetic provides reversible regional loss of sensation and reduces pain perception and global energy expenditure [19]. In some cases, especially in patients with Parkinson's disease undergoing microelectrode implantation of a deep-brain stimulator, local anesthesia might be the only logical anesthetic approach since sedation agents can abolish brain impulses during microelectrode recordings in subcortical areas. These brain areas are highly sensitive to GABAergic anesthetics, even in small doses, and can critically reduce the ability to identify the excision sites [19–21]. When providing local anesthetic, six nerves should be adequately infiltrated:

1. *Auriculotemporal nerve*: This nerve can be blocked with local anesthetic infiltration over the zygomatic process, with an injection 1–1.5 cm anterior to the ear at the level of the tragus. The superficial temporal artery is anterior to the auriculotemporal nerve at the level of the tragus, and should always be palpated and its course identified before injection of local anesthetic.
2. *Zygomaticotemporal nerve*: This nerve can be blocked by infiltrating the supraorbital margin to the posterior part of the zygomatic arch. Arising midway between the auriculotemporal and supraorbital nerves where it emerges above the zygoma, the zygomaicotemporal nerve ramifies as it pierces the temporalis fascia. Both deep and superficial injections are therefore recommended.
3. *Supraorbital nerve*: This nerve can be blocked by infiltrating where it emerges from the orbit. The supraorbital notch is palpated by the finger and the needle is inserted along the upper orbital margin, perpendicular to the skin, approximately 1 cm medial to the supraorbital foramen.
4. *Supratrochlear nerve*: This nerve can be blocked by infiltrating where it emerges above the eyebrow or can be included with a medial extension of the supraorbital block.
5. *Greater occipital nerve*: This nerve can be blocked by infiltrating approximately halfway between the occipital protuberance and the mastoid process, 2.5 cm lateral to the nuchal median line. The best landmark is to palpate the occipital artery, and inject medially after careful aspiration. This should be done to avoid potential intra-arterial injection.
6. *Lesser occipital nerve*: This nerve can be blocked by infiltrating along the superior nuchal line, 2.5 cm lateral to the greater occipital nerve block. It is also recommended that one should infiltrate the sites where the head pins are placed and along the line of surgical incision.

A recent prospective, randomized, placebo-controlled study demonstrated that a selective trigeminal nerve block is more effective than local infiltration for scalp block in controlling the hemodynamic responses to incision and in preventing the increased stress hormone response to skull-pin fixation [23]. Recent studies have confirmed that local anesthetic infiltration of the scalp before craniotomy is effective in reducing tachycardia and hypertension, which could result in increased cerebral blood flow and intracranial pressure [20, 24]. This is especially important for patients with impaired cerebral autoregulation, in whom a small increase in blood pressure could result in large changes in cerebral blood flow and volume, further precipitating intracranial hypertension [20, 25]. Local anesthetic infiltration can also prevent the need for intravenous analgesic agents early in the surgical procedure [24].

12.4 Local Anesthesia Toxicity

A significant complication of local anesthetic infiltration is local anesthesia-induced neurotoxicity and cardiac toxicity. The anesthesiologist should be aware of the maximum local anesthetic dose that can be safely administered and should never administer a dose that exceeds the toxicity level. The volume of local anesthetic at each site necessary to achieve an adequate surgical block can vary from 2 to 5 mL of a local anesthetic mixture of ropivacaine 0.75% and mepivacaine 0.2% [26, 27]. Neurotoxic effects of local anesthesia include drowsiness, circumoral paresthesias, language difficulties, tinnitus, visual disturbances, agitation, coma, and respiratory depression. During the first 15 min after injection of local anesthetics, patients should be carefully monitored for early identification and treatment of local anesthetic-induced neurotoxicity. Furthermore, local anesthetics can have significant negative chronotropic effects. To this end, a recent paper on the anesthetic management for awake craniotomy described a case in which the use of local anesthetic infiltration combined with intravenous antihypertensive agents resulted in significant bradycardia and complete atrioventricular heart block [26]. Neurotoxicity and cardiotoxicity should be treated with intravenous infusion of intralipid emulsion (intralipid 20% 1.5 mL/kg over 1 min followed by 0.25 mL/kg/min).

Another complication of local anesthetic infiltration is transient facial palsy after auriculotemporal nerve block. The exact cause of the transient postoperative facial nerve palsy after auriculotemporal nerve block is unknown and likely multifactorial. This technique may need to be refined to avoid such complications [28]. Many hypotheses have been suggested regarding the etiology of transient facial palsy, including direct nerve injury, nerve compression from a hematoma, edema, or local anesthetic injection that may result in neural ischemia and injury, and direct neurotoxic effects of local anesthetics [26–28].

12.5 Sedation and Analgesia

During awake craniotomy, it is important to plan a dedicated sedation–analgesia protocol. Providing too much sedation can result in an uncooperative patient with or without respiratory depression, whereas providing too little sedation results in an uncomfortable and agitated patient, which can result in arterial hypertension and tachycardia. Providing adequate sedation can make awake anesthesia for craniotomy less physically and emotionally stressful than general anesthesia [20, 29].

Intravenous anesthetic agents that have been described for sedation protocols include propofol–fentanyl, propofol–remifentanil, and dexmedetomidine (Table 12.1). Dexmedetomidine with or without concurrent use of propofol provides sedation that resembles natural sleep, and is especially useful because it does not cause respiratory depression [30]. A bispectral index monitor can be useful when titrating a propofol infusion to a target conscious state [18, 20]. In patients undergoing awake craniotomy, the anesthetic protocol should also achieve adequate postoperative pain control. Remifentanil is a well-tolerated opioid that provides good intraoperative pain control. However, it should be noted that discontinuation of remifentanil has been associated with several postoperative complications, including hyperalgesia, hypertension, and tachycardia [20, 31, 32].

Table 12.1 Perioperative sedation and analgesia protocols for patients undergoing awake craniotomy

Sedation protocol	Premedication	Postoperative analgesia
Propofol 1–3 mg/kg/h; Fentanyl 1–3mcg/kg/h	Fentanyl 1–2mcg/kg	Paracetamol 1 g twice daily
Propofol 1–3 mg/kg/h; Remifentanil 0.01–0.25 mg/kg/h	Midazolam 0.015–0.3 mg/kg	Morphine 0.1–0.3 mg/kg/die
Dexmedetomidine 0.3–0.7 mg/kg/h		

12.6 Hemodynamic Management

One of the most challenging goals in providing anesthesia for awake neurosurgery is the optimization of operating conditions by manipulating systemic and cerebral hemodynamics. Maintenance of normotension or slight hypotension is necessary to reduce bleeding and brain swelling that can occur during brain exposure, and to achieve surgical hemostasis. Severe arterial hypertension and tachycardia are associated with a significant risk of postoperative intracranial hemorrhage and myocardial ischemia, respectively, and should be prevented or promptly treated [20]. Several agents can be used to lower blood pressure, including beta blockers (esmolol, metoprolol, atenolol), calcium-channel blockers (diltiazem and verapamil), alpha blockers (urapidil) mixed alpha and beta blockers (labetalol), and alpha-adrenergic receptor agonists (clonidine). Nitrates should be avoided because they can cause cerebral vasodilation and increased cerebral blood flow [20, 32, 33].

Conclusion

Awake craniotomy is a well-tolerated procedure that requires an extensive knowledge of underlying neuroanesthesia principles, as well as specific strategies of local anesthetic scalp blockade, advanced airway management, a dedicated sedation–analgesia protocol, and skillful management of systemic and cerebral hemodynamics.

References

1. Gruenbaum SE, Meng L, Bilotta F. Recent trends in the anesthetic management of craniotomy for supratentorial tumor resection. Curr Opin Anaesthesiol. 2016;29(5):552–7.
2. Flexman AM, Meng L, Gelb AW. Outcomes in neuroanesthesia: what matters most? Can J Anaesth. 2015;63:205–11.
3. Frost EA, Booij LH. Anesthesia in the patient for awake craniotomy. Curr Opin Anaesthesiol. 2007;20(4):331–5.
4. Sinha PK, Koshy T, Gayatri P, Smitha V, Abraham M, Rathod RC. Anesthesia for awake craniotomy: a retrospective study. Neurol India. 2007;55(4):376–81.
5. Lega BC, Wilfong AA, Goldsmith IL, Verma A, Yoshor D. Cortical resection tailored to awake, intraoperative ictal recordings and motor mapping in the treatment of intractable epilepsia partialis continua: technical case report. Neurosurgery. 2009;64(3 Suppl):ons195–6. ; discussion ons6
6. Erickson KM, Cole DJ. Anesthetic considerations for awake craniotomy for epilepsy. Anesthesiol Clin. 2007;25(3):535–55. ix
7. Cohen-Gadol AA, Britton JW, Collignon FP, Bates LM, Cascino GD, Meyer FB. Nonlesional central lobule seizures: use of awake cortical mapping and subdural grid monitoring for resection of seizure focus. J Neurosurg. 2003;98(6):1255–62.
8. Herrick IA, Craen RA, Blume WT, Novick T, Gelb AW. Sedative doses of remifentanil have minimal effect on ECoG spike activity during awake epilepsy surgery. J Neurosurg Anesthesiol. 2002;14(1):55–8.
9. Hisada K, Morioka T, Fukui K, Nishio S, Kuruma T, Irita K, et al. Effects of sevoflurane and isoflurane on electrocorticographic activities in patients with temporal lobe epilepsy. J Neurosurg Anesthesiol. 2001;13(4):333–7.
10. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. N Engl J Med. 2008;358(1):18–27.
11. Gil Robles S, Gelisse P, Vergani F, Moritz-Gasser S, Rigau V, Coubes P, et al. Discrepancies between preoperative stereoencephalography language stimulation mapping and intraoperative awake mapping during resection of focal cortical dysplasia in eloquent areas. Stereotact Funct Neurosurg. 2008;86(6):382–90.
12. Duffau H. A personal consecutive series of surgically treated 51 cases of insular WHO Grade II glioma: advances and limitations. J Neurosurg. 2009;110(4):696–708.
13. Shinoura N, Yoshida M, Yamada R, Tabei Y, Saito K, Suzuki Y, et al. Awake surgery with continuous motor testing for resection of brain tumors in the primary motor area. J Clin Neurosci. 2009;16(2):188–94.
14. Halpern CH, Wolf JA, Bale TL, Stunkard AJ, Danish SF, Grossman M, et al. Deep brain stimulation in the treatment of obesity. J Neurosurg. 2008;109(4):625–34.
15. Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D, et al. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med. 2008;359(20):2121–34.
16. Kalenka A, Schwarz A. Anaesthesia and Parkinson's disease: how to manage with new therapies? Curr Opin Anaesthesiol. 2009;22(3):419–24.
17. Dinsmore J. Anaesthesia for elective neurosurgery. Br J Anaesth. 2007;99(1):68–74.
18. Gadhinglajkar S, Sreedhar R, Abraham M. Anesthesia management of awake craniotomy performed under asleep-awake-asleep technique using laryngeal mask airway: report of two cases. Neurol India. 2008;56(1):65–7.
19. Osborn I, Sebeo J. "Scalp block" during craniotomy: a classic technique revisited. J Neurosurg Anesthesiol. 2010;22(3):187–94.

20. Bilotta F, Rosa G. 'Anesthesia' for awake neurosurgery. Curr Opin Anaesthesiol. 2009;22(5):560–5.
21. Lee MC, Absalom AR, Menon DK, Smith HL. Awake insertion of the laryngeal mask airway using topical lidocaine and intravenous remifentanil. Anaesthesia. 2006;61(1):32–5.
22. Gonzales J, Lombard FW, Borel CO. Pressure support mode improves ventilation in "asleep-awake-asleep" craniotomy. J Neurosurg Anesthesiol. 2006;18(1):88.
23. Geze S, Yilmaz AA, Tuzuner F. The effect of scalp block and local infiltration on the haemodynamic and stress response to skull-pin placement for craniotomy. Eur J Anaesthesiol. 2009;26(4):298–303.
24. Shiau JM, Chen TY, Tseng CC, Chang PJ, Tsai YC, Chang CL, et al. Combination of bupivacaine scalp circuit infiltration with general anesthesia to control the hemodynamic response in craniotomy patients. Acta Anaesthesiol Sin. 1998;36(4):215–20.
25. Agarwal A, Sinha PK, Pandey CM, Gaur A, Pandey CK, Kaushik S. Effect of a subanesthetic dose of intravenous ketamine and/or local anesthetic infiltration on hemodynamic responses to skull-pin placement: a prospective, placebo-controlled, randomized, double-blind study. J Neurosurg Anesthesiol. 2001;13(3):189–94.
26. Bilotta F, Titi L, Rosa G. Local anesthetic-induced complete atrioventricular block during awake craniotomy. J Neurosurg Anesthesiol. 2012;24(3):238.
27. Bilotta F, Titi L, Rosa G. Prevention and treatment of local anesthetics-induced complete atrioventricular-block during awake craniotomy. J Neurosurg Anesthesiol. 2013;25(3):356.
28. McNicholas E, Bilotta F, Titi L, Chandler J, Rosa G, Koht A. Transient facial nerve palsy after auriculotemporal nerve block in awake craniotomy patients. A A Case Rep. 2014;2(4):40–3.
29. Bilotta F, Titi L, Lanni F, Stazi E, Rosa G. Training anesthesiology residents in providing anesthesia for awake craniotomy: learning curves and estimate of needed case load. J Clin Anesth. 2013;25(5):359–66.
30. Rozet I. Anesthesia for functional neurosurgery: the role of dexmedetomidine. Curr Opin Anaesthesiol. 2008;21(5):537–43.
31. Vinik HR, Kissin I. Rapid development of tolerance to analgesia during remifentanil infusion in humans. Anesth Analg. 1998;86(6):1307–11.
32. Bilotta F, Lam AM, Doronzio A, Cuzzone V, Delfini R, Rosa G. Esmolol blunts postoperative hemodynamic changes after propofol-remifentanil total intravenous fast-track neuroanesthesia for intracranial surgery. J Clin Anesth. 2008;20(6):426–30.
33. Narotam PK, Puri V, Roberts JM, Taylon C, Vora Y, Nathoo N. Management of hypertensive emergencies in acute brain disease: evaluation of the treatment effects of intravenous nicardipine on cerebral oxygenation. J Neurosurg. 2008;109(6):1065–74.

TIVA for Neurosurgery

13

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13.1 Introduction

A tailored anesthesia constitutes a major goal of the modern anesthetic practice based on the patient's individual needs, surgical procedure and outcomes. To better achieve it, the modern anesthesiologist should use drugs with a predictable and favorable profile: a rapid onset and offset, safe and rapid induction, early recovery, easily titratable and without - or minimal - adverse or unwanted effects.

Pending the development of new and "almost-ideal" drugs, the emergence and improvement of systems and devices that allow their safe and accurate delivery, have contributed to the development of our practice.

Hypnotics and opioid drugs of short duration of action, such as propofol and remifentanil, along with target-controlled infusion systems (TCI) have increased the popularity of total intravenous anesthesia (TIVA) and enabled a tailored technique even in different settings such as ambulatory and office-based anesthesia [1].

Thus, the debate continues on intravenous and inhalation anesthesia regarding well-defined clinical endpoints. These are mainly related to the speed and recovery of anesthesia, hemodynamic changes, operative conditions, postoperative nausea and vomiting, recovery of psychomotor and cognitive function, and discharge from hospital.

13.2 TIVA Advantages

TIVA's increasing popularity and its several advantages in the peri-operative setting are listed in Table 13.1.

Table 13.1 TIVA advantages

Less pollution
Control of sedation before induction and at emergence
Safe and accurate titration of drugs
No conflict between airway access and drug delivery
Hypoxic vasoconstrictor reflex intact
No change in surfactant production
No renal toxicity due to fluoride ions
Safe in malignant hyperthermia
Less postoperative nausea and vomiting (PONV)
Postoperative analgesia titration
Less postoperative pain
Early postoperative patient well-being
Less imunossupression

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Beyond the well-known presented clinical endpoints, patient satisfaction is increasingly valued and it has been suggested to be higher after TIVA–TCI, mainly due to the lower incidence of PONV [2].

Furthermore, research on long-term outcomes has shown that intravenous anesthesia with propofol may be more favorable concerning cancer recurrence after surgery [3]. Although several contradictory results have been published concerning immunosuppression, it seems that propofol attenuates surgical stress response without impairment of natural killer cell activity and leading to less significant immunosuppression [4].

Aware of the advantages described, economic impact has been a subject of great interest with insufficient studies until now. Although TIVA–TCI is generally considered more expensive, the associated costs are mainly related to the equipment and consumables. Therefore, all costs and benefits should be considered, related not only to the technique but also the institution, the patient, and the society [5].

Nevertheless, we should not forget the safety and easy titration of volatile anesthetics and recognize the merits of both techniques [6]. Clear indications for the use of each technique are lacking and the choice seems to be more related to the individual experience and familiarity with the technique than based on published studies, without forgetting the availability of the equipment.

13.3 Anesthetic Pharmacology and CNS

For a better understanding of the advantages and disadvantages related to different techniques, the main characteristics of the most commonly used anesthetics drugs are summarized in Tables 13.2 and 13.3.

Propofol has rapid onset and offset, decreases cerebral blood flow (CBF) and cerebral metabolic rate ($CMRO_2$) dose-dependently, with a reduction in intracranial pressure (ICP).

The most commonly used volatile agents, sevoflurane and desflurane, increase CBF dose dependently for MAC greater than 1, with low $CMRO_2$ affecting the CBF–$CMRO_2$ coupling due to cerebral vasodilation. This is more sustained in patients with impairment of cerebral compliance.

Because of its effects on cerebral physiology, propofol has been suggested as the ideal anesthetic for neurosurgery providing better operating conditions, while TIVA is the elected technique [7].

Table 13.2 Effects of intravenous agents respectively on CBF, $CMRO_2$, AND ICP

	CBF	$CMRO_2$	ICP
Propofol	- - -	- - -	- - -
Barbiturates	- - -	- -	- -
Etomidate	- - -	- - -	- - -
Ketamine	+ + +	+ + or =	+ + or + + +
Opioids	- or + or =	- - or =	+ or =
Benzodiazepines	- -	- -	- -
Dexmedetomidine	- -	- - or =	=

+ slight increase, + + increase, + + + marked increase, = no change, - slight decrease, - - decrease, - - - marked decrease

Table 13.3 Effects of volatile agents respectively on CBF, $CMRO_2$, AND ICP

	CBF	$CMRO_2$	ICP
Sevoflurane	- - or = or +	- - or - - -	+ + or + or =
Desflurane	- - or + +	- - -	+ + or =
Isoflurane	+ + or =	- - -	+ or + + or =
N_2O	+ + +	+ + or =	+ + +
Xenon	- - (gray) + + (white)	- -	+ + or =

+ slight increase, + + increase, + + + marked increase, = no change, - slight decrease, - - decrease, - - - marked decrease

13.4 TCI and Modern Practice of TIVA

TCI systems have made TIVA simpler, easier, and safer. The practice of target-controlled anesthesia is based on fundamental pharmacokinetic and pharmacodynamic concepts which deserve a detailed review.

13.4.1 The Compartment Model

Pharmacokinetic models describe a drug's behavior in the body. For most anesthetic drugs, a two or three compartment model can describe it with great accuracy (Fig. 13.1).

In the three compartment model, as shown above, after the drug is injected into the central compartment (V_1), it will have rapid distribution to the second compartment (V_2), slow distribution to the third compartment (V_3), and also redistribution between them. The intercompartmental time constants (K_{12}, K_{21}, K_{23}, K_{32}) describe the proportion of the drug that is undergoing each one of these processes during a unit of time (min^{-1} or h^{-1}). Drug elimination by metabolism from the central compartment corresponds to the constant K_{10}.

It is important to notice that these volumes have no real anatomical correlation. They are theoretical volumes that can be remotely thought as the blood volume (V_1), a "vessel rich" compartment (V_2) and a "vessel poor" compartment (V_3).

In each model, the size of the volumes of distribution reflects the solubility of the drug in that specific compartment. The more the drug is soluble, the higher is the volume.

For pharmacokinetic/pharmacodynamic modeling, an effect-site compartment can be added. Due to its negligible volume, the rate constants for movement in and out of this compartment are the same ($K_{1e} = K_{eo}$).

In the past decades, pharmacokinetic models have been developed and improved, allowing better understanding of the behavior of different drugs and making possible the adjustment to the individual kinetics. These models are the result of arterial or venous sampling with measurement of blood concentration of a drug, after a bolus or infusion, in well-defined populations, using sta-

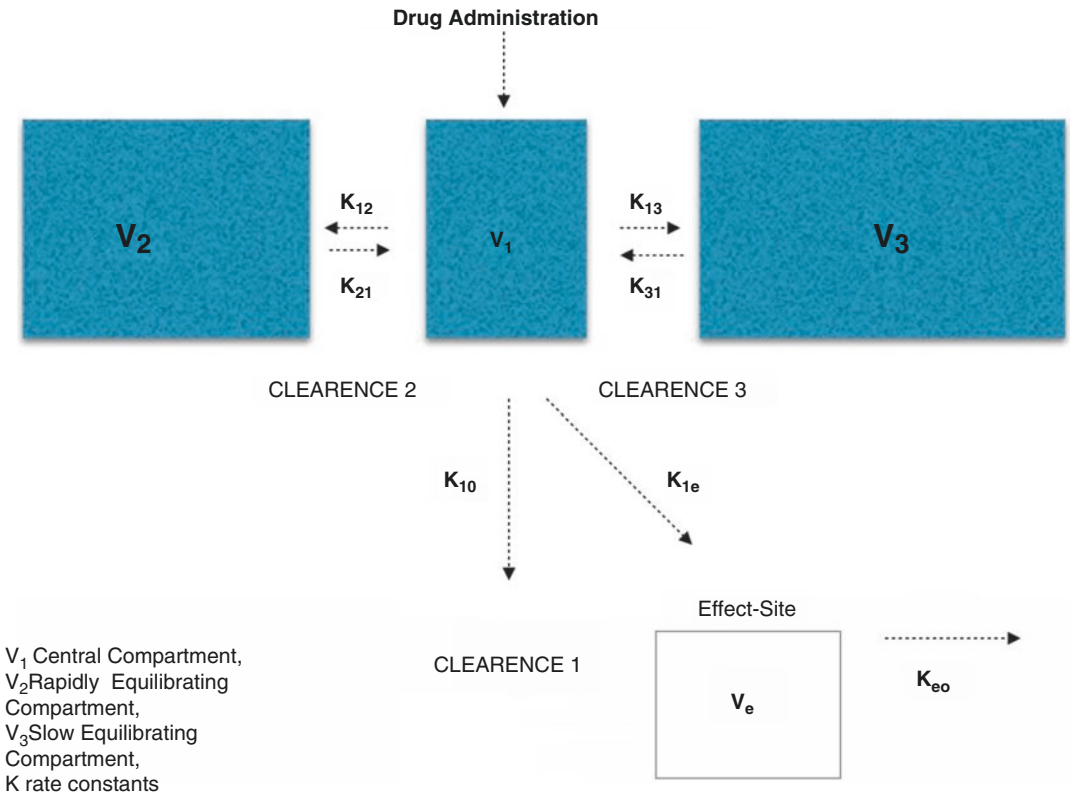

Fig. 13.1 Three compartment pharmacokinetic model with an effect-site compartment

tistical analysis. By knowing the rate constants for each drug, it is possible to predict the concentration in different compartments after a bolus injection of the drug.

TCI systems incorporate this information and, based on individual parameters, allow to predict plasmatic and/or effect-site concentrations (C_p/C_e) controlling drug administration by the infusion pump.

13.4.2 Pharmacokinetic Concepts

Volume of Distribution (V_d) is the volume in which the drug is distributed and its value depends on the time of calculation. Time zero relates to V_1 and at steady state is the sum of V_1, V_2 and V_3. Generally, it can be calculated knowing the dose present in the body (D) and its plasma concentration (C):

$$V_d = D / C \tag{13.1}$$

Although it reflects the distribution of a drug in the body, V_d can exceed the anatomical body volume several times. For e.g., if a drug accumulates in tissues, it will have a low plasma concentration and a consequently high V_d. Drugs with a small V_d are those mainly confined to the intravascular fluid.

This concept allows calculation of the loading dose that the TCI system will deliver to achieve the desired target concentration (C_e or C_p), according to the calculated V_d:

$$\text{Loading Dose} = C \cdot V_d \tag{13.2}$$

If another bolus is required to increase the target concentration,

$$New\,\text{Loading Dose} = \left(Cf - Ci\right) \cdot V_d; \tag{13.3}$$

Cf – final concentration, *Ci* – initial concentration.

Clearance (*Cl*) describes the volume in which the drug is eliminated during a unit of time (mL/min or mL/hr). This particular setting also describes the drug movement between compartments. It can be calculated as:

$$\text{Clearance} = K_{el} \cdot V_d; \tag{13.4}$$

K_{el} – elimination rate constant.

The maintenance infusion rate of TCI systems will compensate the clearance of the drug exciting the body. It is defined as the concentration at steady state multiplied by the clearance value (*Cl*).

$$\begin{aligned}&\text{Maintenance infusion rate}\\ &at\ \text{steady} - \text{state} = C_{ss} \cdot Cl\end{aligned} \tag{13.5}$$

These two concepts can explain the basis of TCI systems, though there are other concepts regarding pharmacokinetics of infusions that assume big importance in this clinical setting.

Half Life ($t_{1/2}$) is the time taken for the concentration of a drug to drop by half its value. However, since most drugs are distributed in more than one compartment and clearance from each one occurs at different rates, the drug will have more than one $t_{1/2.}$ The actual $t_{1/2}$ of a drug is the sum of the individual half-lives.

For this reason, it is preferable to use the *context-sensitive half-time.* This is the time required for a drug's blood concentration to decrease to 50% its previous value after stopping an infusion of a given duration. *Decremental time* is a similar concept that defines the time required for blood concentration to decrease to a desired percentage.

Both concepts are useful predictors of drug concentration decline after an infusion is stopped. TCI systems provide a calculation of the time needed for the measured concentration to decrease to a definable concentration at which recovery is expected.

13.4.3 Pharmacodynamic Concepts

The brain is the site where anesthetic drugs exert their clinical effect, which defines it as the effect site. For this reason it becomes obvious that the main effect is delayed as well as the drug concentration at the effect site when compared to the plasma peak concentration. *Hysteresis* represents this time delay between plasma compartment and effect-site compartment. Mathematically, the time taken for blood–effect-site equilibration is described by the rate constant K_{e0} which is different for different drugs.

Time to peak effect (TTPE) is the time delay between a bolus and maximum effect-site concentration and is independent of size of bolus (Fig. 13.2).

*T*1/2 K_{e0} is the time taken for the drug concentration in the effect site to reach half of the concentration in the blood and can be clinically more useful than K_{e0}. Knowing the K_{e0} and TTPE makes it possible to "target" the effect-site concentration.

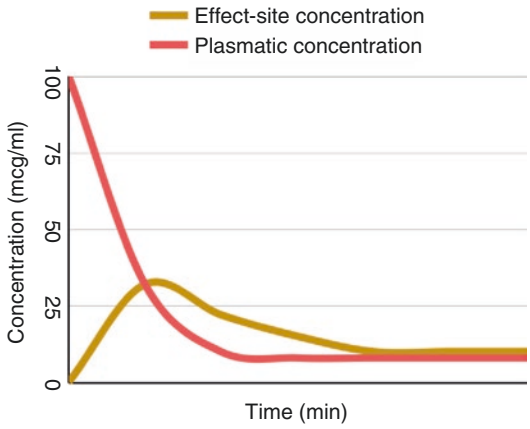

Fig. 13.2 Graphic representation of time to peak effect for a bolus dose of a drug: corresponds to the point where the blood and effect-site concentration curves cross

13.4.4 Target-Controlled Infusion

A target-controlled infusion is an infusion controlled as fast and safe as possible in order to achieve and maintain a defined concentration of a drug in a site of interest as well as the wanted clinical effect.

In clinical practice, the anesthesiologist programs the TCI set-up using the computer interface. First, sets the patient data and then defines the target concentration, plasmatic or in the effect site (C_p/C_e), based on the desired effect and adjusted to the patient's clinical response. The computer system with its mathematical algorithm calculates the specific parameters for each patient, as *Vd* and *Cl*. Accordingly, the infusion pump delivers the bolus dosage and the infusion rates required to achieve and maintain the desired target concentration at steady state. Continuous automatic calculations are made to adjust the infusion rate to the distribution and elimination of the drug. To compensate these processes, the software calculates three superimposed infusion rates decreasing gradually. Target concentrations should be continuously titrated and adjusted to the clinical response.

A TCI system (Fig. 13.3) is composed of a computer, a user interface, and an infusion device. The interface allows the data input according to the pharmacokinetic model incorporated and

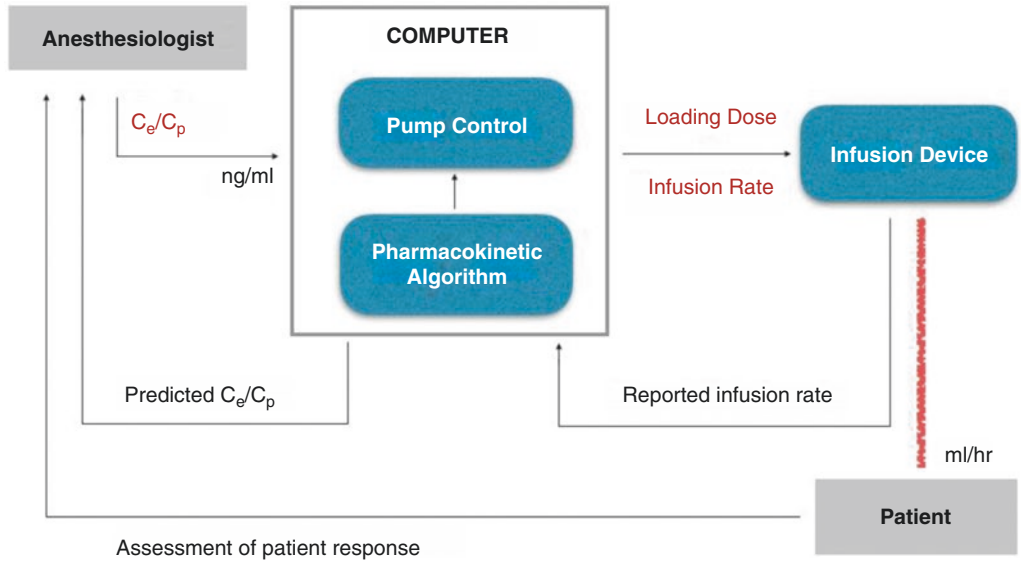

Fig. 13.3 Components of a TCI System

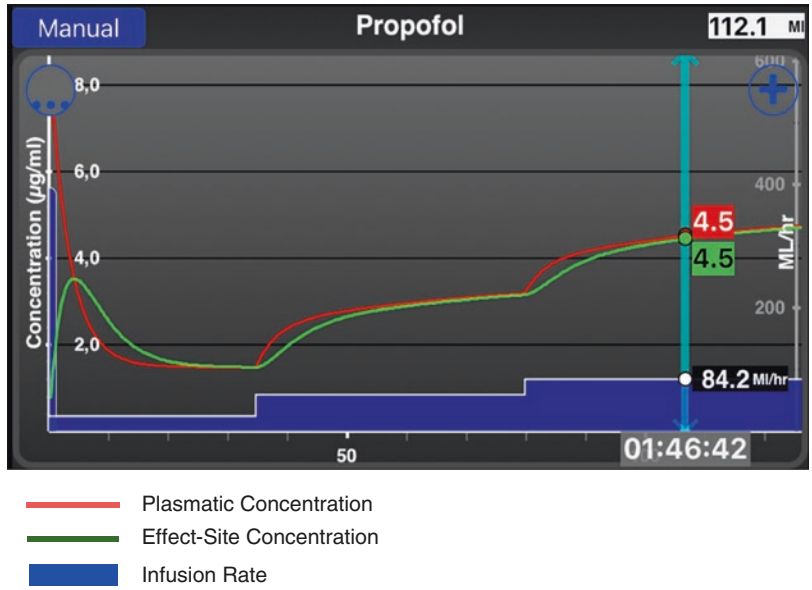

Fig. 13.4 Manually controlled infusion of propofol after an initial bolus

gives numeric and/or graphic information. The computer controls the interface, implements the pharmacokinetic models, controls the infusion device and implements warning systems.

It is important to keep in mind that when using a TCI system, although the user can manage the target concentration, no real concentrations are measured during the infusion and that is why they are called "open-loop" systems.

13.4.4.1 TCI Versus Manual Perfusions

When using a manually controlled infusion, by administering drugs at a fixed rate, it will take a long time to reach steady state, approximately, four to five half-lives, until the drug equilibrates throughout all the tissues in the body. For this reason, the blood concentrations will change very slowly and changes in the infusion rate will not lead to significant changes in plasmatic or effect-site concentration for some time. Also, clinical effect will take too long (Fig. 13.4).

That's why a system of bolus dosing and variable infusion rates is more suitable and effective to better control drug concentration and achieve the desired effect.

However, if a bolus is given and perfusion is controlled randomly by the operator, these doses will be difficult to calculate and to adjust for a rapid and safe control of the target concentrations, potentiating adverse or undesirable effects.

13.4.4.2 Propofol Blood-Targeted TCI

In TCI systems, after setting the desired target concentration, the infusion device will deliver a bolus to quickly fill the central compartment (V_1) with gradual increase in blood concentration. When the system calculates that the targeted blood concentration has been reached, it stops and then starts an infusion at a lower rate. When the operator decreases the target concentration, the system switches off the infusion and starts only when the predicted concentration has reached the target concentration, at a lower rate (Fig. 13.5). If a bolus is delivered to achieve a higher concentration, the system will then adjust the infusion rate to achieve and maintain a new steady-state concentration.

13.4.4.3 Propofol Effect-Site Targeted TCI

When choosing effect-site concentration for TCI, the system manipulates the blood concentration to achieve the effect-site target as quickly as possible. Thus, a large bolus is delivered and a faster rise in effect-site concentration can be seen. After

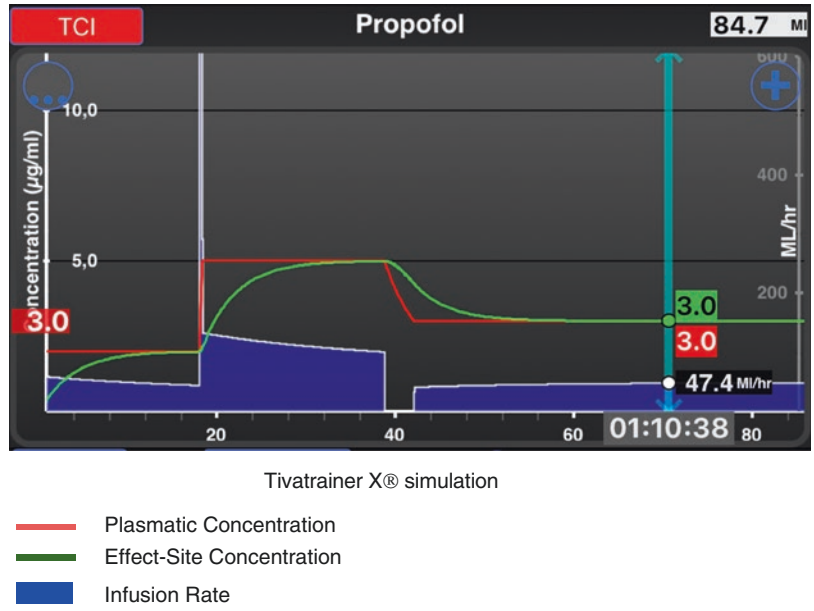

Fig. 13.5 Blood concentration targeted TCI for propofol

the initial bolus, the infusion stops until the declining blood concentration reaches the increasing effect-site concentration. At that point, it restarts at a rate that maintains blood and effect-site concentrations at the desired target concentration. If the target concentration is decreased, the TCI will stop the infusion and effect-site concentration will fall due to the movement of propofol down its concentration gradient out of the effect-site. When the new effect-site concentration has been reached, a different infusion rate starts maintaining a new equilibrium. Thereafter, if a higher effect-site concentration is defined, the system will deliver another bolus followed by the appropriate infusion rate.

13.4.4.4 Propofol and Remifentanil TCI

Pharmacodynamic interactions are common and very important in clinical setting. Total intravenous anesthesia combining the use of propofol with remifentanil shows a synergism meaning that lower concentrations of each drug are needed to achieve the desired effect [8]. As shown in Fig. 13.6, the target concentration of propofol required for maintenance of adequate anesthesia decreases with increasing concentrations of remifentanil.

This synergistic effect allows the combination of moderate doses resulting in optimal concentrations for anesthesia, easily titratable, with rapid awakening times [9]. Although it has a safety margin for side effects, some adverse effects also act synergistically, such as hypotension or apnea, and care must be taken to provide the optimal concentrations and avoid overdosing (Fig. 13.7).

13.4.4.5 Setting the TCI Pump

For a better and safer practice of TIVA/TCI, some recommendations should be followed: (recomendations) Always keep in mind, the paradigm shift of mL/h to ng/mL, while thinking in the individual kinetics and not in the population.

13.5 TIVA and Brain Surgery

In the particular case of neuroanesthesia, the main goals are related with the decrease in cerebral metabolism, maintaining autoregulation ($PaCO_2$ and MAP) and normal intracranial pressure, and also to provide optimal operative conditions with electro-neurophysiological monitoring and a rapid offset preserving cognitive functions.

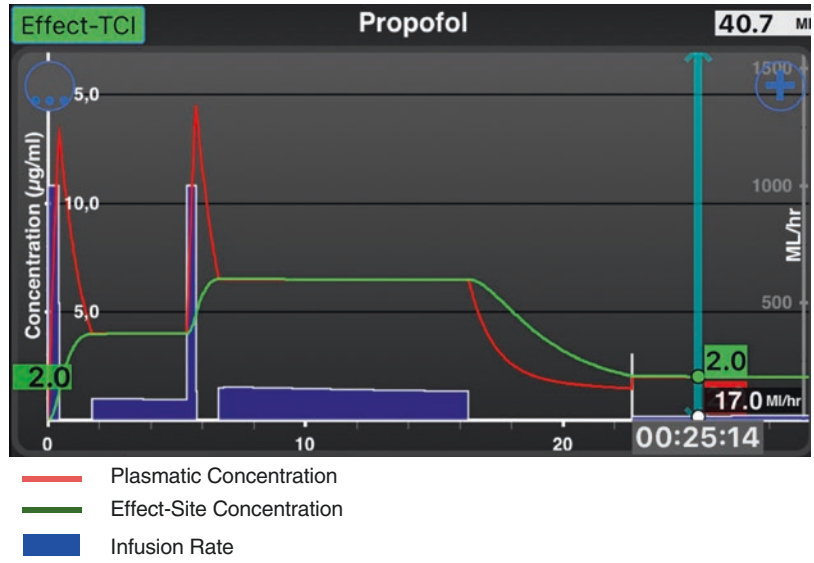

Fig. 13.6 Effect-site concentration targeted TCI for propofol

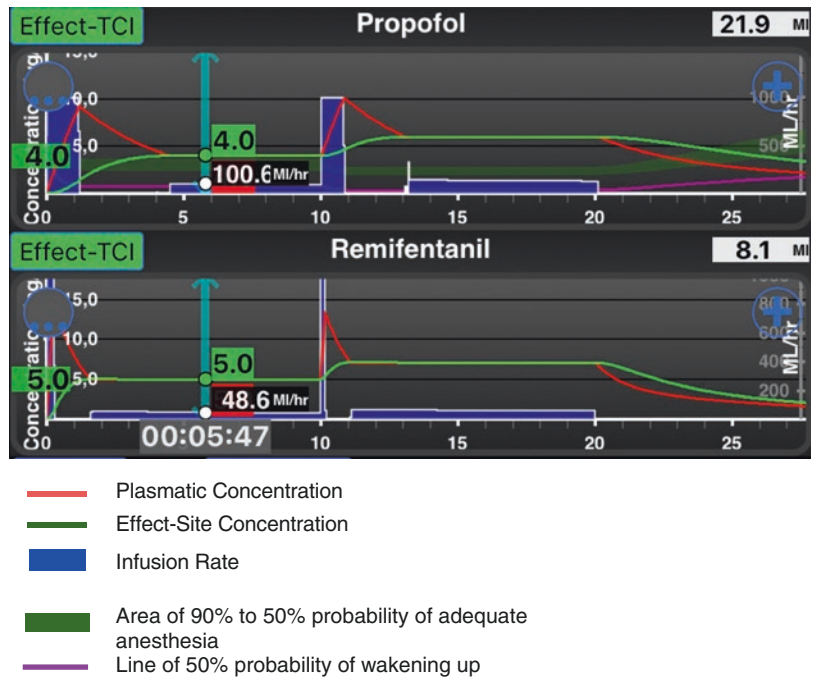

Fig. 13.7 Propofol and remifentanil TCI

Giving particular importance to situations with impaired cerebral autoregulation, e.g. TBI or space-occupying lesions, TIVA seems to be more suitable in those cases [10].

A recently published systematic review and meta-analysis concluded that mean ICP values were lower and cerebral perfusion pressure (CPP) values were higher with propofol-maintained anesthesia [11].

- Programming the pump should be made by an anesthesiologist familiarized with the settings and differences of each pharmacokinetic model;
- Prepare an adequate intravenous system;
- Know the covariates (age, gender, weight, height and lean body mass), its limitations regarding the obese and the extremes of age and the concomitant variations of pharmacokinetics and pharmacodynamics;
- Check the loading doses, steady-state infusion rates and measured concentrations;
- Monitor the targeted effect, e.g., using monitors of processed EEG;
- Titrate the target concentration according to your monitoring and surgical stimulation;
- Know the pharmacologic interactions between drugs used together during TIVA/TCI.

Beneficial effects of anesthetic drugs as neuroprotectants have been inconclusive [12], although a possible role of intravenous agents was recently appraised [13]. Very recently, sevoflurane and isoflurane were shown to induce structural changes in brain endothelial cells, increasing brain barrier permeability, leading to disturbed neuronal function [14].

A suggested approach is to use indirect evidence of different outcomes in fragile brains after exposure to different anesthetic drugs with translational application to the fragile brain under surgery.

Anesthesia-induced developmental disturbances with long-term poor outcomes in young mammalian brain are under debate and research in the last decade with contradicting evidence [15–18] implicating volatile agents, nitrous oxide, ketamine and, in a less extent, propofol. However, a possible protective effect of propofol may be inferred after Jacob et al. [19] showed different cerebral metabolic signatures for sevoflurane and propofol in children undergoing magnetic resonance imaging during sevoflurane- or propofol-based anesthesia, with higher levels of cerebral lactate and glucose in children under sevoflurane anesthesia and a strong and significative association between these metabolites and the occurrence of emergence delirium. Assuming that immediate cognitive disturbances after general anesthesia like delirium or emergence agitation are the result of changes in cerebral physiology, we cannot also forget that propofol significantly decreases the severity and incidence of emergence agitation and delirium in pediatric patients [20], supervening the idea that TIVA will supercede inhalational anesthesia [21].

Sevoflurane has also shown to be associated with negative postoperative behavioral changes in children undergoing adenotonsillectomy while the incidence and severity of cognitive changes were significantly lower when children had propofol-based anesthesia [22].

Also, in vitro studies in animals show that inhalational anesthesia can lead to an increase in amyloid beta peptide deposition as in Alzheimer's disease, which may be related to postoperative cognitive disorder (POCD) [4].

Whether these findings are significant we still don't know but, at least, they trigger doubts about the cerebral health after exposure to volatile agents [23].

A very special case where TIVA–TCI is particularly useful is when an awake patient is required to improve neurosurgical outcome: resection of a tumor or an epileptic focus close to an eloquent area and functional neurosurgery for movement disorders are the paradigm of awake neurosurgery. [24–27]

Although several anesthetic techniques have been described, there is a trend toward the use of a asleep–awake–asleep or asleep–awake approach with TCI of propofol and remifentanil titrated by processed EEG monitors and scalp block, using a laryngeal mask and controlled

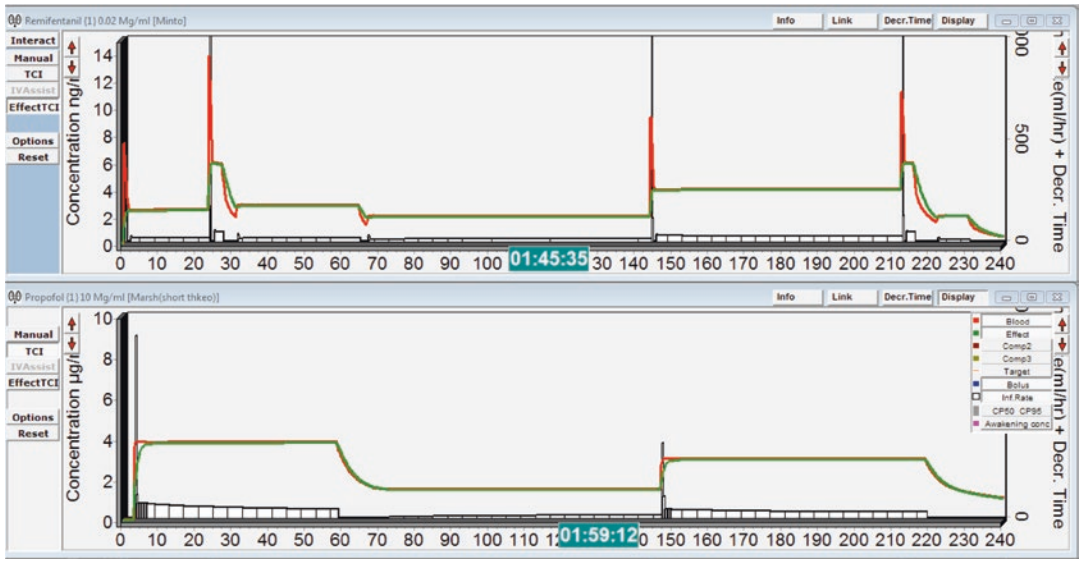

Fig. 13.8 Asleep–awake–asleep technique with propofol and remifentanil TCI

ventilation during craniotomy or, more recently, dexmedetomidine [28–32].

Figure 13.8 shows an example of TCI of propofol and remifentanil for craniotomy with intraoperative awakening for resection of a tumor close to Broca area.

13.6 TIVA and Spine Surgery

As mentioned before, anesthetic drugs used during brain and spine surgery should allow electroneurophysiological monitoring, as electroencephalogram and evoked potentials. During spine surgery, evoked potentials allow to control the integrity of neural pathways. While volatile agents may decrease amplitude and prolong latency of somatosensory evoked potentials (SSEP) in a dose-dependent manner, propofol and other intravenous agents such as dexmedetomidine allow better preservation of evoked responses [33–39].

Propofol and intravenous anesthesia is also associated with a smoother emergence after spine surgery, with less coughing and hemodynamic response and reliable neuro-electrophysiological monitoring [10, 40, 41].

References

1. Rosero E, Joshi GP. Total intravenous anesthesia present and future. Am Soc Anesthesiology Ambulatory Anesthesia. 2015;79(8):10–1.
2. Hofer CK, Zollinger A, Büchi S, Klaghofer R, et al. Patient well-being after general anesthesia: a prospective, randomized, controlled multi-center trail comparing intravenous and inhalation anesthesia. Br J Anaesth. 2003;91(5):631–7.
3. Tavare NA, Perry NJS, Benzonana LL, et al. Cancer recurrence after surgery: direct and indirect effects of anesthetic agents. Int J Cancer. 2012;130:1237–50.
4. Fodale V, Santamaria LB, Schifilliti D, Mandal PK. Anaesthetics and post-operative cognitive dysfunction: a pathological mechanism mimicking Alzheimer's disease. Anaesthesia. 2010;65:388–95.
5. Sneyd JR, Holes KA. Inhalational or total intravenous anaesthesia: is total intravenous anaesthesia useful and are there economic benefits? Curr Opin Anaesthesiol. 2011;24:182–7.
6. Zuleta-Alarcón A, Castellón-Larios K, Nino-de Mejía MC, Bergese S. Total intravenous anesthesia versus inhaled anesthetics in neurosurgery. Rev Colomb Anestesiol. 2015;43(S1):9–14.
7. Hans P, Bonhomme V. Why we still use intravenous drugs as the basic regimen for neurosurgical anaesthesia. Curr Opin Anaesthesiol. 2006;19(5):498–503.
8. Vuyk J, Lim T, Engbers FH, Burm AG, Vletter AA, Bovill JG. The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. Anesthesiology. 1995;83(1):8–22.

9. Vuyk J, Mertens MJ, Olofsen E, Burm AG, Bovill JG. Propofol anesthesia and rational opioid selection: determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. Anesthesiology. 1997;87(6):1549–62.
10. Zuleta-Alarcón A, Castellón-Larios K, Niño-de Mejía MC, Bergese S. Total intravenous anesthesia versus inhaled anesthetics in neurosurgery. Rev Colomb Anestesiol. 2015;43(S1):9–14.
11. Chui J, Mariappan R, Mehta J, Manninen P, Venkatraghavan L. Comparison of propofol and volatile agents for maintenance of anesthesia during elective craniotomy procedures: systematic review and meta-analysis. Can J Anaesth. 2014;61(4):347–56.
12. Bilotta F, Gelb AW, Stazi E, Titi L, Paoloni FP, Rosa G. Pharmacological perioperative brain neuroprotection: a qualitative review of randomized clinical trials. Br J Anaesth. 2013;110(Suppl 1):i113–20.
13. Bilotta F, Stazi E, Zlotnik A, Gruenbaum SE, Rosa G. Neuroprotective effects of intravenous anesthetics: a new critical perspective. Curr Pharm Des. 2014; 20(34):5469–75.
14. Acharya NK, Goldwaser EL, Forsberg MM, Godsey GA, Johnson CA, Sarkar A, DeMarshall C, Kosciuk MC, Dash JM, Hale CP, Leonard DM, Appelt DM, Nagele RG. Sevoflurane and Isoflurane induce structural changes in brain vascular endothelial cells and increase blood-brain barrier permeability: possible link to postoperative delirium and cognitive decline. Brain Res. 1620;2015(16):29–41.
15. Rizzi S, Ori C, Jevtovic-Todorovic V. Timing versus duration: determinants of anesthesia-induced developmental apoptosis in the young mammalian brain. Ann N Y Acad Sci. 2010;1199:43–51.
16. Olsen EA, Brambrink AM. Anesthesia for the young child undergoing ambulatory procedures: current concerns regarding harm to the developing brain. Curr Opin Anaesthesiol. 2013;26(6):677–84.
17. Olsen EA, Brambrink AM. Anesthetic neurotoxicity in the newborn and infant. Curr Opin Anaesthesiol. 2013;26(5):535–42.
18. Sanders RD, Hassell J, Davidson AJ, Robertson NJ, Ma D. Impact of anaesthetics and surgery on neurodevelopment: an update. Br J Anaesth. 2013;110(Suppl 1):i53–72.
19. Jacob Z, Li H, Makaryus R, Zhang S, Reinsel R, Lee H, Feng T, Rothman DL, Benveniste H. Metabolomic profiling of children's brains undergoing general anesthesia with sevoflurane and propofol. Anesthesiology. 2012;117(5):1062–71.
20. Van Hoff SL, O'Neill ES, Cohen LC, Collins BA. Does a prophylactic dose of propofol reduce emergence agitation in children receiving anesthesia? A systematic review and meta-analysis. Paediatr Anaesth. 2015;25(7):668–76.
21. Lauder GR. Total intravenous anesthesia will supercede inhalational anesthesia in pediatric anesthetic practice. Paediatr Anaesth. 2015;25(1):52–64.
22. Stipic SS, Carev M, Kardum G, Roje Z, Litre DM, Elezovic N. Are postoperative behavioural changes after adenotonsillectomy in children influenced by the type of anaesthesia?: a randomised clinical study. Eur J Anaesthesiol. 2015;32(5):311–9.
23. Sanders RD, Hassell J, Davidson AJ, Robertson NJ, Ma D. Impact of anaesthetics and surgery on neurodevelopment: an update. Br J Anaesth. 2013;110(Suppl 1):i53–72.
24. Brown T, Shah AH, Bregy A, Shah NH, Thambuswamy M, Barbarite E, Fuhrman T, Komotar RJ. Awake craniotomy for brain tumor resection: the rule rather than the exception? J Neurosurg Anesthesiol. 2013;25(3):240–7.
25. Erickson KM, Cole DJ. Anesthetic considerations for awake craniotomy for epilepsy and functional neurosurgery. Anesthesiol Clin. 2012;30(2):241–68.
26. Bilotta F, Rosa G. 'Anesthesia' for awake neurosurgery. Curr Opin Anaesthesiol. 2009;22(5):560–5. doi:10.1097/ACO.0b013e3283302339.
27. Meng L, Berger MS, Gelb AW. The potential benefits of awake craniotomy for brain tumor resection: an anesthesiologist's perspective. J Neurosurg Anesthesiol. 2015;27(4):310–7.
28. Lobo F, Beiras A. Propofol and remifentanil effect-site concentrations estimated by pharmacokinetic simulation and bispectral index monitoring during craniotomy with intraoperative awakening for brain tumor resection. J Neurosurg Anesthesiol. 2007;19(3):183–9.
29. Hans P, Bonhomme V, Born JD, Maertens de Noordhoudt A, Brichant JF, Dewandre PY. Target-controlled infusion of propofol and remifentanil combined with bispectral index monitoring for awake craniotomy. Anaesthesia. 2000;55(3):255–9.
30. Deras P, Moulinié G, Maldonado IL, Moritz-Gasser S, Duffau H, Bertram L. Intermittent general anesthesia with controlled ventilation for asleep-awake-asleep brain surgery: a prospective series of 140 gliomas in eloquent areas. Neurosurgery. 2012;71(4):764–71.
31. Sarang A, Dinsmore J. Anaesthesia for awake craniotomy – evolution of a technique that facilitates awake neurological testing. Br J Anaesth. 2003;90(2):161–5.
32. Goettel N, Bharadwaj S, Venkatraghavan L, Mehta J, Bernstein M, Manninen PH. Dexmedetomidine vs propofol-remifentanil conscious sedation for awake craniotomy: a prospective randomized controlled trial. Br J Anaesth. 2016;20
33. Soghomonyan S, Moran KR, Sandhu GS, Bergese SD. Anesthesia and evoked responses in neurosurgery. Front Pharmacol. 2014;5:74.
34. Jameson LC, Sloan TB. Neurophysiologic monitoring in neurosurgery. Anesthesiol Clin. 2012;30(2):311–31.
35. Lotto ML, Banoub M, Schubert A. Effects of anesthetic agents and physiologic changes on intraoperative motor evoked potentials. J Neurosurg Anesthesiol. 2004;16(1):32–42.

36. Banoub M, Tetzlaff JE, Schubert A. Pharmacologic and physiologic influences affecting sensory evoked potentials: implications for perioperative monitoring. Anesthesiology. 2003;99(3):716–37.
37. Clapcich AJ, Emerson RG, Roye Jr DP, Tie H, Gallo EJ, Dowling KC, Ramnath B, Heyer EJ. The effects of propofol, small-dose isoflurane, and nitrous oxide on cortical somatosensory evoked potential and bispectral index monitoring in adolescents undergoing spinal fusion. Anesth Analg. 2004;99(5):1334–40.
38. Rozet I, Metzner J, Brown M, Treggiari MM, Slimp JC, Kinney G, Sharma D, Lee LA, Vavilala MS. Dexmedetomidine does not affect evoked potentials during spine surgery. Anesth Analg. 2015;121(2):492–501.
39. Hermanns H, Lipfert P, Meier S, Jetzek-Zader M, Krauspe R, Stevens MF. Cortical somatosensory-evoked potentials during spine surgery in patients with neuromuscular and idiopathic scoliosis under propofol-remifentanil anaesthesia. Br J Anaesth. 2007;98(3):362–5. Epub 2007 Jan 19
40. Sloan TB, Mongan P, Lyda C, Koht A. Lidocaine infusion adjunct to total intravenous anesthesia reduces the total dose of propofol during intraoperative neurophysiological monitoring. J Clin Monit Comput. 2014;28(2):139–47.
41. Li F, Gorji R, Allott G, Modes K, Lunn R, Yang ZJ. The usefulness of intraoperative neurophysiological monitoring in cervical spine surgery: a retrospective analysis of 200 consecutive patients. J Neurosurg Anesthesiol. 2012;24(3):185–90.

14 Anesthetic Challenges in Pediatric Craniofacial Surgeries

Lucy Chan

14.1 General Problems in Children with Craniofacial Deformities

An understanding of anatomical and physiological alterations arising from craniofacial deformities in children is essential in order to formulate a safe and sensible clinical strategy.

14.1.1 Pathophysiological Alterations

The craniofacial region consists of the skull, forehead, orbits, nose, jaw bones, and oral cavity. The major craniofacial deformities include craniosynostosis and craniofacial clefts. Severe craniofacial malformation, although rare, afflicts one child per 10,000 births and averages about one-fifth of all malformations. When defective ossification of the skull causes faulty development of the skull base as well, three common clinical features may be encountered: craniosynostosis, midface hypoplasia, and exorbitism.

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There are four major (metopic, sagittal, coronal, lambdoid) and several minor sutures, and abnormal ossification can be single or multiple A child with nonsyndromic craniosynostosis has an abnormal cranial vault shape, such as "boat-shaped" (scaphocephaly) from early fusion of sagittal suture. There is greater brain injury with the presence of more premature closure of sutures, resulting in a spectrum of presentations according to the severity of anatomical and functional defects in each patient. A raised intracranial pressure may threaten survival and normal mental development may be impaired. Other natural physiological tasks such as sight, hearing, respiratory, and breathing through the nose may be compromised.

Syndromic craniosynostosis, also known as craniofacial dysostosis, has sutural defects along with systemic or body involvement, for example, associated abnormalities of the limbs, spine, and heart. Genetic mutation studies have evolved rapidly and are able to identify fibroblast growth factor receptor 2 (FGFR2) mutations in Cruzon, Apert, and Pfeiffer syndromes (Fig. 14.1a–c).

Major craniofacial clefts are complex conditions. The array of cases ranges from extensive disfigurement reported in the medical literature to simple cleft lip and cleft palate. The etiology of craniofacial clefts is linked to abnormal development at the embryonic stage and there are various types depending on the site of origin. An example is Treacher Collins Syndrome (Fig. 14.1d) which consists of cleft palate,

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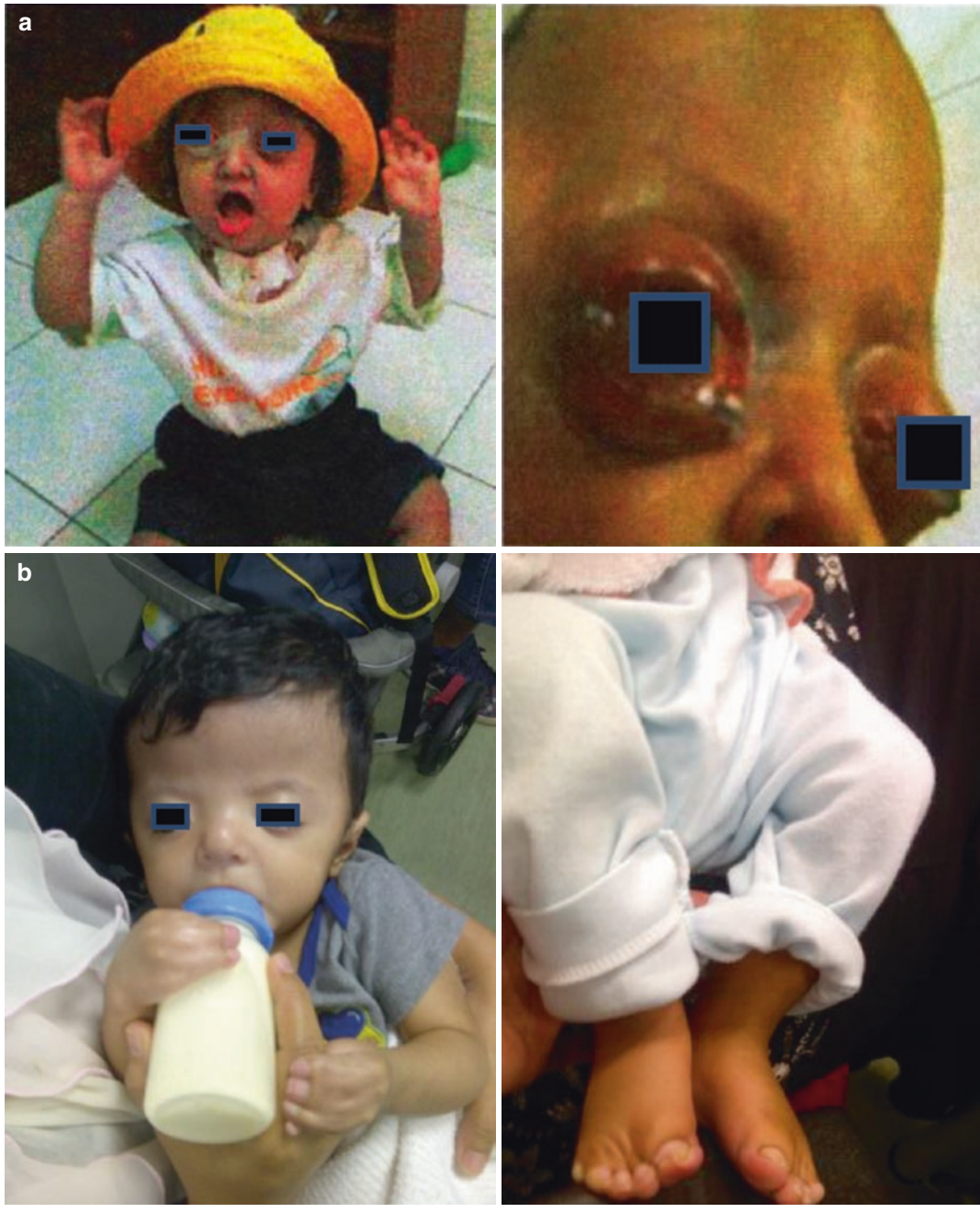

Fig. 14.1 Photographs are courtesy of craniofacial team, University Malaya Medical Centre, Malaysia. (**a**) Cruzon syndrome: (i) At age 1 month, he presented with severe infection in right eye creating scarring of cornea. (ii) After several surgeries in the past, at age 2+ years he was assessed for frontal distraction with monobloc Le Fort III and closure of the incomplete cleft palate (which was successfully carried out when he was 3 years old). (**b**) Apert syndrome. Notice the webbing of fingers (i) and toes (ii) (syndactyly). (**c**) Pfeiffer syndrome. This child had a posterior vault expansion during infancy for raised ICP. At age 6 years, she has stable visual state with pale optic disc. Her ICP is at low to moderate and although there are some cosmetic issues, parents are able to accept at this stage. (**d**) Treacher Collins syndrome or mandibulofacial dysostosis. A 1+-year-old female patient with abnormal facial features, namely, malformed ears, down-sloping eyes, macrostomia, micrognathia, and undeveloped zygoma. These characteristics may be visible with ultrasound examination during the antenatal period

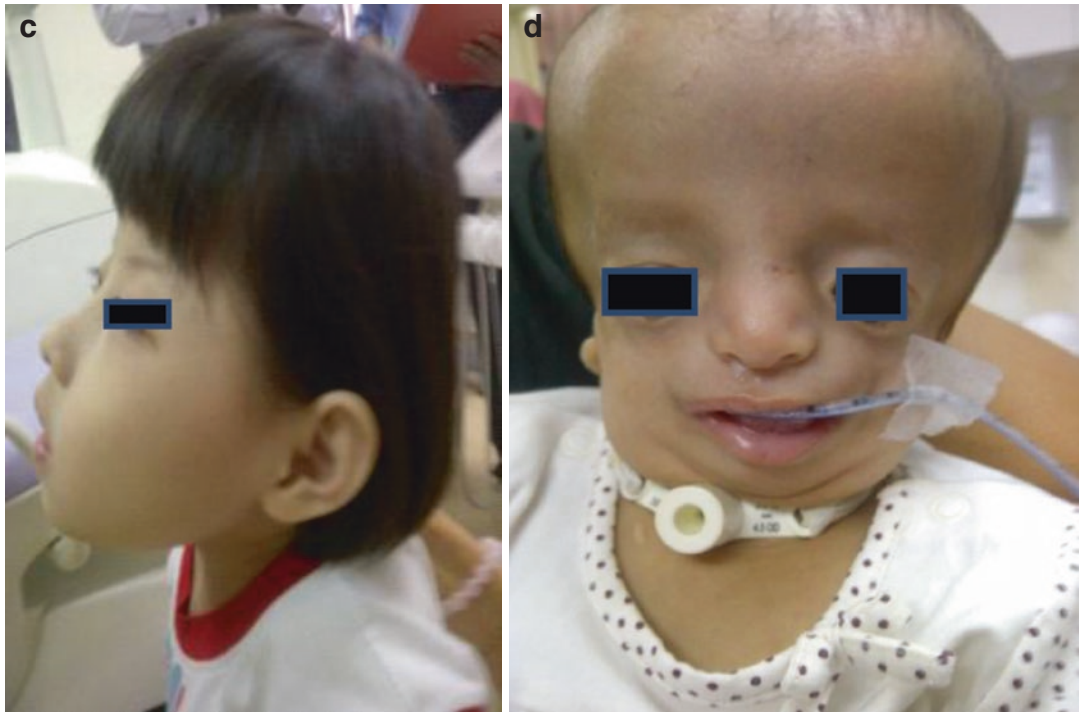

Fig. 14.1 (continued)

absent or deformed ears, down-slanting eyes, underdeveloped or absent zygomatic bone, and a small jaw. There are physiological disruptions in the essential areas of airway and breathing, vision, speech, hearing, and swallowing.

14.1.2 Types of Surgical Corrections

In nonsyndromic deformities the optimal age for elective surgical vault remodeling is unclear. It has been advocated that surgery be carried out as early as possible, taking into consideration the extent of surgery and the expected blood loss. By 12 weeks of age, surgery is possible for closure of one to two sutures that have caused malformed skull appearance or a raised ICP. If the infant has severe protrusion of the eyes, tarsorrhaphy is recommended to sew the eyelids partially together to prevent keratitis or blindness. In a syndrome causing craniosynostosis, early screening is undertaken by a multidisciplinary team so that the comprehensive cooperative effort ensures optimum management in the planning stage, particularly when a staged surgical approach is necessary.

There are a variety of surgical techniques, but meticulous planning is undertaken to choose the treatment that offers the best benefits and the least harm. Surgical procedures range from single suture correction and fronto-orbital remodeling to extensive operative techniques such as, monobloc/frontofacial advancement which is considered as early as 4 years of age. Some patients require several craniotomies and phased distractive strategies with the available tools of modern technology for better correction.

To illustrate the complexity of pediatric craniofacial pathology and surgeries required, an example is given here. Cruzon Syndrome is the most frequent medical condition in syndromic craniosynostosis and is an autosomal dominant genetic disorder. Apart from significant premature suture closure, the list of systemic involvement includes maxillary hypoplasia, exorbitism, hearing loss (55%), C2C3 spinal fusion (30%),

and nasal airway obstruction due to midface hypoplasia and a high-arched palate. Figure 14.1a is a picture of a child with Cruzon Syndrome who was examined at 2+ years of age. He had congenital hydrocephalus, sleep apnea, proptosis of the eyes, bilateral hearing loss, and global developmental delay. Past surgeries included VP shunts from 4 months of age, fronto-orbital advancement surgery at 5 months and adenoidectomy at 2 years. Monobloc Le Fort Type III and distraction osteogenesis via a coronal flap (intracranial approach) were planned for further correction.

14.1.3 Multidisciplinary Approach

Significant improvement in outcome with lowered morbidity and mortality is achieved with a unique dedicated team approach to discuss new cases and review children that have undergone craniofacial surgeries. Decision making is often not straightforward and clinical input from many professionals ensures that planning and implementation are smooth processes. Every referral of a child with craniofacial abnormality is evaluated and investigated by a group of subspecialists: pediatrician, otolaryngologist, neurosurgeon, maxillofacial surgeon, anesthetist, intensivist, plastic surgeon, geneticist, ophthalmologist, speech therapist, and psychologist.

14.2 Preparation for Surgery and Anesthesia

A holistic approach towards management of children selected for major craniofacial surgery includes early optimization and appropriate reviews in the perioperative period. This exercise is certainly the best step to address modifiable risks to reduce morbidity and mortality.

14.2.1 Planning and Optimization

Timing for major surgery depends substantially on the child who has to withstand the stress of prolonged surgery. Factors for consideration include weight, maturity, and severity of blood loss. Optimization of the child can be considered the most important step for a good and safe outcome and reduces the number of "unexpected" challenges for surgery. Every clinician involved has a specific role to play and communication among the members contributes to a sound strategy to care for the child in the perioperative period. The parents are involved too. Proper feeding methods and adequate nutrition are discussed with parents so that proper weight gain is achieved.

Pertinent to the anesthetist's role is emphasis directed at the preparatory stage regarding airway and breathing. A common phenomenon in childhood is upper respiratory tract infections (URTI). The etiology is usually viral in nature but the presence of recurrent episodes of URTI is a cause for concern. Repeated lung infections may be due to frequent aspirations from gastroesophageal reflux, esophageal dysmotility or incoordinate swallowing. Meticulous attention by the multidisciplinary team to obtain the right diagnosis assures appropriate perioperative care to prevent respiratory morbidity in the postoperative period, such as pneumonia and prolonged intubation.

Other significant respiratory signs and symptoms are obstructed breathing, stridorous breathing, snoring, or sleep apnea. Craniofacial abnormality, especially with orofacial cleft, is a significant risk factor for obstructive sleep apnea (OSA) [1] and justifies adequate investigation and planning prior to major surgery. Sleep studies are beneficial to identify and grade the severity of the apneic episodes. Upper and lower airway obstruction reduces survival if untreated because it causes hypoxia, failure to thrive, aspiration, pulmonary hypertension, and cor pulmonale.

A full neurological and skeletal assessment is performed by neurologists and surgical doctors in advance of the surgical date. Three-dimensional reconstruction of the skull and bony features of the face or computer-generated models are useful aids in planning osteotomies as well as to enable nonsurgical clinicians to

understand the rationale and advantages of surgical intervention.

14.2.2 Address Family Concerns

Adequate counseling of family members creates a conducive environment surrounding the child. Parents who are worried and fearful can affect the patient's well-being. The risks and benefits have to be discussed in a language that parents understand. The family of the child are able to trust an anesthetist who has patience and the ability to allay the fears and uncertainties regarding the surgery The perioperative management and complications arising during and after surgery are explained and informed consent taken.

14.3 Preoperative Anesthetic Evaluation

A sound anesthetic plan for perioperative strategy is based on history, physical examination, and investigations. A detailed family history of medical conditions is essential followed by a thorough history and physical examination of the child. Documents regarding important screenings from various disciplines that have been performed at prior evaluations should be available in the patient's folder. Syndromic children should have a full medical check to identify the systemic involvement, such as cardiac, renal, or Chiari malformation. The level of difficulty in anesthetic care greatly depends on the age, weight, type of syndrome diagnosed, and duration of surgery.

Preoperative evaluation is mandatory to consolidate a plan regarding anesthetic technique, surgical needs, back-up options, and postoperative care for each child.

14.3.1 Detailed History

A detailed history establishes a clear background of the pathophysiological changes that the child has experienced from birth. Developmental milestones, previous surgeries, medications, and allergies are noted. Seizures, respiratory disturbances, sleeping and feeding details, and mental perturbations are necessary information to document. Any recent complaint by the parents is seriously attended to. A careful history may elicit chronic respiratory distress for which the ENT specialist would have started treatment before surgery.

14.3.2 Physical Examination

A full general examination is conducted with special focus on neurodevelopment, nutritional status, detailed airway examination, vascular access and other congenital medical conditions. A skeletal system assessment includes an oral examination, temporomandibular joints, mandible, and maxilla. Heart and lungs are auscultated to detect murmurs and altered breath sounds. A syndromic child necessitates further evaluation of the relevant system involved.

14.3.3 Airway and Breathing System

A thorough respiratory assessment of the chest, lungs, oropharynx, nose, and breathing system is essential. Respiratory disorders are common in syndromic and nonsyndromic craniosynostosis. The presence of choanal atresia may have resulted in stenting or corrective procedure prior to major surgery.

Airway management is difficult in midface hypoplasia and obligates examination to ascertain the severity of compromise from potential loss of lower and upper airway patency and plan for safe control during general anesthesia. Attention is crucial in children with skeletal disorders, particularly at the craniocervical region which poses high risks for breathing and intubation difficulty.

14.3.4 Central Nervous System

Records regarding the specific neurological examination and relevant investigations are perused. Neurological examination by the

anesthetist includes assessment of mental status, sensory perceptions, muscle power and tone. Cranial nerve palsies are noted and the spine is carefully examined for deformities. The presence of ventriculo-peritoneal shunts to relieve raised intracranial pressure should not be obstructed.

Drugs that are prescribed are reviewed and anticonvulsants are continued to the morning of surgery.

14.3.5 Cardiovascular Disorders

A congenital heart disease is more common in syndromic conditions than asyndromic and timely referral to the cardiologist for diagnosis and optimization is warranted. OSA can result in repeated episodes of URTI which predisposes to development of pulmonary hypertension or cor pulmonale for which antibiotic prophylaxis is considered.

14.3.6 Hematologic Disorders

A child for major craniofacial surgery is identified as high risk for significant hemorrhage, and careful patient selection is necessary. Blood transfusion is inevitable and the risks of homologous blood transfusion are many, especially with massive blood transfusion (MBT) where complications are more serious and dangerous [2]. Protocols for MBT are less extensively researched in pediatric population compared to adults but useful suggestions are available [3, 4].

Adjuvant therapy has been described for the reduction of homologous blood transfusion during surgery [5]. The following options may be considered at the preoperative stage:

- Iron supplements and erythropoietin injections started 3 weeks prior to elective craniofacial surgery
- Top-up of RBS 1–2 days earlier in the ward to target hemoglobin 13–14 g/dL

In readiness for major surgery, at least one circulation of blood products is available on the day of operation.

14.3.7 Gastrointestinal Disorders

Pediatric growth charts are useful tools that contribute to an overall clinical impression of the child's development. A well-nourished infant has a normal digestive system, adequate central nervous system function, and musculoskeletal strength in order to synchronize efficient sucking, feeding, and swallowing processes. If a part of the physiological integration is deficient, this can progress to poor growth and development, malnutrition, and pulmonary aspiration.

A diagnosis of gastroesophageal reflux disease (GERD) in infants and children is often difficult but is necessary to confirm. Pharmacological treatment is initially with proton-pump inhibitors. GERD can cause recurrent episodes of aspiration and lung infections and it has been linked to OSA.

14.3.8 Investigations

A full blood count is necessary. A hematocrit above 30% is considered acceptable by the author's craniofacial team although this figure may vary according to the age of patient, duration of surgery, and expected blood loss. Surgery can only proceed when a normal coagulation profile is assured. Renal function and serum electrolytes are obtained in view of expected long surgery and large transfusions of fluids. Liver function data and serum albumin may be relevant in poor weight gain children.

A chest X-ray is the simplest film record to identify a normal heart shadow and lung fields. CT scan is also commonly taken and, if applicable, an MRI. X-rays of the cervical or entire spine may be necessary.

Interpretations of the 12-lead ECG and ECHO findings are best confirmed by the cardiologist.

14.3.9 Premedication

The majority of children are uncooperative, restless from fasting, and fearful in a strange environment surrounded by staff in uniform, especially syndromic children who may be mentally challenged. Children are fasted appropriately depending on age (4–6 h) and often receive intravenous fluids to replace fasting losses while in the ward.

Administration of sedation is individualized taking into consideration the risk of respiratory depression in children with airway compromise. In the absence of contraindications, oral midazolam 0.5 mg/kg (maximum 20 mg) for an anxious child is safe. From an age of 6 months and above, parental presence in the operation theatre may be a better sedative and helps the child to achieve a smoother separation from the parent and assists the anesthetist to perform a quiet induction.

14.4 Intraoperative Challenges

There is no optimal anesthetic technique in this category children. The anesthetic management is individualized and dependent on patient's status and surgical demands. A balanced anesthetic technique is frequently able to achieve and maintain the intraoperative needs of children for major surgery. In the presence of increased danger from elevated ICP, the conduct of anesthesia favors the recommendations for neuroanesthetic management of any intracranial lesion.

14.4.1 Intubation

Syndromic craniofacial abnormalities, particularly in children with midface hypoplasia that is present in Apert, Cruzon, and Pfeiffer syndromes, are associated with difficult airways. It is possible that an airway that is assessed as "no airway compromise" may prove to be unexpectedly demanding or unmanageable at laryngoscopy and intubation. Hence, it is prudent to assume that the airway is a suspicious difficult airway until intubation is completed. The difficult intubation cart should always be available with a variety of oral and nasopharyngeal airways, face masks, laryngoscopes, and supraglottic airway devices. Further aids to intubation include video larynscopes and fiberoptic bronchoscope. However, devices for difficult airway management in very small infants are limited.

During the process of induction and intubation, glycopyrrolate is beneficial, particularly in reactive airways that are at risk of bronchospasm and laryngospasm. The intraoperative antisialagogue dose is 0.004 mg/kg intravenously (not exceeding 0.1 mg). A satisfactory and adequate facemask to enable a snug fit can be difficult. Careful head and neck manipulations are needed during induction and intubation to avoid excessive movements in atlantoaxial instability.

Muscle relaxants are best avoided for intubation and can only be administered when the position of the endotracheal tube is confirmed from capnograhy and lung auscultation. The endotracheal tube has to be safely tied down in view of a long surgery or prone position. Packing of the oral pharynx stabilizes the tube and avoids lung contamination from oral bleeding or CSF trickle.

14.4.2 Vascular Access

It is often time-consuming to obtain venous access in smaller infants and large bore catheters, at least two, are inserted before surgery begins. All major craniofacial cases require a central venous line (trilumen or bilumen). The insertion of central lines with ultrasonography is safe in expert hands. Intravenous lines are arranged to ensure free flow and easy access under the drapes. If they are connected to mechanical intravenous pumps, regular inspection of intravenous sites allows early detection of extravasation.

14.4.3 Monitoring

Respiratory and cardiovascular systems are monitored closely. Monitoring of cardiovascular stability is imperative in craniofacial surgery

because of frequent large infusions of fluid and blood and from the potential dangers of metabolic acidosis, hypotension, and coagulopathy. Electrocardiogram, pulse oximetry, and temperature probes (core and skin) are properly connected to the patient. Invasive monitoring includes cannulation of the artery and the jugular or femoral vein. From the arterial line, information on hemodynamic status, acid–base and electrolytes, and laboratory data are obtained. The central venous line helps to monitor volume status, treat air embolism, and administer inotropes, when indicated. The long surgery requires bladder drainage and the urine output aids in evaluation of fluid balance. A useful item is a precordial stethoscope which permits frequent auscultation of breath and heart sounds.

14.4.4 Positioning

Improper protection of pressure points can result in ischemic injury and pressure ulcers following a long surgery. Soft padding material and bolsters aid in weight distribution and adjustment for the abdomen, thorax, and head in the prone and lateral positions. The neck is not unduly stretched to enable unimpeded circulation to and from the head. Limbs are positioned without stretching with support for the knees and ankles. The endotracheal tube is securely tied down and its position is further verified by any change in position of the patient.

14.4.5 Intracranial Pressure

In the majority of surgical cranial vault remodeling, dissection and osteotomies are achieved surgically via an extradural approach. The basic principles of neuroanesthesia are often applied to minimize pressure on the brain and to prevent further rise in ICP. Bradycardia may be a signal of undue pressure on the brain or manipulations on the eyeballs. Attention to fluid status is necessary if the surgeon requests an infusion of mannitol to shrink the brain.

14.4.6 Fluid Balance and Metabolic Changes

Fluid management is important and strategized toward provision for deficit, maintenance, losses into interstitial spaces, and blood loss. Replacement of interstitial fluids or third space losses may require more than 6 ml/kg/hour of isotonic crystalloids. Ringer's lactate (RL) has been shown to have an advantage over normal saline due to the former's lower risk for metabolic acidosis, and it has been reported that hyponatremia is also unlikely [6]. Other fluids for children include 5% albumin and blood products. Large administration of fluids can lead to dilutional coagulopathy, hypothermia, and acidosis. This triad of signs has proven to be serious and dangerous in adult trauma patients [4].

Following each bolus of fluid, an evaluation of the response is necessary before the next bolus is administered. Base deficit and lactate levels are regularly measured to detect metabolic changes that occur. It is not unusual to observe at least one episode of metabolic derangement the longer the surgery. Significant changes in base deficit have been linked to the amount of intraoperative blood loss and replacement. The metabolic derangement can persist into the postoperative period which results in a longer stay in intensive care unit (ICU) [7].

Inadequate or slow correction of massive fluid shift during surgery will inevitably cause deleterious electrolyte changes. It is reported that the combination of hypocalcaemia and hypothermia is harmful and can induce coagulopathy. Significant risk develops when temperature is <34°C and ionized calcium <0.9 mmol/L [8].

Management of fluids is closely guided by base excess, lactate level, and hourly arterial blood gas measurement. Other parameters to aid in cardiovascular stability and normovolemia are urine output (>1 ml/kg/hour), heart rate, arterial blood pressure and capillary return (<2 s).

14.4.7 Hemorrhage and Blood Transfusion

The blood volume in pediatric group varies with age and the commonly accepted values are: 100 ml/kg for preterm neonate, 90 ml/kg for mature neonates, 80 ml/kg for infants and older children. Estimation of blood loss is difficult and depends greatly on the extent of corrective procedures, number of sutures involved, and duration of surgery. It is not uncommon that a blood transfusion is necessary for craniofacial surgery, therefore stressing the necessity to plan carefully for optimal hemostasis.

There are several therapeutic choices to mitigate the complications of homologous blood transfusion in the perioperative period [5]:

- It is practical to accept a lower hematocrit, 21–25% during operation.
- Tranexamic acid, an antifibrinolytic, is beneficial for the reduction of blood loss and blood transfusion. Benefits are reported with the intravenous bolus of 50 mg/kg at induction followed by 5 mg/kg/h [9].
- The use of cell saver is also practiced.
- Other clinical therapies include local hemostatics and bone wax. The surgeon contributes significantly by his meticulous surgical work.

The major cause of morbidity is excessive hemorrhage that can result in cardiac arrest and hypoxic brain damage. Vigilance is a prerequisite. Scalp dissection incurs a fair amount of heavy bleeding, to the extent that 30% of the blood volume can be lost. Profound and acute bleeding is common with damaged venous sinuses. Osteotomies and elevation of the periosteum are significant sources of vascular interruption and blood loss.

Massive blood loss results in massive blood transfusion (MBT). MBT has several meanings: transfusion of >50% total blood volume in 3 h or >100% total blood volume administered in 24 h or transfusion to replace ongoing blood loss of >10% total blood volume in a minute. In an older child, the transfusion of >10 units PRBC in 24 hours is regarded as MBT.

The management of MBT requires urgent and diligent monitoring and evaluation. There is uncertainty regarding MBT guidelines as protocols in children are not as greatly researched as compared to adults and they vary from hospital to hospital, depending on existing resources. The transfusion service department holds a pivotal role for swift supply of blood products, particularly PRBC and FFP. For instance, a mean PRBC:FFP of 1:3 was observed in a study on pediatric MBT [3]. Other products to consider are platelets and clotting factor concentrates such as fibrinogen, prothrombin complex concentrate, recombinant factor VIIa (rFVIIa), and factor XIII.

Perioperative bleeding has to be communicated between surgeon and anesthetist and urgently addressed to reduce complications such as coagulopathies, venous air embolism, transfusion reactions, and acute lung injury. Severe morbidity and death may finally ensue from inadequate attention, monitoring, and intervention.

The availability of rapid laboratory data to assess hemostatic status is quite unlikely but they provide a necessary overview of the coagulation status over time.

14.4.8 Venous Air Embolism

In pediatric craniofacial corrections, venous air embolism (VAE) is a rare phenomenon but it can cause cardiac arrest. The venous channels are not collapsible during dissection and pose a risk, especially in a head-up position, but it can occur in any position of the patient. Tools for detection of VAE include capnogram of end-tidal CO_2, stethoscope, ECG, blood pressure, CVP, pulmonary artery pressure, cardiac output, precordial Doppler, and transesophageal echocardiogram (TEE). The most sensitive modality is the TEE but it may not be easily available. Paradoxical air embolism can occur with a preexisting patent foramen ovale.

When VAE is detected, the surgeon is immediately informed. Prompt actions include flooding

the surgical field with saline, compression of jugular veins, adjusting level of head and supporting the hemodynamics with fluids and inotropic drugs. Aspiration of air emboli via the jugular central venous catheter is recommended.

14.4.9 Hypothermia

A common occurrence in pediatric surgery is inadvertent hypothermia, defined as a core temperature <36°C. Prolonged surgery and extensive operative field exposure with massive fluid shifts during surgery lead to significant heat loss. Moreover, smaller infants have less well-developed thermoregulatory mechanism. There is also greater radiant heat loss and hence, whenever possible, temperature in the operation theatre is adjusted at 23°C or even higher for neonates; but high temperatures for long hours may produce an uncomfortable working environment for surgeons and all personnel. A radiant heater is needed at induction and insertion of lines before surgery begins. Apart from avoiding a cold OT environment, the anesthetist ensures that there is humidification of the breathing systems and availability of warm fluids.

Maintaining normothermia during surgery is by active or passive skin warmers. Passive warming by blankets, drapes or plastic sheets on surface body area contributes to reduction of heat loss by about 30%. The most frequently used device for active warming utilizes forced warm air to circulate around the child but correct placement of the disposable blanket is necessary to avoid burns. It is able to increase heat in the body as much as 0.75 °C per hour.

14.5 Postoperative Complications

An experienced craniofacial team contributes significantly to a reduced rate of morbidity and death in the postoperative period. Multiple factors contribute to problems after surgery depending on the age of child, blood loss, duration of surgery, and the syndromic complexity. In a cohort of 49 children who experienced 57 consecutive craniofacial surgeries, a mortality rate of 1.8% with a 7% incidence of major complications has been reported [10].

14.5.1 High-Risk Airway

A decision for extubation at the end of surgery rests on several criteria. The implication of a high-risk airway necessitates a comprehensive examination of the respiratory and breathing system with respect to whether there is airway edema and recovery of protective reflexes. Other important features to assess prior to extubation are level of consciousness, core temperature, hemodynamic stability, and ongoing blood loss. Following extubation, an overnight stay in the ICU or high dependency unit is safer than discharge to a general ward. Continued monitoring of hemodynamics and respiratory parameters in a child is optimally managed in the ICU.

In prolonged extensive surgery, early extubation is planned in the first (or second) day. The high-risk airway in syndromic children may require a delayed extubation and a longer stay in ICU.

In the ICU, intubated children encounter problems associated with tracheal tube patency and airway obstruction. Regular suctioning prevents atelectasis of alveoli and mucous plugs in the endotracheal tube. Hypoxia and hypercarbia need adjustments on ventilator settings. Relevant to the compromised airway, a reason for sedation is to prevent accidental self-extubation of a restless child. A common sedative is midazolam and its minimum effective dose is 200 mcg/kg and for maintenance, 1–10 mcg/kg/min. Other pharmacological drugs that are prescribed for sedation are lorazepam, chloral hydrate, propofol, clonidine, and ketamine.

14.5.2 Pain Control

Analgo-sedation has a vital supportive role in morbidity reduction, such as agitation, hyperglycemia, and poor wound healing. Osteotomies and large areas of tissue dissection that are performed during surgery expose the child to intense pain.

A multimodal pain control strategy is recommended with the use of centrally and peripherally acting drugs. Paracetamol (suppositories or parenteral) and a continuous infusion of morphine or fentanyl are widely practiced.

14.5.3 Fluids, Electrolytes, Hematocrit Changes

Blood loss may continue after surgery in the ICU. It has been reported that maintenance of hematocrit >30% at the end of surgery was associated with a 50% decrease in the absolute risk of receiving a PRBC transfusion postoperatively [11]. Monitoring of fluid status continues closely in the postoperative period. An important derangement in electrolyte balance is hyponatremia and requires further laboratory investigations for a clear diagnosis to exclude conditions such as syndrome of inappropriate antidiuretic hormone or cerebral salt wasting [12]. Maintenance solution is 5% dextrose ½% normal saline with the addition of KCl (with diuresis).

14.5.4 Nausea and Vomiting

Children are at risk of postoperative nausea and vomiting (PONV) after prolonged surgery. An average risk of 40% is expected in children older than 3 years of age. Current evidence suggests that the best prophylaxis against PONV in children is 5HT3 antagonist and dexamethasone. A recommended combination of intravenous ondansetron (50 mcg/kg) and dexamethasone (150 mcg/kg) has better efficacy than a single antiemetic agent. The 2014 guidelines have no recommendations on rescue antiemetics for a child who has already received dexamethasone and ondansetron [13].

14.5.5 Surgical Complications

When symptoms and signs of cerebral edema or intracranial bleed occur, urgent CT scans are needed. Infection is the commonest complication in the postoperative period. Appropriate antibiotic prevents infections that can lead to osteitis and meningitis. Other frequent problems that can arise after surgery are visual disturbances and persistent CSF leak.

Conclusion

Children with craniofacial abnormalities present with a range of cranial and facial deformities together with complications in the natural processes of sight, hearing, feeding, breathing, and mental development. Syndromic and nonsyndromic children require thorough screening and optimization prior to surgery. The challenging field of pediatric craniofacial subspecialty receives expertise from colleagues who work together for better and safer outcomes. The anesthetist equipped with sound knowledge and skills has a crucial role in the perioperative care.

References

1. Lam DJ, Jensen CC, Mueller BA, Starr JR, Cunningham ML, Weaver EM. Pediatric sleep apnea and craniofacial anomalies: a population-based case-control study. Laryngoscope. 2010;120(10):2098–105. doi:10.1002/lary.21093.
2. Bharadwaj A, Khandelwal M, Bhargava SK. Perioperative neonatal and paediatric blood transfusion. Indian J Anaesth. 2014;58(5):652–7. doi:10.4103/0019-5049.144679.
3. Chidester SJ, Williams N, Wang W, Groner JI. A pediatric massive transfusion protocol. J Trauma Acute Care Surg. 2012;73(5):1273–7. doi:10.1097/TA.0b013e318265d267.
4. Cotton BA, Gunter OL, Isbell J, Au BK, Robertson AM, Morris JA, et al. Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. J Trauma. 2008;64(5):1177–82. ; discussion 1182–3 doi:10.1097/TA.0b013e31816c5c80.
5. Sandra LB, Alexis AT, Charles JC. Review article Intraoperative pediatric blood transfusion therapy: a review of common issues. Part II: transfusion therapy, special considerations, and reduction of allogeneic blood transfusions. Pediatric Anesthesia. 2005;15:814–30.
6. Zunini GS, Rando KA, Cox RG. Fluid replacement in craniofacial pediatric surgery: normal saline or ringer's lactate? J Craniofac Surg. 2011;22(4):1370–4. doi:10.1097/SCS.0b013e31821c94db.

7. Arnwaldy YSC, Nargis SA, David AHB. Metabolic changes during major craniofacial surgery. Pedeiatric Anesthesia. 2010;20:851–5.
8. Stricker PA, Shaw TL, Desouza DG, Hernandez SV, Baetlett SP, Friedman DF, et al. Blood loss, replacement, and associated morbidity in infants and children un-dergoing craniofacial surgery. Pediatric Anesthesia. 2010;20(2):150–9. doi:10.1111/j.1460-9592.2009.03227.x.
9. Goobie SM, Meier PM, Pereira LM, McGowan FX, Prescilla RP, Scharp LM, et al. Efficacy of tranexamic acid in pediatric craniosynostosis surgery: a double-blind, placebo-controlled trial. Anesthesiology. 2011;114(4):862–71. doi:10.1097/ALN.0b013e318210fd8f.
10. Oh AK, Kim S, Wang KC, Park CG, Kim CW, Cho BK. Complications of pediatric craniofacial surgery in the Orient: analysis of a 10-year experience. J Craniofac Surg. 1997;8(5):341–51.
11. Thanh TN, Humphrey VL, Maxie P, Clasherrol E, Thomas MA. Intraoperative optimization to de crease postoperative PRBC transfusion in children undergoing craniofacial reconstruction. Pediatric Anesthesia. 2015;25(3):294–300.
12. Levine JP, Steinicki E, Weiner HL, Bradley JP, McCarthy JG. Hyponatremia in the postoperative craniofacial pediatric patient population: a connection to cerebral salt wasting syndrome and management of the disorder. Plast Reconstr Surg. 2001;108(6):1501–8.
13. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2014;118(1):85–113. doi:10.1213/ANE.0000000000000002.

Acromegalic Patients: Do They Pose Airway Problems?

15

Zahid Hussain Khan and Razmeh Hussain Khan

15.1 Historical Perspective

Acromegaly has been recognized since ancient times as it appears in the Old Testament [1]. However, it was only in 1886 when Pierre Marrie [2] described it as a distinct clinical syndrome and for the first time coined the term "acromegaly" for this entity which was till then referred to as "giants" both among the lay man and the intellectual stratum of the society. Marrie provided clear and vivid clinical descriptions of this malady from his own personal observations of his own two patients. Later, in the first quarter of the twentieth century came in the landmark publication of Harvey Cushing [3] who pointed out that the etiology of this disorder was a pituitary dysfunction or pituitary hypersecretion. He could distinctly observe clinical remission in these patients with acromegaly in whom he had performed hypophysectomy further reinforcing his earlier postulation that the syndrome of acromegaly was in fact related to a "hormone of growth" emanating from the pituitary gland itself.

Others have described with exquisite detail the constellation of features and the different organs and systems affected by the clinical syndrome of acromegaly [4, 5].

Acromegaly affects different systems in the body and has been associated with cardiovascular disorders [6, 7], myopathy [8] diabetes mellitus [9] and thus inevitably adds to induction and airway problems during anesthesia [10, 11, 12, 13].

15.2 Anatomical and Pathophysiologic Changes

In acromegaly, there is oversecretion or overproduction of the growth hormone (GH) which can result from oversecretion of growth hormone releasing hormone from the hypothalamus or else from oversecretion of the hormone from a pituitary tumor. Incidence of acromegaly is 3–4 per million per year, with a prevalence in the population of 50–70 cases per million [4].

Because of the rarity of its occurrence, it is altogether impossible to perform prospective studies. The somatic changes commonly seen in these patients are due to the effects of GH on growth and on insulin metabolism. As the changes are insidious, these patients usually land in the operating room with their typical and classic acromegalic facies including large hands and feet. Symptoms that occur as a result of excess GH include diabetes mellitus, hypertension, cardiac disease (eventually leading to left ventricular hypertrophy, congestive heart failure and global cardiomegaly),

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amenorrhea, hyperhydrosis, sleep apnea and carpal tunnel syndrome. Acral enlargement ends up in the characteristic acromegalic features. The acral enlargement consistently involves upper airway redundancy, which includes pharyngeal and tracheal changes that can lead to airway complications. In addition, coarsening of the features with bony enlargement can concomitantly involve macroglossia; prognathism with malocclusion; and hypertrophy of the laryngeal soft tissue, epiglottis and aryepiglottic folds. Together, all these changes commonly alert the anesthesiologist about the gravity of the situation [14].

Pulmonary function tests are consistent with extrathoracic obstruction as the cause of pulmonary complication. However, there is greater impairment of expiration than inspiration as confirmed by flow-volume loops [15]. As a result of oversecretion of the GH, there is resistance to the effects of insulin, which leads to glucose intolerance. As a result, the glucose concentrations were found to be significantly higher in acromegalics compared to the control group [14]. This aspect is of paramount importance and should be kept in mind since hyperglycemia worsens some types of cerebral ischemia [16]. Acromegaly usually involves the cardiac tissue and can occur with or without concurrent hypertension. However, a correlation between the degree of cardiac enlargement and GH concentrations is lacking [6].

15.3 Difficult Airway and Its Prediction

The ASA Task Force on Management of the Difficult Airway defined it as a clinical situation in which a conventionally trained anesthesiologist experiences difficulty with face mask ventilation of the upper airway, difficulty with tracheal intubation or both [17]. Mallampati et al. [18] introduced their maiden airway screening test that classifies visibility of the oropharyngeal structures. Other tests that are widely used as tools for predicting difficult intubation (DI) include the inter-incisor gap (IIG), the thyromental distance (TMD), the sternomental distance (SMD), the Wilson risk sum score and the upper lip bite test (ULBT) [19, 20, 21, 22, 23]. In an editorial, Yentis [24] questioned whether attempts at prediction are likely to be useful because of the extremely low rate of occurrence of DI.

Having discussed that, obviously the most important drawback in using the TMD, SMD and IIG is the quantitative nature of these tests [25], whereas the classification based on the ULBT is of a qualitative nature, making the differentiation of airway class easy, succinct and precise. Furthermore, the differences between the ULBT and the other tests currently in use are those between continuous and discrete variables. Thus, the ULBT is associated with the least interobserver variability, which gives it an added advantage as an airway screening test [26].

15.4 Incidence and Possible Causes of Difficult Intubation in Acromegalics

The incidence of DI in acromegalic patients has been reported to range from 9.1% to 13% [27–29]. Muchler et al. [30] reported the incidence as 30%. Nemergut and Zuo [31] reported an incidence of 3.8% in acromegalics. They further documented that unanticipated difficulty with airway management was three times more common in acromegalic patients than in patients with nonfunctioning pituitary tumors (9.1% vs. 2.6%) while reviewing the perioperative records of 746 patients that underwent transsphenoidal microsurgery at the University of Virginia between 1995 and 2001. Acromegaly is commonly recognized as a cause of difficulty in airway management and intubation [13]. The causes of difficult intubation include prognathism, macroglossia, thickening of the pharyngeal and laryngeal soft tissues and the vocal cords, fixation of the vocal cords, palsy of the recurrent laryngeal nerve, decrease of the width of the cricoid arch and hypertrophy of the arytenoepiglottic and ventricular folds [32]. We should have a rational explanation of the difficulty. If there does exist a difficulty, It is the most tedious and cumbersome difficulty of all to deal with.

Acromegalics face DI with a prevalence of 12 and 30%. In one study, the Cormack–Lehane

grade (CLG) [33] was 26% [25]. The differences in these and other studies could be attributed to the criteria defined for DI.

Elevated levels of GH cause significant alterations in airway anatomy as seen in acromegalic patients [34]. Hypertrophy of facial bones and coarsening of features are commonly seen in these patients. The mandible becomes thicker leading to significant prognathism. Soft tissues of the nose, mouth and tongue are all affected. There is significant macroglossia and hypertrophy of the laryngeal and pharyngeal soft tissues leading to reduction in the size of the glottic opening, thus contributing to airway obstruction and respiratory disease [10]. In their small series of patients, Hassan et al. [35] reported that the cricoid width and anteroposterior diameter were narrower which were attributed as possible factors of airway problems in acromegalic surgical patients.

15.5 Difficult Mask Ventilation in Acromegalic Patients

Difficult mask ventilation (DMV) is defined as the inability to record a regular carbondioxide waveform. Although Hakala et al. [12] did not encounter DMV, they warned that this risk should be taken into consideration when anesthetizing these patients. Awake intubation under topical anesthesia and sedation is the safest way to proceed if difficulties in ventilation and intubation are expected. Khan and Rasouli [36] in their large series could find DMV in these patients and they would always check the feasibility of face mask ventilation in an apneic patient after premedication and induction doses of thiopental sodium. If feasible, a neuromuscular blocking drug (NMBD) would be given and endotracheal intubation attempted. On the contrary, if mask ventilation would be found difficult, a direct laryngoscopy and intubation would be initiated under the umbrella of a lidocaine spray and without administering an NMBD. The essential part is not to intubate the trachea but to make sure that ventilation and oxygenation are maintained at all cost.

It has been stated that tracheal intubation may be achieved easily in some of the patients in whom DMV is encountered. If mask ventilation is not feasible despite the use of an oral airway, O_2 flush or help of two providers, then attempt a tracheal intubation as the first option and if that also fails, then use the alternative approach, that is, the laryngeal mask airway (LMA) [36].

In the general population, Langeron et al. [37] could find an incidence of DMV as 5%. In cases of DMV, the incidence of DI is increased fourfold, thus warning the anesthesiologist to be more cautious when DMV is encountered.

15.6 A Discrepancy Between Airway Screening Tests and DI

The airway screening tests help the physician in implementing a pragmatic and logical approach in the airway management of acromegalic patients. However, the tests are not totally reliable and can give false positive or negative results, thus adding to our problems in the management of these cases.

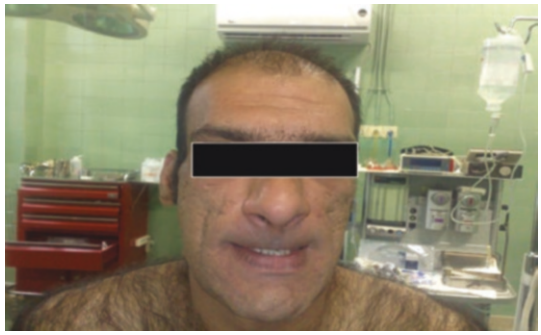
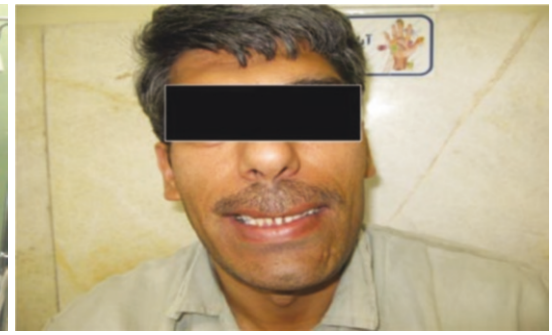
Although preoperative Mallampati scores of 3 and 4 are of value in predicting difficulty, even this test will miss a significant number of patients with a difficult airway [27]. Schmitt et al. [27] defined Mallampati classes 3 and 4 as predictors of difficult laryngoscopy, and found a significant association between Mallampati classes and difficult visualization of laryngeal structures. Using Fisher exact test, they found a p value of 0.001 reflecting strong and significant association, and concluded that the presence of Mallampati classes 3 and 4 served as a predictor of laryngoscopy grade III. They also documented that 20% of acromegalic patients assessed as Mallampati classes 1 and 2 were noted to be difficult to intubate. In the same vein, Edward and Zhiyi [28] found that 4.8% of acromegalic patients assessed as Mallampati classes 1 and 2 were difficult to intubate. These results show that the Mallampati classification has poor negative predictive value in acromegalic patients and DI may be unpredictable. They further documented that of all the 146 patients, the 28 difficult ones were successfully intubated. In their series, although a Mallampati class 3 assessment

was associated with an increased risk of difficulty, 50% of difficult acromegalic patients were evaluated as Mallampati class 1 or 2 during preoperative examination. Both false negative and false positive results are frequently encountered with the Mallampati test. A false negative test can endanger the patient's life because it imparts an erroneous impression that the patient does not have an airway difficulty, whereas in reality the patient does have a difficulty. A false positive result on the contrary gives a false alarm and alerts the physician that a danger does exist, thus prompting the anesthetic team to expand the armamentarium for an expected DI, thus incurring an extra cost for the patient and consuming a good deal of valuable time. Thus, a false alarm does add to our responsibilities regarding patient's management.

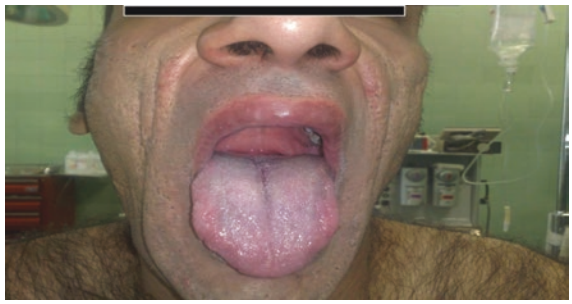
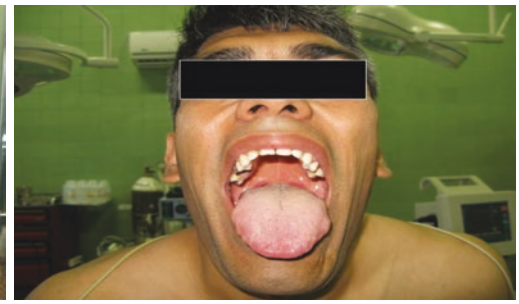
Khan and Rasouli [36] shared their experience in intubating more than 800 patients undergoing transsphenoidal surgery, the largest series of acromegalic patients so far reported in the literature. They say that it is rational to expect DI in patients with acromegaly because of macroglossia, vocal cord hypertrophy and longer TMD. Most of their patients had Mallampati classes 3 and 4 on preoperative evaluation, but they could visualize the glottis during laryngoscopy meaning thereby that a CLG [33] was 1 or 2 and thus intubation was easy. In sharp contrast to the findings of Edward and Zhiyi [28], who found a Mallampati class 1 or 2 in approximately 50% of their patients during preoperative evaluation, Khan and Rasouli [36] preponderantly encountered a Mallampati class 3 or 4 prior to operation. Owing to the fact that acromegalic patients have massive macroglossia, the oropharyngeal structures are totally obscured by the huge hypertrophoid tongue and thus it is natural and logical to find a higher Mallampati class during the preoperative examination. The other explanation that can be forwarded for this discrepancy is that the patients in Khan and Rasouli [36] series had reported when they had a full-blown picture of acromegaly as against that of Edward and Zhiyi [28] series wherein the patients might have reported early, thus reflecting a substantially lesser effect of the GH on the airway architecture. This explanation is highly plausable because screening of patients is not routinely performed in the less affluent population, and as a result such patients are frequently missed and left over till such time when they report on their own for the enormous overgrowth of their hands, feet, mandible and the frontal bones. Later on when Khan and Rasouli [36] included the ULBT and compared it with the Mallampati class, they would frequently find a ULBT class 1 or 2 (Figs. 15.1. and 15.2) as against a Mallampati class of 3 and 4 (Figs. 15.3 and 15.4), and despite widely conflicting variations among the two screening tests, they would frequently encounter an easy intubation except in a small number of patients where external laryngeal pressure would decrease the CLG and thus facilitate endotracheal intubation. A higher class of Mallampati depicts DI probably due to massive macroglossia, vocal cord hypertrophy and longer TMD.

Mandibular length was infrequently found to be longer in patients with acromegaly, and this factor could serve as the dominating factor in predicting DI [32]. The longer mandibular length could serve to provide enough space for the huge tongue to be displaced anteriorly in these patients, thus facilitating good glottic exposure and ease of intubation. As we know, the space anterior to the larynx (the mandibular space) determines how readily the laryngeal axis will fall in line with the pharyngeal axis. When the atlanto-occipital joint is extended, this space can be easily measured by the horizontal length of the mandible. In acromegalic patients, the mandibular length is long pointing toward a large mandibular space, thus affording easy compression of the tongue into this compartment rather than pulling it forward to reveal the larynx [38].

Schmit et al. [27] failed to find a correlation between DI and TMD in acromegalic patients. The large TMD due to prognathism with a mean of 9 cm in their patients clearly exceeds the values reported for nonacromegalic patients [39]. TMD initially introduced to recognize retrognathism may not be appropriate in acromegalic patients [27]. However, this hypothesis has neither being tested nor attested in clinical trials.

Figs. 15.1. and 15.2 Patients asked to take a bite of the upper lip which reveals a ULBT class 1–2

Figs. 15.3 and 15.4 Upon full protrusion of the tongue, a Mallampati class 3–4 is revealed

If your preoperative assessment is accurate, you would be rewarded for the accuracy of your calculations and patient safety. If the assessment is taken lightly, you should be strongly convinced of the worst risks, in store for you as an anesthesiologist and as a care provider.

15.7 Intubation Strategies in Acromegaly

Before induction of anesthesia and intubation, it is incumbent to know that perioperative metabolic problems such as lower urine output are seen during the operation and these disturbances could be because of preoperative hypovolemia, fluid volume dysautoregulation and/or renal dysfunction commonly seen in acromegalic patients as an integral part of the so-called syndrome of acromegaly with a constellation of features and symptoms due to multisystem involvement.

Several authors have focused on airway difficulties in these patients presenting for surgery. To achieve the goals of ventilation and oxygenation, devices such as LMA or laryngeal tubes are employed, or else lighted styles, videolaryngoscopes, and flexible bronchoscopes are used to assist or facilitate intubation. Supraglottic devices are used to achieve the essential goal of ventilation but the problem with them is that they cannot be used in patients with a small IIG. Some are designed primarily to ventilate such as the classic, unique, proseal and supreme LMA, whereas others such as the Fastrach intubating LMA, I-Gel and Cobra PLA can all be used for intubation. Law-Koune et al. [40] in their series used the intubating laryngeal mask airway (ILMA) as a primary tool of ventilation and intubation in acromegalic patients. It was inserted when the bispectral index fell below 50. They concluded that ILMA can be used as a primary airway for oxygenation in acromegalic patients (manual bag ventilation) but the rate of failed blind intubation

precludes its use as a first choice for elective airway management.

Kao et al. [41] on the other hand suggest an awake endotracheal intubation under local anesthesia with the aid of a fiberoptic bronchoscope in these patients because of the commonly held belief of problems with DI.

It has been stated that up to 75% of acromegalic patients have obstructive sleep apnea (OSA) [34, 42]. There is a strong association between OSA and DI [43, 44]. In acromegaly complicated by OSA, there is a high risk of preoperative airway comprise [42], thus such patients need extra vigilance and an extra airway armamentarium as far as their airway and intubation are concerned.

In their experience and based on the airway evaluation, Khan and Rasouli [36] stated that if commonly used strategies fail to achieve a substantial rise in the oxygen saturation, a tracheal intubation should be tried and an LMA inserted if the tracheal intubation cannot be achieved. Moreover, in many studies, successful intubation could be achieved even in the apparently difficult cases [27, 28]. It has been suggested that unnecessary tracheostomy should preferably be avoided in acromegalic patients and fiberoptic intubation tried instead [13]. In their study, Hakala et al. [12] reported that fiberoptic intubation may prove difficult or frankly fail in acromegalic patients. They further claimed that the commonly employed tests for prediction of intubation difficulties do not apply to fiberoptic intubation. They concluded that the method of choice for intubation in acromegalic patients remains unclear.

Although routine tracheostomy had been advocated in the past for acromegalic patients [11], it has been reported that it is rarely necessary [13].

At times when it would be difficult for the surgeon to remove the tumor lying in the pituitary fossa, a transient Valsalva maneuver would help the tumor to pop out from its bed, thus facilitating surgical removal and evacuation. This approach has helped the surgeon in countless occasions in our series of patients [36].

Since DMV is a common occurrence in acromegalic patients as reported [36], the ULBT can serve as a predictor of DMV [39] and a higher ULBT score should serve as a warning sign that DMV most probably would be encountered after the patient has been rendered apneic following a paralyzing dose of muscle relaxant.

15.8 Extubation Strategies

As the nose is packed at the end of transsphenoidal surgery and owing to the fact that breathing via the mouth is grossly impaired because of concomitant macroglossia and OSA, extubation should preferably be attempted in a fully awake and obeying patient. At times after extubation when an adequate oxygen saturation by pulse oximeter could not be obtained while the patient was being positioned supine, a tonsil or a prone position almost always helped the patients in performing an unimpeded respiration and thus helping them in improving their oxygen saturation [36].

Extubation attempted while the patient is still sedated leads to a rapid decline in oxygen saturation, spells of cyanosis and difficulty in maintaining mask ventilation. In such a scenario, if a rapid re-intubation is not performed (which also is exceedingly difficult), severe hypoxia along with acidosis would cause a cardiac arrest. In such life-threatening situations, succinylcholine should be administered and the patient intubated rather than performing futile attempts of mask ventilation in an impending hypoxic and restless patient. This strategy has saved some of our patients who had become hypoxic after extubation. However, the use of succinylcholine is only recommended if the patient had an uncomplicated tracheal intubation prior to surgery.

Conclusion

Acromegaly owing to the constellation of features and involvement of different systems and organs in the body is an anesthetic challenge, and these patients do pose airway problems both during the induction of anesthesia and after extubation. Thus, they need extra surveillance and care as far as their anesthesia management is concerned in general, and their airway in particular.

In the end, I would feel rewarded and get a momentary relief if I have been able to fully

divulge the mystery of airway management difficulty in acromegalic patients, with an explanation that would sound satisfactory to the mind and judgment of a practical anesthesiologist, and I would leave you to repose further on this complicated issue. I reckon the explanations forwarded would sound satisfactory and pragmatic.

References

1. Old Testament. Samuel 17:1–58.
2. Marie P. On two cases of acromegaly. Rev Med. 1886;6:297–333.
3. Cushing H. Partial hypophysectomy for acromegaly: with remarks on the function of the hypophysis. Ann Surg. 1909;50:1002–7.
4. Melmed S, Fagin J. Acromegaly update etiology, diagnosis and management. West J Med. 1987; 146:328–36.
5. Melmed S. Acromegaly. N Engl J Med. 1990; 322:966–77.
6. Fossil L, Thiene G, Caregaro L, Giordano R, Lauro S. Dysrythmias and sudden death in acromegalic heart disease. Chest. 1977;72:495–8.
7. McGuffin Jr WL, Sherman BK, Roth J, et al. Acromegaly and cardiovascular disorders: a prospective study. Ann Intern Med. 1974;81:11–8.
8. Stern LZ, Payne CM, Hannapel LK. Acromegaly: histochemical and electron microscopic changes in deltoid and intercostal muscle. Neurology. 1974;24:589–93.
9. Garcia-Esteves DA, Araujo-Vilar D, Cabesaz-Cerrato J. Non-insulin mediated glucose uptake in several insulin-resistant states in the post-absorptive period. Diabetes Res Clin Pract. 1998;39:107–13.
10. Kitahata LM. Airway difficulties associated with anesthesia in acromegaly. Three case reports. Br J Anaesth. 1971;43:1197–0.
11. Southwick JP, Katz J. Unusual airway difficulty in the acromegalic patient: indications for tracheostomy. Anesthesiology. 1979;51:72–3.
12. Hakala P, Randell T, Valli H. Laryngoscopy and fiberoptic intubation in acromegalic patients. Br J Anaesth. 1998;80:345–7.
13. Ovassapian A, Doka JC, Romsa DE. Acromegaly-use of fiberoptic laryngoscopy to avoid tracheostomy. Anesthesiology. 1981;54:429–30.
14. Seidman PA, Kofke WA, Policare R, Young M. Anesthetic complications of acromegaly. Br J Anaesth. 2000; 84:179–82.
15. Evans CC, Hipkin LJ, Murray GM. Pulmonary function in acromegaly. Thorax. 1977;32:322–7.
16. Siber FE, Traystman RJ. Special issue: glucose and the brain. CCM. 1992;20:104–14.
17. American Society of Anesthesiologists Task Force on Management of the Difficult airway. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology. 2003;98:1269–77.
18. Mallampati SR, Gatt SP, Gugino LD, Desai SP, Warakasa B, Friebeger D, Liu PL. A clinical sign to predict difficult tracheal intubation : a prospective study. Can Anaesth Soc J. 1985;32:429–34.
19. Sava D. Prediction of difficult tracheal intubation. Br J Anaesth. 1994:73149–53.
20. Patil UV, Stechling LC, Zauder HL. Predicting the difficulty of intubation utilizing an intubation guide. Anesthesiology. 1983;10:32.
21. Al Ramadhani S, Mohamed LA, Rocke DA, Gouws E, Ramadhani SA. Sternomental distance as the sole predictor of difficult laryngoscopy in obstetric anaesthesia. Br J Anaesth. 1996;77:312–6.
22. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. Br J Anaesth. 1988;61:211–6.
23. Khan ZH, Kashfi A, Ebrahimkhani E. A comparison of the upper lip bite test (a simple new technique) with modified Mallampati classification in predicting difficulty in endotracheal intubation: a prospective blinded study. Anesth Analg. 2003;96:595–9.
24. Yentis SM. Predicting difficult intubation: worth while exercise or pointless ritual. Anaesthesia. 2002;57:105.
25. Khan ZH, Mohammadi M, Rasouli MR, Farrokhnia F, Khan RH. The diagnostic value of the upper lip bite test combined with sternomental distance, thyromental distance, and interincisor distance for prediction of easy laryngoscopy and intubation: a prospective study. Anesth Analg. 2009;109:822–4.
26. Khan ZH. Airway assessment: a critical appraisal. In: Khan ZH, editor. Airway management. Switzerland: Springer International Publishing; 2014. p. 15–32.
27. Schmitt H, Buchfelder M, Radespiel-Tröger M, Fahlbusch R. Difficult intubation in acromegalic patients: incidence and predictability. Anesthesiology. 2000;93:110–4.
28. Edward CN, Zhiyi Z. Airway management in patients with pituitary disease: a review of 146 patients. J Neurosurg Anesthesiol. 2006;18:73–7.
29. Messick Jr JM, Cucchiara RF, Faust RJ. Airway management in patients with acromegaly. Anesthesiology. 1982;56:157.
30. Müchler HC, Renz D, Ludecke DK. In: Lüdecke DK, Tolis G, editors. Anesthetic management of acromegaly. New York: Raven Press; 1987. p. 267–71.
31. Nemergut EC, Zuo Z. Airway management in patients with pituitary disease: a review of 746 patients. J Neurosurg Anesthesiol. 2006;18:73–7.
32. Murrin KR. Intubation procedure and causes of difficult intubation. In: Latto IP, Rosen M, editors. Difficulties in tracheal intubation. London: Baillière Tindall; 1985. p. 75–89.

33. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. Anaesthesia. 1984;39:1105–11.
34. Fatti LM, Scacchi M, Pincelli AI, et al. Prevalence and pathogenesis of sleep apnea and lung disease in acromegaly. Pituitary. 2001;4:259–62.
35. Hassan SZ, Matz GJ, Lawrence AM, Collins PA. Laryngeal stenosis in acromegaly: a possible cause of airway difficulties associated with anesthesia. Anesth Analg. 1976;55:57–60.
36. Khan ZH, Rasouli MR. Intubation in patients with acromegaly: experience in more than 800 patients. Eur J Anaesthesiol. 2009;26:354–5.
37. Langeron O, Masso E, Huraux C, Guggiari M, Bianchi A, Coriat P, Riou B. Prediction of difficult mask ventilation. Anesthesiology. 2000;92:1229–36.
38. Khan ZH. Long mandibular length in acromegalic patients (Unpublished data).
39. Frerk CM. Predicting difficult intubation: a retrospective study. Anaesthesia. 1991;46:1005–8.
40. Law-Koune JD, Liu N, Szekely B, Fischler M. Using the intubating laryngeal mask airway for ventilation and endotracheal intubation in anesthetized and unparalyzed acromegalic patients. J Neurosurg Anesthesiol. 2004;16:11–3.
41. Kao SC, Chiou Jr H, Hsu JC, Lin CM, Lui PW. Difficult oral endotracheal intubation in an acromegalic patient receiving transsphenoidal surgery-a case report. Acta Anaesthesiol Taiwan. 2006;44:31–4.
42. Weiss MV, Šonka K, Pretl M, et al. Prevalence of the sleep apnea syndrome in acromegaly population. J Endocrinol Invest. 2000;23:515–9.
43. Siyam MA, Benhamou D. Difficult endotracheal intubation in patients with sleep apnea syndrome. Anesth Analg. 2002;95:1098–102.
44. Hiremath AS, Hillman DR, James AL, et al. Relationship between difficult tracheal intubation and obstructive sleep apnoea. Br J Anaesth. 1998; 80:606–11.

Airway and Fluid Management of Patients in a Prone Position

16

Mathieu Asselin and Orlando Hung

16.1 Introduction

Proper patient positioning for surgical procedures is an important consideration for a safe and successful outcome. A proper position provides appropriate surgical access and guards against injury due to pressure points and strain on neurological and musculoskeletal structures.

The prone position is most commonly required for surgical procedures on the spine, and for selected procedures in neurosurgery, urology, and general surgery. This position is complicated by an increased risk of stretch and pressure injury of nerves, eyes, ears, breasts, genitalia, and stoma; postoperative neck pain and limitation of motion; interference with flow in neck vessels; cardiovascular instability; difficulty with ventilation; and problems with providing cardiopulmonary resuscitation as compared with the supine surgical position [1].

Airway considerations for patients placed in the prone position may include difficult access to the airway, migration of the endotracheal tube (ETT) (tip of the ETT moving cephalad or caudad with head extension and flexion, respectively), limited ability to reposition the head and neck for bag-mask- ventilation (BMV), and the potential development of airway edema.

16.2 Preoperative Airway Assessment

Oxygenation of an unconscious patient can be done by four basic methods: bag-mask- ventilation (BMV), tracheal intubation, insertion of an extraglottic device (EGD), and by providing a surgical airway. Different guidelines for the management of the difficult airway [2–5] stress the importance of preoperative airway assessment. Predictors of difficulty should therefore be sought prior to all airway management [4]. However, these guidelines did not discuss the airway management of patients in prone position. Nonetheless, it is obvious that prone position interferes with all four basic methods of airway management, especially with head and neck surgeries. Therefore, the airway strategy should be several-fold: an initial strategy to manage the airway at induction and intubation, safely securing the tracheal tube following intubation, a back-up plan in case of airway loss during the surgical procedure, and an extubation strategy following the surgical procedure.

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While surgically suboptimal, the prone position can sometimes be avoided. If a difficult airway is anticipated, it is important to discuss alternative surgical positions for the procedure with the surgeon. Other positions for the surgical procedures, such as lateral, park bench, or supine positions may be considered to minimize the risk of managing a difficult airway situation (e.g., accidental extubation, airway edema) in a patient placed in prone position with an anticipated difficult airway.

In case of a known or predicted difficult laryngoscopic intubation, the technique utilized to manage the airway will depend on whether or not ventilation can be readily provided by BMV, EGD, or a surgical airway, aspiration risk, the available resources, as well as the expertise of the clinician. The situation becomes more challenging in patients with cervical spine instability or spinal cord damage. For this patient population, some consider that awake bronchoscopic intubation followed by placing the patient in prone position prior to induction of anesthesia provides the widest margin of safety because it allows verification of neurological integrity prior to surgery. However, there is no clinical evidence to support this practice. In a retrospective review of 150 patients with cervical spine injury, Suderman et al. [6] found no difference in neurological outcomes following tracheal intubation awake or under general anesthesia, with or without in-line cervical spine immobilization.

16.3 Intraoperative Management

16.3.1 Choice of Airway Device

During the last two decades, many extraglottic devices (EGD), including the laryngeal mask airway (LMA) and the second-generation EGDs (e.g., LMA-ProSeal) have been shown to be effective and safe in providing ventilation and oxygenation in the supine position. Advantages of these EGDs over tracheal intubation are well-known [7]. Despite the lower seal pressure and a higher frequency of gastric insufflation [7], the incidence of pulmonary aspiration is low, at least for outpatient anesthesia [8].

Oral tracheal intubation has been the traditional choice of airway management for patients in prone position for a surgical procedure and is arguably less likely to dislodge in this setting. Since the availability of EGDs, some clinicians reported the use of an EGD in different positioning settings, including the prone patient even though Benumof [9] and Fisher [10] suggested that it was contraindicated in this setting in 1992. A recent survey of private practice, German anesthesiologists even showed that as high as 48% of them use EGDs in prone position [11]. While it may be reasonable to use an EGD device for surgical procedures requiring prone position in selected situations (e.g., short surgical procedures, non-obese patients, absence of risk factors for a difficult airway, absence of risk factors for pulmonary aspiration), this issue remains controversial [12–14].

A recent review of the literature on induction of general anesthesia (GA) in the prone position and the concurrent use of EGDs concluded that very low complication rates were associated with the use of EGDs after elective induction of anesthesia for prone position in select patients [15]. On the other hand, the investigators also indicated that there is insufficient evidence to suggest the routine use of this technique.

Some reported the use of an EGD for patients in prone position for elective short procedures [16–24]. The EGD was inserted in the supine position before turning prone or after anesthesia induction in prone position. First-attempt success in the prone position was above 90% [21, 24]. Although complications were rare, airway obstruction [17, 18], green emesis regurgitation (without sequelae) [21], inadequate ventilation requiring reinsertion of the LMA in the supine position [21], and a premolar loss have been reported [25]. EGDs used in these studies include the LMA-Classic [16–21], the i-gel [22, 23], and the LMA- Supreme [24].

In three case reports, an EGD was inserted after induction of GA with the patient prone [26–28]. In two of these cases, the anesthesia team used an intubating LMA and blind intubation was

successfully achieved through the device [27, 28]. Anesthesia was uneventful in all those cases.

A few retrospective and prospective studies were published [29–36], studying a total of 914 patients. In general, patients were recruited if they were non-obese, ASA I–II, if a difficult airway was not anticipated, and if the procedures were short. One exception to this rule is the study by Sharma et al. [34] in which patients with a BMI as high as 55 and with documented gastro-esophageal reflux disease were included. The mean duration of surgery was 102 min, but was as long as 5 h. The EGD required repositioning in 13 patients (6.3%) and changed in six patients (2.9%), two patients required more than two attempts at insertion (1%), and four patients (2%) had gastric content regurgitation, but no clinical evidence of pulmonary aspiration. In the other studies, first-attempt success varied from 76% [36] to 99% [31, 33, 35]. BMV was easy in most (up to 96%) of the patients [31, 36]. Malposition of the LMA [29, 31, 35], hypoventilation [29], oropharyngeal bleeding [29, 31, 35], and laryngospasm [29, 35] were reported. No instance of regurgitation was reported in those latter studies. In one study, two patients needed to be turned back in the supine position to proceed to tracheal intubation because complete air seal was not possible in the prone position [36].

Some studied the efficiency of placement of the EGD following induction of general anesthesia with the patient placed in prone position. The traditional supine tracheal intubation followed by prone positioning was compared to GA induction followed by EGD insertion in patients placed in prone position. Weksler et al. [32] noted a significant reduction in requirement for human resources for positioning in the EGD group. The induction–incision time was also significantly reduced in this group by about 10–15 min. In 2014, Olsen et al. [36] did a randomized controlled trial involving 140 patients in which the primary outcome was the total time taken from initial identification to readiness for radiographic examination of the prone and anesthetized patient. There was a 3–5 min reduction in the prone GA induction group. There was no difference in complications (e.g., the presence of blood in the mouth or on the airway devices) between the groups.

While the EGDs used in the studies above were the LMA-Classic and its variants, other extraglottic devices could probably be used while the patient is in prone position, depending on the skill and experience of the clinician, as well as the resources available. However, there are currently no reports in the literature of the successful use of non-LMA-derived EGDs for patients in the prone position.

In our view, to deliberately induce a patient in a position in which airway management can be difficult, especially in case of failure, seems counterintuitive [15]. In fact, since the anesthesia closed claims analysis by Caplan et al. in 1990 [37], difficult airway guidelines have been published [38–40] and revised [2–5] to improve outcomes related to airway management. To optimally position the patient to favor a good denitrogenation and facilitate tracheal intubation is part of the recommendations. While we recognize that it might be reasonable to use an EGD in patients for prone position for repeated radiotherapy sessions in children to avoid potential tracheal trauma associated with tracheal intubation, we believe that routine use of this technique is not to be recommended. Most studies reporting the safety of this technique had small sample size and were underpowered to detect rare events such as “cannot intubate, cannot oxygenate” scenarios, pulmonary aspiration, or to detect any difference in position-related adverse events. Therefore, absence of unfavorable outcomes should not be interpreted as proof of safety. Besides, unfavorable outcomes have been reported. Indeed, at least two prone patients needed to be turned back to supine position [36] for tracheal intubation due to incomplete air seal with the EGD. Moreover, although there was no evidence of aspiration, two different publications report occurrence of regurgitation [21, 34]. Other worrisome adverse events (airway obstruction, laryngospasm, etc.) were also reported. Although there are many proposed benefits [15] of prone induction followed by EGD insertion (lower incidence of pressure injuries, injury to the patient, lines and tubes dislodgement caused by the turn,

operating room personnel injuries [41]; decrease in required human resources for positioning and lifting of patient), they are not supported by clinical studies. The only statistically significant advantage of this approach is a decrease in time before surgical readiness [32, 36]. Based on these two studies, the time saving is approximately 5 to 15 min per case. While we acknowledge the pressure to do more procedures in our settings, we strongly believe that safety cannot be compromised. Finally, some suggest that managing the airway in an anesthetized patient in a prone position is a rescue skill worth acquiring should the tracheal tube become dislodged under anesthesia as turning back the patient to supine position takes time and may not be possible. We acknowledge the usefulness of such a skill, but, in our view, practicing rescue airway management skills (e.g., BMV, use of EGD and tracheal intubation) in a prone position on manikins, or on clinical-grade cadavers, is more prudent and safer. Therefore, we believe that tracheal intubation in the supine position followed by a careful turning to the prone position by experienced personnel remains the gold standard today.

16.3.2 EGD Insertion Technique

A number of studies have reported the EGD insertion technique in a patient placed in a prone position when the use of an EGD is deemed necessary. Patients are first asked to comfortably position themselves prone on the operating table with their head turned to either side. With the cuff completely deflated, the EGD will be inserted following denitrogenation and induction of anesthesia. The preferred insertion technique would be the traditional digital technique, but with the head turned to the side and the head slightly extended. Air seal is obtained by cuff inflation. Following the confirmation of proper placement with end-tidal CO_2, the device should be secured using waterproof tape. In some studies, a gastric tube was inserted through the esophageal port of the second-generation EGDs, such as the LMA-Proseal. The thumb insertion technique has also been described [30]. This technique is similar to the digital technique except that the operator uses the thumb instead of the index finger to advance the EGD. As for the use of EGD in the supine position, the use of neuromuscular blockers remains controversial. A 15° tilt of the operating table has been suggested in helping with airway access for EGD placement [31]. It is important to emphasize that a spare trolley should be available at all time during surgery for patients placed in prone position so that rapid turning to supine position can be achieved for emergency management of a failed airway (e.g., dislodged EGD or ETT) or cardiovascular instability (e.g., cardiac arrest).

16.3.3 How to Secure the Airway Device

To minimize the risk of ETT dislodgement, it is imperative to secure the ETT properly, particularly for patients in a prone position. The most common method of securing the ETT is to tape it to the face. Unfortunately, the presence of facial hair, oily skin, perspiration, oropharyngeal secretions, and surgical skin preparation solutions can impair the adhesiveness of the tape. Generous use of waterproof tape and the use of multiple attachment points can reinforce the bond to the patient's face. The application of tincture of benzoin to the skin may improve tape adhesion. Although adequate taping is required for the prone patient, complete sealing off of the mouth should be avoided, as oropharyngeal secretions should be allowed to drain out. This will minimize pooling of saliva and secretions, which may loosen the tape over time. In addition, the use of an antisialogogue (e.g., glycopyrrolate) may be helpful as a preventive measure to minimize secretions. Placement of a throat pack in the oropharynx or a gauze bite block may also limit the amount of secretions draining out of the oropharynx, which may disrupt the bond between the tape and the skin. However, the clinician must always be aware of the potential for pressure injury (e.g., lingual nerve injury) associated with the use of these throat packs and bite blocks [42, 43]. Following the placement of the throat pack,

personnel working in the operating room should be reminded about its use so that it would be removed prior to extubation at the end of the case.

Patients with facial hair often pose additional problems with securing the airway. For these patients, it may be best to tie the ETT around the neck with an umbilical tape. It is important not to tie the ETT too tightly and thereby obstruct venous return from the head. If the ETT cannot be tied around the neck (e.g., cervical laminectomy or post-fossa craniotomy), other possible options to secure the ETT should be considered. These include suturing the ETT to the lips, tying/suturing the ETT to the upper incisors or nares, and shaving the patient's beard prior to induction of anesthesia.

16.4 Troubleshooting in Airway Issues in the Prone Position

16.4.1 A Leak in the Ventilation System

A leak in the ventilation system is a fairly common occurrence during surgery and is usually easy to manage. However, it is more complex when it occurs in a patient placed in prone position due to the unique challenges it presents to the clinician.

In diagnosing and managing this situation, the source of the leak must be promptly determined. This is usually accomplished by inspecting all portions of the anesthesia circuit in an organized and sequential manner. With the prone patient, it is usually easier to start inspection from the anesthesia machine to the patient, especially if the patient's head is away from the anesthesia workstation. This would include checking flow rates, ventilator/bag volumes, valves, circuit tubing, and connections.

Leaks within the anesthesia machine or circuit may involve circuit disconnects, leaks around circuit connections or valves, and undetected holes in circuit components. Management of such leaks may include increasing the fresh gas flow (for a small leak), or replacing part or all of the anesthesia circuit or machine.

Potential leaks associated with an airway device include partial or complete dislodgement of the device, inadequate volume in the ETT cuff, disruption of the ETT cuff, and a leak from the pilot cuff apparatus (pilot valve or tubing leak).

If there is evidence of tube damage and a significant leak exists, the ETT should be replaced. On the other hand, small air leaks may be overcome by increasing inspired gas flow if the remaining surgical time is short. The benefits of continuing the case without further airway manipulation must be weighed against potential further airway compromise and operating room contamination with anesthetic gases. Therefore, should the clinician decide to proceed, it would be prudent to change the anesthetic technique to total intravenous anesthesia. Larger leaks can be attenuated by the insertion of a throat pack, if not already present. If a throat pack was in place around the faulty ETT immediately following the initial tracheal intubation, it may be possible to remove the faulty ETT and pass a new ETT with a deflated cuff into the trachea through the cast (or track) made by the throat pack or it may be possible to change the ETT over an airway exchange catheter. If these measures fail and the airway has been compromised, ventilation and oxygenation of the patient must be reestablished as soon as possible.

16.4.2 A Dislodged ETT

The goal of management is to resume oxygenation as soon as possible. This situation should be treated as an unanticipated difficult airway emergency and basic principles of established guidelines should be followed [2, 3, 5].

First, operating room personnel must be informed of the emergency situation and additional help should be summoned. The difficult airway cart, the patient's stretcher or bed (should be readily available at all times during anesthesia for prone position patients), and the resuscitation cart should be brought into the operating room immediately. The surgical team should close the surgical wound as soon as possible to allow transfer of the patient to a stretcher in the supine position.

If oxygenation and ventilation remain acceptable and it is still possible to ventilate the patient through the ETT as confirmed by end-tidal CO_2 waveform, the tip of the ETT is likely inside the trachea with the cuff just above the vocal cords. In that situation, the cuff should be deflated and a simple advancement of the tube may be all that is required. If airway equipment is readily available, the ETT can be advanced over a tube exchanger, or a flexible bronchoscope.

If the ETT is completely dislodged, the patient should return to the supine position for definitive airway management. While this would be ideal, it could be difficult to achieve in a timely manner. Moreover, depending on the situation, it might not be without considerable risk to the patient (e.g., potential neurological sequelae during placement of spinal instrumentation [44]), especially if everything will be managed in an unprepared emergency manner. Furthermore, if one waits until the patient returns to supine position to manage the airway, significant delays in oxygenation may occur, which may be associated with catastrophic consequences. Therefore, it is desirable to have several alternative approaches to reestablish oxygenation in this particularly difficult situation. If the patient is turned back to the supine position quickly during the emergency situation, the airway should be managed in the usual manner for any unresponsive or anesthetized patients lying in a supine position.

Options to oxygenate a prone patient are similar to those in the supine patient: BMV, EGD, tracheal intubation, and surgical airway.

BMV should be provided as soon as possible. As discussed above, BMV can be easily achieved in the prone position in the vast majority of elective patients [29, 31, 33, 35]. If possible, rotating the head of the patient to one side may help to achieve an adequate mask for BMV. When difficulties are encountered, oropharyngeal and nasopharyngeal airways can be used. However, BMV in the prone position can be difficult, especially in the emergency setting, due to limited access to the airway, difficult mask seal due to no occipital support to apply counter pressure to the head [45], presence of large amount of secretions, and lack of clinical experience performing BMV in a prone patient. It may be necessary to use a two-hand technique to achieve a mask seal while a second person, or the anesthesia machine, provides ventilation. Provided that a good seal can be maintained, BMV should be reasonably easy in a patient lying prone as gravity tends to move the tongue away from the posterior pharyngeal wall. If BMV is successful, the patient should ideally be turned supine to proceed to tracheal intubation. If turning of the patient is challenging (cervical spine instability, open wound, open skull surgery, etc.), an attempt at tracheal intubation with a flexible bronchoscope is a viable option.

If BMV is impossible, or does not permit effective oxygenation, an EGD can be placed to provide oxygenation and ventilation for the patient in the prone position. Successful use of EGDs has been reported to regain control of the airway and provide positive-pressure ventilation following ETT dislodgement in the prone position [44, 46]. Insertion of the LMA in the prone patient should be attempted using the classic insertion technique recommended for patients in the supine position [47]. Successful insertion of an EGD may actually be easier in the prone position because gravity helps to move the tongue and epiglottis [29] away from the posterior pharyngeal wall and minimizes the risk of down folding of the epiglottis. If EGD insertion is successful and oxygenation is satisfactory, time should be allowed to discuss and decide if the procedure should continue with the EGD in place or if a definitive airway is desired (e.g., prolonged case, risk of aspiration). In the latter scenario, a 6.0-mm ID ETT can pass through a size 4 LMA-Classic (or a 7.0-mm ID ETT through a size 5 LMA-Classic) with flexible bronchoscope (FB) guidance if the "aperture bars" were removed to allow easier passage of the ETT through the opening. Alternatively, the LMA-Classic can be used as a conduit for tracheal intubation using a pediatric bronchoscope loaded with an Aintree Catheter [48]. If immediately available, an intubating LMA (LMA-Fastrach™) can also be placed to provide ventilation and oxygenation and the device can then be used as a conduit for tracheal intubation. However, LMA-Fastrach™ placement, as compared to the LMA-Classic™, can be difficult in the prone position.

In the event that placement of both BMV and EGD fails, tracheal intubation should be attempted. In fact, reintubation while the patient is still in the prone position would eliminate the inherent risks associated with turning the patient. Tracheal intubation by direct laryngoscopy can be performed in the prone patient by the clinician who is positioned at the head of the patient facing caudad. The clinician uses the right hand to insert the laryngoscope into the pharynx and exposes the glottis (Fig. 16.1). Operating the laryngoscope with the right hand while the clinician faces the prone patient allows the laryngoscope blade to displace the tongue away from the right side of the patient's mouth. The clinician then uses the left hand to insert the ETT into the trachea under direct vision. Alternately, direct laryngoscopy and intubation can be performed in a more conventional manner from the right side of the patient (Fig. 16.2). An assistant can turn the patient's head to the right and elevate the right shoulder slightly to facilitate access to the mouth. Tilting the table could improve the accessibility as well. The head and neck can also be placed in the familiar sniffing position. This technique of laryngoscopic intubation in prone patients has been shown to be effective (99% success rate) and safe [49]. In addition to direct laryngoscopic intubation, alternative intubating techniques can be considered. These include the use of a flexible bronchoscope, an intubating LMA (LMA-Fastrach™, LMA North America Inc., San Diego, CA), light-guided intubation using the Trachlight™ (Laerdal Medical Corp., Wappingers Falls, New York), and digital intubation. However, there is limited clinical information with regard to the effectiveness and safety of these intubation techniques in patients in the prone position. The selection of a specific technique will be determined by the experience and skills of the clinician. Baer performed endotracheal intubation under direct laryngoscopy in the prone position in 200 patients undergoing lumbar surgery [49]. Two failed intubations occurred and the tracheas of these patients were then intubated in the lateral or supine positions, with difficulty [49]. Van Zundert et al. [50] successfully intubated the trachea under direct laryngoscopy after induction of general anesthesia in a patient lying prone with a penetrating thoracic spine injury from a pair of scissors. We believe that tracheal intubation of patients in the prone position should be reserved for rescue situations and not used in the elective setting. In principle, there might be an advantage to use video-laryngoscope (VL) to overcome the difficulty of obtaining a direct view in patient lying prone. In practice, if laryngoscopy is performed using the right hand with the clinician facing the patient, visualization of the glottis is difficult as the glottic image is inverted, making the placement of the ETT more challenging (Fig. 16.3).

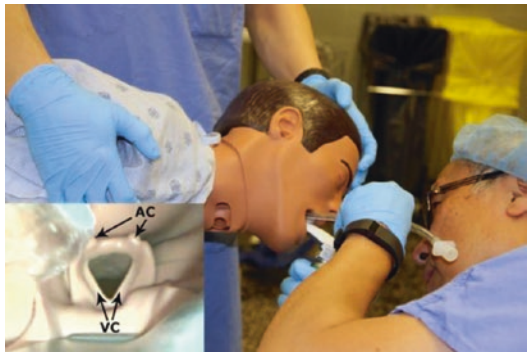

Fig. 16.1 Tracheal intubation of a manikin placed in the prone position: Laryngoscopic intubation using a Macintosh laryngoscope can be performed from the front of the manikin with the right hand holding the laryngoscope. The inset shows the laryngoscopic view of this technique. The vocal cords (*VC*) and the arytenoid cartilages (*AC*) can be visualized easily

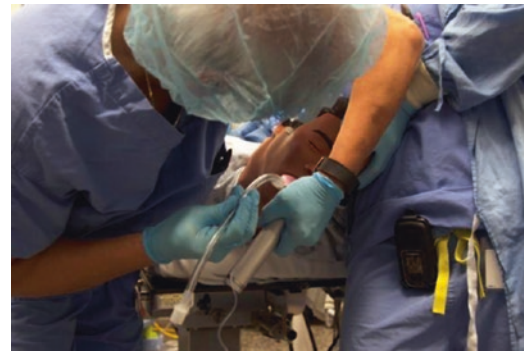

Fig. 16.2 Laryngoscopic intubation of a manikin placed in the prone position: Laryngoscopic intubation can also be performed from the side (*right*) of the manikin

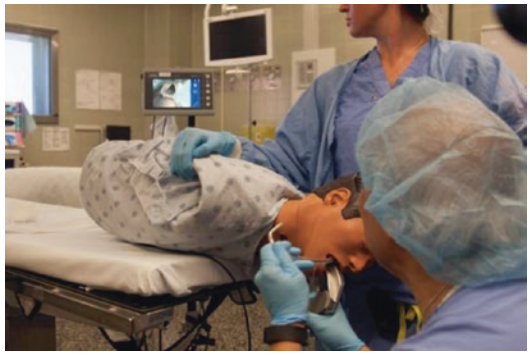

Fig. 16.3 Tracheal intubation of a manikin placed in the prone position: Video-laryngoscopic intubation can be performed from the front of the manikin with the right hand holding the video-laryngoscope (CMAC) and the left hand advancing the ETT. While the inverted image of the vocal cords and the arytenoid cartilages (AC) can be visualized easily on the monitor, the advancement of the ETT is quite challenging because of the inverted images

If BMV, the insertion of an EGD, and tracheal intubation fail, and it is not possible to turn the patient to a supine position (e.g., a lack of a stretcher or bed) and in the presence of hypoxemia, an attempt of surgical airway should be made. The access might be difficult, but turning the patient on his side or tilting the table in addition to turning the patient's head could improve accessibility to the neck. Latest guidelines suggest that a scalpel technique should be the preferred approach unless one is particularly experienced with the needle (Seldinger) technique [3, 5]. Moreover, a few studies have demonstrated that the success rate of identifying the cricothyroid membrane (CTM) is poor (about 30–40%), except in nonobese adult males with the success rate as high as 70% [51–55]. It appears that a vertical incision of the neck followed by digital dissection and palpation of the membrane before CTM incision would be more successful than the needle technique [56]. The simplest technique involves the use of a scalpel with a #10 blade, a tracheal introducer (commonly known as the "bougie"), and a size 6.0-mm ID ETT [5]. In an emergency situation, a simple technique reduces the cognitive load and may increase its success rate [5]. However, it would be prudent for all clinicians to make every effort to turn the patient supine (including lying the patient on the operating room floor on top of a sterile drape if no bed or stretcher is available) so that the airway can be managed properly, and perform a surgical airway in prone position only as a last resort in an emergency situation,

Apart from turning the patient supine, a lateral position can be achieved easily on a regular OR table with the bolsters removed for airway management. The left lateral decubitus is preferred by some clinicians for direct laryngoscopy and intubation, as gravity will help to displace the tongue to the left and facilitate visualization of the glottis [45]. Others prefer the right lateral decubitus position as in this position, the clinician's left arm has more room to maneuver during the procedure. The tongue can still be easily displaced by the laryngoscope in the right lateral decubitus position. However, direct laryngoscopy may be more challenging as the saliva and secretions may obscure the view of the glottis if the patient is in the right lateral decubitus position. Nathanson et al. [57] reported the tracheal intubation of a manikin in the lateral position to be more difficult than in the supine position. The ease of intubation increased with each subsequent attempt, indicating that operator experience was a confounding factor [57]. An assistant may be necessary to stabilize the head, neck, and body while performing an intubation in a patient in the lateral decubitus position. Successful tracheal intubation for patients placed in the lateral position using the intubating LMA (Fastrach™, LMA North America, San Diego) and the lighted stylet have been reported [58–60]. However, skills and experience with these techniques are important to increase the chance of successful intubation. It should be emphasized that blind techniques should only be used after visual techniques have failed as airway anatomic distortion may be present.

In summary, the urgent situation of a dislodged ETT should be clearly communicated to all operating room staff. Additional help and equipment should be summoned. If not contraindicated, the patient should be turned back to the supine position as it makes securing the airway a lot easier. In the meantime, reestablishment of oxygenation should be the priority (BMV, EGD, tracheal intubation, and surgical airway). If oxygenation is reestablished, a planned strategy to secure the airway

should be discussed. If a rescue EGD can provide adequate ventilation and oxygenation in the prone position, the surgical procedure can be resumed under only certain circumstances, such as a short duration procedure or at the end of the surgery and a patient with a low risk of pulmonary aspiration.

16.4.3 Other Airway Considerations

A sudden increase in airway pressure in a patient lying in a prone position is commonly associated with light anesthesia. Simply deepening the anesthesia, or administration of a muscle relaxant would generally be sufficient to mitigate the problem. However, other causes of an increase in airway pressure may be more challenging.

While an increase in airway pressure is generally anticipated in a patient placed in the prone position, scientific evidence is scarce. When comparing different respiratory variables between supine and prone position in non-obese adult patients under general anesthesia, Pelosi et al. [61] reported that there is a small (20%) but statistically significant increase in the respiratory system resistance. This was secondary to increased resistance from the chest wall and was without any clinical consequences. They stated clearly that patients were positioned to assure free abdominal movements. On the other hand, functional residual capacity (FRC) and PaO_2 were significantly increased in the prone position compared to the supine position. In ten obese adult (BMI 30–46) patients, the same investigators showed, again, an increase in FRC and PaO_2 [62]. In those patients, resistance was similar in both positions, lung compliance was higher, and chest wall compliance was lower in prone position, with a resultant unchanged system compliance. In 1959, a study showed a significant decrease in compliance when a patient is mechanically ventilated in the prone position, but the chest and the abdomen wall could not move as freely as in a contemporary prone positioning [63]. Interestingly, prone position ventilation of critically ill patients suffering from ARDS was associated with reduced mortality in a randomized controlled trial [64] in 2013. In other words, the prone position in itself should not increase airway pressures and, therefore, other causes should be determined if it increases under anesthesia in a patient placed in prone position.

Should an increase in airway pressure be detected, an endobronchial intubation is a likely possibility depending on the head and body position. Indeed, the ETT has been shown to migrate toward the carina when the neck is flexed. Slight oxygenation desaturation would accompany the rise in airway pressures if this is secondary to endobronchial intubation. Particular attention should be paid to the position of the ETT cuff which is usually around 1–2 cm below the vocal cords following tracheal intubation and confirmation of the ETT placement.

Another possible cause of an intraoperative increase in airway pressure is tension pneumothorax, especially in surgery of the thoracic spine. If there is a significant leak, the pressure might build up (tension pneumothorax) and there would be serious hemodynamic repercussions. Clinical signs include a decrease in breath sounds ipsilaterally, tracheal deviation, distended neck veins, and subcutaneous emphysema. If tension pneumothorax is promptly recognized and if there are no contraindications, the patient should be turned back to the supine position to proceed to chest decompression [65] as the second intercostal space in the midclavicular line is not readily accessible for needle decompression in the prone position. Similarly, the anterior axillary line which is the usual site to insert a thoracic drainage tube might not be easily accessible. Turning the patient to a lateral position to have access for decompression is a viable option if it is not possible to turn the patient supine. Alternatively, the surgeon can temporarily decompress the pneumothorax posteriorly and a proper thoracic drainage tube can be placed at the end of the procedure after the patient returns to supine position.

16.5 Change in Airway Anatomy

Anatomic distortion of the airway can occur due to factors inherent to the trauma associated with airway management following induction of anesthesia, the surgical procedure (around the cervical

spine), the prone position, or to the airway management of the dislodged ETT. Cervical vertebral fixation and surgical manipulation of oropharyngeal and neck tissues can alter airway anatomy. Bleeding into the airway and hematoma formation can be associated with neck surgery. Prolonged surgical procedures with significant blood loss may be associated with airway edema due to fluid resuscitation. Direct pressure on facial and neck structures and a dependent position compromise venous drainage and contribute to edema formation. Airway edema can alter the appearance of laryngeal structures and can make visualization of the larynx difficult [66–68]. Edematous tissues may also be more easily traumatized. All these are important issues to consider prior to extubation at the conclusion of the surgical procedure.

16.6 Fluid Management for Patients in Prone Position

16.6.1 Fluid Distribution

Total body water (TBW) is approximately 60% of body weight, which is divided into intracellular volume (two-thirds of TBW) and extracellular volume (ECV) (one-third of TBW). The latter can also be divided into intravascular volume (one-fifth of ECV) and interstitial volume (four-fifths of ECV). Sodium-free fluid tends to distribute in TBW, which means that approximately 67 mL of 1 L of D5W (5% dextrose in water) or sterile water will stay in the intravascular space after redistribution (1 L × 1/3 = 333 mL as extracellular volume; 333 mL × 1/5 = 67 mL as intravascular volume). If the solution contains sodium, it tends to distribute in the ECV only, which means that approximately 200 mL of 1 L of Ringer's Lactate or normal saline will stay in the intravascular volume after redistribution (1 L × 1/5 = 200 mL as intravascular volume). Whatever the fluid volume that is outside the intravascular space will be distributed everywhere in the body. In other words, the amount of tissue edema is directly related to the amount of crystalloid fluid administered. Colloids, on the other hand, will at least stay within the intravascular space and, depending on their osmotic pressure, can even attract more free water from the interstitial space.

16.6.2 Fluid Management to Minimize Edema in the Patient in Prone Position

Tissue edema, particularly in the dependent areas, can occur in surgical procedures involving significant fluid shifts secondary to fluid administration to compensate for the blood loss. Tissue fluid tends to accumulate in the face and the upper airway of the patient when placed in prone position. Therefore, to minimize facial and airway edema, all attempts should be made to minimize crystalloid fluid administration during procedures performed in the prone position. Judicious amount of vasopressors (e.g., phenylephrine or norepinephrine) can be used to maintain adequate perfusion to major organs without administration of a large volume of crystalloid. In lieu of large amounts of crystalloid solutions, it would be prudent to administer colloid solutions, such as hydroxyethyl starch solutions or 5% albumin. Although the efficacy of this approach has not been scientifically validated, it is our practice to use colloid solutions judiciously in order to limit crystalloid use to under 2 L in total.

However, colloids may be associated with adverse outcomes in certain populations. The CHEST trial [69] in 2012, concluded that 6% HES increased the necessity for renal replacement therapy in patients in the intensive care units. In a meta-analysis study in 2013, Zarychanski et al. [70] reported that Hydroxyethyl starch is associated with an increased risk of acute kidney injury and mortality in critically ill patients requiring acute volume resuscitation. On the other hand, in the same patient population, 4% albumin was not associated with worse outcomes, although less total fluid volume was administered [71]. However, in patients with traumatic brain injury, albumin is associated with higher mortality [72]. A recent meta-analysis including randomized controlled trials of HES versus crystalloid use in elective noncardiac

surgical patients found a trend toward increased mortality within 90 days [73]. However, studies included in the analysis had small sample size, and more data are needed to draw valid conclusions about the use of colloids.

Venous drainage of the head and neck can be optimized by keeping the head elevated (e.g., reverse Trendelenburg position) if possible and avoiding compression or kinking of internal jugular veins. If the head must be turned to one side for airway or surgical access, the degree of rotation should be minimized.

16.6.3 Assessment and Management of Airway Edema

The development of edema in the hypopharynx and larynx while in the prone position can produce airway obstruction following extubation. Clinical signs, such as facial, orbital, or conjunctival edema, distended neck veins, and venous congestion of the head may indicate the presence of upper airway edema. The use of a flexible nasopharyngoscope to assess the extent of airway edema prior to tracheal extubation may be helpful [74], although there have been no studies to confirm its clinical utility.

Unfortunately, there are no scientifically validated methods to assess the degree of airway edema or to predict postextubation airway obstruction. The performance of a leak test prior to extubation in patients with suspected airway edema has been suggested [75]. The leak test measures the difference between the tidal volume before and after cuff deflation in a mechanically ventilated patient. Confusion persists as to whether a test is positive or negative when a sufficient leak is present. However, a higher cuff leak volume (>88–140 mL or >10–18% of the pre-deflation expired or inspired volume [76]) has been shown to indicate that airway patency is sufficient to tolerate extubation without post-extubation stridor (PES). The leak test can also be performed by deflating the endotracheal tube cuff in a spontaneously breathing patient without ventilator support and then occluding the proximal end of the ETT. A positive leak test is confirmed when there are signs of an audible leak or coughing around the endotracheal tube. The absence of a leak and/or coughing are positive predictors for PES [77]. In 2009, Ochoa et al. [76] published a systematic review and meta-analysis of studies including more than 50 patients and assessing the diagnostic accuracy of the cuff leak test for upper airway obstruction. The pooled sensitivity and specificity were 56% and 92% respectively. This test was therefore deemed useful to alert the clinician of the high risk of upper airway obstruction when the leak was lower than the predefined threshold. However, a leak that is higher than the predefined threshold does not rule out PES. Another systematic review found that the specificity is higher in patients with an endotracheal tube for more than 5 days [78]. Multiple studies have found the leak test to be either helpful for predicting adverse events [79–81] or not helpful [82–86], although they all suffer from many study design limitations. Therefore, clinicians should recognize the potential limitations of the cuff leak test and furthermore, all studies tested patients in intensive care units and may not be applicable for postoperative extubation in the operating room in patients placed in prone position.

Laryngeal ultrasound may be an emerging method for assessing laryngeal anatomy. Lakhal et al. [87] showed a strong correlation between laryngeal ultrasound and MRI for measuring tracheal diameter at the cricoid ring in 27 young adults. Ding et al. [88] reported a pilot study using a laryngeal ultrasound to predict PES in 41 patients. The investigators used real-time ultrasonography to evaluate the air leak and to determine the relationship between the air column width during cuff deflation and the development of PES. The results of this study suggest that laryngeal ultrasonography could be a reliable, noninvasive method in the evaluation of laryngeal morphology and airflow through the upper airway. Unfortunately, a recent prospective study involving 41 critically ill patients concluded that the sensitivity, specificity, and positive predictive value of this method are low [89]. On the other hand, another recent prospective observational study on 101 critically ill patients concluded that ultrasonography is a promising tool to predict

successful extubation regarding laryngeal edema [90]. Clearly, more studies, especially randomized controlled trials, are needed to demonstrate the clinical utility of this approach as part of the pre-extubation airway evaluation.

Other predictors of PES include length of intubation, female gender, body mass index, and ratio of ETT size to laryngeal diameter [85, 91]. Kwon et al. [92] reported total operative time and the volume of crystalloid and transfused blood given to be risk factors for delayed extubation.

If the leak test is positive (sufficient air leak) but there is evidence of facial and possible airway edema, it would be prudent to perform extubation over a tracheal tube exchange catheter (Cook Critical Care, Bloomington, IN) to provide a means for ventilation should post-extubation airway obstruction occur.

If the leak test is negative (i.e., no or minimal air leak), it would be prudent to delay the extubation and continue to ventilate and oxygenate the patient through the existing ETT until the airway edema resolves and a subsequent leak test becomes positive. Although failing the leak test may not predict post-extubation problems with high specificity, using this approach provides the greatest margin of safety for the patient. Appropriate treatment of airway edema includes elevation of the head and the use of steroids and diuretics, although the efficacy of these measures has not yet been validated. Two recent meta-analyses [93, 94] provided a comprehensive review of the effect of steroids on PES and showed that there is evidence to support multiple doses of steroids given 12–24 h prior to extubation for prevention of PES in high-risk adult patients (as determined by the cuff leak test). Although the evidence for prophylactic steroids in neonates or children is less clear, there is a trend toward benefit and therefore should be considered for high-risk patients [94]. While there is evidence to support that steroids may reduce the amount of airway edema and decrease the risk of post-extubation airway obstruction and a decreased rate of reintubation, this only applies to the pediatric population [95–99]. Moreover, airway edema in the prone patient is mostly related to excessive amount of fluid that accumulates in dependent areas of the body rather than inflammation caused by trauma and infection.

Conclusion

The clinician dealing with a patient in prone position should proceed with tracheal intubation while the patient is in supine position and secure the ETT with appropriate ties or tapes. A careful turn to prone position then follows. The use of EGDs in this position should be limited to select cases.

If the ETT is dislodged during the procedure, operating room personnel should be informed and appropriate equipment should be summoned. Every effort should be made to ensure a rapid return to the supine position in order to deal with the airway. However, if turning to supine position is not possible, immediate airway management to ensure continuous oxygenation should include BMV, the use of an EGD, tracheal intubation, and surgical airway.

To minimize airway edema judicious amount of crystalloid solutions, colloids, and blood products, as well as vasopressors should be administered. Prior to extubation, nasopharyngoscopic examination and a leak test may be useful to assess airway edema. If there are concerns with airway edema, the ETT should be left in place with the patient placed in a semi-sitting position, and appropriate amount of diuretics should be administered. Airway edema should be reassessed prior to extubation.

References

1. Edgcombe H, Carter K, Yarrow S. Anaesthesia in the prone position. Br J Anaesth. 2008;100:165–83.
2. Apfelbaum JL, Hagberg CA, Caplan RA, et al. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology. 2013; 118:251–70.
3. Law JA, Broemling N, Cooper RM, et al. The difficult airway with recommendations for management – part 1 – difficult tracheal intubation encountered in an unconscious/induced patient. Can J Anaesth. 2013;60:1089–118.
4. Law JA, Broemling N, Cooper RM, et al. The difficult airway with recommendations for management – part

2 – the anticipated difficult airway. Can J Anaesth. 2013;60:1119–38.
5. Frerk C, Mitchell VS, McNarry AF, et al. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. Br J Anaesth. 2015;115:827–48.
6. Suderman VS, Crosby ET, Lui A. Elective oral tracheal intubation in cervical spine-injured adults. Can J Anaesth. 1991;38:785–9.
7. Brimacombe J. The advantages of the LMA over the tracheal tube or facemask: a meta-analysis. Can J Anaesth. 1995;42:1017–23.
8. Brimacombe JR, Berry A. The incidence of aspiration associated with the laryngeal mask airway: a meta-analysis of published literature. J Clin Anesth. 1995;7:297–305.
9. Benumof JL. Laryngeal mask airway. Indications and contraindications. Anesthesiology. 1992;77:843–6.
10. Fisher JA, Ananthanarayan C, Edelist G. Role of the laryngeal mask in airway management. Can J Anaesth. 1992;39:1–3.
11. St. Pierre M, Merkens E, Schaffartzik W, Scleppers A. Laryngeal mask placement in the porne position. An online-survey among German anaesthetists in private practice. Anesthesiologie und Intensivmedizin. 2013;54:181–91.
12. Hinkelbein J. PRO: laryngeal masks can be used for surgery in the prone position. Eur J Anaesthesiol. 2014;31:253–5.
13. Kranke P. Penny wise, pound foolish? Trade-offs when using the laryngeal mask airway for spine surgery in the prone position. Eur J Anaesthesiol. 2014;31:249–52.
14. Staender S. CON: laryngeal masks must not be used for surgery in the prone position. Eur J Anaesthesiol. 2014;31:256–8.
15. Ellard L, Wong DT. Should we induce general anesthesia in the prone position? Curr Opin Anaesthesiol. 2014;27:635–42.
16. Wilson IG, Eastley R. A modification of the laryngeal mask airway. Anesthesiology. 1991;74:1157.
17. Herrick MJ, Kennedy DJ. Airway obstruction and the laryngeal mask airway in paediatric radiotherapy. Anaesthesia. 1992;47:910.
18. Ngan Kee WD. Laryngeal mask airway for radiotherapy in the prone position. Anaesthesia. 1992;47:446–7.
19. McCaughey W, Bhanumurthy S. Laryngeal mask placement in the prone position. Anaesthesia. 1993;48:1104–5.
20. Milligan KA. Laryngeal mask in the prone position. Anaesthesia. 1994;49:449.
21. Stevens WC, Mehta PD. Use of the Laryngeal Mask Airway in patients positioned prone for short surgical cases in an ambulatory surgery unit in the United States. J Clin Anesth. 2008;20:487–8.
22. Senthil Kumar M, Pandey R, Khanna P. Successful use of I-gel airway in prone position surgery. Paediatr Anaesth. 2009;19:176–7.
23. Taxak S, Gopinath A. Insertion of the i-gel airway in prone position. Minerva Anestesiol. 2010;76:381.
24. Thomas M, Bhorkar NM, D'Silva JA, Chilgar RM. Prone induction of anesthesia using laryngeal mask airway in liposculpting surgery. Plast Reconstr Surg. 2012;129:599e–600e.
25. Chau SW, Wang FY, Wu CW, et al. Premolar loss following insertion of a Classic Laryngeal Mask Airway in a patient in the prone position. J Clin Anesth. 2011;23:588–9.
26. Valero R, Serrano S, Adalia R, et al. Anesthetic management of a patient in prone position with a drill bit penetrating the spinal canal at C1-C2, using a laryngeal mask. Anesth Analg. 2004;98:1447–50.
27. Samantaray A. Tracheal intubation in the prone position with an intubating laryngeal mask airway following posterior spine impaled knife injury. Saudi J Anaesth. 2011;5:329–31.
28. Agrawal S, Sharma JP, Jindal P, Sharma UC, Rajan M. Airway management in prone position with an intubating Laryngeal Mask Airway. J Clin Anesth. 2007;19:293–5.
29. Ng A, Raitt DG, Smith G. Induction of anesthesia and insertion of a laryngeal mask airway in the prone position for minor surgery. Anesth Analg. 2002;94:1194–8.
30. Osborn IP, Cohen J, Soper RJ, Roth LA. Laryngeal mask airway – a novel method of airway protection during ERCP: comparison with endotracheal intubation. Gastrointest Endosc. 2002;56:122–8.
31. Brimacombe JR, Wenzel V, Keller C. The proseal laryngeal mask airway in prone patients: a retrospective audit of 245 patients. Anaesth Intensive Care. 2007;35:222–5.
32. Weksler N, Klein M, Rozentsveig V, et al. Laryngeal mask in prone position: pure exhibitionism or a valid technique. Minerva Anestesiol. 2007;73:33–7.
33. Lopez AM, Valero R, Brimacombe J. Insertion and use of the LMA Supreme in the prone position. Anaesthesia. 2010;65:154–7.
34. Sharma V, Verghese C, McKenna PJ. Prospective audit on the use of the LMA-Supreme for airway management of adult patients undergoing elective orthopaedic surgery in prone position. Br J Anaesth. 2010;105:228–32.
35. Lopez AM, Valero R, Hurtado P, Gambus P, Pons M, Anglada T. Comparison of the LMA Supreme with the LMA Proseal for airway management in patients anaesthetized in prone position. Br J Anaesth. 2011;107:265–71.
36. Olsen KS, Petersen JT, Pedersen NA, Rovsing L. Self-positioning followed by induction of anaesthesia and insertion of a laryngeal mask airway versus endotracheal intubation and subsequent positioning for spinal surgery in the prone position: a randomised clinical trial. Eur J Anaesthesiol. 2014;31:259–65.
37. Caplan RA, Posner KL, Ward RJ, Cheney FW. Adverse respiratory events in anesthesia: a closed claims analysis. Anesthesiology. 1990;72:828–33.
38. Practice guidelines for management of the difficult airway. A report by the American Society of

Anesthesiologists Task Force on management of the difficult airway. Anesthesiology. 1993;78:597–602.
39. Crosby ET, Cooper RM, Douglas MJ, et al. The unanticipated difficult airway with recommendations for management. Can J Anaesth. 1998;45:757–76.
40. Henderson JJ, Popat MT, Latto IP, Pearce AC, Difficult AS. Difficult Airway Society guidelines for management of the unanticipated difficult intubation. Anaesthesia. 2004;59:675–94.
41. Pompeii LA, Lipscomb HJ, Schoenfisch AL, Dement JM. Musculoskeletal injuries resulting from patient handling tasks among hospital workers. Am J Ind Med. 2009;52:571–8.
42. Evers KA, Eindhoven GB, Wierda JM. Transient nerve damage following intubation for trans-sphenoidal hypophysectomy. Can J Anaesth. 1999;46:1143–5.
43. Wang KC, Chan WS, Tsai CT, Wu GJ, Chang Y, Tseng HC. Lingual nerve injury following the use of an oropharyngeal airway under endotracheal general anesthesia. Acta Anaesthesiol Taiwan. 2006; 44:119–22.
44. Raphael J, Rosenthal-Ganon T, Gozal Y. Emergency airway management with a laryngeal mask airway in a patient placed in the prone position. J Clin Anesth. 2004;16:560–1.
45. Cupitt JM. Induction of anaesthesia in morbidly obese patients. Br J Anaesth. 1999;83:964–5.
46. Dingeman RS, Goumnerova LC, Goobie SM. The use of a laryngeal mask airway for emergent airway management in a prone child. Anesth Analg. 2005; 100:670–1.
47. Brain A. Proper technique for insertion of the laryngeal mask. Anesthesiology. 1990;73:1053–4.
48. Cook TM, Silsby J, Simpson TP. Airway rescue in acute upper airway obstruction using a ProSeal Laryngeal mask airway and an Aintree catheter: a review of the ProSeal Laryngeal mask airway in the management of the difficult airway. Anaesthesia. 2005;60:1129–36.
49. Baer K. Is it much more difficult to intubate in prone position? Lakartidningen. 1992;89:3657–60.
50. van Zundert A, Kuczkowski KM, Tijssen F, Weber E. Direct laryngoscopy and endotracheal intubation in the prone position following traumatic thoracic spine injury. J Anesth. 2008;22:170–2.
51. Elliott DS, Baker PA, Scott MR, Birch CW, Thompson JM. Accuracy of surface landmark identification for cannula cricothyroidotomy. Anaesthesia. 2010;65:889–94.
52. Aslani A, Ng SC, Hurley M, McCarthy KF, McNicholas M, McCaul CL. Accuracy of identification of the cricothyroid membrane in female subjects using palpation: an observational study. Anesth Analg. 2012;114:987–92.
53. Bair AE, Chima R. The inaccuracy of using landmark techniques for cricothyroid membrane identification: a comparison of three techniques. Acad Emerg Med. 2015;22:908–14.
54. Lamb A, Zhang J, Hung O, et al. Accuracy of identifying the cricothyroid membrane by anesthesia trainees and staff in a Canadian institution. Can J Anaesth. 2015;62:495–503.
55. You-Ten KE, Desai D, Postonogova T, Siddiqui N. Accuracy of conventional digital palpation and ultrasound of the cricothyroid membrane in obese women in labour. Anaesthesia. 2015;70:1230–4.
56. Lockey D, Crewdson K, Weaver A, Davies G. Observational study of the success rates of intubation and failed intubation airway rescue techniques in 7256 attempted intubations of trauma patients by pre-hospital physicians. Br J Anaesth. 2014; 113:220–5.
57. Nathanson MH, Gajraj NM, Newson CD. Tracheal intubation in a manikin: comparison of supine and left lateral positions. Br J Anaesth. 1994;73: 690–1.
58. Dimitriou V, Voyagis GS, Iatrou C, Brimacombe J. Flexible lightwand-guided intubation using the intubating laryngeal mask airway in the supine, right, and left lateral positions in healthy patients by experienced users. Anesth Analg. 2003;96: 896–8.
59. Cheng KI, Chu KS, Chau SW, et al. Lightwand-assisted intubation of patients in the lateral decubitus position. Anesth Analg. 2004;99:279–83.
60. Komatsu R, Nagata O, Sessler DI, Ozaki M. The intubating laryngeal mask airway facilitates tracheal intubation in the lateral position. Anesth Analg. 2004;98:858–61.
61. Pelosi P, Croci M, Calappi E, et al. The prone positioning during general anesthesia minimally affects respiratory mechanics while improving functional residual capacity and increasing oxygen tension. Anesth Analg. 1995;80:955–60.
62. Pelosi P, Croci M, Calappi E, et al. Prone positioning improves pulmonary function in obese patients during general anesthesia. Anesth Analg. 1996;83:578–83.
63. Lynch S, Brand L, Levy A. Changes in lung thorax compliance during orthopedic surgery. Anesthesiology. 1959;20:278–82.
64. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368:2159–68.
65. Rankin D, Mathew PS, Kurnutala LN, Soghomonyan S, Bergese SD. Tension pneumothorax during surgery for thoracic spine stabilization in prone position: a case report and review of literature. J Investig Med High Impact Case Rep. 2014;2: 2324709614537233.
66. Mallampati SR. Clinical sign to predict difficult tracheal intubation (hypothesis). Can Anaesth Soc J. 1983;30:316–7.
67. Samsoon GL, Young JR. Difficult tracheal intubation: a retrospective study. Anaesthesia. 1987;42: 487–90.
68. Farcon EL, Kim MH, Marx GF. Changing Mallampati score during labour. Can J Anaesth. 1994;41:50–1.
69. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901–11.

70. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA. 2013;309:678–88.
71. Finfer S, Norton R, Bellomo R, Boyce N, French J, Myburgh J. The SAFE study: saline vs. albumin for fluid resuscitation in the critically ill. Vox Sang. 2004;87(Suppl 2):123–31.
72. Investigators SS, Australian, New Zealand Intensive Care Society Clinical Trials G, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med. 2007;357:874–84.
73. Raiman M, Mitchell CG, Biccard BM, Rodseth RN. Comparison of hydroxyethyl starch colloids with crystalloids for surgical patients: a systematic review and meta-analysis. Eur J Anaesthesiol. 2016;33:42–8.
74. Bentsianov BL, Parhiscar A, Azer M, Har-El G. The role of fiberoptic nasopharyngoscopy in the management of the acute airway in angioneurotic edema. Laryngoscope. 2000;110:2016–9.
75. Miller RL, Cole RP. Association between reduced cuff leak volume and postextubation stridor. Chest. 1996;110:1035–40.
76. Ochoa ME, Marin Mdel C, Frutos-Vivar F, et al. Cuff-leak test for the diagnosis of upper airway obstruction in adults: a systematic review and meta-analysis. Intensive Care Med. 2009;35:1171–9.
77. Maury E, Guglielminotti J, Alzieu M, Qureshi T, Guidet B, Offenstadt G. How to identify patients with no risk for postextubation stridor? J Crit Care. 2004;19:23–8.
78. Zhou T, Zhang HP, Chen WW, et al. Cuff-leak test for predicting postextubation airway complications: a systematic review. J Evid Based Med. 2011;4:242–54.
79. Chung YH, Chao TY, Chiu CT, Lin MC. The cuff-leak test is a simple tool to verify severe laryngeal edema in patients undergoing long-term mechanical ventilation. Crit Care Med. 2006;34:409–14.
80. Suominen P, Taivainen T, Tuominen N, et al. Optimally fitted tracheal tubes decrease the probability of postextubation adverse events in children undergoing general anesthesia. Paediatr Anaesth. 2006;16:641–7.
81. Wang CL, Tsai YH, Huang CC, et al. The role of the cuff leak test in predicting the effects of corticosteroid treatment on postextubation stridor. Chang Gung Med J. 2007;30:53–61.
82. Suominen PK, Tuominen NA, Salminen JT, et al. The air-leak test is not a good predictor of postextubation adverse events in children undergoing cardiac surgery. J Cardiothorac Vasc Anesth. 2007;21:197–202.
83. Shin SH, Heath K, Reed S, Collins J, Weireter LJ, Britt LD. The cuff leak test is not predictive of successful extubation. Am Surg. 2008;74:1182–5.
84. Wratney AT, Benjamin Jr DK, Slonim AD, He J, Hamel DS, Cheifetz IM. The endotracheal tube air leak test does not predict extubation outcome in critically ill pediatric patients. Pediatr Crit Care Med. 2008;9:490–6.
85. Kriner EJ, Shafazand S, Colice GL. The endotracheal tube cuff-leak test as a predictor for postextubation stridor. Respir Care. 2005;50:1632–8.
86. Patel AB, Ani C, Feeney C. Cuff leak test and laryngeal survey for predicting post-extubation stridor. Indian J Anaesth. 2015;59:96–102.
87. Lakhal K, Delplace X, Cottier JP, et al. The feasibility of ultrasound to assess subglottic diameter. Anesth Analg. 2007;104:611–4.
88. Ding LW, Wang HC, Wu HD, Chang CJ, Yang PC. Laryngeal ultrasound: a useful method in predicting post-extubation stridor. A pilot study. Eur Respir J. 2006;27:384–9.
89. Mikaeili H, Yazdchi M, Tarzamni MK, Ansarin K, Ghasemzadeh M. Laryngeal ultrasonography versus cuff leak test in predicting postextubation stridor. J Cardiovasc Thorac Res. 2014;6:25–8.
90. Sutherasan Y, Theerawit P, Hongphanut T, Kiatboonsri C, Kiatboonsri S. Predicting laryngeal edema in intubated patients by portable intensive care unit ultrasound. J Crit Care. 2013;28:675–80.
91. Erginel S, Ucgun I, Yildirim H, Metintas M, Parspour S. High body mass index and long duration of intubation increase post-extubation stridor in patients with mechanical ventilation. Tohoku J Exp Med. 2005;207:125–32.
92. Kwon B, Yoo JU, Furey CG, Rowbottom J, Emery SE. Risk factors for delayed extubation after single-stage, multi-level anterior cervical decompression and posterior fusion. J Spinal Disord Tech. 2006;19:389–93.
93. Jaber S, Jung B, Chanques G, Bonnet F, Marret E. Effects of steroids on reintubation and post-extubation stridor in adults: meta-analysis of randomised controlled trials. Crit Care. 2009;13:R49.
94. Khemani RG, Randolph A, Markovitz B. Corticosteroids for the prevention and treatment of post-extubation stridor in neonates, children and adults. Cochrane Database Syst Rev. 2009;3:CD001000.
95. Darmon JY, Rauss A, Dreyfuss D, et al. Evaluation of risk factors for laryngeal edema after tracheal extubation in adults and its prevention by dexamethasone. A placebo-controlled, double-blind, multicenter study. Anesthesiology. 1992;77:245–51.
96. Anene O, Meert KL, Uy H, Simpson P, Sarnaik AP. Dexamethasone for the prevention of postextubation airway obstruction: a prospective, randomized, double-blind, placebo-controlled trial. Crit Care Med. 1996;24:1666–9.
97. Meade MO, Guyatt GH, Cook DJ, Sinuff T, Butler R. Trials of corticosteroids to prevent postextubation airway complications. Chest. 2001;120:464S–8S.
98. Markovitz BP, Randolph AG. Corticosteroids for the prevention of reintubation and postextubation stridor in pediatric patients: a meta-analysis. Pediatr Crit Care Med. 2002;3:223–6.
99. Lukkassen IM, Hassing MB, Markhorst DG. Dexamethasone reduces reintubation rate due to postextubation stridor in a high-risk paediatric population. Acta Paediatr. 2006;95:74–6.

Anaesthetic Considerations in Posterior Fossa Surgery

17

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17.1 Introduction

Posterior fossa accords significant neurological status since it houses very important structures of the brain which are packed in a very constricted space. The lesions of this area, thus, cause significant morbidity and mortality just by virtue of being in a very adverse location [1]. However, with advances in medical and surgical technologies, increasingly large number of patients are undergoing successful surgeries for posterior fossa pathologies. These surgeries are extremely challenging for both the surgeon as well as the anaesthesiologist because of the demanding, delicate nature of the surgical procedure and the long hours involved. The main challenges faced by the anaesthesiologist are due to peculiar patient positioning, chances of excessive bleeding owing to venous sinus injury, intraoperative risk of cranial nerve dysfunction, high probability of venous air embolism and predisposition to upper airway oedema necessitating postoperative ventilatory support [2].

17.2 Posterior Fossa: Boundaries [3]

The base of the skull is divided into anterior, middle and posterior cranial fossae. Posterior fossa is the deepest cranial fossa and is surrounded anteriorly by the dorsum sellae and basilar portion of the occipital bone (clivus), posteriorly and inferiorly by the occipital bone, superiorly by the dural layer (tentorium cerebelli) and laterally there are the petrosal and mastoid components of the temporal bone. It is limited posteriorly and inferiorly by the foramen magnum, which is the largest opening of the posterior fossa. Other openings in

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the posterior fossa include the internal acoustic meatus, condylar canal and the jugular foramen. Important structures occupying posterior fossa include the cerebellum, pons, medulla oblongata and lower cranial nerves. The sigmoid, transverse and occipital sinuses also traverse the fossa.

17.2.1 Clinical Relevance of Posterior Fossa Anatomy

The anatomical location of posterior fossa, also known as the infratentorial fossa, makes it a difficult site to be surgically accessed. Further, it is a rigid and compact compartment with poor compliance. Thus, even a small volume addition to this non-compliant space, in the form of tumours or haematoma, can result in significant elevation of the compartmental pressure, resulting in life-threatening brainstem compression.

17.3 Posterior Fossa Pathologies [4–6]

Posterior fossa neurosurgical disorders can be classified on the basis of aetiology and location (Table 17.1).

Table 17.1 Classification of posterior fossa pathologies

I. Aetiology	
Tumour pathology:	
A. Anterior compartment tumours:	Intra-axial: gliomas
	Extra-axial: acoustic schwannoma, meningioma, epidermoid tumours, cysts, glomus tumours and metastases
B. Posterior compartment tumours:	Predominantly intra-axial tumours: cerebellar astrocytoma , medulloblastoma , ependymoma, haemangioblastoma, lymphoma and metastases.
Vascular pathology:	Includes aneurysms and arterio-venous malformations which can arise from the vertebro-basilar system and the arteries of the posterior inferior cerebellar system
Traumatic pathology	
Infectious pathology	
II. Location	
Midline syndrome Cerebellar hemisphere-syndrome Ponto-cerebellar angle syndrome Brainstem syndrome	

17.4 Anaesthetic Challenges in Posterior Fossa Surgeries [3, 7, 8]

1. *Presence of vital structures*: The presence of vital structures in the posterior fossa, particularly the brainstem, cerebellum and cranial nerves along with the limited space, makes performing surgical procedures in this area challenging.
2. *Difficult surgical access*: Surgical access to the posterior fossa, due to its anatomical location, is particularly difficult. Adding to the difficulty is the fact that the compartment is compact and poorly compliant.
3. *Extreme positions*: Posterior fossa surgeries are performed in extreme positions, including the lateral, park-bench, sitting or prone position. Each surgical approach is associated with its set of advantages and inherent risks.
4. *Long operative durations*: Long duration of surgery in extreme positions poses a challenge to both the surgeon as well as the anaesthesiologist. Important considerations include securing and maintaining the airway, maintenance of adequate anaesthetic depth, haemodynamic stability and oxygenation. Also important are preservation of invasive monitors and intravenous catheters, and protecting the patient against pressure injuries to the skin, peripheral nerves and pressure-sensitive organs such as eyes.
5. *Venous air embolism* (*VAE*): This is a potentially fatal complication of posterior fossa surgery, especially seen in surgeries performed in sitting position (though VAE is possible in lateral and prone positions as well). Its incidence ranges from 25 to 50% in studies using precor-

dial Doppler monitoring. However, investigators using a more sensitive transoesophageal echocardiography monitoring have reported an incidence of VAE as high as 76%.

6. *Postoperative ventilatory support*: Patients undergoing posterior fossa surgeries are at a higher risk to need postoperative ventilatory support. The main indications for this are brainstem handling, lower cranial nerve palsies resulting in absence of gag and cough reflex, prolonged surgical duration, hypothermia, intraoperative tense brain and unresponsive patients at the end of procedure.

17.5 Goals of Anaesthesia [2, 9]

In all neurosurgical procedures, in addition to the pathological and surgical processes, anaesthetic agents also interact with brain structures and functions. In addition to maintaining systemic haemodynamic stability, the aims of anaesthetic technique include:

1. Ensuring optimal cerebral perfusion pressure (CPP)
2. Maintaining a stable intracranial pressure (ICP)
3. Maintaining cerebrovascular reactivity to changes in $PaCO_2$
4. Cerebral protection
5. Preserving cardiovascular responsiveness to surgical manipulation of brainstem structures
6. Rapid patient awakening for early postoperative neurological assessment
7. Early detection and management of complications

17.6 Preoperative Evaluation and Preparation [2, 3, 9]

In addition to applying the basic principles for assessment of general health for any surgical procedure, a thorough preoperative evaluation of neurological condition, cardiorespiratory status and assessment of co-existing medical condition with a view to optimization needs to be performed for the safe conduct of anaesthesia for posterior fossa surgery. Some of the vital aspects of preoperative evaluation include:

1. *Detailed medical history*: A detailed medical history needs to be elucidated with special emphasis on assessment of the signs, symptoms and complications related to posterior fossa lesion. Children having posterior fossa tumours need to be assessed for presence of complications such as diabetes insipidus. In hypertensive patients, the limits of cerebral autoregulation are shifted towards right, thus identification of such patients is important so as to avert inadvertent cerebral ischaemia.
2. *Evaluation of hydration status*: Dehydration and associated electrolyte disturbances are common in this patient group and its origin is multifactorial. It could be due to reduced oral intake following decreased conscious level, vomiting, diuretic administration, diabetes insipidus and use of intravenous contrast agents. Incremental administration of intravenous fluids before induction may limit hypotension during anaesthesia induction and positioning. Application of lower limb compression stockings may also limit venous pooling in the legs.
3. *Evaluation of cranial nerve and cerebellar dysfunction*: Presence of lower cranial nerve compression and dysfunction may result in the loss of gag reflex or impaired cough and aspiration pneumonitis. In some patients with bulbar dysfunction, postoperative ventilation or tracheostomy may be necessary to protect the airway. Signs of cerebellar dysfunction such as ataxia, dysarthria, gait disturbances and intentional tremors should be looked for and recorded.
4. *Evaluation for presence of raised intracranial pressure* (*ICP*): Decreased level of consciousness and altered respiratory pattern may indicate the presence of raised ICP, predicting tight brain and difficult operating conditions. Prior to the definitive posterior fossa surgery, management of hydrocephalus by external ventricular drainage or other shunt procedures may be required in such patients.

5. *Evaluation for intraoperative patient positioning*: Patients should be carefully assessed for optimal intraoperative patient positioning. Sitting position is contraindicated in patients with patent foramen ovale (PFO), which has an incidence of 10–35%.
6. *Airway assessment*: Assessment of difficulty in airway management is important. Craniovertebral junctional abnormalities can lead to instability of the spine or reduced neck movements posing a challenge for securing the airway for anaesthesia.
7. *Assessment of vascular access*: Suitability of vascular access for right atrial catheter placement helps determine the most promising route. Obese patients, those with poor vasculature due to disease or chronic intravenous cannulation, or patients with short, thick necks need to be identified early so that necessary time may be allotted for catheter placement.

17.7 Premedication

Administration of premedication depends on the patient's physical status, level of anxiety and presence of raised ICP. Narcotic premedication is avoided in patients with space-occupying lesions or hydrocephalus as narcotics may result in hypoventilation and CO_2 retention, thus elevating ICP. Mild anxiolysis provided by low-dose benzodiazepines is often prescribed.

17.8 Intraoperative Monitoring [10–15]

17.8.1 Goals of Monitoring

1. Ensure adequate cerebral perfusion
2. Maintain cardiorespiratory stability
3. Detect and treat air embolism

Table 17.2 lists the monitors used in patients undergoing posterior fossa surgery.

Routine Monitoring This should include five-lead electrocardiogram, pulse oximetry, capnography, temperature, urine output, non-invasive and invasive blood pressure monitoring. Invasive arterial monitoring is mandatory and allows measurement of beat-to-beat variability. The arterial transducer should be placed at the level of external auditory meatus to correlate with cerebral perfusion. Central venous catheters are also routinely inserted in these patients, especially in those undergoing surgery in sitting position. In addition to allowing assessment of volume status, central venous catheters allow aspiration of air during venous air embolism.

Table 17.2 Monitors for posterior fossa surgery

Routine monitors
Five-lead electrocardiogram
Pulse oximetry
Capnography
Blood pressure monitoring (non-invasive and invasive)
Temperature monitoring
Urine output
Central venous catheter
Special monitors
Neurophysiological monitoring (somatosensory and brain stem auditory-evoked potentials, electroencephalogram, EMG monitoring)
Precordial Doppler
Transoesophageal echocardiography and Doppler
Pulmonary artery (PA) catheter
End-tidal nitrogen (ETN_2) monitoring

Special Monitoring These include monitors that are not routinely used but provide specialized information during certain procedures.

Neurophysiological Monitoring Due to the concentration of the nerve structures in the brain stem, minor damage in the brain stem can cause devastating complications. Various neurological monitoring techniques such as somatosensory-evoked potentials (SSEPs) and brain stem auditory-evoked potentials can help to avert such potential complications. SSEP can be used to monitor spinal cord ischaemia in the sitting position and brainstem auditory-evoked potentials to monitor the function of the VIII cranial nerve and are particularly important for cerebellopontine angle surgery and/or for microvascular decompression. The electroencephalogram can be used to detect cerebral hypoperfusion and cortical ischaemia. Continuous EMG

monitoring of the VIth and VIIth cranial nerves enhances operative safety and facilitates aggressive monitoring during microvascular decompression, surgery for fourth ventricle tumours and during acoustic neuroma surgery.

17.9 Anaesthesia Technique [9, 16–19]

Induction Invasive blood pressure monitoring established prior to anaesthesia induction allows tight control of blood pressure and cerebral perfusion pressure during induction and intubation, especially in patients with elevated ICP. Induction can be achieved by administering a judicious dose of induction agent, either thiopental or propofol, an opiate and a muscle relaxant. The need for vasopressor administration may arise following induction of anaesthesia or positioning, especially in chronically hypertensive or debilitated patients. Further, verification of correct endotracheal tube placement is important after final positioning, as intraoperative access to the airway is limited.

Armoured endotracheal tube should be preferred over PVC endotracheal tubes since these are less liable to kinking in the prone or sitting positions. Verification of appropriate placement of the endotracheal tube after final positioning, but before surgical incision, is very important, regardless of the position employed.

Intraoperative access to the airway is limited and neck flexion or extension can produce caudad or cephalad displacement of the endotracheal tube, respectively, by as much as 2 cm.

Maintenance The technique used to maintain anaesthesia should be chosen keeping the following goals in mind:

1. Maintaining adequate analgesia and amnesia
2. Preserving adequate cerebral perfusion pressure
3. Preventing increases in ICP
4. Preservation of autonomic system activity
5. Rapid awakening after discontinuation of anaesthetic agents

Controlled positive-pressure ventilation with muscle paralysis is the most common technique employed since this allows maintaining lighter planes of anaesthesia and hyperventilation and eliminates chances of patient movement.

Anaesthesia can be maintained with either volatile agents or infusion of propofol, depending on the preference of individual anaesthetist. However, propofol infusion owing to its property of reducing cerebral blood volume (CBV) and ICP and preserving autoregulation and vascular reactivity is often relied upon by most neuroanaesthesiologists. While using volatile agents, care should be taken to avoid using concentrations greater than 1 MAC as increase in ICP may result. In patients with a high risk of VAE or pneumocephalus, nitrous oxide is often avoided.

Liberal fluid administration may be required in posterior fossa surgeries being performed in head-elevated, prone position. Further, one should be careful as administration of osmotic and loop diuretics often required intra-operatively may predispose patients to electrolyte disturbances or cardiovascular instability.

Emergence Emergence from anaesthesia should be smooth, minimizing coughing and straining on the endotracheal tube, ensuring rapid awakening and return of adequate motor strength. Decision to keep the patient on postoperative ventilatory support can be made based on the presence of one or more of the following:

1. Extensive brainstem manipulation with increased probability of postoperative brainstem oedema
2. Brainstem injury caused by difficult tumour resection
3. Preoperative lower cranial nerve dysfunction and potential for aspiration pneumonia
4. Failure of return of gag reflex
5. Extensive intraoperative dissection, particularly in the floor of the fourth ventricle and around the cranial nerve nuclei, resulting in postoperative airway compromise
6. Presence of preoperative co-morbidities
7. Presence of airway oedema after prolonged prone positioning and tongue swelling after the sitting position

Inputs from Neurosurgeon are invaluable and close communication between surgeon and anaesthesiologist is essential to make a plan for postoperative ventilation. Patients who are kept on elective postoperative ventilation should be sedated so as to avoid coughing on the endotracheal tube which induces increases in ICP.

ICP monitoring should be considered if postoperative ventilation is required because hydrocephalus remains a risk. Postoperative hypertension should be carefully managed to avoid intracranial bleeding and haematoma formation. Failure to recover from anaesthesia should prompt further investigations such as imaging of the brain stem to exclude any complications.

17.10 Postoperative Management [9, 10]

The main concerns in the postoperative period following posterior fossa surgery are:

1. *Pain*: Occipital and infratentorial approaches are associated with severe postoperative pain due do extensive muscle cutting.
2. *Postoperative nausea and vomiting (PONV)*: All patients undergoing surgery on the posterior fossa should be considered to be at high risk of PONV because of the proximity of the vomiting centre to the surgical site.

Any deterioration in the neurological status should be promptly noted and investigated.

17.11 Patient Positioning [12, 20, 21]

A number of different patient positions can be used to obtain surgical access to the posterior fossa (Table 17.3). Patients should be positioned gradually, so that the cardiovascular system adapts to the physiological changes associated with positioning and thus, hypotension can be prevented or mitigated.

Table 17.3 Patient positions in posterior fossa surgeries

Supine position with maximal rotation to the contralateral side
Lateral position
Park-bench position
Prone position
Sitting position

17.11.1 Supine Position with Maximal Rotation to the Contralateral Side

This position is used for access to the lateral structures of the posterior fossa.

Up to 45° can be achieved by lateral rotation and anything beyond that can be achieved by elevation of the ipsilateral shoulder using a roll or a pillow. This might, however, not be possible in patients with impaired neck movement. Reverse Trendelenburg positioning is also usually done to improve venous drainage from the brain. We need to remember that each 2.5-cm increase in vertical height of the head above the level of the heart leads to a 2-mmHg reduction in cerebral perfusion.

Disadvantages

1. Lateral rotation is associated with reduced venous return from the brain due to compression of internal jugular vein, thereby theoretically increasing the chances for raised intracranial pressure.
2. Extreme lateral rotation for a prolonged period can cause macroglossia, so a soft block should be placed to avoid injury by the teeth.
3. Risk of brachial plexus stretch and injury. To reduce this complication, use of supporting pad under the ipsilateral shoulder is advisable.

17.11.2 Lateral Position

The lateral position is suitable for unilateral procedures of the posterior fossa, as it improves surgical access by gravitational retraction of the cerebellum, and drainage of CSF and blood from the operating field. Drainage can be improved further by placing the table in a head-up position.

Advantages

1. The incidence of venous air embolism is lower than with the prone position.
2. Haemodynamic stability is better when compared to the supine and sitting position.

Disadvantages

1. Peripheral nerve injuries.
2. Gravitational ventilation perfusion mismatch in the dependent lung

17.11.3 Park-Bench Position

This is the variation of the lateral position, with the patient being placed semi-prone (three-quarters prone), with the head rotated and neck flexed, resulting in the brow facing the floor.

Advantages

1. Better access to the posterior fossa, especially the midline structures. In selected patients, the park-bench position avoids the need for prone position.
2. Less chances of VAE than sitting position.

Disadvantages

1. Peripheral nerve injuries, especially injuries to brachial plexus
2. Macroglossia
3. Venous engorgement

17.11.4 Prone Position

The prone position facilitates access to the posterior fossa, craniocervical junction and the upper spinal cord.

Advantages

1. Lower incidence of VAE. However, as the patient's head is usually elevated above the heart level, so as to decrease venous bleeding, the risk of VAE is not completely eliminated.
2. Extreme care and meticulous planning is required for making this position, with due precautions taken to avoid diaphragmatic splinting.

Disadvantages

1. Eye compression can produce blindness from retinal artery thrombosis or ischaemic optic neuropathy.
2. In patients where the lower limbs lie below the level of the right atrium, venous pooling may occur, impairing venous return to the heart.
3. Increased chances of hypotension at the time of putting the patient into prone position.

17.11.5 Sitting Position

The sitting position facilitates surgical access but presents unique physiological challenges for the anaesthesiologist.

This is actually a modified recumbent position, with the patient's skull secured in a three-pin head holder, legs kept as high as possible to promote venous return, arms supported to prevent shoulder traction. In order to prevent cervical cord stretching and obstruction of venous drainage from the face and tongue, it is necessary to maintain at least 1-inch space between the chin and chest, avoid excessive neck rotation and avoid large airways and bite blocks in the pharynx. It is also important to avoid excessive flexion of the knees towards the chest, so as to prevent lower extremity ischaemia, sciatic nerve injury and abdominal compression.

Advantages of sitting position for the surgeon are:

1. This patient position provides optimum access to craniovertebral junction and the posterior fossa, particularly midline structures and the cerebellopontine angle.
2. Improves cerebral venous decompression and lowers ICP.
3. Accumulated blood drains away from the operative site in the sitting position, thus

allowing a cleaner surgical field and rapid access to bleeding points.
4. Unobstructed view of patient's face provides easy access to the airway.
5. Favourable changes in ventilatory mechanics because abdominal viscera is no longer pushing the diaphragm up so there is no restriction to inspiration. Adoption of the sitting position results in increase in functional residual capacity (FRC), but the associated reduction in perfusion obviates the expected benefits in oxygenation. As there is better diaphragmatic excursion, ventilation is unimpeded. Though pulmonary vital capacity is improved in sitting position, decreased perfusion of upper lung may lead to ventilation or perfusion abnormalities and hypoxemia.

17.11.5.1 Physiological Changes in Sitting Position

Sitting position is associated with several characteristic physiological changes:

17.11.5.2 Cardiovascular System

Cardiovascular effects include increase in pulmonary and systemic vascular resistance and decrease in venous return, cardiac output and cerebral perfusion pressure. Negative effects on cardiac output, such as dysrhythmias, resulting from manipulation or retraction of cranial nerves or the brainstem may be more pronounced for patients in sitting position rather than supine position.

17.11.5.3 Respiratory System

Adoption of sitting position results in increase in functional residual capacity (FRC), but the associated reduction in perfusion obviates the expected benefits in oxygenation. As there is better diaphragmatic excursion, ventilation is unimpeded. Though pulmonary vital capacity is improved in sitting position, decreased perfusion of upper lung may lead to ventilation or perfusion abnormalities and hypoxemia.

17.11.5.4 Cerebral Perfusion and Intracranial Pressure

Sitting position is associated with reduction in arterial and venous pressures due to gravitational effect of head positioning above heart level. General anaesthesia and induced hypocapnia are known to reduce cerebral blood flow by 34% in supine position. Assumption of sitting position further reduces this flow by 14%. The consequence of such a reduction in cerebral blood flow may be offset by the reduction in cerebral metabolic rate for oxygen ($CMRO_2$) and consequent lowering of ischaemic threshold associated with anaesthesia.

17.11.5.5 Complications of Sitting Position [1, 11]

17.11.5.6 Hypotension and Dysrhythmias

Cardiovascular effects of sitting position include increase in pulmonary and systemic vascular resistance and decrease in venous return, cardiac output and cerebral perfusion pressure. Negative effects on cardiac output, such as dysrhythmias, resulting from manipulation or retraction of cranial nerves or the brainstem may be more pronounced for patients in sitting position rather than supine position.

17.11.5.7 Venous Air Embolism (VAE)

VAE is a potentially life-threatening complication, caused by the entry of air into peripheral or central vasculature. The incidence of VAE varies from 25 to 75% during surgery in the sitting position depending on the sensitivity of the monitoring used. In the sitting position, the site of surgery is above the level of the heart, which results in a negative venous pressure at the level of surgical wound. Open veins and venous sinuses thus, may entrain atmospheric air into the circulation, resulting in VAE. Dehydration exacerbates the low venous pressure and increases the risk of air entrainment.

Clinical Features Morbidity and mortality are directly related to the amount and rate of air entry, with lethal dose in humans being between 200 and 300 ml, or 3–5 ml/kg. The spectrum of manifestations includes cardiovascular, respiratory and neurological changes. Symptoms appear late and

one should rely on the monitors mentioned above in the text for early identification of VAE.

VAE usually results in elevated right atrial pressure resulting in decreased venous return, hypotension and shock. Tachyarrhythmia and myocardial ischaemia may ensue. A large embolus obstructing the outlet of the right ventricle can result in a sudden onset of right heart failure and cardiac arrest. Pulmonary signs of VAE include wheeze, crepitations, and sudden decrease in end-tidal carbon dioxide ($EtCO_2$). Arterial blood gas analysis may reveal hypoxia and hypercapnia. Neurological manifestations include cerebral hypoperfusion as a result of shock and stroke in the event of a paradoxical embolus.

Monitoring for Venous Air Embolism (VAE):

1. Precordial Doppler: Precordial probe can be fixed onto the patient's chest. It is the most sensitive non-invasive monitoring device used to detect VAE.
2. Transoesophageal echocardiography (TEE) and Doppler: TEE is more sensitive than precordial Doppler, but is invasive and expensive and expert personnel are required to use it.
3. Pulmonary artery (PA) catheter: Detects pulmonary hypertension resulting from mechanical obstruction and reflex vasoconstriction from local hypoxemia caused by transpulmonary air. However, it is more invasive, with the PA catheter's small lumen making air aspiration difficult. It is not often used due to unfavourable risk–benefit ratio. It may be used in patients with impaired cardiac function in whom the indications are to monitor cardiac function rather than for monitoring for VAE.
4. Capnography ($ETCO_2$ monitoring): Enables detection of increased arterial-to-end-tidal CO_2 gradient associated with the occurrence of VAE. However, it is non-specific for air and less sensitive than Doppler.
5. End-tidal nitrogen (ETN_2) monitoring: This technique is specific for air and detects air earlier than capnography. However, the sensitivity of currently available N_2 monitoring technology may not be sufficient to detect subclinical VAE and it is not useful if O_2:air is used during anaesthesia.

Prevention and Treatment The risk of VAE can be reduced by careful planning of the surgery, meticulous surgical technique and liberal use of bone wax, vigilance, avoidance of N_2O and maximization of intravascular pressure.

The treatment includes:

1. 100% oxygen and increasing the flows.
2. Discontinuation of nitrous oxide.
3. Having the surgeon flood the surgical field with fluids.
4. Patient position should be changed to lower the head below heart level, if feasible.
5. Placing the patient in the left lateral decubitus position to reduce the gas lock effect, though the efficacy of this manoeuvre has been questioned recently.
6. Jugular venous compression.
7. Attempted aspiration of air from the right atrium.
8. Haemodynamic support (with intravenous fluids, inotropes and anti-arrhythmics) and cardiopulmonary resuscitation.

17.11.5.8 Pneumocephalus

Pneumocephalus occurs when air enters the brain or spaces around the brain after dural incision. Tension pneumocephalus may follow air entry into the epidural or dural spaces in sufficient volumes to exert a mass effect with the potential for life-threatening brain herniation. Pneumocephalus can present after operation as delayed recovery, neurological deficit, headache, confusion, agitation or convulsion, with CT scan enabling early diagnosis. The management includes drainage of air via a burr hole, ventilation with 100% oxygen, and avoidance of nitrous oxide.

17.11.5.9 Macroglossia

Macroglossia, causing postoperative respiratory obstruction, can occur as a result of obstruction to the venous and lymphatic drainage of the tongue because of a flexed neck during prolonged surgery in the sitting position.

17.11.5.10 Quadriplegia

Quadriplegia is a rare but potentially disastrous complication that is caused by prolonged focal

pressure on the spinal cord secondary to the acute flexion of the head in the sitting position. Ischaemic damage to the spinal cord can result from compromised regional spinal cord blood flow, particularly during episodes of significant hypotension. Meticulous attention during positioning and avoiding significant and prolonged hypotension during surgery can help avoid this complication.

Conclusion

Anaesthetic management of patients undergoing posterior fossa surgery is challenging for the anaesthesiologist in terms of preoperative evaluation, extreme patient positioning, choice of anaesthetic agents, prolonged surgical duration, type of monitoring, maintaining haemodynamic stability, preserving neurologic function and prevention, early detection and management of complications. Meticulous planning and extreme care throughout the perioperative period help in successfully overcoming these challenges.

References

1. Gale T, Leslie K. Anaesthesia for neurosurgery in the sitting position. J Clin Neurosci. 2004;11(7):693–6.
2. Culley DJ, Crosby G. Anesthesia for posterior fossa surgery. Hand book of neuroanesthesia. 4th ed. vol. 236. Philadelphia: Lippincott Williams and Wilkens; 2007. p. 133–42.
3. Smith DS. Anesthetic management for posterior fossa surgery. In: Cotrell J, Young WL, editors. Cotrell and young's neuroanesthesia. 5th ed. Philadelphia: Mosby Elsevir; 2010. p. 203.
4. Morantz RA, Walsh JW, editors. Brain tumors : a comprehensive text. 1st ed. New York: Informa Health Care; 1993.
5. Wilson M, Davies NP, Brundle MA, McConville C, Grundy R, Peet A. High resolution magic angle spinning 1H NMR of childhood brain and nervous system tumours. Mol Cancer. 2009;8:6.
6. Choi IS, David C. Giant intracranial aneurysms: development, clinical presentation and treatment. Eur J Radiol. 2003;46(3):178–94.
7. Bhardwaj A, Long DM, Ducker TB, Toung TJ. Neurological deficits after cervical laminectomy in the prone position. J Neurosurg Anesthesiol. 2001;13:314–9.
8. Haisa T, Kondo T. Midcervical flexion myelopathy after posterior fossa surgery in the sitting position: case report. Neurosurgery. 1996;38:819–21.
9. Gheorghita E, Ciurea J, Balanescu B. Considerations on anesthesia for posterior fossa-surgery. Romanian Neurosurgery. 2012;3:183–92.
10. Duffy C. Anaesthesia for posterior fossa surgery. In: Matta BF, Menon DK, Turner MJ, editors. Textbook of neuroanaesthesia and critical care. London: Greenwich Medical Media Ltd; 2000. p. 269–80.
11. Jagannathan S, Krovvidi H. Anaesthetic considerations for posterior fossa surgery. Contin Educ Anaesth Crit Care Pain. 2014;14(5):202–6.
12. Porter JM, Pidgeon C, Cunningham AJ. The sitting position in neurosurgery: a critical appraisal. Br J Anaesth. 1999;82:117–28.
13. Gildenberg PL, O'Brien RP, Britt WJ, Frost EA. The efficacy of Doppler monitoring for the detection of venous air embolism. J Neurosurg. 1981;54(1):75–8.
14. Schubert A, Deogaonkar A, Drummond JC. Precordial Doppler probe placement for optimal detection of venous air embolism during craniotomy. Anesth Analg. 2006;102:1543–7.
15. Sala F, Manganotti P, Tramontano V, Bricolo A, Gerosa M. Monitoring of motor pathways during brain stem surgery: what we have achieved and what we still miss? Neurophysiol Clin. 2007;37(6): 399–406.
16. Drummond JC, Todd MM, Scheller MS, Shapiro HM. A comparison of the direct cerebral vasodilating potencies of halothane and isoflurane in the New Zealand white rabbit. Anesthesiology. 1996;65(5): 462–7.
17. Fraga M, Rama Maceiras P, Rodino S, Aymerich H, Pose P, Belda J. The effects of isoflurane and desflurane on intracranial pressure, cerebral perfusion pressure and cerebral arteriovenous oxygen content difference in normocapnic patients with supratentorial brain tumors. Anesthesiology. 2003;98:1085–90.
18. Miura Y, Kamiya K, Kanazawa K, Okada M, Nakane M, Kumasaka A, Kawamae K. Superior recovery profiles of propofol-based regimen as compared to isoflurane based regimen in patients undergoing craniotomy for primary brain tumor excision: a retrospective study. J Anesth. 2012;26(5):721–7.
19. Newell DW, Weber JP, Watson R, Aaslid R, Winn HR. Effect of transient moderate hyperventilation on dynamic cerebral autoregulation after severe head injury. Neurosurgery. 1996;39(1):35–43.
20. Elton RJ, Howell RS. The sitting position in neurosurgical anaesthesia: a survey of British practice in 1991. Br J Anaesth. 1994;73(2):247–8.
21. Rath GP, Bithal PK, Chaturvedi A, Dash HH. Complications related to positioning in posterior fossa craniectomy. J Clin Neurosci. 2007;14(6):520–5.

Anesthesia for Pituitary Surgery

18

Fauzia Khan and Faraz Shafiq

18.1 Introduction

Anesthetic management for pituitary surgery demands a thorough knowledge of anatomy, endocrinology and pathophysiology of pituitary gland as well as a multidisciplinary approach involving endocrinologists, anesthesiologists, and neurosurgeons. Preoperative assessment should focus on the identification of hormonal and metabolic disturbances and planning the intraoperative care based on this. The postoperative period requires careful monitoring in the recovery units and close collaboration between the teams.

The aim of this chapter is to review the key concepts required for safe conduct and perioperative management of patients requiring pituitary surgery, and an update on its current management.

18.2 Review of Anatomy and Physiology

The pituitary gland (Fig. 18.1) is approximately 8 mm in diameter and lies in the middle cranial fossa at the base of skull in a cavity of the sphenoid bone (*sella turcica*). The gland is surrounded by the bone in its anterior, posterior and inferior aspects. The optic chaisma lies superiorly and is separated from the pituitary by a sheet of dura known as "*diaphragma sellae*". The lateral relationship has internal carotid artery, cavernous sinus along with the third, fourth and sixth cranial nerves [1].

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18.3 Pathophysiology

The pituitary gland consists of two lobes. The larger anterior lobe, (*adeno-hypophysis*) secretes several hormones as shown in Table 18.1. The posterior lobe (*neuro-hypophysis*) is responsible for secretion of antidiuretic hormone *(ADH)* and oxytocin. The gland is connected through a fold of dura to the hypothalamus, which regulates the hormones secreted by the anterior pituitary, by several hypothalamic releasing and inhibiting factors. The factors released by hypothalamus are thyrotropin-releasing hormone *(TRH)*, corticotropin-releasing hormone *(CRH)*, gonadotropin-releasing hormone *(GnRH)*, growth hormone *(GHRH),* and prolactin-releasing hormone *(PRLH).* The control of posterior pituitary hormone ADH is through plasma osmolality and the circulating blood volume, whereas suckling reflex stimulates oxytocin release.

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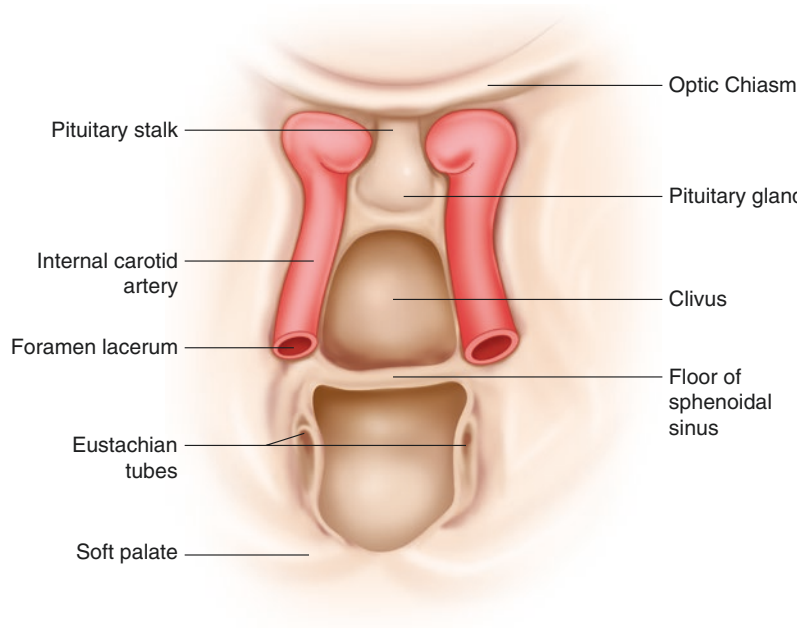

Fig. 18.1 Diagrammatic representation showing the suprasellar and parasellar anatomical relationship of the pituitary gland through the endoscopic approach

Table 18.1 Hormones and functions of pituitary gland

Hormones secreted by anterior pituitary	*Functions*
Thyroid-stimulating hormone (TSH)	Stimulates the synthesis and release of thyroid hormones
Adrenocorticotrophic hormone (ACTH)	Stimulates the adrenal gland for the production of stress hormones i.e., glucocorticoids, and mineralo-corticoids.
Melanocyte-stimulating hormone (MSH)	Causes skin pigmentation
Follicle-stimulating hormone (FSH)	Stimulates the gonads for the production of testosterone and estrogen
Luteinizing hormone (LH)	Helps in spermatogenesis in males and luteinization of ovarian follicles in females
Growth hormone (GH)	Anabolic effects and synthesis of proteins, skeletal growth, gluconeogenesis, and lipolysis
Prolactin (PRL)	Stimulates milk production and reduces fertility
Hormones secreted by posterior pituitary	
Antidiuretic hormone (ADH)	Maintaining circulating volume and plasma osmolality
Oxytocin	Secretion of milk

18.3.1 Classification of Pituitary Tumors

Pituitary tumors can be classified either as *micro-adenomas* having a diameter of less than 10 mm, or *macro-adenomas* with diameter more than 10 mm [2]. The clinical presentation depends upon either the size or the hormones produced (*functioning or nonfunctioning tumors*) [3].

Nonfunctioning tumors These are macro-adenomas which produce symptoms due to mass effect e.g., visual disturbances due to pressure on optic chaisma. They are usually nonsecretory [4]. The signs and symptoms include headache, nausea, or vomiting, which indicate raised intracranial pressure. As the tumor grows it can cause pituitary hypo functioning due to direct compressive effect on the gland. This is also called *stalk effect* [5]. These patients may present with infertility, panhypopituitarism, and epilepsy.

Functioning tumors These are micro-adenomas which present much earlier because of the hor-

monal disturbances. The commonest are prolactin-secreting (35%), followed by GH-secreting (20%) and ACTH-secreting tumors (7%). One percent of the tumors secrete more than one hormone [6].

18.3.2 Metabolic Disturbances Associated with Pituitary Tumors

Acromegaly and Gigantism These clinical conditions are caused by excessive GH secretion by a functioning adenoma, and rarely by oversecretion of GHRH. The process is insidious at onset and causes enlargement of mandible, hands, and feet. In adults it leads to acromegaly, whereas if it occurs before the closure of long bone epiphyses it results in gigantism [7]. Diabetes, hypertension, obstructive sleep apnea (OSA), and peripheral nerve compression are associated problems. GH has an anti-insulin effect leading to diabetes mellitus (DM). Other associated conditions are hypertension, obstructive sleep apnea, premature coronary artery disease, cardiomyopathy, and osteoarthritis. OSA can effect up to 97% of these patients [8].

Cushing's disease This condition is due to excessive secretion of cortisol secondary to excess ACTH secreted by a pituitary adenoma. Typical features of Cushing's disease are central obesity, cushingoid facies also called moon face, hyponatremia, hypokalemia, abdominal striae, thin skin, easy bruisability, proximal myopathy, and osteoporosis [9]. These patients are also prone to gastroesophageal reflux disease, diabetes mellitus, hypertension, left ventricular hypertrophy (LVH), and proximal myopathy.

Diabetes Mellitus Diabetes is associated with 60% of patients with Cushing's disease and 25% with acromegaly. The perioperative management of these patients is similar to other surgical patients with diabetes.

Thyroid Disease Thyroid functions may alter in patients with pituitary tumors. These patients need thyroid function tests done preoperatively.

Cardiovascular disease Sixty percent of deaths in patients with acromegaly are directly related to cardiovascular complications [10]. Association of left ventricular hypertrophy, coronary artery disease, arrhythmias, cardiomyopathy, and heart failure may be features of functioning pituitary tumors [11].

Sexual Disturbances Prolactinomas may present with problems that are associated with menstrual disturbance, and galactorrhea in females and hypogonadism, loss of libido, or erectile dysfunction in males [12]. Patients may be on bromocriptine as part of medical management. Premature puberty or earlier onset of menstrual cycles may be an incidental finding of tumors secreting FSH and LH in females [4].

Pituitary Apoplexy This condition occurs due to acute deficiency of the secretory functions of anterior pituitary gland. Sudden hemorrhage in the tumor is responsible for deterioration in the blood supply of the gland. The condition is acute and patient may present with signs and symptoms of raised intracranial pressure or cranial nerve palsies [13]. The treatment is supportive with fluid management and hormone replacement therapy; however, at times surgical exploration is required for the evacuation of hematoma [14]. Females may present with postpartum pituitary infarction (Sheehan's syndrome).

18.4 Preoperative Assessment

18.4.1 General Assessment

Preoperative assessment should focus on overall health status, comorbid conditions, medical/surgical history, medication, and allergy. In addition, an endocrinologist should evaluate these patients.

18.4.2 Endocrinological Review

It is important to evaluate the signs and symptoms associated with the pituitary pathology. This includes detailed evaluation of the patients having acromegaly or Cushing's disease specifically or any other hormonal abnormality in general.

Hypertension and DM are commonly associated with acromegaly and Cushing's disease and need thorough evaluation, workup, and preoperative optimization. Obstructive sleep apnea (OSA) may complicate the perioperative course of 50% patients with acromegaly [15]. Presence of OSA can increase the incidence of postoperative complications. A history of snoring and daytime somnolence is suggestive of severe disease.

Patients with Cushing's need careful assessment in terms of organ involvement and complications such as osteoporosis, glucose intolerance, myopathy, and obstructive sleep apnea [16]. Hypokalemic metabolic acidosis, if present, should be corrected preoperatively. Patients with prolactinomas are on bromocriptine agonists that may cause hypotension during anesthesia [17]. Patients with panhypopituitarism are prone to water intoxication and hypoglycemia.

18.4.3 Cardiovascular System Evaluation

Eighty to 85% patients with Cushing's disease and 30–35% with acromegaly have hypertension requiring treatment [10]. Coronary artery disease, conduction disturbances, and arrhythmias may also be present both in patients with acromegaly and Cushing's disease [18]. Patients with OSA may develop right heart failure.

18.4.4 Neurological Evaluation

Patient should be evaluated for any neurological complications associated with the tumor. History of nausea, vomiting, and headache indicates raised intracranial pressure. Visual field defects on examination indicate that the tumor is compressing the optic chiasma in such cases. Bitemporal hemianopia is the classical presentation.

18.4.5 Airway Assessment

Excessive secretion of GH causes the renin-angiotensin-dependent sodium and water retention, which in turn causes hypertrophy of pharyngeal and laryngeal soft tissues including macroglossia [19]. This excess in GH is also responsible for extracellular matrix protein synthesis and cartilage production [20], both of which are responsible for typical facial features of these patients. These facial features may lead to difficulty in mask ventilation and/or intubation. Table 18.2 summarizes the airway abnormalities in these patients [21]. Any hoarseness or change in voice indicates the involvement of glottic opening, due to thickening of aeri-epiglottic folds and should be taken as an alert for difficult intubation. Paresis of recurrent laryngeal nerve may be present. Routine airway assessment is done by Mallampati examination, which has been reported as a reliable tool for predicting difficult airway [21]. Recently a study done by Bindra et al. failed to show any superiority of modified Mallampati (MMP) alone or in combination with extended Mallampati for prediction of difficult intubation in acromegaly patients [22]. Sharma et al. [23] compared upper lip bile test (ULBT) with modified Mallampati test (MMPC) in 64 acromegalic and 63 nonacromegalic patients. ULBT failed to predict 73% and MMPC failed to predict 33% of difficult laryngoscopies. MMPC was found to be more sensitive whereas ULBT was more specific. Accuracy of both tests was less in patients with acromegaly. The authors recommend using ULBT routinely in addition to MMPC in these patients.

Airway assessment is also important in patients with Cushing's disease. These patients have fat deposition on the upper back (buffalo hump), which may interfere with positioning for tracheal intubation. Obesity and gastrointestinal reflux can also affect airway control.

Table 18.2 Features of acromegaly that make the airway difficult

Thick mandible
Prognathism
Coarse features
Macroglossia
Hypertrophy of soft tissues of upper airway
Hypertrophy of laryngeal and pharyngeal tissues
Reduced size of glottis opening

18.4.6 Respiratory System Evaluation

In addition to the airway abnormalities, acromegaly leads to impaired respiratory function due to the involvement of bones of rib cage, intercostal muscles, and lung elasticity. Lung volumes are increased and these patients may have subclinical hypoxemia [24].

18.5 Investigations

From the anesthetic perspective it is important to have the following information at hand before proceeding with the case.

Endocrine Function-Related Tests: Hormonal studies should be performed on the basis of history and clinical findings. These include serum cortisol level, ACTH, T4 and TSH, basal prolactin, LH, FSH, testosterone, GH and insulin-like growth factor 1 (*IGF-1*). An endocrinologist should be involved in interpretation and further management of these results.

Electrolytes: Serum electrolyte abnormalities may be associated features of conditions such as Cushing's disease and need to be corrected before proceeding with anesthesia.

Blood glucose: Diabetes is associated with both acromegaly and Cushing's disease.

Complete blood count: To evaluate for anemia.

Electrocardiography and Echocardiography: Routine bedside ECG should be performed in all patients. Echocardiography is useful in assessing global function. Left ventricular hypertrophy can be present in 50% of acromegalics [25] due to interstitial myocardial fibrosis [26].

Airway-related investigations: Indirect laryngoscopy or X-ray of the neck may be needed in severe form of the disease and should be left at the discretion of the consultant anesthetist.

Blood group and save: Major hemorrhage is rare but bleeding can occur from venous sinuses or carotid artery due to accidental injury. Only blood group and save is sufficient preoperatively.

Radiological investigations: *MRI* is the gold standard for diagnosing pituitary tumors and is superior to CT scan. MRI findings help in differentiating micro from macro-adenomas, as well as identifying the extent and location of tumors. It can also predict the severity and outcome of the disease, as the tumors with suprasellar extension indicate difficulty in surgical approach and higher chances of recurrence [27]. Complications like involvement of pituitary stalk by infiltrative process of craniopharyngoma are the main cause of panhypopituitarism and can be detected on the MRI scan.

18.6 Premedication

Patients should continue hormone replacement therapy [2], antihypertensives, and steroids until the day of surgery. Oral hypoglycemic medications need to be replaced by the shorter acting insulin therapy in the perioperative period. Although the incidence of preoperative anxiety in the neurosurgical patients is high, long-acting sedative medications are usually not recommended due to the concern of raised ICP and requirement of rapid emergence and neurological assessment postoperatively [28]. Incremental boluses of short-acting sedative can be given under controlled environment where facilities of monitoring are available [16]. If obesity and gastroesophageal reflux are present, patient should be administered aspiration prophylaxis.

18.7 Preoperative Management

Anesthetic plan should be discussed with the patient. Similarly, explanation about conduct of fiberoptic intubation is mandatory before proceeding with suspected difficult airway. The patient should be instructed preoperatively regarding nasal obstruction [29] due to nasal packing and mouth breathing at the time of awakening.

Table 18.3 Goals of anesthetic management in pituitary surgery

Preserve and optimize cerebral perfusion and oxygenation
Maintain hemodynamic stability
Facilitate surgical exposure
Prevent and manage intraoperative complications
Rapid smooth emergence
Early assessment of neurological function

18.8 Goals of Intraoperative Management

18.8.1 Goals

The goals of anesthetic management in pituitary surgery are given in Table 18.3.

18.9 Surgical Approaches

18.9.1 Direct Endonasal Approach

Trans-sphenoidal is the safest and the most commonly used approach. The surgeon follows midline of nose, removes bone and floor of pituitary fossa. The tumor is removed using an operative microscope (microsurgery) or an endoscope [6].

The advantages of trans-sphenoidal approach are an extracranial approach with minimal surgical trauma and blood loss, and avoidance of hazards of craniotomy [1]. It is also associated with decreased length of hospital stay and lower mortality. Mortality of 0.2% has been reported with micro-adenoma and 0.9% with a macro-adenoma [30]. Endoscopic surgery can also be carried out with the help of intraoperative MRI, which helps in gauging the extent of surgical resection. In one study of 229 patients, intraoperative MRI led to further resection in 20.5% patients [31]. In another series of 18 patients, intraoperative MRI showed 50% patients having residual tumor [31]. Computer-assisted navigation has improved endoscopic approach by helping direct the angle of the scope [3]. Trans-sphenoidal endoscopic approach was also used for surgery of pituitary abscess in 18 patients [32].

In a meta-analysis of 38 studies of endoscopic versus microscopic approach, endoscopy was associated with a higher risk of vascular complications [33]. Endoscopic resection was also associated with an increased incidence of CSF leak [34].

Complications of trans-sphenoidal approach are persistent CSF rhinorrhea, risk of postoperative meningitis, transient diabetes insipidus, panhypopituitarism, vascular damage, cranial nerve injury, cerebral ischemia, and stroke secondary to vasospasm [35].

18.9.2 Trans-cranial Approach

Bifrontal craniotomy is indicated in case of giant pituitary tumors, failure of trans-sphenoidal surgery or if there is no intrasellar tumor [16]. This approach is associated with less surgical stimulation compared to trans-sphenoidal.

18.9.3 Sublabial Approach

This approach is sometimes undertaken in children or adults with large tumors [3].

18.10 Antibiotics at Induction

This is a debatable issue. The consensus policy in the UK recommends a cephalosporin at induction and every 3 h during surgery [36] with no further doses postoperatively.

18.11 Glucocorticoid Therapy at Induction

Regimens of glucocorticoid therapy differ in different hospitals but generally 100 mg of IV hydrocortisone therapy at induction is required in majority of patients unless basal cortisol (8 a.m.) and short synacthen tests are normal [5, 6, 17]. Therapy is continued for the next 2–3 days reducing the dose gradually [6]. Patients with Cushing's disease will require perioperative replacement therapy as well as postoperative therapy for several weeks.

18.12 Induction and Airway Management

Intravenous access may be technically difficult in patients with Cushing's disease.

18.12.1 If a Difficult Airway Is Not Expected

Routine induction with thiopentone or propofol followed by a short-acting narcotic and a long-acting muscle relaxant (Vecuronium or Atracurium) is acceptable. A reinforced endotracheal tube is positioned in the left corner of the mouth to give unimpeded access to surgeon who stands on the right [36]. A saline-soaked throat pack is inserted which prevents blood and secretions from going into the stomach and larynx [5]. It also stabilizes the tracheal tube [3]. If unexpected difficulty in bag-mask ventilation occurs, an oral airway can be inserted to overcome obstruction.

18.12.2 If a Difficult Airway Is Expected

The airway can be difficult in cases of acromegaly or Cushing's disease. The features of acromegaly that make the airway difficult are given in Table 18.1 [15]. Southwick et al. have described four grades of airway management in acromegalic patients [37]. Historically preoperative tracheostomy has been recommended for grades 3 and 4 [36–38], but nowadays it is rarely necessary. Most authors now recommend fiberoptic tracheal intubation with patient awake or asleep [1, 36]. Acromegaly is an independent risk factor for difficult intubation (DI) and difficulty in these patients can be quite unpredictable [39]. In one retrospective review of 746 such patients, the incidence of DI was reported as 9.1% [38]. Schmitt et al. reported a 10% incidence [21] and Messick et al. as 13% [38]. Authors experienced no problems with mask ventilation and intubation in acromegalic patients if large facemask and long blade of laryngoscope was used [5]. Intubating laryngeal mask (LMA) was also successfully used in these patients [38]. Bougie was found to be useful equipment in the management [48]. In another study of 32 acromegalic patients, a video laryngoscope was required in seven (22%), and fiberoptic intubation in four (12.5%) [40]. Use of external laryngeal pressure was found useful in improving laryngoscopic view [24]. In Cushing's disease difficult intubation may occur because of obesity. These patients have a moon face due to fat deposits in cheeks and temporal region. Obstructive sleep apnea (OSA) is present in 33% [41]. Fat deposits at the nape of neck may interfere with optimal positioning for tracheal intubation. Intraoperatively, approach to airway during trans-sphenoidal surgery is further restricted due to the presence of operating microscope, endoscopic equipment, C arm, and portable X-ray [1].

18.13 Preparation of Nasal Mucosa

Following induction local anesthetic solution with epinephrine injection is used to provide topical anesthesia and minimize bleeding from the nasal mucosa. A commonly used combination is 1–2% lignocaine with 1:200,000 epinephrine [1, 3, 6]. Epinephrine can cause an exaggerated hemodynamic response in acromegalic patients and in Cushing's disease. Chelliah et al. have reported a case of hypertensive crisis following lidocaine epinephrine injection into nasal mucosa [42]. In a comparison of 1:200,000 and 1:400,000 epinephrine with 2% lignocaine, the former produced less hemodynamic response compared to the latter and provided similar operating conditions [43]. In a retrospective review of 100 cases of trans-sphenoidal pituitary surgery, large blood pressure increases were common following intranasal injection [42]. In some centers, a mixture of cocaine and epinephrine is preferred [44]. Use of cocaine is associated with risk of arrhythmias. Alternative solutions to epinephrine and lignocaine combinations that have been used are xylometazoline [45], a long-acting sympathomimetic, or co-phenylcaine (5% lidocaine and 0.5% phenylephrine) [1].

18.14 Placement of Lumbar Catheter

Placement of lumbar catheter is done after induction and before surgery by some surgeons. A 16 G epidural catheter is inserted in L3/4 lumbar interspace and 10 cm is fed in the cephalic direction [36]. The purpose is to manipulate CSF pressure that is helpful in case of large tumors with significant suprasellar extension. Injection of 10 ml of normal saline using a sterile technique produces a temporary increase in CSF pressure causing a downward shift of tumor [6], hence making trans-sphenoidal resection easier [46]. The catheter can also be left in place postoperatively to drain the CSF if dura is breached [46].

18.15 Controlled Hypercapnia

Controlled hypercapnia was assessed for its effectiveness in raising CSF to enable descent of suprasellar position of pituitary in pituitary surgery by Korula et al. and was found effective but is not practiced universally [47].

18.16 Positioning

For trans-sphenoidal approach, the patient is kept in the classic "deck chair" position [31] i.e., supine with head up, neck extended and turned slightly to left to facilitate access to the surgeon standing on the right side [5, 36]. For geriatric patients with stiff necks, the operating table can be tilted laterally toward the surgeon [36]. Head-up position optimizes venous drainage and decreases bleeding; however, it increases the incidence of venous air embolism (VAE) [3]. Risk is more if head is elevated more than 40° above the heart [48]. The eyes should be padded and anesthetic circuit kept away from the surgical field toward the left of the patient. For transcranial surgery, the patient lies in supine position and the head is kept in the midline [5]. Presence of Cushing's disease and associated osteoporosis increase the risk of pathological fractures intraoperatively.

18.17 Perioperative Monitoring

ECG, pulse oximetry, end tidal CO_2, temperature, and non invasive blood pressure (NIBP) should be monitored routinely [17, 36]. Some authors prefer to use additional invasive BP monitoring routinely [1] whereas others reserve it for high-risk cases only [5]. In acromegalic patients the ulnar artery circulation is compromised [14]. Pulse oximetry may be difficult because of enlarged fingers. CVP is indicated if cavernous sinus invasion is suspected and if the surgeon plans head-up position more than 40° above the heart [5]. Visual evoked potential (*VAP*) monitoring has been used by some if the tumor compromises visual fields [36] but it is costly and waveforms are unstable for practical use. Incidence of false positives and negatives is high [49].

18.18 Anesthetic Drugs and Technique

Anesthetic drugs and techniques depend on individual preference and are similar to other intracranial procedures depending on patient's comorbidity. A meticulous approach is more important than use of specific agents [5, 36]. Both balanced anesthesia with short-acting narcotics and inhalational agents or total intravenous anesthesia (*TIVA*) has been used. Some authors prefer TIVA combining propofol and remifentanil [3] if the ICP is high [50, 51]. Neither technique is superior [52]. Nitrous oxide is avoided in case of raised ICP.

Trans-sphenoidal surgery is associated with periods of intense sympathetic stimulation, especially during access to the pituitary fossa during nasal fracture, sphenoid drilling, and sellar dissection [53]. A shorter acting opioid like remifentanil, if available, is preferred as it can be titrated to the hemodynamic effects [54]. In addition, it has rapid emergence and is not associated with respiratory depression [55]. Use of intraoperative paracetamol has an opioid sparing effect [56]. Bilateral maxillary nerve block for intraoperative analgesia has also been described [57].

A single bolus dose of a long-acting opioid like IV morphine or intramuscular codeine is recommended 20–30 min before the end of surgery [58] to prevent rebound hypertension and pain at emergence if a short-acting opioid like Remifentanil is chosen for intraoperative pain relief [6, 16]. Tramadol has also been used but it causes more sedation and PONV compared to codeine [59]. NSAIDS are best avoided because of the risk of hematoma formation [60]. Desflurane has also been used instead of sevoflurane [6].

In one study, comparison of remifentanil–propofol versus remifentanil–sevoflurane anesthesia showed similar hemodynamic stability but earlier recovery with remifentanil–sevoflurane combination [61]. Ali et al. compared three techniques of GA in an RCT with 90 patients. The patients either received propofol, isoflurane, or sevoflurane anesthesia and BIS monitoring keeping the BIS index range between 40 and 60. Presser responses were significantly less with propofol and N_2O and better recovery profile was observed with propofol and sevoflurane group [62].

Gopala and colleagues compared 46 patients, 18–65 years of age undergoing trans-sphenoidal resection of pituitary tumor to receive a continuous infusion of dexmeditomidine, an alpha 2 adrenergic agonist or normal saline. Dexmeditomidine increased hemodynamic stability, decreased anesthetic and narcotic requirement by 40% and 33% respectively and led to lesser bleeding [54]. In another study of 60 patients 18–65 years, authors used a continuous infusion of 0.6 μg kg^{-1} h^{-1} dexmeditomidine versus normal saline [63]. Total blood loss was less and resulted in a reduction in propofol maintenance dose and total fentanyl. Mean arterial pressure (MAP) and HR were lower and surgeon's satisfaction was higher. Other authors have also supported this fact [64]. In trans-sphenoidal surgery particular attention should be paid to maintaining normocapnia as hypocapnia will decrease ICP, reduce brain size, and make suprasellar extension less accessible [5].

Before wound closure, the surgeon may ask for a Valsalva maneuver to check for CSF leak [17]. Sella turcica is then packed with autologous fat. All personnel should also take adequate precautious from radiation exposure [5]. Patients with panhypopituitarism are extremely sensitive to anesthetic agents and other CNS depressants [38].

18.19 Intraoperative Complication

Trans-sphenoidal approach can be associated with several complications shown in Table 18.4.

Bleeding is a rare but catastrophic complication. Carotid artery or cavernous sinus injury is a possibility [65]. Carotid injury can lead to pseudo aneurysm and fistula postoperatively [66]. Venous air embolism can occur but is uncommon [1, 36]. CSF fistula can persist postoperatively and may require repair [67]. Damage to olfactory nerve, cranial nerve II to VI can occur due to their proximity to the pituitary [17]. Complications with intracranial approach are similar to other intracranial procedures. Specific complications are frontal lobe ischemia, trauma to carotid artery and optic chiasma [5]. A case report of short sudden asystole probably due to severe vagal response secondary to hypothalamic stimulation has also been described [68]. Diabetes insipidus usually occurs postoperatively but can rarely present intraoperatively as well.

Table 18.4 Perioperative complications of pituitary surgery

Route	Complication
Trans-sphenoidal approach	Carotid artery injury
	Cavernous sinus injury
	Corticocavernous fistula
	Optic nerve, optic chiasma injury
	Pseudo aneurysm
	Hypothalamic injury
	Olfactory nerve injury
	Other cranial nerve injuries (3–6) CSF rhinorrhea
	Venous air embolism
	Seizures
Trans-cranial approach	Frontal lobe ischemia
	Trauma to carotid artery
	Trauma to optic chaisma
	Seizures

18.20 Emergence

The goal of emergence is rapid and smooth emergence without bucking and coughing [36, 69]. Pharyngeal suction should be done under vision and pharyngeal pack removed. The patient's trachea should be extubated once pharyngeal reflexes return and the patient is able to maintain airway. Positive-pressure ventilation at this stage should be avoided because of the risk of tension pneumoencepholus, venous embolism, and introduction of bacteria in the subarachnoid space [70] [56]. Care should be taken that nasal packs inserted at the end of surgery are not dislodged [5]. Special nasal packs incorporating ventilating tubes are also available [36].

Routine antiemetic prophylaxis is advisable [5] and it is acceptable to give prophylactic antiemetics [6]. Standard prophylaxis is dexamethasone; however, in a recent retrospective study of 136 patients, this dose was shown to suppress the adrenocorticotrophic axis [71].

18.21 Postoperative Monitoring

Following surgery, in addition to cardiovascular and respiratory functions, the patients should be closely monitored for any neurological deterioration and cranial nerve dysfunction, especially cranial nerves 2–6. Eye movements and visual field acuity should be charted [4]. This can be done in the recovery room or in the ward if the patient does not have any comorbid disease. In case of acromegalic patients with OSA, particular attention should be given to signs of hypoventilation and these patients should be nursed in a high dependency unit for 24 h [5].

18.22 Postoperative Analgesia

Trans-sphenoidal surgery is associated with moderate pain; in addition, nasal packs cause considerable discomfort. In UK, the traditional analgesia has been codeine but currently narcotics are also acceptable [5]. The median postoperative requirements are low. In a retrospective study of 900 patients for trans-sphenoidal surgery the median requirement was less than 4 mg of morphine [72]. NSAIDS like ketorolac have been used but can be associated with higher risk of bleeding [16, 73]. Pain is more severe following trans-cranial surgery and narcotic requirement is increased in these cases. Use of intravenous morphine with patient-controlled intravenous analgesia (*PCIA*) has been described [4, 73]. Paracetamol is used as a co-analgesic [16]. Bilateral infra-orbital nerve block has also been used for postoperative pain management [73].

18.22.1 Postoperative Nausea and Vomiting (PONV)

PONV after neurosurgical procedures merits special attention as it can lead to raised ICP and CPP resulting in CSF leaks and hemorrhage [74]. Several antiemetic drugs such as metoclopramide, dexamethasone, ondensetron, granisetron, or dropenidol have been used to prevent PONV post neurosurgery [75]. A recent retrospective study of 136 patients has shown that dexamethasone 4 mg IV perioperatively led to the suppression of hypothalamic-pituitary-adrenal axis after pituitary surgery [72].

18.23 Postoperative Complications

In addition to surgical complications, the following can occur:

18.23.1 CSF Leak

CSF leak can present immediately after nasal pack removal or later [4, 6]; as a consequence patients present with low-pressure headaches and rhinorrhea. Confirmation is done by testing the leaked fluid for alpha transpherase [4]. Treatment is lumbar drain for 24–48 h [31] or surgical placement of autologous fat pad [4, 6].

18.23.2 Diabetes Insipidus (DI)

The direct surgical stimulation of the pituitary stalk or hypothalamus is responsible for the development of DI. The overall incidence for this complication is 16% [15]. It is commonly associated with the resection involving the transcranial approach. Similarly, patients having craniopharyngioma, large adenoma, or suprasellar extension are at a high risk of having this complication [28]. Presenting symptoms are increased urine output in the absence of other causes of polyuria. The management plan should include the evaluation of serum sodium along with the osmolality workup, on the basis of which the patient may need adequate fluid replacement to overcome the losses, or in severe cases treatment option is the administration of desmopressin.

18.23.3 Inappropriate Secretion of Anti Diuretic Hormone (SIADH)

It is another rare complication of the pituitary surgery. The overall incidence is 8%, and is due to nonspecific release of ADH causing unregulated water retention and loss of urinary sodium [76]. The diagnostic feature is hyponatremia secondary to extracellular volume expansion. In contrast to DI, it usually presents with the hyponatremia secondary to unregulated water retention and loss of urinary sodium. The diagnostic workup is the same as DI, but the treatment option here is fluid restriction.

18.23.4 Cerebral Salt Wasting Syndrome

It is a rare cause of hyponatremia in neurosurgical patients associated with excessive diuresis, causing significant reduction in the extracellular and intravascular volumes [5]. The condition is very much similar to SIADH, but diagnosis is crucial from the treatment point of view, which is different for both conditions. Hypertonic saline is the treatment of choice here to overcome the volume-depleted status of the patient.

18.23.5 Rare Complications

Case reports of intracranial placement of nasogastric tube have been described [77, 78]. Complications can occur as the bony defect persists for 2–3 weeks postoperatively.

18.24 Special Topics

18.24.1 Pituitary Apoplexy

Pituitary apoplexy is a rare emergency, which often occurs in clinically nonfunctioning macroadenoma. Its incidence is between 2% and 7%. Patients usually present in the fifth or sixth decade as an emergency. Precipitating factors have been identified as hypertension, major surgery, coagulopathy, estrogen therapy, pregnancy, and head trauma. The British Society of Endocrinology has published UK Guidelines for the management of pituitary apoplexy in 2011 [13]. These guidelines cover definition, initial assessment, indications of medical or surgical management, and postoperative care.

Conclusion

Anesthesia for pituitary disease presents several challenges to the anesthetists. Preoperative assessment needs to focus on endocrinological, cardiovascular, respiratory/airway, and neurological assessment. Perioperative management requires hemodynamic control and optimization of cerebral perfusion and oxygenation as well as facilitating surgical exposure. Extubation should be smooth and rapid and requires early assessment of neurological function. A multidisciplinary approach is fundamental in successful management.

Take Home Messages

- Anterior pituitary secretes TSH, ACTH, GH, FSH, LH, PRL, MSH.
- Posterior pituitary secretes ADH and oxytocin.
- Pituitary tumors present with mass or hormonal effects.
- Tumors can be classified as microadenoma (<10 mm diameter) or macroadenoma (>10 mm diameter) and functioning or nonfunctioning.
- Preoperative assessment should focus on endocrinological review, cardiovascular, respiratory/airway assessment, and neurological assessment.
- The goals of intraoperative management are to optimize cerebral perfusion and oxygenation, maintain hemodynamic stability, and facilitate surgical exposure.
- Airway can be difficult with acromegaly and Cushing's disease.
- Anesthetic drugs and techniques depend on individual preference and are similar to other intracranial procedures.
- Goal of emergence is smooth and rapid emergence and early assessment of neurological function.
- Acromegalic patients with OSA and those diagnosed with Cushing's disease should be nursed on a high dependency unit postoperatively.
- CSF leak, DI, SIADH, and cerebral salt wasting syndrome can occur postoperatively.

References

1. Menon R, Murphy PG, Lindley AM. Anesthesia and pituitary disease. Contin Educ Anaesth Crit Care Pain. 2011;11:133–7.
2. Vance ML. Perioperative management of patients undergoing pituitary surgery. Endocrinol Metab Clin North Am. 2003;32(2):355–65.
3. Dunn LK, Nemergut EC. Anesthesia for transphenoidal pituitary surgery. Curr Opin Anaesthesiol. 2013;26(5):549–54.
4. Bajwa SJS, Bajwa SK. Anesthesia and intensive care implications for pituitary surgery: recent trends and advancements. Indian J Endocrinol Metab. 2011;15(3):224–32.
5. Smith N, Hirsch NP. Pituitary disease and anesthesia. Br J Anaesth. 2000;85(1):3–14.
6. Griffiths S. Tutorial of the week. The hypothalamic pituitary axis part 2: anesthesia for pituitary surgery. Anesthesia tutorial of the week. 2010. http://www.frca.co.uk/Documents/186%20The%20hypothalamic-pituitary%20axis%20part%201%20-%20anatomy%20&%20physiology.pdf.
7. Chanson P, Saleneve S. Acromegaly. Orphanet J Rare Dis. 2008;3:17.
8. Hernández-Gordillo D, Ortega-Gómez Mdel R, Galicia-Polo L, Castorena-Maldonado A, Vergara-López A, Guillén-González MÁ, et al. Sleep apnea in patients with acromegaly. Frequency, characterization and positive pressure titration. Open Respir Med J. 2012;6:28–33.
9. Kabayegit OY, Soysal D, Oruk G, Ustaoglu B, Kosan U, Solmaz S, et al. Adrenocortical oncocytic neoplasm presenting with Cushing's syndrome: a case report. J Med Case Reports. 2008;13:228.
10. Salaun C, Foubert L, Vialatou M, Kujas M, Turpin G. Prognostic factors of surgical cure of growth hormone secreting pituitary adenomas. Ann Med Interne (Paris). 1999;150(3):195–8.
11. Herrmaan BL, Bruch C, Saller B, Bartel T, Ferdin S, Erbel R, et al. Acromegaly: evidence for a direct relation between disease activity and cardiac dysfunction in patients without ventricular hypertrophy. Clin Endocrinol (Oxf). 2002;56(5):596–602.
12. Ellegala DB, Alden TD, Coture DE, Vance ML, Maartens NF, Laws Jr ER. Anemia, testosterone and pituitary adenoma in men. J Neurosurg. 2003;98(5):974–7.
13. Rajasekaran S, Vanderpump M, Baldeweg S, Drake W, Reddy N, Lanyon M, et al. UK guidelines for the management of pituitary apoplexy. Pituitary Apoplexy Guideline Development Group. Clin Endocrinol (Oxf). 2010;74:9–20.
14. Randeva HS, Schoebel J, Byrne J, Esiri M, Adams CB, Wass JA. Classical pituitary apoplexy: clinical features, management and outcome. Clin Endocrinol (Oxf). 1999;51:181–8.
15. Nemergut EC, Zuo Z. Airway management in patients with pituitary disease. A review of 746 patients. J Neurosurg Anaesthesiol. 2006;18(1):73–7.
16. Sivanaser V, Manninen P. Preoperative assessment of adult patients for intracranial surgery. Anesthesiol Res Pract. 2010; doi:10.1155/2010/241307. Epub Mar 31.
17. Horvat A, Kolak J, Gopcevic A, Ilej M, Zivko G. Anesthesia management of patients undergoing pituitary surgery. Acta Clin Croat. 2011;50(2):209–16.
18. Mulesan ML, Lupia M, Salvetti M, Grigoletto C, Sonino N, Boscaro M, et al. Left ventricular structural

and functional characteristics in Cushing's syndrome. J Am Coll Cardiol. 2003;41(12):2275–9.
19. Katznelson L. Alterations in body composition in acromegaly. Pituitary. 2009;12(2):136–42.
20. Dostalova S, Sonka K, Smahel Z, Weiss V, Marek J. Cephalometric assessment of cranial abnormalities in patients with acromegaly. J Craniomaxillofac Surg. 2003;31(2):80–7.
21. Schmitt H, Buchfelder M, Radespiel-Tröger M, Fahlbusch R. Difficult intubation in acromegalic patients: incidence and predictability. Anesthesiology. 2000;93(1):110–4.
22. Bindra A, Prabhakar H, Bithal PK, Singh GP, Chowdhury T. Predicting difficult laryngoscopy in acromegalic patients undergoing surgery for excision of pituitary tumors: a comparison of extended Mallampati score with modified Mallampati classification. J Anaesthesiol Clin Pharmacol. 2013;29(2):187–90.
23. Sharma D, Prabhakar H, Pramod K, Ali Z, Singh GP, Rath GP, et al. Predicting difficult laryngoscopy in acromegaly: a comparison of upper lip bite test with modified Mallampatti classification. J Neurosurg Anesthesiol. 2010;22(2):138–43.
24. Lungo G, Pena L, Cordido F. Clinical manifestations and diagnosis of acromegaly. Int J Endocrinol. 2012;2012 doi:10.1155/2012/540398. Epub 2012 Feb 1.
25. Lopez-velasco R, Escobar-Mooreale HF, Vega B, Villa E, Sancho JM, Moya-Mur JL, et al. Cardiac involvement in acromegaly: specific-myocardiopathy or consequences of systemic hypertension. J Clin Endocrinol Metab. 1997;82(4):1047–53.
26. Rossie E, Zuppi P, Biasucci LM, Lombardo A, De Marinis L, Loperfido F. Acromegalic cardiomyopathy: left ventricular filling and hypertrophy in active and surgically treated disease. Chest. 1992;102(4):1204–8.
27. Bourdelot AJ, Coste V, Hazebroucq V, Gaillard S, Cazabat L, Bertagna X, et al. Clinical hormonal and magnetic resonance imaging (MRI) predictors of transphenoidal surgery outcome in acromegaly. Eur J Endocrinol. 2004;150(6):763–71.
28. Korttila K, Tarkkanen L, Kuurne T, Himberg JJ, Abbondati G. Unpredictable central nervous system effects after lorazepam premedication for neurosurgery. Acta Anaesthesiol Scand. 1982;26(3):213–6.
29. John R, Hirsch N. Pituitary disease and anesthesia. Anesth Intens Care Med. 2014;15(4):185–8.
30. Kim EH, Oh MC, Kim SH. Application of low field intraoperative magnetic resonance imaging in transphenoidal surgery for pituitary adenomas: technical points to improve the visibility of the tumour resection margin. Acta Neuochir (Wein). 2013;155:485–93.
31. Tabakow P, Czyz M, Jarmundowicz W, Lechowicz-Glogowska E. Surgical treatment of pituitary adenomas using low field intraoperative magnetic resonance imaging. Adv Clin Exp Med. 2012;21(4):495–503.
32. Yu H, Lin G. Transphenoidal endoscopic endonasal approach for the surgery of pituitary abscess. Chinese J Otorhinol Head Neck Surg. 2014;49(1):16–9.
33. Ensenat J, de Notaris M, Sanchez M, Fernandez C, Ferrer E, Bernal-Sprekelsen M, et al. Endoscopic endonasal surgery for skull base tumours: technique and preliminary results in a consecutive care series report. Rhinology. 2013;51(1):37–46.
34. D'Haens J, Van Rompey K, Staduck T, Haentjens P, Poppe K, Velkeniers B. Fully endoscopic transphenoidal surgery for functioning pituitary adenomas a retrospective comparison with traditional trans sphenoidal microsurgery in the same institution. Surg Neurol. 2009;72:336–40.
35. Lim M, Williams D, Maartens N. Anesthesia for pituitary surgery. J Clin Neurosci. 2006;13(4):413–8.
36. Antimicrobial prophylaxis in neurosurgery and after head injury. Infection in neurosurgery working party of the British Society for Antimicrobial Chemotherapy. Lancet. 1994;344(8936):1547–51.
37. Southwick JP, Katz J. Unusual airway difficulty in the acromegalic patient: indications of tracheostomy. Anesthesiology. 1979;51(1):72–3.
38. Messick JM, Cucchiara RF, Faust RJ. Airway management in patients with acromegaly. Anesthesiology. 1982;56(2):157.
39. Shing J, Avidan S, Ing R, Pott L. Awake intubation of the difficult airway with the intubating laryngeal mask airway. Anesthesia. 1998;53(7):645–9.
40. Fiedel ME, Johnston DR, Singhal S, Al Khalili K, Farrell CJ, Evans JJ, et al. Airway management and perioperative concerns in acromegaly patients undergoing endoscopic trans-spehnoidal surgery for pituitary tunours. Otolaryngol Head Neck Surg. 2013;149(6):840–4.
41. Pasternak JJ, Atkinson JLD, Kasperbauer JL. Hemodynamic responses to epinephrine containing local anesthetic injection and to emergence from general anesthesia in transphenoidal hypophysectomy patients. J Neurosurg Anesthesiol. 2004;16:189–95.
42. Chelliah YR, Mawnimen PH. Hazards of epinephrine in trans sphenoidal pituitary surgery. J Neurosurg Anesthesiol. 2002;14(1):43–6.
43. Bhatia N, Ghai B, Mangal K, Wig J, Mukherjee KK. Effect of intramucosal infiltration of different concentrations of adrenaline on hemodynamics during trans-spehnoidal surgery. J Anaesthesiol Clin Pharmacol. 2014;30(4):520–5.
44. Cambell JP, Campbell CD, Warren DW, Prazma TU, Pillsbury 3rd HC. Comparison of the vasoconstrictive and anesthetic effects of intranasally applied cocaine vs. xylometazoline/lidocaine solution. Otolaryngol Head Neck Surg. 1992;107(5):697–700.
45. Razis PA. Anesthesia for surgery of pituitary tumours. Int Anesthesiol Clin. 1997;35(4):23–34.
46. Powell M, Lightman SL. The management of pituitary tumours: a handbook. London: Churchill Livingstone; 1996. p. 145–58.
47. Korula G, George SP, Rajshekkar V, Haran RP, Jeyaseelan L. Effect of controlled hypercapnia on cerebrospinal fluid pressure and operating conditions during transphenoidal operations for pituitary mac-

roadenoma. J Neurosurg Anesthesiol. 2001;13: 255–9.
48. Nemergut EC, Dumont AS, Barry UT, Laws ER. Perioperative management of patients undergoing trans sphenoidal pituitary surgery. Anesth Analg. 2005;101:1170–81.
49. Feinsod M, Selhorst JB, Hoyt WF, Wilson CB. Monitoring optic nerve function during craniotomy. J Neurosurg. 1976;44(1):29–31.
50. Matta BF, Menon DK. Management of head injury: part 1. In: Kaufman L, Ginsberg R, editors. Anesthesia review. London: Churchill Livingstone; 1991. p. 163–78.
51. Van AH. Anesthetic agents: total intravenous and inhalational anesthesia. In: Van Aken H, editor. Neuroanesthetic practice. London: BMJ Publishing Group; 1995. p. 91–132.
52. Todd MM, Warner DS, Sokoll MD, Maktabi MA, Hindman BJ, Scamman FL, et al. A prospective comparative trial of three anesthetics for elective supratentorial craniotomy. Propofol/ fentanyl, Isoflurane / nitrous oxide, and fentanyl/ nitrous oxide. Anesthesiology. 1993;78(6):1005–20.
53. Gopalakrishna KN, Dash PK, Chatterjee N, Easwer HV, Ganesamoorthi A. Dexmedetomidine as an anesthetic adjuvant in patients undergoing trans sphenoidal resection of pituitary tumor. J Neuro Surg Anesthesiol. 2015;27(3):209–15.
54. Guy J, Hindman BJ, Bkaer KZ, Borel CO, Maktabi M, Ostapkovich N, et al. Comparison of remifentanil and fentanyl in patients undergoing craniotomy for supratentorial space-occupying lesions. Anesthesiology. 1997;86(3):514–24.
55. Gemma M, Tommasino C, Cozzi S, Narcisi S, Mortini P, Losa M, et al. Remifentanil provides hemodynamic stability and faster awakening time in trans sphenoidal surgery. Anesth Analg. 2002;94(1):163–8.
56. Hyllested M, Jones S, Pederson JL, Kehlet H. Comparative effect of paracetamol, NSAIDS or their combination in postoperative pain management: a qualitative review. Br J Anaesth. 2002;88(2):199–214.
57. Chadha R, Padmanabhan V, Rout A, Waikar HD. Prevention of hypertension during trans sphenoidal surgery the effect of bilateral maxillary nerve block with local anesthetics. Acta Anaesthesiol Scand. 1997;41:35–40.
58. Leno EM, Tomlinson AA. Anesthesia for supratentorial surgery: current issues. Curr Anaesth Crit Care. 1997;8:270–4.
59. Jeffery H, Charlton P, Mellor D, Moss E, Vucevic M. Analgesia after intracranial surgery: a double blind prospective comparison of codeine and tramadol. Br J Anaesth. 1999;83(2):245–9.
60. Palmer J, Sparrow O, Lannotti F. Postoperative haematoma: a 5-year survey and identification of avoidable risk factors. Neurosurgery. 1994;35(6):1061–4.
61. Cafiero T, Cavallo LM, Frangiosa A, Burrelli R, Gargiulo G, Cappabianca P, et al. Clinical comparison of remifentanil-sevoflurane vs remifentanil-propofol for endoscopic endonasal trans sphenoidal surgery. En J Anaesthesiol. 2007;24(5):441–6.
62. Ali Z, Prabhakar H, Bithal PK, Dash HH. Bispectral index-guided administration of anesthesia for transspheniodal resection of pituitary tumours: a comparison of 3 anesthetic techniques. J Neurosurg Anesthesiol. 2009;21(1):10–5.
63. Salini A, Sharifi G, Bahrani H, Mohajerani S, Jafari A, Safari F, et al. Dexmedetomidine could enhance surgical satisfaction in trans sphenoidal resection of pituitary adenoma. J Neurosurg Sci. 2017;61:46–52.
64. Brady T. Anesthetic management of a pituitary tumor resection with dexmeditomidine. AANA J. 2010;78(2):125–8.
65. Gadhinglajkar SV, Sreedhar R, Bhattacharya RN. Carotid artery injury during transsphenoidal resection of pituitary tumour: anesthesia perspective. J Neurosurg Anesthesiol. 2003;15:323–6.
66. Fukushima T, Maroon JC. Repair of carotid artery perforations during transsphenoidal surgery. Surg Neurol. 1998;50(2):174–7.
67. Hirsch N, Jewke D. Anesthesia for pituitary surgery. In: Oowell H, Lightman SL, editors. The management of pituitary tumours: a handbook. Edinburgh: Churchill Livingstone; 1996. p. 141–4.
68. Rath GP, Chaturverdi A, Chouhan RS, Prabhakar H. Transient cardiac asytole in trans sphenoidal pituitary surgery. A case report. J Neurosurg Anesthesiol. 2004;16(4):299–301.
69. Koga T, Mijao M, Sato M, Hirota K, Kakuyama M, Tanabe H, et al. Pituitary apoplexy during general anesthesia in beach chair position for shoulder joint arthoplasty. J Anesth. 2010;24(3):476–8.
70. Sawka AM, Aniszewski JP, Young Jr WF, Nippoldt TB, Yanez P, Ebersold MJ. Tension pheumocranium a rare complication of trans sphenoidal pituitary surgery: Mayo clinic experience 1976–1998. J Clin Endocrinol Metab. 1999;84(12):4731–4.
71. Burkhardt T, Rotermund R, Schmidt NO, Kiefmann R, Flitsch J. Dexmethasone PONV prophylaxis alters the hypothalamic pituitary adrenal axis after transsphenoidal pituitary surgery. J Neurosurg Anesthesiol. 2014;26:216–9.
72. Flym BC, Nemergut EC. Postoperative nausea vomiting and pain after trans spheniodal surgery: a review of 877 patients. Anesth Analg. 2006;103(1):162–7.
73. Stoneham MD, Cooper R, Qurney NF, Walters FJ. Pain following craniotomy: a preliminary study comparing PCA morphine with intramuscular codeine phosphate. Anesthesia. 1996;51(12):1176–8.
74. Habib AS, Keifer JC, Borel CO, White WD, Gan TJ. A comparison of the combination of aprepitant and dexamethasone versus the combination of ondensetron and dexamethasone for the prevention of post-operative nausea and vomiting in patients undergoing craniotomy. Anesth Analg. 2011;112(4):813–8.
75. Neufield SM, Newborn-Cook CV. The efficacy if 5-HT 3 receptor antagonists for the prevention of

postoperative nausea and vomiting after craniotomy: a meta-analysis. J Neurosurg Anesthesiol. 2007;19(1):10–7.
76. Kelly DF, Laws ER, Fossett D. Delayed hypornatremia after transphenoidal surgery for pituitary adenoma. Report of nine cases. J Neurosurg. 1995;83(2):363–7.
77. Hande A, Nagpal R. Intracranial malportion of nasogastric tube following transnasal transsphenoidal operation. Br J Neurosurg. 1991;5(2):205–7.
78. Paul M, Dueck M, Kampe S, Petzke F, Ladra A. Intracranial placement of a nasotracheal tube after trans nasal trans sphenoidal surgery. Br J Anaesth. 2003;91(4):601–4.

Venous Air Embolism in Neurosurgical Patients

19

S.K. Malhotra

19.1 Introduction

Vascular air embolism (VAE) has been known for the last 100 years but its reporting and awareness have considerably increased in the last 40 years [1]. In the last three decades alone, over 3000 articles covering VAE have been published, highlighting the seriousness of this vascular phenomenon. With the help of technological advances, most events of VAE may be prevented.

Vascular air embolism is the entrainment of air from the operative field or other communication with the environment into the venous or arterial vasculature, producing systemic effects [2]. It is difficult to know the exact incidence of VAE, since a variety of techniques are used to detect the phenomenon. Some subclinical events may not be detected and reported.

VAE is one of the most severe complications in neurosurgery. The reported incidence of VAE is between 16% and 86% in the literature [3]. This wide range is due to various kinds of surgical procedures undertaken and techniques of anesthesia employed. There is no precise data of mortality except some reports following substantial amount of VAE [4]. The occurrence is more in procedures carried out in sitting or semisitting positions [5, 6] such as posterior fossa surgery. Air may enter the circulation through opened veins or dural sinuses and burr holes [7]. For the last one century, VAE has been documented in various articles.

19.2 Epidemiology

Since the clinical features of VAE are nonspecific, subclinical cases may go undetected; hence it is not easy to assess the precise incidence of air embolism. The incidence of VAE in neurosurgical procedures may be 10–80% [8]. About 2% of the patients may experience air embolism while undergoing central venous catheter insertion. In cases of severe lung trauma, there are 4–14% chances of VAE [9]. In patients undergoing laparoscopic procedures, the incidence is reported to be 69% [10]. The incidence of VAE in scuba divers is 7 in 100,000 dives [11]. No racial, sex, or particular age tendency has been noticed for venous air embolism.

19.3 Pathophysiology

When the venous system is exposed to environment and there is a difference of 5 cm of H_2O between the two, the air inflow occurs [12]. It

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has been postulated that air bubbles lead to a kind of reperfusion injury following air embolism. The air is entrained and dissolved in lung circulation. A reflex vasoconstriction occurs due to hypoxia following local obstruction by the air. The microbubbles result in release of cytokine and production of complement. This leads to hypoxia, reduced gas exchange, decreased $ETCO_2$ and pulmonary hypertension [13]. The airway pressures are increased following bronchospasm. There is fall in blood pressure due to low venous return leading to even myocardial ischemia [14]. If the amount of air entrained is more than 5 ml/kg, airlock may occur in right heart causing the block of outflow of right ventricle, dilatation of right heart, decrease in cardiac output, and myocardial ischemia [15]. The "Lethal dose" of air causing symptoms has not been clearly mentioned in literature but 50–300 ml air has been quoted, based on many studies. In an adult, the volume of air that may cause clinical manifestations is around 100 ml [16]. The severity of features depends on the surgical site, such as posterior fossa and the degree of head elevation [17]. When the CVP is lowered following hypovolemia, negative pressure gradient is raised between the right side of the heart and elevated head. Hemodynamic disturbances are more in pediatric age group, hence VAE is more difficult to manage in this group [18]. The use of bone wax, careful dissection, and hemostasis may reduce the incidence of VAE.

19.4 Clinical Etiology

Though venous air embolism may happen in any neurosurgical procedure, the risk is greater in situations where sitting or head-up position is mandatory (Table 19.1). However, it may occur in any position, including prone or supine position [19]. In neurosurgery, sitting or semisitting position is becoming less popular, not because of VAE alone but other problems, such as macroglossia, sciatic nerve injury, and tension pneumocephalus. However, sitting position is still preferred in some countries for posterior fossa surgery [20]. Even the surgery for Parkinson's disease carries a substantial risk of VAE ranging from 1.3% to 3.2%, owing to the stimulation of deep brain [21, 22].

Table 19.1 Neurosurgical procedures related to venous air embolism

Craniotomies in sitting position
Posterior fossa surgery
Stereotactic surgery
Deep brain stimulation
Craniosynostosis repair
Torticollis corrective surgery
Cervical laminectomy
Spinal fusion procedures

Another situation where VAE is likely to occur is stereotactic surgery, where clinical features of air embolism have been observed in 8.3% cases, which underwent this procedure in raised head position [23].

In pediatric age group, craniosynostosis repair surgery is more likely to result in VAE, thereby leading to higher chances of fatalities [24]. Procedures such as cervical laminectomy [25], spinal fusion surgery [26], and torticollis corrective surgery [27] have also been associated with venous air embolism.

19.5 Clinical Presentation

The clinical manifestation depends on the amount and rate of air entry into the systemic circulation. There are many more factors that contribute to this event (Table 19.2). The VAE mainly leads to respiratory, cardiovascular, and neurological problems.

In case the patient is conscious, the features of venous air embolism may include sudden and continuous coughing event [28]. In addition, there may be fall in blood pressure and oxygen saturation as well as wheezing, "gasp reflex," pain in the chest and difficulty in breathing [29]. There may be hypercarbia due to decreased pulmonary compliance and increase in dead space [30].

Moreover, mill-wheel murmur on auscultation may be a common feature [31]. However, the

Table 19.2 Etiological factors related to venous air embolism

Factors
Level of right atrium as related to surgical field
Exposure of large surgical site
Abdominal decompression
Irrigation of wound with hydrogen peroxide
Introduction of gas for investigations
Underlying hypovolemia
Patient on spontaneous breathing

esophageal stethoscope is considered to be a low sensitivity monitor to detect this murmur.

Cardiovascular problems may include pulmonary hypertension, pulmonary congestion, bradyarrhythmias, tachycardia, or features of myocardial ischemia [32]. The ECG may show changes in ST segment or right ventricular strain pattern [33]. Due to the right heart failure, there may be raised central venous pressure, too.

The neurological disorders may range from focal neurological deficits to even coma. These are usually due to cerebral embolism or cerebral hypoperfusion, secondary to decreased cardiac output [34], particularly if there is patent foramen ovale that is present in 20% of adult population. In the patients at risk, there may be change in mental status due to air embolism and cerebral ischemia.

The air embolism may affect the pulmonary vasculature, which in turn leads to discharge of inflammatory factors leading to coagulation disorders such as fall in platelet count [35].

19.6 Risks of Air Embolism

The risk of VAE is higher when the site of operative field is more than 5 cm above the right atrium. At the craniotomy site, air may enter opened venous channels leading to VAE. It depends on the pressure gradient between the right atrium and cerebral veins. In case the CVP falls, there are more chances of air embolism. If the detection of air embolism is faster and management is immediate, the hazards may be minimized [36].

A lot of stress has been laid on paradoxical air embolism (PAE), its detection, and subsequent management. The ischemia of myocardium and brain may follow PAE which may be distressing. The common cause of PAE is right-to-left shunt due to congenital cardiac anomaly, such as patent foramen ovale that is present in 25–30% cases [37]. The reversal of shunt, i.e., from right to left, occurs when right side pressure increases. The shunt reversal takes place in about half of the cases and that too within an hour. The risk of PAE is not more than 10% and not all the patients with patent foramen ovale are likely to experience it as, echocardiography has revealed in many studies [38]. In such cases, cerebral and myocardial ischemia can result due to embolization of cerebral (Fig. 19.1) or coronary circulation. In case a patient gets a sudden postoperative neurological dysfunction, particularly after a surgical procedure likely to have air embolism, PAE should be suspected. The role of hypovolemia is vital in occurrence of PAE as well as VAE, since lower CVP may lead to right-to-left shunt, hence patient should be well hydrated, particularly if the procedure is performed in sitting position [39]. Since PEEP may increase pressure in the right atrium, it may reduce the chances of VAE. But at the same time it may increase the chances of PAE by causing right-to-left shunting at the level of atrium [40]. Therefore,

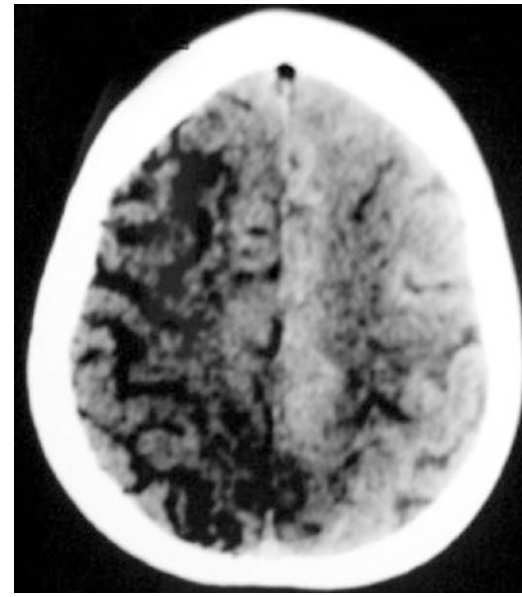

Fig. 19.1 Cerebral paradoxical air embolism

PEEP should be better avoided in such cases, especially in sitting position.

Hypovolemia, up-right position, and deep inspiration are few factors that may increase the risk of VAE when a central venous catheter is being inserted or removed.

19.7 Diagnosis

Patients at high risk for venous air embolism undergoing neurosurgical procedures are monitored routinely with ECG, pulse oximetry, ABG analysis, and direct arterial pressure measurement. In addition, some specific monitors for timely detection of VAE are employed (Table 19.3).

19.7.1 Precordial Doppler Ultrasound

To detect the entrained air in the right heart, precordial Doppler ultrasound is the most accurate and useful tool [41]. Even a small amount of air, as little as 0.25 ml, may be easily detected [42]. It is much more sensitive than capnography. The location and removal of air is affected by morbid obesity as well as the prone or lateral position. The probe is placed above the xiphoid and on the right side of the sternum [43]. Since it is a subjective method, it may give false negative results. The sound artifacts may be noted while using electrocautery at the same time. The probe generates a signal reflected by circulating blood. The change in frequency between this reflected and the transmitted signal is translated into sound that is easily heard [44]. Before starting the procedure, 0.25–1 ml of CO_2 or 3–5 ml of stirred saline should be injected into the central catheter so that the change in the Doppler tones may be well appreciated and a reference point may be noted.

19.7.2 Capnography

This is the most frequent and easily accessible monitoring, which can detect abrupt fall in $ETCO_2$, in case VAE occurs [45]. It has a defi-

Table 19.3 Monitors to detect venous air embolism

Doppler ultrasound	Very sensitive, noninvasive, early detection of VAE Difficult placement in obese, chest wall deformity, prone position Ineffective during electrocautery I.V.mannitol may imitate vascular air
Pulmonary artery catheter	More sensitive than $ETCO_2$ Commonly available Minimal difficulty in placement Detects RA pressure more than PACP Lumen small, air aspiration difficult
Transesophageal Echocardiography	Very sensitive Detects air in left heart Costly, invasive Needs continuous observation Not quantitative Interferes with Doppler
Capnography	Easily available Quite sensitive Noninvasive Less sensitive than Doppler Affected by tachypnea, COPD
End-tidal nitrogen	Precisely for air Early detection than $ETCO_2$ No detection of subclinical air embolism Premature air clearance from pulmonary circulation Hypotension affects precision
Right atrial catheter	Removal of air assists in diagnosing VAE Electrocautery can be concurrently used Useful in measuring CVP (increased in air embolism) Lumen is large, sufficient amount of air aspirated May get displaced when patient's position changed Multiple lumen catheter more useful

nite part to play in locating the air embolism. It helps by detecting the rise in arterial to $ETCO_2$ gradient. Various conditions such as COPD, the fall in cardiac output, and tachypnea may affect the accuracy of results by capnography. A fall of $ETCO_2$, as little as 2 mmHg may indicate the presence of air embolism [46]. However, capnography is not so precise, especially in the presence of hypotension. Also, in a patient with spontaneous ventilation, capnography may be unpredictable, particularly when upper airway is obstructed or if respiratory rate is varying.

19.7.3 End-Tidal Nitrogen

End-tidal nitrogen (ETN_2), though not commonly provided in anesthesia machines, is quite a specific device to detect air embolism [47]. If nitrogen is present in expired gas while patient is on 100% oxygen, there is likely to be VAE. It may measure rise in ETN_2 as small as 0.04%. The changes in ETN_2 may occur 30–90 seconds earlier than those in $ETCO_2$, especially when the volume of the air entrained is large [48]. However, this method is not recommended when nitrous oxide is being used, concurrently.

19.7.4 Transesophageal Echocardiography (TEE)

This method helps to obtain an accurate diagnosis and the information provided is substantial [49]. It also assists in diagnosing patent foramen ovale that is a vital cause of central embolism and is present in about 35% of subjects [50]. Out of invasive techniques, TEE is the most accurate method, not only to detect air embolism but paradoxical embolism, too [51]. As small volume of air as 0.01–0.19 ml/kg, may be detected by TEE [52]. One study showed that in case TEE detects air embolism without an associated fall in $ETCO_2$, there would not be any hemodynamic changes [53]. However, TEE is expensive and the learning curve is steep and requires expertise. Moreover, it is not certain that it may not miss the presence of air embolism. TEE is used in about 38% of patients undergoing neurosurgical procedures as compared to Doppler ultrasound that is practiced in almost all the patients [54].

19.7.5 Pulmonary Artery Catheter

The pulmonary artery catheter would show an increase in PA pressure. It is not so sensitive method for monitoring of air embolism (0.25/kg) as its sensitivity is only 15% [55]. As in pulmonary thromboembolism, ventilation–perfusion scan is same. The perfusion defect found in air embolism disappears within a day. It is quite invasive a technique and much less useful as compared to Doppler ultrasound. Since its lumen is narrow, it is less able to remove the entrained air.

Unless the patient has coexistent cardiac diseases that may require pulmonary artery catheter to assess cardiac output, its use is not recommended.

19.7.6 Right Atrial Catheter

In case the right atrial catheter has been in place, the entrained air may assist in diagnosing VAE, especially when electrocautery is concurrently used and Doppler signals are obstructed [56]. It would also be useful in measuring CVP that is increased in air embolism. The catheter orifice kept at air-blood interface is the correct site for placement. Since the lumen is large, a sufficient amount of air may be withdrawn but the problem is that the catheter may get displaced when the patient's position is changed [57]. Multiple lumen catheters are more useful than single lumen [58].

19.7.7 Transcranial Doppler

Transcranial Doppler has been successfully used to detect air bubbles present in the cerebral artery. Its sensitivity is 91.3% and specificity 93.8%. In a patient of patent foramen ovale, transcranial Doppler is helpful in monitoring intracranial air embolism [59].

19.7.8 Electrocardiography (ECG)

Changes in ECG following venous air embolism are not so sensitive. These are appreciated well when air inflow is fast. Findings may include ST-T changes that appear first. There may be ST depression in L1 and avL and ST elevation in inferior leads. Tachyarrythmias, bradycardia, and right ventricular strain pattern are also observed [60].

19.7.9 Pulse Oximetry

The change in oxygen saturation as shown by pulse oximeter appears late in the event of venous air embolism. Change is not appreciated until there is physiological imbalance of a severe type because patient receives high concentration of inspired oxygen after VAE is established. Both oximetry and capnography do not come under the category of sensitive monitors.

19.7.10 Miscellaneous Methods

Currently, Doppler ultrasound is being employed to monitor cerebral circulation. Perioperatively, monitoring of middle cerebral artery has been used successfully using transcranial Doppler ultrasound. Studies are underway to measure the quantity of air and make the device more manageable.

Some studies regarding the changes in bispectral index following VAE can be found in the literature [61]. But such changes may not only be due to air embolism but other factors such as increase in depth of anesthesia, too.,

Doppler ultrasonographic monitoring of the cerebral circulation uses the same technology currently in use for VAE detection. Routine carotid Doppler monitoring may not be specific in the case of PAE, because any air in the adjacent internal jugular veins would also be detected by the probe. Transcranial Doppler ultrasonographic monitoring of the middle cerebral artery has become increasingly useful in the perioperative setting. Efforts continue to enable quantification of embolic air and to make the equipment less cumbersome.

During posterior fossa surgery, it is essential to monitor the status of cerebral functions. Some kinds of monitoring like brainstem auditory-evoked potential (BAEP), motor nerve stimulation, and electroencephalogram (EEG) are being practiced. These monitors are employed in specific spinal and intracranial surgical procedures [62].

19.7.11 Complications Following Venous Air Embolism

The complications that occur following venous air embolism mainly involve three systems, i.e., cardiovascular, pulmonary and central nervous system (Table 19.4). During surgical procedure, there may be premature ventricular complexes in addition to murmurs, bradycardia, and tachycardia [63]. Substantial hemodynamic effects and heart sound changes occur only when the air embolism is massive. Fall in blood pressure occurs due to decreased cardiac output owing to massive venous air embolism, while other cardiac features do not last beyond 5 min [64]. The changes in ECG come late and may show myocardial ischemic changes, in case the air embolism affects the coronary arteries [65]. The occlusion of pulmonary outflow may result in right heart failure. Even cardiac arrest may follow if airlock occurs in the right atrium or ventricle. "Gasp reflex" has been described when a

Table 19.4 Complications of venous air embolism

System	Complications
Pulmonary	Hypoxemia Hypercarbia Pulmonary edema Pulmonary hypertension
Cardiovascular	Arrhythmias Hypo-/hypertension Right ventricular failure Mill-wheel murmur Ischemic ECG changes Cardiovascular collapse
Central nervous system	Increased cerebral flow Brain edema Neurologic disorders Stroke, coma

large bolus of air gets entrained in pulmonary circulation leading to sudden hypoxia [66]. Other important complication is the development of pulmonary edema that may occur due to air emboli and is not of neurogenic origin in which pulmonary artery wedge pressure remains unchanged. Persistent rise in pulmonary artery pressure may damage the vascular endothelium.

After the surgery, various complications may be expected. Neurological disorders may occur due to cerebral ischemia, hypoxia, or air embolism leading to rise in ICP, stroke, or even coma. Morbidity or mortality has not been established as related to VAE, but cerebral trauma may definitely occur due to cerebral air embolism [67]. Convulsions, hemiplegia, nystagmus, and strabismus have also been reported. Postoperative cardiovascular problems may include right heart failure owing to pulmonary hypertension as well as myocardial ischemia following air embolism in coronary arteries. Pulmonary edema in postoperative period may occur and responds to conventional treatment, such as diuretics and oxygen [68].

19.7.12 Prophylaxis

The first vital factor is the surgical position in preventing air embolism. In place of sitting position, another position such as "Park-bench" position or a low head-up position should be preferred. Other recommended position is semi-sitting, where the head is at a lower level than legs. This causes a positive pressure in transverse as well as sigmoid sinuses. The legs raised to the level of heart can also facilitate to decrease the pressure gradient between the right atrium and the surgical field.

In case of preexisting right-to-left shunt, additional precautions and detailed monitoring must be undertaken [69]. While inserting or removal of central venous catheter, all the risk factors must be kept in mind [70]. Keeping the patient well hydrated would prevent high pressure gradient between cerebral veins and right atrium, therefore decreasing the chances of VAE, though no measures fully ensure its prevention [71].

It is suggested that the right atrial pressure should be kept between 10 and 15 cm H_2O.

In the anesthetic technique, ventilation should be controlled and nitrous oxide must be avoided to prevent air embolism. Drugs that cause vasodilatation, such as nitroglycerine should be avoided. Use of PEEP in preventing VAE is not established. It may decrease blood pressure and may increase the risk of PAE.

One must avoid hyperventilation, particularly in sitting position. The lower extremities should be thoroughly wrapped. Surgical dissection must be careful and the use of bone wax be made.

19.7.13 Management

The aims of management of air embolism during operative procedure include prevention of further inflow of air and aspiration of the air already present. The treatment of hypotension, hypercapnia and hypoxia must be undertaken.

If Doppler monitoring and $ETCO_2$ changes indicate VAE, it should be communicated to the operating surgeon so that he should irrigate the surgical field with saline and saline-soaked dressing and use liberal wax to cover the opened blood vessels.

In case there are chances of air embolism, bilateral jugular venous compression should be employed irrespective of the patient's surgical position [72]. This is a controversial maneuver since it may increase the intracranial pressure causing cerebral congestion and reduction in cerebral perfusion. Keep in mind that jugular compression may compress carotid arteries and carotid sinus compression may result in bradycardia.

Once the air is detected by recommended monitors, any air collected in the right atrium and superior vena cava must be aspirated immediately through central venous catheter to prevent further damage [73]. It is recommended that air is best aspirated with the tip of catheter placed 2 cm below the SA node.

Sufficient fluids need to be administered to maintain adequate blood pressure. Inotropes such as ephedrine, dobutamine, norepinephrine, and epinephrine should be kept ready.

Nitrous oxide increases the size of entrained air bubbles, therefore it is rational to discontinue its use in high-risk procedures, particularly those with intracardiac septal defects. Hundred percent oxygen must be started and anesthetic technique duly modified [74].

The patient should be given left lateral position (Durant maneuver) with head low (Trendelenburg position) so that the entrapped air is localized in right atrium and spares the right ventricular outflow tract.

In high-risk surgical procedures, the employment of controlled ventilation is suggested, intraoperatively.

Adding PEEP is controversial and is generally avoided. It may result in paradoxical air emboli in a patient with a patent foramen ovale and may lead to hemodynamic instability by reducing right ventricular preload and venous return. Hence, PEEP should not be added unless strongly indicated [75].

In case of a massive embolism or cardiac arrest, ACLS protocol must be followed and advanced resuscitation should be promptly commenced [76].

In postanesthesia care unit, management of air embolism includes detection and treatment of myocardial ischemia as well as avoiding any respiratory distress. If PAE is detected, it should be duly managed. Routine investigations such as ABG and ECG should be undertaken. The examination of fundus and CT scan is mandatory to rule out air in the cerebral circulation. Though MRI is considered to be more accurate, its use in critically ill patients is questionable [77]. If feasible, hyperbaric oxygen may be employed in case of cerebral embolism as it reduces the size of air bubble, promotes nitrogen reabsorption and the passage of dissolved oxygen into the blood [78].

Conclusion

Venous air embolism is most frequently observed in neurological procedures in sitting or semi-sitting posture. Clinically, it is crucial to anticipate and prevent this risky event. The ideal preparation for this life-threatening complication is to keep constant vigilance toward the possibility of venous air embolism, particularly in the high-risk neurosurgical procedures. Timely detection and quick intervention are vital factors in improving the outcome. The most reliable and widely practiced monitors to detect air embolism include Doppler ultrasound and capnography. Once venous air embolism is established, further entrainment of air should be prevented, nitrous oxide discontinued, 100% oxygen supplemented, and the aspiration of air from right atrium carried out. Head down with a left lateral position is recommended to spare the right ventricular outflow tract. Hemodynamic stability must be ensured by administering intravenous fluids and inotropes. Adequate advanced resuscitation measures are essential in case of a massive air embolism.

References

1. Muth CM, Shank ES. Gas embolism. N Engl J Med. 2000;342:476–82.
2. Mirski MA, Lele AV, Fitzsimmons L, Toung TJK. Diagnosis and treatment of vascular air embolism. Anesthesiology. 2007;106:164–77.
3. Ganslandt O, Merkel A, Schmitt H, Tzabazis A, Buchfelder M, Eyupoglu I, et al. The sitting position in neurosurgery: indications, complications and results. a single institution experience of 600 cases. ActaNeurochir (Wien). 2013;155:1887–93.
4. Wei S-T, Chen D-C. Catastrophic venous air embolism duringcraniotomy in the supine position: the bleeding pattern as awarning sign? J Craniofac Surg. 2013;24:228–9.
5. Chang EF, Cheng JS, Richardson RM, Lee C, Starr PA, Larson PS. Incidence and management of venous air embolisms during awake deep brain stimulation surgery in a large clinical series. Stereotact Funct Neurosurg. 2011;89:76–82.
6. Felema GG, Bryskin RB, Heger IM, Saswata R. Venous air embolism from Tisseel use during endoscopic cranial vault remodeling for craniosynostosis repair: a case report. Paediatr Anaesth. 2013;23:754–6.
7. Edelman JD, Wingard DW. Air embolism arising from burrholes. Anesthesiology. 1980;53:167–8.
8. Tobias JD, Johnson JO, Jimenez DF, Barone CM, DS Jr MB. Venous air embolism during endoscopic strip craniotomy for repair of craniosynostosis in infant. Anesthesiology. 2001;95:340–2.
9. Baker CC, Thomas AN, Turnkey DD. The role of emergency roomthrocotomy in trauma. J Trauma. 1990;20:848–55.

10. Derouin M, Couture P, Boudreault D, Girard D, Gravel D. Detection of gas embolism by transesophageal echocardiography during laparoscopic cholecystectomy. Anesth Analg. 1996;82:119–24.
11. Leitch DR, Green RD. Pulmonary barotruama in divers and treatment of gas embolism. Aviat Space Environ Med. 1986;57:931.
12. Paladino MA. Eventosintraoperatorios en neurocirugia. Rev Arg Anest. 2004;62:133–51.
13. Pfitzner J, Petito SP, McLean AG. Hypoxaemia following sustained low-volume venous air embolism in sheep. Anaesth Intensive Care. 1988;16:164–70.
14. Van Hulst RA, Klein J, Lachmann B. Gas embolism: pathophysiology and treatment. Clin Physiol Funct Imaging. 2003;23:237–46.
15. Durant TM, Long J, Oppenheimer MJ. Pulmonary (venous) air embolism. Am Heart J. 1947;33:269–81.
16. Pahnon SC, Toung T. Special article SP venous air embolism: a review. 1997;8180:97.
17. CabezudoJM GF, Vaquero J, et al. Air embolism from wounds from a pin-type head-holder as a complication of posterior fossa surgery in the sitting position. J Neurosurg. 1981;55:147–8.
18. Matjasko J, Petrozza P, Cohen M, et al. Anesthesia and surgery in the seated position: Analysis of 554 cases. Neurosurgery. 1985;17:695–702.
19. Hassan WMNW, Zainuddin A, Ali S. Venous air embolism during elective craniotomy for parasagittal meningioma. Med J Malaysia. 2013;68:69–70.
20. Misra BK. Neurosurgery in the semisitting position in patients with a Patent Foramen Ovale. World Neurosurg. 2013;3:7–8.
21. Ammirati M, Lamki TT, Shaw AB, Forde B, Nakano I, Mani M. A streamlined protocol for the use of the semi-sitting position in neurosurgery: a report on 48 consecutive procedures. J Clin Neurosci. 2013;20:1–6.
22. Hooper AK, Okun MS, Foote KD, Haq IU, Fernandez HH, Hegland D, et al. Venous air embolism in deep brain stimulation. Stereotact Funct Neurosurg. 2009;87:25–30.
23. Deogaonkar A, Avitsian R, Henderson JM, Schubert A. Venous air embolism during deep brain stimulation surgery in an awake supine patient. Stereotact Funct Neurosurg. 2005;83:32–5.
24. Faberowski LW, Black S, Mickle JP. Incidence of venous air embolism during craniectomy for craniosynostosis repair. Anesthesiology. 2000;92:20–3.
25. Lopez LM, Traves N, Napal M. Fatal gas embolism during corrective surgery for scoliosis using the posterior approach. Rev Esp Anestesiol Reanim. 1999;46:267–70.
26. Latson TW. Venous air embolism during spinal instrumentation and fusion in the prone position. Anesth Analg. 1992;75:152–3.
27. Lobato EB, Black S, De Soto H. Venous air embolism and selective denervation for torticollis. Anesth Analg. 1997;84:551–3.
28. Balki M, Manninen PH, McGuire GP, El-Behereiry H, Bernstein M. Venous air embolism during awake craniotomy in a supine patient. Can J Anesth. 2003;50:835–8.
29. Bithal PK, Pandia MP, Dash HH, Chouhan RS, Mohanty B, Padhy N. Comparative incidence of venous air embolism and associated hypotension in adults and children operated for neurosurgery in the sitting position. Eur J Anaesthesiol. 2004;21:517–22.
30. Siviri S, Woods WP, Van Heerden PV. Air embolism; A case series and review. Crit Care Resusc. 2004;6:271–6.
31. Kumar R, Goyal V, Chauhan RS. Venous air embolism during microelectrode recording in deep brain stimulation surgery in an awake supine patient. Br J Neurosurg. 2009;23:446–8.
32. Arora R, Chablani D, Rath GP, Prabhakar H. Pulmonary oedema following venous air embolism during transsphenoidal pituitary surgery. Acta Neurochir. 2007;149:1177–8.
33. Orebough SL. Venous air embolism. Clinical and experimental considerations. Crit Care Med. 1992;20:1169–70.
34. Palmon SC, Moore LE, Lundberg J, Toung T. Venous air embolism: a review. J Clin Anesth. 1997;9:251–7.
35. Schafer ST, Sandalcioglu IE, Stegen B, Neumann A, Asgari S, Peters J. Venous air embolism during semisitting craniotomy evokes thrombocytopenia. Anaesthesia. 2011;66:25–30.
36. Bedford RF. Perioperative venous air embolism. Semin Anesth. 1987;6:163–70.
37. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramenovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc. 1984;59:17–23.
38. Artru AA, Cucchiara RF, Messick JM. Cardiorespiratory and cranial nerve sequelae of surgical procedures involving the posterior fossa. Anesthesiology. 1980;52:83–6.
39. Colohan ART, Perkins NAK, Bedford RF, et al. Intravenous fluid loading as prophylaxis for paradoxical air embolism. J Neurosurg. 1985;62:839–42.
40. Giebler R, Kollenberg B, Pohlen G, et al. Effect of positive end-expiratory pressure on the incidence of venous air embolism and on the cardiovascular response to the sitting position during neurosurgery. Br J Anaesth. 1998;80:30–5.
41. Gildenberg PL, O'Brien RP, Britt WJ, et al. The efficacy of Doppler monitoring for the detection of venous air embolism. J Neurosurg. 1981;54:75–8.
42. Chang JL, Albin MS, BuneginL HTK. Analysis and comparison of venous air embolism detection methods. Neurosurgery. 1980;7:135–41.
43. Schubert A, Deogaonkar A, Drummond JC. Precordial Doppler probe placement for optimal detection of venous air embolism during craniotomy. Anesth Analg. 2006;102:1543–7.
44. Michenfelder JD, Miller RH, Gronert GA. Evaluation of an ultrasonic device (Doppler) for the diagnosis of venous air embolism. Anesthesiology. 1972;36:164–8.

45. Brechner TM, Brechner VL. An audible alarm for monitoring air embolism during neurosurgery. J Neurosurg. 1977;47:201–4.
46. Smelt WLH. Capnography and air embolism. Can Anaesth Soc J. 1986;33:113–5.
47. Harrison EA, Mackersie A, McEwan A, Facer E. The sitting position for neurosurgery in children: a review of 16 years'experience. Br J Anaesth. 2002;88:12–7.
48. Matjasko J, Petrozza P, Mackenzie CF. Sensitivity of end-tidal nitrogen invenous air embolism detection in dogs. Anesthesiology. 1985;63:418–23.
49. Feigl GC, Decker K, Wurms M, Krischek B, Ritz R, Unertl K, et al. Neurosurgical procedures in the semisitting position: evaluation of the risk of paradoxical venous air embolism in-patients with a Patent Foramen Ovale. World Neurosurg. 2013:1–6. Elsevier Inc.
50. Shaikh N, Ummunisa F. Acute management of vascular air embolism. J Emerg Trauma Shock. 2009;2:180–5.
51. Vinay B, Sriganesh K, Gopala Krishna KN. An abrupt reduction in end-tidal carbon-dioxide during neurosurgery is not always due to venous air embolism: a capnograph artefact. J Clin Monit Comput. 2013;31:5–7.
52. Jaffe RA, Siegel LC, Schnittger I, Propst JW, Brock-Utne JG. Epidural air injection assessed by transesophageal echocardiography. Reg Anesth. 1995;20:152–5.
53. Pandia MP, Bithal PK, Dash HH, Chaturvedi A. Comparative incidence of cardiovascular changes during venous air embolism as detected by transesophageal echocardiographyalone or in combination with end tidal carbon dioxide tension monitoring. J Clin Neurosci. 2011;18:1206–9.
54. Himmelseher S, Pfenninger E, Werner C. Intraoperative monitoring in neuroanesthesia: a national comparison between two surveys in Germany in 1991 and 1997. Scientific Neuroanesthesia Research Group of the German Society of Anesthesia and Intensive Care Medicine. Anesth Analg. 2001;92:166–71.
55. Soriano SG, McManus ML, Sullivan LJ, Scott RM, Rockoff MA. Doppler sensor placement during neurosurgical procedures for children in the prone position. J Neurosurg Anesthesiol. 1994;6:153–5.
56. Alvaran SB, Toung JK, Graff TE, et al. Venous air embolism: comparative merits of external cardiac massage, intracardiac aspiration, and left lateral decubitus position. Anesth Analg. 1978;57:166–70.
57. Lee DS, Kuhn J, Shaffer MJ, et al. Migration of tips of central venouscatheters in seated patients. Anesth Analg. 1984;63:949–52.
58. Albin MS, Carroll RG, Maroon JC. Clinical considerations concerningdetection of venous air embolism. Neurosurgery. 1978;3:380–4.
59. Stendel R, Gramm HJ, Schroder K, Lober C, Brock M. Transcranial Doppler ultrasonography as a screeningtechnique for detection of a patent foramen ovale before surgery in the sitting position. Anesthesiology. 2000;93:971–5.
60. Boussuges A, Molenat F, Carturan D, Gerbeaux P, Sainty JM. Venous gas embolism: detection with pulsed Doppler guided by two-dimensional echocardiography. Acta Anaesthesiol Scand. 1999;43:328–32.
61. Kin N, Konstadt SN, Sato K, et al. Reduction of bispectral index value associated with clinically significant air embolism. J Cardiothorac Vasc Anesth. 2004;18:82–4.
62. Schramm J, Watanabe E, Strauss C, et al. Neurophysiologic monitoring in posterior fossa surgery. I: Technical principles, applicability and limitations. Acta Neurochir. 1989;98:9–18.
63. Michenfelder JD, Martin JT, Altenburg BM, et al. Air embolism during neurosurgery: an evaluation of right atrial catheters for diagnosis and treatment. JAMA. 1969;208:1353–8.
64. Adornato DC, Gildenberg PL, Ferrario CM, et al. Pathophysiology ofintra venous air embolism in dogs. Anesthesiology. 1978;49:120–7.
65. Durant TM, Oppenheimer MJ, Webster MR, et al. Arterial air embolism. Am Heart J. 1949;38:481–500.
66. Lesky E. Notes on the history of air embolism. German Med Monthly. 1961;6:159–61.
67. Mills NL, Ochsner JL. Massive air embolism during cardiopulmonary bypass: causes, prevention, and management. J Thorac Cardiovasc Surg. 1980;80:708–17.
68. Perschau RA, Munson ES, Chapin JC. Pulmonary interstitial edema after multiple venous air emboli. Anesthesiology. 1976;45:364–6.
69. Mam motto T, Hayashi Y, Obnishi Y, Kurno M. Incidence of venous and paradoxical air embolism in neurosurgical patients in sitting position; Detection by trasesophgeal echocardiography. Acta Anesthesiolo Scand. 1998;42:643–5.
70. Brouns R, De Surgeloose D, Neetens I, De Deyn PP. Fatal venous cerebral air embolism secondary to a disconnected central venous catheter. Cerebro Vasc Dis. 2006;21:212–4.
71. Dominique CM. Anesthesia for neurosurgery in sitting position; a case series. Anesth Intens Care. 2005;33:332–5.
72. Grady MS, Bedford RF, Park TS. Changes in superior sagittal sinus pressure in children with head elevation, jugular venous compression and PEEP. J Neurosurg. 1986;65:199–202.
73. Colley PS, Artru AA. Bunegin-Albin catheter improves air retrieval and resuscitation from lethal venous air embolism in upright dogs. Anesth Analg. 1989;68:298–301.
74. Pasternak JJ, Lanier WL. Is nitrous oxide use appropriate in neurosurgical and neurologically at-risk patients? Curr Opin Anaesthesiol. 2010;23:544–50.
75. Kronik G, Mosslacher H. Positive contrast echocardiography in patients with patent foramen ovale and normal right heart hemodynamics. Am J Cardiol. 1982;49:1806–9.
76. Toung TJ, Rossberg MI, Hutchins GM. Volume of air in a lethal venous air embolism. Anesthesiology. 2001;94:360–1.
77. Warren Jr LP, Djang WT, Moon RE, et al. Neuroimaging of scuba diving injuries to the CNS. Am J Roentgenol. 1988;151:1003–8.
78. Kjeld T, Hansen EG, Holler NG, Rottensten H, Hyldegaard O, Jansen EC. Resuscitation by hyperbaric exposure from a venous gas emboli following laparoscopic surgery. Scand J Trauma Resusc Emerg Med. 2012;20:51.

Blood Glucose Concentration Management in Neuro-Patients

20

Federico Bilotta and Elisabetta Stazi

20.1 Brain Metabolism

The energy requirements of the brain are amazingly high; indeed, while representing only about 2% of the body weight, its oxygen and glucose utilization accounts for approximately 20% of that of the whole organism, almost ten times more than what would be predicted on a weight basis. A similar mismatch is also observed for blood flow destined to the brain, which represents over 10% of the cardiac output [1–3]. Glucose is the obligate energetic fuel of the brain, but under particular conditions such as fasting or uncontrolled diabetes, ketone bodies sustain the energetic requirements of the brain [4, 5]. Most of the energy (~80%) is oxidatively produced and consumed by neurons to support neuron-to-neuron signaling and the majority of the energy used appears to be consumed at the synapse [6].

Insulin is a peptide hormone produced by b cells of the pancreas; the secretion is regulated by blood glucose concentration (BGC) and it exerts its effects through insulin receptors (IRs). The b-IRs are heterodimeric transmembrane glycoproteins that belong to the subfamily of tyrosine kinase receptors. The b-IRs have a particular distribution in the brain, with the highest concentrations in the thalamus, caudate–putamen, hippocampus, amygdala, and parahippocampal gyrus. This distribution suggests that the functions of b-IRs may relate to memory, cognition, and neuromodulation [7–10].

Insulin traverses the blood–brain barrier (BBB) via receptor-mediated transport which is an active adenosine triphosphate (ATP)-dependent process that decreases with increasing plasma insulin levels. The other major route of entry from the circulation is through the epithelium of the choroid plexus. The presence of lipopolysaccharide-containing bacterial cell membrane enhances insulin transport (although insulin's effects are diminished) and resultant insulin resistance, often seen during bacterial infections. Conversely, steroid therapy inhibits insulin transport through the BBB [11–15].

Insulin plays an important role in brain metabolism inducing a time- and dose-dependent stimulation of glycogen synthesis. In glial cells, insulin increases norepinephrine concentration by inhibiting its reuptake culminating in enhanced glucose release from glycogen stores. Contemporaneously, insulin causes a rise in expression of glucose transporters. In addition to its effect on neuronal metabolism, insulin acts as a neuropeptide with a neuromodulatory role regulating the activities of excitatory and inhibitory receptors, such as glutamate and g-aminobutyric acid (GABA) receptors [16–18].

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20.2 Blood Glucose Concentration (BGC) Variation in Neurocritical Patients

20.2.1 Hyperglycemia

The American Diabetes Association consensus recently established the presence of hyperglycemia when blood glucose concentration (BGC) exceeds 140 mg/dL (7.8 mmol/L) in two or more plasma samples [19].

Hyperglycemia at the time of acute brain injury such as ischemic stroke, cerebral hemorrhage, or cerebral trauma, is associated with increased morbidity and mortality and a significant relation has been reported between hyperglycemia and longer intensive care unit (ICU) stay, increased infections rate, and worse neurologic outcome. Animal study shows that during cerebral ischemia BGC higher than 170 mg/dL contributes to extend neuronal injury [20–24].

Stress-induced hyperglycemia and insulin resistance are common among critically ill patients with or without a history of diabetes mellitus. Stress associated with critical illness is characterized by activation of neuroendocrine response that antagonizes the action of insulin and causes hyperglycemia and ketoacidosis. Insulin levels are usually normal or decreased, despite peripheral insulin resistance. Stress-induced neuroendocrine response is a consequence of the activation of the hypothalamic–pituitary–adrenal (HPA) axis with the release of cortisol from the adrenal gland and of a marked increase in the release of norepinephrine and epinephrine as well as glucagon and growth hormone. In addition to causing insulin resistance, interleukin-6 (IL-6) and tumor necrosis factor-a (TNF- α) inhibit insulin release, an effect that appears to be concentration dependent. The low to normal insulin levels together with insulin resistance in the presence of increased secretion of the counter-regulatory hormones result in stress hyperglycemia. In the neurocritical care setting, another factor that exacerbates hyperglycemia is the use of glucorticoids [25–29].

Stress-induced hyperglycemia may cause endothelial cell dysfunction, defects in immune function, increased oxidative stress, prothrombotic changes, cardiovascular effect, and insular cortex injury or a direct hypothalamic damage of glucose regulatory centers. Hyperglycemia exacerbates brain injury through several mechanisms including activation of the hypothalamo–hypophyseal–adrenal (HHA) axis, inflammation, peripheral and hepatic insulin resistance, reduction in perfusion, production of lactic acid and free radicals, raised excitatory amino acids and intracellular calcium, mitochondrial abnormalities, and endothelial dysfunction. Glucose has been shown to induce an increase in superoxide generation by leukocytes, proinflammatory transcription factors, and extrinsic pathways of coagulation. This dysregulation disrupts the microcirculation, thus up-regulating the inflammatory and related thrombotic-fibrinolytic mechanisms in the brain. In experimental studies, the injection of intraperitoneal glucose to produce hyperglycemia during induced brain ischemia was associated with a 24% reduction in regional blood flow. Moreover, glucose-induced reactive oxygen species neutralize nitric oxide in the vessel wall and reduce cerebral perfusion. Hyperglycemia and subsequent lactic acidosis extend the neuronal injury and worsen the neurologic outcome. During an ischemic event, a local increase in anaerobic glycolysis leads to intracellular acidosis occurring shortly after the ischemic insult. The most acidic mean cortical pH and high cerebral lactate concentrations developed in animals with acute hyperglycemia thus increase neuronal and glial injury. Enhanced acidosis may exaggerate ischemic injury through various mechanisms, for example by increasing free radical formation, perturbing intracellular signal transduction, and activating endonucleases. Studies showing that lactic acid injected into the cerebral cortex causes histologic changes resembling ischemic infarction led some to propose that lactic acid accumulation has a direct effect on neuronal necrosis [30–33].

20.2.2 Hypoglycemia

Hypoglycemia is defined as a BGC of <50 mg/dL (<2.78 mmol/L) in adults and <30 mg/dL in neonates (1.67 mmol/L). Hypoglycemia is a

multifactorial event—often as a consequence of a strict glycemic control—that can occur under any circumstances, although diabetes patients are most susceptible. Hypoglycemia is related to an increased risk of death, even after a single episode of mild hypoglycemia, and to an increase in intensive care unit (ICU) length of stay [19, 34].

Hypoglycemia has three important effects on the brain: it induces a systemic stress response (increased sympathetic tone), increases cerebral blood flow (CBF), and alters cerebral metabolism.

- Systemic stress response induction. A systemic, counter-regulatory stress response during acute hypoglycemia leads to an increase in blood norepinephrine, epinephrine, glucagon, growth hormone, and cortisol concentrations. Neurologic symptoms with slow EEG waves, impaired cognitive functions, and seizures are related to counter-regulatory stress response. The mechanism underlying the appearance of these stress-related hypoglycemic symptoms is unclear but it may be related to neurotransmitter failure secondary to altered amino acids and acetylcholine synthesis [35, 36].
- Cerebral blood flow (CBF) increase. Hypoglycemia is associated with loss of cerebral autoregulation (reactivity of CBF to changes in cerebral perfusion pressure), cerebral vasoreactivity (reactivity of CBF to changes in $PaCO_2$), and b-adrenoceptor stimulation. During severe hypoglycemia, CBF may increase by 300%. The negative effects of hypoglycemia on CBF are potentiated when hypocapnia coexists [37, 38].
- Disturbance in cerebral metabolism. The lack of glucose causes changes in neuronal protein synthesis, amino acid metabolism, neurotransmitter release, membrane function, and pH homeostasis. As hypoglycemia progresses, cerebral glucose, glycogen, and lactate concentrations decrease. Hypoglycemia-induced somnolence and hypoglycemic seizures and coma are accompanied by a decrease in cerebral glucose uptake [39].

Preventing hypoglycemia and its related neuronal damage is especially important in patients receiving neurocritical care. Evidence suggests that even moderate hypoglycemia (<70 mg/dL) induces derangements in brain metabolism and cerebrovascular autoregulation. Furthermore, in patients with acute brain injury, BGC below 80 mg/dL is associated with microdialysis markers of brain metabolic distress (increased glutamate and lactate/pyruvate ratio) that may be potentially detrimental [40].

20.3 BGC Monitoring

Glucose measurements in critical ill patients are based on intermittent central laboratory analysis (CLA) and blood gas analyzer, but obtaining them requires extreme precautions to avoid contamination with parenteral solutions, and some blood gas analyzers that allow obtaining fast and reliable glucose values are not always available in the ICU or operating room. Point of care (POC) devices, although potentially attractive because of easy handling and rapid results, are not suitable in ICU patients due to inaccuracy (differences in results exceeding 20% of a reference value) related to several clinical and laboratory variables—including inadequate cardiac output, arterial hypotension, hypoxia, hematocrit values, pH, associated therapies—that may lead to excessive insulin administration with resultant hypoglycemia which is a major concern in the ICU or operating room. However, intermittent measurements are limited by the workload associated with the sampling process and the potential that between-measurement events may be missed. In recent years, continuous glucose monitoring (CGM) and closed-loop glycemic control systems have been developed, at first for ambulatory patients with type I diabetes, in which minimally or non-invasive measurements can be obtained with tissue probes. With CGM, glucose is continuously monitored and it can further be combined with a closed-loop glycemic control system, in which computer-regulated algorithms incorporate the real-time glucose information to administer

insulin and glucose to meet predefined target blood glucose concentrations. These systems have several potential benefits, such as reduction of labor of nursing staff and a knowledge about trends in a patient's blood glucose concentration as well as a patient's insulin requirements. The use of CGM systems has yielded inconsistent results. Many trials report accurate glucose measurements compared with intermittent arterial blood glucose measurements, whereas other studies demonstrate that while CGM technology can be useful in the ICU, current CGM systems are not yet reliable enough to be used in critically ill patients [34, 41–48].

Techniques currently used for CGM are based on the following:

- Glucose-oxidase technique is based on the sensing of hydrogen peroxide (H_2O_2) released when glucose is converted to glucolactone: the greater the concentration of glucose, the more H_2O_2 will be released and the stronger the signal.
- Mid-infrared spectroscopy detects an absorption spectrum for glucose in plasma using different wavelength filters.
- Fluorescence techniques rely on quenched chemical fluorescence to measure glucose concentration.

CGM can be performed in whole blood, plasma, interstitial fluid, and microdialysis fluid and the degree of invasiveness of a CGM technique varies from highly invasive (for example, intravascular devices) through the minimally invasive subcutaneous techniques, to non-invasive transdermal devices. The type of monitor selected should be adjusted to patient characteristics, including the severity of illness of the patient and the type of access available. A critical and unstable ICU patient will have arterial and/or central venous lines allowing invasive intravascular monitoring, whereas a stable patient ready for ward transfer can be monitored using a less or non-invasive device [49].

20.4 Glycemia Management in Neuro-Patients

BGC management and control in critical care (CC) patients and neurocritical care (NCC) patients, in particular, has evolved dramatically over the past years and remains under active investigation and debate about the ideal target range and impact of dysglycemia (hyperglycemia, hypoglycemia, and variable glucose levels) on outcome in the heterogeneous ICU population. Traditionally, BGC management in critical care patients was mostly overlooked and "permissive" hyperglycemia was the standard of care. Afterwards, several reports have proposed the intensive insulin infusion therapy (IIT) targeted to tighten glycemia control (T-GC, i.e. target blood glucose concentration 80–110 mg/dL) for glycemia management in critical care patients. However, this approach increases episodes of hypoglycemia and is potentially associated to worsened long-term functional status [35, 50–54]. According to the NICE-SUGAR data results, there is no additional benefit from lowering BGC levels below a "moderate" target range (140–180 mg/dL); this range is associated with lower 90-days mortality compared to "tight" BGC (target range 80–110 mg/dL) and to a lower risk of episodes of severe hypoglycemia. In a more recent prospective nested cohort study in 523 medical/surgical ICU patients assigned to 1 out of 6 BGC target range group treatments (group1 BCG <108 mg/dL; group 2 BGC 108–114 mg/dL; group 3 BGC 115–128 mg/dL; group 4 BGC 129–145 mg/dL; groups 5 BGC 146–181 mg/dL; group 6 BGC >181 mg/dL), the 129–145 mg/dL target range was associated with the lowest mortality rate. The authors concluded that targeting BGC to <146 mg/dL ("advanced" BGC target range: 129–145 mg/dL) is associated with less risk of inadvertent hypoglycemia and represents an optimal BGC level in critically ill patients [55–59].

Blood glucose management in NCC patients, addressed to actively maintain BGC within defined thresholds, is based on two major therapeutic

interventions: to supply an adequate calorie load and, when necessary, to continuously infuse insulin titrated to patients' needs.

Initiating a strategy of blood glucose control with a nutritional protocol—with the preferential use of the enteral route—and adequate provision of calories and carbohydrates decreases the risk of severe hypoglycemia. This strategy of BGC control should be carefully coordinated with the level of nutritional support and metabolic status, which changes frequently in NCC patients. A recent study evaluated the nutrition protocol's influence on brain metabolism using microdialysis in patients with SAH. Two hours after 250 Kcal by nasojejunal tube feeding, there were simultaneous increments in glucose levels in the blood and cerebral extracellular space without a change of glutamate concentration or the L/P ratio. Stress hyperglycemia exacerbates the disorders in gastric motility as a result of several factors such as cytokines produced by inflammation, oxidative stress, vasoactive intestinal peptides, splanchnic hypoperfusion, and drugs such as phenytoin, steroids, and opioids. Acute gastroparesis differs from diabetic gastroparesis in that it is reversible and sensitive to prokinetics. Acute gastroparesis causes an interruption of appropriate feeding, which contributes in a wider variability in blood glucose levels, showing an increase in insult severity. However, solid clinical evidence and practical considerations are not provided for nutrition support regimens to minimize stress hyperglycemia and assist glucose management. Actual guidelines are based on small patient series and expert opinion only. Current recommendations for good glucose control and nutritional support are (1) prefer enteral route; (2) nutrition should be initiated in all patients who are not expected to be on a full oral diet within 3 days of stay; (3) early nutrition (<24 h) should be started in CC patients who are hemodynamically stable and have a functioning gastrointestinal tract; (4) in patients who cannot be fed sufficient enterally, the deficit should be supplemented parenterally while in those who are intolerant to enteral nutrition, parenteral nutrition may be proposed at a unique route; (5) avoid excessive caloric intake, especially carbohydrates—no more than 25–30 calories per kg body weight per day; (6) 25% of intake in the form of lipids; (7) insulin therapy according to needs [60–65].

High serum glucose variability and differences in complexity of the glycemic profile predict increased risk of death in ICU patients. Sudden changes in BGC should be minimized and therefore, insulin bolus injections—both intravenous and subcutaneous—and the infusion of solutions containing high glucose concentration—sometimes prescribed to correct iatrogenic induced hypoglycemia—should be avoided. The target BGC level is not the only variable that affects the relationship between insulin infusion, the risk of iatrogenic hypoglycemia, and ICU outcome. Among the most relevant variables that contribute to determine the effects of insulin infusion on BGC are duration of insulin infusion and the changes in insulin sensitivity over time. The duration of insulin infusion is a predictor of severe hypoglycemia (BGC <40 mg/dL), as demonstrated in a retrospective analysis in 1118 ICU surgical patients treated with tight BGC (target BGC 80–110 mg/dL). This study confirmed the increased odds for death among patients even after a single episode of hypoglycemia (26.9% vs 15.3%, $P = 0.03$) and showed how occurrence of severe hypoglycemia does not reflect illness severity or demographic features but is related to the time of insulin infusion. The relationship of length of insulin infusion can possibly be explained by the induced changes in insulin sensitivity [34, 66–68].

Clinical application of IIT is usually accomplished with regular human insulin (Hlin) continuous infusion. Shorter acting insulin formulations, such as lispro insulin (Hlog) have faster onset and offset kinetics than Hlin and are thus more suitable for IIT in critical care patients. The molecular structure of Hlog is characterized by a change in the amino acid sequence of the insulin B chain—with proline in position 28 and lysine in position 29 inverted Lys(B28),Pro(B29).

This pharmacokinetic profile leads to a faster rise in plasma concentration, a higher peak concentration, and a shorter duration of action than Hlin. The use of Hlog in patients receiving IIT is associated with a faster BGC reduction when infusion is started while after insulin discontinuation, the extent and duration of carryover effect were more limited and the rate of BGC increase was more rapid. In the NCC setting, shorter acting insulin analogs such as Hlog have a safer profile when used as continuous infusion for glycemic control as decreased risk of hypoglycemia in the carryover phase and the risk of high glucose variability [69, 70].

20.5 BGC Management and Specific Neurocritical Conditions

20.5.1 Intracerebral Hemorrhage

Current guidelines from the American Heart Association recommend BGC strict monitoring to avoid hypoglycemia episodes and high BGC variation.

20.5.2 Subarachnoid Hemorrhage

Recently published guidelines from the American Heart Association emphasize the importance of avoiding hyperglycemia in patients with aneurysmal SAH, but without providing specific recommendations on target glucose levels.

20.5.3 Traumatic Brain Injury

Guidelines from the Brain Trauma Foundation and the European Brain Injury Consortium [84] highlight the association of hyperglycemia with worse prognosis after severe brain trauma, but these documents do not specify which glucose level should be considered as a trigger for initiating insulin therapy.

20.5.4 Acute Spinal Cord Injury

The consortium for Spinal Cord Medicine recommend maintaining serum glucose values between 80 and 110 mg/dL (4.4–6.2 mmol/L), albeit acknowledging a low level of evidence to support such recommendation [71–73].

Conclusion

In conclusion, BGC management is a demanding task that includes specific and unique aspects when accomplished in patients with acute brain damage. Among the relevant aspects, some deserve extra attention: in patients with acute subarachnoid hemorrhage, a BGC <110 mg/dL is associated with brain metabolic derangement, in patients with traumatic brain injury, stress hyperglycemia is frequent, it complicates up to 20–30% of the cases and is associated with higher incidence of in-hospital morbidity and mortality and worse neurological follow-up. The use of short-acting insulin induces shorter carry over effects and is possibly associated with lower risk of induced hypoglycemia. Nutritional supply to be established the sooner after acute brain damage is a prerequisite for continuous insulin infusion.

References

1. Jolivet R, Magistretti PJ, Weber B. Deciphering neuron-glia compartmentalization in cortical energy metabolism. Front Neuroendocrinol. 2009;1:4.
2. Kety SS. The general metabolism of the brain in vivo. In: Richter D, editor. Metabolism of the nervous system. Pergamon: London; 1957. p. 221–37.
3. Magistretti PJ. Brain energy metabolism. In: Squire LR, Bloom FE, Spitzer NC, editors. Fundamental neuroscience. 3rd ed. Academic Press: San Diego; 2008. p. 271–96.
4. Magistretti PJ, Pellerin L, Rothman DL, Shulman RG. Energy on demand. Science. 1999;283:496–7.
5. Siesjo BK. Brain energy metalolism. New York: John Wiley & Sons; 1978.
6. Magistretti PJ, Allaman I. A cellular perspective on brain energy metabolism and functional imaging. Neuron. 2015;86:883–901.
7. Raizada MK, Shemer J, Judkins JH, Clarke DW, Masters BA, LeRoith D. Insulin receptors in the brain:

structural and physiological characterization. Neurochem Res. 1988;13:297–303.
8. Schulingkamp RJ, Pagano TC, Hung D, Raffa RB. Insulin receptors and insulin action in the brain: review and clinical implications. Neurosci Biobehav Rev. 2000;24(8):855–72.
9. Benedict C, Frey II WH, Schio¨th HB, Schultes B, Born J, Hallschmid M. Intranasal insulin as a therapeutic option in the treatment of cognitive impairments. Exp Gerontol. 2011;46:112–5.
10. Potau N, Escofet MA, Martinez MC. Ontogenesis of insulin receptors in human cerebral cortex. J Endocrinol Investig. 1991;14:53–8.
11. King GL, Johnson SM. Receptor-mediated transport of insulin across endothelial cells. Science. 1985;227:1583–6.
12. Schwartz MW, Sipols AJ, Kahn SE, et al. Kinetics and specificity of insulin uptake from plasma into cerebrospinal fluid. Am J Phys. 1990;259:E378–83.
13. Pardridge WM, Kang YS, Buciak JL, Yang J. Human insulin receptor monoclonal antibody undergoes high affinity binding to human brain capillaries in vitro and rapid transcytosis through the blood–brain barrier in vivo in the primate. Pharm Res. 1995;12:807–16.
14. Xaio H, Banks WA, Niehoff ML, Morley JE. Effect of LPS on the permeability of the blood–brain barrier to insulin. Brain Res. 2001;896:36–42.
15. Baura GD, Foster DM, Kaiyala K, Porte Jr D, Kahn SE, Schwartz MW. Insulin transport from plasma into the central nervous system is inhibited by dexamethasone in dogs. Diabetes. 1996;45:86–90.
16. Yang JW, Fellows RE. Characterization of insulin stimulation of the incorporation of radioactive precursors into macromolecules in cultured rat brain cells. Endocrinology. 1980;107:1717–24.
17. Wozniak M, Rydzewski B, Baker SP, Raizada MK. The cellular and physiological actions of insulin in the central nervous system. Neurochem Int. 1993;22:1–10.
18. Heidenreich KA. Insulin and IGF-I receptor signaling in cultured neurons. Ann N Y Acad Sci. 1993;692:72–88.
19. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, Inzucchi SE, Ismail-Beigi F, Kirkman MS, Umpierrez GE; American Association of Clinical Endocrinologists, American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care. 2009;32: 1119–1131.
20. Bilotta F, Spinelli A, Giovannini F, Doronzio A, Delfini R, Rosa G. The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: a randomized prospective pilot trial. J Neurosurg Anesthesiol. 2007;19:156–60.
21. Rovilas A, Kotsou S. The influence of hyperglycemia on neurological outcome in patients with severe head injury. Neurosurgery. 2000;46:335–42.
22. Jeremitsky E, Omert LA, Dunham CM, Wilberger J, Rodriguez A. The impact of hyperglycemia on patients with severe brain injury. J Trauma. 2005;58:47–50.
23. Godoy DA, Pin˜ ero GR, Svampa S, Papa F, Di Napoli M. Hyperglycemia and short term outcome in patients with spontaneous intracerebral hemorrhage. Neurocrit Care. 2008;9: 217–229.
24. Li PA, He QP, Csiszar K, Siesjö BK, et al. Does long term glucose infusion reduce brain damage after transient cerebral ischemia? Brain Res. 2001;912:203–5.
25. Godoy DA, Di Napoli M, Biestro A, Lenhardt R. Perioperative glucose control in neurosurgical patients. Anesthesiol Res Pract. 2012;2012:690362.
26. McCowen KC, Malhotra A, Bistrian BR. Stress induced hyperglycemia. Crit Care Clin. 2001;17:107–24.
27. Nylen ES, Muller B. Endocrine changes in critical illness. J Intensive Care Med. 2004;19:67–82.
28. Marik PE, Raghavan M. Stress-hyperglycemia, insulin and immunomodulation in sepsis. Intensive Care Med. 2004;30:748–56.
29. Sapolsky RM, Pulsinelli WA. Glucocorticoids potentiate ischemic injury to neurons: therapeutic implications. Science. 1985;229:1397–400.
30. Allport LE, Butcher KS, Baird TA, MacGregor L, Desmond PM, Tress BM, Colman P, Davis SM. Insular cortical ischemia is independently associated with acute stress hyperglycemia. Stroke. 2004;35:1886–91.
31. Duckrow RB, Beard DC, Brennan RW. Regional cerebral blood flow decreases during hyperglycemia. Ann Neurol. 1985;17:267–72.
32. Xiang Z, Yuan M, Hassen GW, Gampel M, Bergold PJ. Lactate induced excitotoxicity in hippocampal slice cultures. Exp Neurol. 2004;186:70–7.
33. Kraig RP, Petito CK, Plum F, Pulsinelli WA. Hydrogen ions kill brain at concentrations reached in ischemia. J Cereb Blood Flow Metab. 1987;7:379–86.
34. Bilotta F, Rosa G. Glycemia management in critical care patients. World J Diabetes. 2012;3:130–4.
35. Sieber FE, Traystman RJ. Special issues: glucose and the brain. Crit Care Med. 1992;20:104–14.
36. Goldfien A, Zieli MS, Despointes RH, et al. The effects of hypoglycemia on the adrenal secretion of epinephrine and norepinephrine in the dog. Endocrinology. 1958;62:749–57.
37. De Feo P, Perriello G, De Cosmo S, et al. Comparison of glucose counter-regulation during short-term and prolonged hypoglycemia in normal humans. Diabetes. 1986;35:563–9.
38. Siesjo˜ BK, Ingvar M, Pelligrino D. Regional differences in vascular autoregulation in the rat brain in severe insulin-induced hypoglycemia. J Cereb Blood Flow Metab 1983;3: 478–85.
39. Tews JK, Carter SH, Stone WE. Chemical changes in the brain during insulin hypoglycemia and recovery. J Neurochem. 1965;12:679–93.

40. Vespa PM, McArthur D, O'Phelan K, et al. Persistently low extracellular glucose correlates with poor outcome 6 months after human traumatic brain injury despite a lack of increased lactate: a microdialysis study. J Cereb Blood Flow Metab. 2003;23:865–77.
41. Finfer S, Wernerman J, Preiser JC, Cass T, Desaive T, Hovorka R, Joseph JI, Kosiborod M, Krinsley JS, MacKenzie I, Mesotten D, Schulz M, Scott MG, Slingerland R, van den Berghe G, Van Herpe T. Consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults. Crit Care. 2013;17:229.
42. Miller M, Skladany MJ, Ludwig CR, Guthermann JS. Convergence of continuous glucose monitoring and in-hospital tight glycemic control: closing the gap between caregivers and industry. J Diabetes Sci Technol. 2007;1:903–6.
43. Widom B, Simonson DC. Glycemic control and neuropsycologic function during hypoglycemia in patients with insulin-dependent diabetes mellitus. Ann Intern Med. 1990;112:904–12.
44. Okabayashi T, Nishimori I, Maeda H, et al. Effect of intensive insulin therapy using a closed-loop glycemic control system in hepatic resection patients: a prospective randomized clinical trial. Diabetes Care. 2009;32:425–7.
45. Goldberg PA, Siegel MD, Russell RR, et al. Experience with the continuous glucose monitoring system in a medical intensive care unit. Diabetes Technol Ther. 2004;6:339–47.
46. Bridges BC, Preissig CM, Maher KO, Rigby MR. Continuous glucose monitors prove highly accurate in critically ill children. Crit Care. 2010;14:R176.
47. Jacobs B, Phan K, Bertheau L, et al. Continuous glucose monitoring system in a rural intensive care unit: a pilot study evaluating accuracy and acceptance. J Diabetes Sci Technol. 2010;4:636–44.
48. Logtenberg SJ, Kleefstra N, Snellen FT, et al. Pre- and postoperative accuracy and safety of a real-time continuous glucose monitoring system in cardiac surgical patients: a randomized pilot study. Diabetes Technol Ther. 2009;11:31–7.
49. Wernerman J, Desaive T, Finfer S, et al. Continuous glucose control in the ICU: report of a 2013 round table meeting. Crit Care. 2014;18:226.
50. Walia S, Sutcliffe AJ. The relationship between blood glucose, mean arterial pressure and outcome after severe head injury: an observational study. Injury. 2002;33:339–44.
51. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critical ill patients. N Engl J Med. 2001;345:1359–67.
52. Bilotta F, Caramia R, Cernak I, Paoloni PP, Doronzio A, Cuzzone V, Santoro A, Rosa G. Intensive insulin therapy after severe traumatic brain injury: a randomized clinical trial. Neurocrit Care. 2008;9:159–66.
53. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy .in the medical ICU. N Engl J Med. 2006;354:449–61.
54. Mechanick JI, Handelsman Y, Bloomgarden ZT. Hypoglycemia in the intensive care unit. Curr Opin Clin Nutr Metab Care. 2007;10:193–6.
55. Study Investigators NICE-SUGAR, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
56. Rodbard HW, Blonde L, Braithwaite SS, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract. 2007;13:1–68.
57. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hell-man R, Hirsch IB, Inzucchi SE, Ismail-Beigi F, Kirkman MS, Umpierrez GE, American Association of Clinical Endocrinol-ogists, American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Endocr Pract. 2009;15:353–69.
58. Qaseem A, Humphrey LL, Chou R, Snow V, Shekelle P. Clinical Guidelines Committee of the American College of Physicians. Use of intensive insulin therapy for the manage- ment of glycemic control in hospitalized patients: A clinical practice guideline from the American College of Physicians. Ann Intern Med. 2011;154:260–7.
59. Al-Tarifi A, Abou-Shala N, Tamim HM, Rishu AH, Arabi YM. What is the optimal blood glucose target in critically ill patients? A nested cohort study. Ann Thorac Med. 2011;6:207–11.
60. Marik PE, Preiser JC. Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis. Chest. 2010;137:544–51.
61. Dhinsa BS, Khan WS, Puri A. Management of the patient with diabetes in the perioperative period. J Perioper Pract. 2010;10:364–7.
62. Girard M, Schricker T. Perioperative glucose control: living in uncertain times-continuing professional development. Can J Anesth. 2011;58:312–29.
63. Kinoshita T, Moriya A. Utagawa, et al. Change in brain glucose after enteral nutrition in subarachnoid hemorrhage. J Surg Res. 2010;162:221–4.
64. Krenitsky J. Glucose control in the intensive care unit: a nutrition support perspective. Nutr Clin Pract. 2011;26:31–43.
65. Kreymanna KG, Bergerb MM, Deutzc NEP, et al. ESPEN Guidelines on Enteral Nutrition: Intensive care. Clin Nutr. 2006;25:210–23.
66. Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, Devries JH. Glucose variability is associated with intensive care unit mortality. Crit Care Med. 2010;38:838–42.
67. Lundelin K, Vigil L, Bua S, Gomez-Mestre I, Honrubia T, Varela M. Differences in complexity of

glycemic profile in survivors and nonsurvivors in an intensive care unit: a pilot study. Crit Care Med. 2010;38:849–54.
68. Mowery NT, Gunter OL, Kauffmann RM, Diaz JJ, Collier BC, May AK. Duration of time on intensive insulin therapy predicts severe hypoglycemia in the surgically critically ill population. World J Surg. 2012;36:270–7.
69. Bilotta F, Badenes R, Lolli S, Belda FJ, Einav S, Rosa G. Insulin infusion therapy in critical care patients: regular insulin vs short-acting insulin. A prospective, crossover, randomized, multicenter blind study. J Crit Care. 2015;30:437.
70. Bilotta F, Guerra C, Badenes R, Lolli S, Rosa G. Short acting insulin analogues in intensive care unit patients. World J Diabetes. 2014;5:230–4.
71. Hemphill 3rd JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, Fung GL, Goldstein JN, Macdonald RL, Mitchell PH, Scott PA, Selim MH, Woo D, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/ American Stroke Association. Stroke. 2015;46:2032–60.
72. Bederson JB, ConnollyJr ES, Batjeretal HH, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the stroke council, American heart association. Stroke. 2009;40:994–1025.
73. Guidelines for the management of severe traumatic brain injury. J Neurotrauma. 2007; 24(Suppl 1): S1–106.

Anaesthesia for Deep Brain Stimulation

21

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21.1 Introduction

In the 1980s, the first commercially developed deep brain stimulation (DBS) system became available. This coincided with the awareness that permanent destructive brain lesions performed intentionally was less favourable compared to a system that was reversible and adjustable. In a short matter of time, it was found that pallidal activity could be suppressed with DBS, hence, relieving dystonic symptoms of Parkinson's disease [1].

Currently, DBS is increasingly being used not only in the treatment of chronic movement disorders but also in psychiatric disorders and chronic pain. As the brain targets are deep and small, stereotactic frames are used to increase accuracy of electrode placement. Improvement of symptoms is assessed intra-operatively via electrophysiological guidance using mircroelectrode recordings (MER) and macrostimulation testing. This further enhances results while reducing the occurrences of side effects.

Brain targets vary depending on the intended aim of treatment. Movement disorder targets are the subthalamic nucleus (STN), globus pallidus internal (GPi) and ventralis intermedius nucleus of the thalamus. Target sites are chosen to attain the best therapeutic effect.

Currently, approved conditions and respective locations, treatable by deep brain stimulation by the Food and Drug Administration, are as follows:

Condition	Location
Parkinson's disease	Subthalamic nucleus, globus pallidus internus
Essential tremor	Ventral intermediate thalamus
Dystonia	Anterior limb of internal capsule
Obsessive compulsive disease	Anterior nucleus of thalamus
Epilepsy	Ventrocaudal thalamus, periventricular grey

On the other hand, DBS has been investigated for the treatment of depression, Tourette syndrome, headaches, obesity, Alzheimer's disease and minimally conscious states [2]. The target sites vary from the subcallosal cingulate gyrus to the hypothalamus.

Thus, the choice of anaesthetic technique must have the least interference during the procedure while ensuring patient safety and comfort.

21.2 Technique

The entire process is very time consuming but definitely fulfilling not only for the patient but also for the health care personnel. Implantation

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may be performed in either a single or two-staged operation. The two-staged operation arose from fears of infection.

The process begins with the application of a stereotactic frame, which is usually placed under a local anaesthetic technique. Both scalp blocks and local infiltration at potential pin sites areas have been performed and reported. Local anaesthetics that have been used are bupivacaine (0.5%), levobupivacaine (0.5%) and ropivacaine (0.75%), supplemented with adrenaline to reduce toxicity and prolong drug action [3]. This is followed by a magnetic resonance imaging (MRI) or computed tomography to obtain target coordinates based on anatomical imaging using computer software.

The patient returns to the operating theatre where the frame is attached and a geometric arch is placed. Further local anaesthetic is given prior to making a planned incision and drilling of a burr hole is performed. The dura is incised and intraoperative electrodes are inserted to a location 10–25 mm above the targeted site. Microelectrode and macrostimulation during the procedure allows accurate localization. A neurologist is present to assess the improvement of symptoms with different levels of stimulation through an external pacing device. Attention is also paid to occurrence of side effects such as speech impairment, eye deviation, weakness and tonic movements. Optimal target implantation is based on the variation in spontaneous background firing, spike discharges and movement-related changes in firing rate [2].

Recently, studies combining interventional MRI (iMRI) with special aiming systems and software have alluded to the future of DBS surgery. Hence, allowing the procedure to be performed under general anaesthesia as no macrostimulation is needed and the absence of a bulky stereotactic frame.

21.3 Pre-operative Assessment

A good post-operative outcome is always determined by prudent patient selection. As this process involves many aspects of patient care and well-being, a multidisciplinary team approach would be appropriate for such a complex task. Suitability for surgery is dependent on the patient's general physical condition with attention to cardiopulmonary comorbidities, psychiatric history and cognitive function [4]. Contraindication to DBS includes an increased bleeding risk with brain penetration, patients who may need to be exposed to MRI, patients who require the use of shortwave, microwave or therapeutic ultrasound diathermy.

An "awake" technique not only requires a cooperative patient but also the ability to remain fairly still. Perioperative neurological status should be documented in view of the possibility of deterioration post-operatively. Medication regimes should also be scrutinized and the patient made aware of medications to be taken on the day of surgery.

21.4 Anaesthetics

The anaesthetic aim for deep brain electrode insertion is to:

1. Provide optimal surgical conditions without sacrificing patient comfort and safety
2. Facilitate intraoperative monitoring which includes neuromonitoring for target localization
3. Ensuring patient safety by detecting and treating life-threatening complications

Anxiolytic premedication such as benzodiazepines should be used cautiously as they can result in not only over-sedation but also paradoxical agitation [5] and dyskinesia [6]. Anti-emetics such as metoclopramide should also be avoided in Parkinson's/dystonia as they can exacerbate symptoms [5]. Suitable first-line anti-emetics would be ondansetron and dexamethasone [7]. However, one should be aware that ondansetron can also cause extrapyramidal side effect. Further reading on the advantages and disadvantages of drugs used in deep brain stimulaton can be found a review article by Ryan Gant and collegues [8].

Provision of sedation is usually welcomed by both the surgeon and the patient. Conscious sedation where the patient is able to carry out verbal commands and communicate during macrostimulation is the preferred type of sedation. There is however a small group of surgeons who request

for no sedation at all. Deep sedation increases the risk of respiratory compromise, which, when compounded by the presence of the frame, severely jeopardizes patient safety. General anaesthesia, for the entire procedure, has also been reported by some centres with comparably good outcomes.

The two major conscious sedation techniques are the asleep–awake–asleep (AAA) and monitored anaesthetic care (MAC) with sedation [5]. The paediatric population commonly use the AAA technique not only because of obvious age-related challenges but also due to poorly controlled dystonia making awake positioning difficult [9]. There are however certain centres that perform the entire procedure for adults under general anaesthesia with favourable end results [5].

Many studies have been done with regard to the best technique in order to achieve optimal surgical conditions with sedative agents without impacting the alertness or respiratory effort of the patient. The anaesthetic technique ranges from conscious sedation with drugs such as propofol and/or dexmedetomidine, small amounts of remifentanil, to general anaesthesia (achieved with either inhalational agents or intravenous agents) [2].

Propofol requires special mention due to its peculiar pharmacokinetic behaviour in patients with Parkinson's disease, thus resulting in a different steady state of plasma for optimal sedation without airway compromise [10]. Another unusual side effect is its tendency to cause sneezing in certain occasions.

Blood pressure control is essential during DBS surgery. This is complicated by the fact that many of the diseases requiring DBS surgery have autonomic dysfunction, which can potentially result in a fluctuating blood pressure. Acid aspiration prophylaxis should also be considered in view of possibility of nausea and vomiting [11].

21.5 Side Effects

Stimulation itself has its own side effects such as induction of paraesthesia, involuntary movements or cognitive and mood changes. Fortunately, precise electrode placement and adjustment of stimulation parameters can abolish them.

Based on studies by Khatib, Venkatraghavan and colleagues, the overall complication rate ranges from 11.6 to 16% [12, 13]. Neurological complications rate the highest with a reported 3.6% [12]. A seizure rate of 4.5% was reported by Venkatraghavan and colleagues. The next commonest neurological complication was decreased consciousness and confusion in 2.8% [12]. Haemorrhage was reported between 0.3 and 0.6% [13, 14].

Respiratory complications rate ranged from 1.1 to 1.6% [12, 13]. The complications ranged from the need for mechanical ventilation to airway obstruction [12, 13]. The commonest cardiovascular complication was hypertension and its incidence ranged from 0.4 to 3.9% [12–14]. Finally, other forms of complications, for example, blood loss, coughing/sneezing, ranged from 0.6 to 1.2% [12–14].

21.6 Neurological

The major surgery-related risk is intracranial haemorrhage with a reported incidence as high as 5%; of which in 2.1% result in permanent neurological deficit and in 1.1% in death [15]. Seizures generally occur within 48 h of surgery with an estimated incidence of 2.4% [16, 17]. An eightfold increase in incidence of seizures occurs in patients with multiple sclerosis, hence suggesting the need for the use of anticonvulsants in this group of patients [18]. Venous air embolism though rare has also been reported. Chronic changes such as mania, depression, apathy, panic, impulsivity, anxiety, hallucinations and even suicidal ideation are multifactorial in origin, hence management should be approached in a multidisciplinary approach.

21.7 Respiratory

Its incidence has been shown to occur between 1.6 and 2.2% patients [19]. Respiratory depression can result from either over-sedation or neurological insult as a result of the procedure. This problem is complicated by the presence of the stereotactic frame, which can impede respiratory resuscitation intervention. Parkinson's disease can also affect the respiratory system.

21.8 Anaesthetic Considerations for Patients with DBS Implant

As DBS becomes a more common form of treatment for patients with not only Parkinson's disease and other movement disorder, the anaesthetist will inevitably be faced with such patients needing to undergo some surgical procedure requiring anaesthesia.

Poon and Irwin give a concise table on potential devices that can cause interference with DBS implants [19]. The use of short-wave diathermy can cause brain damage as the electrodes get heated; hence, its use is absolutely contraindicated. Phacoemulsification, peripheral nerve stimulation and electroconvulsive therapy (with the ECT electrodes placed away from the DBS hardware) appear to report no interference. Similar electrical devices such as pacemakers, electrocautery, external defibrillators and internal cardioverter defibrillator (ICD) can be used with special caution as dangerous interactions can occur. MRI safety guidelines are also available for patients with DBS implants.

Conclusion

The anaesthetist plays a very important role during DBS electrode insertion. A sound knowledge of pharmacological agents to be used to ensure optimal condition for electrode insertion and patient comfort is needed. Patient safety is enhanced by an awareness of potential complications of the procedure. Finally, as this mode of treatment becomes more accessible, the knowledge of potential interaction is useful when faced with patients who come into theatre for other procedures.

References

1. Patrick Dobbs, James Hoyle, Rowe J. Anaesthesia and deep brain stimulation. Continuing education Continuing Education in Anaesthesia. Critical Care Pain. 2009;9(5):157–61.
2. Venkatraghavan L, Manninen P. Anaesthesia for deep brain stimulation. Curr Opin Anesthesiol. 2011;24: 495–9.
3. Kerscher C, Zimmermann M, Graf BM, Hansen E. Scalp blocks. A useful technique for neurosurgery, dermatology, plastic surgery and pain therapy. Anaesthesist. 2009;58:949–58.
4. Tarsy D, Vitek JL, Lozano AM. Surgical treatment of Parkinson's Disease and other movement disorders. Totowa: Humana; 2003.
5. Erickson KM, Cole DJ. Anesthetic considerations for awake craniotomy for epilepsy and functional neurosurgery. Anesthesiol Clin. 2012;30:241–68.
6. Venkatraghavan L, Luciano M, Manninen P. Anesthetic management of patients undergoing deep brain stimulation insertion. Anesth Analg. 2010;110: 1138–45.
7. Chen MS, Hong CL, Chung HS, et al. Dexamethasone effectively reduces postoperative nausea and vomiting in a general surgical adult patient population. Chang Gung Med J. 2006;29:175–81.
8. Grant R, Gruenbaum SE, Gerrard J. Anaesthesia for deep brain stimulation : a review. Curr Opin Anaesthesiol. 2015;28:505–10.
9. Hippard HK, Watcha M, Stocco AJ, Curry D. Preservationofmicroelectrode recordings with nongabaergic drugs during deep brain stimulator placement in children. J Neurosurg Pediatr. 2014;14:279–86.
10. Fabregas N, Rapado J, Gambus PL, et al. Modeling of the sedative and airway obstruction effects of propofol in patients with Parkinson's disease undergoing stereotactic surgery. Anesthesiology. 2002;97:1378–86.
11. Shaikh SI, Verma H. Parkinson's disease and anaesthesia. Indian J Anaesth. 2011;55:228–34.
12. Khatib R, Ebrahim Z, Rezai A, et al. Perioperative events during deep brain stimulation: the experience at Cleveland clinic. J Neurosurg Anesthesiol. 2008;20:36–40.
13. Venkatraghavan L, Manninen P, Mak P, Lukitto K, Hodaie M, Lozano A. Anesthesia for functional neurosurgery: review of complications. J Neurosurg Anesthesiol. 2006;8:64–7.
14. Kenney C, Simpson R, Hunter C, et al. Short-term and long-term safety of deep brain stimulation in the treatment of movement disorders. J Neurosurg. 2007;106:621–5.
15. Zrinzo L, Foltynie T, Limousin P, Hariz MI. Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. J Neurosurg. 2012;116:84–94.
16. Pouratian N, Reames DL, Frysinger R, Elias WJ. Comprehensive analysis of risk factors for seizures after deep brain stimulation surgery. Clinical article. J Neurosurg. 2011;115:310–5.
17. Coley E, Farhadi R, Lewis S, Whittle IR. The incidence of seizures following deep brain stimulating electrode implantation for movement disorders, pain and psychiatric conditions. Br J Neurosurg. 2009;23:179–83.
18. Johnson RD, Qadri SR, Joint C, et al. Perioperative seizures following deep brain stimulation in patients with multiple sclerosis. Br J Neurosurg. 2010;24: 289–90.
19. Poon CCM, Irwin MG. Anaesthesia for deep brain stimulation and in patients with implanted neurostimulation devices. Br J Anaesthesia. 2009;2:152–65.

Intraoperative Magnetic Resonance Imaging

22

Pui-San Loh and Ramani Vijayan

22.1 Introduction

The advent of intraoperative magnetic resonance imaging (iMRI) since the 1990s has revolutionized modern neurosurgery to what it is today [1]. By combining the non-invasive imaging capability of MRI with an operative space, surgeons can now locate and excise lesions precisely, gaining instant quality control over every step in their workflow [2].

Neuronavigation no longer needs to depend on archived images but appropriately timed scans uploaded for real-time guidance. This improves precision in the surgical field that is affected by intraoperative brain shift and distortion from multiple factors such as position changes, anaesthetic effects, cerebral spinal fluid (CSF) loss, tissue type, resected mass and of course, surgical duration [3]. Patients benefit from not only improved overall gross tumour resection rates but also preserved vital neurovascular structures and eloquent areas; an advantage most prominently seen in glioma craniotomy and pituitary tumour resection. With this technology, more than a third of gliomas and a fifth of pituitary adenomas were reportedly requiring further resection. Furthermore, biopsies and implantations can be performed with minimal surgical damage [4]. In the younger age group, the need for additional resection in the immediate post-operative period of 2 weeks is also reduced [5].

However, intraoperative imaging comes with its own set of challenges with regard to both costs and logistics. This chapter focuses on the challenges faced with providing anaesthesia for iMRI in neurosurgery.

22.2 Types of iMRI

The set-up of iMRI has followed two general concepts: operating within the magnet with continuously refreshed images and a dual-room suite offering both surgical and diagnostic facilities. Either magnet or patient can be stationary in the dual-room concept.

22.2.1 Open

The original 'open' system started with a stationary magnet (0.5 T) and a stationary patient [6]. The main advantage is its ability to obtain frequent 'real-time' images but despite this, there are several setbacks. First of all, working space is limited for both surgeons and anaesthetists. Second, all equipment including surgical instruments must be MRI safe. These tools are not only costly but their quality is also often inferior to

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conventional instruments [7]. Newer systems then progressively looked into improving the resolution with a stronger magnetic field compared to the prototype.

22.2.2 Dual-Room

Later development has seen the growth in the concept of having two independent rooms, one with a MRI machine of 1.5–3.0 T, separated by an air lock chamber that could be linked when iMRI is needed in the adjacent operating suite. The initial cost for such a system can be prohibitive but may have a better cost: benefit ratio eventually because ongoing diagnostic scans can be carried out until imaging is needed for the surgical case. In this way, either magnet or patient can be placed stationary with the other moving towards it.

The additional advantages of utilizing a dual-room iMRI will be a less impaired surgical access and allowance for normal surgical instruments such as regular microscopes, drills, retractors and conventional navigation reference frame [7]. However, intraoperative imaging for craniotomy lengthens the procedure as image acquisition can only occur after the patient has been placed within the magnet [8]. With an open cranium, it is imperative to maintain sterility throughout the process of transfer and allowance made for head positioning within the isocentre of the scanner.

Apart from common advantages in the dual-room system, when the magnet is mobile, meticulous care is taken to ensure all ferromagnetic items such as the operating microscope, high-speed drill and bipolar cautery are secured beyond the 5 Gauss (5-G) line. All electric circuits entering the radiofrequency cabin will be filtered with the data and video lines transferred to the control room via a fibre-optic cable [9].

The major setback of having the patient mobile instead of the magnet lies in the need to transfer an anaesthetized patient in a process involving docking onto a MRI compatible trolley and ensuring adequate monitoring plus ventilator support throughout the scanning process in the MRI suite [7]. As an added advantage, such a system provides an opportunity to include several different modalities such as positron emission tomography and biplanar fluoroscopy.

22.3 Providing Anaesthesia for iMRI

The anaesthesia provided for a surgery with iMRI planned is different compared to those with no such requirements. The planning starts much earlier for the neurosurgical case and additional steps have to be taken to ensure MRI safety and efficient workflow which will not interrupt the duration of the surgery nor compromise patient safety. As a comparison, the flow chart below in Fig. 22.1 demonstrates the workflow of providing anaesthesia for a normal neurosurgical case and another with iMRI planned in a dual-room system where either the magnet or patient is mobile.

The practice of iMRI should follow recommended inernational guidelines in anaesthetic care for MRI. In the most recent Practice Advisory on Anaesthetic Care for MRI by the American Society of Anaesthesiologists Special Task Force, several items have been highlighted

Fig. 22.1 The iMRI dual-room suite with the docking trolley in front and an MRI-compatible ventilator by the side of the stationary magnet (Picture courtesy of *C*entre of *I*mage *G*uided and *M*inimally *I*nvasive *T*herapy – *CIGMIT*, University Malaya Medical Centre)

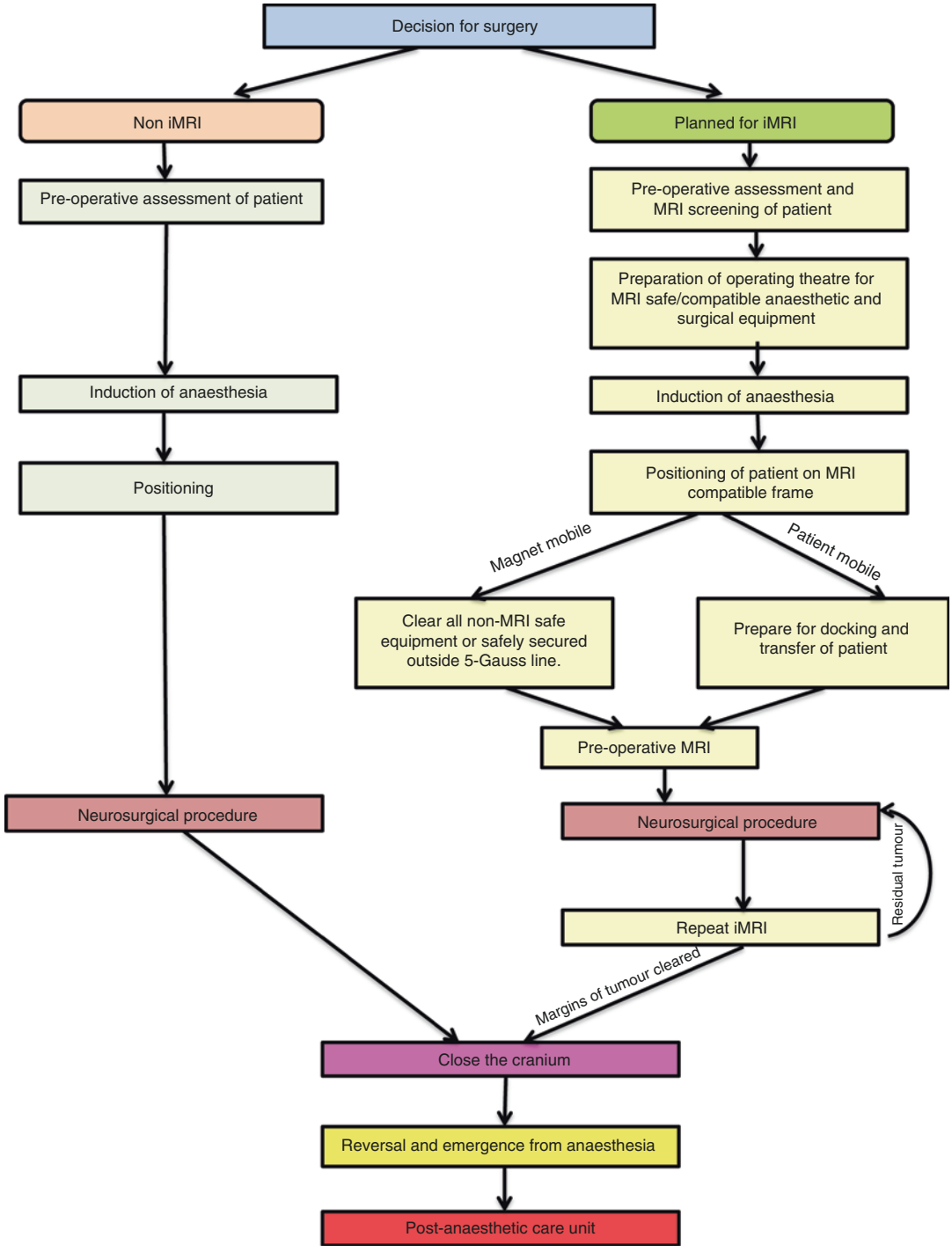

Fig. 22.2 Workflow to compare a non-iMRI case on the left and iMRI on the right

which can be adopted in iMRI [10]. The Practice Advisory differs from documents published previously by focusing specifically on anaesthetic care of patients in the MRI environment compared to broader safety issues by other organizations' guidelines (Figs. 22.2 and 22.3).

1. Education
2. Screening of anaesthetic care providers and ancillary support personnel
3. Patient screening
4. Preparation –
   - Plan for providing optimal anaesthetic care
5. Management during MRI –
   - Monitoring
   - Anaesthetic care
   - Airway management
   - Emergencies
6. Post-procedure care

Fig. 22.3 A summary of the highlights from the ASA task force in 2015 [10]

22.4 Anaesthetic Concerns

22.4.1 Training

Specific training modules must be developed to orientate the whole team working together in the MRI suite [7]. Basic information on work safety in an MRI environment and special considerations for iMRI such as steps in docking and transferring a patient or mobile magnet must be included. The team members who need to undergo this training include surgeons, anaesthesiologists, nurses and the radiographers. An MRI safety officer as the Chief in Training should be selected to document the training records and the list of trained personnel so that only dedicated staff is allowed to manage iMRI cases. Access ought to be restricted to those who are untrained or who are not involved in the surgery.

22.4.2 Planning and Communication

Although the neurosurgeons take the lead to decide for iMRI in their cases, planning and timing must be communicated to the anaesthetic team and other care providers to facilitate preparations for MRI safe equipment, longer lines and placement of monitoring items. Vigilant care must be applied for clear reasons to ensure MRI safety and the sterility of an open cranium. Hence, good communication is vital and with time, the process becomes smoother and faster to accomplish.

22.4.3 Equipment Safety

Preparation of an MRI-safe environment includes labelling and identifying items and devices that are safe to be used and positioned within the magnetic field or otherwise. Specific terminology has been established to describe the relative safety of items in an MRI environment. MRI safe describes an item that poses no risk and likewise MRI unsafe means the item is a hazard in such an environment. MRI conditional refers to items that have no known hazards under specific conditions of use in a specified MRI environment. Such an example would be an MRI conditional anaesthetic machine specified for use under condition for 100 Gauss in a 1.5-T magnet which means it would be unsafe beyond that field strength [11]. Similarly, certain infusion pumps, warming blankets, temperature probes and even pacemakers are available as MRI conditional now. Another terminology is MRI compatibility, a requirement that the magnetic field does not affect a device and vice versa, the device should not interfere with the imaging process (Table 22.1).

22.4.4 Checklist

An important concept to remember is that the magnet is always on [13]. A checklist is used to ensure all appropriate steps are followed for a safe transfer of the patient to the MRI suite or

Table 22.1 Common equipment and devices used in the operating theatre (OT) that need to be located outside the 5-G line before iMRI

Anaesthetic equipment
Anaesthesia machine (unless MRI compatible)
Anaesthesia cart
Resuscitation trolley
Monitoring – Pulse oximetry, ECG, blood pressure (unless MRI compatible)
Desflurane vaporizer [12]
Invasive monitoring transducers
Needles and guidewires
Armoured tracheal tubes
Stethoscopes
Warming blanket device
Intravenous fluid warmer
Nerve stimulators
Temperature probe
Poles for intravenous fluids
Oxygen tanks, regulators and holder (unless MRI safe)
Surgical items
Diathermy – foot pedals, cautery pads and cords
Unsafe instruments – clamps, retractors
Microscope
Headlights, loops
Neuronavigation equipment
General use
Garbage bins
Buckets
Stools and steps
Patient folders
Pens
Handphones, pagers

the transfer of the magnet into the operating suite which must be done with extra caution. When iMRI is undertaken, only designated anaesthetic care providers and MRI staff should be involved. An assigned officer, who may be the nurse manager, takes the lead to call for time out and reads the checklist aloud to tick off all necessary items in the presence and attention of the whole team. When the scanner is not in use for the surgical case, the connecting door should remain closed at all times for the two rooms to function separately (Table 22.2).

Table 22.2 Example of an iMRI anaesthetic checklist for a stationary magnet and mobile patient system

Pre-induction	(✓)
Patient particulars and consent checked	
Surgical position confirmed	
Both ventilators and circuits in OT and MRI checked	
MRI compatible ECG dots/ lead and SpO_2 probe/ cable available	
MRI compatible oxygen tank with resuscitator bag/ T-piece available	
Anaesthetic personnel cleared of electrical/ ferromagnetic items	
Induction	
MRI compatible ECG dots placed	
Plain PVC tracheal tube	
Intubate patient on trolley	
NO ferromagnetic items on patient canvas and OT table before transfer	
Before sterile draping	
Monitoring lines, catheters and circuit that need to be removed before the transfer to MRI are assessable	
Perfusor tubings and intravenous lines secured and adequate in length	
Docking	
Arterial, CVP monitoring lines, hotline and forced air warmer disconnected, temperature probe removed	
Catheter bladder drain, lines and any other tubes removed from sides of OT table	
Manual ventilation taken over	
Oxygenation maintained before removing non-MRI compatible SpO_2	
Transfer from OT to MRI	
Confirm patient's haemodynamic stability for transfer	
MRI ventilator, circuit and monitor checked and complete	
NO electrical/ ferromagnetic items on patient, trolley and anaesthetists/ assistants	
Pathway of transfer cleared	
MRI suite	
IPPV ventilation instituted	
MRI-compatible SpO_2, ECG and NIBP monitoring on	
Intravenous line and drug perfusion running well	
Back in OT	
IPPV ventilation re-instituted	
Arterial, CVP monitoring lines, hotline and forced air warmer reconnected	
Non-MRI compatible SpO_2, ECG and NIBP monitoring on	

OT operating theatre, *IPPV* intermittent positive ventilation, *SpO_2* pulse oximetry, *ECG* electrocardiograph, *NIBP* non-invasive blood pressure, *CVP* central venous pressure

Conclusion

The iMRI suite is considered a hybrid, combining elements of an MRI interventional radiology unit with an operating room. In an increasingly technology driven field of medicine and science, the human factor remains the most critical. Therefore, communication remains the most important element to stress upon with all respective roles in iMRI clearly outlined for such a practice to be useful and safe in neurosurgery.

References

1. Black PM, Moriarty T, Alexander III E, Stieg P, Woodard EJ, Gleason PL, et al. Development and implementation of intraoperative magnetic resonance imaging and its neurosurgical applications. Neurosurgery. 1997;41(4):831–45.
2. Bradley WG. Achieving gross total resection of brain tumors: intraoperative MR imaging can make a big difference. Am J Neuroradiol. 2002;23(3):348–9.
3. Nimsky C, Ganslandt O, Cerny S, Hastreiter P, Greiner G, Fahlbusch R. Quantification of, visualization of, and compensation for brain shift using intraoperative magnetic resonance imaging. Neurosurgery. 2000;47(5):1070–80.
4. Qiu T, Yao C, Wu J, Pan Z, Zhuang D, Xu G, et al. Clinical experience of 3 T intraoperative magnetic resonance imaging integrated neurosurgical suite in Shanghai Huashan Hospital. Chin Med J. 2012;125(24):4328–33.
5. Shah MN, Leonard JR, Inder G, Gao F, Geske M, Haydon DH, et al. Intraoperative magnetic resonance imaging to reduce the rate of early reoperation for lesion resection in pediatric neurosurgery: clinical article. J Neurosurg Pediatr. 2012;9(3):259–64.
6. Kollias SS, Bernays R, Marugg RA, Romanowski B, Yonekawa Y, Valavanis A. Target definition and trajectory optimization for interactive MR-guided biopsies of brain tumors in an open configuration MRI system. J Magn Reson Imaging. 1998;8(1):143–59.
7. McClain CD, Rockoff MA, Soriano SG. Anesthetic concerns for pediatric patients in an intraoperative MRI suite. Curr Opin Anesthesiol. 2011;24(5):480–6.
8. Archer DP, Cowan RAM, Falkenstein RJ, Sutherland GR. Intraoperative mobile magnetic resonance imaging for craniotomy lengthens the procedure but does not increase morbidity. Can J Anaesth. 2002;49(4):420–6.
9. Chen X, Xu BN, Meng X, Zhang J, Yu X, Zhou D. Dual-room 1.5-T intraoperative magnetic resonance imaging suite with a movable magnet: implementation and preliminary experience. Neurosurg Rev. 2012;35(1):95–110.
10. Borghi L. Practice advisory on anesthetic care for magnetic resonance imaging an updated report by the American Society of anesthesiologists task force on anesthetic care for magnetic resonance imaging. Anesthesiology. 2015;122(3):495–520.
11. Shellock FG, Woods TO, Crues III JV. MR labeling information for implants and devices: explanation of terminology 1. Radiology. 2009;253(1):26–30.
12. Bergese SD, Puente EG. Anesthesia in the intraoperative MRI environment. Neurosurg Clin N Am. 2009;20(2):155–62.
13. Henrichs B, Walsh RP. Intraoperative magnetic resonance imaging for neurosurgical procedures: anesthetic implications. AANA J. 2011;79(1):71–7.

Sedation in Neurocritical Units

23

Rafael Badenes and Mario De Fez

23.1 Introduction

Sedation is an essential component of treatment in intensive care units (ICU). The patients admitted to the ICU are sedated using intravenous drugs: propofol and midazolam. This has been observed in review studies [1–3] and clinical guidelines [4]. However, these agents have pharmacological characteristics that make them far from ideal [5]. Neurocritical patients with brain injury tend to be found subject to complex neuromonitoring and instrumentation such as external ventricular drains, intracranial monitors, and multimodal monitors for hemodynamic and respiratory control that may lead to discomfort and irritation in a patient among whose main needs is getting enough brain rest to prevent secondary damage that may arise after trauma. This type of patients deserves special consideration with regard to the current trend of early cessation of sedation. For patients with elevated intracranial pressure (ICP), those who require muscular relaxation for any reason or patients in status epilepticus, the temporary or permanent cessation of sedation would not be recommended [6, 7].

Sedoanalgesic drugs with an ideal profile for a patient with intracranial hypertension (IH) should be capable of decreasing this ICP, maintaining adequate cerebral perfusion and hemodynamics without interfering with its autoregulation if it has been preserved, decreasing cerebral metabolic rate for oxygen (CMRO2), and it should possess neuroprotective and anticonvulsant properties. It should have a pharmacokinetic and pharmacodynamic profile that makes it possible to achieve a rapid onset of the desired clinical effect and a rapid wake-up time for neurological assessment after interruption of sedation (IS) with a predictable dose–response, without or with minimal accumulation in the organism, minimal secondary effects, and non-toxicity. We have currently not found any drug that meets these characteristics, and the best option has been to establish some sedation protocols guided by objectives and thorough knowledge on how to manage the drug so as not to compromise its efficacy and safety.

23.2 Needs for Sedation

Sedation in neurocritical patients has its benefits and drawbacks. It is currently essential to relieve both pain and anxiety, reduce ICP, decrease oxygen consumption, tolerate therapeutic maneuvers (fibrobronchoscopies, lung recruitment maneuvers, catheter placement, dressings, etc.) as well

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as improve adaptation to tracheal intubation and mechanical ventilation, reducing the sympathetic shock resulting from all these experiences. However, it complicates or prevents serial clinical neurological evaluation. Changes in the brain state are difficult to detect, decreasing prognostic capacity.

Likewise, sedation may bring about vasodilation leading to hypotension, reducing cerebral perfusion pressure (CPP), and possibly resulting in a "steal" phenomenon that would bring blood to ischemic areas. Despite the vasoreactivity mechanisms generated in protective autoregulation, it has been seen that both the CBF and the supply of oxygen to the brain are decreased in injured brains [8–14], with a marked decline in CBF in the first 24 h [15, 16]. In 31% of the patients with CET [12], CBF was found below the ischemic threshold where ischemia and cellular death may occur [17].

Prolonged deep sedation may possibly worsen cognitive results after its cessation and contribute to polyneuropathy in critical patients. In neurocritical patients, many therapeutic decisions or procedures are carried out after neurological examinations in awake patients and in many cases, whenever possible, sedation is avoided in patients with unstable injuries that may progress provided that it is safe.

Sometimes, the need for sedation does not consider the challenges of the benefit–risk evaluation and is found within the therapeutic arsenal. Asynchronies during mechanical ventilation, injuries that the patient has, agitation, anxiety, and ICP elevation are the complications of inadequate sedation [18–31]. Correct sedation is found present in all the treatment algorithms for increased intracranial pressure (ICP) [22, 23]. We know that anxiety, pain, and sympathetic shock generated by stress have negative effects on the ICP, CBF, CPP, and CMRO2. Correct sedoanalgesia is our instrument to prevent or minimize secondary brain injury despite the lack of evidence that proves that neurological outcomes may improve by its use alone [22]. In intensive care units, excessive sedation has been proven to lead to an increase in the days with mechanical ventilation, a longer stay in the unit, and in hospitalization days [24–27] together with an increase in rates of depression, post-traumatic stress disorder, infections, and long-term neurocognitive deterioration [27–29].

There are patients for whom sedation cessation is not possible, such as for cases of status epilepticus or refractory IH, in which a reduction in the level of sedation may be counterproductive. Unless deep sedation or general anesthesia is necessary, analgesia must precede sedation. Sedation based on analgesia with opioids is a new trend in intensive care units, which has been seen to improve the outcomes of mechanical ventilation in patients under analgesics and with no sedation [30]. Many patients with adequate pain control do not need sedation and many sedative agents do not provide analgesia, which may cause delirium in intensive care units. Short-acting analgesics would also allow serial neurological assessment. Environmental stimuli cause agitation. A calm and soothing environment, attentive to circadian rhythms, and the presence of family and friends may decrease anxiety and agitation [31]. Injuries caused by aphasia may lead to anxiety and agitation after failures to communicate. It is advisable to employing staff who can reorient agitated patient toward using sedative medication. Patients with severe brain injury may show deficits in short-term memory, concentration, and emotional control, and this confusion may cause agitation. Patiently and calmly reorienting the situation and circumstances may avoid sedative medication.

The guidelines for sedoanalgesia in massive cerebral infarction establish the following recommendations [32]:

- Analgesia and sedation are recommended if signs of pain, anxiety, or agitation arise (strong recommendation, very low quality of evidence).
- The lowest possible sedation intensity and earliest possible sedation cessation is recommended, while avoiding physiologic instability and discomfort (strong recommendation, very low quality of evidence).
- The routine use of daily wake-up trials is not recommended. Caution is particularly warranted in patients prone to ICP crises.

Neuromonitoring of at least ICP and CPP is recommended to guide sedation, and daily wake-up trials should be abandoned or postponed at signs of physiological compromise or discomfort (strong recommendation, very low quality of evidence).

23.3 Sedation Assessment

To achieve efficient sedation and avoid the deleterious effects resulting from inadequate sedation to the extent possible, it is necessary to carry out a careful assessment of sedation. Neurophysiological monitoring should be considered a routine practice for neurocritical patients requiring sedation.

Doses not adjusted to sedation targets, whether due to infradosification or overdosification, may affect neurological assessment and lead to the wrong diagnosis. Oversedation increases the risk of infections, delays the removal of mechanical ventilation, and increases the length of stay in ICUs. In contrast, infrasedation causes agitation, anxiety, and risk of accidents such as self-extubation, pulling out of catheters, discomfort, or ventilator asynchronies [33] and has prevented neurologic deterioration [26, 34] .

There are different scales used to evaluate arousal, depth of sedation, and response to stimuli [35].

The Ramsay Scale evaluates consciousness, while the Richmond Agitation Sedation Scale (RASS) examines cognition, Sedation Agitation Scale (SAS) and the Motor Activity Assessment Scale (MAAS) monitor sedation and arousal. The use of sedation scales can reduce the amount of sedatives given to achieve a specific sedation target, decreasing the number of days on mechanical ventilation and cost of hospital stay [25], but no validation is available in the neuro ICU environment.

When assessment is not possible using scales such as in the case of patients requiring muscular relaxation or when burst-suppression is desired, an electrophysiological endpoint must be used instead. Recently, processed electroencephalogram (EEG) algorithms have been introduced into clinical practice as a method to monitor objectively and quantitatively the level of consciousness in ICU patients. One example is the determination of bispectral index (BIS) [36], which has been associated with a decrease in sedative use in intraoperative care [37]. Although there are no randomized studies that validate it as ideal in neurocritically ill patients, sedation assessment using BIS monitoring has made adjustments possible, reducing the doses of propofol required for an adequate level of sedation. In comparison with those patients evaluated using subjective sedation scales, BIS monitoring leads to shorter wake-up times after sedation cessation. No differences can be seen between BIS monitoring and sedation scales with regard to infrasedation, and it seems a reliable monitor for sedation assessment. The BIS may have a role in monitoring deeply sedated patients in the neurointensive care unit (NICU) [38–41].

Regarding assessment of delirium, no assessment tools have been validated in neurocritical care patients, though several studies that used the Intensive Care Delirium Screening Checklist enrolled NICU patients [40, 42, 43]. Recent, highly insightful reviews of the topic are also available [44]. Several studies have addressed the sedation monitoring approaches and medication choices for NICU patients.

23.4 Need to Wake Up

Neurological assessment remains a valuable tool for monitoring severely brain-injured patients and the need for a reliable evaluation conflicts with sedation, routinely administered to severely brain-injured patient. For the clinical assessment of neurocritical patients, interruption of continuous sedation (IS) is therefore necessary. This interruption is usually short term, aimed to evaluate the patients and plan further management strategies, including the definitive sedation interruption once the clinical picture and ICP are no longer a concern and IS does not provoke patients' distress and metabolic imbalance. Close patient observation during IS is therefore strongly suggested.

The interruption of sedation may have negative effects because it could also induce a stress response. ICP and the CPP levels can increase during interruption of sedation, when compared to baseline levels recorded during continuous sedation. In the majority of patients, these changes are transient and tolerable [45]. However, in a subset of patients with very low cerebral compliance, the interruption of continuous sedation can induce marked ICP and CPP changes that can produce secondary injuries [22]. Those patients should be excluded from repeated evaluations, and information should instead be gathered from other multimodality monitoring methods in combination with neuroimaging [24].

Not all patients can be safely woken up. The benefit of having clinical evolution clues in the more severe subset is overwhelmed by the possible negative effect on ICP and, consequently, on cerebral blood flow. In this setting, multimodality monitoring and neuroimaging remain the clinicians' guide, and we have to postpone clinical evaluations that could cause secondary insults.

During the maneuver for the interruption of sedation (IS), CPP and ICP usually show slight and tolerable increases during IS. In the majority of patients, these changes are mild, transient, and acceptable, and they do not preclude repeating IS in the neurointensive care setting. Nevertheless, IS is a stressful condition [46].

Of all IS events performed, the trial had to be stopped frequently (i.e., in one-third) due to ICP surge, agitation, or systemic desaturation. In the aborted IS trials, a decrease in brain tissue oxygen tension and a tendency to brain metabolic distress were observed. A better risk stratification [47] needs to be defined accordingly.

One of the major strengths of daily awakening trials is the additional information gained from a reliable clinical assessment in those patients who tolerate IS. Unfortunately, this was not the case: evidence for a new focal neurologic deficit was found in only one (2%) patient with known cerebral vasospasm who developed motor weakness of the lower limb.

Patients with exhausted ICP compliance may pose a high risk for critical ICP increase during wake-up trials. Recent studies have failed to confirm a benefit associated with daily wake-up protocols [48]. Sedation interruption in other neurocritical care populations—traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH)—was associated with potentially negative effects such as transient rises in ICP and stress hormone levels [22, 46].

Interruption of sedation revealed new relevant clinical information in only one trial and a large number of trials could not be performed or had to be stopped due to safety issues. Weighing pros and cons of IS trials in patients with acute brain injury seems important as related side effects may overcome the clinical benefit [49].

IS trials in patients with acute brain injury are not well studied and the only case series, including 12 patients with traumatic brain injury (TBI) and 9 subarachnoid hemorrhage (SAH) patients, showed that the risk of elevated ICP and low CPP is evident during these trials [22, 50]. Cerebral hypoperfusion and raised ICP may result in an imbalance of energy supply and demand especially for the injured brain and, therefore, aggravate the risk for metabolic distress and brain tissue hypoxia [51–57].

We observed a sympathetic stress response with increased heart rate, respiratory rate and mean arterial pressure (MAP) during all IS trials, which is in line with a recent report showing an excess of endogenous catecholamines and corticoids during neurologic wake-up tests [46].

In patients who failed the trial, we observed a decrease in $PbtO_2$ to critical values (<20 mmHg) in 67% of IS trials. In parallel, elevation in ICP was observed, which may increase the demand of oxygen and, therefore, decrease brain tissue oxygen tension [49].

The neurological wake-up test (NWT) was performed in order to assess and evaluate the motor component of the glasgow coma scale (GCS) (glagow motor score (GMS)) score, and during the test, pupil size and reactivity to light were also assessed. One primary aim of the NWT is to detect neuroworsening and the level of consciousness, and the presence of focal deficits as well as the pupil reaction to light must be evaluated [58].

Karin Skoglund et al. evaluated the effects of the NWT using cerebral microdialysis (MD),

brain tissue oxygenation ($PbtiO_2$), jugular venous oxygen saturation ($SjvO_2$), and/or arterial-venous difference (AVD) for glucose, lactate, and oxygen in patients with severe TBI. The NWT-induced stress response resulted in increased ICP and CPP levels although it did not negatively alter focal neurochemistry or cerebral oxygenation in TBI patients [59]. The NWT does not induce a significant secondary insult on the injured brain when applied during neurocritical care of TBI patients, provided that NWTs are avoided in unstable patients with marked ICP elevations.

Given the current little knowledge about the benefits of IS in brain-injured patients, it is extremely important to adopt multiple monitoring modalities in neurocritical care in order to escape IS in those patients who will potentially be harmed by this procedure.

23.4.1 Ideal Sedative Drug

Nevertheless, no clear data on the best sedative choice for acute brain damaged patients are available.

Properties of an Ideal Agent for Neurointensive Care Sedation [24]

- Rapid onset and rapid recovery, allowing prompt neurologic evaluation
- Predictable clearance independent of end-organ function, avoiding the problem of drug accumulation
- Easy titration to achieve adequate levels of sedation
- Reduced intracranial pressure by cerebral blood volume (CBV) reduction or cerebral vasoconstriction
- Reduced cerebral blood flow and cerebral metabolic rate of oxygen consumption, maintaining their coupling
- Maintenance of cerebral autoregulation and normal cerebral vascular reactivity to changes in arterial carbon dioxide tension
- Minimal cardiovascular depressant effects
- Inexpensive

23.4.2 Pharmacological Targets

23.4.2.1 Reduction of Cerebral Metabolic Rate of Oxygen Consumption

To maintain adequate oxygen availability and energy balance at the neuronal level, treatment is directed at both increasing oxygen delivery by optimizing cerebral and systemic hemodynamics and reducing cerebral metabolic demand [60–67]. Selected sedatives used in NICU offer a protective effect by reducing oxygen demand and increasing oxygen delivery [68–70]. The γ-aminobutyric acid (GABA) type A receptor system, the main fast-acting inhibitory neurotransmitter system in the brain, is the pharmacological target for many drugs used clinically to treat, for example, anxiety disorders and epilepsy, and to induce and maintain sedation titrated to the desired effect. GABA type A receptor stimulation results in a reduction of cerebral metabolism of O2 ($CMRO_2$).

23.4.2.2 Effects on Cerebral Blood Flow

When selecting sedative drugs, the maintenance of sufficient cerebral blood flow and at the same time the provision of sedation are of paramount importance and should be considered.

All sedative agents may cause a decrease in mean arterial blood pressure by inducing both cardiac depression and peripheral vasodilatation. The decrease in blood pressure can cause an increase in ICP as a result of autoregulatory compensation and, consequently, a reduction in CPP.

23.4.2.3 Intracranial Pressure Control

Adequate control of the ICP is one of the main therapeutic goals of managing the critically ill neurologic patient: Sedatives may reduce ICP by different mechanisms. As previously described, most of the sedatives used in the NICU decrease the cerebral metabolic rate of oxygen consumption ($CMRO_2$), producing a reduction in CBF, a reduction of cerebral blood volume (CBV), and a decrease in ICP. The applicability of this concept not only is limited to traumatic brain injury

patients but also can be extended to patients with stroke and subarachnoid hemorrhage [65].

23.4.2.4 Seizures Suppression

Seizures are a frequent event in neuroinjury patients [71–73]. Convulsive and nonconvulsive seizures occurred in 22% of the traumatic brain injury cohort and in 15% of patients with intracerebral hemorrhage or subarachnoid hemorrhage [65]. Seizures produce a massive increase in cerebral metabolism and possibly a mismatch between oxygen delivery and metabolism in the affected brain area. Together with antiepileptic drugs, sedation appears to be an attractive option in reducing seizures in the NICU.

23.5 Drugs Used in Intravenous Sedation

23.5.1 Propofol

It is a short-acting anesthetic. Pharmacologically, its lipid formulation allows for rapid penetration of the blood–brain barrier, resulting in rapid onset and cessation of action. Though allowing rapid awakening after short-term use, propofol also appeared to unpredictably accumulate after long-term use and to cause prolonged sedation [74].

Cerebral blood flow measured by positron emission tomography is reduced with propofol [76, 77]. Propofol further decreases CBV and, in turn, ICP. This makes propofol most suitable for patients with reduced intracranial compliance [75–77].

The ability of propofol to protect against seizures has provided conflicting data [78]. More recent studies showed that standard or high-dose propofol infusion (2 mg/kg induction bolus followed by 150–200 μg/kg/min infusion) can be reliably used as an anticonvulsant, even for the control of status epilepticus [79–82]. Experimental data have shown propofol to have strong anticonvulsant properties, which have proved to be very effective in controlling refractory status epilepticus. A recent statement by the European Federation of Neurological Societies included the use of propofol as an antiepileptic for convulsive epileptic status in the ICU setting [81].

Soon after its introduction, a serious adverse effect, the propofol infusion syndrome (PRIS), was recognized. PRIS was characterized by rhabdomyolysis, hyperkalemia, metabolic acidosis, and renal and cardiac failure and is associated with a high mortality. A lot of case reports describe cardiac failure in head injury patients receiving long-term propofol infusions [83–85].

Morgan et al. identified that initiation of propofol in patients with a baseline MAP between 60 and 70 mmHg independently predicted hypotension. Propofol has been shown in several studies to cause both venous and arterial vasodilation, potentially resulting in an increased risk of hypotension in patients with a lower MAP at baseline [86]. The hypotension-inducing mechanisms of propofol are multifactorial [87–90] and administration of antihypertensive agents may increase the hemodynamic response to propofol. Severe propofol-associated hypotension occurred in 26.2% of patients studied. They identified a baseline MAP 60–70 mmHg, increasing propofol infusion rate changes, and requirement for renal replacement therapy (RRT) as factors independently associated with the development of hypotension.

23.5.2 Opioids

In general, opioids slightly decrease $CMRO_2$, CBF, and ICP, as long as normocapnia is maintained by mechanical ventilation. Opioids can produce short-lasting, mild decreases in mean arterial pressure, followed by decreases in CPP. In a study, Roberts DJ found that morphine, fentanyl, sufentanil, and alfentanil significantly increased ICP and decreased CPP and MAP after bolus administration [91]. They tend to have a transient effect, although CPP and MAP remained decreased in a study [92].

23.5.3 Remifentanil

Because of its short half-life, remifentanil has unique pharmacokinetic properties that make it

attractive for use in neurocritical care. It is a mu-opioid agonist exhibiting analgesic effects with a rapid onset and a short duration of action. It is an agent which can be used as a part of a combined sedative analgesic approach. In particular, remifentanil may cause decrease in both cerebral metabolic rate and ICP, with minimal changes in CPP and cerebral blood flow [93]. It may facilitate frequent awakening to evaluate neurologic and respiratory parameters [39]. In a study of patients with traumatic brain injury who were mechanically ventilated, remifentanil was used for on-top analgesia in head trauma patients without adverse effects on cerebrovascular hemodynamics, CPP, or ICP [94].

23.5.4 Benzodiazepines

The use of benzodiazepines as sedatives in intensive care significantly increases delirium incidence, which has a very negative effect on the patients' progress. Midazolam is an appealing sedative option given the rapid onset of action and short duration of effect with bolus administration, making it an ideal agent for procedural sedation. Additionally, due to its potent gamma-aminobutyric acid (GABA) activity and relatively benign hemodynamic profile, midazolam is an important drug in refractory status epilepticus. Benzodiazepines increase the seizure threshold and are useful anticonvulsants [95, 96]. In fact, in all settings benzodiazepines are a first-line treatment of a new onset of seizures.

As a long-term sedative for general ICU use, midazolam accumulates in adipose tissues, significantly prolonging duration of action unless interruptions or down-titration of dose are routinely utilized. Bolus-dose midazolam is a good choice for intermittent agitation in an NICU population. Conversely, midazolam infusion has been associated with prolonged mechanical ventilation [97, 98].

Though most studies suggest that the impact of midazolam on hemodynamics is similar compared to dexmedetomidine (DEX) or propofol, a recent report suggests less instability compared to dexmedetomidine [98]. Lorazepam is a longer-acting benzodiazepine when used in the short term, but its duration of action is shorter than midazolam when infused for more than 1–2 days. The strong GABA activity of lorazepam suppresses electrical and metabolic brain activity. Unlike midazolam, lorazepam is formulated in propylene glycol, which can accumulate to toxic levels causing metabolic acidosis and kidney injury. At lorazepam infusion rates above 3 mg/h or daily doses approaching 1 mg/kg, the osmolar gap should be followed, and alternative agents should be used if the osmolar gap rises above 10–12 mOsm/L [99, 100].

23.5.5 Barbiturates

Use of barbiturates as a sedative in the neurocritical care unit is limited due to its undesirable side effect profile. Immunosuppressant properties and negative inotropic effects are among the more concerning limitations. Pentobarbital serves as a potent agent for deep sedation in patients with refractory status epilepticus or elevated ICP [101–103]. Barbiturates remain second-line therapy for the control of ICP after propofol. They remain in widespread use to control refractory status epilepticus, and their potent effects on cerebral metabolic and electrical activity make them an appealing class of agents for sedation in the NICU.

23.5.6 Dexmedetomidine

Dexmedetomidine (DEX) is a centrally acting alpha agonist similar to clonidine, but more specific for the alpha-2 receptor. It is increasingly utilized for ICU sedation. Desirable properties include rapid onset and termination of activity, mild to moderate sedation without significant respiratory depressant action, analgesic effects, and less delirium than the benzodiazepines [99]. Undesirable properties include a high incidence of bradycardia and hypotension [98]. Bradycardia is the most typical hemodynamic effect associated with DEX [104–112]. In addition to bradycardia, hypertension and hypotension have been

reported as adverse events in clinical applications of DEX, especially during loading infusion [106, 107, 109–111, 113, 114].

Grof et al. demonstrated that neurocritically ill patients may require high doses of dexmedetomidine to achieve desired levels of sedation and to wean off adjunctive analgesic and/or sedative agents. Dexmedetomidine infusions may be started at doses from 0.4 to 1 mcg/kg/h in neurocritical care patients to achieve target levels of sedation and/or to wean off other sedative and analgesic infusions. Dexmedetomidine appears to be an effective sedative agent in the neurocritical care patients [101]. In the study by Erdman et al., limiting dose titrations to every 30 min and omitting a bolus dose, there was no significant difference found in the prevalence of hypotension or bradycardia between DEX and propofol.

In ICU, dexmedetomidine has been shown to be non-inferior to both midazolam and propofol in maintaining light to moderate sedation [115, 116]. It appears to shorten time to extubation and enhance arousability and patient's ability to communicate with caregivers. Dexmedetomidine may reduce delirium after long-term sedation as compared with midazolam [115] and also reduce the overall neurocognitive adverse events of sedation, such as agitation, anxiety, and delirium, when compared with propofol [116].

The safety and efficacy of dexmedetomidine, however, have not been evaluated in some ICU patient groups, such as patients with acute neurologic disorder (e.g., stroke and head trauma).

23.5.7 Etomidate

In the absence of long-term safety data, familiarity with short-term use and its apparent safety profile led to the introduction of etomidate as a continuous infusion for ICU sedation, with resulting adverse events including adrenal suppression and a 19% absolute increase in mortality in trauma patients [117, 118].

23.6 New Trends: Toward Inhalation Sedation

Although still off-label, inhalative ICU sedation is currently spreading all over Europe and has been recommended as an alternative in a recent German consensus guideline [119].

The device named AnaConDa (Anesthetic Conserving Device, Sedana Medical, Uppsland Väsby, Sweden) makes it possible to administer inhaled anesthetic agents—isoflurane and sevoflurane—using any ventilator commonly found in Intensive Care Units [120–122], only requiring an infusion pump and a respiratory gas monitor to control the amount of administered drug. This is a major impetus for inhalation sedation as an alternative to intravenous sedation [121].

Among the inhaled anesthetic agents that are currently used, isoflurane, sevoflurane, and desflurane have been occasionally used in resuscitation units to carry out sedation in critical patients, which have been proven to offer benefits compared to intravenous sedation [121–125]. Metabolism is minimal, and due to their low solubility, they are quickly eliminated through the lungs. Because of these characteristics, it has been proven that they lead to shorter and more predictable wake-up times than intravenous agents when used as sedatives in intensive care [121–124]. At the physiological level, inhaled anesthetic agents can prevent the development of bronchospasm [120, 125] and have been proven to have cardioprotective effects [121]. In addition, the commonly used doses for sedation are hemodynamically stable drugs [122] that enable good control over ventilation. All of this bring them much closer to the ideal sedatives, as recently acknowledged by an important article in the British Journal of Anaesthesia [126]. Volatile anesthetics may be considered for mechanically ventilated patients, if short wake-up durations are desired [121, 127–131].

It has been shown that some volatile anesthetics abolish cerebral autoregulation at high doses, whereas sevoflurane, at high doses of 1.5 minimum alveolar concentration (MAC), is associated with an intact autoregulation in humans with

normal $PaCO_2$ values. Cerebral blood flow and the metabolic rate for oxygen consumption remain tied to cerebrovascular reactivity to CO_2 and do not worsen with the administration of sevoflurane. It has been reported that at 1.0 MAC of sevoflurane, the autoregulation of cerebral blood flow remained intact, but that this was impaired at 2.0 MAC.

The $PaCO_2$ threshold for a significant alteration of autoregulation is in the range of 50–66 mmHg. The average threshold during anesthesia using sevoflurane was 56 ± 4 mmHg. Mild chronic hypercapnia should be avoided if we are attempting to preserve cerebral autoregulation.

Previous studies have shown that after the hypoperfusion period, a hyperperfusion period follows for the recovery of the ischemic brain from ischemia. Cerebral blood flow is closely related with brain injury. Bundgaard et al. [132] found that sevoflurane increased cerebral blood flow and decreased cerebrovascular resistance.

Volatile anesthetics have a direct neuroprotective effect when found present in periods of in vitro [133] and in vivo [134] ischemia or administered prior to it (anesthetic conditioning) [135]. Preconditioning has already been described for the heart [136] and more recently, in vitro [137] and in vivo [138] models of cerebral ischemia. More specifically, sevoflurane has reduced hippocampal damage caused by hypoxia in vitro [137] and in vivo after a global cerebral ischemia [139].

Codaccioni et al. conclude that sevoflurane is capable of reducing infarct size and it decreases ischemia-induced apoptosis more than 7 days from the injury in rats.

The mechanism of the induction of tolerance to ischemia and neuroprotection is still under investigation. Current evidence would suggest that it is inducible nitric oxide synthase dependent [140]. Other factors that could be involved are the inhibition of excitatory neurotransmission and regulation of intracellular calcium responses during ischemia and the attenuation of ubiquitin-conjugated protein aggregation [141–144]. Surprisingly, recent animal studies have shown that isoflurane preconditioning response is attenuated by estradiol and that is androgen dependent in male mice and is gender specific [145, 146].

Sevoflurane also has a role in postconditioning; its application could be of interest once cerebral ischemia has occurred. In 2003, the concept of ischemic postconditioning was proven for the purpose of improving outcomes of cardiac events after ischemia [147], and in 2006, its neuroprotective effects on rats were shown. Lee et al. [148] found that isoflurane postconditioning reduced brain injury due to ischemia in rats. More recent studies have shown its role in the inhibition of apoptosis in hearts and brains. Adamczyk et al. reported that sevoflurane postconditioning for 15 min 1 h after ischemia led to neuroprotection in rats. Jun-kuan Wang [149] obtained good results in sevoflurane postconditioning at 1.0 and 1.5 MAC, with a decrease in neurologic deficits, cerebral infarction volume, improvement in learning, memory, and cerebral edema in rats that had suffered focal lesions due to ischemia reperfusion. At 0.5 MAC, adequate neuroprotective is not obtained, which means that the effect of sevoflurane postconditioning in focal ischemic lesions is dose dependent [150]. Sevoflurane at 1.0 and 1.5 MAC is very similar to that widely used in clinical practice, and in fact, 1.5 MAC does not achieve greater neuroprotection than 1.0 MAC, for which sevoflurane postconditioning could have potential clinical applications.

Apoptosis has a fundamental role in the mechanism that causes the death of cells found in the ischemic penumbra in ischemia-reperfusion brain injuries. Sevoflurane postconditioning inhibits this apoptosis. Similar results in this direction were found by Xing et al. [151] wherein a significant decrease in apoptotic cells was found after postconditioning.

Sevoflurane postconditioning increases the levels of anti-apoptotic proteins Bcl-2 and inhibits the expression of pro-apoptotic proteins Bax. Several signaling pathways are involved in cell death due to apoptosis. The induction of P53 protein is involved in neuronal cell death due to apoptosis. The P53 protein can interact with the Bcl-2 family of proteins and cause apoptosis.

Sevoflurane postconditioning inhibits the expression of P53 [150].

The neuroprotective role played by sevoflurane postconditioning in spinal cord ischemia-reperfusion injuries has also been proved in rabbits. It appears to carry out its action by increasing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), with an optimal concentration for sevoflurane postconditioning at 1.0 MAC [152–154]. Sevoflurane postconditioning can be clinically useful for the prevention of ischemia–reperfusion injuries in surgical procedures such as aortic aneurysm repair and spinal cord surgery.

Purrucker et al. in a prospective study of sevoflurane sedation in patients with acute stroke or subarachnoid hemorrhage, sufficient sedation levels without clinically relevant ICP increase were achieved in 68% of the patients. However, serious adverse events observed in the remaining 32% raise considerable safety concerns. Mean arterial pressure (MAP) had to be stabilized actively to maintain CPP. Based on these observations, they concluded that they do not feel that the alleged neuroprotective potential of sevoflurane outweighs the risk of adverse events and sevoflurane sedation should probably not be used in this specific patient population. [155].

Isoflurane at effective sedation doses did not compromise cerebral oxygenation (short term), blood flow (short term), or ICP (short term and long term) to clinically relevant extents. It has shown neuroprotective effects when used prior to (preconditioning) [156, 157] or during [158, 159] ischemic insults in a considerable number of experimental studies [160].

Isoflurane significantly decreased cerebral and systemic oxygen extraction, which might reflect isoflurane's well-known ability to reduce the metabolic rate and thus cerebral and systemic oxygen consumption without relevant increases in ICP, if baseline ICP values are low or only moderately elevated. However, the observation of substantial MAP/CPP reductions and other adverse effects are concerning and warrant caution in this off-label treatment.

In terms of neurotoxicity, one single neuropathological work-up revealed no signs of basal ganglia injuries [161]. Intrapulmonary shunt in two patients was probably caused by blunting of hypoxic pulmonary vasoconstriction that is more common with isoflurane than with propofol [162].

Two patients developed anisocoria without changes in ICP or on a control CT scan that disappeared after cessation of isoflurane. Suggested mechanisms with other volatile agents are local pupilomotor effects and dysregulation of sympathetic tone [163], not attributable to ICP crises and unnecessary transports for CT scanning.

Bösel and colleagues [164] enrolled ischemic stroke, intracerebral and subarachnoid hemorrhage patients, sedated initially with an intravenous sedative agent (propofol or midazolam) and switched to inhalative isoflurane at a minimal alveolar concentration (MAC) of 0.5 for 3 days. They observed a clinically irrelevant increase in ICP; also, cerebral artery flow velocity did not change significantly. This result is interesting and is consistent with the results of other studies; a possible explanation could be that isoflurane causes a reduction in vascular resistance in the microcirculation and in the intraparenchymal arterioles rather than large vessels as the mean cerebral artery that is explored by transcranial Doppler [165]. Recent studies suggest that large vessel vasospasm may not be the only factor in predicting outcome in SAH, in particular, intracerebral arterioles have an important role in the regulation of distal CBF [166–171].

The onset of isoflurane also caused a decrease in core temperature, presumably caused by peripheral vasodilatation [172].

Selected patients with good systemic circulatory stability but compromised cerebral microcirculation (e.g., vasospasms in SAH, ischemic penumbra in large vessel occlusion) might benefit from volatile sedation. Transient application of isoflurane might provide the reported protective "preconditioning" effect to ameliorate secondary ischemia without risking neurotoxicity potentially associated with longer-term application.

Volatile sedation historically has been considered unsafe in acute brain damaged patients and confined outside neuroICUs. As suggested in the

animal studies, the potential neuroprotective benefit of inhalation sedation is huge and unexplored. Until recently, surpassing this boundary seemed foolhardy. We have to find ways to exploit it, while, driven by monitoring, avoiding the side effects. Continuous monitoring of ICP and CBF and the demarcation of safety thresholds have allowed securely setting sailing for this adventure.

Conclusion

Sedation is fundamental in the management of the critically ill patient. Recent emphasis on weaning from the ventilator and reducing ventilator-associated pneumonia has produced improved sedation guidelines that assure comfort, has reduced time on the ventilator, has resulted in a decreased ICU length of stay (LOS), and has prevented neurologic deterioration. The NICU, when compared to the general ICU, requires special considerations. Sedation used in the general ICU limits the stress response to critical illness, provides anxiolysis, improves patient–ventilator synchrony, and facilitates care. However, when used in the NICU, sedation is fundamental as a therapeutic strategy. To achieve efficient sedation and avoid the deleterious effects resulting from inadequate sedation to the extent possible, it is necessary to carry out a careful assessment of sedation. Neurological assessment remains a valuable tool for monitoring severely brain-injured patients and there is a need for a reliable evaluation of conflicts with sedation, routinely administered to severely brain-injured patient. Nevertheless, no clear data on the best sedative choice for acute brain-damaged patients are available.

References

1. Crippen DW. The role of sedation in the ICU patient with pain and agitation. Crit Care Clin. 1990;6:369–92.
2. Kong KL, Bion JF. Sedating patients undergoing mechanical ventilation in the intensive care unit--winds of change? Br J Anaesth. 2003;90:267–9.
3. Ghatge S, Lee J, Smith I. Sevoflurane: an ideal agent for adult day-case anesthesia? Acta Anaesthesiol Scand. 2003;47:917–31.
4. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, Chalfin DB, Masica MF, Bjerke HS, Coplin WM, Crippen DW, Fuchs BD, Kelleher RM, Marik PE, Nasraway SA Jr, Murray MJ, Peruzzi WT, Lumb PD; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists (ASHP), American College of Chest Physicians. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med. 2002; 30:119–41.
5. Smith HA, Fuchs DC, Pandharipande PP, Barr FE, Ely EW. Delirium: an emerging frontier in the management of critically ill children. Crit Care Clin. 2009;25:593–614.
6. Bailey P, Thomsen GE, Spuhler VJ, et al. Early activity is feasible and safe in respiratory failure patients. Crit Care Med. 2007;35:139–45.
7. Stiller K. Safety issues that should be considered when mobilizing critically ill patients. Crit Care Clin. 2007;23:35–53.
8. Diringer MN, Videen TO, Yundt K, et al. Regional cerebrovascular and metabolic effects of hyperventilation after severe traumatic brain injury. J Neurosurg. 2002;96:103–8.
9. Imberti R, Bellinzona G, Langer M. Cerebral tissue PO2 and SjvO2 changes during moderate hyperventilation in patients with severe traumatic brain injury. J Neurosurg. 2002;96:97–102.
10. Bouma GJ, Muizelaar JP. Cerebral blood flow, cerebral blood volume, and cerebrovascular reactivity after severe head injury. J Neurotrauma. 1992;9(Suppl 1):S333–48.
11. Fieschi C, Battistini N, Beduschi A, et al. Regional cerebral blood flow and intraventricular pressure in acute head injuries. J Neurol Neurosurg Psychiatry. 1974;37:1378–88.
12. Bouma GJ, Muizelaar JP, Stringer WA, et al. Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. J Neurosurg. 1992;77:360–8.
13. Bouma GJ, Muizelaar JP, Choi SC, et al. Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. J Neurosurg. 1991;75:685–93.
14. Obrist WD, Langfitt TW, Jaggi JL, et al. Cerebral blood flow and metabolism in comatose patients with acute head injury. Relationship to intracranial hypertension. J Neurosurg. 1984;61:241–53.
15. Epstein HM, Linde HW, Crampton AR, Ciric IS, Eckenhoff JE. The vertebral venous plexus as a major cerebral venous outflow tract. Anesthesiology. 1970;32:332–8.
16. Eckenhoff JE. The physiologic significance of the vertebral venous plexus. Surg Gynecol Obstet. 1970;131:72–8.

17. Heiss WD, Rosner G. Functional recovery of cortical neurons as related to degree and duration of ischemia. Ann Neurol. 1983;14:294–301.
18. Samaniego EA, Mlynash M, Caulfield AF, Eyngorn I, Wijman CA. Sedation confounds outcome prediction in cardiac arrest survivors treated with hypothermia. Neurocrit Care. 2011;15:113–9.
19. Riker RR, Fraser GL. Altering intensive care sedation paradigms to improve patient outcomes. Anesthesiol Clin. 2011;29:663–74.
20. Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med. 2002;30:119–41.
21. Fraser GL, Riker RR, Prato BS, Wilkins ML. The frequency and cost of patient-initiated device removal in the ICU. Pharmacotherapy. 2001;21:1–6.
22. Skoglund K, Enblad P, Marklund N. Effects of the neurological wake-up test on intracranial pressure and cerebral perfusion pressure in brain-injured patients. Neurocrit Care. 2009;11:135–42.
23. Brain TF, American Association of Neurological S, Congress of Neurological S, et al. Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. J Neurotrauma. 2007;24(Suppl 1):S37–44.
24. Citerio G, Cormio M. Sedation in neurointensive care: advances in understanding and practice. Curr Opin Crit Care. 2003;9:120–6.
25. Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursingimplemented sedation protocol on the duration of mechanical ventilation. Crit Care Med. 1999;27:2609–15.
26. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000;342:1471–7.
27. Treggiari MM, Romand JA, Yanez ND, et al. Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med. 2009;37:2527–34.
28. Mehta S, Burry L, Martinez-Motta JC, et al. A randomized trial of daily awakening in critically ill patients managed with a sedation protocol: a pilot trial. Crit Care Med. 2008;36:2092–9.
29. Jones C, Backman C, Capuzzo M, Flaatten H, Rylander C, Griffiths RD. Precipitants of posttraumatic stress disorder following intensive care: a hypothesis generating study of diversity in care. Intensive Care Med. 2007;33:978–85.
30. Hopkins RO, Jackson JC. Long-term neurocognitive function after critical illness. Chest. 2006;130: 869–78.
31. Al MJ, Hakkaart L, Tan SS, Bakker J. Cost-consequence analysis of remifentanil-based analgosedation vs conventional analgesia and sedation for patients on mechanical ventilation in the Netherlands. Crit Care. 2010;14:R195.
32. Evidence-based guidelines for the management of large hemispheric infarction. A Statement for health care professionals from the Neurocritical Care Society and the German Society for Neuro-Intensive Care and Emergency Medicin. Neurocrit Care. 2015;22:146–64.
33. Olson DWM, Thoyre SM. A randomized evaluation of bispectral index-augmented sedation assessment in neurological patients. Neurocrit Care. 2009;11:20–7.
34. Hogarth DK, Hall J. Management of sedation in mechanically ventilated patients. Curr Opin Crit Care. 2004;10(1):40–6.
35. DeJonge B, Cook D, Appere-De-Vecchi C, et al. Using and understanding sedation scoring systems: a systematic review. Intensive Care Med. 2000;26:275–85.
36. Riess ML, Graefe UA, Goeters C, et al. Sedation assessment in critically ill patients with bispectral index. Eur J Anesthesiol. 2002;19:18–22.
37. Klopman MA, Sebel PS. Cost-effectiveness of bispectral index monitoring. Curr Opin Anaesthesiol. 2011;24:177–81.
38. Teitelbaum JS, Ayoub O, Skrobik Y. A critical appraisal of sedation, analgesia and delirium in neurocritical care. Can J Neurol Sci. 2011;38:815–25.
39. Karabinis A, Mandragos K, Stergiopoulos S, et al. Safety and efficacy of analgesia-based sedation with remifentanil versus standard hypnotic-based regimens in intensive care unit patients with brain injuries: a randomised, controlled trial [ISRCTN50308308]. Crit Care. 2004;8:R268–80.
40. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med. 1999;27:1325–9.
41. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166:1338–44.
42. Deogaonkar A, Gupta R, DeGeorgia M, et al. Bispectral Index monitoring correlates with sedation scales in brain-injured patients. Crit Care Med. 2004;32:2403–6.
43. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med. 2001;27:859–64.
44. Van Rompaey B, Elseviers MM, Schuurmans MJ, ShortridgeBaggett LM, Truijen S, Bossaert L. Risk factors for delirium in intensive care patients: a prospective cohort study. Crit Care. 2009;13:R77.
45. Prisco L, Citerio G. To wake-up, or not to wake-up: that is the Hamletic neurocritical care question. Crit Care. 2012;16:190.
46. Skoglund K, Enblad P, Hillered L, Marklund N. The neurological wake-up test increases stress hormone levels in patients with severe traumatic brain injury. Crit Care Med. 2012;40:216–22.
47. Stover JF. Arousal from sedation in wake-up tests requires careful risk stratification. Crit Care Med. 2012;40:338–40.
48. Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA. 2012;308(19):1985–92.

49. Helbok R, Kurtz P, Schmidt MJ, et al. Effects of the neurological wake-up test on clinical examination, intracranial pressure, brain metabolism and brain tissue oxygenation in severely brain-injured patients. Crit Care. 2012;16:R226.
50. Helbok R, Badjatia N. Is daily awakening always safe in severely brain injured patients? Neurocrit Care. 2009;11:133–4.
51. Helbok R, Ko SB, Schmidt JM, Kurtz P, Fernandez L, Choi HA, Connolly ES, Lee K, Badjatia N, Mayer SA, Claassen J. Global cerebral edema and brain metabolism after subarachnoid hemorrhage. Stroke. 2011;42:1534–9.
52. Helbok R, Kurtz P, Schmidt JM, Stuart RM, Fernandez L, Malhotra R, Presciutti M, Ostapkovich ND, Connolly ES, Lee K, Badjatia N, Mayer SA, Claassen J. Effect of mannitol on brain metabolism and tissue oxygenation in severe haemorrhagic stroke. J Neurol Neurosurg Psychiatry. 2011;82:378–83.
53. Hillered L, Vespa PM, Hovda DA. Translational neurochemical research in acute human brain injury: the current status and potential future for cerebral microdialysis. J Neurotrauma. 2005;22:3–41.
54. Vespa PM, Miller C, McArthur D, Eliseo M, Etchepare M, Hirt D, Glenn TC, Martin N, Hovda D. Nonconvulsive electrographic seizures after traumatic brain injury result in a delayed, prolonged increase in intracranial pressure and metabolic crisis. Crit Care Med. 2007;35:2830–6.
55. Vespa PM. Metabolic penumbra in intracerebral hemorrhage. Stroke. 2009;40:1547–8.
56. Vespa P, Bergsneider M, Hattori N, Wu HM, Huang SC, Martin NA, Glenn TC, McArthur DL, Hovda DA. Metabolic crisis without brain ischemia is common after traumatic brain injury: a combined microdialysis and positron emission tomography study. J Cereb Blood Flow Metab. 2005;25:763–74.
57. Oddo M, Frangos S, Maloney-Wilensky E, Andrew Kofke W, Le Roux PD, Levine JM. Effect of shivering on brain tissue oxygenation during induced normothermia in patients with severe brain injury. Neurocrit Care. 2010;12:10–6.
58. Skoglund K, Enblad P, Marklund N. Effects of the neurological wake-up test on intracranial pressure and cerebral perfusion pressure in brain-injured patients. Neurocrit Care. 2009;11:135–42.
59. Karin Skoglund, Lars Hillered, Karlis Purins, et al. The neurological wake-up test does not alter cerebral energy metabolism and oxygenation in patients with severe traumatic brain injury. Neurocrit Care. doi:10.1007/s12028–013–9876-4.
60. Gehlbach BK, Kress JP. Sedation in the intensive care unit. Curr Opin Crit Care. 2002;8:290–8.
61. Kress JP, Pohlman AS, Hall JB. Sedation and analgesia in the intensive care unit. Am J Respir Crit Care Med. 2002;166:1024–8.
62. Ostermann ME, Keenan SP, Seiferling RA, et al. Sedation in the intensive care unit: a systematic review. JAMA. 2000;283:1451–9.
63. Mirski MA, Muffelman B, Ulatowski JA, et al. Sedation for the critically ill neurologic patient. Crit Care Med. 1995;23:2038–53.
64. Prielipp RC, Coursin DB. Sedative and neuromuscular blocking drug use in critically ill patients with head injuries. New Horiz. 1995;3:458–68.
65. Kraus JJ, Metzler MD, Coplin WM. Critical care issues in stroke and subarachnoid hemorrhage. Neurol Res. 2002;24(suppl 1):S47–57.
66. Oertel M, Kelly DF, Lee JH, et al. Metabolic suppressive therapy as a treatment for intracranial hypertension—why it works and when it fails. Acta Neurochir Suppl. 2002;81:69–70.
67. Robertson CS, Cormio M. Cerebral metabolic management. New Horiz. 1995;3:410–22.
68. Clausen T, Bullock R. Medical treatment and neuroprotection in traumatic brain injury. Curr Pharm Des. 2001;7:1517–32.
69. Grasshoff C, Gillessen T. The effect of propofol on increased superoxide concentration in cultured rat cerebrocortical neurons after stimulation of N-methyl-d-aspartate receptors. Anesth Analg. 2002;95:920–2.
70. Starbuck VN, Kay GG, Platenberg RC, et al. Functional magnetic resonance imaging refl ects changes in brain functioning with sedation. Hum Psychopharmacol. 2000;15:613–8.
71. Bladin CF, Alexandrov AV, Bellavance A, et al. Seizure after stroke: a prospective multicenter study. Arch Neurol. 2000;57:1617–22.
72. Reith J, Jorgensen HS, Raaschou HO, et al. Seizure in acute stroke: predictors and prognostic signifi cance. Copenhagen Stroke Study Stroke. 1997;28:1585–9.
73. Vespa PM, Nuwer MR, Nenov V, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. J Neurosurg. 1999;91:750–60.
74. Barr J, Egan TD, Sandoval NF, Zomorodi K, Cohane C, Gambus PL, Shafer SL. Propofol dosing regimens for ICU sedation based upon an integrated pharmacokinetic–pharmacodynamic model. Anesthesiology. 2001;95:324–33.
75. Oshima T, Karasawa F, Satoh T. Effects of propofol on cerebral blood fl ow and the metabolic rate of oxygen in humans. Acta Anaesthesiol Scand. 2002;46(7):831–5.
76. Engelhard K, Werner C. Inhalational or intravenous anesthetics for craniotomies? Pro inhalational. Curr Opin Anaesthesiol. 2006;19:504–8.
77. Trescot AM, Datta S, Lee M, et al. Opioid pharmacology. Pain Physician. 2008;11(2 Suppl):S133–53.
78. Magarey JM. Propofol or midazolam – which is best for the sedation of adult ventilated patients in intensive care units? A systematic review. Aust Crit Care. 2001;14:147–54.
79. Weinbroum AA, Halpern P, Rudick V, et al. Midazolam versus propofol for long-term sedation in the ICU: a randomized prospective comparison. Intensive Care Med. 1997;23:1258–63.
80. Power KN, Flaatten H, Gilhus NE, Engelsen BA. Propofol treatment in adult refractory status epilepticus. Mortality risk and outcome. Epilepsy Res. 2011;94(1–2):53–60.
81. Meierkord H, Boon P, Engelsen B, Göcke K, Shorvon S, Tinuper P, Holtkamp M. European Federation of

Neurological Societies. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol. 2010;17(3):348–55.
82. Marik PE, Varon J. The management of status epilepticus. Chest. 2004;126(2):582–91.
83. Rosow C. Remifentanil: a unique opioid analgesic. Anesthesiology. 1993;79:875–6.
84. Pitsiu M, Wilmer A, Bodenham A, et al. Pharmacokinetics of remifentanil and its major metabolite, remifentanil acid, in ICU patients with renal impairment. Br J Anaesth. 2004;92:493–503.
85. Dumont L, Picard V, Marti RA, et al. Use of remifentanil in a patient with chronic hepatic failure. Br J Anaesth. 1998;81:265–7.
86. Morgan Jones G, Doepker BA, et al. Predictors of severe hypotension in neurocritical care patients sedated with propofol. Neurocrit Care. 2014;20:270–6.
87. Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP. Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. Anesthesiology. 1992;76:725–33.
88. Gonzalez-Correa JA, Cruz-Andreotti E, et al. Effects of propofol on the leukocyte nitric oxide pathway: in vitro and ex vivo studies in surgical patients. Naunyn Schmiedeberg's Arch Pharmacol. 2008;376:331–9.
89. Doursout MF, Joseph PM, Liang YY, Hartley CJ, Chelly JE. Role of propofol and its solvent, intralipid, in nitric oxide-induced peripheral vasodilatation in dogs. Br J Anaesth. 2002;89:492–8.
90. Samain E, Bouillier H, Marty J, Safar M, Dagher G. The effect of propofol on angiotensin II-induced Ca(2+) mobilization in aortic smooth muscle cells from normotensive and hypertensive rats. Anesth Analg. 2000;90:546–52.
91. Roberts DJ, Hall RI, Kramer AH, et al. Sedation for critically ill adults with severe traumatic brain injury: a systematic review of randomized controlled trials. Crit Care Med. 2011;39(12):2743–51.
92. Albanese J, Viviand X, Potie F, et al. Sufentanil and alfafentanil in head trauma patients: a study on cerebral hemodynamics. Crit Care Med. 1999;27(2):407–11.
93. Peeters MY, Bras LJ, DeJongh J, et al. Disease severity is a major determinant for the pharmacodynamics of propofol in critically ill patients. Clin Pharmacol Ther. 2008;83(3):443–51.
94. Engelhard K, Reeker W, Kochs E, et al. Effect of remifentanil on intracranial pres- sure and cerebral blood fl ow velocity in patients with head trauma. Acta Anaesthesiol Scand. 2004;48:396–9.
95. Hanley DF, Pozo M. Treatment of status epilepticus with midazolam in the critical care setting. Int J Clin Pract. 2000;54:30–5.
96. Walder B, Tramer MR, Seeck M. Seizure-like phenomena and propofol: a systematic review. Neurology. 2002;58:1327–32.
97. Iyer VN, Hoel R, Rabinstein AA. Propofol infusion syndrome in patients with refractory status epilepticus: an 11-year clinical experience. Crit Care Med. 2009;37:3024–30.
98. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA. 2012;307:1151–60.
99. Yahwak JA, Riker RR, Fraser GL, Subak-Sharpe S. Determination of a lorazepam dose threshold for using the osmol gap to monitor for propylene glycol toxicity. Pharmacotherapy. 2008;28:984–91.
100. Horinek EL, Kiser TH, Fish DN, MacLaren R. Propylene glycol accumulation in critically ill patients receiving continuous intravenous lorazepam infusions. Ann Pharmacother. 2009;43:1964–71.
101. Grof TM, Bledsoe KA. Evaluating the use of dexmedetomidine in neurocritical care patients. Neurocrit Care. 2010;12:356–61.
102. Chen HI, Malhotra NR, Oddo M, Heuer GG, Levine JM, LeRoux PD. Barbiturate infusion for intractable intracranial hypertension and its effect on brain oxygenation. Neurosurgery. 2008;63:880–6.
103. Marshall GT, James RF, Landman MP, et al. Pentobarbital coma for refractory intra-cranial hypertension after severe traumatic brain injury: mortality predictions and one-year outcomes in 55 patients. J Trauma. 2010;69:275–83.
104. Bekker A, Sturaitis MK. Dexmedetomidine for neurological surgery. Neurosurgery. 2005;57:1–10.
105. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg. 2000;90:699–705.
106. Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg. 2004;98:153–8.
107. Venn RM, Bradshaw CJ, Spencer R, et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia. 1999;54:1136–42.
108. Prielipp RC, Wall MH, Tobin JR, et al. Dexmedetomidineinduced sedation in volunteers decreases regional and global cerebral blood flow. Anesth Analg. 2002;95:1052–9.
109. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301:489–99.
110. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA. 2007;298:2644–53.
111. Venn RM, Bryant A, Hall GM, Grounds RM. Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit. Br J Anaesth. 2001;86:650–6.
112. Aho M, Lehtinen AM, Erkola O, Kallio A, Korttila K. The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. Anesthesiology. 1991;74:997–1002.

113. Kamibayashi T, Maze M. Clinical uses of alpha2-adrenergic agonists. Anesthesiology. 2000;93:1345–9.
114. Herr DL, Sum-Ping ST, England M. ICU sedation after coronary artery bypass graft surgery: dexmedetomidine-based versus propofol-based sedation regimens. J Cardiothorac Vasc Anesth. 2003;17:576–84.
115. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, Rocha MG. SEDCOM (Safety and Effi cacy of Dexmedetomidine Compared With Midazolam) Study Group: Dexmedetomidine vs. midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301:11.
116. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR, Takala J. Dexmedetomidine for Long-Term Sedation Investigators: Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA. 2012;307:10.
117. Ledingham IMA, Watt I. Infl uence of sedation on mortality in critically ill multiple trauma patients. Lancet. 1983;1:1270.
118. Albert SG, Ariyan S, Rather A. The eff ect of etomidate on adrenal function in critical illness: a systematic review. Intensive Care Med. 2011;37:901–10.
119. Martin J, Heymann A, Basell K, et al. Evidence and consensus-based German guidelines for the management of analgesia, sedation and delirium in intensive care–short version. Ger Med Sci. 2010;8:Doc02.
120. Millane TA, Bennet ED, Grounds RM. Isoflurane and propofol for long-term sedation in the intensive care unit a crossover study. Anaesthesia. 1992;47:768–74.
121. Spencer EM, Willatts SM. Isoflurane for prolonged sedation in the intensive care unit; efficacy and safety. Intensive Care Med. 1992;18:415–21.
122. Meiser A, Sirtl C, Bellgardt M, Lohmann S, Garthoff A, Kaiser J, Hügler P, Laubenthal HJ. Desflurane compared with propofol for postoperative sedation in the intensive care unit. Br J Anaesth. 2003;90:273–80.
123. Halpenny D. Sevoflurane sedation. Can J Anaesth. 2000;47:193–4.
124. Ibrahim AE, Ghoneim MM, Kharasch ED, et al. Sevoflurane sedation Study Group. Speed of recovery and side-effect profile of sevoflurane sedation compared with midazolam. Anesthesiology. 2001;94:87–94.
125. Kong KL, Willatts SM, Prys-Roberts C. Isoflurane compared with midazolam for sedation in the intensive care unit. BMJ. 1989;298:1277–80.
126. Johnston RG, Noseworthy TW, Friesen EG, Yule HA, Shustack A. Isoflurane therapy for status asthmaticus in children and adults. Chest. 1990;97:698–701.
127. Kong KL. Inhalational anesthetics in the intensive care unit. Crit Care Clin. 1995; 11:887–902 97.
128. Bedi A, Murray JM, Dingley J, et al. Use of xenon as a sedative for patients receiving critical care. Crit Care Med. 2003;31:2470–7.
129. Meiser ALH. Inhalational anaesthetics in the ICU: theory and practice of inhalational sedation in the ICU, economics, risk-benefit. Best Pract Res Clin Anaesthesiol. 2005;19:523–38.
130. Sackey PVMC, Granath F, Radell PJ. Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device. Crit Care Med. 2004;32:2241–6.
131. Hanafy M. Clinical evaluation of inhalational sedation following coronary artery bypass grafting. Egypt J Anaesth. 2005;21:237–2.
132. Bundgaard H, von Oettingen G, Larsen KM, Landsfeldt U, Jensen KA, Nielsen E, Cold GE. Effects of sevoflurane on intracranial pressure, cerebral blood flow and cerebral metabolism. A dose-response study in patients subjected to craniotomy for cerebral tumours. Acta Anaesthesiol Scand. 1998;42:621–7.
133. Kalenka A, Gross B, Isoflurane MH. Anesthesia Elicits Protein Pattern Changes in Rat Hippocampus. J Neurosurg Anesthesiol. 2010;22:144–54.
134. Tanzi RE, Bertram L. Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. Cell. 2005;120:545–55.
135. Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. Physiol Rev. 2001;81:741–66.
136. Eckenhoff RG, Johansson JS, Wei H, Carnini A, Kang B, Wei W. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. Anesthesiology. 2004;101:703–9.
137. Pidikiti R, Keller JM, Eckenhoff MF. Anesthesiology. 2004;101:703–9.
138. Xie Z, Dong Y, Maeda U, Alfille P, Culley DJ, Crosby G, Tanzi RE. Anesthesiology. 2006;104:988–94.
139. Xie Z, Dong Y, Maeda U, Moir R, Inouye SK, Culley DJ, Crosby G, Tanzi RE. Isoflurane-induced apoptosis: a potential pathogenic link between delirium and dementia. J Gerontol A Biol Sci Med Sci. 2006;61:1300–6.
140. McAuliffe JJ, Joseph B, Vorhees CV. Isoflurane-delayed preconditioning reduces immediate mortality and improves striatal function in adult mice after neonatal hypoxia-ischemia. Anesth Analg. 2007;104:1066–77.
141. Clarkson AN. Anesthetic-mediated protection/preconditioning during cerebral ischemia. Life Sci. 2007;80:1157–75.
142. Kitano H, Kirsch JR, Hurn PD, et al. Inhalational anesthetics as neuroprotectants or chemical preconditioning agents in ischemic brain. J Cereb Blood Flow Metab. 2007;27:1108–28.
143. Wang L, Traystman RJ, Murphy SJ. Inhalational anesthetics as preconditioning agents in ischemic brain. Curr Opin Pharmacol. 2008;8:104–10.
144. Zhang HP, Yuan LB, Zhao RN, et al. Isoflurane preconditioning induces neuroprotection by attenuating ubiquitin-conjugated protein aggregation in a mouse model of transient global cerebral ischemia. Anesth Analg. 2010;111:506–14.
145. Zhu W, Wang L, Zhang L, et al. Isoflurane preconditioning neuroprotection in experimental focal stroke

is androgen-dependent in male mice. Neuroscience. 2010;169:758–69.
146. Kitano H, Young JM, Cheng J, et al. Genderspecific response to isoflurane preconditioning in focal cerebral ischemia. J Cereb Blood Flow Metab. 2007;27:1377–86.
147. Zhao H. Ischemic postconditioning as a novel avenue to protect against brain injury after stroke. J Cereb Blood Flow Metab. 2009;29:873–85.
148. Lee JJ, Li L, Jung HH, Zuo Z. Postconditioning with isoflurane reduced ischemia-induced brain injury in rats. Anesthesiology. 2008;108:1055–62.
149. Wang JK, Yu LN, Zhang FJ, Yang MJ, Yu J, Yan M, Chen G. Postconditioning with sevofluorane protects against focal cerebral ischemia and reperfusion injury via PI3K/Akt pathway. Brain Res. 2010;1357:142–51.
150. Xie Z, Dong Y, Maeda U, Moir RD, Xia RE. The inhalation anesthetic isoflurane induces a vicious cycle of apoptosis and amyloid beta-protein accumulation. J Neurosci. 2007;27:1247–54.
151. Xing B, Chen H, Zhang M, Zhao D, Jiang R, Liu X, Zhang S. Ischemic postconditioning inhibits apoptosis after focal cerebral ischemia/reperfusion injury in the rat. Stroke. 2008;39:2362–9.
152. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci. 2003;23:876–82.
153. Bin Zhang, Yuanlin Dong. The inhalation anesthetic desflurane induces caspase activation and increases amyloid β-protein levels under hypoxic conditions. J Biol Chem. 283(18):11866–75.
154. Canas P, Velly L, Labrande C, Guillet B, Sautou-Miranda V, Masmejean F, Nieoullon A, Gouin F, Bruder N, Pisano P. Sevoflurane protects rat mixed cerebrocortical neuronal glial cell cultures against transient oxygen-glucose deprivation:Involvement of glutamate uptake and reactive oxygen species. Anesthesiology. 2006;105:990–8.
155. Purrucker JC, Renzland J, Uhlmann L. Volatile sedation with sevoflurane in intensive care patients with acute stroke or subarachnoid haemorrhage using AnaConDa®: an observational study. Br J Anaesth. 2015;114(6):934–43.
156. Gray JJ, Bickler PE, Fahlman CS, Zhan X, Schuyler JA. Isoflurane neuroprotection in hypoxic hippocampal slice cultures involves increases in intracellular Ca2? and mitogen-activated protein kinases. Anesthesiology. 2005;102:606–15.
157. Kapinya KJ, Prass K, Dirnagl U. Isoflurane induced prolonged protection against cerebral ischemia in mice: a redox sensitive mechanism? Neuroreport. 2002;13:1431–5.
158. Engelhard K, Werner C, Reeker W, Lu H, Mollenberg O, Mielke L, Kochs E. Desflurane and isoflurane improve neurological outcome after incomplete cerebral ischaemia in rats. Br J Anaesth. 1999;83:415–21.
159. Sakai H, Sheng H, Yates RB, Ishida K, Pearlstein RD, Warner DS. Isoflurane provides long-term protection against focal cerebral ischemia in the rat. Anesthesiology. 2007;106:92–9. (discussion 98–10)
160. Kitano H, Kirsch JR, Hurn PD, Murphy SJ. Inhalational anesthetics as neuroprotectants or chemical preconditioning agents in ischemic brain. J Cereb Blood Flow Metab. 2007;27:1108–28.
161. Fugate JE, Burns JD, Wijdicks EF, Warner DO, Jankowski CJ, Rabinstein AA. Prolonged high-dose isoflurane for refractory status epilepticus: is it safe? Anesth Analg. 2010;111:1520–4.
162. Kellow NH, Scott AD, White SA, Feneck RO. Comparison of the effects of propofol and isoflurane anaesthesia on right ventricular function and shunt fraction during thoracic surgery. Br J Anaesth. 1995;75:578–82.
163. Tayefeh F, Larson MD, Sessler DI, Eger 2nd EI, Bowland T. Timedependent changes in heart rate and pupil size during desflurane or sevoflurane anesthesia. Anesth Analg. 1997;85:1362–6.
164. Bösel J, Purrucker JC, Nowak F, Renzland J, Schiller P, Pérez EB, Poli S, Brunn B, Hacke W, Steiner T. Volatile isoflurane sedation in cerebrovascular intensive care patients using AnaConDa(®): effects on cerebral oxygenation, circulation, and pressure. Intensive Care Med. 2012;38:1955–64.
165. Villa F, Iacca C, Molinari AF, Giussani C, Aletti G, Pesenti A, Citerio G. Inhalation versus endovenous sedation in subarachnoid hemorrhage patients: effects on regional cerebral blood flow. Crit Care Med. 2012;40(10):2797–804.
166. Faraci FM, Heistad DD. Regulation of large cerebral arteries and cerebral microvascular pressure. Circ Res. 1990;66:8–17.
167. Nishimura N, Schaffer CB, Friedman B, et al. Penetrating arterioles are a bottleneck in the perfusion of neocortex. Proc Natl Acad Sci U S A. 2007;104:365–70.
168. Nystoriak MA, O'Connor KP, Sonkusare SK, et al. Fundamental increase in pressuredependent constriction of brain parenchymal arterioles from subarachnoid hemorrhage model rats due to membrane depolarization. Am J Physiol Heart Circ Physiol. 2011;300:H803–12.
169. Park IS, Meno JR, Witt CE, et al. Impairment of intracerebral arteriole dilation responses after subarachnoid hemorrhage. Laboratory investigation. J Neurosurg. 2009;111:1008–13.
170. Ohkuma H, Manabe H, Tanaka M, et al. Impact of cerebral microcirculatory changes on cerebral blood flow during cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke. 2000;31:1621–7.
171. Park KW, Metais C, Dai HB, et al. Microvascular endothelial dysfunction and its mechanism in a rat model of subarachnoid hemorrhage. Anesth Analg. 2001;92:990–6.
172. Federico Villa MD. Cosimo Iacca. inhalation versus endovenous sedation in subarachnoid hemorrhage patients: effects on regional cerebral blood flow. Crit Care Med. 2012;40:2797–804.

24 Transcranial Doppler and Transcranial Color-Coded Duplex Sonography

Chiara Robba and Andrea Rigamonti

24.1 Basic Principles of Transcranial Doppler

Transcranial Doppler (TCD) ultrasonography was first described by Aaslid and collaborators in 1982 [1]. It is a noninvasive technique able to monitor dynamics of cerebral blood flow (CBF) and vessel pulsatility in the basal cerebral arteries, such as middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA) (Fig. 24.1).

TCD technique is based on the phenomenon described by the physicist Christian Andreas Doppler in the nineteenth century, called Doppler Effect. According to this principle, when a sound wave with a certain frequency strikes a moving object (such as red blood cell inside an insonated artery), it is reflected with a different frequency, the Doppler shift, fd, which is directly proportional to the velocity of the object (V). Echoes received by the ultrasound (US) probe are processed to produce a spectral waveform with peak systolic velocity and diastolic velocity values (Fig. 24.2).

$$V = \frac{(c \times fd)}{2 \times f0 \times \cos\theta}$$

(c is the speed of the incident wave, $f0$ is the incident pulse frequency, and θ is the angle of the reflector relative to the US probe).

The spectral waveform is then processed and combined with indices derived from cerebral blood flow velocity (FV) (such as Gosling's and spectral pulsatility index) allowing the calculation of secondary indices (including autoregulation, critical closing pressure (CrCP), noninvasive intracranial pressure [ICP]) useful for the analysis of cerebral hemodynamics.

The main obstacle to vessel insonation and ultrasound penetration of the skull is the bone. Therefore, TCD is performed through acoustic windows representing specific points of the skull where the bone is thin enough to allow ultrasound waves to penetrate.

The equipment used is a duplex US color flow mapper. The probe is either a sector or phased array cardiac or dedicated probe with a small imaging footprint and a Doppler frequency of 1.8 or 2 MHz.

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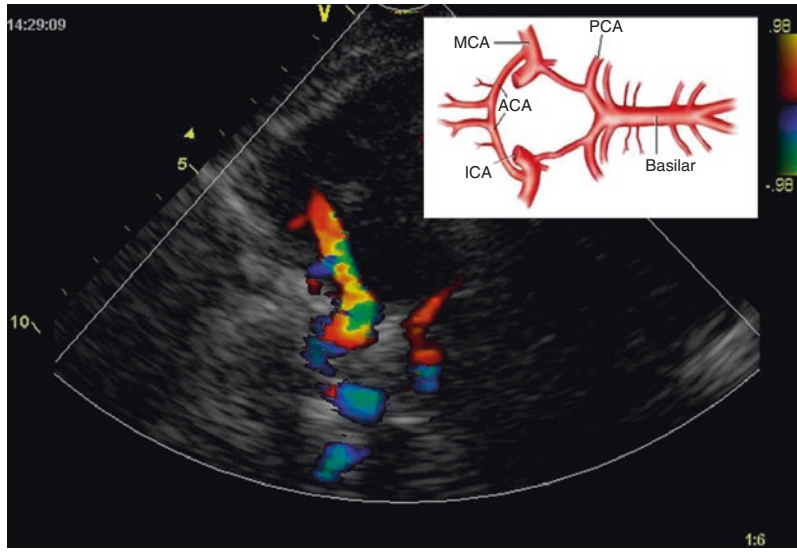


Fig. 24.1 Typical transcranial color-coded duplex sonography (TCCS) view of the circle of Willis

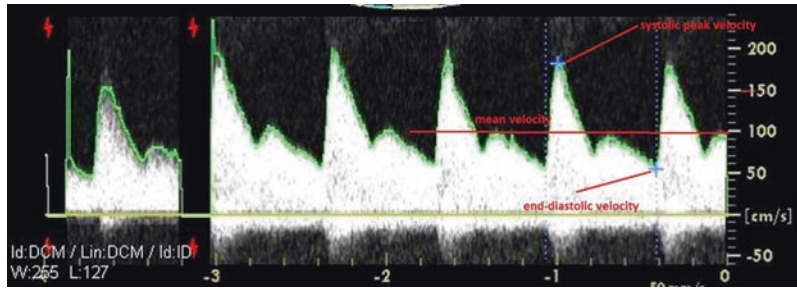


Fig. 24.2 Spectral waveform highlighting the peak systolic and the diastolic velocity values

24.2 Acoustic Windows

The acoustic windows used to insonate the vessels are transtemporal, suboccipital, transorbital, and retromandibular (Fig. 24.3). The temporal window is the most commonly used for the insonation of the MCA (responsible for the 75% of the brain blood flow and it is the vessel of choice for most of the TCD derived signals), ACA, and PCA (Fig. 24.4). The posterior circulation, in particular terminal segments of the vertebral and basilar arteries, can be visualized via the suboccipital (transforaminal) window. Transorbital examination allows the insonation of the ophthalmic arteries and carotid siphons, as well as the measurement of the optic nerve sheath diameters [2]. In patients with subarachnoid hemorrhage (SAH) and suspect of vasospasm, a submandibular approach can be used to insonate the extracranial portion of the internal carotid artery (ICA) to calculate the mean flow velocity ratio between the MCA and ICA (Lindegaard index). Finally, in newborns, open fontanelles provide a good acoustic window to the intracranial circulation; internal carotid vessels and the branches of the circle of Willis can be insonated through the anterior fontanelle in sagittal and coronal planes [3].

The identification of each intracranial vessel is based on the depth of signal capture, velocity and direction of the vessel, possibility of following

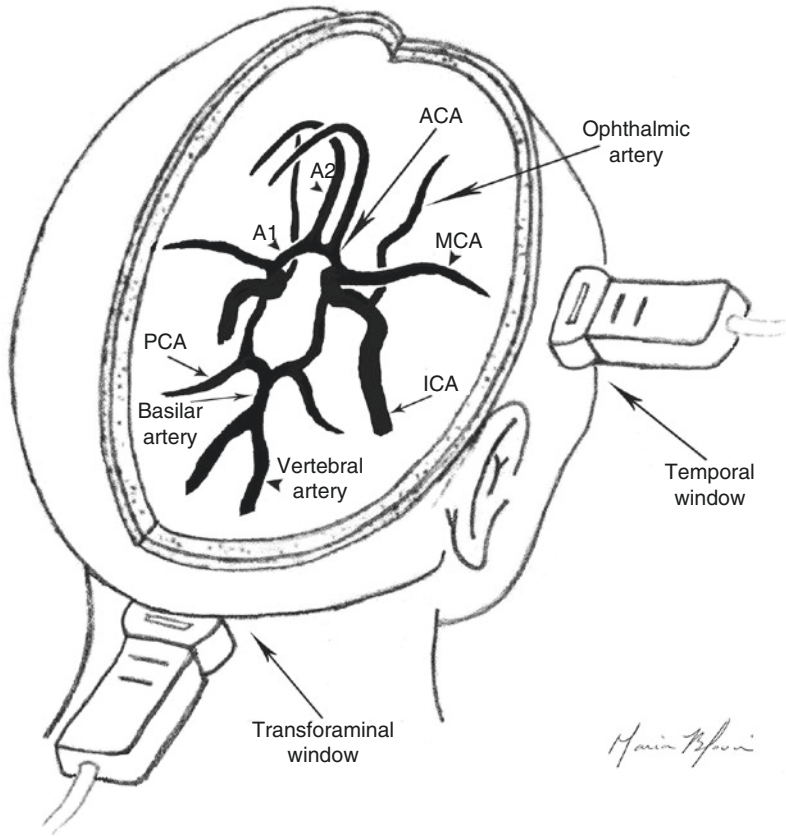


Fig. 24.3 Transtemporal and suboccipital (or transforaminal) windows and vascular cerebral anatomy (Courtesy of Maria Blouin)

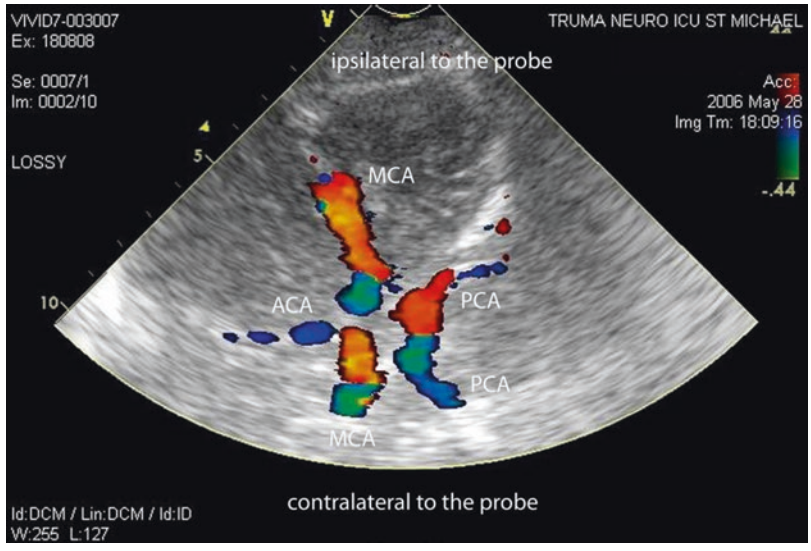


Fig. 24.4 Typical view through the temporal window

Table 24.1 Normal values of flow velocities of the main cerebral vessels detected by transcranial doppler in adults

	Acoustic window	Mean FV (cm/s)	Depth (mm)	Direction of flow
MCA	Transtemporal	55 ± 12	30–65	Toward
ACA	Transtemporal	50 ± 11	60–75	Away
PCA	Transtemporal	40 ± 10	60–70	Toward (P1), Away (P2)
BA	Occipital	41 ± 10	80–120	Away
VA	Occipital	38 ± 10	60–75	Away
OA	Transorbital	21 ± 5	45–55	Toward
ICA	Retromandibular	30 ± 9	45–50	Away

Abbreviations: MCA middle cerebral artery, *ACA* anterior cerebral artery, *PCA* posterior cerebral artery, *BA* basilar artery, *VA* vertebral artery, *OA* ophthalmic artery, *ICA* internal carotid artery

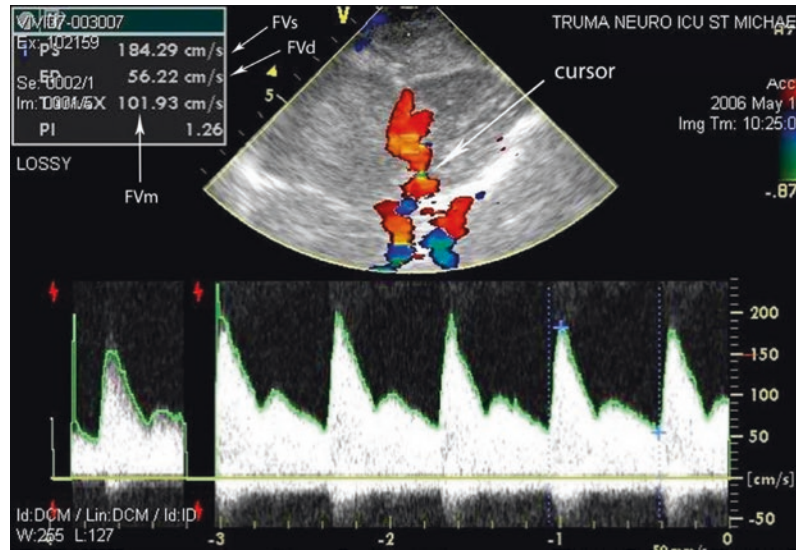


Fig. 24.5 Systolic (FVs), diastolic (FVd), and mean (FVm) flow velocities generated by spectral analysis

the vessel its whole length and anatomical relationship with other vessels (Table 24.1).

Transcranial color-duplex sonography (TCCS) combines pulsed-wave Doppler with two-dimensional, real-time B mode imaging. It allows the direct visualization of basal cerebral arteries anatomy; therefore, it allows precise placement of the Doppler sample volume in the vessel. Compared to conventional TCD, TCCS is more reliable and accurate.

24.3 TCD-Derived Signals

The processing of the echoes received by the US probe produces a spectral waveform. Systolic (FVs), diastolic (FVd), and mean (FVm) flow velocities will be then generated by the analysis of the waveform (Fig. 24.5).

Pulsatility index (PI) is a TCD-derived parameter able to provide information about cerebral vascular resistance and changes in the morphology of the TCD waveform resulting from cerebral perfusion pressure (CPP) changes.

Mathematically, PI is calculated as the relationship between the difference of FVs and FVd divided by mean flow velocity (FVm) [4] (Figs. 24.6 and 24.7)

$$PI = \frac{FVs - FVd}{FVm}$$

PI has been widely investigated as noninvasive estimator of ICP. Some authors demonstrated that ICP and PI are positively correlated during

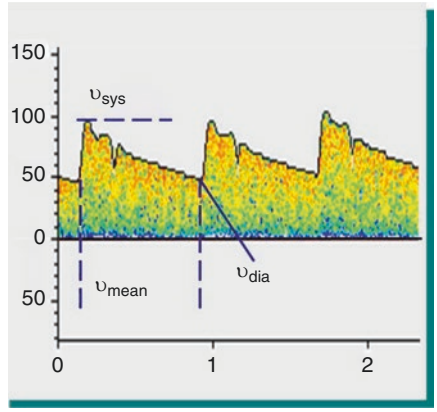


Fig. 24.6 Pulsatility index (PI) and resistivity index (RI)

Pulsatility index (gosling)

$$PI = \frac{FV_s - FV_d}{FV_m}$$

Resistivity index (pourcelot)

$$PI = \frac{FV_s - FV_d}{FV_m}$$

Both indices tend to increase with age

Fig. 24.7 Normal and abnormal PI

Pulsatility index

- **PI < 0.5 – Below normal resistance**
  May suggest a proximal narrowing / occlusin or an artero-venous malformation
- **0.5 < PI < 1.0 – Normal resistance**
- **1.1 < PI < 1.5 – Above normal resistance**
- **PI > 1.5 – Abnormal resistance**
  PIs > 1.1 may be caused by a distal occlusion.When blood flow hits the occlusion it causes flow to stop abruptly. The result is a decrease in diastolic flow or a reversal of flow in early diastole and little or no flow in late diastole. Arterial constriction 9i.e. vasospasm) will also cause PL to elevate

increases of ICP [5], demonstrating a strong correlation coefficient with invasively measured ICP ($R = 0.94$ $p < 0.05$) [6]. However, other authors found less positive results finding a weak correlation between PI and ICP [6, 7]. However, PI is not specific for increase in ICP. When a drop in CPP occurs, PI presents an increasing trend, which can be related to increases in ICP but also to decreases in cerebrovascular resistance (CVR). Similarly, during hypocapnia, both CVR and PI increase significantly [8]. Many studies have supported the idea that PI can reflect distal CVR, attributing greater PI to higher CVR [9].

However, experimental data showed that hypercapnia can cause a decrease in both CVR and PI while a reduction in CPP with intact autoregulation induces a decrease in CVR but an increase in PI [10]; therefore, PI is dependent on numerous factors, including ICP, ABP, on CPP and vascular tone (consequently CO_2).

In summary, changes in PI are correlated to changes both in ICP and ABP. Although a few manuscripts favor PI as a surrogate ICP, the sensitivity of PI to identify raised ICP is high, but its specificity is low.

24.4 Cerebral Blood Flow

Under normal conditions, FV is proportional to the cerebral blood flow (CBF). Although TCD is not appropriate to yield an absolute value of CBF, changes over time in FV are related to changes in CBF. Therefore, since TCD gives a quantitative

measurement of FVs, the measurement of changes in FV provides a quantitative measurement of changes in CBF.

TCD-derived cerebral blood FVs are commonly measured in clinical and experimental environment. The simultaneous monitoring of these signals as well as intracranial pressure (ICP) and arterial blood pressure (ABP) can give valuable information regarding the state of cerebral hemodynamics in different intracranial pathologies. Through the analysis of TCD waveform, many authors attempted to investigate the relationship between the cerebral blood flow (CBF) and cerebrospinal fluid (CSF) dynamics, proposing several mathematical and hydrodynamic models [12–14].

24.5 Anesthetic Agents and Intracranial Blood Flow Velocity

24.5.1 Volatile Agents

Cerebral vasodilatory effects of volatile agents have been extensively studied [11]; according to most authors, the vasodilatory effect of volatile agents on cerebral vessels is dose dependent and less evident with sevoflurane when compared with other inhalational agents [12]. Conversely, propofol is not associated with a significant modification of cerebral hemodynamics and demonstrates possible avoidance of the undesirable effects in brain-injured patients [13, 14].

During general anesthesia, in patients without neurological disease, the cerebrovascular autoregulation seems to be maintained between 0.5 and 1.0 minimum alveolar concentration (MAC) of sevoflurane, although the autoregulation is slightly impaired with MAC above 1.0. However, some authors suggested that cerebral autoregulation is maintained even with higher MAC (1.2 and 1.5 MAC) [15]. Compared to sevoflurane, the use of halothane [16] is associated with lower vessel resistance and higher mean flow velocity during general anesthesia. The effect of isoflurane on cerebral FVs however is discordant [17, 18]. Many authors consider the use of isoflurane [24] on cerebral hemodynamics as safe; however, Nishiyama et al. [25] compared cerebrovascular carbon dioxide reactivity assessed through TCD during general anesthesia with sevoflurane and isoflurane in patients without known cerebral disease and found that FV was significantly lower in the isoflurane group at PCO_2 = 20–40 mm Hg than in the sevoflurane group. Moreover, they found that the rate of change in cerebral blood flow caused by variations of CO_2 tension was greater during the administration of isoflurane anesthesia compared with sevoflurane.

Holmström et al. [19] assessed the dose-dependent vasodilatory effects at hypocapnia of desflurane, sevoflurane, and isoflurane administered in a randomized order at 0.5 and 1.0 MAC in a pig experimental model. Cerebral and systemic variables were recorded at two different levels of CO_2 (normocapnia vs. hypocapnia). At 0.5 MAC, all the agents had similar effects on CBF at hypocapnia. However, the authors found a more pronounced cerebral vasodilation at hypocapnia with higher doses of desflurane than with sevoflurane or isoflurane, concluding that desflurane might be less suitable than other agents in neurosurgical procedures.

Among volatile agents, sevoflurane seems to have the least effect on middle cerebral artery blood flow velocities; however, it has shown to determinate a reduction in cerebrovascular carbon dioxide reactivity at and above CO_2 of 45 mm Hg at 1.0 and 1.5 MAC, which is even reduced with the addition of nitrous oxide [20].

The addition of nitrous oxide can also determinate significant increase in CBF and reduction in autoregulatory indices and needs to be avoided [21].

24.5.2 Intravenous Anesthetics

Intravenous anesthesia is considered the technique of choice for neurosurgical procedures since, compared to inhalation technique, is associated with less pronounced vasodilating effect on cerebral vessels [22].

However, investigations comparing the cerebral hemodynamic effects during inhalation or intravenous anesthesia are conflicting.

Recent findings confirm that the use of sevoflurane, compared to propofol sedation, can decrease more significantly MAP and CPP in neurocritical care population, with consequent ICP increases [23]. However, Marval et al. [24] found that estimated CPP (eCPP), calculated using an established formula, decreased significantly in the propofol group (median, from 58 to 41 mm Hg) but not in the sevoflurane group (from 60 to 62 mm Hg) in 23 healthy patients undergoing non-neurosurgical procedures monitored with TCD.

Finally, some authors demonstrated [25] that, in patients undergoing intracranial tumors resection, cerebral blood flow velocity was not significantly different between sevoflurane- and propofol-anesthetized patients at the comparable depth of anesthesia, suggesting a role of inhalation anesthesia in neurosurgical procedures.

Propofol is the intravenous anesthetic drug of choice and it is commonly used as a first-line therapy for sedation and control of intracranial pressure in head-injured patients. Compared to thiopental, the use of propofol during electroconvulsive therapy resulted in minor cerebral blood flow velocity changes [26].

Steiner et al. [27] examined the effect of increasing propofol plasmatic concentration on pressure autoregulation in head-injured patients. They administered norepinephrine to achieve CPP of 70 and 85 mm Hg at each different propofol concentration. The authors found that at high propofol concentration TCD-derived flow velocities were significantly lower than at the moderate concentration, but that autoregulation was impaired. In their study, Steiner et al. therefore demonstrated that the cerebrovascular effects of propofol in head-injured patients are different from those observed in healthy individuals, and large doses of propofol should be used cautiously in this group of patients.

Opioids are frequently used in patients with cerebral injury despite clinical reports suggest that these compounds may increase ICP. Some authors suggest that fentanyl and sufentanil can elevate ICP [28]. However, increases in ICP along with infusion of opioids are generally associated with decreases in MAP, and a rise in ICP is related to autoregulatory vasodilation and increased cerebral blood volume secondary to systemic hypotension.

Indeed, de Nadal et al. demonstrated that morphine and fentanyl transiently increase ICP in response to ABP decrease in patients with preserved and impaired cerebrovascular autoregulation but induced no significant variations in CBF estimated by TCD sonography. [29]

24.6 Transcranial Doppler Ultrasonography in Neurocritical Care Monitoring

TCD presents a wide range of clinical application in the neurointensive care settings (Table 24.2).

24.6.1 Non-invasive ICP and CPP Assessment

Monitoring and targeted management of ICP and CPP are widely advocated for patients with severe head injuries as intracranial hypertension is an important cause of morbidity and mortality [30]. Therefore, ICP and CPP evaluation is crucial in many neurological diseases such as traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), and stroke [31].

The gold standard for ICP measurement is invasive. However, invasive ICP monitoring is associated with a wide range of possible complications including infection and hemorrhage [32]; therefore, a noninvasive measurement of ICP can be invaluable in the management of many neurological patients [33]. TCD is one possible tool to assess noninvasive ICP (nICP) and CPP, as increased ICP produces specific changes in cerebral blood FV, with diastolic FV being particularly sensitive [10].

Gosling pulsatility index (gPI) is one of the first measures derived from the TCD waveform that has been studied to assess ICP (Fig. 24.7),

Table 24.2 Clinical applications of transcranial Doppler

Traumatic brain injury	Noninvasive ICP and CPP estimation
	Autoregulation
	Compliance and cerebrovascular dynamics
SAH (Aneurysms and AVM)	Vasospasm
	Autoregulation
Stroke	Diagnosis and treatment of ischemic stroke
Hydrocephalus	Infusion study and cerebral reserve and compliance
	Noninvasive ICP and CPP
Brain death	Diagnosis of brain death
Sickle cell disease	Risk from a spectrum of brain injuries that include subclinical infarction, acute stroke and hemorrhage; screening of children between 2- and 6-years old is recommended on a 6–12 monthly basis, involving measurement of the time-averaged mean FV in bilateral MCA, bifurcation, distal ICA, ACA, PCA, and BA
Right to left CARDIAC shunt	Evaluation of paradoxical embolism through right to left cardiopulmonary shunts (e.g., patent foramen ovale)
Central nervous system infections	Noninvasive ICP and cerebrovascular dynamic
Peri-procedural/operative	Autoregulation Noninvasive ICP and CPP
Liver failure and Hepatic encephalopathy	Noninvasive ICP estimation and prognosis for acute liver failure
Preeclampsia	Assessment of autoregulation and FV as prognostic for preeclampsia
Sepsis	Assessing cerebral perfusion changes in septic patients as risk of sepsis-associated encephalopathy

but reports on its usefulness for predicting ICP and CPP are discordant [6, 8].

Bellner [6] found a significant correlation (R = 0.94, $p < 0.0001$) between ICP and PI but other authors found weak correlation between PI and ICP [9]. Some other studies proposed methods based on the primarily intended calculation of noninvasive cerebral perfusion pressure (nCPP), and secondarily calculating noninvasive ICP based on the assumption that nICP = ABP – nCPP [42, 43].

Czosnyka et al. [34] proposed a similar but modified formula for estimation of CPP and demonstrated that the correlation between noninvasive CPP (nCPP) and measured CPP was 0.73 ($p < 10^{-6}$). The absolute difference between real CPP and nCPP was less than 10 mm Hg in 89% of measurements and less than 13 mm Hg in 92% of measurements.

Recently, Varsos et al. proposed a method to estimate CPP based on critical closing pressure (CrCP) which represents a threshold of ABP, below which the blood pressure in the brain vasculature is inadequate to prevent the collapse and cessation of blood flow [35]. The authors found a good correlation between nCPP and measured CPP (R = 0.85, $p < 0.001$), with a mean (±SD) difference of 4.02 ± 6.01 mmHg. In 83.3% of the cases, the estimation error was below 10 mmHg.

In summary, there is a considerable variability in the results from studies assessing the accuracy of TCD in the detection of ICP and CPP. None of these methods seem to be accurate enough to be used as a replacement for invasive ICP measurement, but TCD can still be useful in many situations, including when the patient presents contraindication for the insertion or invasive ICP monitoring or when the indications for ICP are not met (Fig. 24.8).

24.6.2 Vasospasm and SAH

Aneurysmal subarachnoid hemorrhage (aSAH) occurs with an incidence of 6–10 per 100,000 cases per years [36] and represents an important cause of morbidity and mortality.

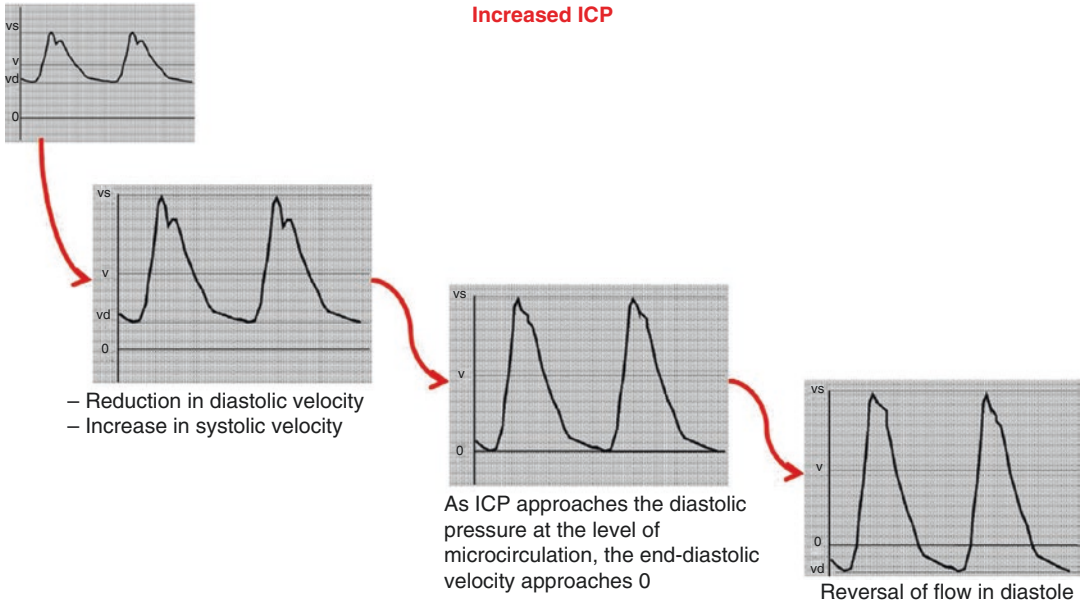


Fig. 24.8 How increased may affect cerebral blood flow velocities as demonstrated by TCCS

Table 24.3 Grading of vasospasm

Vasospasm of the MCA	FVm (cm/s)
Mild (<25% narrowing)	<120
Moderate (25–50% narrowing)	120–200
Severe (>50% narrowing)	>200

Abbreviations: MCA middle cerebral artery, *FVm* mean flow velocity

Vasospasm after aSAH is another important cause of mortality and morbidity. It usually occurs 3–14 days following aSAH, and it is known to be one of the causes leading to new ischemic neurological deficits [37]. Despite angiography still being the gold standard for the detection of vasospasm, TCD can be used for the assessment and detection of vasospasm after aSAH [38] as the constriction of the cerebral vessels leads to an increase of the cerebral blood flow velocities.

TCD has a good ability in the prediction of vasospasm. In particular, mean flow velocity >120 cm/s on the MCA was found to have a specificity of 72% and sensitivity of 88% for angiographic vasospasm (Table 24.3) [39].

The Lindegaard ratio (LR) is a TCD-derived index which is normally used to differentiate between the increase in FV related to systemic hyperdynamic flow and the increase secondary to vasospasm, by comparing intra-extra cranial blood flow velocities.

LR is calculated according to the following formula:

$$LR = \frac{MCA\,MFV}{\text{extracranial}\,ICA\,MFV}$$

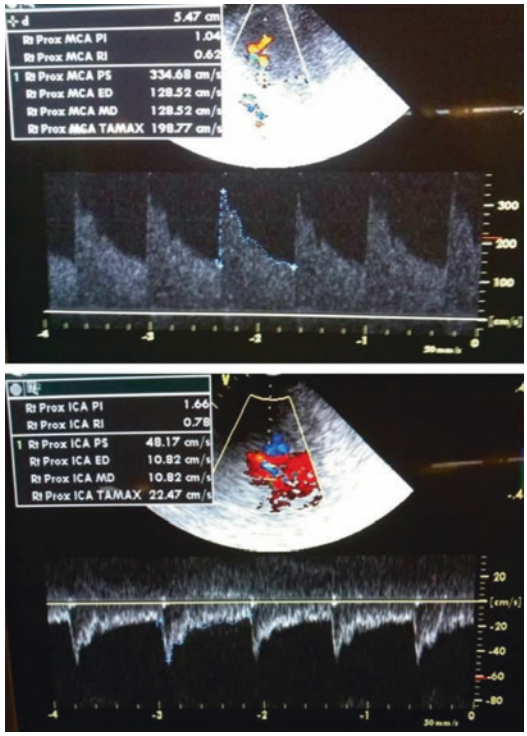
When increased flow velocity is related to hyperemia, it affects both intracranial and extracranial portion of the ICA (LR < 3); when vasospasm is the cause of increased flow velocity, the extracranial portion of the ICA is unaffected and LR is >3 (Fig. 24.9). In the posterior circulation, a modified LI is generally used with a value >2 as threshold to indicate vasospasm [40]:

Modified LR = BA (FVm)/VA (FVm).

An approach to the interpretation of the flow velocities and the Lindegaard index in the context of vasospasm is presented in Fig. 24.10.

24.6.3 Autoregulation

Cerebral autoregulation is the intrinsic ability of the brain to maintain a stable CBF despite



Lindegaard index

$$LI = \frac{FV_{MCA}}{FV_{eclCA}}$$

- The Lindegaard ration helps determine whether the increase in MCA velocity is due to vasospasm or due to hyper – dynamic flow

- 3.00 ≤ LI ≤ 5.99: mild to moderate
- LI ≥ 6.00: severe

Lindegaard index: 8:8 (198.77/22.47)

Fig. 24.9 Lindegaard index (*LI*) formula and example of severely elevated LI

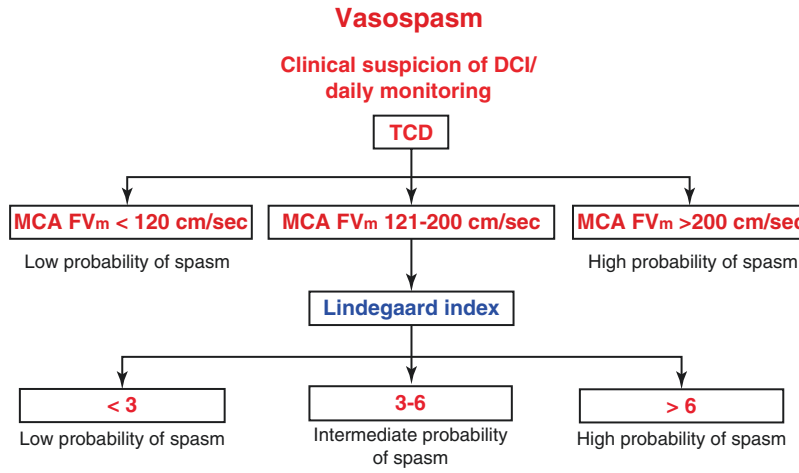


Fig. 24.10 Approach to the interpretation of the flow velocities and the Lindegaard index in the context of vasospasm

variations in cerebral perfusion pressure between certain limits of pressure (50–150 mmHg in normotensive patients) [41]. Impairment of autoregulation has been demonstrated in many neurocritical care conditions, and it is related to poor outcome.

Monitoring of cerebral autoregulation has been performed for decades under steady-state conditions in clinical practice. TCD has been applied as a static model to autoregulatory testing in patients using the static autoregulatory index (sARI) or static rate of regulation (sROR),

defined as the percentage of change in CVR with respect to the percentage of change in CPP [42].

However, static assessment of autoregulation is often too simplistic as it does not take in account a number of factors including the different upper and lower limits of autoregulation or different slopes of the "autoregulatory zone" among different individuals.

A recent approach used TCD for the investigation of dynamic cerebral autoregulation given its high temporal resolution, which allows to measure the timing of the changes of CBF to the CPP/(ABP) challenge [43].

TCD can allow the calculation of an index of autoregulation called mean flow index (Mx), which is calculated as the correlation coefficient between FVm and CPP; an Mx value of zero or negative indicates preserved autoregulation, whereas a positive correlation between ABP (or CPP) and CBF indicates impaired autoregulation.

The study of autoregulation through TCD has been applied in many clinical scenarios.

In patients with stroke, TCD has demonstrated to be able to detect an impairment in cerebral autoregulation of the pathologic hemisphere and showed an association of this impairment with poor outcome [44]. Moreover, impaired autoregulation assessed with Mx index has shown to be strongly associated with poor outcome at 6 months in patients after TBI [45].

Similarly to TBI, impaired cerebral autoregulation seems to play a significant role in the pathophysiology of vasospasm and delayed cerebral ischemia (DCI) after SAH. Budohoski et al. demonstrated that patients with worse autoregulation after SAH are more likely to develop delayed cerebral ischemia (DCI) independently to the incidence of vasospasm [46] and that impairment of autoregulation can be detected before vasospasm occurs.

Finally, in patients with ICA stenosis, impaired autoregulation assessed by Mx observed in the pathological stenotic or occlusive arteries has shown to be correlated with the degree of stenosis and is considered as a tool to identify patients at risk for need of surgical decompressive craniectomy [47].

24.6.4 Brain Death

Brain death is an irreversible cessation of the brain and brainstem functions. Its diagnosis implies several medical, ethical, and legal implications.

Currently, brain death is diagnosed by clinical neurological examination and confirmatory instrumental tests in some clinical cases, such as EEG, angiography with multi-slice computed tomography (CTA), brain scintigraphy or TCD, according to the legal requirements in each individual country.

The use of TCD in brain dead has been first described in 1974, and it is an alternative confirmatory test. It is able to demonstrate cerebral circulatory arrest associated to brain death, especially when neurological examination is not possible.

The conditions for establishing a diagnosis of cerebral circulatory arrest using TCD include the knowledge of the cause of coma, and the exclusion of factors that may alter the neurological findings, including hypothermia, metabolic alterations, and intoxications. Moreover, during the TCD measurements, the patient has to be hemodynamically stable with a blood pressure no lower than 90/50 mmHg, and $PaCO_2$ 35–45 mmHg.

Published criteria [48] for the diagnosis of cerebral circulatory arrest on TCD state that one of the following waveforms must be observed in the middle cerebral artery, basilar artery, and internal carotid artery bilaterally by two expert sonographers:

1. An oscillating waveform (equal systolic forward flow and diastolic reversed flow) (Fig. 24.11)
2. Small systolic spikes of < 200 ms duration and < 50 cm/s PSV with no diastolic flow (Fig. 24.12), or
3. Disappearance of intracranial flow

The examinations should be repeated twice at least 30 min apart.

Despite the large number of limitations in the use of TCD for the diagnosis of brain dead (operator-dependent technique, absence of acoustic window in 10–20% of patients, difficulty exploring posterior circulation in critically ill patients, false-negative results in patients with anoxia or with open skull), a meta-analysis

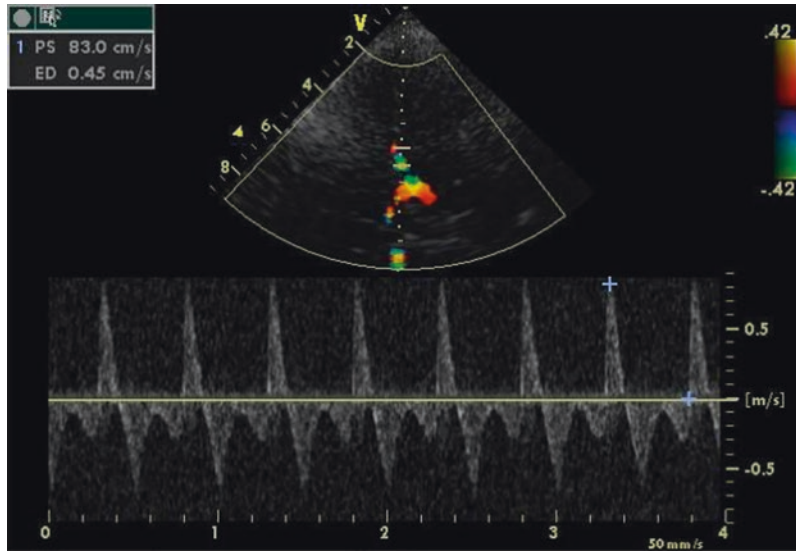


Fig. 24.11 Example of diastolic flow reversal in the context of malignant intracranial hypertension

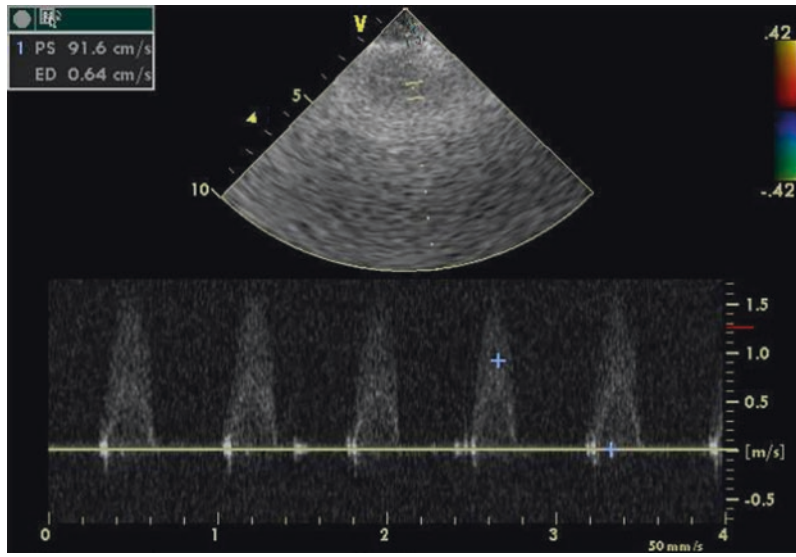


Fig. 24.12 Example of absence of diastolic flow in the context of malignant intracranial hypertension

published in 2006 [49] reported a sensitivity of 95% and a specificity of 99%.

24.7 Other Applications

TCD has been used for the diagnosis, prognosis, and treatment of ischemic stroke.

It has been demonstrated to be a reliable prognostic indicator in MCA occlusive stroke [50] and may also have a role in the prediction of outcome in these patients, according to the site and severity of occlusion observed.

Besides the common previously described applications in neurointensive care settings, TCD has been successfully applied even in the intraoperative settings, in order to assess nCPP and nICP in surgical procedures at risk to increase intracranial hypertension [5] such as laparoscopic procedures with pneumoperitoneum and Trendelenburg position, as well as for neuromonitoring during cardiac surgery or carotid endarterectomy . Finally, growing and

recent evidences support the use of TCD even in metabolic coma (such as during liver transplant or hepatic encephalopathy) or in pregnant patients, to assess autoregulation and cerebrovascular changes as prognostic factor for preeclampsia.

24.7.1 Limitations of TCD and TCCS

TCD presents several technical limitations. First, the two main assumptions and limitations that govern the use of TCD as an indirect measure of CBF are a constant vessel diameter and an unchanged angle of insonation during the measurements (despite TCCS allows correction of angle of insonation). As demonstrated by Clark et al. [51], MCA blood-flow velocity is a useful index of CBF response to changes in arterial PCO_2 during O_2 breathing at rest. However, FV evaluated by TCD is proportional to CBF only when vessel cross-sectional area remains constant. Thus, the results of any TCD study of CBF should always be interpreted with caution, keeping in mind the possibility that cerebral vessel diameter has changed. With every ultrasound exam, there is an operator-dependent variability, despite the intra-observer and inter-observer variability during TCD examinations has been reported to be good [52].

In a recent study on healthy volunteers and patients with aSAH, TCCS measurement variability resulted to be wider in patient measurements than in healthy volunteers (Bland-Altman limits of agreement 0.62–1.61 in patients and 0.67–1.50 in controls). This discrepancy can be explained by a higher degree of error in patients with angiographic vasospasm, where the caliber of the vessels is altered

Another limitation is that up to 20% of patients do not have a proper temporal window which prevents US transmission [52].

Moreover, since measurements are frequently only taken from the MCA, cerebrovascular changes in the posterior circulation may not be detected [44].

Finally, there are several anatomical variants and the direction and anatomy of the vessels can vary up to 52% of patients [53].

Conclusion

TCD is a noninvasive, safe, accessible technique for the bedside monitoring of static and dynamic cerebral flow and treatment response.

In neurointensive care settings, real-time monitoring of TCD-derived indices may provide important information regarding the onset of cerebrovascular alterations and facilitate clinical management of cerebral pathologies. Despite it presents several limitations, TCD remains an important tool for the assessment of cerebral hemodynamics in critically ill patients.

References

1. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg [Internet]. 1982;57(6):769–74. Available from: <Go to ISI>://WOS:A1982PR90500007.
2. You Y, Hao Q, Leung T, Mok V, Chen X, Lau A, et al. Detection of the siphon internal carotid artery stenosis: transcranial Doppler versus digital subtraction angiography. J Neuroimaging. 2010;20:234–9.
3. Lowe LH, Bulas DI. Transcranial Doppler imaging in children: Sickle cell screening and beyond. Pediatr Radiol. 2005;35(1):54–65.
4. Naqvi J, Yap KH, Ahmad G, Ghosh J. Transcranial Doppler ultrasound: a review of the physical principles and major applications in critical care. Int J Vasc Med. 2013;2013:629378.
5. Cardim D, Robba C, Bohdanowicz M, Donnelly J, Cabella B, Liu X, et al. Non-invasive monitoring of intracranial pressure using transcranial Doppler ultrasonography: is it possible? Neurocrit Care. 2016;1–19
6. Bellner J, Romner B, Reinstrup P, Kristiansson KA, Ryding E, Brandt L. Transcranial Doppler sonography pulsatility index (PI) reflects intracranial pressure (ICP). Surg Neurol. 2004;62(1):45–51.
7. Robba C, Donnelly J, Bertuetti R, Cardim D, Sekhon MS, Aries M, et al. Doppler non-invasive monitoring of ICP in an animal model of acute intracranial hypertension. Neurocrit Care. 2015;23(3):419–26.
8. De Riva N, Budohoski KP, Smielewski P, Kasprowicz M, Zweifel C, Steiner LA, et al. Transcranial doppler pulsatility index: what it is and what it isn't. Neurocrit Care. 2012;17(1):58–66.
9. Giller CA, Hodges K, Batjer HH. Transcranial Doppler pulsatility in vasodilation and stenosis. J Neurosurg. 1990;72:901–6.
10. Czosnyka M, Richards HK, Whitehouse HE, Pickard JD. Relationship between transcranial Doppler-determined pulsatility index and cerebrovascular resistance: an experimental study. J Neurosurg. 1996;84(1):79–84.
11. Bundgaard H, von Oettingen G, Larsen KM, Landsfeldt U, Jensen KA, Nielsen E, et al. Effects of sevoflurane on intracranial pressure, cerebral blood flow and cerebral metabolism. A dose-response study in patients subjected to craniotomy for cerebral tumours. Acta Anaesthesiol Scand. 1998;42(6):621–7.

12. Matta BF, Heath KJ, Tipping K, Summors AC. Direct cerebral vasodilatory effects of sevoflurane and isoflurane. Anesthesiology. 1999;91(3):677–80.
13. Kaisti KK, Långsjö JW, Aalto S, Oikonen V, Sipilä H, Teräs M, et al. Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. Anesthesiology [Internet]. 2003;99(3):603–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12960544.
14. Kaisti KK, Metsahonkala L, Teras M, Oikonen V, Aalto S, Jaaskelainen S, et al. Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. Anesthesiology [Internet]. 2002;96(6):1358–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12170048.
15. Ogawa Y, Iwasaki KI, Shibata S, Kato J, Ogawa S, Oi Y. The effect of sevoflurane on dynamic cerebral blood flow autoregulation assessed by spectral and transfer function analysis. Anesth Analg. 2006;102(2):552–9.
16. Monkhoff M, Schwarz U, Gerber A, Fanconi S, Banziger O. The effects of sevoflurane and halothane anesthesia on cerebral blood flow velocity in children [Internet]. Anesth Analg. 2001;92(4):891–6. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11273920.
17. Brosnan RJ, Steffey EP, LeCouteur RA, Esteller-Vico A, Vaughan B, Liu IKM. Effects of isoflurane anesthesia on cerebrovascular autoregulation in horses. Am J Vet Res. 2011;72(1):18–24.
18. Nishiyama T, Matsukawa T, Yokoyama T, Hanaoka K. Cerebrovascular carbon dioxide reactivity during general anesthesia: a comparison between sevoflurane and isoflurane. Anesth Analg [Internet]. 1999;89(6):1437–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10589623.
19. Holmström A, Rosén I, Åkeson J. Desflurane results in higher cerebral blood flow than sevoflurane or isoflurane at hypocapnia in pigs. Acta Anaesthesiol Scand. 2004;48(4):400–4.
20. Wilson-Smith E, Karsli C, Luginbuehl I, Bissonnette B. Effect of nitrous oxide on cerebrovascular reactivity to carbon dioxide in children during sevoflurane anaesthesia. Br J Anaesth. 2003;91(2):190–5.
21. Iacopino DG, Conti A, Battaglia C, Siliotti C, Lucanto T, Santamaria LB, et al. Transcranial Doppler ultrasound study of the effects of nitrous oxide on cerebral autoregulation during neurosurgical anesthesia: a randomized controlled trial. J Neurosurg [Internet]. 2003;99(1):58–64. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12854745.
22. Villa F, Iacca C, Molinari AF, Giussani C, Aletti G, Pesenti A, et al. Inhalation versus endovenous sedation in subarachnoid hemorrhage patients: effects on regional cerebral blood flow. Crit Care Med [Internet]. 2012;40(10):2797–804. . Available from: http://www.ncbi.nlm.nih.gov/pubmed/22824929.
23. Purrucker JC, Renzland J, Uhlmann L, Bruckner T, Hacke W, Steiner T, et al. Volatile sedation with sevoflurane in intensive care patients with acute stroke or subarachnoid haemorrhage using AnaConDa(R): an observational study. Br J Anaesth [Internet]. 2015;114(March):934–43. Available from: http://bja.oxfordjournals.org/lookup/doi/10.1093/bja/aev070.
24. Marval PD, Perrin ME, Hancock SM, Mahajan RP. The effects of propofol or sevoflurane on the estimated cerebral perfusion pressure and zero flow pressure. Anesth Analg. 2005;100(3):835–40.
25. Banevičius G, Rugytė D, Macas A, Tamašauskas A, Stankevičius E. The effects of sevoflurane and propofol on cerebral hemodynamics during intracranial tumors surgery under monitoring the depth of anesthesia. Medicina (Kaunas) [Internet]. 2010;46(11):743–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21467832.
26. Saito S, Kadoi Y, Nara T, Sudo M, Obata H, Morita T, et al. The comparative effects of propofol versus thiopental on middle cerebral artery blood flow velocity during electroconvulsive therapy [Internet]. Anesth Analg. 2000;91(6):1531–6. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11094013.
27. Steiner LA, Johnston AJ, Chatfield DA, Czosnyka M, Coleman MR, Coles JP, et al. The effects of large-dose propofol on cerebrovascular pressure autoregulation in head-injured patients. Anesth Analg. 2003;97:572–6. table of contents
28. Albanese J, Durbec O, Viviand X, Potie F, Alliez B, Martin C. Sufentanil increases intracranial pressure in patients with head trauma. Anesthesiology. 1993;79(3):493–7.
29. de Nadal M, Munar F, Poca MA, Sahuquillo J, Garnacho A, Rosselló J. Cerebral hemodynamic effects of morphine and fentanyl in patients with severe head injury: absence of correlation to cerebral autoregulation. Anesthesiology. 2000;92(1):11–9.
30. Marmarou A, Anderson RL, Ward JD, Choi SC, Young HF, Eisenberg HM, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J Neurosurg. 1991;75(Supplement):S59–66.
31. Miller JD, Becker DP, Ward JD. Significance of intracranial hypertension in severe head injury. J Neurosurg [Internet]. 1977;47(4):503. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L8193896\nhttp://sfx.library.uu.nl/utrecht?sid=EMBASE&issn=00223085&id=doi:&atitle=Significance+of+intracranial+hypertension+in+severe+head+injury&stitle=J.+NEUROSURG.&title=Journal+.
32. Holloway KL, Barnes T, Choi S, Bullock R, Marshall LF, Eisenberg HM, et al. Ventriculostomy infections: the effect of monitoring duration and catheter exchange in 584 patients. J Neurosurg. 1996;85(3):419–24.
33. Robba C, Bacigaluppi S, Cardim D, Donnelly J, Bertuccio A, Czosnyka M. Non-invasive assessment of intracranial pressure. Acta Neurologica Scand. 2016;134(1):4–21.

34. Czosnyka M, Matta BF, Smielewski P, Kirkpatrick PJ, Pickard JD. Cerebral perfusion pressure in head-injured patients: a noninvasive assessment using transcranial Doppler ultrasonography. J Neurosurg. 1998;88(5):802–8.
35. Varsos GV, Kolias AG, Smielewski P, Brady KM, Varsos VG, Hutchinson PJ, et al. A noninvasive estimation of cerebral perfusion pressure using critical closing pressure. J Neurosurg. 2015;123(3):638–48.
36. Rincon F, Rossenwasser RH, Dumont A. The epidemiology of admissions of nontraumatic subarachnoid hemorrhage in the United States. Neurosurgery. 2013;73(2):217–22.
37. Diringer MN, Bleck TP, Claude Hemphill J, Menon D, Shutter L, Vespa P, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care [Internet]. 2011; [cited 2014 Nov 25];15(2):211–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21773873.
38. Kistka H, Dewan MC, Mocco J. Evidence-based cerebral vasospasm surveillance. Neurol Res Int [Internet]. 2013;2013:256713. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3686086&tool=pmcentrez&rendertype=abstract.
39. Marshall SA, Nyquist P, Ziai WC. The role of transcranial Doppler ultrasonography in the diagnosis and management of vasospasm after aneurysmal subarachnoid hemorrhage. Neurosurg Clin N Am. 2010;21(2):291–303.
40. Soustiel JF, Shik V, Feinsod M. Basilar vasospasm following spontaneous and traumatic subarachnoid haemorrhage: clinical implications. Acta Neurochir 2002;144 (2):137–44.
41. Czosnyka M, Smielewski P, Piechnik S, Pickard JD. Clinical significance of cerebral autoregulation. Acta Neurochir Suppl [Internet]. 2002;81:117–9. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12168280.
42. Panerai RB. Transcranial Doppler for evaluation of cerebral autoregulation. Clin Auton Res [Internet]. 2009 [cited 2014 Nov 18];19(4):197–211. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19370374.
43. Donnelly J, Aries MJ, Czosnyka M. Further understanding of cerebral autoregulation at the bedside: possible implications for future therapy. Expert Rev Neurother [Internet]. 2015;15(2):169–85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25614952.
44. Aries MJH, Elting JW, De Keyser J, Kremer BPH, Vroomen PCAJ. Cerebral autoregulation in stroke: a review of transcranial doppler studies. Stroke. 2010;41(11):2697–704.
45. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD. Monitoring of cerebral autoregulation in head-injured patients. Stroke [Internet]. 1996;27(10):1829–34. Available from: http://acs.hcn.com.au?acc=36422&url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=8841340.
46. Budohoski KP, Czosnyka M, Smielewski P, Kasprowicz M, Helmy A, Bulters D, et al. Impairment of cerebral autoregulation predicts delayed cerebral ischemia after subarachnoid hemorrhage: a prospective observational study. Stroke [Internet]. 2012; [cited 2014 Jun 16];43(12):3230–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23150652.
47. Reinhard M, Roth M, Müller T, Czosnyka M, Timmer J, Hetzel A. Cerebral autoregulation in carotid artery occlusive disease assessed from spontaneous blood pressure fluctuations by the correlation coefficient index. Stroke. 2003;34(9):2138–44.
48. Powers AD, Graeber MC, Smith RR. Transcranial Doppler ultrasonography in the determination of brain death. Neurosurgery. 1989;24(6):884–9.
49. Monteiro LM, Bollen CW, Van Huffelen AC, Ackerstaff RGA, Jansen NJG, Van Vught AJ. Transcranial Doppler ultrasonography to confirm brain death: a meta-analysis. Intensive Care Med. 2006;32(12):1937–44.
50. Alexandrov AV, Burgin WS, Demchuk AM, El-Mitwalli A, Grotta JC. Speed of intracranial clot lysis with intravenous tissue plasminogen activator therapy: sonographic classification and short-term improvement. Circulation. 2001;103(24):2897–902.
51. Clark JM, Skolnick BE, Gelfand R, Farber RE, Stierheim M, Stevens WC, et al. Relationship of 133Xe cerebral blood flow to middle cerebral arterial flow velocity in men at rest. J Cereb Blood Flow Metab. 1996;16:1255–62.
52. Bazan R, Braga GP, Luvizutto GJ, Hueb JC, Hokama NK, Zanati Bazan SG, et al. Evaluation of the temporal acoustic window for transcranial Doppler in a multi-ethnic population in Brazil. Ultrasound Med Biol. 2015;41(8):2131–4.
53. Iqbal S. A comprehensive study of the anatomical variations of the circle of Willis in adult human brains. J Clin Diagn Res. 2013;7(11):2423–7.

The Conundrum of Postoperative Hematoma in Intracranial Surgery

25

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25.1 Incidence and Outcome

Postoperative intracranial hemorrhage hence named postoperative hematoma (POH) is a devastating neurosurgical complication with an incidence ranging from 0.08 to 6.2% per craniotomy [1, 2]. POH as stated above is one of the most serious complications of any cranial neurosurgical procedure and is associated with significant morbidity and mortality [3].

Although significant advances have been made in timely interventions, the occurrence of POH always looms after a seemingly successful intracranial surgery and is a feared complication. The prognosis of POH unfortunately is dismal and disappointing with hardly 13% having a good outcome, and 55% of patients severely disabled or else dead at 6 months [1]. In another study, an overall mortality of 32% has been reported, and even higher for intraparenchymal clots [4]. In another study comprising 6668 procedures, the incidence of POH was 1.1% [5]. The incidence however varies in different studies depending on whether the figures are based on clinical deterioration or else routine radiological monitoring. Based on the latter tool, the incidence ranges between 10.8 and 50.0% [6].

POH evolving at the site of operation however differs from the one occurring at a site far away or remote from the site of operation. The one occurring distant from the site of operation has a different etiology and frequently occurs following evacuation of subdural collections [7], posterior fossa surgery [8, 9], intercerebral hemorrhage [10]and shunting procedures [11]. The two hematomas are distinct entities each having its own risk factors but factors such as brain atrophy, hypertension, and upright positioning [9] may be common for both POH and hematomas occurring at places far distant from the site of operation. Since our objective is to dilate on the subject of POH, that is, hematomas occurring following intracranial surgery, hematomas occurring at remote areas would not be discussed further.

25.2 Etiology

Because of its high incidence, a downhill course of the patient postoperatively is commonly regarded as a subtle and consistent sign of an evolving POH, and surgeons regard it as a grave sign necessitating speedy exploration and evacuation. Delay is perilous, thus timely surgery is the hallmark of a successful outcome of POH.

Among the causes cited for the occurrence of POH, hyperfibrinolysis has been cited as the

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principal mechanism for such hemorrhagic abnormalities [1, 12].

The underlying pathological event involves release of plasminogen-activating factors from the tumor cells, or tissue factors released from the injured parenchyma during the process of surgery itself [13, 14].

It is however to be kept in mind that the process of coagulopathy is triggered by the release of thromboplastins from the injured brain [12, 15]. Meningiomas have been cited as the benign brain tumors capable of releasing the highest amount of tissue thromboplastins and thus demanding an ever increase vigilance in executing timely and adequate surgical hemostasis.

Besides meningiomas, thromboembolic complications, hyperfibrinolysis, disseminated intravascular coagulopathy, and hemorrhage have been frequently observed in patients with all brain tumors [16–18].

25.3 Demography Factors

Demographic factors such as age and sex have not been found to influence the occurrence or gravity of POH. Although the aging process would go parallel with some of the brain atrophy, there is no study so far to provide an unequivocal evidence that age or gender would be influencing factors [1, 4].

25.4 Predisposing Conditions/ Factors and Underlying Pathophysiologic Mechanisms

Intracranial hemorrhage can be serious and sometimes fatal complication when it occurs during or after intracranial surgery. It is likely the result of many predisposing conditions such as surgical hemostasis, venous pressure, coagulation status, genetic predisposition, and hemodynamic state.

Acute blood pressure (BP) elevations frequently occur prior to postcraniotomy intracranial hemorrhage. Postoperative hypertension has been cited as a major factor for the development of POH. This is of course based on substantial evidence as most cases of bleeding occur within the first 6 h of surgery. Patients who succumb to the catastrophic complication of POH, in all probability had either an episode of hypertension in the intraoperative period or in the early postoperative period. It is also likely that such patients had remained hypertensive in the intraoperative and early postoperative period and had either remained unattended or else had failed to respond to the antihypertensive treatment. Other contributing factors could be tracheal intubation right at the initiation of anesthesia which is frequently associated with coughing and straining causing an alarming increase in cerebral venous pressure and eventually leading to the development of POH. In the same vein, tracheal intubation if not conducted at an appropriate depth of anesthesia could also activate the sympathetic nervous system and bring in an incalculable harm to the meticulous homeostasis achieved during surgery, and result in an early POH formation. Although not the subject of this chapter, but just to make a passing reference to the fact that labile hypertension and intraoperative swings in the blood pressure may also contribute to the development of intracranial hemorrhage, quite remote from the site of operation following neurosurgical procedure which again entail time for reoperation and increase both morbidity and mortality [10].

Patients who have hypertension, coronary artery disease, preoperative labile hypertension, and surgery planned for intracranial mass may carry the risk of intracranial hematoma during the perioperative period. Perioperatively and during extubation, sudden spikes in blood pressure must be avoided. Surgical stress and erratic hemodynamic responses during the induction of anesthesia must be controlled with anesthetics or other additional agents. Emergence from anesthesia should preferably be smooth and without any surges in blood pressure. Prompt and effective management of hypertension remains the most effective prevention strategy for POH, given both the relatively high prevalence of hypertension with in the community and the strong

association between hypertension and intracranial hypertension [19].

In most of the studies conducted so for, hypertension is commonly implicated in the development of both intra and postoperative hemorrhage. Furthermore, it is associated with hemorrhage both at the operative site and at sites quite distant from the site of operation.

The association between hypertension and POH formation is so compelling that authors have emphasized on the point that precautionary pharmacological therapies should be initiated to circumvent or attenuate the stress responses to surgery and to strictly obviate wide fluctuations in blood pressure that are commonly encountered during surgery and during the waxing and waning actions of the anesthetic agents commonly employed for intracranial surgery [2].

Apart from causing POH, it could be argued that an increase in mean arterial pressure (MAP) can be transmitted to the capillary bed, thus increasing hydrostatic pressure and thus aggravating intracranial hypertension by increasing transcapillary fluid filtration [20].

Although such a scenario is specially seen in head injury patients in whom the blood brain barrier is disrupted, theoretically it is not far from conceivable assumption that it can possibly occur in patients undergoing routine intracranial tumor resection on the valid and scientific grounds that intracranial tumors do in fact disrupt the blood brain barrier to a certain degree.

A raised blood pressure coupled with intracranial hypertension can further compound the already complicated situation and make matters worse. Potential pathophysiologic mechanisms of elevated blood pressure in patients with POH include stress activation of the neuroendocrine system (sympathetic nervous system, renin–angiotensin axis, or glucocorticoid system) and increased intracranial pressure (ICP). Hypertension could theoretically contribute to hydrostatic expansion of the hematoma thus enhancing the size of an already progressing hematoma, bringing about peri-hematoma edema formation and activating bleeding, all of which may contribute to the cascade of adverse outcomes.

25.5 Emergence from Anesthesia

Tapering the anesthetic agents towards the end of surgery commonly referred to as emergence from anesthesia is frequently associated with a surge or a rise in blood pressure and this systemic hypertension in turn ushers in the intracranial bleeding and the much feared POH and cerebral edema following craniotomy [21–23]. It has been demonstrated that a high blood pressure was a correlate of intracranial hemorrhage following craniotomy [24]. Perioperative hypertension has been reported to range from 54% to as high a figure as 91% [25–28]. Rises in blood pressure have been attributed to a surge in catecholamine levels after craniotomy [13], activation of the renin–angiotensin system and perhaps other metabolic stresses that occur during surgery. POH is commonly seen when recovery from anesthesia is not smooth and is associated with systemic hypertension [28]. Some studies have related hypertension to intracerebral hemorrhage in patients who had normal coagulation profile [4, 6] highlighting the fact that hypertension in itself could cause POH. It is quite logical to assume that an elevated blood pressure would cause cerebral hyperemia with a propensity for hemorrhaging. If the autoregulatory levels are trespassed, the increased blood pressure might overwhelm the reserves of autoregulation and usher in a devastating cerebral hyperemia eventually ending up in a POH. There is also a strong possibility that vasomotor paralysis might have occurred at the site of surgical manipulation either because of excessive use of surgical retractors or because of remnants of the tumor. In the setting of such a fragile and vulnerable state of cerebral autoregulation, it is but natural that an episode of hypertension no matter how transient it may be would cause a sudden increase in cerebral blood flow (CBF) and eventually lead to the formation of POH.

In one study, metoprolol and ketanserin were employed to tide over the rising blood pressure, but the drugs failed to counteract the rise in CBF both during and after craniotomies [29]. In another study, the authors could find an increase in CBF despite the fact that the hemodynamics were adequately controlled during the

perioperative period [30]. It is difficult to explain as to why should there be rises in CBF during apparently quiescent periods when the hemodynamics were well controlled and why should such patients develop POH. There is paucity of well-controlled, prospective, randomized trials to explicitly demonstrate clear benefits accrued from keeping the blood pressure within the acceptable range during the perioperative period and translating them into a statistically significant reduction in the incidence of POH. The results obtained from the above studies, no matter how few they are, failed to have a substantial impact on preventing rises in CBF, revealing thereby that the control of blood pressure might not have the desired effect that it was intended to bring about such as preventing any surges in CBF.

Thus, there conceivably might be additional mechanisms in play besides the often talked about rises in blood pressure that might be responsible for the development of POH following intracranial surgeries. It could also be well argued that the hypertension that is frequently encountered and which many a times fail to respond to the various pharmacological and antihypertensive agents could possibly be a sign of yet an unknown phenomenon that is activated primarily by the intracranial surgery itself and which possibly could be temporally related to the development of POH. Perhaps other factors such as gross or partial excision of the tumor, transgression of the tumor or its frank invasion to adjacent structures such as the sinuses, any inadvertent alternations in cerebral venous pressures during the course of surgery, the degree of surgical hemostasis achieved before dural closure, and finally, the duration of surgery could also in all probability be of dire importance in the occurrence of POH.

Intubation of the trachea in itself might incur an incalculable harm in terms of raised central venous pressures that could predispose to the development of POH [30]. Antihypertensive agents currently in vogue are accompanied with cerebral vasodilation and thus usher in hyperemia which could also possibly be an incriminating factor in the development of POH.

25.6 The Dilemma of Emergence Hypertension

Although there is no solid proof that emergence hypertension would cause intracranial hemorrhage and finally end up in POH, it is prudent to prevent any surges and obviate any spikes in blood pressure during the highly critical and susceptible period of emergence from anesthesia.

To help conduct a smooth emergence and tracheal extubation after the culmination of surgery, various drugs such as beta blockers [31], Angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers have been tried with some limited success, but they are not totally safe and are associated with side effects such as conduction defects, bradycardia, hypotension, and autoregulation impairment [32, 33].

Hydralazine provenly causes cerebral vasodilation and thus causes an inevitable rise in ICP [34].

Lidocaine has served to be a useful agent in blunting the airway reflexes prior to both intubation and extubation and thus curtails or altogether prevents coughing and straining, events that are highly hazardous in neurosurgery.

A hemodynamic stability has been reported with dexmedetomidine when used as an adjuvant drug during neuroanesthesia [35, 36].

Although hypertension per se might be associated with POH, it is hard to establish a temporal relationship between the two on valid scientific grounds. Establishing a cause and effect relationship between the two needs additional well-conducted randomized clinical trials.

25.7 Intracranial Surgery and Hemostasis

In all other types of surgeries, the bleeders are ligated and thus surgical hemostasis is achieved, but this type of hemostasis does not hold true in the brain where hemostasis is achieved by methods other than ligation and this brings down the accuracy of adequate hemostasis. It has been accepted by all that an inadequate hemostasis in the brain has disastrous repercussions. Following intracranial surgery, meticulous hemostasis and a

clean surgical field is imperative before dural closure to prevent the highly devastating complication of POH. Different techniques such as timely utilization of topical hemostats have been of some help in achieving surgical hemostasis [37].

Perioperative factors such as patient positioning, blood pressure, and Valsalva maneuver can be of help in preventing the development of a POH and thus help in conducting a seemingly successful intracranial surgery. When there is still an ooze and visible bleeding at the end of surgery, a thin sheet of oxidized cellulose is frequently employed to cover the surgical field as the final hemostasis is being accomplished [38, 39]. Prior to the placement of oxidized cellulose, bipolar forceps are invariably used to coagulate bleeders at the capillary level. Undoubtedly, oxidized cellulose has had its wide application in intracranial surgery and has proved to be successful in bringing a substantial reduction in the development of POH, but the problem is that it could swell up and cause severe neurological deficits [40, 41]. Its use has also been accompanied with granuloma formation [42]. Large slices of cellulose are thus being avoided for evident and obvious complications. Some surgeons used either oxidized cellulose or else gelatin simply out of habit even if there is no oozing in the tumor bed. In cases of oozing, they are helpful but under no circumstances would they be of any help in stopping more active bleeding at the site of the operation.

The powder form of cellulose which was sprinkled on the surface in 107 patients resulted in only 2.8% postoperative bleeding with only three of the patients developing a POH, and all the 3 were operated for meningiomas which has been cited as causing consumptive coagulopathy and thus promoting the development of a POH. These authors consider it a better option compared to oxidized cellulose and recommend it as a safe product for homeostasis [43].

It has been widely upheld that the practice of neurosurgery inherently was more sensitive to any deficit in homeostasis than many of the surgical disciplines [44]. This statement in itself highlights an extra vigilance and spending an extra time in achieving adequate homeostasis in all cranial surgeries because the rate of POH could range from figures as low as 0.8% to figures as high as 50.0% [4, 6, 45]. The exact volume of POH necessitating urgent evacuation has not been cited and would differ from case to case and determined by other factors such as location of the POH and the clinical deterioration of the patient.

All efforts should be focused on all possible remedies to prevent the occurrence of POH. Thromboelastography when combined with the standard laboratory tests is of value in assessing platelet function and likewise in detecting other coagulation deficiencies such as abnormal prothrombin time (PT) and partial thromboplastin times (PTT) which would not be detected by other tests unless they are reduced by more than 50%. It is thus suggested to initiate replacement of clothing factors and platelets even before the laboratory tests are known to counteract the occurrence of POH [46].

Many factors can be of vital importance in an adequate surgical homeostasis such as an adequate number of functioning platelets, normal blood coagulation profile, and the nonexistence of excessive fibrinolysis [1]. Lack of these factors leads to abnormal coagulation, thus enhancing the risk of postoperative complications. Platelets are essential for plug formation and a sudden reduction in platelet count (normal 100,000–124,000/μL) in the postoperative period is significantly associated with POH formation [47].

In the same vein, it has been said that an episode of acute thrombocytopenia increases the chances of POH [47]. Thrombocytopenia usually occurs from blood transfusions, platelet consumption, or coagulopathies [48]. Alcohol consumption also significantly impairs platelet function and increases the risk for postoperative bleeding following major surgery [49].

The chances of POH further increase when disseminated intravascular coagulopathy, depletion of coagulation factors, and platelets set in along with excessive fibrinolysis [50]. Factor XIII deficiency which occurs either because of excessive consumption or else impaired synthesis initiates excessive fibrinolysis, thus leading to postoperative bleeding [51, 52]; therefore its

levels should preferably be determined in patients with POH. Administration of antiplatelet agents is commonly associated with the development of POH [1] and both aspirin and clopidogrel should be stopped 7 days before surgery as they inhibit platelet aggregation and significantly increase the bleeding time. Again, caution should be exercised in recommending low-dose heparin or low molecular weight heparin before craniotomy as they increase the risk of postoperative bleeding [53]. Bleeding that does not respond to other treatments is reduced with recombinant activated factor VII (rFVIIa) [54, 55], but thromboembolic events do occur as have been reported [55, 56]. Excessive blood loss during surgery for unknown reasons has been incriminated as a risk factor for POH [57], thus logically antifibrinolytics such as tranexamic acid and epsilon aminocaproic acid that decrease blood loss would be of potential value. But these agents are also not totally safe and carry an inherent risk of deep vein thrombosis [56]. Aprotonin is of value in reducing perioperative blood loss without increasing the risk of thromboembolic complications [58].

To attain neurosurgical hemostasis, topical hemostats [1] including oxidized cellulose, gel foam, fibrin glue, and aprotinin are required [59]. Bipolar cautery is extensively employed in neurosurgery, but it is believed that the vessels that are being cauterized may retract and thus initiate hemorrhage [6]. Postoperative hemorrhage paradoxically also occurs in operative sites with seemingly meticulous hemostasis being conducted at the time of closure [2] making us to think that there might be some unidentified factors at play in the development of POH. Some propose Valsalva maneuver at the end of operation which besides raising intrathoracic pressure and intracranial pressure, also raises the blood pressure (BP) that normally occurs during extubation and weaning from anesthesia [60]. An increase in the blood pressure alerts the surgeon to potential bleeders at the site of the operation. An upright position adapted for cerebellopontine angle or posterior fossa tumors may predispose to hemorrhage [9, 61]. It is also argued that the reduced blood flow in an upright position may induce ischemia [57], and then upon adopting supine position postoperatively, hyperperfusion breakthrough occurs in the previously induced ischemic tissue [9].

An increase in intraoperative blood loss has been associated with a high incidence of POH. The likely explanation is depletion of platelets and other coagulation factors that occur during extensive intraoperative blood loss [57]. Thus, it is logical that intraoperative blood loss be replaced with FFP and platelets, and if such losses are anticipated to occur such as in major surgeries, prophylactic transfusions should be initiated well ahead of the event.

It has been stressed that sudden swings in blood pressure and hypertensive episodes in the perioperative period are associated with an increased risk of POH [28, 62]. This is all the more important and particularly evident when the blood–brain barrier is disrupted as in vasogenic edema when the rise in blood pressure is transmitted directly to the microvasculature causing an increase in intracranial volume, intracranial pressure thus predisposing to POH. Blood pressure levels above 160/90 mmHg have a significant correlation with POH [28]. Thus, a smooth or gentle extubation and emergence from anesthesia would be helpful in attenuating the stress responses to surgical trauma and extubation [2, 9].

For diagnosis, intraoperative magnetic resonance imaging (iMR) is of value in detecting POH [63], but owing to its high cost, intraoperative computed tomography (iCT) would perhaps be a plausable option [64]. iMR has a very low sensitivity with very few patients requiring evacuation. Thus, although the role of intraoperative monitoring is of considerable importance, it has to be kept in mind that POH may appear long after the patient has been shifted from the operative room substantiating this point that a continued vigilance and monitoring is needed to correctly and timely diagnose an evolving POH [3]. Postoperative imaging is always needed and has been routinely conducted with 24 h [2], 48 h [65], and up to 7 days postoperatively [6, 7].

Taking the grave prognosis of POH into consideration, ICP monitoring has been advocated following brain surgery [66, 67] on the assumption that it has direct correlation with poor prognosis.

25.8 A Novel Approach in Identifying Occult Bleeders

In an interventional study on 37 patients with parasagittal or parafalcian meningiomas, Khan et al. [68] attempted a novel approach to curtail the incidence of POH which is of course high after intracranial meningioma surgery (Figs. 25.1 and 25.2).

After tumor resection and having accomplished primary hemostasis, group I received a bolus of ketamine hydrochloride 1.5 mg/kg intravenously, group II received a free infusion of an extra isotonic saline (15 mg/kg) at the rate of 100 ml/min, and group III received 2 ml of normal saline as a placebo. Ketamine and hypervolemia were both employed with an intent to induce hyperdynamic stress, and it was postulated that with this method, the surgeon having finished the

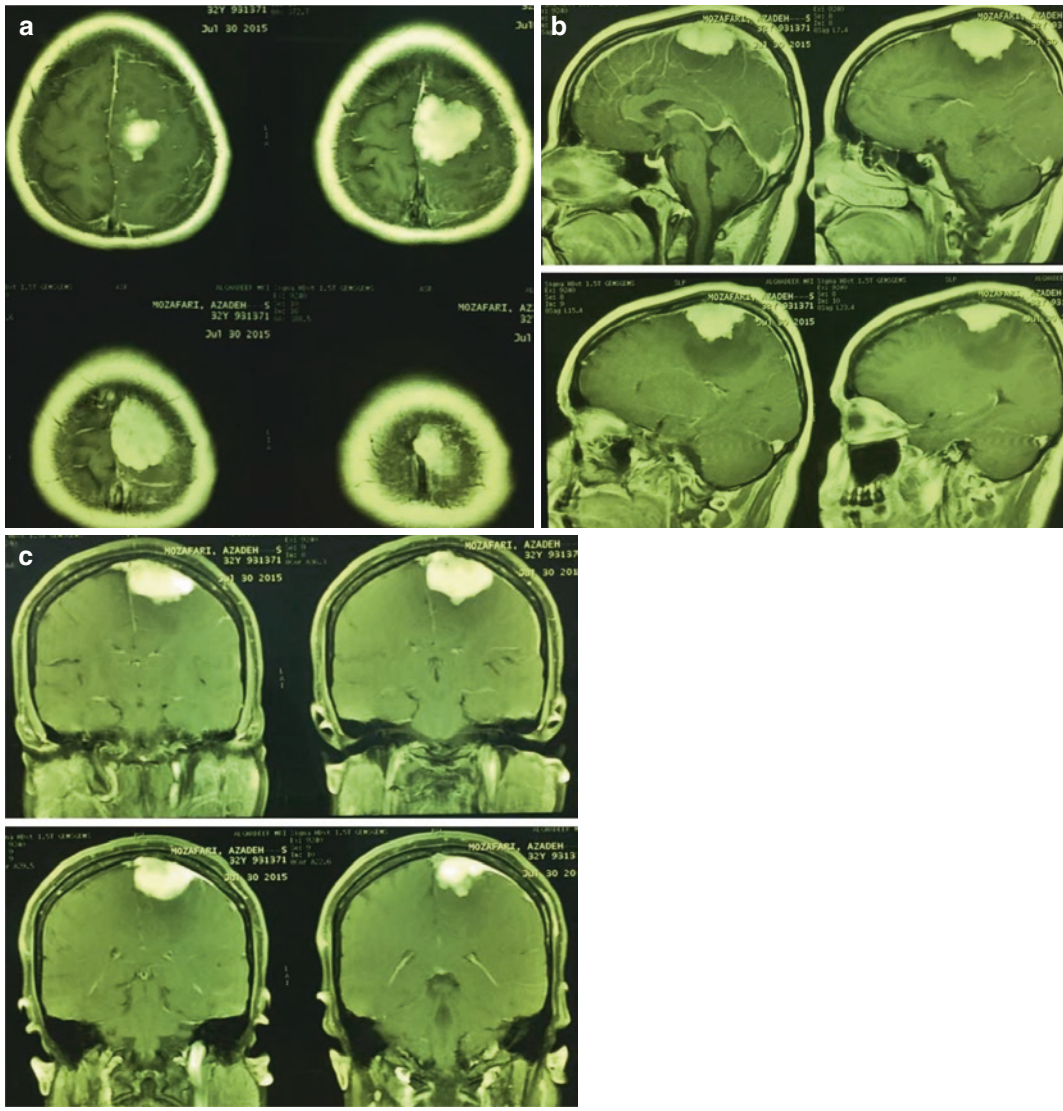

Fig. 25.1 Contrast-enhanced axial (**a**), coronal (**b**), and sagittal (**c**), T1–weighted images of the tumor showing parasagittal meningioma, which has filled the convexity falx angle. Superior sagittal sinus is patent

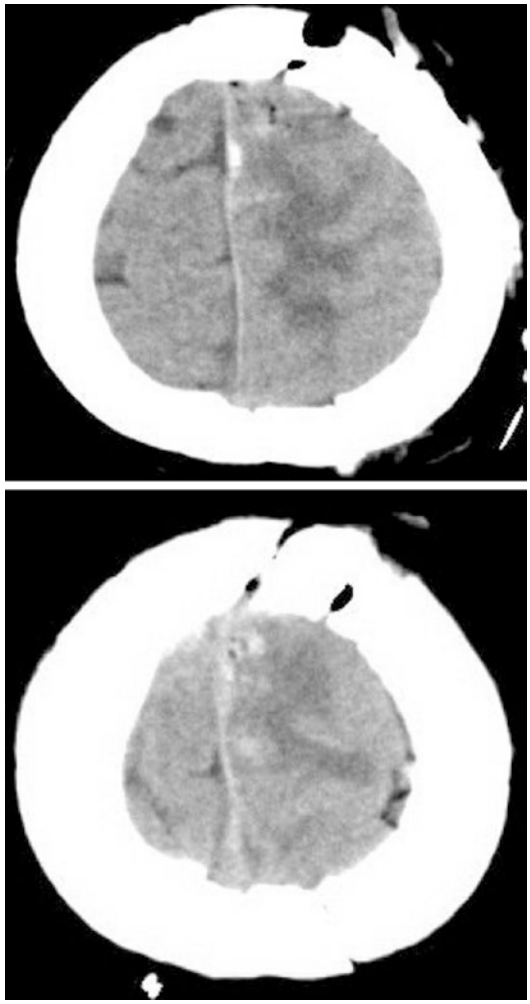

Fig. 25.2 Postoperative CT scan showing gross total tumor removal after a right-side parietal craniotomy

primary hemostasis and having controlled pre-stress hemorrhage or bleeding vessels conducts another secondary or vigilant hemostasis after the hemodynamic stress. The basis of this novel theory was that the surgeon normally conducts surgical hemostasis of the pre-stress hemorrhage under circumstances when the patient is deeply anesthetized and at the same time might be hypocapnic, hypotensive, and hypovolemic and thus the surgeon might inadvertently miss or fail to microscopically visualize some of the dormant or camouflaged bleeders. It is expected and quite natural that owing to the low intraluminal pressure under circumstances as mentioned above, the occult bleeders would be impossible to visualize and thus would remain uncoagulated in the lax and sagging brain.

As is the custom, the tumor bed is covered by a gel foam with an intent to having executed meticulous hemostasis. Also, at the completion of surgery, the tumor bed is re-checked for any renewed bleeders after raising the intrathoracic pressure or else employing Valsalva maneuver [4], suffice it to say that this maneuver exclusively helps only in identifying the venous bleeders by increasing the cerebral blood volume, the arterial bleeders however remain dormant and would start spurting again if a hemodynamic stress, that is, administration of ketamine I.V. or an additional load of isotonic saline is utilized [68]. By employing I.V. ketamine or an additional load of normal saline, they in fact promoted the potential arteriolar bleeders to spurt again enabling the surgeon to tackle these bleeders by conducting a renewed intraoperative re-hemostasis. Colloids were avoided in this study to induce hypervolemia because they have a trend in reducing the fibrinogen component of the clot. Crystalloids on the other hand do not affect primary platelet-mediated hemostasis [69]. Brain edema is a matter of concern [70] when hypervolemia is employed, but an increase in edema score was not seen in the hypervolemia group compared to the control group [68]. It could be argued that as hemodilution tends to increase the cardiac output and capillary flow [71, 72], if severe enough, it could cause left ventricular failure [73]. The purpose of infusing an extra isotonic saline after the completion of primary hemostasis in our study [68] was to boost the cardiac output to promote or else enhance arteriolar/capillary circulation to identify the occult bleeders, thus enabling the surgeon to conduct renewed hemostasis of the newly spurting bleeders.

As a caution, it is to be emphasized that a rise in central venous pressure (CVP) after a hemodynamic stress reflects an impending heart failure [72]. Such a scenario in itself limits an increase in cardiac output and thus fails to activate arteriolar bleeders. The fluid challenge in our study not only helped to activate arteriolar bleeders subsequent to an increase in cardiac output but also

failed to cause significant rises in central venous pressure. This shows that the fluid challenge employed in these patients was large enough to bring about modest increases in cardiac output, yet not big enough to cause a reduction in cardiac output secondary to an impending heart failure. This fluid challenge totally differs from an acute normovolemic hemodilution where large volumes of fluid are infused to replace the quantity of the blood withdrawn with an intent to maintain hemodynamic stability.

The positive inotropic effects of ketamine, an N-methyl-D-aspartate receptor antagonist in the form of an increase in heart rate, blood pressure, and cardiac output [73], were clearly noticeable in the ketamine group and this sterling effect allowed the arteriolar bleeders to spurt again after the primary or initial hemostasis, and it was distinctly evident by a significantly longer time needed to conduct secondary hemostasis, thus promoting an efficient and meticulous hemostasis culminating in reducing POH and postoperative edema. Some studies have incriminated ketamine in causing significant rises in CBF while others have found ketamine to curtail CBF or else exhibit no effect on cerebral hemodynamics [74–76]. The increase in CBF following ketamine administration depended on the increase in MAP [77] and the effect on cerebral hemodynamics was secondary to an increase in cerebral metabolic rate of oxygen ($CMRO_2$) [78]. Nevertheless, these changes also depended and were influenced by the degree of controlled ventilation and the use of background anesthetics [79].

25.9 Intracranial Hematoma and Nonsurgical Treatment

Intracranial hematomas carry a worse prognosis unless evacuated because of cerebral ischemia caused the expanding lesions. Before surgical evacuation of the hematoma, many therapies such as mannitol, hyperventilation, and volume expansion with fluids or pressor drugs are advocated to lower the rising ICP. The MAP under such circumstances should preferably be at least 80 mmHg [80] because mortality rate is increased when the MAP declines below 80 mmHg [81].

Jugular venous saturation ($Sjvo_2$) monitoring might give a useful clue regarding the adequacy of cerebral perfusion [81, 82] and should ideally be kept above 50%. A fiberoptic oxygen catheter is placed in the dominant internal jugular vein with its tip positioned in the jugular bulb. The $Sjvo_2$ can serve as a useful adjunct to maintain cerebral perfusion in the setting of increased ICP because of an intracranial hematoma [83].

Conclusion

Unlike spontaneous intracranial hemorrhage which is preceded by a transient ischemic attack, and where treatment regimens are limited, intracranial hemorrhage that occurs during or after intracranial surgery can be a devastating and fatal complication if timely intervention and surgical evacuation of the POH is not attempted.

There does exist an impending risk for the development of intracranial hematoma following any intracranial surgical operation. Since postoperative hematoma is associated with a high mortality, all measures should be instituted to prevent its occurrence. Hence, it should become a prerogative that these patients are catered for in the intensive care unit for an overnight. Together with the list of remedial measures outlined above, we recommend that the occult bleeders should be reactivated by a hemodynamic stress following the initial surgical hemostasis and then a re-hemostasis of the bleeders achieved. A hemodynamic stress encourages occult bleeders to spurt again, thus providing a chance to the surgeon to conduct a vigilant re-hemostasis which substantially decreases the risk of postoperative hematoma formation.

References

1. Palmer JD, Sparrow OC, Iannotti F. Postoperative hematoma: a 5-year survey and identification of avoidable risk factors. Neurosurgery. 1994;35(6):1061–5.
2. Vassilouthis J, Anagnostaras S, Papandreou A, Dourdounas E. Is postoperative haematoma an avoidable complication of intracranial surgery? Br J Nurosurg. 1999;13(2):154–7.

3. Seifman MA, Lewis PM, Rosenfeld JV, Hwang PY. Postoperative intracranial haemorrhage: a review. Neurosurg Rev. 2011;34(4):393–407.
4. Kalfas IH, Little JR. Postoperative hemorrhage: a survey of 4992 intracranial procedures. Neurosurgery. 1988;23(3):343–7.
5. Taylor WA, Thomas NW, Wellings JA, Bell BA. Timing of postoperative intracranial hematoma development and implications for the best use of neurosurgical intensive care. J Neurosurg. 1995;82(1): 48–50.
6. Fukamachi A, Koizumi H, Nukui H. Postoperative intracerebral hemorrhages: a survey of computed tomographic findings after 1074 intracranial operations. Surg Neurol. 1985;23(6):575–80.
7. Koizumi H, Fukamachi A, Nukui H. Postoperative subdural fluid collections in neurosurgery. Surg Neurol. 1987;27(2):147–53.
8. Haines SJ, Maroon JC, Jannetta PJ. Supratentorial intracerebral hemorrhage following posterior fossa surgery. J Neurosurg. 1978;49(6):881–6.
9. Harders A, Gilsbach J, Weigel K. Supratentorial space occupying lesions following infratentorial surgery early diagnosis and treatment. Acta Neurochir. 1985;74(1–2):57–60.
10. Waga S, Shimosaka S, Sakakura M. Intracerebral hemorrhage remote from the site of the initial neurosurgical procedure. Neurosurgery. 1983;13(6):662–5.
11. Waga S, Shimizu T, Shimosaka S, Tochio H. Intratumoral hemorrhage after a ventriculoperitoneal shunting procedure. Neurosurgery. 1981;9(3):249–52.
12. Palmer JD, Francis DA, Roath OS, Francis JL, Iannotti F. Hyperfibrinolysis during intracranial surgery: effect of high dose aprotinin. J Neurol Neurosurg Psychiatry. 1995;58(1):104–6.
13. Olsen KS, Pedersen CB, Madsen JB, Ravn LI, Schifter S. Vasoactive modulators during and after craniotomy: relation to postoperative hypertension. J Neurosurg Anesth. 2002;14(3):171–9.
14. Singh VP, Jain D, Mohan R, Bhatia R, Bhargava M. Haemostatic abnormalities in brain tumours. Acta Neurochir. 1990;102(3-4):103–7.
15. Manjunath Prasad KS, Sharma BS, Marwaha N, Sarode RS, Kak VK. Haemostatic derangement in patients with intracranial tumours. Br J Neurosurg. 1994;8(6):695–702.
16. Sawaya R, Donlon JA. Chronic disseminated intravascular coagulation and metastatic brain tumor: a case report and review of the literature. Neurosurgery. 1983;12(5):580–4.
17. Sawaya R, Glas-Greenwalt P. Postoperative venous thromboembolism and brain tumors. J Neurooncol. 1992;14:127–34.
18. Oka K, Tsuda H, Kamikaseda K, Nakamura R, Fukui M, Nouzuka Y, Sueishi K. Meningiomas and hemorrhagic diathesis. J Neurosurg. 1988;69(3):356–60. 80
19. Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population a systematic review. Stroke. 2003;34(8):2060–5.
20. Kongstad L, Grände PO. Arterial hypertension increases intracranial pressure in cat after opening of the blood-brain barrier. J Trauma Acute Care Surg. 2001;51(3):490–6.
21. Mayhan WG. Disruption of blood-brain barrier during acute hypertension in adult and aged rats. Am J Physiol Heart Circ Physiol. 1990;258(6):H1735–8.
22. Hatashita S, Hoff JT, Ishii S. Focal brain edema associated with acute arterial hypertension. J Neurosurg. 1986;64(4):643–9.
23. Forster A, Van Horn K, Marshall LF, Shapiro HM. Anesthetic Effects on Blood—brain barrier function during acute arterial hypertension. Anesthesiology. 1978;49(1):26–30.
24. Leweh W, Hummel R, Littlewood K. Recovery from anesthe-sia and cerebral blood flow velocity. Anesth Analg. 1992;74:S186.
25. Gibson BE, Black S, Maass L, Cucchiara RF. Esmolol for the control of hypertension after neurologic surgery. Clin Pharmacol Ther. 1988;44(6):650–3.
26. Mackenzie AF, Colvin JR, Kenny GN, Bisset WI. Closed loop control of arterial hypertension following intracranial surgery using sodium nitroprusside. Anaesthesia. 1993;48(3):202–4.
27. Todd MM, Warner DS, Sokoll MD, Maktabi MA, Hindman BJ, Scamman FL, Kirschner J. A prospective, comparative trial of three anesthetics for elective supratentorial craniotomy. Propofol/fentanyl, isoflurane/nitrous oxide, and fentanyl/nitrous oxide. Anesthesiology. 1993;78(6):1005–20.
28. Basali A, Mascha EJ, Kalfas I, Schubert A. Relation between perioperative hypertension and intracranial hemorrhage after craniotomy. Anesthesiology. 2000; 93(1):48–54.
29. Felding M, Cold GE, Jagobsen CJ, Stjernholm P, Voss K. The effect of ketanserin upon postoperative blood pressure, cerebral blood flow and oxygen metabolism in patients subjected to craniotomy for cerebral tumours. Acta Anaesthesiol Scand. 1995;39(5):582–5.
30. Bruder N, Ravussin P. Recovery from anesthesia and postoperative extubation of neurosurgical patients: a review. J Neurosurg Anesth. 1999;11(4):282–93.
31. Grillo P, Bruder N, Auquier P, Pellissier D, Gouin F. Esmolol blunts the cerebral blood flow velocity increase during emergence from anesthesia in neurosurgical patients. Anesth Analg. 2003;96(4):1145–9.
32. Kovac AL, Masiongale A. Comparison of nicardipine versus esmolol in attenuating the hemodynamic responses to anesthesia emergence and extubation. J Cardiothorac Vasc Anesth. 2007;21(1):45–50.
33. Haas CE, LeBlanc JM. Acute postoperative hypertension: a review of therapeutic options. Am J Health Syst Pharm. 2004;61(16):1661–75.
34. Puchstein C. Treatment of hypertensive crisis in neurosurgery. Ann Fr Anesth Reanim. 1989;8:598–602.
35. Bekker A, Sturaitis MK. Dexmedetomidine for neurological surgery. Operative Neurosurgery. 2005;57(1): 1–10.

36. Günes Y, Gündüz M, Özcengiz D, Özbek H, Isik G. Dexmedetomidine-remifentanil or propofol-remifentanil anesthesia in patients undergoing intracranial surgery. Neurosurgery Quarterly. 2005;15(2): 122–6.
37. Owen Jr CA, Bowie EW. Surgical hemostasis. J Neurosurg. 1979;51(2):137–46.
38. Levy ML, Amar AP. The use of oxidized regenerated cellulose in neurosurgical procedures. Surg Technol Int. 1998;7:467.
39. Scarff JE, Stookey B, Garcia F. The use of dry oxidized cellulose as a primary hemostatic agent in neurosurgery. J Neurosurg. 1949;6(4):304–6.
40. Dutton JJ, David TT, Anderson RL. Compressive optic neuropathy following use of intracranial oxidized cellulose hemostat. Ophthalmic Surg, Lasers Imaging Retina. 1983;14(6):487–90.
41. Menovsky T, Plazier M, Rasschaert R, Maas AI, Parizel PM, Verbeke S. Massive swelling of Surgicel® Fibrillar™ hemostat after spinal surgery. Case report and a review of the literature. Minim Invasive Neurosurg MIN. 2011;54(5–6):257–9.
42. Kothbauer KF, Jallo JI, Stiffert J, Jimenez E, Allen JC, Epstein FJ. Foreign body reaction to hemostatic materials mimicking recurrent brain tumor. Report of three cases. J Neurosurg. 2001;95:503–6.
43. Menovsky T, Kamerling N, Sener S, Parizel PM, Maas AIR. New hemostatic powder (Gelitacel Ca Powder TM) and its application in cranial neurosurgery. Open J Modern Neurosurg. 2014;4:142–9.
44. Merriman E, Bell W, Long DM. Surgical postoperative bleeding associated with aspirin ingestion: report of two cases. J Neurosurg. 1979;50(5):682–4.
45. Touho H, Hirakawa K, Hino A, Karasawa J, Ohno Y. Relationship between abnormalities of coagulation and fibrinolysis and postoperative intracranial hemorrhage in head injury. Neurosurgery. 1986;19(4): 523–31.
46. Go Y-C, Tsoi WC, Feng CS, Wickham N, Poon WS. Hemostatic changes during surgery for primary brain tumors. J Neurol Neurosurg Psychiatry. 1997;63:334–8.
47. Chan KH, Mann KS, Chan TK. The significance of thrombocytopenia in the development of postoperative intracranial hematoma. J Neurosurg. 1989;71(1):38–41.
48. Kwaan HC. Diseases of hemostasis. In: Beal JM, editor. Critical care for surgical patients. New York: Macmillan; 1982. p. 588–98.
49. Bullock R, Hannemann CO, Murray L, Teasdale GM. Recurrent hematomas following craniotomy for traumatic intracranial mass. J Neurosurg. 1990;72(1): 9–14.
50. Colman RW, Robboy SJ, Minna JD. Disseminated intravascular coagulation (DIC): an approach. Am J Med. 1972;52(5):679–89.
51. Gerlach R, Raabe A, Zimmermann M, Siegemund A, Seifert V. Factor XIII deficiency and postoperative hemorrhage after neurosurgical procedures. Surg Neurol. 2000;54(3):260–6.
52. Gerlach R, Tölle F, Raabe A, Zimmermann M, Siegemund A, Seifert V. Increased risk for postoperative hemorrhage after intracranial surgery in patients with decreased factor XIII activity implications of a prospective study. Stroke. 2002;33(6):1618–23.
53. Dickinson LD, Miller LD, Patel CP, Gupta SK. Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors. Neurosurgery. 1998;43(5):1074–9.
54. Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. Lancet. 1999;354(9193):1879.
55. Khan ZH, Soltani AE, Rahmani P. Postoperative pulmonary thromboembolism possibly associated with recombinant activated factor VII infusion for the treatment of uncontrolled hemorrhage during vertebral instrumentation. J Anesth. 2007;21(2):258–60.
56. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. Recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med. 2005;352(8):777–85.
57. Zetterling M, Ronne-Engström E. High intraoperative blood loss may be a risk factor for postoperative hematoma. J Neorosurg Anesthesiol. 2004;16(2): 151–5.
58. Palmer JD, Francis JL, Pickard JD, Iannotti F. The efficacy and safety of aprotinin for hemostasis during intracranial surgery. J Neurosurg. 2003;98(6):1208–16.
59. Arand AG, Sawaya R. Intraoperative chemical hemostasis in neurosurgery. Neurosurgery. 1986;18(2): 223–33.
60. Wilson C. General considerations. In: Apuzzo M, editor. Brain surgery: complication, avoidance and management. New York: Churchill Livingston; 1993. p. 177–85.
61. Seiler RW, Zurbrügg HR. Supratentorial intracerebral hemorrhage after posterior fossa operation. Neurosurgery. 1986;18(4):472–4.
62. Thiarajah S. Postoperative care of neurosurgical patients. Int Anesth clin. 1983;21(1):139–56.
63. Rohde V, Rohde I, Thiex R, Küker W, Ince A, Gilsbach JM. The role of intraoperative magnetic resonance imaging for the detection of hemorrhagic complications during surgery for intracerebral lesions an experimental approach. Surg Neurol. 2001;56(4): 266–74.
64. Butler WE, Piaggio CM, Constantinou C, Niklason L, Gonzalez RG, Cosgrove GR, Zervas NT. A mobile computed tomographic scanner with intraoperative and intensive care unit applications. Neurosurgery. 1998;42(6):1304–10.
65. Izumihara A, Ishihara T, Iwamoto N, Yamashita K, Ito H. Postoperative outcome of 37 patients with lobar intracerebral hemorrhage related to cerebral amyloid angiopathy. Stroke. 1999;30(1):29–33.
66. Johnston IH, Jennett B. The place of continuous intracranial pressure monitoring in neurosurgical practice. Acta Neurochir. 1973;29(1–2):53–63.

67. Kaye AH, Brownbill D. Postoperative intracranial pressure in patients operated on for cerebral aneurysms following subarachnoid hemorrhage. J Neurosurg. 1981;54(6):726–32.
68. Khan ZH, Tabatabai SA, Saberi H, Aliari M. Vigilant surgical hemostasis challenged by ketamine or hypervolemia induced hemodynamic stress to minimize postoperative hemorrhage in patients with parasagittal/or parafalcian meningiomas: an interventional study. Acta Anaesthesiol Taiwan. 2005;43(4):217–22.
69. Innerhofer P, Fries D, Margreiter J, Klingler A, Kühbacher G, Wachter B, Oswald E, Salner E, Frischhut B, Schobersberger W. The effects of perioperatively administered colloids and crystalloids on primary platelet-mediated hemostasis and clot formation. Anesth Analg. 2002;95(4):858–65.
70. Bruder N, Cohen B, Pellissier D, Francois G. The effect of hemodilution on cerebral blood flow velocity in anesthetized patients. Anesth Analg. 1998;86(2): 320–4.
71. Boldt J, Knothe C, Zickmann B, Andres P, Dapper F, Hempelmann G. Influence of different intravascular volume therapies on platelet function in patients undergoing cardiopulmonary bypass. Anesth Analg. 1993;76(6):1185–90.
72. Mielke LL, Entholzner EK, Kling M, Breinbauer BE, Burgkart R, Hargasser SR, Hipp RF. Preoperative acute hypervolemic hemodilution with hydroxyethylstarch: an alternative to acute normovolemic hemodilution. Anesth Analg. 1997;84(1):26–30.
73. Lindahl SG. Thinner than blood. Anesth Analg. 1995; 80(2), 217–18. Marlow R, Reich DL, Neustein S, Silvay G. Haemodynamic response to induction of anaesthesia with ketamine/midazolam. Can J of Anaesth. 1991;38(7):844–8.
74. Strebel S, Kaufmann M, MAÎRE L, Schaefer HG. Effects of ketamine on cerebral blood flow velocity in humans Influence of pretreatment with midazolam or esmolol. Anaesthesia. 1995;50(3):223–8.
75. Åkeson J, Björkman S, Messeter K, Rosen I, Helfer M. Cerebral pharmacodynamics of anaesthetic and subanaesthetic doses of ketamine in the normoventilated pig. Acta Anaesthesiol Scand. 1993;37(2): 211–8.
76. Albanese J, Arnaud S, Rey M, Thomachot L, Alliez B, Martin C. Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. Anesthesiology. 1997;87(6):1328–34.
77. Gardner AE, Olson BE, Lichticer M. Cerebrospinal-fluid pressure during dissociative anesthesia with ketamine. Anesthesiology. 1971;35(2):226–8.
78. Cavazzuti M, Porro CA, Biral GP, Benassi C, Barbieri GC. Ketamine effects on local cerebral blood flow and metabolism in the rat. J Cereb Blood Flow Metab. 1987;7(6):806–11.
79. Ohata H, Iida H, Nagase K, Dohi S. The effects of topical and intravenous ketamine on cerebral arterioles in dogs receiving pentobarbital or isoflurane anesthesia. Anesth Analg. 2001;93(3):697–702.
80. Shapiro HM, Drummond JC. Neurosurgical anesthesia. In: Miller RD, et al., editors. Anesthesia. New York: Churchill Livingstone; 1994. p. 1897–946.
81. Gopinath SP, Robertson CS, Contant CF, Hayes C, Feldman Z, Narayan RK, Grossman RG. Jugular venous desaturation and outcome after head injury. J Neurol Neurosurg Psychiatry. 1994;57(6):717–23.
82. Dearden NM. Jugular bulb venous oxygen saturation in the management of severe head injury. Cur Opin Anesth. 1991;4(2):279–86.
83. Gopinath S, Cormio M, Ziegler J, Raty S, Valadka A, Robertson C. Intraoperative jugular desaturation during surgery for traumatic intracranial hematomas. Anesth Analg. 1996;83(5):1014–21.

26 Neuroprotection in Neuroanesthesia and Neurocritical Care

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26.1 Introduction

It is well-known that patients undergoing neurosurgical procedures and patients with acute neurological injury are at high risk for developing long-term neurological deficits [1]. Providing neuroprotection after brain surgery and neurological injury is the primary goal of neuroanesthesia and neurocritical care and has been the subject of significant research and interest [2].

When considering the optimal timing and method of providing neuroprotection, there is great importance in understanding the underlying physiology of perioperative and traumatic neurological injury. Mechanistically, the neurological injury can be classified into two classifications that differ in their time course: primary and secondary injury [3]. While the primary injury is immediate and results from the direct mechanical injury, secondary injury typically progresses over hours to days after the primary injury and results from a subsequent cascade of mechanical and chemical events that significantly alters the normal cerebral physiology. The mechanism of secondary brain injury is attributed to changes in cerebral blood flow and intracranial pressure (ICP), hypoxemia, systemic hypotension, and cerebral edema.

In recent years, the neuroprotective effects of several pharmacological and nonpharmacological agents have been investigated with mixed results. In this chapter, we review the clinical evidence on neuroprotective strategies in patients undergoing neurosurgical procedures and in neurocritically ill patients (particularly after stroke and traumatic brain injury [TBI]). Although there has been a plethora of preclinical studies in recent years that have examined the neuroprotective effects of numerous agents, this chapter focuses on therapeutic modalities that have been investigated in human studies.

26.2 Perioperative Neuroprotection in Patients Undergoing Neurological Surgery

Patients undergoing neurological surgery are at high risk for developing new neurological deficits related to the underlying neurological to disease as well as procedure-related complications. However, there have been few clinical studies

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that have investigated neuroprotective agents for patients undergoing neurological surgery. Moreover, because patients undergoing neurological surgery are vastly heterogeneous in their underlying physiology and surgery, most studies that have investigated neuroprotective agents have been limited to studying specific patient populations, surgery types, or specific postoperative complications. Importantly, despite promising preclinical studies, studies in human patients have failed to demonstrate that one single agent provides neuroprotection in all patients undergoing neurosurgery.

26.2.1 Blockade of Endogenous Opioids

Recent clinical studies that have examined the neuroprotective effects of various agents in patients undergoing neurosurgical procedures have followed promising results in animal models, and have all targeted various components of the complex mechanisms thought to play an important role in the development of secondary brain injury. The release of endogenous opioids after an acute neurological event is one such mechanism that is thought to propagate secondary brain, and preclinical studies have suggested that opiate receptor blockade or minimizing endogenous opioid release may provide neuroprotection after neurological injury [4]. A recent retrospective study examined the neuroprotective effects of the opiate receptor antagonist nalmefene after brain surgery complicated by intracranial hemorrhage [5]. Although the administration of nalmefene was found to be safe, the study failed to demonstrate any improvement in short-term consciousness or long-term function outcomes. A second recent retrospective study investigated the neuroprotective effects of remifentanil in more than 4500 patients undergoing surgical clipping of intracranial aneurysm [6]. Although the authors demonstrated a difference in mortality (4.7 vs. 7.7%) in patients with a ruptured aneurysm, they otherwise demonstrated no differences in postoperative length of stay, or in the postoperative neurological, cardiovascular, or pulmonary complications.

26.2.2 Propofol

Propofol is commonly used in neurosurgical procedures because of its effects on reducing cerebral metabolism and blood flow, and some studies have investigated whether propofol may offer neuroprotective advantages over other general anesthetic agents [2]. After two randomized controlled trials (RCTs) failed to demonstrate neuroprotective effects of propofol in patients undergoing cardiac surgery [7, 8], a recent RCT in 66 patients undergoing open aneurysm clipping failed to demonstrate any improvement in postoperative neurological outcomes or cognitive function when propofol was administered to attain burst suppression [9].

26.2.3 Brain Relaxation

The achievement of adequate brain relaxation during brain surgery for intracranial tumor resection is thought to improve surgical exposure and improve cerebral perfusion. It is unclear, however, whether the choice of hyperosmotic agent is superior in achieving brain relaxation, or whether an improvement in brain relaxation translates to improved neurological outcomes after surgery. To this end, a recent RCT in 74 patients examined whether equivolume, equiosmolar solutions of mannitol versus hypertonic saline was superior in achieving adequate brain relaxation and minimizing postoperative complications. Although patients who were administered hypertonic saline achieved more brain relaxation compared with mannitol, there were no differences between groups with regard to postoperative complications, length of hospital stay, or length of intensive care unit stay.

26.3 Traumatic Brain Injury

TBI is a leading cause of morbidity and mortality worldwide [10]. Despite a significant reduction in TBI-associated deaths over the past decade [11], severe TBI results in a poor neurological outcome or death in more than 50% of patients [12]. Therefore, therapeutic interventions that

improve neurological outcomes and reduce mortality after TBI are greatly needed.

The urgent pursuit of neuroprotective agents to treat TBI has generated more interest and literature than perhaps any other area in neuroanesthesia and neurocritical care. Currently, treatment of acute TBI aims at reducing ICP and maximizing cerebral perfusion, and agents that target secondary brain injury have largely failed to unequivocally improve outcomes. In the past few years, clinical studies that investigated the neuroprotective effects of dozens of agents after TBI have undergone extensive investigation, with varying degrees of success. The evidence provided by these studies were recently reviewed at length [3], and the summary of the individual studies is shown in Table 26.1. While there were no agents that unequivocally improved outcomes in all patients, several agents have demonstrated possible neuroprotective effects. Importantly, however, many of the studies with demonstrated positive results were limited by small sample sizes or retrospective study designs. In this chapter, we summarize some of the recent studies in which agents were shown to demonstrate potential neuroprotective effects. We also review some agents in which conflicting evidence has been demonstrated in the literature. Although the following list is not exhaustive, it highlights some of the agents in which further investigation is likely warranted.

26.3.1 Growth Hormone

Growth hormone deficiency is common after TBI and is associated with dysfunction in behavior and cognition [13]. Moreover, even in the absence of growth hormone deficiency, growth hormone treatment is thought to play an important role in facilitating neuronal recovery after TBI [3]. Recently, three studies demonstrated potential neuroprotective effects of growth hormone therapy [14–16]. Specifically, these studies demonstrated that growth hormone treatment resulted in improvements in most cognitive functions such as attention and executive function [17], improvements in daily living tasks [17], and an improvement in quality of life that was sustained for several years [17]. Importantly, patients were not randomized in any of these three studies, and the studies were limited by a small sample size. Moreover, only one of the studies demonstrated improvements in cognition and behavior when growth hormone was administered in absence of growth hormone deficiency. Therefore, while these studies suggest a possible neuroprotective role of growth hormone replacement therapy after TBI, it is unclear who might benefit from its use.

26.3.2 Statins

Studies in animal models of TBI have suggested that statin therapy improves neuronal survival in the hippocampus and improves functional outcomes [18], possibly by inducing neurogenesis and angiogenesis after TBI [19]. A recent RCT demonstrated 10-day treatment of rosuvastatin after TBI was associated with a reduction in disability score and improved functional outcomes compared with placebo-treated patients at 3 and 6 months post-TBI [20]. Moreover, a second retrospective study showed that statin discontinuation on hospital admission after TBI was associated with fourfold higher mortality compared with patients in whom statins were continued [21]. These recent studies suggest that the neuroprotective effects of statins are worth further investigation, and larger RCTs are needed to identify who might benefit from its use.

26.3.3 Marijuana

Preclinical animal studies have demonstrated that cannabinoid analogues offer neuroprotection by reduction of brain glutamate excitotoxicity, free radical damage, and inflammation [22], and may improve outcomes after TBI [23]. Moreover, a recent retrospective study in humans showed that a positive THC screen was associated with a decreased incidence of mortality after TBI [24]. Although phase I [25] and phase II [26] clinical trials suggested that dexanabinol is safe and may help improve ICP after TBI, a multicenter phase III trial failed to show an improvement in

Table 26.1 Recent studies from 2013 to 2015 that have demonstrated neuroprotective effects or mixed results of various agents to improve outcomes after traumatic brain injury

Study	Study design	*n*	Intervention	Primary end points	Conclusions
Demonstrated neuroprotection					
Moreau, 2013 [14]	Case control	50	Growth hormone	Cognition, ADL, and QoL after 1 year of treatment	GH therapy in TBI patients with GH deficiency may improve cognitive functions, ADL, and QoL functions.
Devesa, 2013 [15]	Case series	13	growth hormone	Cognitive and behavioral function	GH therapy may improve cognitive and behavioral function after TBI regardless of whether or not the patient is GH-deficient.
Gardner, 2015 [16]	Retrospective chart review	564	Growth Hormone	QoL scores and dimensions	GH replacement therapy resulted in long-term benefit in QoL in patients with TBI
Sanchez-Aguilar, 2013 [20]	Randomized controlled trial	36	Rosuvastatin	1. Effect of rosuvastatin on plasma levels of TNF, IL 1, 6 and 10 after 72 h after TBI 2. Amnesia, disorientation and disability at 6 month after TBI	Statins may partially reduce proinflammatory mediators and may improve functional recovery after TBI
Orlando, 2013 [21]	Retrospective chart review	93	Statins	In-hospital mortality, having at least one complication, and hospital length of stay >1 week	Abrupt, unintended discontinuation of statin therapy is associated with an increased risk of mortality in the elderly TBI population
Nguyen, 2014 [24]	Retrospective chart review	446	Marijuana	Mortality	A positive THC screen is associated with a decreased mortality after TBI
Mohseni, 2014 [29]	Retrospective chart review	662	Beta blockers	In-hospital mortality	Pre-injury beta blockade improves survival following isolated severe TBI
Hoffer, 2013 [33]	Randomized controlled trial	70	N-acetyl cysteine	Balance dysfunction, confusion, sensorineural hearing loss, headache, impaired memory and sleep disturbances	NAC has beneficial effects on the severity and resolution of sequelae of blast-induced mild TBI (especially with early intervention)

Theadom, 2013 [35]	Randomized controlled trial	60	Enzogenol	Cognitive failures and working and episodic memory at baseline, 6, 12, and 16 weeks	Enzogenol might reduce self-perceived cognitive failures 3–12 months after mild TBI
Chen, 2013 [37]	Randomized controlled trial	32	Cerebrolysin	Differences in cognitive function including MMSE, CASI scores at week 1, between baseline and week 4, and between baseline and week 12	Cerebrolysin improves cognitive function in patients with mild TBI at 3 months after injury, especially for long-term memory and drawing function
Stover, 2014 [40]	Randomized controlled trial	32	Nitric oxide synthase inhibitor 4-amino-tetrahydrobiopterin (VAS203)	ICP, CPP, brain metabolism, the therapy intensity level, and GOS-E after 6 months	The significant improvement in clinical outcome indicates VAS203-mediated neuroprotection after TBI, but was associated with a risk of acute kidney injury at the highest dose
Mixed results					
Shakeri, 2013 [43]	Randomized controlled trial	76	Progesterone	Mortality rate, GCS on discharge, and GOS 3 months after discharge	Progesterone improves neurological outcome in patients with severe TBI
Skolnick, 2014 [46]	Randomized controlled trial	1195	Progesterone	GOS at 3 and 6 month, mortality rate at 1 and 3 month; Short-Form Health Survey scale at 3 and 6 months	Progesterone treatment has no effect on clinical outcome in patients with moderate TBI
Wright, 2014 [45]	Randomized controlled trial	882	Progesterone	Extended GOS at 6 months, mortality rate, disability rating scale score	Progesterone did not improve the outcome of patients with acute moderate-to-severe TBI

(continued)

Table 26.1 (continued)

Study	Study design	*n*	Intervention	Primary end points	Conclusions
Raj, 2015 [48]	Retrospective chart review	405	Ethanol	6-month mortality and unfavorable neurological outcome (GOS 1–3)	Low admission BAC (<2.3%) demonstrated an independent risk reduction of 6-month morality, and a trend toward improved long-term neurological outcome in BAC-positive patients
Pandit, 2014 [49]	Retrospective chart review	23,983	Ethanol	Mortality	Ethanol intoxication is an independent predictor for mortality in patients with severe TBI, and is associated with higher complication rates
Scheyerer, 2014 [50]	Retrospective chart review	383	Ethanol	Mortality	Patients with positive ethanol have a higher incidence of severe TBI and worse initial physiological parameters, but similar survival and hospital course, suggesting a possible neuroprotective role of ethanol
Majdan, 2013 [56]	Retrospective chart review	1172	Barbiturates	ICP use of vasopressors, and short and long-term outcomes including injury severity and treatment factors, mortality, and GOS	The benefits of reduced ICP with barbiturates after TBI may be offset by marked hemodynamic instability. The use of barbiturates did not improve short or long-term outcomes after TBI

Aloizos, 2015 [59]	Randomized controlled trial	42	Erythropoietin	Unfavorable neurological outcomes at 6 months (GOS-E 2–4 or death), probability of an equal, greater, or lesser GOS-E at 6 months, proportion of surviving patients with unfavorable neurological outcome (GOS-E 2–4) at 6 months, 6-month mortality	Epo may be effective in limiting neuronal damage after TBI, resulting in lower mortality and improved neurological outcomes
Robertson, 2014 [60]	Randomized controlled trial	200	Erythropoietin	GOS at 6 months after TBI, incidence of pulmonary complications, DVT, and pulmonary embolism	Epo administration in patients with TBI does not improve neurological outcomes or mortality Maintenance of Hb concentration with hemotransfusions above 10 g/dl in TBI patients is not beneficial and may even be harmful
Nichol, 2015 [61]	Randomized controlled trial	606	Erythropoietin	Improvement in patients' neurological status, summarized as a reduction in the proportion of patients with a GOS-E of 1–4	After moderate or severe TBI, Epo did not reduce the number of patients with severe neurological dysfunction or increase the incidence of DVT

Adapted with permission from Gruenbaum et al. [3]
TBI traumatic brain injury

functional outcomes, mortality, ICP, or quality of life [27]. As such, despite the neuroprotective properties of marijuana demonstrated in animal models, it is impossible at this point to draw conclusions on whether these properties translate to humans with TBI. Moreover, the timing, dose, and route of administration to best exploit these properties and improve outcomes are unknown at this time.

26.3.4 Beta Blockers

In the first few weeks after TBI, it is well known that the associated catecholamine surge results in cerebral vasoconstriction, brain hypoperfusion, resulting in worsening of secondary brain injury and multi-organ failure [3, 28]. In recent years, some studies have suggested that the administration of beta blockers may provide neuroprotection by blocking the catecholamine surge and its associated effects after TBI [29]. Moreover, a recent retrospective study demonstrated that pre-TBI treatment with beta blockers may also improve survival after severe TBI [30]. Importantly, however, the differences in mortality demonstrated were correlative, the mechanisms of neuroprotection were speculative, and a causative link between beta blockade and improved survival could be determined. At this time, further investigations with clinical trials are needed before any specific recommendations can be made regarding the use of beta blockers in patients with TBI.

26.3.5 N-acetyl-L-cysteine

It is well known that N-acetyl-L-cysteine (NAC) has antioxidant and anti-inflammatory properties, and previous studies have demonstrated neuroprotective effects of NAC in animal models of both stroke and TBI [31, 32]. A recent RCT [33] suggested that soldiers with mild TBI after blast injury had a higher resolution of TBI-related symptoms within 7 days of NAC treatment. These findings suggest a possible role of NAC in the treatment of mild TBI, although it should be pointed out that the study had a small sample size (81 patients) and was limited to patients with mild TBI after blast injury. The neuroprotective effects of NAC should be further investigated in larger RCTs before recommendations can be made regarding their use.

26.3.6 Enzogenol

The neuroprotective effects of enzogenol, a pine bark extract that is known to possess antioxidant and anti-inflammatory properties [34], were investigated in a recent phase II RCT [35]. In the study, 60 patients with cognitive dysfunction 3–12 months after mild TBI were randomized to receive either enzogenol or placebo for 6 weeks. The authors demonstrated an improvement in cognitive failures and in the frequency of self-reported cognitive failures. Despite promising results, the study was limited by a small sample size, and only included patients with mild TBI and specific cognitive disorders. Therefore, before it is possible to draw meaningful conclusions about the neuroprotective effects of enzogenol at this time, larger RCTs in other patient populations are needed.

26.3.7 Cerebrolysin

Cerebrolysin is a neurotrophic agent that mimics the actions of endogenous neurotrophic effects on repair after injury, and studies have successfully shown that cerebrolysin improves cognitive function in patients with Alzheimer's dementia and after stroke [36]. A recent phase II pilot RCT demonstrated that 5 days of cerebrolysin treatment in patients with mild TBI resulted in improved cognition, drawing function, and memory [37]. The study did not investigate cerebrolysin's effects on mortality, however, and the study was limited by a small sample size. However, the demonstrated effects warrant further study with larger RCTs.

26.3.8 Nitric Oxide Synthase Inhibitor

Nitric oxide (NO) is thought to promote cellular injury after TBI by dilating cerebral vessels and the contributing to the production of reactive nitrogen species [38]. Blockade of the NO-mediated pathways has previously been shown to decrease ICP and improve outcomes in animal models of TBI [39]. A recent RCT demonstrated that treatment with 4-amino-tetrahydrobiopterin (VAS203) in 32 patients with TBI resulted in improvements in functional outcomes after 6 months [40]. Like cerebrolysin, however, the study was limited by a small sample size, and the effects on mortality were not studied. As such, larger future studies are needed.

26.3.9 Progesterone

The possible neuroprotective effects of progesterone have yielded much interest and scrutiny in recent years [41, 42]. Several properties of progesterone make for a highly attractive agent in treating TBI: It rapidly crosses the blood brain barrier and has antioxidant, anti-inflammatory, and remyelination effects after brain injury [43]. After phase I and phase II RCTs demonstrated improved outcomes in TBI patients treated with progesterone [43–45], the recent larger phase III RCTs have failed to replicate the neuroprotective effects demonstrated in earlier studies [45, 46]. Therefore, until larger RCTs demonstrate which patients may benefit from progesterone treatment therapy after TBI, progesterone treatment cannot be recommended at this time to treat TBI.

26.3.10 Ethanol

Ethanol is a well-known inhibitor of glutamate receptors, and some studies have suggested that ethanol may have neuroprotective effects after TBI [47]. However, human studies in TBI patients with acute ethanol intoxication, or in patients who regularly consume ethanol, have been largely inconsistent. While one recent retrospective study demonstrated that TBI patients with a low blood alcohol concentration (BAC) at the time of hospital admission was associated with a lower 6-month mortality after TBI compared with BAC-negative patients [48], more recent studies have demonstrated that ethanol intoxication was an independent predictor for mortality [49], was associated with higher complication rates [49], and resulted in worse functional outcomes compared with BAC-negative patients after TBI [50]. It should be noted that these recent studies were all retrospective in design, and in each study, ethanol use was limited to before the injury. Therefore, at this time, it is difficult to ascertain which patients, if any, may benefit from alcohol after TBI. Importantly, designing an RCT that examines the neuroprotective effects of ethanol would be difficult for ethical reasons.

26.3.11 Barbiturates

Elevated ICP is common in patients TBI [51] and is associated with worsened secondary brain injury and poor outcomes. Barbiturates have long been used to treat intracranial hypertension after TBI [52], and they are thought to lower ICP by reducing cerebral oxygen consumption and metabolism and by scavenging free oxygen radical species [53]. However, because barbiturate use in patients after TBI is associated with an increased risk in infectious, pulmonary, and cardiovascular complications [54, 55], indiscriminate use in TBI patients is not recommended. Two recent retrospective studies with barbiturate therapy after TBI have yielded conflicting results. In the first study, high-dose barbiturate therapy resulted in a 69% decrease in ICP, but more importantly resulted in significant hemodynamic instability and no differences in mortality or long-term outcomes [56]. In the second study, barbiturate therapy in TBI patients with refractory intracranial hypertension resulted in improved neurological outcomes [57]. At this time, it is unclear who might benefit from barbiturate therapy after TBI.

26.3.12 Erythropoietin

Studies in animal models of TBI have demonstrated neuroprotective effects of erythropoietin (Epo) [58], which have been largely attributed to its anti-inflammatory and anti-apoptotic properties. Although early, smaller studies that showed that Epo may limit neurological damage after TBI, improve neurological outcomes, and lower mortality [59], more recent larger RCTs failed to demonstrate neuroprotective effects of Epo [60, 61], and even suggested that Epo treatment in TBI patients may even increase the incidence of thromboembolic events [60]. Therefore, in light of these recent studies, Epo treatment after TBI cannot be recommended at this time.

26.4 Stroke

Acute stroke is a leading cause of death and disability worldwide [1], and the Society for Neuroscience in Anesthesiology and Critical Care (SNACC) has created a task force to provide expert recommendation on the anesthetic management of patients admitted for surgical treatment of acute stroke [62]. Providing pharmacological and nonpharmacological therapies that result in neuroprotection is the primary goal in the clinical management of patients after acute stroke. However, although approximately 1500 clinical trials have been included in the Internet Stroke Trials Registry, there have been few studies that have been shown to consistently improve outcomes in patients after acute stroke [6]. Recent studies have similarly yielded mixed results. Here, we will review some of the recent studies that have shed some light on potential neuroprotective strategies that have been employed to improve clinical outcomes after stroke.

26.4.1 Magnesium Sulfate

Preclinical animal studies have suggested possible neuroprotective properties of magnesium [63]. A recent large, phase III RCT (Field Administration of Stroke Therapy–Magnesium [FAST MAG] study) showed that prehospital administration of magnesium therapy was safe when administered within 2 h after onset of stroke symptoms, but was ineffective in improving disability outcomes at 90 days after stroke [64]. Therefore, magnesium sulfate cannot be recommended at this time in the treatment of acute stroke.

26.4.2 Progesterone

Despite showing much promise in preclinical and early clinical trials, recent phase III RCTs have failed to demonstrate any improvement in outcomes with progesterone treatment after TBI as highlighted above. However, there is a plethora of evidence that suggests that progesterone therapy may have neuroprotective effects for other types of brain injury, including stroke, and many experts have highlighted whether progesterone therapy may play an important neuroprotective role after acute stroke [65]. However, the neuroprotective effects of progesterone therapy in stroke patients are largely unknown at this time.

26.4.3 General Anesthesia Versus Conscious Sedation for Clot Evacuation

While intra-arterial therapy is known to improve outcomes when initiated in the early time course after ischemic stroke, the decision of whether to perform this therapy under general anesthesia versus conscious is highly variable and largely institution and clinician dependent. In a recent, large retrospective study that included 348 patients undergoing intra-arterial therapy for treatment of ischemic stroke, patients who underwent general anesthesia had significantly worsened clinical outcomes compared with patients who underwent conscious sedation [66]. While the results of this study have important clinical implications, it should be pointed out that the study was not randomized, which introduces many potential important biases

[67]. As such, an RCT is urgently needed to determine whether these differences in outcomes are actually related to the type of anesthetic, or if the differences can be attributed to other confounding variables.

26.4.4 Extracorporeal Methods of Blood Glutamate Reduction

Recently, there has been much interest in exploring various methods of blood glutamate reduction, which has been suggested to increase the brain-to-blood glutamate efflux and improve neurological outcomes across a wide spectrum of acute brain insults [68]. Pharmacological experimental agents, termed blood glutamate scavengers, have been shown to improve outcomes in animal models of stroke [69], but may have unknown side effects in humans. Recently, extracorporeal methods of blood glutamate reduction, including hemofiltration, have been proposed as a safe alternative to pharmacological agents [70]. Currently, a phase II, prospective RCT is underway that is evaluating the effects of hemofiltration in the treatment of acute stroke [70].

Conclusions

Providing neuroprotection is the primary goal of neuroanesthesia and neurocritical care, and the discovery of therapeutic agents that meet these goals is urgently needed for patients with brain injury. To date, numerous agents have been studied across a wide spectrum of acute and chronic brain insults, many of which we have reviewed in this chapter. Although science has yet to identify a specific agent that provides neuroprotection in every context and patient population, there are several agents that have demonstrated promising results that should be investigated in future. These promising results, in combination with the devastating global impact of brain injury, justify the enormous time and costs required to move forward in the pursuit of discovering highly effective neuroprotective agents.

References

1. Badenes R, Gruenbaum SE, Bilotta F. Cerebral protection during neurosurgery and stroke. Curr Opin Anaesthesiol. 2015;28(5):532–6.
2. Bilotta F, Stazi E, Zlotnik A, Gruenbaum SE, Rosa G. Neuroprotective effects of intravenous anesthetics: a new critical perspective. Curr Pharm Des. 2014;20(34):5469–75.
3. Gruenbaum SE, Zlotnik A, Gruenbaum BF, Hersey D, Bilotta F. Pharmacologic neuroprotection for functional outcomes after traumatic brain injury: a systematic review of the clinical literature. CNS Drugs. 2016;30(9):791–806.
4. Faden AI, Shirane R, Chang LH, James TL, Lemke M, Weinstein PR. Opiate-receptor antagonist improves metabolic recovery and limits neurochemical alterations associated with reperfusion after global brain ischemia in rats. J Pharmacol Exp Ther. 1990;255(2):451–8.
5. Zheng J, Li H, Guo R, Chen R, Lin S, Liu M, et al. Neuroprotection of nalmefene for postoperative patients with spontaneous intracerebral hemorrhage. Int J Neurosci. 2015;125(12):918–23.
6. Uchida K, Yasunaga H, Sumitani M, Horiguchi H, Fushimi K, Yamada Y. Effects of remifentanil on in-hospital mortality and length of stay following clipping of intracranial aneurysm: a propensity score-matched analysis. J Neurosurg Anesthesiol. 2014;26(4):291–8.
7. Roach GW, Newman MF, Murkin JM, Martzke J, Ruskin A, Li J, et al. Ineffectiveness of burst suppression therapy in mitigating perioperative cerebrovascular dysfunction. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Anesthesiology. 1999;90(5):1255–64.
8. Kanbak M, Saricaoglu F, Avci A, Ocal T, Koray Z, Aypar U. Propofol offers no advantage over isoflurane anesthesia for cerebral protection during cardiopulmonary bypass: a preliminary study of S-100beta protein levels. Canadian journal of anaesthesia =. Journal canadien d'anesthesie. 2004;51(7):712–7.
9. Abdelmalak BB, Knittel J, Abdelmalak JB, Dalton JE, Christiansen E, Foss J, et al. Preoperative blood glucose concentrations and postoperative outcomes after elective non-cardiac surgery: an observational study. Br J Anaesth. 2014;112(1):79–88.
10. Waxweiler RJ, Thurman D, Sniezek J, Sosin D, O'Neil J. Monitoring the impact of traumatic brain injury: a review and update. J Neurotrauma. 1995;12(4):509–16.
11. Gerber LM, Chiu YL, Carney N, Hartl R, Ghajar J. Marked reduction in mortality in patients with severe traumatic brain injury. J Neurosurg. 2013;119(6):1583–90.
12. Marmarou A, Lu J, Butcher I, McHugh GS, Mushkudiani NA, Murray GD, et al. IMPACT database of traumatic brain injury: design and description. J Neurotrauma. 2007;24(2):239–50.

13. Falleti MG, Maruff P, Burman P, Harris A. The effects of growth hormone (GH) deficiency and GH replacement on cognitive performance in adults: a meta-analysis of the current literature. Psychoneuroendocrinology. 2006;31(6):681–91.
14. Moreau OK, Cortet-Rudelli C, Yollin E, Merlen E, Daveluy W, Rousseaux M. Growth hormone replacement therapy in patients with traumatic brain injury. J Neurotrauma. 2013;30(11):998–1006.
15. Devesa J, Reimunde P, Devesa P, Barbera M, Arce V. Growth hormone (GH) and brain trauma. Horm Behav. 2013;63(2):331–44.
16. Gardner CJ, Mattsson AF, Daousi C, Korbonits M, Koltowska-Haggstrom M, Cuthbertson DJ. GH deficiency after traumatic brain injury: improvement in quality of life with GH therapy: analysis of the KIMS database. Eur J Endocrinol. 2015;172(4):371–81.
17. Agha A, Rogers B, Sherlock M, O'Kelly P, Tormey W, Phillips J, et al. Anterior pituitary dysfunction in survivors of traumatic brain injury. J Clin Endocrinol Metab. 2004;89(10):4929–36.
18. Mahmood A, Goussev A, Kazmi H, Qu C, Lu D, Chopp M. Long-term benefits after treatment of traumatic brain injury with simvastatin in rats. Neurosurgery. 2009;65(1):187–91; discussion 91–2.
19. Lu D, Goussev A, Chen J, Pannu P, Li Y, Mahmood A, et al. Atorvastatin reduces neurological deficit and increases synaptogenesis, angiogenesis, and neuronal survival in rats subjected to traumatic brain injury. J Neurotrauma. 2004;21(1):21–32.
20. Sanchez-Aguilar M, Tapia-Perez JH, Sanchez-Rodriguez JJ, Vinas-Rios JM, Martinez-Perez P, de la Cruz-Mendoza E, et al. Effect of rosuvastatin on cytokines after traumatic head injury. J Neurosurg. 2013;118(3):669–75.
21. Orlando A, Bar-Or D, Salottolo K, Levy AS, Mains CW, Slone DS, et al. Unintentional discontinuation of statins may increase mortality after traumatic brain injury in elderly patients: a preliminary observation. J Clin Med Res. 2013;5(3):168–73.
22. Yoles E, Belkin M, Schwartz M. HU-211, a nonpsychotropic cannabinoid, produces short- and long-term neuroprotection after optic nerve axotomy. J Neurotrauma. 1996;13(1):49–57.
23. Shohami E, Biegon A. Novel approach to the role of NMDA receptors in traumatic brain injury. CNS Neurol Disord Drug Targets. 2014;13(4):567–73.
24. Nguyen BM, Kim D, Bricker S, Bongard F, Neville A, Putnam B, et al. Effect of marijuana use on outcomes in traumatic brain injury. Am Surg. 2014;80(10):979–83.
25. Brewster ME, Pop E, Foltz RL, Reuschel S, Griffith W, Amselem S, et al. Clinical pharmacokinetics of escalating i.v. doses of dexanabinol (HU-211), a neuroprotectant agent, in normal volunteers. Int J Clin Pharmacol Ther. 1997;35(9):361–5.
26. Knoller N, Levi L, Shoshan I, Reichenthal E, Razon N, Rappaport ZH, et al. Dexanabinol (HU-211) in the treatment of severe closed head injury: a randomized, placebo-controlled, phase II clinical trial. Crit Care Med. 2002;30(3):548–54.
27. Maas AI, Murray G, Henney 3rd H, Kassem N, Legrand V, Mangelus M, et al. Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial. Lancet Neurol. 2006;5(1):38–45.
28. Clifton GL, Ziegler MG, Grossman RG. Circulating catecholamines and sympathetic activity after head injury. Neurosurgery. 1981;8(1):10–4.
29. Mohseni S, Talving P, Wallin G, Ljungqvist O, Riddez L. Preinjury beta-blockade is protective in isolated severe traumatic brain injury. J Trauma Acute Care Surg. 2014;76(3):804–8.
30. Arbabi S, Campion EM, Hemmila MR, Barker M, Dimo M, Ahrns KS, et al. Beta-blocker use is associated with improved outcomes in adult trauma patients. J Trauma. 2007;62(1):56–61; discussion 60–2.
31. Sekhon B, Sekhon C, Khan M, Patel SJ, Singh I, Singh AK. N-Acetyl cysteine protects against injury in a rat model of focal cerebral ischemia. Brain Res. 2003;971(1):1–8.
32. Hicdonmez T, Kanter M, Tiryaki M, Parsak T, Cobanoglu S. Neuroprotective effects of N-acetylcysteine on experimental closed head trauma in rats. Neurochem Res. 2006;31(4):473–81.
33. Hoffer ME, Balaban C, Slade MD, Tsao JW, Hoffer B. Amelioration of acute sequelae of blast induced mild trauamatic brain injury by N-acetyl cysteine: a double-blind, placebo controlled study. PloS one. 2013;8(1):e54163.
34. Shand B, Strey C, Scott R, Morrison Z, Gieseg S. Pilot study on the clinical effects of dietary supplementation with Enzogenol, a flavonoid extract of pine bark and vitamin C. Phytotherapy Res. 2003;17(5):490–4.
35. Theadom A, Mahon S, Barker-Collo S, McPherson K, Rush E, Vandal AC, et al. Enzogenol for cognitive functioning in traumatic brain injury: a pilot placebo-controlled RCT. Eur J Neurol Off J Eur Fed Neurol Soc. 2013;20(8):1135–44.
36. Masliah E, Diez-Tejedor E. The pharmacology of neurotrophic treatment with Cerebrolysin: brain protection and repair to counteract pathologies of acute and chronic neurological disorders. Drugs Today (Barc). 2012;48 Suppl A:3–24.
37. Chen CC, Wei ST, Tsaia SC, Chen XX, Cho DY. Cerebrolysin enhances cognitive recovery of mild traumatic brain injury patients: double-blind, placebo-controlled, randomized study. Br J Neurosurg. 2013; 27(6):803–7.
38. Guzik TJ, West NE, Pillai R, Taggart DP, Channon KM. Nitric oxide modulates superoxide release and peroxynitrite formation in human blood vessels. Hypertension. 2002;39(6):1088–94.
39. Terpolilli NA, Zweckberger K, Trabold R, Schilling L, Schinzel R, Tegtmeier F, et al. The novel nitric oxide synthase inhibitor 4-amino-tetrahydro-L-biopterine prevents brain edema formation and intracranial hypertension following traumatic brain injury in mice. J Neurotrauma. 2009;26(11):1963–75.
40. Stover JF, Belli A, Boret H, Bulters D, Sahuquillo J, Schmutzhard E, et al. Nitric oxide synthase inhibition

with the antipterin VAS203 improves outcome in moderate and severe traumatic brain injury: a placebo-controlled randomized Phase IIa trial (NOSTRA). J Neurotrauma. 2014;31(19):1599–606.
41. Deutsch ER, Espinoza TR, Atif F, Woodall E, Kaylor J, Wright DW. Progesterone's role in neuroprotection, a review of the evidence. Brain Res. 2013;1530: 82–105.
42. Wei J, Xiao GM. The neuroprotective effects of progesterone on traumatic brain injury: current status and future prospects. Acta Pharmacol Sin. 2013;34(12): 1485–90.
43. Shakeri M, Boustani MR, Pak N, Panahi F, Salehpour F, Lotfinia I, et al. Effect of progesterone administration on prognosis of patients with diffuse axonal injury due to severe head trauma. Clin Neurol Neurosurg. 2013;115(10):2019–22.
44. Xiao G, Wei J, Yan W, Wang W, Lu Z. Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: a randomized controlled trial. Critical care (London, England). 2008;12(2):R61.
45. Wright DW, Kellermann AL, Hertzberg VS, Clark PL, Frankel M, Goldstein FC, et al. ProTECT: a randomized clinical trial of progesterone for acute traumatic brain injury. Ann Emerg Med. 2007;49(4):391–402, e1–2.
46. Skolnick BE, Maas AI, Narayan RK, van der Hoop RG, MacAllister T, Ward JD, et al. A clinical trial of progesterone for severe traumatic brain injury. N Engl J Med. 2014;371(26):2467–76.
47. Kelly DF. Alcohol and head injury: an issue revisited. J Neurotrauma. 1995;12(5):883–90.
48. Raj R, Skrifvars MB, Kivisaari R, Hernesniemi J, Lappalainen J, Siironen J. Acute alcohol intoxication and long-term outcome in patients with traumatic brain injury. J Neurotrauma. 2015;32(2):95–100.
49. Pandit V, Patel N, Rhee P, Kulvatunyou N, Aziz H, Green DJ, et al. Effect of alcohol in traumatic brain injury: is it really protective? J Surg Res. 2014;190(2): 634–9.
50. Scheyerer MJ, Dutschler J, Billeter A, Zimmermann SM, Sprengel K, Werner CM, et al. Effect of elevated serum alcohol level on the outcome of severely injured patients. Emerg Med J. 2014;31(10):813–7.
51. Cormio M, Gopinath SP, Valadka A, Robertson CS. Cerebral hemodynamic effects of pentobarbital coma in head-injured patients. J Neurotrauma. 1999; 16(10):927–36.
52. Levin AB, Duff TA, Javid MJ. Treatment of increased intracranial pressure: a comparison of different hyperosmotic agents and the use of thiopental. Neurosurgery. 1979;5(5):570–5.
53. Chen HI, Malhotra NR, Oddo M, Heuer GG, Levine JM, LeRoux PD. Barbiturate infusion for intractable intracranial hypertension and its effect on brain oxygenation. Neurosurgery. 2008;63(5):880–6; discussion 6–7.
54. Schwartz ML, Tator CH, Rowed DW, Reid SR, Meguro K, Andrews DF. The University of Toronto head injury treatment study: a prospective, randomized comparison of pentobarbital and mannitol. Can J Neurol Sci. 1984;11(4):434–40.
55. Ward JD, Becker DP, Miller JD, Choi SC, Marmarou A, Wood C, et al. Failure of prophylactic barbiturate coma in the treatment of severe head injury. J Neurosurg. 1985;62(3):383–8.
56. Majdan M, Mauritz W, Wilbacher I, Brazinova A, Rusnak M, Leitgeb J. Barbiturates use and its effects in patients with severe traumatic brain injury in five European countries. J Neurotrauma. 2013;30(1): 23–9.
57. Mellion SA, Bennett KS, Ellsworth GL, Moore K, Riva-Cambrin J, Metzger RR, et al. High-dose barbiturates for refractory intracranial hypertension in children with severe traumatic brain injury. Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 2013;14(3):239–47.
58. Siren AL, Fratelli M, Brines M, Goemans C, Casagrande S, Lewczuk P, et al. Erythropoietin prevents neuronal apoptosis after cerebral ischemia and metabolic stress. Proc Natl Acad Sci U S A. 2001; 98(7):4044–9.
59. Aloizos S, Evodia E, Gourgiotis S, Isaia EC, Seretis C, Baltopoulos GJ. Neuroprotective effects of erythropoietin in patients with severe closed brain injury. Turk Neurosurg. 2015;25(4):552–8.
60. Robertson CS, Hannay HJ, Yamal JM, Gopinath S, Goodman JC, Tilley BC, et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: a randomized clinical trial. JAMA. 2014;312(1):36–47.
61. Nichol A, French C, Little L, Haddad S, Presneill J, Arabi Y, et al. Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. Lancet. 2015;386(10012):2499–506.
62. Talke PO, Sharma D, Heyer EJ, Bergese SD, Blackham KA, Stevens RD. Republished: Society for Neuroscience in Anesthesiology and Critical Care expert consensus statement: anesthetic management of endovascular treatment for acute ischemic stroke. Stroke J Cereb Circ. 2014;45(8):e138–50.
63. Huang Z, Filipovic Z, Mp N, Ung C, Troy EL, Colburn RW, et al. AC105 increases extracellular magnesium delivery and reduces excitotoxic glutamate exposure within injured spinal cords in rats. J Neurotrauma. 2016.
64. Saver JL, Starkman S, Eckstein M, Stratton SJ, Pratt FD, Hamilton S, et al. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. N Engl J Med. 2015;372(6):528–36.
65. Gibson CL, Bath PM. Feasibility of progesterone treatment for ischaemic stroke. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab. 2016;36(3):487–91.
66. van den Berg LA, Koelman DL, Berkhemer OA, Rozeman AD, Fransen PS, Beumer D, et al. Type of anesthesia and differences in clinical outcome after intra-arterial treatment for ischemic stroke. Stroke J Cereb Circ. 2015;46(5):1257–62.

67. van den Berg LA, Roos YB. Response to letter regarding article, "type of anesthesia and differences in clinical outcome after intra-arterial treatment for ischemic stroke". Stroke J Cereb Circ. 2015;46(9):e218.
68. Boyko M, Gruenbaum SE, Gruenbaum BF, Shapira Y, Zlotnik A. Brain to blood glutamate scavenging as a novel therapeutic modality: a review. J Neural Transm (Vienna, Austria : 1996). 2014;121(8):971–9.
69. Boyko M, Zlotnik A, Gruenbaum BF, Gruenbaum SE, Ohayon S, Kuts R, et al. Pyruvate's blood glutamate scavenging activity contributes to the spectrum of its neuroprotective mechanisms in a rat model of stroke. Eur J Neurosci. 2011;34(9):1432–41.
70. Zhumadilov A, Boyko M, Gruenbaum SE, Brotfain E, Bilotta F, Zlotnik A. Extracorporeal methods of blood glutamate scavenging: a novel therapeutic modality. Expert Rev Neurother. 2015;15(5):501–8.

Sepsis and Septic Shock

27

Piero Ceriana

27.1 Introduction

The word sepsis derives from the ancient Greek language and means "rot" or "putrescence," carrying inside the concept of tissue disruptive action of bacteria, a phenomenon that at the time of Hippocrates and Galen was considered in some cases necessary for subsequent wound healing [1]. With the development of new knowledge about germs in the nineteenth century, sepsis was reconsidered as a systemic infection, i.e., the result of aggression of the body carried by microorganisms that, after initial colonization of a body site, then diffuse into the bloodstream. Now even this concept has been further revised, since we know that infection per se is necessary but not sufficient to generate sepsis, being this the result of the interaction between microorganism and host reaction. Another important aspect is that sepsis must be viewed in the majority of cases as one step of a complex and multiphase pathological process that can be elicited even by a noninfectious cause.

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27.2 Epidemiology

Precise data about the real incidence of sepsis are lacking, due to inhomogeneous diagnostic criteria, accuracy of filling medical records, and absence of centralized systems of data collection in many countries. Data from North American hospitals indicate that sepsis accounts for about 2% and 10%, respectively, for hospital and intensive care unit (ICU) admissions, every year. Therefore, an estimate of more than 750,000 cases per year in the United States and 19 million all over the world can be considered reasonable, albeit probably underestimated [2, 3]. With respect to the kind of patient more exposed to the risk of developing sepsis, we observe from epidemiological data that there is a peak of incidence in the first year of life, a relatively low incidence in adolescents and young adults, then cases become progressively more frequent around the early 50s, with the highest incidence between 55 and 65 years of age, with a slight prevalence of males over females and of blacks over whites [4]. Hospitalized patients are far more at risk for sepsis than ambulatory ones, especially after trauma or surgical procedure, or when immunosuppression of any cause and debilitating chronic disease is present.

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27.3 Terminology and Definition

A great contribution to the definition of sepsis has been given in 1991 during the joint meeting between the American College of Chest Physicians and the Society of Critical Care Medicine [5]. The greatest innovation was the introduction of a new clinical entity, the systemic inflammatory response syndrome (SIRS) that is now adopted and accepted by clinicians and researchers as the preliminary and early stage of sepsis. This acronym identifies a clinical state characterized by the presence of at least two of the following findings: fever (body temperature > 38 °C) or hypothermia (body temperature < 36 °C), tachycardia (heart rate > 90 beats/min) taking into account defects of cardiac conduction or administration of beta-blockers or calcium channel blockers, hyperventilation (respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg or an expired minute volume > 10 l/min if the patient is mechanically ventilated), and leukocytosis or leucopenia (white blood cells > 12,000 cells/μLor < 4000 cells/μL). The idea that more than one of these criteria should be present for the definition of SIRS has recently been questioned [6]: actually it was observed in a cohort of over 100,000 patients admitted in different ICUs from Australia and New Zealand that one out of eight patients with SIRS can be overlooked applying the rule of "more than two criteria." Hence this concept should not be considered too strictly when considering if a patient has SIRS or not. Therefore, we can assume that SIRS can be considered the result of the activation of the innate immune system and at the same time a sort of big "umbrella" under which many different clinical states can be housed: local or systemic infection, but also noninfectious processes such as trauma, pancreatitis, or thermal injury.

SIRS is thus the first step of a complex and potentially lethal clinical cascade: the association of SIRS and infection is sepsis, severe sepsis is the result of sepsis plus acute organ dysfunction, while septic shock is considered as a state of sepsis plus arterial hypotension (systolic blood pressure < 90 mmHg or mean arterial pressure < 60 mmHg or a reduction of >40 mmHg compared to baseline) despite adequate volume replacement and in absence of any other possible cause of hypotension (Fig. 27.1).

27.4 Initial Clinical Presentation

Despite the multiple and extremely variable causes, sepsis and severe sepsis have a relatively uniform pattern of clinical presentation and the diagnosis is mainly achieved from the clinical observation of the patient, with the necessary support from laboratory and microbiological data. The triad of fever, tachycardia, and tachypnea must alert the attending physician of a possible impending SIRS or sepsis: fever is present in the majority of cases, unless in very old

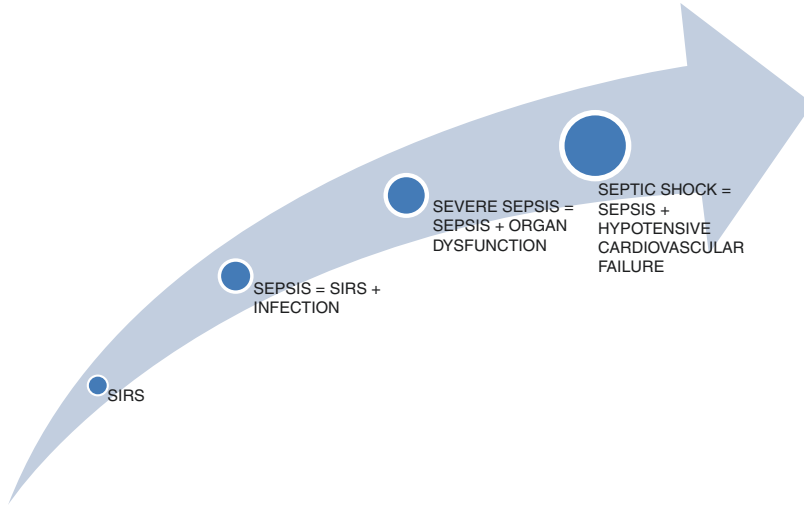

Fig. 27.1 The clinical cascade from SIRS to septic shock. SIRS – systemic inflammatory response syndrome

patients or those under immunosuppressive drugs; hypothermia is present in very few cases (< 10%) and can be considered a predictive sign of poor outcome. Tachycardia is an important sign, but must be viewed taking into account rhythm pattern and underlying cardiac disease, together with the use of drugs potentially interfering with heart rate, while an increased respiratory rate is a key and sometimes early warning. Besides tachypnea, typical of all patients, hypoxemia is present in the vast majority of them ($PaO_2/FiO_2 < 300$), so that oxygen administration and mechanical ventilation are, respectively, always and very often necessary.

27.5 Subsequent Clinical Evolution

When the systemic inflammatory reaction triggered by the interaction between the noxious agent and the host become widespread, any possible body site can be involved, and subsequent organ failures can ensue. It is a rather shared opinion that mortality rate for severe sepsis is directly proportional to the number of failing organs, going from a death rate of about 15% with one failing organ up to 80% with failure of five organs; each new organ failure increases the risk of death of about 15–20% in a cumulative manner. Besides the number of failing organs, the criteria of failure severity can be considered equally important for prognostic purposes, and this can be specific for every involved organ: amount of inotropic drugs required to relieve circulatory failure, degree of lactic acidosis, grade of acute respiratory distress syndrome (ARDS) [7] for lung dysfunction, and creatinine blood values for kidney failure. The typical clinical scenario of severe sepsis is a patient with respiratory and circulatory failure; then, it is very common for hypotensive patients to develop oliguria or overt renal failure in cases of persistent shock or use of nephrotoxic drugs. During the subsequent evolution of severe sepsis, coagulation abnormalities are found very often, ranging from low platelet count to intravascular disseminated coagulation, as well as signs of liver, brain, and bowel failure.

The *lung* is generally the first organ to be involved in SIRS and sepsis, since it receives the entire cardiac output and consequently the whole amount of the inflammatory and coagulation cascades; the extremely thin alveolar/capillary barrier and the wide vascular area make this organ the first-line target of severe sepsis. The respiratory involvement in the majority of cases has all the features of ARDS, i.e., hypoxemia with bilateral infiltrates whose origin is not secondary to heart failure. Alveolar filling with inflammatory exudates and capillary clotting are only two of the main pathological findings; the functional result is worsened oxygenation, increased airway resistance, and decreased compliance with overall increased respiratory load. The coexistence of hypotension and circulatory failure decreases blood flow to the respiratory muscles with consequent ventilatory pump failure and need for artificial respiratory support. Besides conventional diagnostic tools for the diagnosis and monitoring of lung involvement (chest X ray, oxymetry and arterial blood gas analysis), the use of lung ultrasound is at present a well-recognized and reliable noninvasive tool [8].

The *cardiovascular system* is involved in the majority of patients suffering from severe sepsis and in all patients with septic shock. The typical circulatory profile includes hypotension, reduced central venous and capillary wedge pressure, and these are generally the consequences of increased vascular permeability with interstitial fluid shift, together with reduced intake and increased loss (sweating, fever, tachypnea, vomiting etc.). Cardiac output is typically normal or increased together with low systemic vascular resistance; however, due to the possible myocardial depressant effect of circulating toxins, it is not uncommon to find a picture with low cardiac output and high filling pressure, or simply a flattened cardiac performance/filling pressure slope after optimal fluid replacement, indicating limited cardiac reserve. The initial assessment of the patient with septic shock is based on optimal fluid administration, even 4–6 l of crystalloids within the first

hours and choice of optimal vasopressors, generally norepinephrine for maintenance of systemic vascular resistance and tissue perfusion and dobutamine when an inotropic agent is required. In order to maintain adequate oxygen delivery and to avoid excessive hemodilution, transfusion of packed red blood cells must be considered in order to maintain hemoglobin concentration in the range between 7 and 9 g/dl.

Renal function during severe sepsis shows a variable degree of impairment; oliguria and rise of blood creatinine up to 2.5–3 mg/dl is quite common and generally treated in a conservative manner with fluid expansion and judicious use of diuretics. The protective use of low-dose dopamine lacks strong clinical evidence and is rarely used. The avoidance of nephrotoxic agents and drugs is mandatory, together with the maintenance of adequate blood volume and perfusion pressure. Renal replacement therapy can be applied through different techniques and is strictly necessary only in a minority of cases and for a limited period of time, with restoration of normal kidney function in almost all survivors, even if this is strongly influenced by previous renal function, being patients with diabetes and multisite atherosclerotic vascular disease at increased risk to need long-term dialysis.

The dysfunction of the *central nervous system* becomes evident as a state of obtundation; it is not generally an early sign of severe sepsis, since in most cases it arises at a later stage and its recognition is sometimes hampered by the contemporary use of sedatives. Sepsis is a risk factor for the development of delirium, a form of brain dysfunction that affects up to 70% of patients admitted in ICU and responsible for an increased morbidity, mortality, and subsequent institutionalization [9]. In recent years the problem of long-term sequelae after ICU discharge has received increasing attention and a significant degree of neurocognitive deterioration among survivors of severe sepsis has been observed [10]. Sepsis and long stay in ICU is also a risk factor for the development of critical illness neuropathy and myopathy [11], a condition affecting both sensory and motor peripheral nervous fibers with the possible generation of a state of quadriplegia with the subsequent need for prolonged rehabilitative treatments.

The *bowel* and the *liver* generally display signs of failure during severe sepsis. Hypotension and reduced visceral perfusion impair gastrointestinal motility with the subsequent development of ileus; furthermore, bowel ischemia is sometimes responsible for gastrointestinal bleeding, facilitated by the frequent withholding of enteral feeding with consequent lack of the trophic effect of enteral formulas on the gut mucosa. Great emphasis has been given in the last years to a possible active role of the gut in the generation and amplification of sepsis due to migration of bacteria from the enteral lumen to the bloodstream, through a mechanism of translocation to the portal circulation facilitated by gut ischemia and increased epithelial permeability with consequent leakage across the loose cellular junctions. An increase in blood levels of bilirubin and transaminases is the sign of liver damage occurring during septic shock and low splanchnic perfusion.

Metabolic acidosis and coagulation disorders are frequently seen during septic shock; elevated lactate blood levels can be considered as the expression of anaerobic metabolism secondary to low peripheral oxygen delivery or inadequate tissue oxygen extraction due to cellular dysfunction at the mitochondrial level. In Fig. 27.2 there is a simple description of the pathogenetic mechanisms underlying the development of organ and cellular failure during sepsis and septic shock. Other endocrinological abnormalities include hyperglycemia, adrenal dysfunction, and euthyroid sick syndrome. Mild coagulation abnormalities are very common, since almost all patients display low levels of clotting and anticlotting proteins, low platelet count, elevated clotting degradation products and d-dimer, and prolongation of prothrombin time. In most severe cases, full-blown disseminated intravascular coagulation is a rare but possible complication of septic shock.

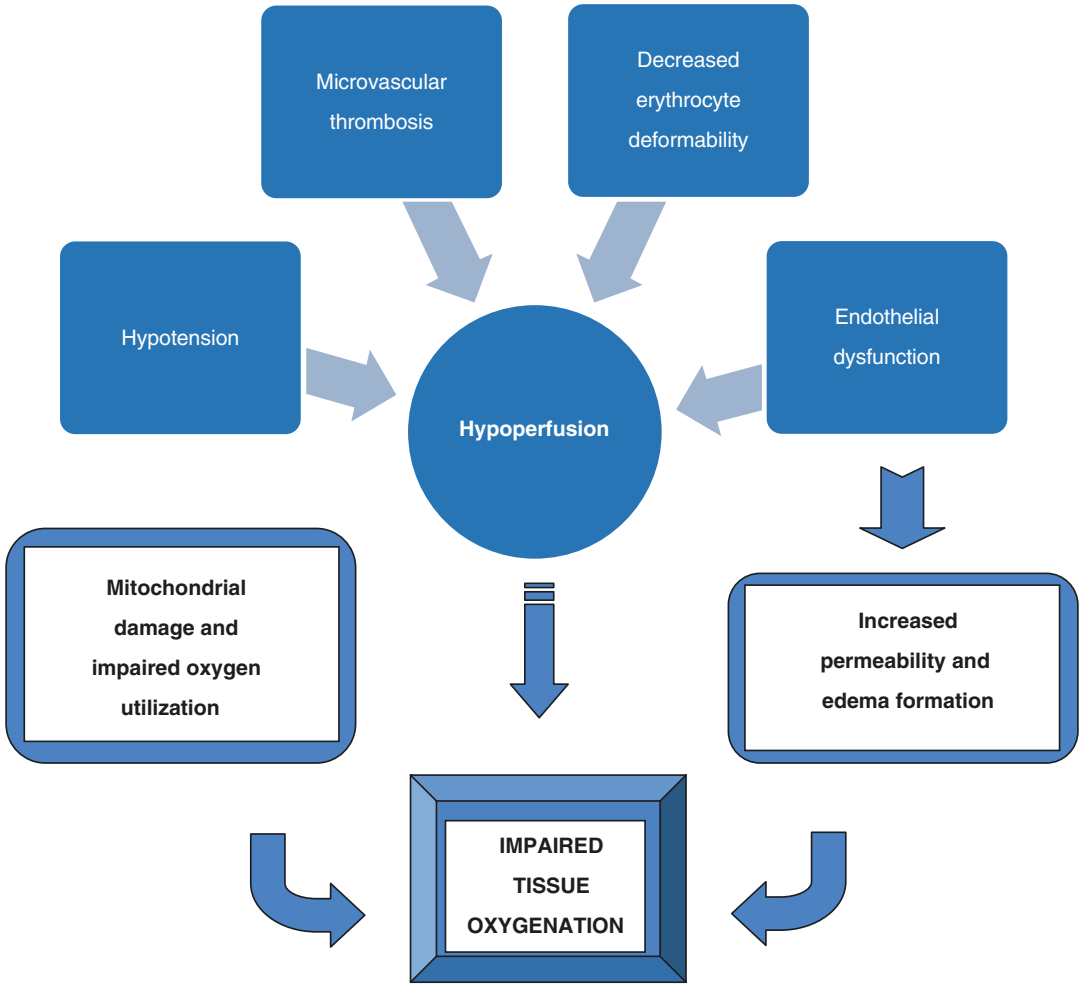

Fig. 27.2 Mechanism of development of tissue damage and organ dysfunction

27.6 Pathogenesis of Sepsis

Bacteria most commonly responsible for sepsis are almost equally represented among gram-negative and gram-positive strains; Klebsiella, *Escherichia coli*, and Pseudomonas are the most represented in the former group while Streptococci and Staphylococci among gram-negative ones. Emerging new strains characterized by multiple antibiotic resistance and responsible for particularly severe cases are *Klebsiella pneumoniae* carbapemenase-producing (KPC), *Acinetobacter baumannii* and vancomycin-resistant Enterococcus. Fungi, mainly Candida, account for no more than 5–10% of the cases, especially in immunocompromised patients and those with longer ICU stay. Viruses can be also involved, alone or superimposed on bacterial infections, but precise data are lacking for the intrinsic limitations of diagnostic techniques. Infection can be originated in any possible body site, on a theoretical basis, but sites most commonly involved are the lungs in about 50% of cases, the abdomen in 20–25% of cases, the urinary tract in about 10–15% of cases, and the remaining 10–20% in other body sites (skin, subcutaneous tissue, bones, etc.).

As already stated, microorganisms alone cannot be entirely responsible for sepsis, since the host response plays a pivotal role. The classical view of the inflammatory cascade developing at sequential steps with great emphasis on cytokines like tumor necrosis factor (TNF) and interleukin-1 (IL-1) has been widely revised; besides, it is now clear how immune system is not the only effector, since the coagulation system as well plays a fundamental role in the evolution of sepsis.

Interaction between microorganisms and the innate immune system is the preliminary step: parts of bacterial cell wall (pathogen-associated molecular patterns) react with specific molecules located on the surface of immune cells (pattern recognition receptors) called toll-like receptors; the following step is the activation of intracellular transcription factors and signaling pathways leading to the activation of immune response genes and generation of circulating mediators [12]. Pathogen-associated molecular patterns include endotoxins, peptidoglycan lipopeptides, lipoteichoic acid, and so on. Lipopolysaccharide is the endotoxin present on gram-negative bacterial cell wall and binds specifically to toll-like receptor 4 located on the surface of innate immune cells; this attachment and the subsequent intracellular activation of the second messengers and transcription factors requires the contemporary action of protein CD14 that facilitates both receptor binding and intracellular transport. On the other hand, gram-positive bacteria can generate sepsis through a mechanism similar to that of gram-negative strains, when some cell wall structures (lipopeptides, peptidoglycans, and lipoteichoic acid) interact with the specific toll-like receptor 2, or when they produce exotoxins that bind to major histocompatibility complex (MHC) class II molecules and to T-cell receptors with the subsequent generation of pro-inflammatory cytokines.

The variable clinical picture of sepsis according to the strain of bacteria involved and the body site of infection is also dependent on the different expression and generation of inflammatory cytokines. This complex microorganism–host interaction, together with the specific binding of certain pathogen-associated molecular pattern to specific toll-like receptors, supports the concept that the immune response will be different according to the specific bacterial biochemical composition and that also the different distribution and pattern of expression of toll-like receptors on different tissues and organs could be responsible for a greater or lesser susceptibility of the organ itself to the effects of microorganism aggression.

Global dysfunction of the coagulation system is an integral part of sepsis, with the coexistence of both impaired thrombolysis and enhanced coagulation. Expression of tissue factor, a glycoprotein present on different cell types, stimulates clotting factors V and VIII and leads to the enhanced production of thrombin, while natural anticlotting proteins (protein C, protein S, and antithrombin) try to counterbalance this increased clotting process. However, due to the impaired conversion of inactive anticlotting precursors to functioning proteins, this coagulation balance is shifted toward increased clotting also because the fibrinolytic system is impaired. Therefore, a complex interplay between dysregulated inflammation and coagulation abnormalities is at the base of the pathogenesis and development of sepsis; the link between these two systems are the G-protein-coupled receptors called protease-activated receptors (PARs) [13]. Among the four known subtypes, PAR1 appears to be involved in the mechanism of sepsis, since it can show cytoprotective actions when stimulated by protein C or cause damage to the endothelial barrier when stimulated by excessive thrombin.

27.7 Treatment of Sepsis and Septic Shock

The main pillars of sepsis and septic shock treatment are cardiovascular and respiratory support, plus early treatment of underlying infection. Almost equal importance must be paid to support kidney failure even with depurative techniques, to nutrition and glucose control, and to therapies targeted to blunt the inflammatory and coagulation cascades. A great contribution to the

generation of shared and evidence-based protocols for the treatment of sepsis has been given by the Surviving Sepsis Campaign [14], a panel of scientific societies involved in the field of critical care and emergency medicine and infectious diseases.

Respiratory support is based on the use of invasive mechanical ventilation, since rarely conventional oxygen therapy or noninvasive mechanical ventilation can be sufficient to reverse hypoxemia and impending hypercapnic respiratory failure. Being ARDS the most frequent picture of respiratory involvement during sepsis, it should be advisable to start with a tidal volume of about 5–7 ml/Kg of ideal body weight with an inspired oxygen fraction (FiO_2) sufficient to achieve an acceptable oxygen saturation (generally between 40 and 70%) and a value of positive end expiratory pressure in the range 8–10 cmH_2O. Most severe cases, generally sepsis-induced ARDS, may require pronation maneuvers, protecting ventilatory strategy with low tidal volume (maintaining the inspiratory plateau pressure below 30 cmH_20), in order to minimize alveolar stretching and ventilation-induced biotrauma [15] and a conservative fluid strategy if peripheral perfusion defects are absent. Additional prescriptions should be the elevation of the head of the bed, the avoidance of neuromuscular blockers (unless for a very short course), and the use of targeted and daily interrupted sedation and weaning protocols, once the patient meets the requirement for a spontaneous breathing trial.

Support of the *circulation* requires an early (within the first 6 h) and aggressive volume replacement. The clinical and scientific debate about the optimal kind of infusing solution (crystalloids or colloids) lasted for many years, and at present, given for accepted that both kinds of solutions lack the advantage to be confined inside the intravascular compartment, crystalloids are the preferred choice, for reasons of reduced allergic reactions and costs, with the possible addition of albumin when relevant amounts of crystalloids are needed. Precise directions about the amount of fluids required cannot be stated, since this figure is the result of clinical and instrumental monitoring and underlying cause of sepsis, but generally the average septic patient can receive up to 4–6 l of crystalloids in the first 6–12 h or anyway until the achievement of hemodynamic improvement. Possible transfusion of packed red cells can be considered in order to maintain a hemoglobin value between 7 and 9 g/dl, or even higher if the patient has coronary heart disease. Once adequate volume replacement has been carried out, a vasopressor agent, generally norepinephrine, can be added in order to maintain an adequate blood pressure, while the infusion of an inotropic agent, generally dobutamine, is started in cases of concomitant myocardial dysfunction. With respect to the definition of "adequate volume replacement" or "adequate perfusion," a range of central venous pressure between 8 and 12 mmHg of mean arterial pressure > 65 mmHg, a urine output >0.5 ml/Kg/h, and a central venous (superior vena cava) oxygen saturation > 70% can be considered. The gold standard for hemodynamic monitoring has for a long time been considered the pulmonary artery thermodilution Swan-Ganz catheter, still widely used even with the option of continuous SvO_2 monitoring, but this practice is anyway widely influenced by local and individual preference and practice. The use of ultrasound is rapidly growing for the ease of use, bedside performance, and repeatability, since the simultaneous view of ventricular motion and inferior vena cava diameter can give a reasonable estimate of myocardial dysfunction and volume status.

As far as the treatment of *infection* is concerned, this should also be started as early as possible, always within the first hour after diagnosis of severe sepsis or septic shock and after the performance of blood cultures and imaging studies in order to understand the possible source of infection. Antibiotic infusion should be done in parallel with the surgical treatment of a possible localized site of infection (wound, abscess, intravascular infected device, etc.), and an agent with a spectrum as broad as possible and targeted to the possible agents involved according to the possible site and to the patient provenience (community, hospital, nursing home, etc.) should be chosen. A reasonable first-line empiric antibiotic

choice could be the association of a third-generation cephalosporin plus a quinolone or aminoglycoside if a pulmonary or intra-abdominal infection is suspected, while in case of presence of intravascular infected device or meningeal infection the use of vancomycin should be considered and when there is the possible presence of anaerobic microorganisms, metronidazole or clindamycin should be added. Use of antifungal agents should be used empirically only in patients at high risk of fungal infections (prolonged hospital stay, immunosuppressed, post-surgical, etc.). Re-assessment of antimicrobial therapy must be done as soon as the blood results and imaging studies give more data about the origin of infection, in order to change therapy accordingly, switching from the initial empiric treatment to a more targeted one. Length of treatment is guided by clinical and laboratory data, since in recent years great consideration has been given to blood values of procalcitonin as a tool to guide antibiotic treatment duration [16].

Transient kidney failure is quite common during sepsis and septic shock, with reduction of urine output and increase of creatinine; the most important protective measures are adequate blood volume restoration and maintenance of adequate perfusion pressure with vasopressors, and avoidance of nephrotoxic drugs. Use of low-dose dopamine in order to increase renal blood flow has never shown a definite advantage and is not among the suggested therapies, as well as the use of diuretics in the oliguric phase, at least on a routine basis. When indicated, extracorporeal depurative treatments must be carried out, either under the form of intermittent hemodialysis or continuous hemofiltration. Tight glycemic control is advisable, since hyperglycemia can exert adverse effects on neutrophil function, can influence blood coagulation with increased clotting formation, and can be a risk factor for the subsequent development of the critical illness polyneuropathy. If blood glucose levels are repeatedly above 180 mg/dl, insulin therapy should be started, preferably as a continuous infusion. Prophylaxis against stress-ulcers with H_2 blockers or proton pump inhibitors and deep vein thrombosis should be carried out, preferably with low-dose unfractioned heparin, due to the unpredictable half-life of low-molecular weight heparin in case of renal failure. Bicarbonate infusion should not be used in order to increase blood pH in case of acidemia with increased lactate levels due to hypoperfusion. As far as the nutritional support is concerned, the current and reasonable practice is to prefer the enteral route, mainly for the beneficial effects on gut mucosal trophism, to start nutrition once hemodynamic stability has been achieved (1–2 days after the onset of septic shock), and to switch to the parenteral route only in cases of prolonged bowel dysfunction with depressed motility. With respect to therapies with a potential impact on the inflammatory and coagulation cascade, the use of steroids can be recommended in cases of septic shock if hypotension responds poorly to fluid replacement and vasoactive drugs, choosing hydrocortisone at a dose of 200–250 mg/day for up to 7 days or until hemodynamic stability. In cases of sepsis without shock, the use of hydrocortisone should be limited to those patients with adrenal insufficiency documented or strongly suspected. The use of human recombinant activated protein C is one of the most promising advances in the treatment of septic shock in the last years; it can modulate the coagulation cascade and the complex interplay between coagulation and inflammation mainly stimulating the protease-activated receptors 1 (PAR1). It should be administered by continuous infusion for 96 h at a dose of 24 μg/Kg of body weight. Due to the increased bleeding risk with its use, activated protein C should be avoided in patients with low platelet count (<30,000 platelets/mm^3), recent trauma or surgery, or active bleeding. After initial enthusiasm due to the promising data on reduced mortality (20% of cases) [17] especially in most severe patients (shock with two or more failing organs), recent data failed to show a reduction in the early (28 days) and late (90 days) mortality in patients with septic shock treated with activated protein C compared to those treated with placebo [18].

Besides the overall approach to the septic patient with the peculiarities of single organ support mentioned above, the most important innovation in the treatment of sepsis of the last few years

has been the introduction of "bundles" of care, i.e. [14] a group of evidence-based diagnostic and therapeutic measures that, carried out together and within a limited timeframe, are far more effective than the same interventions performed individually and without a tight time constraint. The whole series of interventions to be carried out in cases of sepsis are organized into two bundles: an initial bundle to be applied within the first 6 h after patient admission and including six items: (1) early recognition of sepsis also based on the presence of SIRS criteria, (2) obtainment of blood cultures and early start of IV antibiotic therapy, (3) aggressive treatment of hypotension with crystalloids, (4) use of vasopressors in cases not responding to volume replacement, (5) monitoring central venous pressure (CVP) and venous oxygen saturation (SvO_2) in order to achieve the goal of a CVP > 8 mmHg and an SvO_2 > 70% and (6) consider the use of inotropes in case of low cardiac output and packed red blood cells in case of low hematocrit. The second bundle of treatments is put in practice after the admission of the patient to the ICU: ventilation with lung protective strategy in cases of ARDS, monitoring and support of organ function, avoidance of complications, possible use of steroids, tight glycemic control, and de-escalation of initial broad-spectrum antibiotic therapy. The application of the first bundle of care, generally applied in the emergency department, received the name of "early goal-directed therapy" (EGDT) since the protocol included the insertion of a central venous catheter for monitoring of CVP and SvO_2, whose values acted as a guide for the administration of fluids, inotropes, vasopressors, packed red cells in order to achieve predefined hemodynamic targets. In 2001, it was reported [19] that septic patients treated according to the EGDT had a lower mortality rate compared to patients treated with usual care (30.5% vs 46.5%).

The "bundles" approach to the patient with septic shock turned out to be, on a theoretical basis, of great educational relevance for the staff working in emergency departments and ICU, generating the drive for an increased adherence to these procedures [20]. However, despite its sound clinical basis, this protocol has not received a uniform and widespread application and, in the last decade, some concern has been raised about the EGDT, arguing that maybe not all the elements of the protocol are strictly needed, especially central venous catheterization, since the same information can be gathered with less invasive means, like lactate level measurement [21]. The hypothesis of the nonsuperiority of the EGDT over usual care has been confirmed in two recent trials [22, 23].

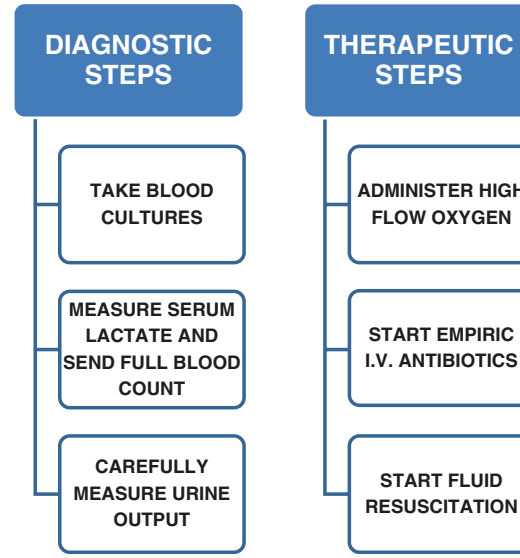

Fig. 27.3 The "sepsis six" bundle, including three diagnostic and three therapeutic steps to be performed within the first hour

Despite these unexpected results, most clinicians remain convinced of the validity of the bundles methodology and, in the attempt to simplify the initial sepsis approach, a modified protocol has been proposed, called the "sepsis six," based on three diagnostic steps and three therapeutic actions (Fig. 27.3). These actions are to be put in place within the first hour of clinical recognition and have already been adopted by many centers with promising results [24].

Conclusion

Laboratory research over the past 30 years has made several attempts to develop new strategies to treat sepsis and septic shock, investigating drugs potentially interfering with the activated inflammatory system: TNF antibodies

and receptor antagonists, anti-endotoxins drugs, interleukin-1 antagonists, and antioxidant molecules. Despite the great expectations on this research area, results were disappointing and none of the studied drugs reached clinical approval. More interest and potential usefulness was attributed to the human recombinant activated protein C, that at the beginning of the twenty-first century seemed a drug with the potential to modify the clinical story of septic shock, but unfortunately results have been disappointing and it was withdrawn from the market. In terms of sepsis treatment, the most significant innovation of the last years, therefore, is still the introduction of the bundles of care, although this is only an advancement in the area of clinical organization and patient approach, and not a real therapeutic innovation. More knowledge has been gained about the interaction between bacteria and host cells through specific receptors and about the clarification of the role of intracellular second messengers in the activation of immune response genes. It is likely that future developments will bring advancements in the process of stratification of patients' severity with the use of blood biomarkers and in casting new insights on genomic aspects of sepsis, including studies on gene polymorphisms with different susceptibility to sepsis and on personalized immunomodulatory treatments.

Take Home Messages

- Sepsis and septic shock are challenging pathological conditions with still high mortality rates, around 30% and 60%, respectively.
- Sepsis must not be considered as an isolated clinical entity, but as part of a continuum, from SIRS to septic shock.
- Gram-positive and negative bacteria are almost equally responsible for septic cases, while fungi are less represented.
- Interactions between microorganisms and host are fundamental for the development of sepsis.
- Contact of bacterial cell wall parts with specific host cell receptors triggers immune and coagulation cascades through intracellular second messengers.
- Systemic and multiorgan involvement is typical of sepsis and septic shock.
- Early antimicrobial treatment, cardiorespiratory support, and prevention of organ failure are the main pillars of sepsis and septic shock treatment.
- Aggregation of diagnostic and therapeutic measures in "bundles" has improved the care of patients with sepsis and septic shock.

References

1. Majno G. The ancient riddle of sigma eta psi iota sigma (sepsis). J Infect Dis. 1991;163:937–45.
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome and associated costs of care. Crit Care Med. 2001;29:1303–10.
3. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. Lancet. 2010;376:1339–46.
4. Mayr FB, Yende S, Linde-Zwirble WT, et al. Infection rate and acute organ dysfunction risk as explanations for racial differences in severe sepsis. JAMA. 2010;303:2495–503.
5. Members of the American College of Chest Physicians/Society of Critical Care Med Consensus Conference Committee: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20:864–74.
6. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med. 2015;372:1629–38.
7. ARDS definition task force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutski AS. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307(23):2526–33.
8. Lichtenstein DA. Lung ultrasound in the critically ill. Curr Opin Crit Care. 2014;20(3):315–22.
9. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization and dementia: a meta-analysis. JAMA. 2010;304(4):443–51.

10. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304:1787–94.
11. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DL. Neuromuscular dysfunction acquired in critical illness: a systematic review. Intensive Care Med. 2007;33:1876–91.
12. Calandra T, Bochud PY, Heumann D. Cytokines in septic shock. In: Remington JS, Swartz MN, editors. Current clinical topics in infectious diseases. Oxford: Blackwell Publishing; 2002. p. 1–23.
13. Levi M, van der Poll T. Inflammation and coagulation. Crit Care Med. 2010;38(Suppl):S26–34.
14. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med. 2008;34:17–60.
15. Slutsky SA, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2013;369:2126–36.
16. Bréchot N, Hékimian G, Chastre J, Luyt CE. Procalcitonin to guide antibiotic therapy in the ICU. Int J Antimicrob Agents. 2015;46(Suppl 1):S19–24.
17. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001;344:699–709.
18. Ranieri VM, Taylor Thompson B, Barie PS, Dhainaut JF, Douglas IS, Finfer S, et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012;366:2055–64.
19. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368–77.
20. Ferrer R, Artigas A, Levy MM, et al. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. JAMA. 2008;299:2294–303.
21. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA. 2010;303:739–46.
22. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372:1301–11.
23. The ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370:1683–93.
24. Daniels R, Nutbeam T, McNamara G, Galvin C. The sepsis six and the severe sepsis resuscitation bundle: a prospective observational cohort study. Emerg Med J. 2011;28(6):507–12.

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