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THE EFFECT OF BRIEF PROFOUND HYPOXIA UPON THE ARTERIAL AND VENOUS OXYGEN TENSIONS IN MAN

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The partial pressure of oxygen in the alveolar gas may be reduced either by decreasing the total pressure of the environment or by replacing the oxygen normally present in the inspired air by an inert gas. The severe anoxia induced by rapid decompression from 565 to 155 mm Hg absolute, whilst breathing air, may be terminated by the delivery of 100 % oxygen to the respiratory tract. The effects of such brief profound anoxia upon the alveolar and arterial gas tensions and upon the central nervous system have been studied extensively (Ernsting & McHardy, 1963; Ernsting, Gedye & McHardy, 1960; Ernsting, 1962). The effect of the resultant severe but short-lived arterial hypoxaemia upon the supply of oxygen to various organs of the body is of considerable interest. The oxygen content of the venous blood flowing from a region reflects the balance between the supply of oxygen to it and its metabolic oxygen consumption. Continuous measurements of the oxygen content of the venous blood flowing from several regions have been made in subjects exposed to brief but profound hypoxia. In the experiments described in this paper a short period of overventilation, nitrogen being used as the inspired gas, was employed in place of rapid decompression to induce hypoxia. This method allowed more extensive observations to be made than were considered practical in a decompression chamber.

METHODS

Induction of hypoxia. Three healthy men, aged from 33 to 38 years, were used. The subject lay on a couch and breathed through a valve box, to the inlet of which two taps were connected in series. The side arm of the tap next to the box was open to the atmosphere. One arm of the second tap was connected to a demand valve which was supplied with nitrogen, whilst the other arm was connected to a second demand valve supplied with oxygen. Before the experiment was started the hoses between the two demand regulators and the second tap were purged with the gas delivered by the corresponding regulator. The dead space between the two taps was purged with nitrogen to ensure that 100 % nitrogen was delivered directly the first tap was operated. During each rest period the first tap was positioned so that the subject breathed air. Nitrogen was administered by instructing the subject to expire maximally at the end of a normal expiration, and at this instant the first tap was turned so that the subject breathed from the demand valve which supplied nitrogen.

During the period of breathing nitrogen the subject was instructed to breathe as deeply as possible at a rate of about 20 breaths per minute. After 7–20 sec over-ventilation with nitrogen the first tap was returned to its original position so that air was breathed again. At the same time the subject was told to cease over-breathing.

Respired gas tensions. The partial pressures of oxygen and carbon dioxide in the gas passing the subject's lips were recorded continuously in all the experiments by means of a respiratory mass spectrometer (Fowler & Hugh-Jones, 1957). Preliminary studies showed that the output of the instrument was linearly related to the partial pressure of each of these gases. The delay between a sudden change of partial pressure of either at the sampling tip and the beginning of the response of the recording pen motor was 0·2 sec and 90 % of the total response occurred in a further 0·1 sec. Calibrations employing gas mixtures of known composition were performed at intervals throughout each experiment. Over a 30 min period no significant change occurred in the sensitivity of the instrument. The pulmonary ventilation was recorded in some of the experiments by collecting the expired gas in a recording Tissot spirometer.

Blood sampling. In separate experiments blood was sampled continuously from various sites in the cardiovascular system. Blood was obtained from the brachial artery and the femoral vein through a Cournand needle introduced into the vessel after local analgesia had been produced with 2 % lignocaine. A catheter was introduced into the right side of the heart through a large-bore needle which had been inserted into a vein in the antecubital fossa. The position of the catheter was determined during its introduction by recording the pressure at the tip by means of a strain-gauge pressure transducer. The catheter was advanced until its tip lay in the pulmonary artery. Blood flowing through the internal jugular vein was sampled by means of a radio-opaque catheter which was introduced into a vein which had been exposed through an incision in the right antecubital fossa. This catheter was advanced under direct fluoroscopic control with the subject's head held against his left shoulder. The catheter entered the right internal jugular vein and was placed so that its end lay above the level of the tip of the right mastoid process. When in place, the patency of the Cournand needle or the intravascular catheter was maintained when sampling was not in progress by a flow of sterile physiological saline (NaCl 0·9 g/100 ml.), approximately 2 ml./min containing heparin (200 i.u./100 ml.).

Recording of blood oxygen saturation and pH. The blood from the intravascular needle or catheter flowed through a tubular cuvette oximeter (Fig. 1) and was then diluted 1:10 with neutral physiological saline to which heparin had been added (Sherwood-Jones, Robinson & Cooke, 1960). The diluted suspension of blood was then passed through a microflow-glass-electrode–calomel-reference-electrode system. The saline reservoir and microflow-electrode system were immersed in a water-bath which was maintained at 38° C. The flow of blood and the desired dilution of the blood with saline were produced by means of a two-cylinder pump with a single piston, the velocity of which could be varied. The pump was constructed so that the cross-sectional area of one cylinder, which was charged with saline, was 10/11 of that of the other cylinder into which the mixture of saline and blood was drawn after it had passed through the glass-electrode system. In all the experiments a blood sampling rate of 20 ml./min was used.

The outputs of the oximeter amplifier and of the pH meter were fed on to two of the pen motors of a recorder. Preliminary experiments showed that the output of the oximeter amplifier was linearly related to the oxygen saturation of the blood flowing through the cuvette. At the beginning and end of each period of recording the output of the oximeter was calibrated by drawing a fully saturated sample of blood and a second sample of a known degree of unsaturation through the cuvette. A linear relation was also found between the pH of the blood and the output of the pH meter. The output of the latter was calibrated at intervals by using two phosphate buffers (pH 6·84 and 7·60). The time course of the response of the entire measuring system to a sudden change in the oxygen saturation and pH of the blood entering the sampling system was determined at the end of each experiment.

When sampling was required the drip of heparinized saline was turned off and the speed of the sampling pump was increased until blood was withdrawn at 20 ml./min. Sampling was continued for 1 min before the subject breathed nitrogen and was maintained until all the disturbances produced by the procedure had subsided.

Electroencephalogram (e.e.g.) and electrocardiogram (e.c.g.) recording. In many of the experiments the e.e.g. was recorded. Two pairs of saline pad electrodes were placed on the scalp over the frontal and occipital regions of the left side of the head. The potential changes from each pair of electrodes were amplified and recorded at a high paper speed. In addition, lead II of the e.c.g. was recorded.

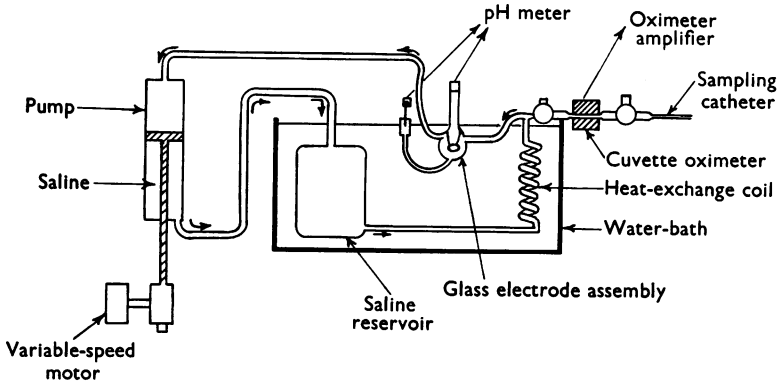

Fig. 1. Apparatus for the continuous measurement of the oxygen saturation and pH of blood. Blood is drawn into the apparatus through a catheter and then it passes through the cuvette oximeter. Saline at 38° C driven by the pump in the direction indicated by the arrows mixes with the blood and the diluted blood flows through the pH electrode assembly back to the pump.

Arterial pressure and calf blood flow. The arterial blood pressure was recorded through a Riley needle by means of an unbonded strain-gauge pressure transducer which was filled with physiological saline containing heparin. The needle was connected to the transducer by means of a 3 cm length of polyethylene tubing with an internal diameter of 1 mm. Preliminary measurements demonstrated that the complete recording system faithfully reproduced the magnitude and phase of sinusoidal pressure fluctuations at frequencies of up to 20 c/s. The Riley needle was inserted into the brachial artery and the transducer was placed on the same horizontal plane as the tip of the needle. The output of the amplifier connected to the transducer, which was fed to one channel of the recorder, was calibrated by means of a mercury manometer before and after each series of measurements. Blood flow through the calf was measured by means of venous occlusion plethysmography, with a mercury-in-rubber strain gauge (Whitney, 1953) to measure changes in the circumference of the calf. The lower limb was supported so that the lower border of the calf was just above the horizontal level of the sternal angle. The circulation to the foot was occluded by means of a cuff placed around the ankle, which was inflated to 250 mm Hg 1 min before the calf blood-flow measurements were started. The venous outflow from the calf was obstructed for 5 sec of every 10 sec period by inflating the cuff placed around the lower part of the thigh to between 30 and 40 mm Hg. The exact pressure used in the venous cuff was adjusted at the beginning of each experiment so that the circumference of the calf increased at a constant rate during each collection period. The output of the gauge was calibrated while it was in position by producing a known reduction of its length. The circumference of the calf at the level at which the gauge was fixed was measured at the end of each experiment.

In all the experiments the subject was carefully observed during and following the period of over-ventilation with nitrogen. If any severe disturbance of consciousness or respiration occurred, oxygen was administered.

RESULTS

Effect upon consciousness. The increase of pulmonary ventilation achieved by each subject during nitrogen breathing was measured from the spirometer records. The mean pulmonary ventilation of the three subjects was increased to 80 l./min at b.t.p.s. during the period of over-ventilation. When the duration of over-ventilation with nitrogen was greater than 8–10 sec the subject reported a transient dimming of vision. In the experiments in which nitrogen breathing was carried out for 15–16 sec the subject experienced some general clouding of consciousness and impairment of vision. Vision was frequently lost in these experiments for a short period. In the few experiments in which nitrogen was breathed for 17–20 sec unconsciousness supervened and was accompanied on most occasions by a generalized convulsion. The duration of the interval between the start of over-ventilation with nitrogen and the onset of symptoms was 12–14 sec.

End-tidal gas tensions. A typical record of the partial pressures of oxygen and carbon dioxide in the gases flowing through the mouth-piece is presented in Fig. 2. The end-tidal oxygen tension fell very rapidly when the subject commenced over-ventilation with nitrogen. It reached a value of less than 10 mm Hg at the end of the third expiration and remained below this level until air was inspired after 16 sec of nitrogen breathing. During the over-ventilation period the end-tidal carbon dioxide tension also fell rapidly. With the restoration of air breathing and the cessation of over-breathing the end-tidal oxygen and carbon dioxide tensions rose gradually to regain their control values. Each of the three subjects over-ventilated, whilst breathing nitrogen for a period of 15–16 sec on six separate occasions. The time course of the changes of the end-tidal tensions of oxygen and carbon dioxide has been measured for each of these 18 experiments and mean curves for each of these variables are presented in Fig. 3.

Arterial blood oxygen saturation and pH. Blood was sampled from the brachial artery of each subject on three separate occasions during which the subject over-ventilated with nitrogen for 16 sec. The records of the response of the entire system to a sudden change in the composition of blood at the tip of the Cournand needle showed a mean delay of 0·7 sec to the beginning of the response of the pen motor recording oxygen saturation and a further 0·9 sec elapsed before 90 % of the total response had occurred. The corresponding times for the response of the pH recording system were 1·4 sec and 2·0 sec respectively. Corrections for these delays in response were applied to the recorded values of oxygen saturation and pH. A

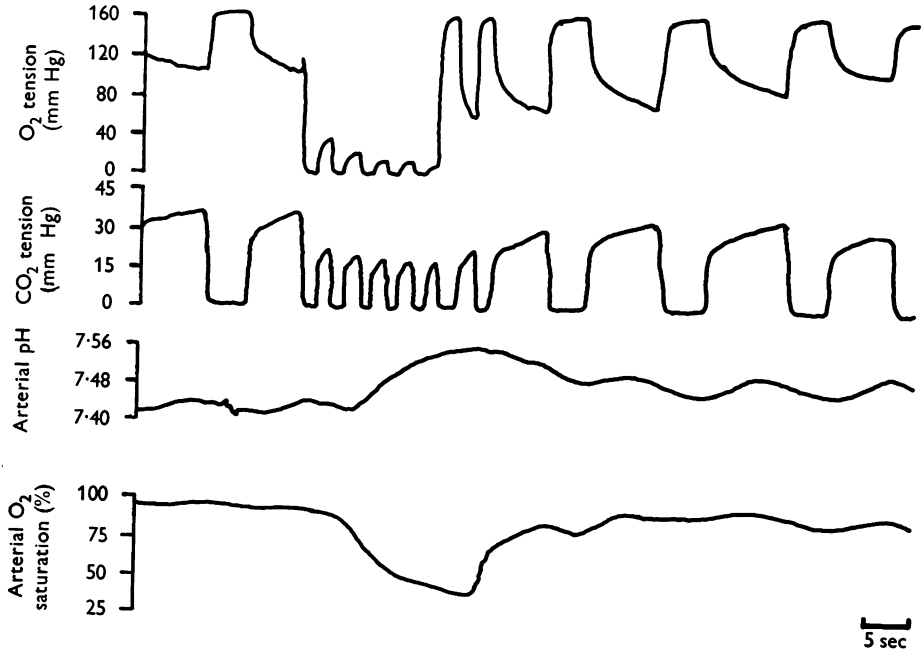

Fig. 2. Respiratory gas tensions and systemic arterial oxygen saturation and pH before, during and after 16 sec over-ventilation with nitrogen. The tensions of oxygen and carbon dioxide were recorded at the lips, whilst the blood was sampled continuously from the brachial artery. Delay time of oxygen saturation record, 0·7 sec of pH record, 1·5 sec.

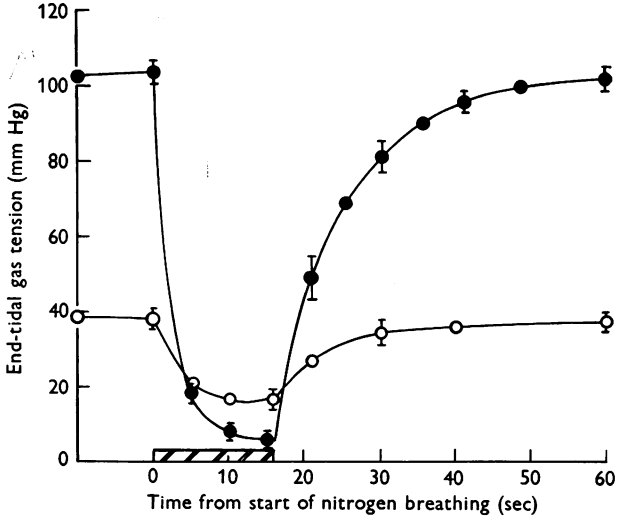

Fig. 3. Effect of over-ventilation with nitrogen upon end-tidal tensions of oxygen (●) and carbon dioxide (○). Each point represents the mean of eighteen values from three subjects; each bar represents ± 1 S.E. of the mean. The period of over-ventilation with nitrogen is indicated by the hatched bar.

typical experimental record of the arterial oxygen saturation and pH is presented in Fig. 2. The arterial oxygen saturation and hydrogen-ion concentration began to fall 4–5 sec after the commencement of nitrogen breathing and both fell very rapidly at first and then more slowly until air breathing was started again at 16 sec. The oxygen saturation then increased rapidly whilst the pH gradually returned to its control value. The mean time courses of the changes of arterial oxygen saturation and pH have been calculated for the nine experiments and these values together with their standard errors are shown in Fig. 4.

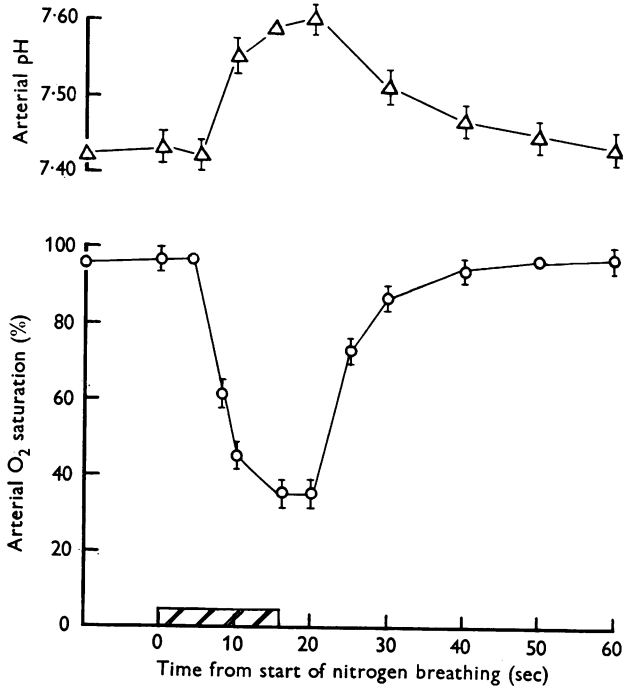

Fig. 4. Effect of over-ventilation with nitrogen upon arterial oxygen saturation (○) and arterial pH (△). Each point represents the mean of nine values from three subjects; each bar represents ±1 S.E. of the mean.

Venous blood oxygen saturation and pH. Blood was sampled from the femoral vein, the pulmonary artery and the right jugular bulb on separate occasions in each of the subjects. The delay in the response of the recording systems was lengthened considerably when intravascular catheters were employed. On none of these occasions did any significant change of pH occur during the period of nitrogen breathing. The mean time courses of the oxygen saturation of the venous blood drawn from these three sites are presented in Fig. 5.

Electroencephalogram changes. The resting e.e.g. shows no specific electrical activity and no change occurred in any experiment until 15–18 sec after the beginning of the period of over-ventilation with nitrogen. When nitrogen over-breathing was carried out for 8–12 sec low voltage

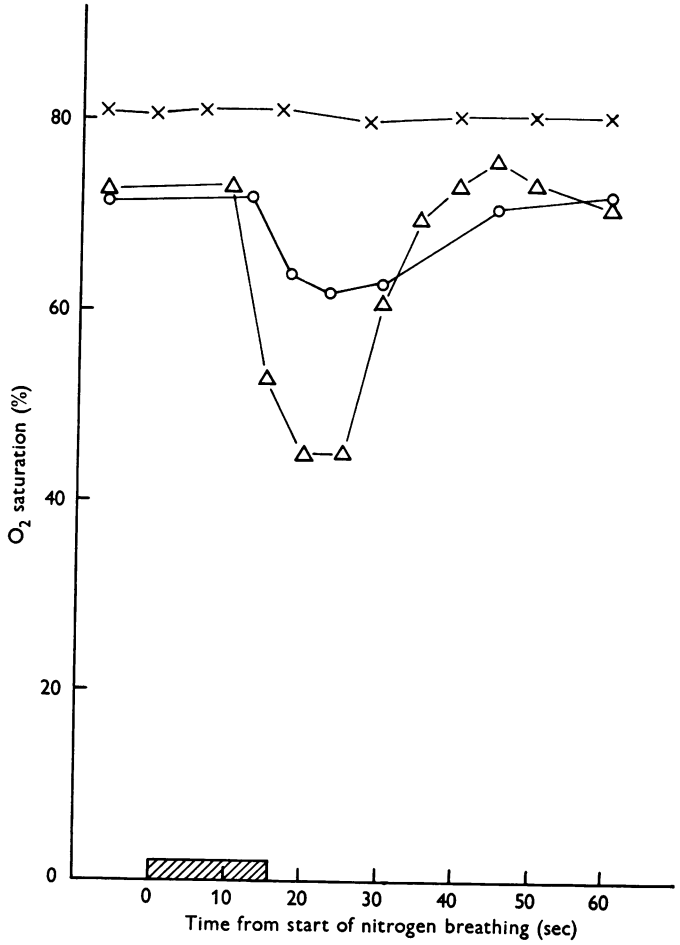

Fig. 5. Effect of over-ventilation with nitrogen upon the oxygen saturation of blood flowing through the femoral (×) and internal jugular (△) veins and the pulmonary artery (○). Each point represents the mean of three values obtained from three subjects.

activity at 11–13 c/s appeared in both channels of the e.e.g. 15 sec after the beginning of the procedure and persisted for 7–9 sec. When the duration of nitrogen over-ventilation was extended to 15–16 sec, similar changes arose in the e.e.g. but they persisted for slightly longer. Occasionally the

11–13 c/s activity was replaced by high-voltage 2–4 c/s activity, which appeared 4–6 sec after the beginning of the change of the e.e.g. This slow activity generally persisted for 4–6 sec. When nitrogen breathing was extended to 18–20 sec the initial fast, low-voltage activity was always replaced by high-voltage 2–4 c/s activity after 5 sec, which lasted for about 10 sec. Control experiments in which a subject over-ventilated for a similar period whilst breathing air produced no change of e.e.g. activity.

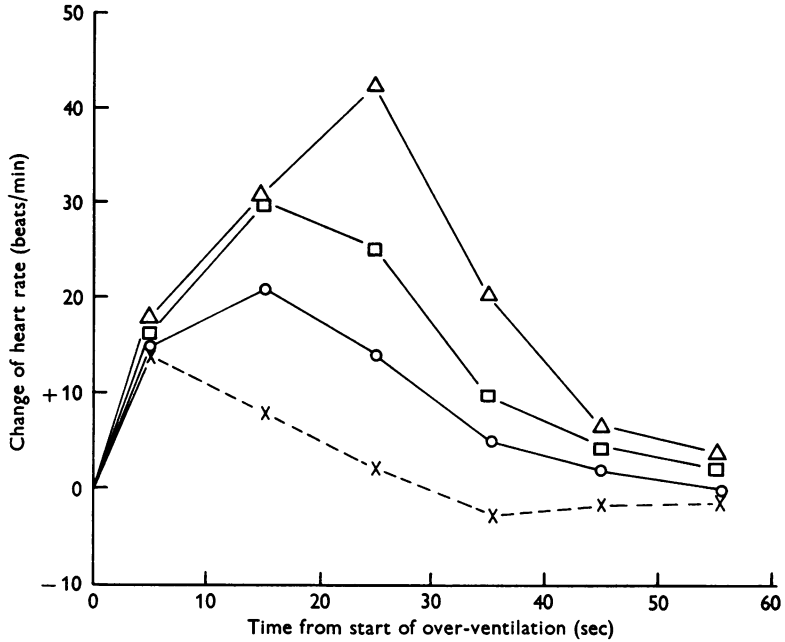

Fig. 6. Effect of over-ventilation with nitrogen for various periods upon the heart rate. △, nitrogen for 17 sec; □, nitrogen for 11 sec; ○, nitrogen for 8 sec; ×, air for 15 sec. Each point represents the mean of three values obtained from three subjects.

Cardiovascular changes. The period of over-ventilation with nitrogen produced a transient acceleration of the heart rate. This commenced at the beginning of the period of over-ventilation and reached a maximum about 30 sec later. The magnitude of the increase varied directly with the duration of the nitrogen over-ventilation. The mean changes of the heart rate for the three subjects when they over-ventilated with nitrogen for various periods are presented in Fig. 6. There were no consistent changes in the shape of the e.c.g. in these experiments. In one subject, however, there was a transient flattening of the 'T' wave, which started 5 sec after the beginning of the nitrogen over-ventilation and persisted for 10 sec. In

several experiments the subjects over-ventilated whilst breathing air. This caused a relatively small and transient increase of heart rate which had subsided 10 sec after the end of the over-ventilation period (Fig. 6).

The period of over-ventilation produced marked respiratory variations of the arterial blood pressure. The mean and pulse pressure were both increased during the deep expiratory efforts and decreased during each inspiration. The mean blood pressure was increased by about 20 mm Hg during the period of over-breathing. Directly the subject ceased over-ventilation the arterial pressure fell and reached a minimum after some 15 sec from the beginning of nitrogen breathing. The minimal value was less than the mean blood pressure before the over-ventilation period. The fall of mean pressure was accompanied by a reduction of the pulse pressure. It was followed by a secondary rise of pressure and an increase of pulse pressure, both of which reached a maximum at about 30 sec after the beginning of the period of over-ventilation with nitrogen. In all, two separate periods of over-ventilation with nitrogen were studied for each of the three subjects and the mean values of arterial pressure before, during and after the period of over-ventilation with nitrogen are presented in Fig. 7. The blood flow through the calf was calculated from the rate at which the circumference of the part increased during each venous-congestion period (Whitney, 1953). The mean value for the calf blood flow obtained in twelve separate periods of over-ventilation with nitrogen in the three subjects are shown in Fig. 7. The flow of blood into the calf was increased during the period of over-ventilation, following which it returned to the resting level, to increase again between 20 and 40 sec after the beginning of over-ventilation.

DISCUSSION

Preliminary experiments in which the subjects over-ventilated with nitrogen for various periods showed that unconsciousness supervened if the duration of this procedure exceeded 16–17 sec. In the majority of these experiments, therefore, the period of over-ventilation with nitrogen was limited to 16 sec. This period of nitrogen over-breathing produced only a transient disturbance of the e.e.g. The low-voltage 8–13 c/s activity was generally associated with a transient dimming of vision and could not be distinguished from that produced by closure of the eyelids. Further, apart from a transient flattening of the 'T' wave on one occasion, no significant change was seen in the e.c.g., although only a standard limb lead (II) was recorded. In view of these findings it was considered that the degree of hypoxia induced by over-ventilation with nitrogen for 15–16 sec was within acceptable limits for resting subjects.

The concentration of oxygen in the gas contained within the respiratory tract at the beginning of the nitrogen breathing period was reduced very rapidly by the very large voluntary increase of pulmonary ventilation. The reduction of the lung volume to a minimum before the first breath of nitrogen was taken decreased the quantity of oxygen to be washed out. The combination of these two manoeuvres resulted in a very rapid fall of end-tidal oxygen tension to 10 mm Hg after 8 sec of over-ventilation. The rate of rise of the end-tidal oxygen tension following the cessation of nitrogen over-ventilation and the return to breathing air was considerably less than the rate at which it had fallen. This difference reflects the reduction of alveolar ventilation associated with the resumption of a more normal breathing pattern.

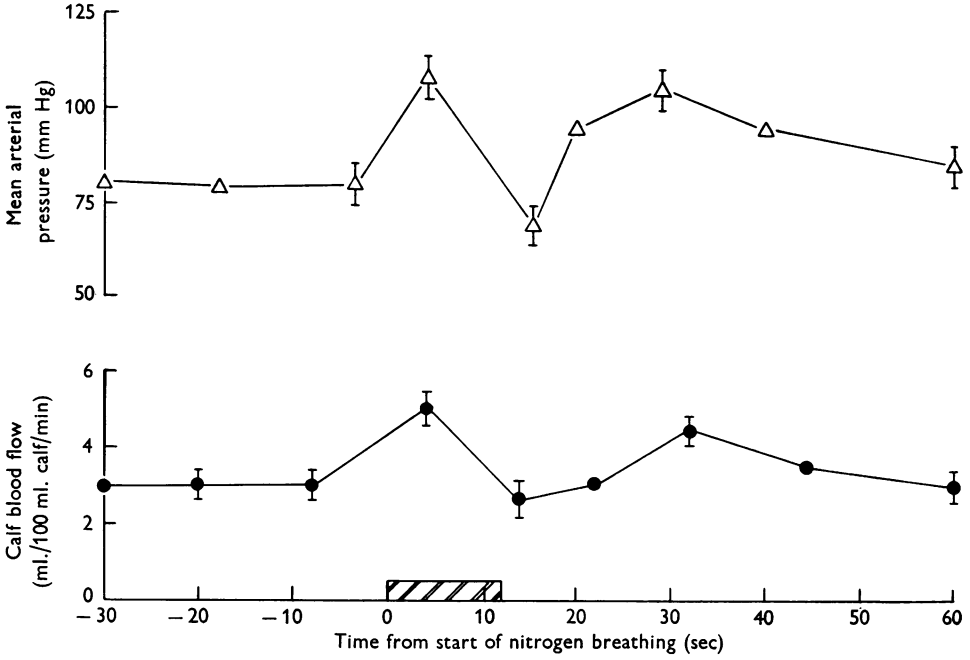

Fig. 7. Effect of over-ventilation with nitrogen upon the mean systemic arterial pressure (△) and the blood flow through the calf (●). The results are from three subjects, each pressure point representing the mean of six values whilst each blood flow point is the mean of twelve values; each bar depicts ±1 S.E. of the mean value.

Arterial oxygen saturation and pH

The delay of 4–5 sec between the beginning of nitrogen breathing and the reduction of the oxygen saturation of the brachial artery blood was a reflexion of the circulation time from the pulmonary capillaries to the sampling point in the systemic arterial tree. A similar delay occurred

between the restitution of air breathing and the subsequent increase of the arterial oxygen saturation. The reduction of the end-tidal oxygen tension to below 10 mm Hg was associated with an arterial oxygen saturation of less than 40 %. The increase of the pH of the arterial blood was related to the fall of the alveolar carbon-dioxide tension and the reduction of the blood oxygen saturation (Christiansen, Douglas & Haldane, 1914). The mean increase of the arterial pH produced by the over-ventilation amounted to 0·18 unit. This gave a calculated value for the minimal arterial carbon-dioxide tension of 22·5 mm Hg as compared with the observed end-tidal value of 17 mm Hg. The changes of arterial oxygen tension produced by over-breathing with nitrogen have been calculated from the simultaneous measurements of the oxygen saturation and pH of the arterial blood by means of standard oxygen dissociation curves (Dill, 1944). The mean time course of the oxygen tension for all the experiments is presented in Fig. 8. together with the curve for the end-tidal oxygen tension. During over-ventilation the end-tidal oxygen tension may be taken as representative of the mean alveolar tension of this gas. When allowance is made for the 4 sec delay between the change of alveolar gas composition and the resultant change of the oxygen tension of the arterial blood at the sampling point, it is apparent that the arterial oxygen tension fell in the same manner as the alveolar oxygen tension until this was less than 16 mm Hg. Beyond this point the systemic arterial oxygen tension was consistently greater than that of the alveolar gas until air breathing was restored. There was a statistically significant difference ($P < 0{\cdot}01$; $n = 9$) between the oxygen tensions of the arterial blood and of the alveolar gas for the last 7 sec of the period of nitrogen breathing. The oxygen tension of the mixed venous blood during nitrogen breathing was between 35 and 40 mm Hg (Fig. 9), and hence the oxygen tension of the alveolar gas was less than that of the blood entering the pulmonary capillaries for nearly the whole period of nitrogen over-ventilation. During this procedure, therefore, there was a reversal of the normal oxygen-tension gradient between the alveolar gas and the mixed venous blood. Since the oxygen saturation of the systemic arterial blood was considerably less than that of the mixed venous blood, oxygen must have passed from the blood flowing through the pulmonary capillaries into the alveolar gas during the latter part of the nitrogen-breathing period. Such a reversal of the normal direction of passage of oxygen across the alveolar capillary membrane has been demonstrated following rapid decompression to high altitude (Luft, Clamann & Adler, 1949; Ernsting & McHardy, 1960) and during rapid ascent following a breath-holding dive to a water depth of 60–100 ft. (18–30 m; Rahn, 1963). In both these situations the oxygen tension of the alveolar gas is reduced rapidly below that of the mixed venous blood.

Venous pH and oxygen saturation

The absence of any detectable change of the pH of the blood sampled from the three venous sites following the period of over-ventilation with nitrogen demonstrated the marked carbon dioxide buffering power of the peripheral tissues and the rapid diffusibility of this gas. The constancy of the venous pH was unexpected, since the reduction of the oxygen saturation of the venous blood would of itself have produced an increase of pH (Christiansen *et al.* 1914). At a constant carbon-dioxide tension the greatest increase of pH due to this mechanism, associated with the decrease of

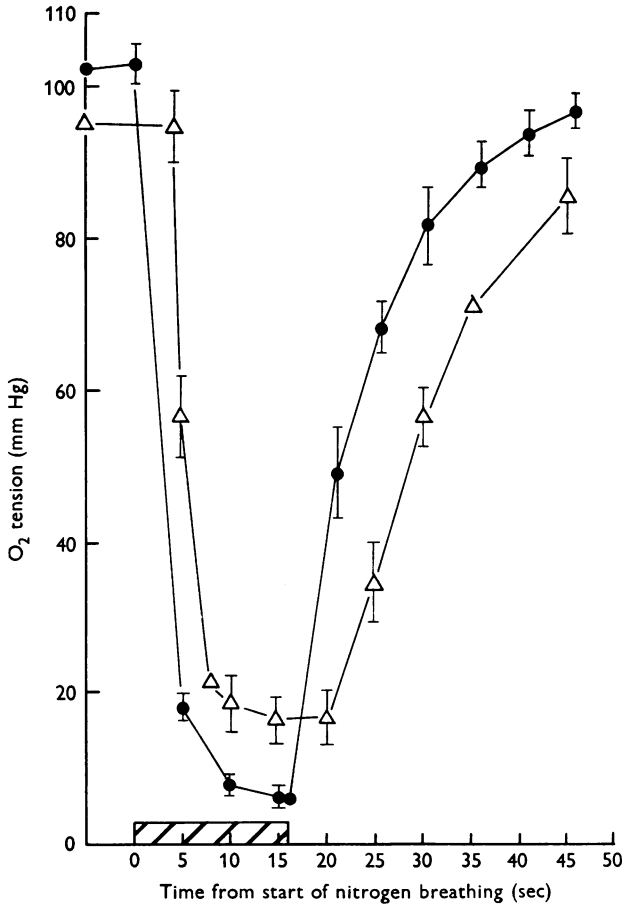

Fig. 8. Effect of over-ventilation with nitrogen upon end-tidal oxygen tension (●) and systemic arterial oxygen tension (△). Each point represents the mean of eighteen end-tidal values and nine arterial values. Each bar denotes ± 1 S.E. of the mean value.

oxygen saturation of the cerebral venous blood by 27 %, was calculated to be of the order of 0·012 unit. The over-all sensitivity of the system used for the measurement of the pH of the venous blood was such, however, that a change of this magnitude might not have been detected.

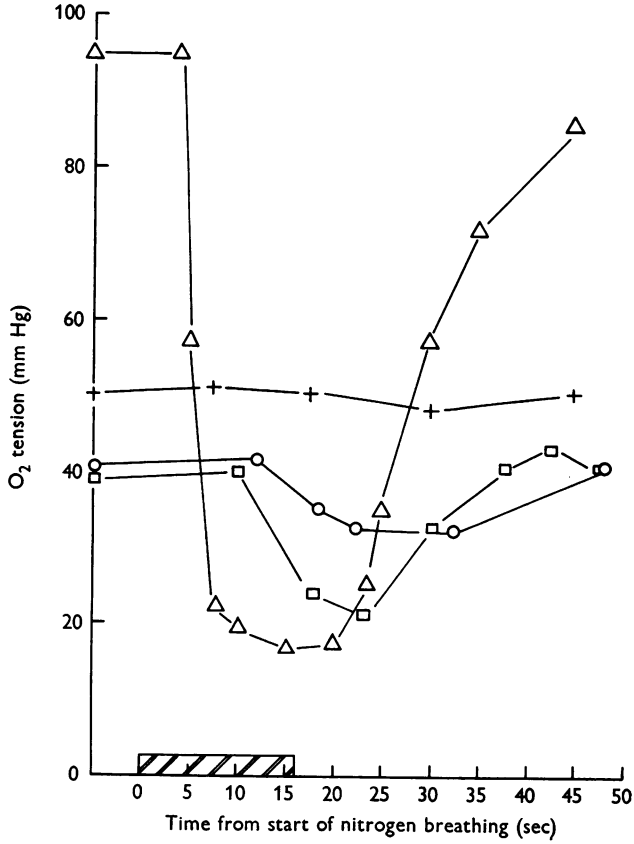

Fig. 9. Effect of over-ventilation with nitrogen upon the oxygen tension of the systemic arterial (△), femoral venous (+), internal jugular (□) and pulmonary arterial (○) blood. Each point represents the mean of the values obtained from three subjects.

The pattern of the reduction of the oxygen saturation of the venous blood produced by the period of nitrogen breathing varies markedly with the site of sampling (Fig. 5). The oxygen content of the jugular venous blood was the first to change and it exhibited the greatest reduction and the most rapid recovery. In contrast the oxygen saturation of the femoral venous blood started to fall last, was reduced by the smallest amount and recovered the most slowly. Mixed venous blood showed changes which

were intermediate between those of the jugular and femoral venous bloods. The maximal fall of the oxygen saturation of the femoral venous blood was half that which occurred in the blood sampled from the pulmonary artery, whilst the maximal reduction of the oxygen content of the jugular blood was more than twice the latter. The changes of the oxygen tension of the blood sampled from these venous sites have been calculated from the measured values of oxygen saturation and pH and the mean curves are presented in Fig. 9, together with the mean curve for the arterial oxygen tension. It is apparent that during the period of severe hypoxia the oxygen tension of the blood flowing from the lower limbs, the brain and the whole body was greater than that of the arterial blood flowing into these regions.

Cardiovascular effects of profound hypoxia

The limited measurements made in this study demonstrate that the period of over-ventilation with nitrogen produced significant changes in the cardiovascular system. The control experiments in which the subject over-breathed with air make it possible to distinguish two phases in the cardiovascular response. First, during the period in which the pulmonary ventilation was increased there was a moderate rise of heart rate and the arterial pressure and calf blood flow were raised (Fig. 7). Immediately the over-ventilation ceased the arterial pressure and calf blood flow returned to their resting values. These changes occurred when either air or nitrogen was breathed. When the over-breathing was performed with nitrogen the rise of heart rate persisted for considerably longer and there was a secondary increase of arterial pressure and calf blood flow. These secondary changes were absent when air was substituted for nitrogen and were due, therefore, to the severe hypoxia induced by the nitrogen. Throughout each experiment the calf blood flow was directly proportional to the mean systemic arterial pressure. Thus the observed changes of calf blood flow were a result of the concomitant changes of arterial pressure. The secondary changes which occurred after over-ventilation with nitrogen were probably the result of an increase of cardiac output and of systemic arteriolar constriction which were produced reflexly by chemoreceptor stimulation. It is apparent that the arterioles of the calf did not contribute to this vasoconstriction, and the most probable sites for the increase of peripheral resistance were the splanchnic and cutaneous circulations. The rise of the oxygen saturation of the jugular venous blood above the control value when air breathing was restored (Fig. 5) suggests that there was an increase of the over-all cerebral blood flow at this time. In the steady state moderate arterial hypoxaemia, even when accompanied by hypocapnia, is known to produce a dilatation of the cerebral vessels (Kety &

Schmidt, 1948). The rate at which the cerebral vasodilatation develops when arterial hypoxaemia is induced suddenly is not known, but the present experiments suggest that the cerebral vessels respond to a fall of arterial oxygen tension within 20 sec.

Pulmonary gas exchange in profound hypoxia

The arterial oxygen-tension values derived in this study demonstrated that during over-ventilation with nitrogen the oxygen tension of the arterial blood was significantly greater than that of the alveolar gas. The time for which this state existed was only 7–8 sec, although during this period the rates of change of alveolar and arterial oxygen tensions were relatively slow. Furthermore, this length of time is large relative to the average transit time of 0·73 sec (Roughton, 1945; Roughton & Forster, 1957) for a red cell through the pulmonary capillaries lining ventilated alveoli. It would appear, therefore, that the observed difference between systemic arterial and alveolar oxygen tensions cannot be accounted for on the basis of the short period for which the condition existed. Such a difference could be produced by the presence of either a shunt of venous blood into the systemic arterial tree or a higher tension of oxygen in the blood leaving the pulmonary capillaries than in the alveolar gas. Mixed venous blood flowing into the systemic arterial tree without having transversed the capillaries of ventilated alveoli would raise the oxygen tension of the systemic arterial blood above that of the alveolar gas. The effect of the normal quantity of venous admixture upon the arterial oxygen tension would be insignificant, because of the relative steepness of the blood-oxygen dissociation curve over the range concerned here. If, however, the proportion of the cardiac output perfusing ventilated alveoli was reduced during nitrogen breathing, this effect could become significant. In order for this mechanism to account for the total observed oxygen-tension gradient the venous-arterial shunt would have to amount to at least half of the total cardiac output. There is at present no evidence in favour of such a degree of shunting during severe hypoxia. It would appear probable, therefore, that the tension of oxygen in the blood leaving the pulmonary capillaries is considerably greater than that in the alveolar gas during over-ventilation with nitrogen.

Since no measurements were made of the rate of gaseous exchange during the period of over-ventilation with nitrogen it is impossible to examine quantitatively the factors affecting the exchange of oxygen between the pulmonary capillary blood and the alveolar gas. It is of value, however, to compare the effects of over-ventilation with nitrogen with those produced by moderate hypoxia in the steady state. Thus, Lilienthal, Riley, Proemmel & Franke (1946) found that at an alveolar

oxygen tension of 46 mm Hg at rest the difference between the tensions of oxygen in the alveolar gas and the systemic arterial blood amounted to 9·1 mm Hg. They calculated that under these circumstances the oxygen tension of the mixed venous blood was 19 mm Hg less than that of the alveolar gas and that the oxygen tension of the blood leaving the pulmonary capillaries was about 8 mm Hg less than that of the alveolar gas. Although in the nitrogen over-ventilation experiments the oxygen tension gradient between the alveolar gas and the mixed venous blood was reversed, it was of the same order as that which existed in the experiments performed by Lilienthal *et al.* (1946). Furthermore, the mean difference between the oxygen tensions of the arterial blood and the alveolar gas obtained in the present study, which amounted to 11 mm Hg, was only slightly greater than that found in moderate hypoxia by Lilienthal *et al.* (1946). The arterial–alveolar oxygen-tension difference observed in nitrogen over-ventilation experiments was probably due, therefore, to a mechanism analogous to that which was deduced by Lilienthal *et al.* (1946) to be responsible for the existence of an alveolar to end-pulmonary capillary blood-oxygen tension difference in moderate hypoxia. The limited rate at which oxygen was transferred from chemical combination in the pulmonary blood into the alveolar gas under the circumstances which existed in the nitrogen-breathing experiments gave rise to a large oxygen-tension difference between the blood leaving the pulmonary capillaries and the alveolar gas.

Exchange of oxygen between blood and peripheral tissues in profound hypoxia

The reduction in the rate at which oxygen is carried to a part caused by a short period of arterial hypoxaemia depends upon the degree and duration of the desaturation of the arterial blood and the arterial flow to the part. In the resting state the total blood flow to the brain is over twice that to the lower limbs. Thus in the present experiments the deficit of the oxygen supply to the brain was twice that to the lower limbs. The effect of such a deficit in the oxygen supply to a region upon the oxygen content of the blood flowing from it will be determined in part by the relation between the magnitude and nature of its oxygen store and its metabolic oxygen consumption. Where the available oxygen store is small in relation to the oxygen uptake, the venous oxygen saturation will be reduced to a greater extent than when the store is large in relation to the oxygen consumption. Quantitatively the most important oxygen store is that contained by the blood, and the greater proportion of this resides in the small and large veins. Muscle possesses in addition a specific oxygen storage mechanism in the form of oxymyoglobin. The amount of oxygen stored in this manner in man is, however, relatively small (Drabkin, 1950)

and the oxygen tension in muscle must be reduced below 10 mm Hg before a significant proportion of the oxygen held in this form is liberated (Hill, 1936). Finally, all tissues contain oxygen in simple physical solution, although quantitatively this store is relatively small. The brain, in contrast to the lower limbs and the body as a whole, has a high arterial inflow, a high oxygen consumption and a small oxygen store. For a specified transient arterial hypoxaemia all these factors tend to produce a greater fall of the oxygen saturation in the jugular blood than in the blood flowing from the lower limbs.

The pattern of the fall of the saturation of venous blood caused by a transient arterial hypoxaemia will be modified by changes of blood flow into the region and of the capacity of its vascular bed. In the present experiments there were transient changes of calf blood flow during and after the period of hypoxaemia. There was also evidence which suggested that the cerebral blood flow changed, although no direct measurements of this quantity were made. If an increase of blood flow occurred during the period of hypoxaemia, the deficit of the oxygen supply would have been increased. If, however, the increase of blood flow did not occur until the arterial oxygen saturation was rising, it would have produced a more rapid recovery of the venous oxygen saturation, or even a rise to above the control value. Although no direct measurements of the capacity of the vessels of the calf were made, it was noted that the volume of this region was decreased by the period of over-ventilation with nitrogen. Eckstein, Hamilton & McCammond (1958) have shown that the reflex reduction of the distensibility of the capacity vessels produced by over-ventilation is in part due to the hypocapnia and in part a result of the intrathoracic pressure changes associated with the over-ventilation. Such a reduction of the blood content of the calf would have tended to increase the venous desaturation produced by the arterial hypoxaemia.

During the period of over-ventilation with nitrogen, the oxygen tension of the arterial blood was reduced to 20–30 mm Hg below that of the venous blood normally flowing from the regions studied. Thus the oxygen tension of the arterial blood during this period was lower than the mean capillary oxygen tension (Barcroft, 1938) which existed before nitrogen breathing was commenced. Furthermore, during the period of profound hypoxaemia the oxygen tension of the blood flowing from the regions under investigation was greater than that of the arterial blood perfusing them. Although the oxygen content of the blood leaving the tissue capillaries was probably raised by admixture with the blood already present in the venules and veins of the part, it is apparent that during the period of severe hypoxaemia the oxygen tension of the capillary blood was markedly reduced. Thus the diffusion of oxygen into the various tissues from the blood flowing through

them was severely reduced by the period of hypoxia. Indeed, in some areas, especially those with a relatively high capillary blood flow, the capillary oxygen tension may have been reduced below that of the surrounding tissues, so that oxygen actually diffused into the blood as it flowed through them. Thus direct measurements of the oxygen tension of the grey matter of the cerebral cortex in animals breathing air have given values of the order of 18–25 mm Hg (Cater, Garattini, Marina & Silver, 1962), whilst in the present experiments the arterial oxygen tension was reduced to about 17 mm Hg. The effect of a given reduction of the rate at which oxygen diffuses into a tissue upon the cellular oxygen tension will depend upon the relation between the cellular oxygen consumption and the extravascular oxygen store. There is considerable evidence that the cellular oxidative enzyme systems will continue to function normally until the local oxygen tension is reduced to below 5 mm Hg (Keilin, 1930). Thus the cellular metabolic oxygen uptake will probably remain unchanged until severe hypoxia is induced. In the brain, where the only extravascular oxygen store is oxygen dissolved in tissue fluid, and the metabolic oxygen uptake is high, sudden arterial hypoxaemia will produce a very rapid fall of the cellular oxygen tension.

In the present series of experiments it was found that unconsciousness ensued if over-ventilation with nitrogen was continued for longer than 17 sec. A more rapid fall of arterial oxygen tension can be produced by sudden reduction of the environmental pressure to below 140 mm Hg whilst air is breathed. Thus in one series of experiments in which the arterial oxygen tension was reduced to below 20 mm Hg in about 1 sec, unconsciousness ensued 8 sec after the induction of arterial hypoxaemia (Ernsting *et al.* 1960). The delay between a sudden occlusion of the cerebral circulation and loss of consciousness in man also amounts to between 7 and 8 sec (Rossen, Kabat & Anderson, 1943). Thus the time which elapses between a sudden reduction of the arterial oxygen tension to below 20 mm Hg and the onset of unconsciousness is very similar to the interval which occurs between sudden occlusion of the cerebral circulation and loss of consciousness. Kety (1950) has calculated that at any one moment the total oxygen content of the brain and of the cerebral capillary blood is about 7 ml. Thus at the normal level of cerebral oxygen consumption the oxygen tension of the brain following cessation of the supply of this substance would be reduced to zero in about 8 sec. These results suggest that when unconsciousness supervenes following the sudden induction of severe cerebral hypoxia the cellular oxygen tension in many regions of the brain will be virtually zero. This conclusion is in close agreement with the results of calculations made by Thews (1962) with respect to hypoxia of slow onset. His calculations suggest that when the arterial oxygen tension is

reduced to the level which produces unconsciousness, the oxygen tension of the neurones which are furthest from their vascular supply will be of the order of 2–4 mm Hg.

SUMMARY

1. Brief profound hypoxia was induced by voluntary over-ventilation whilst breathing nitrogen. Unconsciousness ensued when this procedure was performed for longer than 16 sec. Voluntary over-ventilation with nitrogen for 16 sec reduced the end-tidal oxygen tension to below 10 mm Hg for 8 sec.

2. Continuous recordings were made of the systemic arterial oxygen saturation and pH during 16 sec of nitrogen over-ventilation. The calculated minimal arterial oxygen tension was 16 mm Hg. There was therefore a reversal of the normal alveolar-arterial oxygen tension difference.

3. The oxygen saturation and pH of venous blood flowing through the jugular bulb, the femoral vein and the pulmonary artery were recorded continuously. The oxygen tension of the jugular blood exhibited the most rapid and most profound reduction when nitrogen was breathed. The femoral-vein oxygen tension exhibited only a very transient and slight fall, whilst the oxygen tension of the blood flowing through the pulmonary artery exhibited a moderate fall.

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REFERENCES

BARCROFT, J. (1938). *Architecture of Physiological Function*, 2nd ed. p. 244. London: Cambridge University Press.

CATER, D. B., GARATTINI, S., MARINA, F. & SILVER, I. A. (1962). Changes of oxygen tension in brain and somatic tissues induced by vasodilator and vasoconstrictor drugs. *Proc. Roy. Soc.* B, **155**, 136–157.

CHRISTIANSEN, J., DOUGLAS, C. G. & HALDANE, J. S. (1914). The absorption and dissociation of carbon dioxide by human blood. *J. Physiol.* **48**, 244–271.

DILL, D. B. (1944). Oxygen dissociation curves for human blood at 37° C. In BRONK, D. W. *Handbook of Respiratory Data in Aviation*. Washington: Committee on Medical Research.

DRABKIN, D. L. (1950). The distribution of the chromoproteins, haemoglobin, myoglobin and cytochrome in the tissues of different species, and the relationship of the total content of each chromoprotein to body mass. *J. biol. Chem.* **182**, 317–333.

ECKSTEIN, J. W., HAMILTON, W. K. & MCCAMMOND, J. M. (1958). Pressure-volume changes in the forearm veins of man during hyperventilation. *J. clin. Invest.* **37**, 956–961.

ERNSTING, J. (1962). Some effects of brief profound anoxia upon the central nervous system. In MCMENEMEY, W. H. and SCHADE, J. P., *Selective Vulnerability of the Brain in Hypoxaemia*. Oxford: Blackwell.

ERNSTING, J., GEDYE, J. L. & MCHARDY,. J. R. (1960). Anoxia subsequent to rapid decompression. *Flying Personnel Research Committee Report*, No. 1141. London: Air Ministry.

ERNSTING, J. & MCHARDY, G. J. R. (1960). Brief anoxia following rapid decompression from 560 to 150 mm Hg. *J. Physiol.* **153**, 73*P*.

ERNSTING, J. & MCHARDY, G. J. R. (1963). The oxygen saturation and pH of the arterial blood during brief profound anoxia induced by rapid decompression from 560 to 140 mm Hg. In CUNNINGHAM, D. J. C. and LLOYD, B. B., *The Regulation of Human Respiration*. Oxford: Blackwell.

FOWLER, K. T. & HUGH-JONES, P. (1957). Mass spectrometry applied to clinical practice and research. *Brit. med. J.* i, 1205–1211.

HILL, R. (1936). Oxygen dissociation curves of muscle haemoglobin. *Proc. Roy. Soc.* B, **130**, 472–483.

KEILIN, D. (1939). Cytochrome and intra-cellular oxidase. *Proc. Roy. Soc.* B, **106**, 418–444.

KETY, S. S. (1950). Circulation and metabolism of the human brain in health and disease. *Amer. J. Med.* **8**, 205–217.

KETY, S. S. & SCHMIDT, C. F. (1948). The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. *J. clin. Invest.* **27**, 484–492.

LILIENTHAL, J. L., RILEY, R. L., PROEMMEL, D. D. & FRANKE, R. E. (1946). An experimental analysis in man of the oxygen pressure gradient from alveolar air to arterial blood during rest and exercise at sea level and at altitude. *Amer. J. Physiol.* **147**, 199–216.

LUFT, U. C., CLAMANN, H. G. & ADLER, H. F. (1949). Alveolar gases in rapid decompressions to high altitudes. *J. appl. Physiol.* **2**, 37–48.

RAHN, H. (1963). Lessons from breath holding. In CUNNINGHAM, D. J. C. and LLOYD, B. B. *The Regulation of human respiration.* Oxford: Blackwell.

ROSSEN, R., KABAT, H. & ANDERSON, J. P. (1943). Acute arrest of the cerebral circulation in man. *Arch. Neurol. Psychiat., Chicago*, **50**, 510–528.

ROUGHTON, F. J. W. (1945). The average time spent by the blood in the human lung capillary and its relation to the rate of CO uptake and elimination in man. *Amer. J. Physiol.* **143**, 621–633.

ROUGHTON, F. J. W. & FORSTER, R. E. (1957). Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. *J. appl. Physiol.* **11**, 290–302.

SHERWOOD-JONES, E., ROBINSON, J. S. & COOKE, W. H. (1960). A device for the continuous measurement and recording of intravascular pH. *Lancet*, **278**, 1329.

THEWS, G. (1962). Implications of the physiology and pathology of oxygen diffusion at the capillary level. In MCMENEMEY, W. H. & SCHADE, J. P. *Selective Vulnerability of the Brain in Hypoxaemia.* Oxford: Blackwell.

WHITNEY, R. J. (1953). The measurement of volume changes in human limbs. *J. Physiol.* **121**, 1–27.