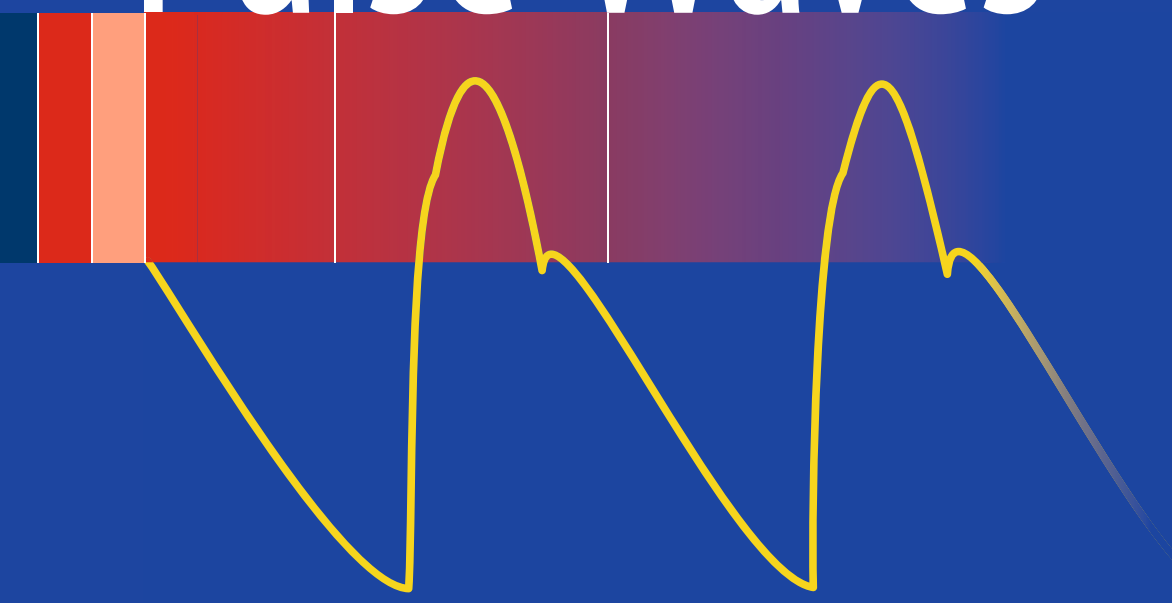
Paolo Salvi

Pulse Waves



How Vascular Hemodynamics Affects Blood Pressure

Second Edition

Springer

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To my wife Marna
I thank my Lord for this wonderful gift

Foreword by Alberto Zanchetti

I am delighted to introduce this new updated edition of Paolo Salvi's volume on *Pulse Waves*, brilliantly summarizing the hemodynamics of hypertension and its implications for treatment. The publication of the second edition at a relatively short distance from the first one witnessed the success of the work and its timely appearance.

The founding fathers of cardiovascular physiology were well aware of the complexity of the hemodynamic mechanisms underlying arterial blood pressure, and the models they developed tried to keep all known mechanisms under consideration. During the second half of the twentieth century, when blood pressure became an object of increasing clinical interest and a target for therapeutic intervention, the operational model being used was simplified and reduced to a pump working against a peripheral vascular resistance. Although certainly oversimplified, it cannot be denied that this model helped in achieving one of the greatest medical successes of the past century, that is the ability to effectively lower the most important risk factor for cardiovascular disease, high blood pressure.

With increasing attention being paid nowadays to hypertension in the elderly, it was too easy to understand that the simplified model that had been so beneficial in developing current antihypertensive therapy had obvious limitations, and that in order to understand blood pressure increase with aging additional hemodynamic complexities had to be added to the model. Paolo Salvi, who has been and is in the forefront of new research in this area, deserves the highest appreciation for calling the doctors' attention to the reality of the complexities of hemodynamics and for doing that in such a clear and efficacious way. Readers will find here a clear explanation of the role of large arteries in addition to those of the cardiac pump and vascular resistances, the role of pulse wave reflection, the possible differences between peripheral and central blood pressure, the new techniques and equipments allowing a more precise evaluation of hemodynamic patterns.

Scientific progress naturally generates not only knowledge but challenges. The major challenge in front of hypertension experts is demonstrating that the new

models, the new equipments, and the new measurements can effectively improve the way we are diagnosing and treating hypertensive patients and further improve their survival.

Istituto Auxologico Italiano
Milan, Italy

Alberto Zanchetti

Foreword by Michel E. Safar

A young clinical research worker in the fields of hypertension during the 1970s had principally to focus on the etiological aspects of hypertension, namely the renin–angiotensin–aldosterone system and the kidney structure and function, which seemed, at this period, the dominant scientific problems of high blood pressure. Drug treatment of hypertension was emerging, and the most important outcomes of therapeutic trials were just becoming to be investigated. Hypertension was described as a mosaic of various pathophysiological alterations, involving numerous organs and/or functions, including kidney, adrenal glands, renin, sympathetic nervous system, and arterioles. In fact, it seemed that any part of the body was involved in the mechanisms of hypertension. However, the conduit arteries, which were the precise site where the diagnosis of high blood pressure was established, were not considered of primary interest. Only the arterioles, a part of the vascular tree in which blood pressure was poorly measured, were considered of great importance. Furthermore, the large arteries, i.e., the precise and specific site of the complications (rupture, thrombosis and aneurysms) of the disease, were considered important only as the location of atherosclerosis, a specific process very similar to, but in fact substantially different from that of hypertension itself.

In that period, however, systemic hemodynamic studies were considered as a necessary basis for any understanding of the mechanisms of hypertension. This notion was widely accepted both in clinical and experimental situations, but in both fields, the hemodynamic description of hypertension referred almost exclusively to linear models of circulation with simple measurements of steady flow. Only Poiseuille's and Laplace's laws were considered to be relevant to investigate the hemodynamic alterations. The evolution of the disease was presented as some kind of "struggle" between two exclusive components of blood circulation: heart and arterioles. No other component of the circulation had to be extensively investigated. To be more specific, large arteries had no substantial role to be clarified within the mechanisms of hypertension. Nevertheless, at that time (1970), the weight of evidence suggested that conduit arteries were clearly involved in both the diagnosis of the disease and mainly its complications. It was evident that the description of this important aspect of circulation in hypertensive subjects required a considerable modification of our conceptual approach of this disease.

In the traditional approach, the vascular system is considered as a steady-flow conduit network, which is mainly characterized by mean blood pressure. However, this model focuses on the end product, the steady flow that is vital for tissue perfusion and ignores the process that comes before it which regards the pulsatile nature of the arterial system and the buffering function of large arteries and their Windkessel function. This process is the conversion of the intermittent, high-flow ejection by the left ventricle into the continuous peripheral flow and functions through the elastic properties of the aorta and large arteries already described in cardiovascular physiology. Taking into account both steady and pulsatile hemodynamics phenomena, the pressure waveform may be conceived as a fluctuation, whose peak is systolic blood pressure and nadir the diastolic blood pressure, around a mean value, mean blood pressure. Furthermore, large arteries may be investigated not only on the basis of viscoelastic properties of the arterial wall but also on the basis of presence of wave reflections.

In fact, all these new properties of the cardiovascular system could not be described without new goals in the development of hypertension: not only the research for the causes of the disease but also the definition of its main purpose, the reduction of cardiovascular risk, conceived both within its steady and pulsatile aspects. The association of hemodynamic development and of cardiovascular epidemiology has now turned our concepts about hypertension towards several major noninvasive investigations in men. First, aortic stiffness using aortic pulse wave velocity (PWV) measurement becomes a common evaluation of cardiovascular risk. Second, wave reflections may be explored using augmentation index and pressure. Third, blood pressure variability becomes an important study in the long term. Quarter, brachial artery blood pressure may be investigated in parallel with central blood pressure measurements, which are closer from organs generating the higher risk. All these determinations may be repeated using nowadays adequate drug treatments. Finally, all these novel aspects are detailed in the present book, Pulse Waves, done by Paolo Salvi.

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Preface to the Second Edition

Over the last 20 years, the outcomes of important clinical trials have pointed out some peculiar aspects of vascular hemodynamics, stressing the importance of the mechanical properties of the aorta and large arterial vessels, of central blood pressure, of the amplification phenomenon, of incremental pressure, etc. To understand these elements, the basics of cardiovascular pathophysiology are required, particularly vascular hemodynamics.

This book aims to be a clear and easy tool, providing the reader with the basic principles of vascular hemodynamic physiopathology, to offer a better approach to the hypertensive patient. Sometimes this teaching method needs to simplify things in a way that could seem even banal, but the purpose is always to give intelligible messages to everybody.

The author will try to take the reader by the hand, to describe the elements of blood pressure, starting from the definition of mean arterial pressure, going on with the analysis of the basic principles of pulse pressure, and familiarizing the reader with a "dynamic" concept of blood pressure. Then, the forward and reflected components of the central pressure wave will be analyzed, providing the reader with self-study material to read the central blood pressure waveform and to understand the relationship between peripheral and central blood pressure.

There have been significant changes in this second version. This is mainly due to the fact that Springer preferred an e-book to a paper book. Personally, I do not agree with this decision as I continue appreciating the direct relationship with the old paper book, where one can take notes and underline sentences. Paper books can be read and zealously stored in a book case. The new edition of the book has a number of color images. All the chapters have been updated. Two new chapters concerning the relationship between arterial stiffness and pressure variability and the interrelation between arteriosclerosis and chronic renal disease have been added.

Please point me out incomplete or unclear parts or even possible mistakes. Thank you in advance for your suggestions and comments. Any suggestion will be taken into consideration in the next editions, always to improve the quality of the book. Please send them to this e-mail: *salvi.pulsewaves@gmail.com*.

Paolo Salvi

Contents

Vascular Hemodynamics and Blood Pressure

1

1.1 Mean Arterial Pressure

In the study of vascular hemodynamics, the cardiovascular system is usually considered to be a simple hydraulic circuit, composed of a pump (heart) with a rhythmic activity (systole → diastole → systole → diastole → systole…) that pushes a liquid (blood) into a tube (the aorta), which divides over and over again (peripheral arteries → arterioles → capillaries) to be able to reach the farthest extremes (tissues).

This hydraulic circuit is very similar to a simple electric circuit and we have to stress that electrical models are often used to verify cardiovascular hemodynamic phenomena (Fig. 1.1).

According to Ohm's law, the potential difference between the extreme points of an electric circuit ($\Delta V = V_1 - V_2$) is defined by multiplying the current (I) by the resistance of the circuit (R).

$$\Delta V = I \times R.$$

The cardiovascular system can be considered in a similar way, and the law which defines blood pressure comes directly from Ohm's law:

- The difference in blood pressure values between the extreme points of the systemic circulation ($\Delta P = P_1 - P_2$) represents the potential difference between the extreme points of an electric circuit ($\Delta V = V_1 - V_2$)
- CO (cardiac output) represents the current (I)
- SVR (systemic vascular resistance) represents the resistance of the circuit (R)

$$\Delta P = \mathrm{CO} \times \mathrm{SVR}.$$

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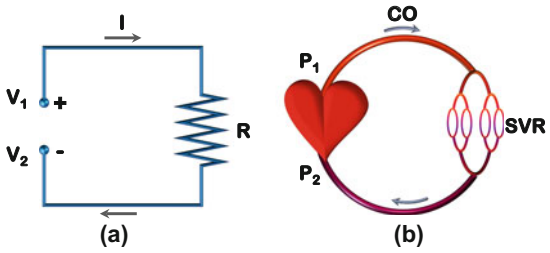

Fig. 1.1 Similarities between a simple electric circuit and the circulatory system. (**a**) Simple electric circuit: $V_1 - V_2$ is the potential difference measured across the conductor; I is the current through the conductor; R is the resistance of the conductor. (**b**) Systemic circulation system model: $P_1 - P_2$ is the difference in blood pressure values between the extreme points of the systemic circulation; *CO* stands for cardiac output; *SVR* stands for systemic vascular resistance

As blood pressure back to the heart is very low, let us consider the pressure value as the value of blood pressure in the ascending aorta (P); therefore, the formula can be simplified by writing:

$$P = \text{CO} \times \text{SVR}.$$

As cardiac output (CO) is given by multiplying stroke volume (SV) by heart rate (HR), the formula can be rewritten as:

$$P = \text{SV} \times \text{HR} \times \text{SVR}$$

$$(\text{blood pressure} = \text{stroke volume} \times \text{heart rate} \times \text{systemic vascular resistance}).$$

However, we must point out that blood pressure values change during the cardiac cycle, so the term "P", defined by the formula above, refers to mean arterial pressure (MAP). Therefore,[1]

$$\text{MAP} = \text{SV} \times \text{HR} \times \text{SVR}.$$

According to this formula, mean blood pressure values depend on just three parameters: stroke volume, heart rate and systemic vascular resistance (Fig. 1.2). It

[1] *How can mean arterial pressure be calculated?*

Mean arterial pressure is generally calculated from brachial systolic and diastolic blood pressure (DBP), according to the following formula: MAP = DBP + 33 % of pulse pressure (or +40 % of pulse pressure, as recently proposed). For more accurate calculation of mean arterial pressure, the brachial artery pressure curve can also be recorded by means of a tonometer. Once the brachial artery pressure curve is taken, the integral of the pressure curve is calculated, corresponding to the real mean arterial pressure. Now the exact ratio between mean arterial pressure and pulse pressure can be easily obtained; this topic will be dealt with later. Nowadays, automated oscillometric blood pressure devices have become increasingly popular in the measurement of mean arterial pressure, which corresponds to the maximum pulse amplitude in cuff pressure.

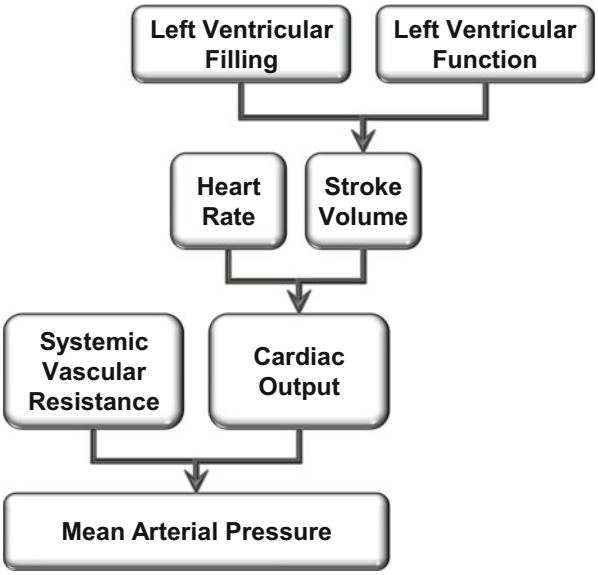

Fig. 1.2 Factors defining mean arterial pressure

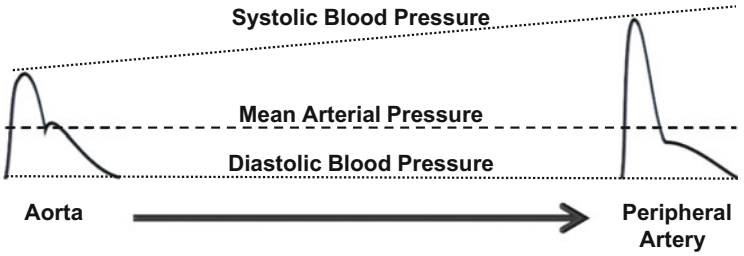

Fig. 1.3 Change in blood pressure values from the center to the periphery of the arterial system

is important to note that, for decades, both research and clinical application focused their attention on these three factors affecting mean arterial pressure.

Mean arterial pressure is a key parameter and its most important aspect is associated with its relative "stability" in the arterial tree. Mean arterial pressure tends to remain unchanged in the arterial system, from the ascending aorta to peripheral arteries (Fig. 1.3).

Are these three parameters (SV, HR, and SVR) sufficient to explain the changes in pressure found in both physiological and pathological conditions?

Let us analyze Fig. 1.4. In this figure, we can see the condition of two subjects with very different blood pressure levels. The subject on the left (a) has 80 mmHg diastolic blood pressure and 130 mmHg systolic blood pressure. On the contrary, the subject on the right (b) has 60 mmHg diastolic blood pressure and 160 mmHg systolic blood pressure.

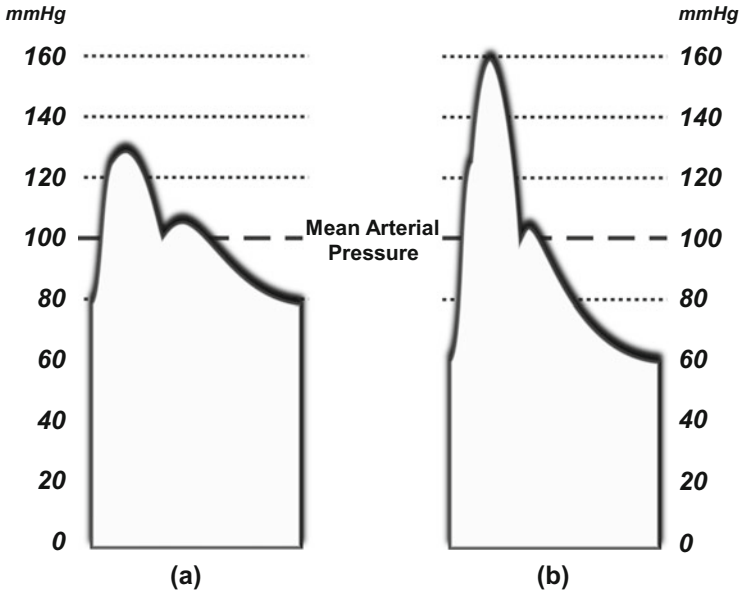

Fig. 1.4 Example of two subjects with the same mean arterial pressure values: (**a**) normotensive and (**b**) patient with isolated systolic hypertension. Waveforms were recorded in the brachial artery

Therefore, subject (a) has blood pressure values within the normal range, while subject (b) is characterized by a condition of true isolated systolic hypertension. However, both of these subjects present the same mean arterial pressure value (100 mmHg). They both could have the same values of heart rate, stroke volume, and systemic vascular resistance.

We can conclude that different pressure values can correspond to the same mean arterial pressure value. This example is sufficient to answer the question above. The three parameters: heart rate, stroke volume and systemic vascular resistance, define mean arterial pressure, but they are not sufficient, in themselves, to justify blood pressure values.

1.2 Pulse Pressure

Accurate analysis of cardiovascular hemodynamics cannot ignore that blood pressure has two distinct but interdependent components (Fig. 1.5):

- A steady component, namely, mean arterial pressure.
- A pulsatile component, defined as pulse pressure (PP), which represents the fluctuation in pressure values around the mean value of arterial pressure.

As we have already seen, the steady component, mean arterial pressure, depends on three factors:

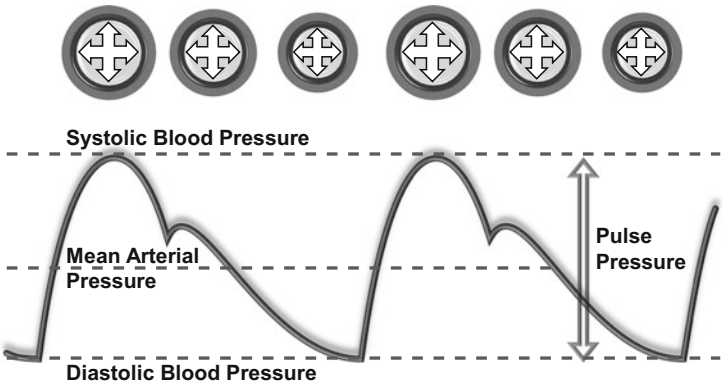

Fig. 1.5 Mean arterial pressure and pulse pressure. Variation of the section of a large artery during a cardiac cycle is schematized in the *upper panel* of the figure

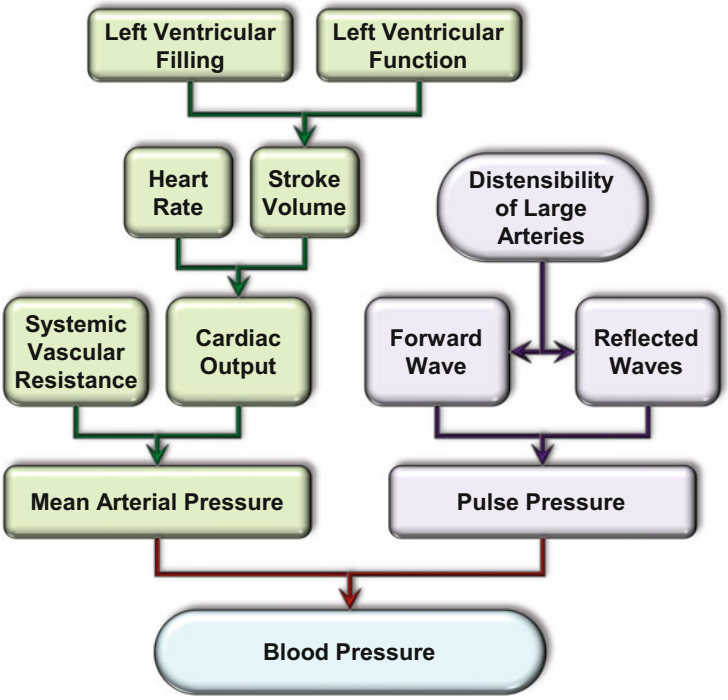

Fig. 1.6 Factors defining blood pressure

1. Heart rate
2. Stroke volume
3. Systemic vascular resistance

The pulsatile component, pulse pressure, depends on two factors (Fig. 1.6):

1. The blood pressure wave originating from the interaction between the left ventricular ejection activity and the mechanical properties of large arteries (forward wave).
2. Reflected waves.

However, both the steady and pulsatile components of blood pressure should not be thought of as self-contained areas. In fact, there are a number of interactions between the elements defining mean arterial pressure and the ones defining pulse pressure. These interactions will be analyzed later.

1.3 Systemic Circulation: Only One Engine, Two Pumps

When we think of systemic circulation, we bear in mind a clear-cut scheme. We tend to consider systemic circulation as a pump, the left ventricle, which pumps blood into the aorta intermittently (stroke volume) and, from here, to the whole body arterial system, which conveys blood to peripheral tissues. Then blood is sent back to the heart through the veins.

Now, we are going to see that this is a gross oversimplification of the facts and learn that systemic circulation has not only a pump (the left ventricle), which is active only in the systolic phase, but that systemic circulation is composed of two pumps:

1. The left ventricle, which represents the systolic pump. The left ventricle guarantees the pumping action of the circulating system during the systolic phase of the cardiac cycle
2. The aorta and large elastic arteries, which represent the diastolic pump. Large elastic arteries guarantee the pumping activity of the circulating system during the diastolic phase of the cardiac cycle

The interaction between these two pumps guarantees the normal supply of oxygen and nutrients to tissues. This new view of the physiology of the systemic circulation will be of great help to us not only to understand the hemodynamic process at the basis of the regulation of blood pressure but also to clarify the pathophysiological mechanism of diastolic dysfunction and left ventricular failure [1].

1.3.1 The Aorta and Large Elastic Arteries

Throughout the 20th century, the assessment of arterial blood pressure was carried out by taking into account, on the one hand, the heart, namely, the pumping action of the left ventricle (stroke volume and heart rate), and, on the other hand, systemic vascular resistance.

The conduction system of large arteries was totally ignored (Fig. 1.7).

Still today, a lot of physicians and, unfortunately, even a number of cardiologists consider the aorta and large arteries as mere “inert tubes” connecting the left

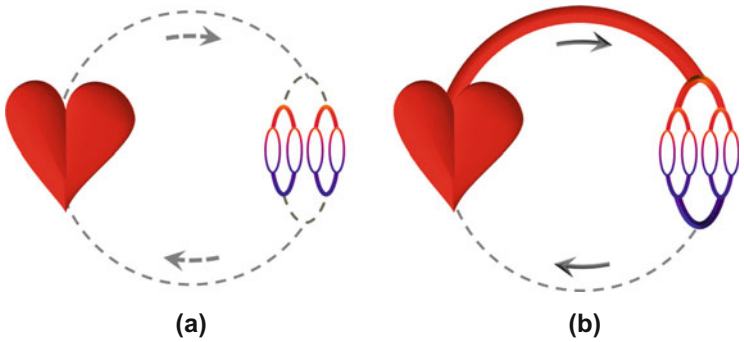

Fig. 1.7 (**a**) Considering blood pressure exclusively as the product of cardiac output multiplied by peripheral vascular resistance means that only the left ventricle and peripheral resistance functions are taken into account and that the role of large arteries is totally ignored. (**b**) On the contrary, an accurate evaluation of blood pressure also needs to analyze the viscoelastic properties of the aorta and large arteries

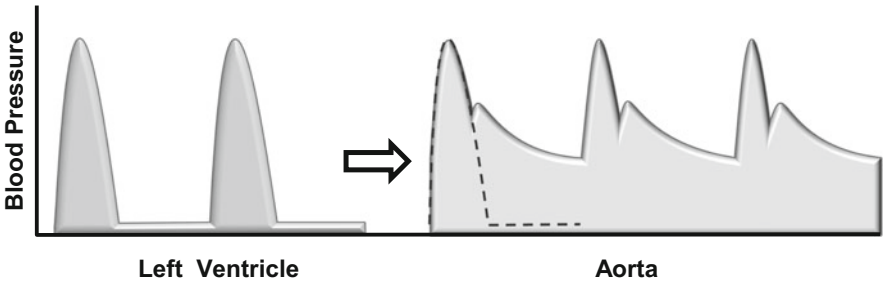

Fig. 1.8 From intermittent pressure (left ventricle) to continuous pressure (aorta)

ventricle with peripheral resistance. These "tubes" are taken into account just when they run the risk of being broken or closed, namely, with patients at increased risk of thrombosis or bleeding events, respectively.

We are about to see that this concept is totally wrong, and we will reevaluate the important and essential role of the aorta and large arteries in the hemodynamics of the cardiovascular system and in assessing blood pressure values.

Actually, large arteries play a major role in the regulation of blood pressure and peripheral blood flow. It is well known that the aorta and large arteries have not only a passive transfer function of oxygenated blood from the heart to the periphery but also a "buffer" function, as they are able to amortize left ventricular stroke volume, thanks to their viscoelastic properties. In fact, each cardiac cycle alternates between a left ventricular contraction phase, in which a given amount of blood is forcibly pushed into the arterial system (systole), and a relaxation phase (diastole), in which ventricular filling occurs.

Large elastic arteries, therefore, have the task of damping the pulsatile output of the left ventricle and of changing the rhythmic, intermittent, and discontinuous activity of the cardiac pump into a continuous one (Fig. 1.8). Actually, when the stroke volume

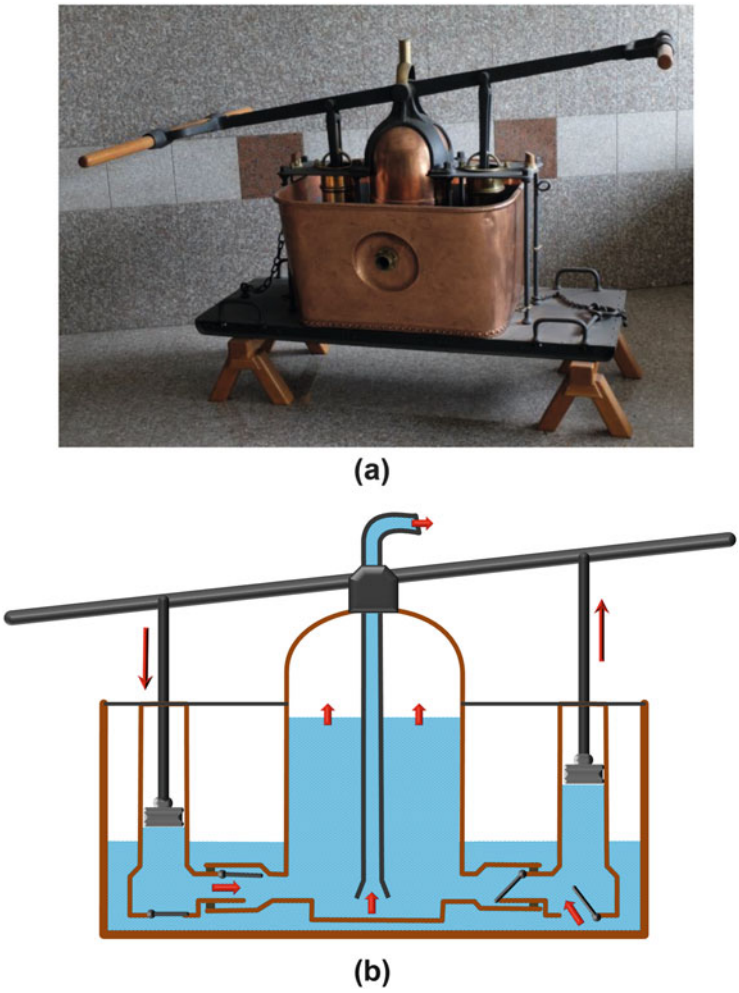

Fig. 1.9 The Windkessel phenomenon. "Windkessel", in German, literally means "air chamber". This term refers to the system used in old fire engines until the beginning of last century. Given a pump with intermittent activity, water was provided at a steady flow, thanks to an ingenious system, whereby, during the ejection phase of the pump, some water was pumped out, whereas most of it was stored in a closed tank, which also contained some air that became compressed. During the aspiration phase, water was pushed out by the compressed air, thereby maintaining a continuous and regular flow. (**a**) Hand pump used in the 19th century to be founded at Forlì-Cesena Fire Department. (**b**) Scheme reproducing the functioning of this hand pump

and the closure of the aortic valves occur, a great quantity of blood remains "stored up" in the aorta and large elastic arteries, to be released afterwards (*Windkessel* effect) so that proper pressure values are maintained in diastole as well (Fig. 1.9).

1.3.2 The Aorta as Diastolic Pump

The change from intermittent flow (on leaving the heart) to continuous flow (in the organs and tissues) occurs thanks to the viscoelastic properties of the aorta and large arteries.

When the viscoelastic properties of the aorta are undamaged, in systolic phase, only a fraction of the stroke volume is sent directly to the periphery, while most of it is stored in the system of large elastic arteries (Fig. 1.10a).

In diastole, at the closure of the aortic valves, the aorta, which has been filled and "blown up" like a balloon in systole, tends to return to its basal state, causing a propelling thrust towards the periphery (Fig. 1.10b). In other words, the potential energy stored in the aortic wall during the systolic phase turns into kinetic energy during the diastolic phase of the cardiac cycle, pushing the stored blood into the bloodstream. In this way, the aorta behaves like a sort of "pump in diastole". This is exactly what happens in the *Windkessel* phenomenon, when the compressed air pushes water out of the system.

In order to accurately understand cardiovascular hemodynamics, let us get rid of any knowledge we have gained so far about the circulatory system. At university,

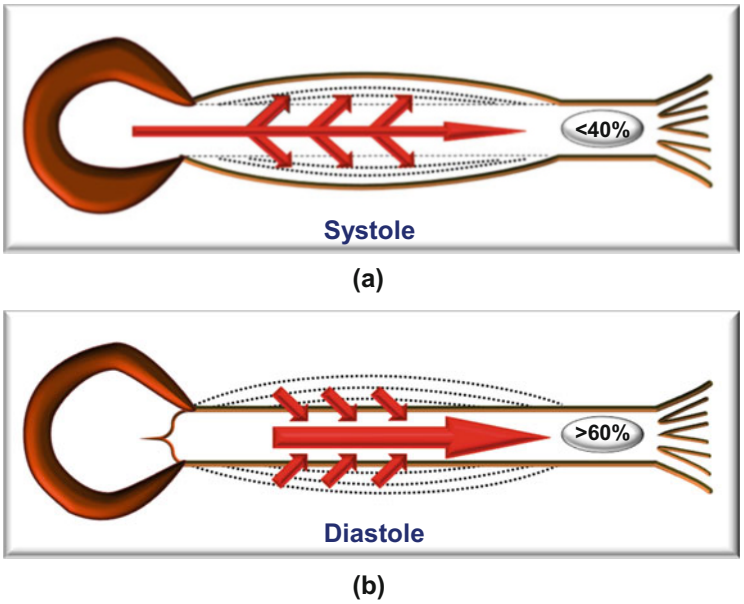

Fig. 1.10 The Windkessel phenomenon under normal vascular distensibility conditions. (**a**) The left ventricle acts as a pump during the systolic phase of the cardiac cycle whereas (**b**) the aorta acts as a pump during the diastolic phase of the cardiac cycle

we learnt that systemic circulation of the cardiovascular system is made up of a pump (the left ventricle), a vascular system (carrying blood throughout the body and delivering oxygen and nutrients to tissues), and a venous system (taking back blood to the heart).

Yet, it is important to stress that this circulatory system model is incomplete and misleading. Firstly, it does not take into account that the left ventricle performs an intermittent activity. Secondly, blood is pumped into the vascular system only during the systolic phase.

Therefore, let us consider that the systemic circulation system is made up of two pumps: the left ventricle is the pump working during the systolic phase whereas the aorta and large elastic arteries are the diastolic pump of the systemic circulation system (Fig. 1.11). Nevertheless, I would like you not to make the mistake of considering these two pumps as two independent and separate structures. In fact, the activity of the systolic pump (the left ventricle) is closely linked to the activity of the diastolic pump (the aorta and large arteries) in a mutually dependent relationship.

The viscoelastic properties of the aorta and large elastic arteries depend on the relationship between the principal components of the arterial wall: elastin and collagen. The functional and structural state of the arterial wall, therefore, affects and defines its ability to damp the systolic wave.

$$\text{Viscoelastic properties of the aorta} = \frac{\text{elastin fibers}}{\text{collagen fibers}}$$

1.3.3 Aortic Stiffness and Diastolic Pump Failure

If we consider the aorta as a pump that guarantees a normal supply of blood in diastole, when the normal viscolelastic properties of large arteries are somehow altered, diastolic dysfunction occurs. Let us now introduce the concept of aortic pump failure in diastole.

Several paraphysiological or pathological conditions such as aging, hypertension, inflammation, media calcifications, and metabolic alterations can change the anatomical, structural, and functional properties of large elastic arteries, thereby degrading their mechanical properties.

Arterial viscoelastic properties change with age. The aging process causes well-known histological alterations in the elastic large arteries. An increased elastase activity and a reduced elastin synthesis cause thinning and breakage of elastin fibers, and the result is a decrease in the elastin/collagen ratio.

An accelerated vascular aging characterizes chronic kidney disease and diabetes. In these patients, calcifications in the arterial medial layer changes in the extracellular matrix and endothelial dysfunction are early phenomena, causing conditions that predispose to arterial stiffening.

In hypertension, a permanent increase in mean arterial pressure may cause structural changes in viscoelastic properties of arterial walls. An increased

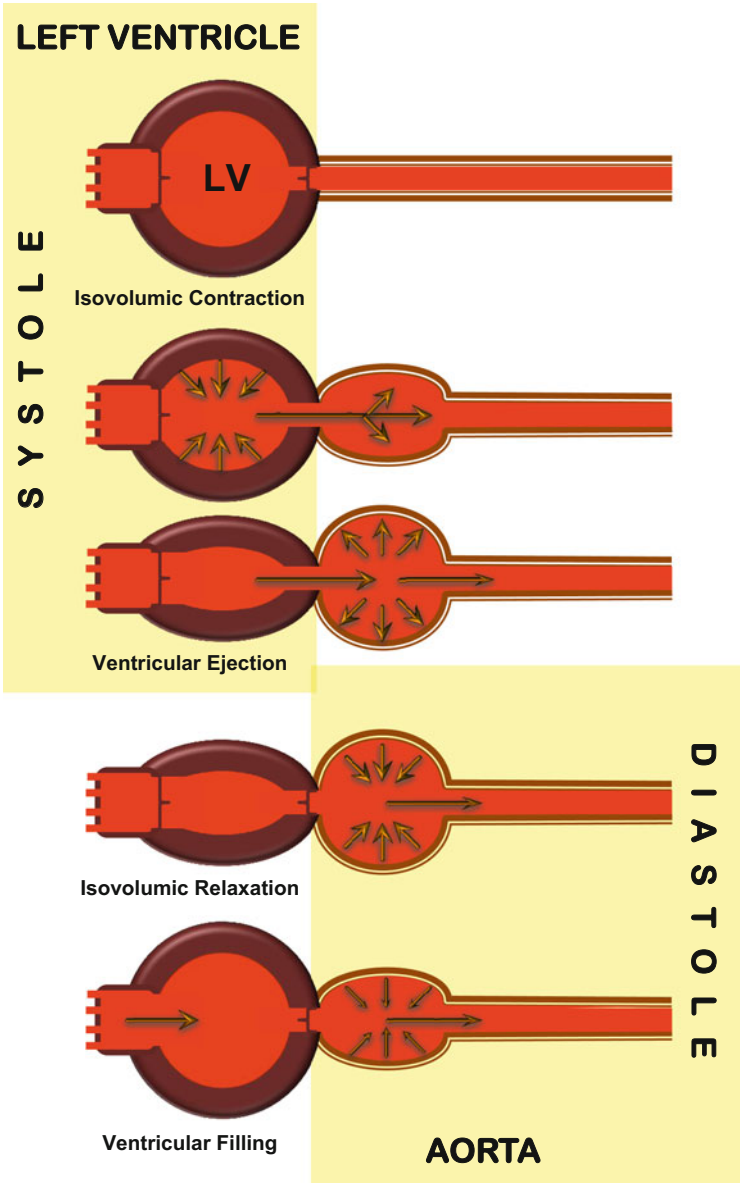

Fig. 1.11 The scheme highlights that the left ventricle acts as a pump during the systolic phase of the cardiac cycle whereas large elastic arteries act as a pump during the diastolic phase of the cardiac cycle

biosynthesis of collagen occurs in order to counterbalance the increase in transmural pressure. This process can be associated with alterations in the endothelial function and with a remodeling process of the arterial wall, characterized by

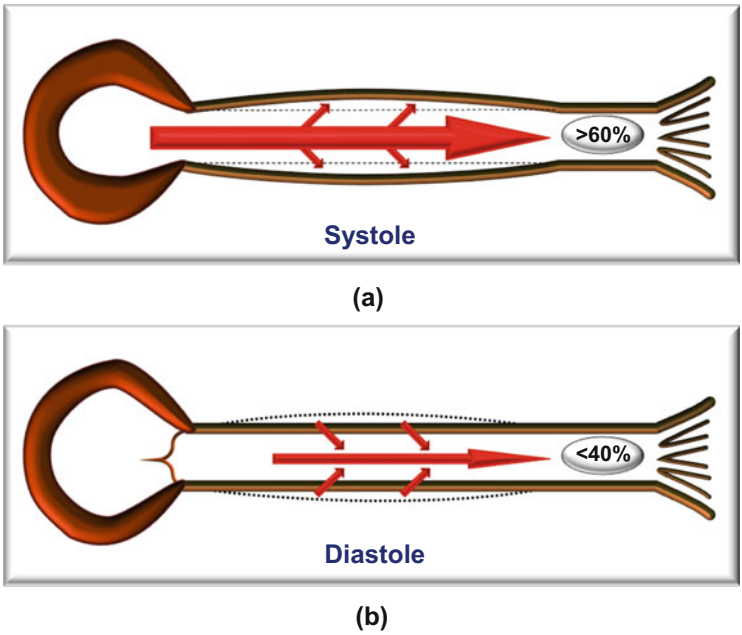

Fig. 1.12 The Windkessel phenomenon in patient with reduced vascular distensibility. Reduction in the aortic pump function during the diastolic phase of the cardiac cycle

hypertrophy and hyperplasia of smooth muscle cells. These alterations in mechanical properties of the arterial wall cause a permanent reduction in arterial distensibility.

Alterations in the viscoelastic properties of large arteries cause marked parietal stiffness and reduced elasticity in the aorta and large arteries. Under these conditions, the amount of stroke volume that is stored by the aorta during the systolic ejection time decreases, even drastically, while most of it is "pushed" directly towards the periphery of the vascular system (Fig. 1.12a). As a consequence, the propulsive effect of the aorta, in diastole, is reduced (Fig. 1.12b).

This phenomenon has three important consequences for blood pressure (Fig. 1.13):

1. Increase in systolic blood pressure.
   The increase in systolic blood pressure leads to an increase in the left ventricular afterload. This can cause left ventricular hypertrophy and predispose to left ventricular failure.
2. Decrease in diastolic blood pressure.
   Subendocardial perfusion occurs only during the diastolic phase of the cardiac cycle because of the development of extravascular compressive forces; therefore, a reduction in diastolic blood pressure in the aorta can lead to a reduction in subendocardial diastolic perfusion. A coronary syndrome, with undamaged

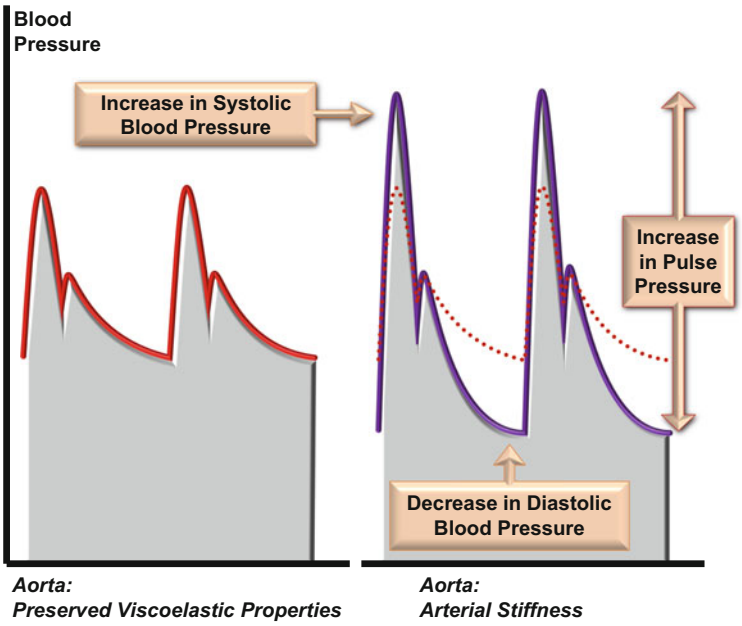

Fig. 1.13 Impact of aortic stiffness on blood pressure

coronaries, may be a symptom of diastolic pump failure and of irregular ratio between blood supply to the subendocardium and subendocardial oxygen needs. This is the reason why, in diastolic pump failure secondary to arterial stiffness, the supply of blood to the subendocardium decreases in diastole and the heart works harder as afterload increases (Fig 1.14).

3. Increase in pulse pressure.

   An increase in pulse pressure can lead to blood hyperflow in organs such as kidney and brain, characterized by high blood perfusion, reduced impedance, and reduced vascular resistance. In a kidney, this can lead to microvascular damage and to chronic kidney disease.

1.4 Systolic, Diastolic, and Pulse Pressure

Until the late 1980s, diastolic blood pressure was considered to be very important whereas systolic blood pressure was not considered to be of clinical relevance (Fig. 1.15) because blood pressure was conceived as a consequence of the interaction between cardiac output and systemic vascular resistance. As diastolic blood pressure reflects the conditions of peripheral resistance, it was considered the reference point for accurate assessment of blood pressure values. Therefore, in the assessment of blood pressure values, there was the strong conviction that "...

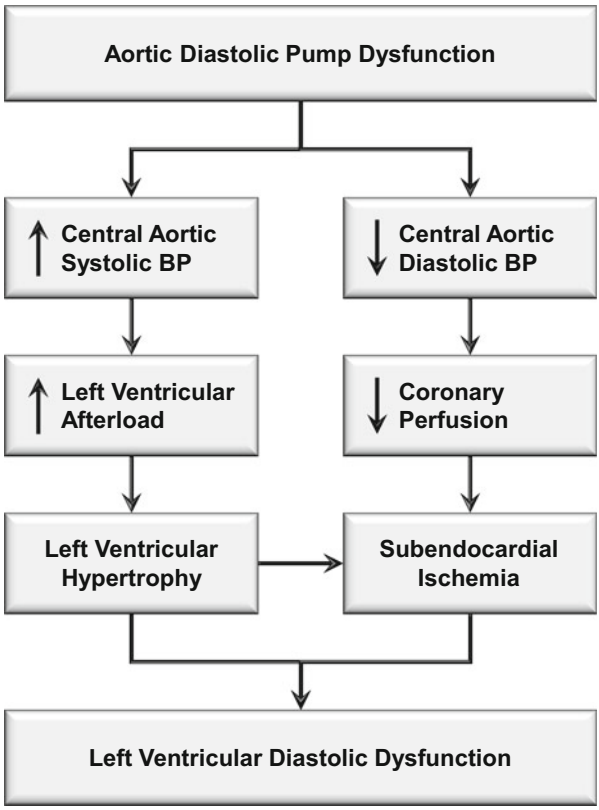

Fig. 1.14 Clinical implications of aortic diastolic pump dysfunction. Left ventricular hypertrophy and subendocardial ischemia are the major alterations determined by aortic stiffness. Both factors may cause left ventricular impaired relaxation and myocardial fibrosis, which are the main factors determining the left ventricular diastolic dysfunction. BP, blood pressure

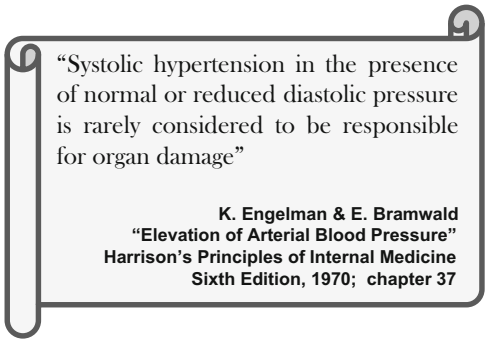

Fig. 1.15 Concept of systolic blood pressure and diastolic blood pressure in the 1970s, in the judgment of most authoritative cardiologists and most authoritative medical textbooks

the most important parameter is diastolic blood pressure . . ." and that "*. . . the right systolic blood pressure is 100 mmHg + the subject age . . .*". As a consequence, 170 mmHg systolic blood pressure in a 70-year-old subject was considered to be absolutely normal, better if accompanied by low values of diastolic blood pressure.

The hemodynamic approach to the assessment of the hypertension phenomenon has dramatically changed the interpretation of blood pressure values.

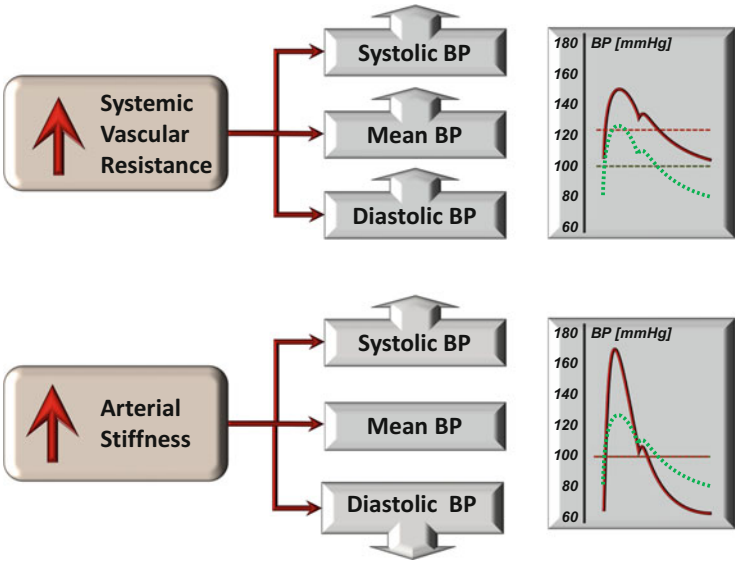

Fig. 1.16 Different consequences of the increase in systemic vascular resistance or of arterial stiffness on blood pressure

Therefore, while an increase in systemic vascular resistance causes an increase in both systolic blood pressure and diastolic blood pressure, higher arterial stiffness is accompanied by a decrease in the "buffer function" of the aorta on the cardiac output. This causes an increase in systolic blood pressure values and a decrease in diastolic blood pressure and, therefore, an increase in pulse pressure (Fig. 1.16). To sum up, in general, high values of pulse pressure are an expression of alteration of the viscoelastic properties of the aorta and large elastic arteries.

This phenomenon helps us to understand the leading role of systolic blood pressure and pulse pressure in the evaluation of cardiovascular risk, most of all in adult and elderly subjects.

Several authoritative studies have shown the importance of the control of systolic blood pressure values in cardiovascular prevention. The Framingham Study [2] has clearly shown that the risk of acute coronary events progressively increases with rise in pulse pressure values (Fig. 1.17).

To sum up, we can note that, with high systolic blood pressure values, the risk of acute coronary events is inversely proportional to the diastolic blood pressure value. Let us consider an example from the left panel of Fig. 1.17. With 170 mmHg systolic blood pressure, the hazard ratio (which represents an estimate of the relative risk, that is to say, the risk ratio for an event per person per unit of time) is 1.5 if diastolic blood pressure is 110 mmHg, but it rises to 2.8 if diastolic blood pressure is 70 mmHg. In short, it is "better" to have 170/110 mmHg blood pressure than 170/70 mmHg. These outcomes are really amazing and have highlighted the role of pulse pressure in the risk of coronary heart disease: the risk is strictly

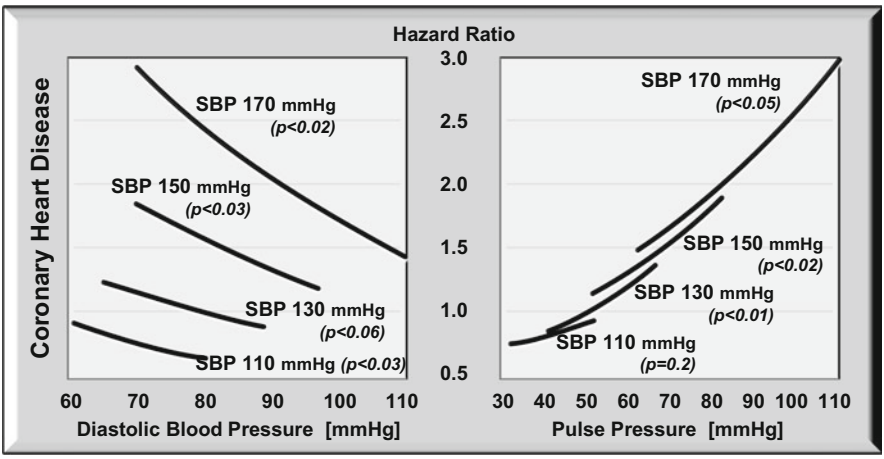

Fig. 1.17 Importance of systolic blood pressure and pulse pressure for prevalence of acute coronary events. *Left panel*: relationship between diastolic blood pressure and prevalence of coronary heart diseases for given systolic blood pressure (SBP). *Right panel*: relationship between pulse pressure (systolic—diastolic blood pressure) and prevalence of acute coronary events for given systolic blood pressure. From the outcomes of the Framingham Study [2]

correlated with pulse pressure values, regardless of systolic blood pressure values (Fig. 1.17, right panel).

1.5 Clinical Perspectives: New Concept of "Arterial Hypertension"

Over the past 20 years, there has been a radical change in scientific knowledge, thanks to clinical and epidemiological research, and this has dramatically changed the approach to the hypertensive patient.

Past: Hypertension Considered as a "Disease"
Arterial hypertension was considered to be a serious disease whose even fatal complications were an everyday occurrence. Nowadays, medical knowledge and scientific research have improved greatly, providing increasingly effective tools to assess pressure values. Moreover, health training and culture always emphasize that blood pressure must be kept under control.

Present: Hypertension Considered as a "Risk Factor"
Currently, we consider blood pressure as part of a wider prevention context and no longer as an isolated pathological event. As a consequence, nowadays, hypertension is considered to be one of the main risk factors for cardiovascular diseases, particularly myocardial infarction and cerebral stroke.

Future: Hypertension Considered as a "Symptom"

In the future, there will be further evolution in the concept of hypertension as it will be mainly considered as a symptom. This concept will revolutionize the approach to hypertensive patients as it leads to the exploration of the pathophysiological events underlying increased blood pressure values [3]. To understand these events, the basics of cardiovascular pathophysiology are required, particularly vascular hemodynamics.

Faced with a patient who is suffering from high blood pressure, not only will we have to normalize the pressure values but we will also try to understand, and possibly solve, the hemodynamic causes of the increased blood pressure values. In this way, the aim of the therapy will even be to face the hemodynamic elements and resolve the main factors leading to hypertension.

Pills for Growing

1. Mottram PM, Haluska BA, Leano R, Carlier S, Case C, Marwick TH (2005) Relation of arterial stiffness to diastolic dysfunction in hypertensive heart disease. Heart 91:1551–1556
2. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D (1999) Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham heart study. Circulation 100:354–360
3. Benetos A, Salvi P, Lacolley P (2011) Blood pressure regulation during the aging process: the end of the 'hypertension era'? J Hypertens 29:646–652

Pulse Wave Velocity and Arterial Stiffness Assessment

2

2.1 Arterial Stiffness and Cardiovascular Risk

Cardiovascular diseases are currently the main cause of death in developed countries. One of the main goals of Healthcare systems is, therefore, the prevention of cardiovascular diseases and the reduction in major cardiovascular events such as myocardial infarction and cerebral stroke.

Throughout the 20th century, the vascular disease was considered synonymous with atherosclerosis. Consequently, only the factors able to favor or inhibit the process of atherosclerosis were taken into account in cardiovascular prevention and the assessment of cardiovascular risk last century. Actually, the arterial system has always been considered to be made of inert "tubes", which connect the left ventricle to peripheral tissues. These "tubes" assume clinical significance only when they tend to narrow (infarction) or break (bleeding).

Arteriosclerosis, namely the stiffening of large elastic arteries, was, therefore, considered insignificant in the assessment of cardiovascular risk. It was only at the beginning of the new millennium that several epidemiological studies started to show the predictive value of aortic stiffening (aortosclerosis, i.e., arteriosclerosis of the aorta) for cardiovascular diseases, over and above other traditional major risk factors. Below you will find some of the most important outcomes from the main epidemiological and clinical studies where aortic stiffening was assessed by measuring aortic pulse wave velocity (PWV), the velocity by which pulse wave travels along the aorta.

- An higher relative risk of cardiovascular mortality was shown in hypertensive patients characterized by high aortic PWV values [1]. In this population, an increase in PWV by 5 m/s increases the relative risk of cardiovascular event as much as 10 years of aging.
- Aortic stiffness has been shown to be an independent predictor of primary coronary events in patients with essential hypertension [2]. The risk of developing a coronary heart disease event rose with each tertile of PWV and remained

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significant after adjustment for Framingham risk score or all cardiovascular risk factors (Fig. 2.1). The increase in risk of coronary heart disease events with tertiles of PWV was particularly steep for patients traditionally considered at low risk.

- A 1 m/s increase in aortic PWV was associated with a 7 % higher risk of a cardiovascular event for a 60-year-old man without other known cardiovascular risk factors [3].
- Aortic stiffness was significantly associated with the risk of stroke death in patients with essential hypertension. In these patients, arterial stiffness, measured through PWV, predicted the occurrence of fatal stroke beyond the prediction provided by classic risk factors. PWV was significantly associated with a 72 % increase in stroke risk for each 4 m/s increase in PWV [4].
- Aortic PWV was a significant predictor of cardiovascular complications, above and beyond 24-h mean arterial pressure and traditional risk factors, including sex, age, body mass index, current smoking and alcohol intake (Figs. 2.2 and 2.3) [5].
- More recently, data from the Framingham Heart Study [6] clearly showed that higher aortic stiffness assessed by PWV is associated with higher risk for a first cardiovascular event. Aortic PWV improves risk prediction when added to standard risk factors and may represent a valuable biomarker of cardiovascular disease risk in the community (Fig. 2.4).

Thus, at present, an increase in aortic PWV, expression of aortic stiffness (aortosclerosis), is considered to be an independent predictor of cardiovascular

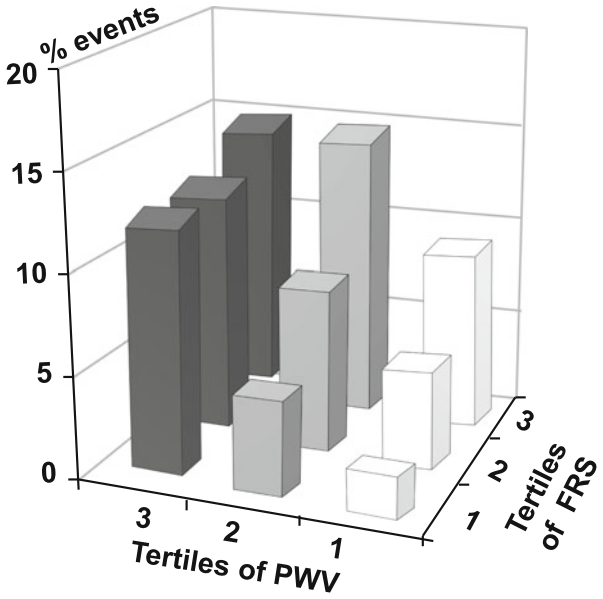

Fig. 2.1 The observed incidence of coronary heart disease events parallels the incidence of coronary heart disease, which has been predicted from the Framingham risk score (FRS), except for the highest values of FRS. Pulse wave velocity (PWV) significantly ($p = 0.002$) predicted all cardiovascular events in patients considered at low risk, i.e., belonging to the first and second tertiles of the FRS, even after full adjustment for all cardiovascular risk factors [2]

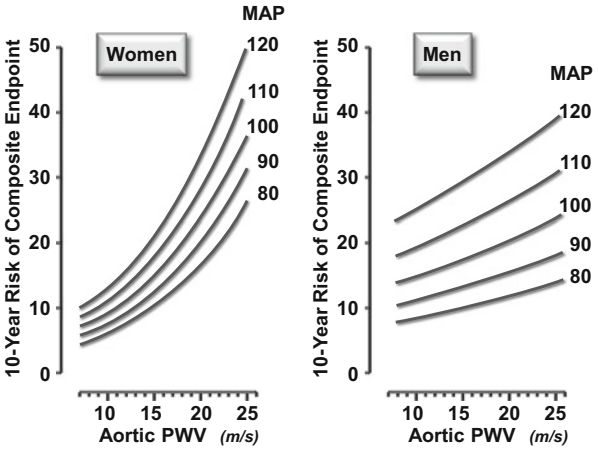

Fig. 2.2 Absolute risk associated with aortic pulse wave velocity (PWV) in women and men at different levels of mean arterial pressure in the office controlling for age, body mass index, current smoking, and alcohol intake. At any level of mean arterial pressure, the absolute risk of a composite cardiovascular outcome increased in relation to aortic PWV, more in women than in men [5]

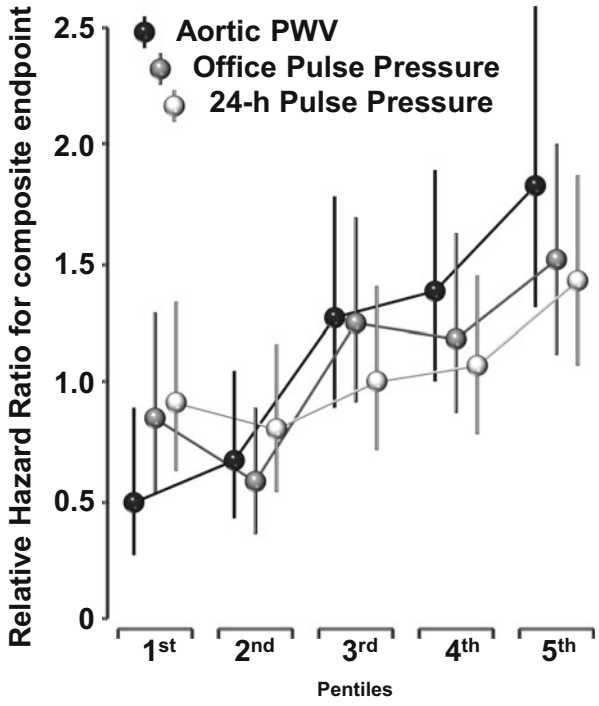

Fig. 2.3 Relative hazard ratios for the composite cardiovascular end point by quintiles of the distribution of aortic pulse wave velocity (PWV) and office and 24-h pulse pressures adjusted for sex and age. The hazard ratios express the risk in each quintile vs. the average risk in the whole population [5]

mortality. This implies that not only the phenomena of atherosclerosis but also the factors associated with arteriosclerosis, namely with the reduction in the

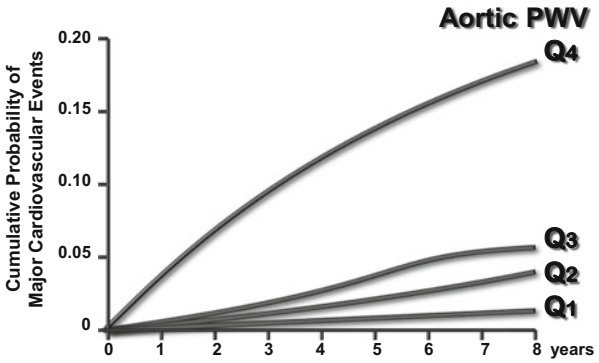

Fig. 2.4 Kaplan–Meier plot of cumulative probability of a first major cardiovascular event. Participants were grouped according to quartiles of carotid–femoral (aortic) pulse wave velocity (PWV). When individuals in the highest (≥11.8 m/s) aortic PWV group were compared with those in the lowest (<7.8 m/s) aortic PWV group after adjustment for age, sex, and standard risk factors, individuals in the highest quartile had an adjusted Hazard Ratio of 3.4 ($p = 0.008$) Data from Framingham Heart Study [6]

viscoelastic properties of large arteries, must be taken into account in the assessment of cardiovascular risk.

2.2 Aortic Pulse Wave Velocity

Measurement of pulse wave velocity (PWV) represents the simplest way to measure the stiffness of a specific arterial segment, as it is noninvasive, reproducible, and supported by considerable scientific literature.

The pulse wave is transmitted through the arterial vessels, and its speed is inversely related to the viscoelastic properties of the wall itself; the higher the velocity, the less elastic the wall.

The concept of pulse wave velocity is not always clear (it is not clear to many "experts" either). Therefore, let us clear up the most common misunderstanding:

pulse wave velocity is not blood flow velocity.

Blood flow velocity changes in the cardiac cycle and is on the order of cm/s (a mean blood velocity of 22 cm/s corresponds to <0.8 km/h, i.e., <0.5 mph) whereas pulse wave velocity is on the order of m/s, PWV values ranging from 4 to over 30 m/s, i.e., from 14 km/h (=9 mph) to over 108 km/h (=67 mph).

However, the term "velocity" evokes the image of something which moves and travels. This is the reason why, when speaking about velocity in the arterial system, red blood cells tend to be considered as a lot of red Ferrari racing cars whizzing down the aorta at high speed.

But . . . this is not pulse wave velocity.

To provide better understanding of pulse wave velocity, let us change the term to "pulse wave transmission", which evokes something which is propagated from segment to segment, rather than something which moves and travels, just like the velocity at which the vibrations of violin or guitar strings are transmitted.

We must conceive pulse wave velocity as a shock wave.

To see what "shock wave propagation" means, let us imagine arterial circulation as a series of "units", where each unit represents the stroke volume, that is, the amount of blood ejected from the heart at each systole. Each of these "unit" can be considered similar to the carriage of a train. Each systole represents a railway engine that arrives at the station and crashes into the carriages that are there, thereby generating a shock wave that is transmitted along the track (arterial system).

Another example which can help us to understand the meaning of the shock wave characterizing pulse wave velocity is the Newton's cradle. This is a toy consisting of a number of steel pinball-sized balls hanging in a row from a rigid bar (Fig. 2.5).

Even in this case, we can consider our vascular system as a series of "units" (our balls), where each "unit" is correlated with the stroke volume, i.e., the amount of blood ejected from the heart at each systole. Each systole represents a "unit" (a ball)

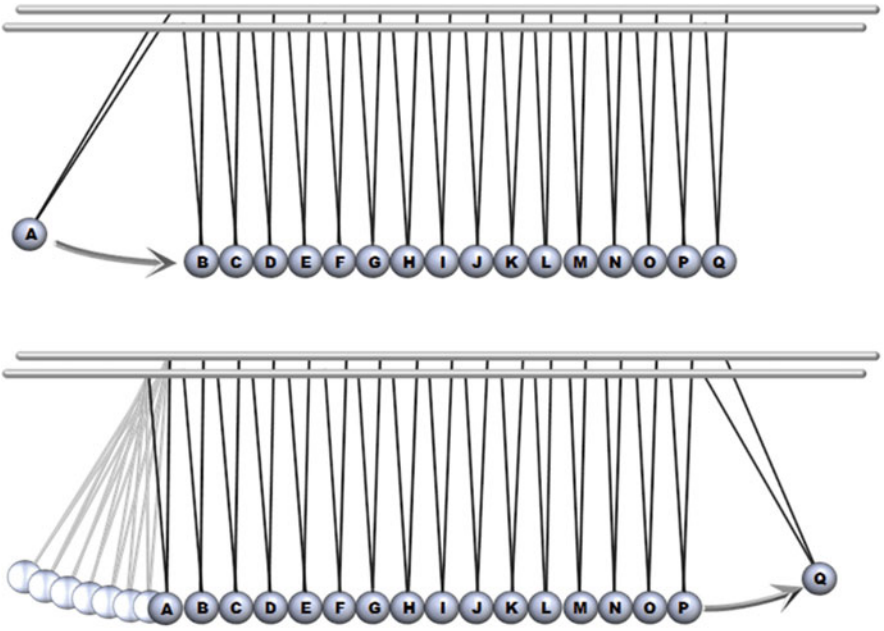

Fig. 2.5 Newton's cradle: example of shock wave velocity. If we take the first ball ("A"), raise it, and then let it fall again to hit the next ball ("B"), a shock wave is generated. As a result, the last ball ("Q") almost immediately breaks away from the row. The time elapsed between the impact of the first ball ("A") with the second one ("B") and the time when the last ball ("Q") breaks away from the row is a thousandth of a second and is unrelated to the speed at which the first ball hits the second one

which is thrown against the others, generating a shock wave which is transmitted along the arterial system.

If we do not merely let the first ball fall against the second one, but rather push it with all our strength or let it fall from a higher position, we can see that the corresponding greater impact is not accompanied by a change in the latency period between the impact of the first ball with the second one and the time that the last ball takes to break away from the row. Shock wave velocity, therefore, is unrelated to the strength (pressure) exerted. Similarly, the relationship between pulse wave and blood pressure is secondary to the organic alterations caused by blood pressure on the structure of the arterial wall, that is, the elastin and collagen fibers ratio, but depends only partially on blood pressure values recorded at the time the test is carried out. However, some conditions characterized by high blood pressure values cause a state of strain and distensibility of the vascular wall, which affects its elastic capabilities and can influence pulse wave transmission. If we replace our metal balls with cotton or styrofoam balls, we can easily see that, in this case, with respect to the series of steel balls, the latency time between the impact of the first ball with the second one and the time the last ball breaks away from the series increases. This leads us to the concepts of vascular "stiffness" and "elasticity".

2.2.1 Methodological Aspects

Technically, it is possible to assess pulse wave velocity by simultaneously recording the pressure waveform at two different sites in the arterial tree: a proximal site and a distal, peripheral one. This enables the time delay between pressure waveforms recorded in the distal segment with respect to the proximal one to be calculated.

We know that velocity is equal to displacement/time. As a consequence, pulse wave velocity is calculated using the following formula:

$$\text{Pulse Wave Velocity}\,(\text{mm/s}) = \frac{\text{Distance between the two arterial segments}}{\Delta T}$$

where ΔT represents the time delay of the distal pulse pressure waveform with respect to the proximal one.

The possibility of establishing a correlation between PWV and artery distensibility is based on the calculation of the speed of transmission of transverse elastic waves. According to the law for transmission of transverse waves, as applied for the first time by Moens (1878) and later modified by Bramwell and Hill [7], this concept has been formalized in a mathematical model that connects the elasticity of the arterial wall with the inverse of the square of PWV.

$$\text{Distensibility} = (3.57/\text{PWV})^2,$$

where distensibility is defined as the percentage variation in diameter for each increase in blood pressure of 1 mmHg. Therefore, according to this formula, for each increase in blood pressure of 1 mmHg:

- PWV of 4 m/s corresponds to distensibility of 0.80 %
- PWV of 6 m/s corresponds to distensibility of 0.35 %
- PWV of 8 m/s corresponds to distensibility of 0.20 %
- PWV of 10 m/s corresponds to distensibility of 0.13 %
- PWV of 12 m/s corresponds to distensibility of 0.09 %
- PWV of 14 m/s corresponds to distensibility of 0.06 %
- PWV of 16 m/s corresponds to distensibility of 0.05 %

Carotid–femoral pulse wave velocity (aortic PWV) is considered the gold-standard method for assessing arterial stiffness [8].

The proximal transducer is placed on the carotid artery and the distal transducer on the femoral artery. In this way, the PWV along the aorta is measured. Therefore, the carotid–femoral PWV reflects the viscoelastic properties of the aorta.

Carotid–femoral PWV measurement can be easily carried out and two different methods are possible:

1. At one time (Figs. 2.6 and 2.7), two transducers are simultaneously used (tonometers, ultrasound probes, oscillometers, mechanotransducers):

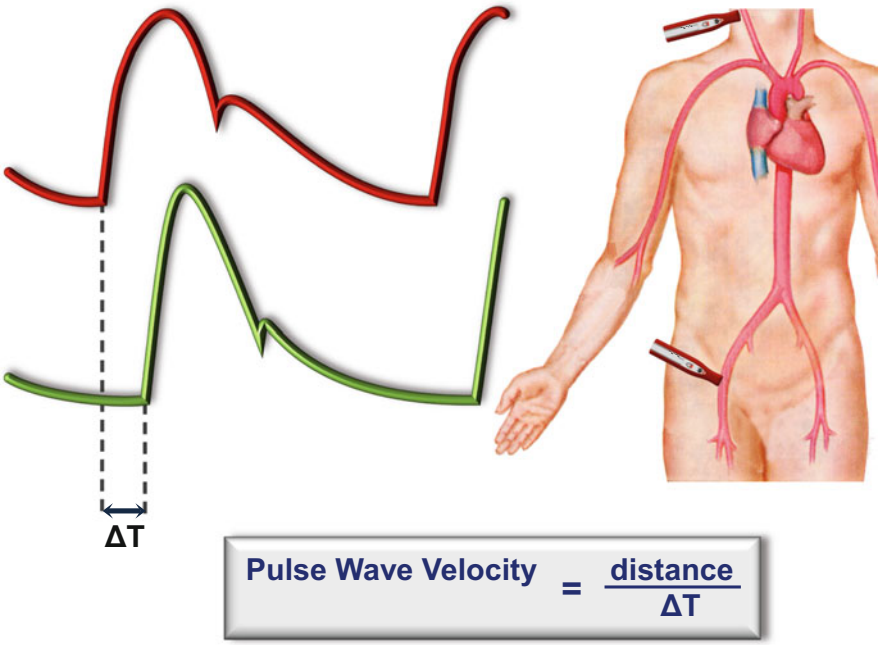

Fig. 2.6 Carotid–femoral pulse wave velocity assessed all at once: carotid and femoral pressure waveforms are recorded simultaneously

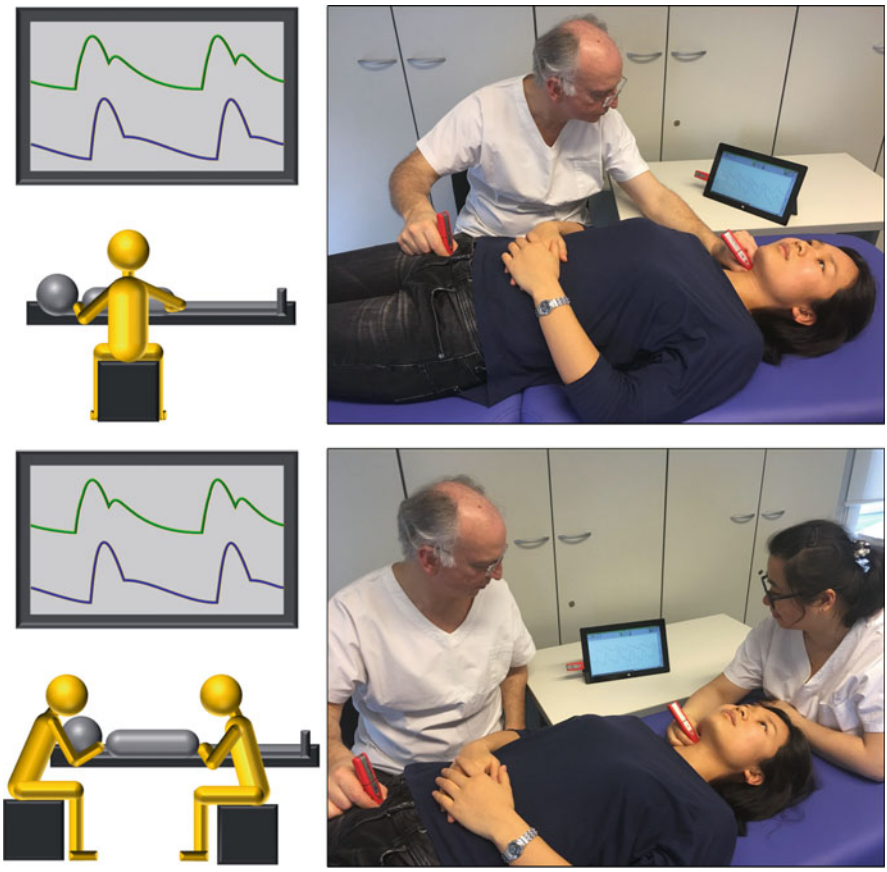

Fig. 2.7 When carotid–femoral pulse wave velocity is assessed all at once, carotid and femoral may be recorded simultaneously both by one expert operator (*upper panels*) and by two operators (*lower panels*). Tests performed using a PulsePen device are shown in the images on the *right*

- The first transducer records the proximal pulse wave curve (the proximal transducer is placed on the common carotid artery, considered as central detection site).
- The second transducer records the pulse wave curve simultaneously in the peripheral artery (femoral, brachial, radial, posterior tibial arteries, etc.).

This method enables the calculation of the time delay between the distal pulse wave curve and the proximal pulse wave curve and it is being used by several devices on the market:

- The Coplior Analyse® (Alam Medical, Vincennes, France) uses two piezoelectric sensors, which record pressure waveforms

- The PulsePen® WPP-ETT (DiaTecne srl, Milan, Italy), which uses two tonometers. This model also allows the recording of central aortic blood pressure and pulse wave analysis
- The PulsePenLab® (DiaTecne srl, Milan, Italy), a model derived from the PulsePen® and targeted at the study of small animals and newborns
- The SphygmoCor® XCEL PWV Measurement System (AtCor Medical Pty Ltd, Sydney, Australia) measures carotid pulse pressure with a tonometer, while the femoral pulse is measured through pulsations in a cuff placed around the thigh

2. At two times (Figs. 2.8 and 2.9), just one transducer combined with electrocardiographic tracing is used. In this way, PWV can be assessed at two times, separated by a short interval, taking the R wave of the QRS complex of the electrocardiogram (ECG) as a reference point. ΔT will be given by the difference between the time delay of the distal (femoral, brachial, radial, posterior tibial arteries, etc.) pulse wave with relation to the R wave belonging to the QRS complex of the ECG and the time delay of the proximal pulse wave in relation to the R wave of the QRS complex of the ECG.

   This second method provides outcomes that are exactly superimposable on the first method. However, being carried out at two times, significant variation in heart rate or systolic blood pressure between the recording of the proximal and distal pulse waveform curves must not occur. This is an important reason why blood pressure and heart rate must be recorded by means of a traditional validated sphygmomanometer at the same time of both proximal and distal pulse wave acquisition. Measurements of PWV where the difference between the mean values of the heart period (defined by the R′–R′ interval of the ECG) recorded in carotid and peripheral arteries is over 10 % are not considered reliable.

   This method is used by two devices; they both use a tonometer to record the pulse wave:

   - The PulsePen® WPP-ET (DiaTecne srl, Milan)
   - The SphygmoCor® CPV System (AtCor Medical Pty. Ltd., Sydney)

2.2.1.1 How to Measure the Distance

Pulse wave velocity is given by the ratio between the distance between two artery points and the delay in the peripheral artery pressure wave with respect to the proximal pressure wave. However, how can we measure this distance?

To measure distances, it is possible to use a rigid bar, which must be graduated, equipped with diastimeters at the ends, similar to the one used to measure a newborn's height. Such an instrument can be useful especially when measuring the distance in overweight or pregnant subjects. Actually, in these cases, if we used a classic flexible tape measure, we would run the risk of overestimating the distance; it is very important to take the tape measure distance in a straight line.

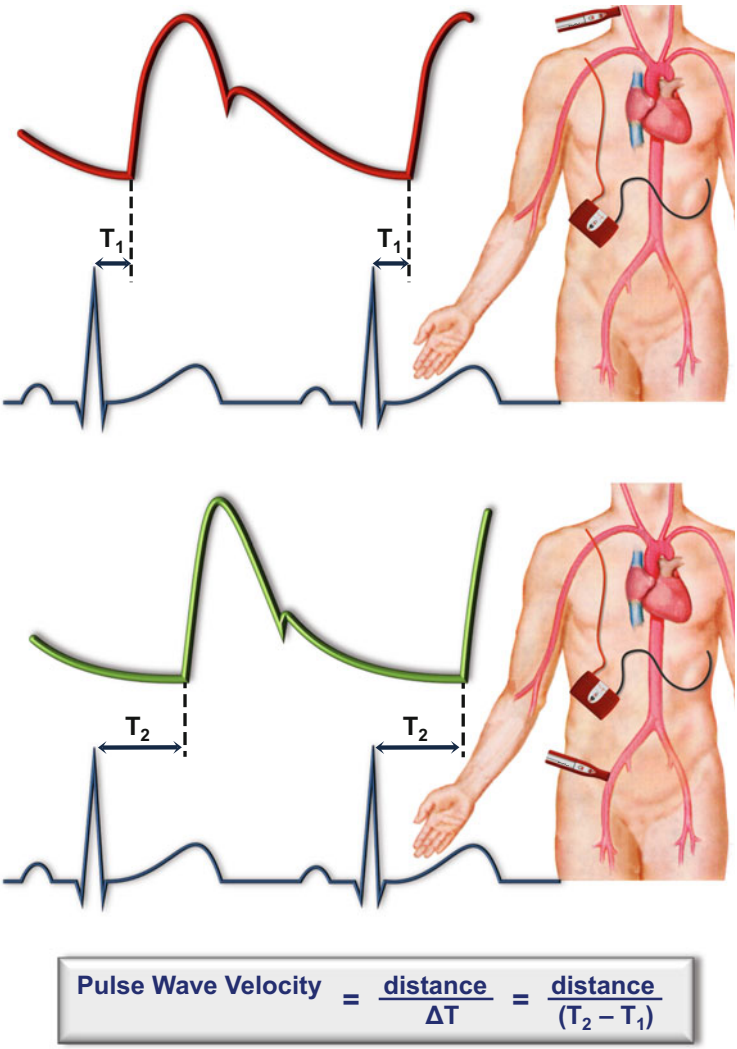

Fig. 2.8 Carotid–femoral pulse wave velocity assessed at two times. (I) *Upper panel*: carotid pressure waveform recording and assessment of the time delay of the waveform with respect to the R wave of the QRS complex of the ECG recording. (II) *Lower panel*: pressure waveform recording in the femoral artery and assessment of the time delay of the waveform with respect to the R wave of the QRS complex of the ECG

As for carotid–femoral PWV, direct measurement of the distance between the carotid and femoral artery pressure wave has been used for years (Fig. 2.10a).

Distance can also be measured with the so-called subtractive method (Figs. 2.10b and 2.11), which is more accurate. This method seems to be better correlated with the real anatomical distance between the two analyzed arterial sites.

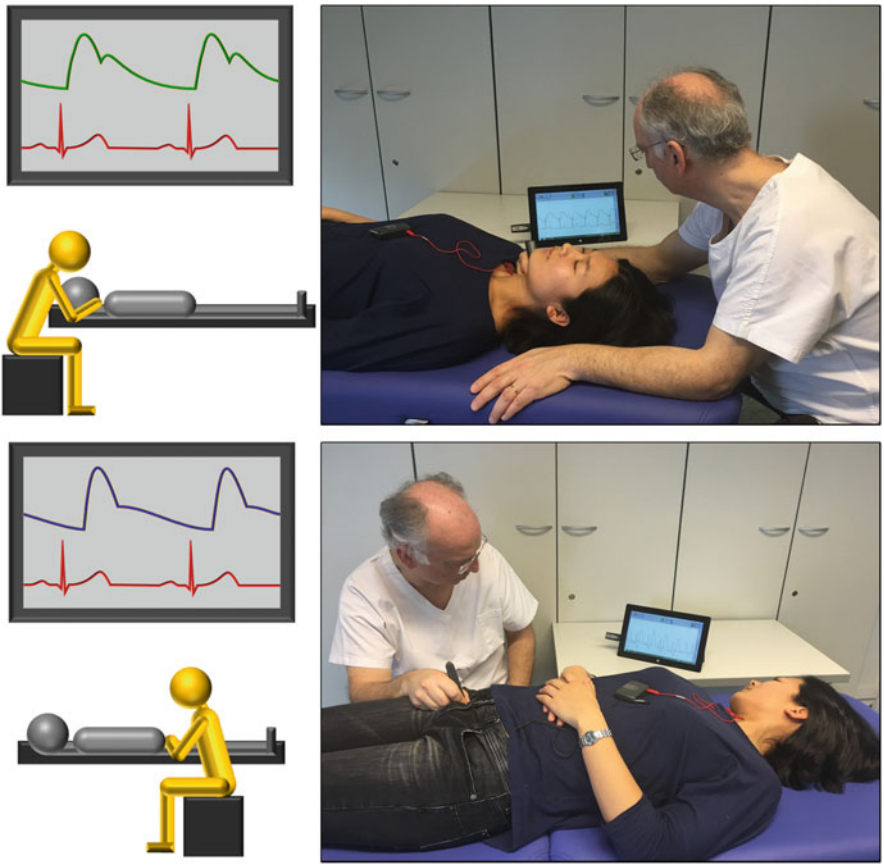

Fig. 2.9 When carotid–femoral pulse wave velocity is assessed at two times, firstly pulse pressure wave is recorded in carotid artery simultaneously with ECG (*upper panels*); secondly, pulse pressure wave is simultaneously recorded with ECG in femoral artery (*lower panels*). Tests performed using a PulsePen® device are shown in the images on the *right*. It is worth noting that, thanks to the high sensitivity of the PulsePen® tonometer, the femoral pressure waveform can be recorded by placing the probe on the patients' clothes, so that they are not required to undress

Distance is a basic parameter for the assessment of PWV, and its importance should not be underestimated; for example, let us consider a subject with a delay of 100 ms in the femoral artery pressure wave in relation to the carotid pressure wave, with carotid-to-femoral distance of 650 mm, suprasternal notch-to-carotid distance of 100 mm, and suprasternal notch-to-femoral distance of 560 mm. If PWV is, calculated using the "direct" method, it is 6.5 m/s [PWV = 650/100]. On the contrary, if PWV is calculated using the "subtractive" method, it is 4.6 m/s [PWV = (560 − 100)/100]. In this case, PWV is 32 % greater using the "direct" method than the "subtractive" method.

A newly published expert consensus document on the measurement of aortic stiffness [9] provides advice on the use of 80 % of the direct carotid-to-femoral tape measure distance as new standard for daily practice:

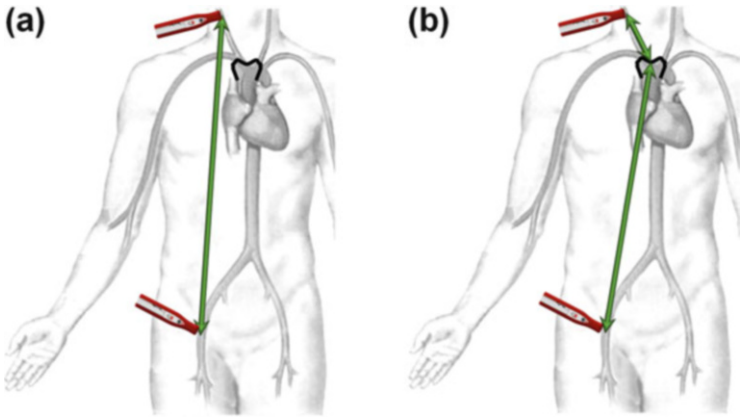

Fig. 2.10 Main methods to evaluate carotid–femoral distance in assessing PWV. (**a**) "Direct" measurement of carotid–femoral distance. (**b**) Measurement of carotid–femoral distance with the "subtractive" method. Firstly, the suprasternal notch is taken as a reference point. Secondly, the distance between the suprasternal notch and the femoral artery is measured. Thirdly, from this measure, the distance between the suprasternal notch and the carotid sampling site is subtracted

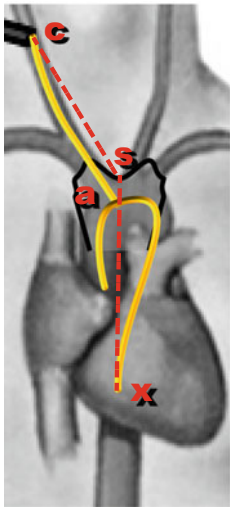

Fig. 2.11 The "subtractive method" is based on the knowledge that, while the pressure wave reaches the carotid pressure landmark (distance $a \rightarrow c$ in the figure), it would cover the same distance in the aorta (distance $a \rightarrow x$). This path coincides with segment "sx", which corresponds to segment "cs", i.e., the distance between the suprasternal notch and the carotid sampling site

$$\text{Recommended distance} = \text{Direct carotid-to-femoral distance} \times 0.8$$

A more accurate, simple and acceptable modification of this formula, taking into account age, was proposed, too. This tested formula adjusts this distance for age by

adding 1 mm/year for an age above 50 and subtracting 1 mm/year for an age below 50, respectively:

$$\text{Age corrected distance} = \text{Carotid-to-femoral distance} \times 0.8 + 0.1 \times (\text{age} - 50).$$

I always suggest considering all the three measures: carotid-to-femoral, suprasternal notch-to-carotid, and suprasternal-to-femoral. In this way, you can always compare your own findings with those reported in literature, regardless of the method used by the authors.

When you read scientific papers or articles concerning PWV, you should always pay attention to the method used to define distance in the calculation of PWV. This is the reason why you are totally bewildered when scientific publications and official guidelines express cutoff values for PWV without specifying the method used to obtain them.

2.2.1.2 How to Measure the Transit Time Delay

The foot of the pulse pressure wave represents the landmark for the calculation of the time delay of the pulse wave, which is the time delay between two waves on a simultaneous recording (Fig. 2.12a) or the time delay with respect to the R wave of

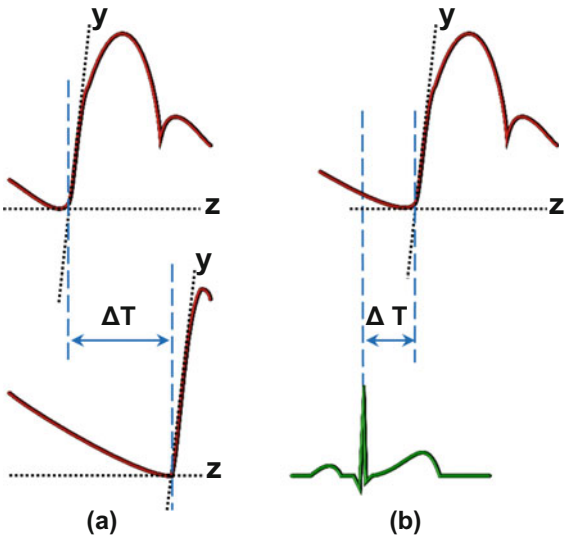

Fig. 2.12 (**a**) Pulse waves foot-to-foot transit time assessment using the interpolating intersecting algorithm. Measurement of the time delay of the peripheral pressure waveform (*bottom*) in relation to the central pressure waveform (*top*). The foot of the pressure waveform curve is estimated by the intersection of the *horizontal line* tangent to the lowest point of the pressure waveform (*line* "*z*") with the prolongation of the *straight line* that minimizes the standard deviation of the points building up the initial protosystolic rapid ascending phase of the pressure waveform curve (*line* "*y*"). (**b**) Measurement of the time delay of the pressure waveform (*top*) in relation to the R wave of the ECG complex (*bottom*). The latter occurs when pulse wave velocity is recorded at two times

the ECG recorded at two intervals (Fig. 2.12b). This is the method used by the PulsePen® (interpolating intersecting algorithm), the Complior Analyse® and the SphygmoCor® (tangent intersecting algorithm), providing PWV values that are superimposable between them. On the contrary, the old model Complior SP® used an algorithm based on a derivative of the change in arterial wall motion, secondary to pulse pressure. The Complior SP® supplies PWV values inferior to the PulsePen® and the SphygmoCor®.

Several formulas for converting one measurement system into another have been suggested. The most commonly used method suggests conversion of the carotid–femoral pulse transit time (c-fTT), according to the following formula:

$$\text{PulsePen TT} = \text{SphygmoCor TT} = (\text{Complior} - \text{SP TT} - 14.96)/0.8486$$

2.2.1.3 Pulse Wave Velocity in Subjects with Arrhythmias

Is the PWV value recorded in a subject with arrhythmias or with atrial fibrillation reliable? What are the rules to follow? This is one of the most frequent questions that operators using this method in clinical practice ask themselves.

Arrhythmias and atrial fibrillation, in particular, are probably the only clinical conditions where central and peripheral pressure waveforms are strongly recommended to be recorded simultaneously to define PWV.

Yet, PWV, recorded at two times in subjects with *atrial fibrillation*, may be considered reliable under the following conditions:

- In subjects where fibrillation is rather regular and with no significant changes in the R′–R′ interval on ECG. Measurements where the standard deviation of the R′–R′ intervals is less than 20 % of the mean value can be accepted.
- If PWV is to be recorded at two times, it is always important to verify that the difference between the mean value of the cardiac period of the R′–R′ interval recorded in the carotid artery and that recorded in the peripheral artery is less than 10 %.
- If the previous conditions are fulfilled, it is advisable to carry out at least two measurements in subjects with atrial fibrillation and to use the mean of the recorded measurements.

Assessment of PWV is easier in subjects with *premature atrial or ventricular complexes*.

- In fact, it is strongly recommended that the analysis of the foot of the pulse pressure waveform corresponding to the extrasystole and to the next one should be excluded when assessing PWV.
- On the contrary, as for pulse wave analysis, it is advisable to exclude not only the pressure curve generated by the extrasystole but also the previous and the following ones.

2.2.1.4 Sampling Rate

Sampling rate is a very important parameter for a device that aims to accurately calculate PWV and accurately define pulse wave analysis. Figures 2.13 and 2.14 illustrate what the pressure waveform and the ECG would look like if there were no interpolation process and the signal was recorded point by point at different sample rates. The low sensitivity of the recordings with a low sampling rate is evident. However, the processes of interpolation ensure a phenomenon of cosmetics of the recordings, and the waves acquired at low sampling rate often appear cleaner and more linear than waves acquired point-to-point, without the aid of an interpolation process. At low sampling rates, many details of the pulse waveform are lost. Moreover, the definition of the peak of the R wave in the QRS complex is obviously inaccurate, as well as the definition of the PWV.

The ARTERY Society Guidelines for a standard methodology for assessing PWV, suggested a sampling rate of 1 kHz (=1000 Hz), with a minimum recording time of 10 cardiac cycles. At present, this recommended sampling rate is used by

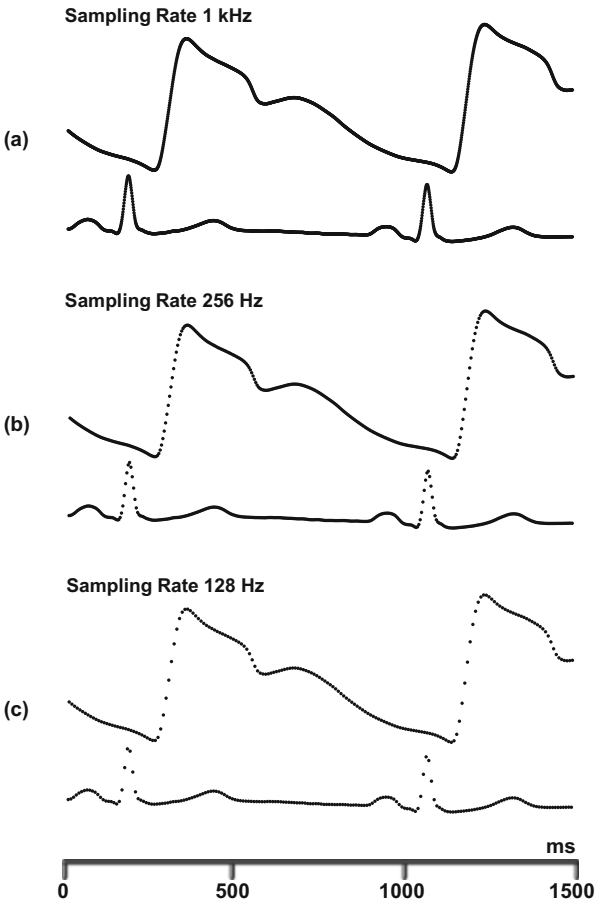

Fig. 2.13 Importance of sampling rate in defining the pulse pressure waveform and the parameters required for calculating the pulse wave velocity (heart rate: 60 beats/min). (**a**) *Upper panel*: pulse wave and ECG signal are acquired with 1 kHz sampling rate (each signal every 1 ms). This sampling rate is used by the PulsePen®, the PulsePenLab®, and the Complior Analyse® devices. (**b**) *Medium panel*: pulse wave and ECG signal are acquired with 256 Hz sampling rate (each signal every 3.9 ms). This sampling rate is used by the SphygmoCor® XCEL device. (c) *Lower panel*: pulse wave and ECG signal are acquired with 128 Hz sampling rate (each signal every 7.8 ms). This sampling rate is used by the SphygmoCor® device

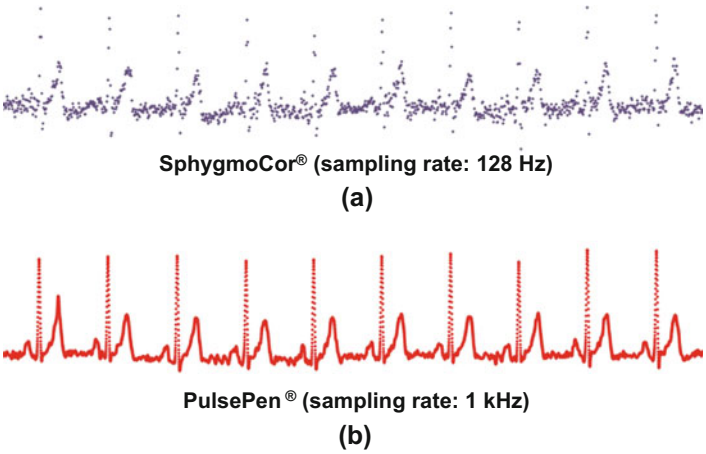

Fig. 2.14 (**a**) ECG tracing simultaneously recorded by SphygmoCor®, characterized by a 128 Hz sampling rate and (**b**) by PulsePen®, characterized by a 1 kHz sampling rate. Only single signals acquired during recording are shown, without interpolation

both the Complior Analyse® system and the PulsePen® system. On the contrary, the SphygmoCor® system acquires signals with a sampling rate of 128 Hz or 256 Hz (XCEL system).

2.2.1.5 Arterial Distensibility and Pulse Wave Velocity Evaluated by MRI

Aortic PWV can also be measured by Magnetic Resonance Imaging (MRI). This procedure allows the user to select two regions of interest along the aorta, recording a flow-time curve (Fig. 2.15). As a matter of fact, PWV can be given by the ratio of the distance between two artery points and the time delay between the two aortic flow curves (Fig. 2.16) [10]. MRI can also measure PWV at a single aortic location (ascending aorta, aorta arch, or descending aorta), providing useful hemodynamic information in different vascular diseases. However, the evaluation of the aortic blood flows by MRI appears to be very general and, consequently, the acquisition of PWV inaccurate (Figs. 2.17 and 2.18). This is the reason why MRI cannot be considered as a standard reference method, but it is a reliable procedure for the segmental evaluation of arterial compliance as it permits an accurate measurement of the variation of the vascular diameter during the cardiac cycle.

2.2.2 Factors Affecting Pulse Wave Velocity

PWV depends on structural alterations and transient functional changes in the arterial wall.

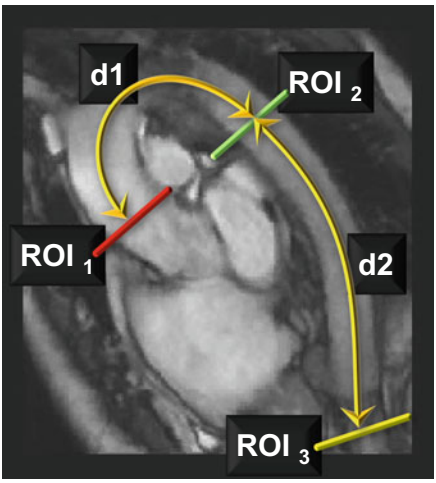

Fig. 2.15 Assessment of pulse wave velocity (PWV) by magnetic resonance imaging (MRI). In this case, three regions of interest (ROIs) have been considered. Sagittal scout MRI showing the aortic arch and the descending aorta. Two sections separated by a fixed distance of 15 cm are positioned perpendicularly to the thoracic aorta determining the three ROIs. MRI Proximal-PWV is determined with distance d_1, and the MRI Distal-PWV is determined with distance d_2; MRI Thoracic-PWV is determined by using the total arterial length ($d_1 + d_2$)

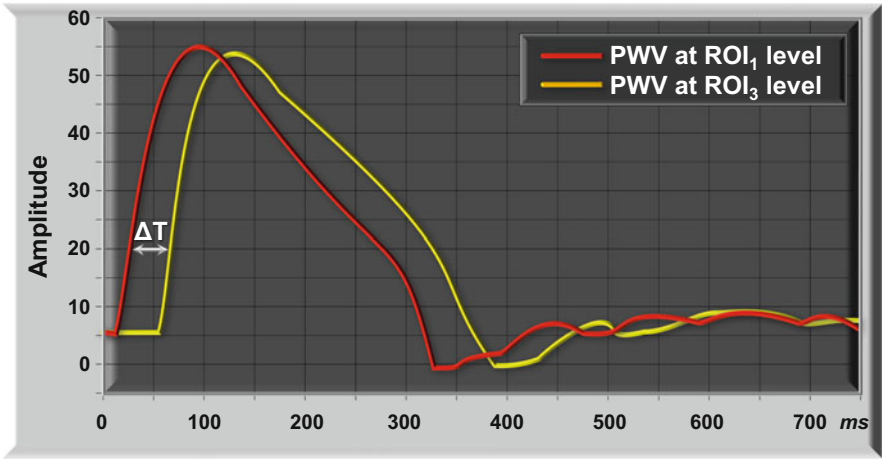

Fig. 2.16 Example of two normalized (or amplitude) blood velocity–time curves generated from two intra-aortic ROIs (ROI 1 and 3). The curves are scaled to represent the same peak velocity value. Time-delay calculation is based on superimposition and minimization of the square deviation between waveforms

2.2.2.1 Structural Factors

Structural alterations are stable and due to the change in the elastin and collagen fiber ratio in the arterial wall (Fig. 2.19).

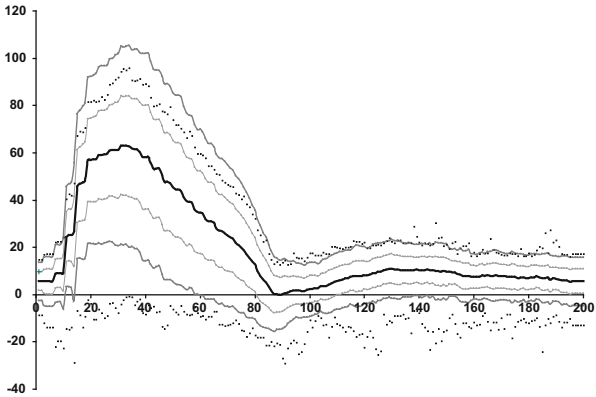

Fig. 2.17 Large spread of values in the data set acquired using magnetic resonance imaging (MRI) in the recording of aortic blood velocity–time curves. The figure highlights the curves corresponding to the mean (*central thick curve*), to the standard deviation (SD), and to 2SD of the data acquired

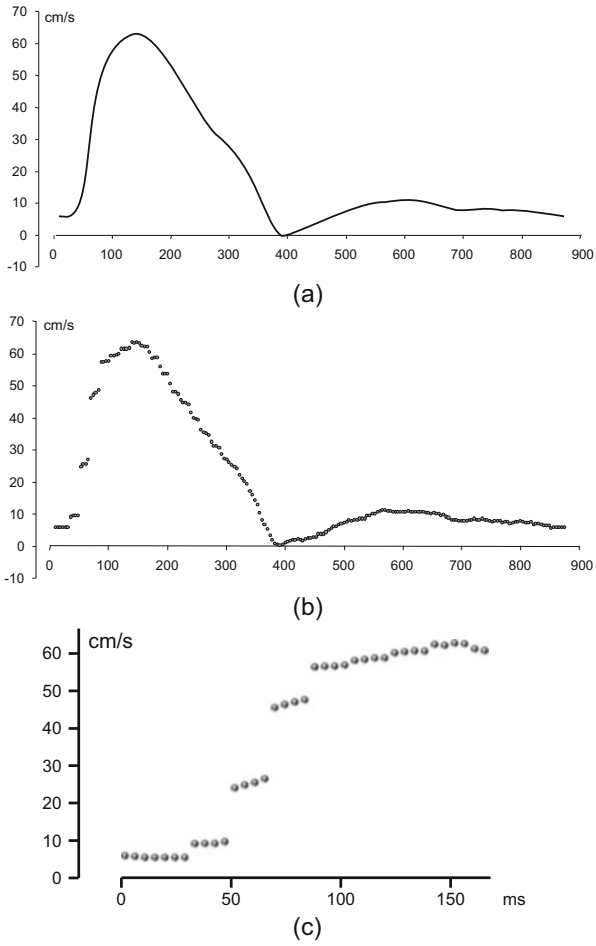

Fig. 2.18 Aortic blood velocity–time curves recorded by magnetic resonance imaging (MRI). (**a**) Curve of the blood flows as it is shown by the test. The curve is the result of the interpolation of the mean of the single points acquired. (**b**) Mean values of the single points acquired without interpolation. (**c**) A detail of the proto-meso-systolic phase of the picture shown above

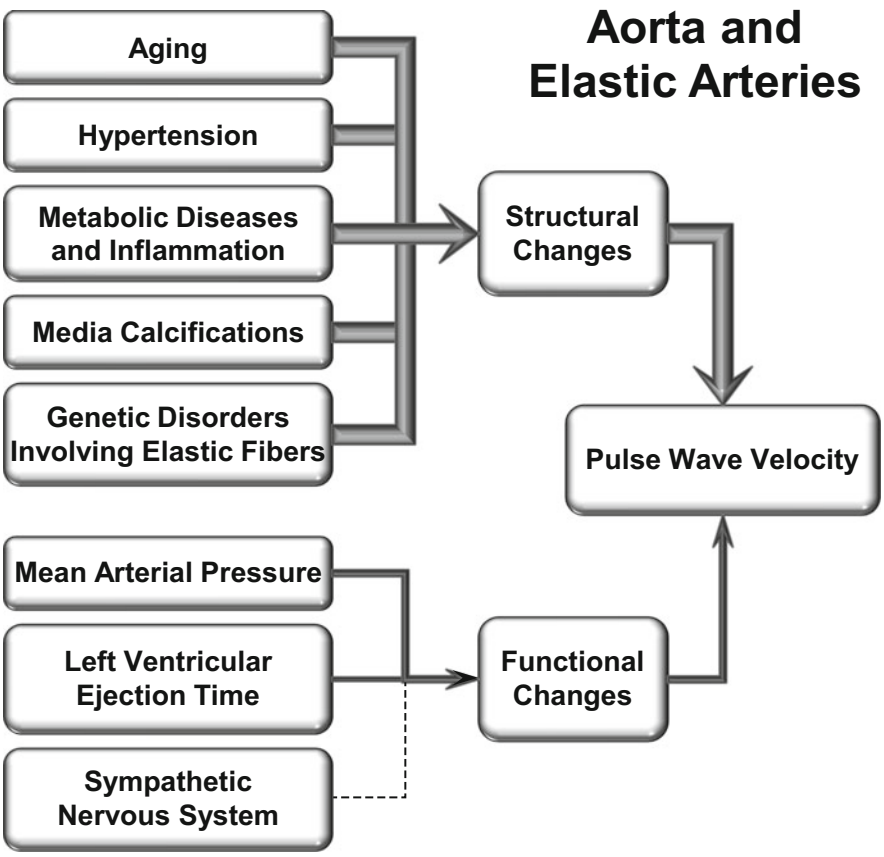

Fig. 2.19 Structural and functional factors affecting pulse wave velocity in the aorta and large elastic arteries. The thickness of the *arrow* shows how much every single factor affects pulse wave velocity

An increase in PWV with *age* is well established. Aging is characterized by generalized increase in arterial wall stiffness related to structural alterations. The aging process causes histological alterations in the arterial wall, and the degeneration of elastin fibers is accompanied by a boost in collagen fibers. Increased elastase activity and reduced elastin synthesis cause thinning and breakage of elastin fibers, and the result is a decrease in the elastin and collagen ratio. It was calculated (Faber and Moller-Hou 1954) that in the age range of 20–80 years, the percentage, in dry weight, of elastin fibers in the thoracic aorta decreases from 32 to 20 % whereas the percentage of collagen fibers increases from 21 to 32 %. However, the relationship between age and PWV is not linear. PWV values change insignificantly in the first decades of life then they tend to increase as age advances, by an average of 0.07 m/s per year from 45 to 65 years and of 0.2 m/s per year after 65 years.

As a matter of fact, it is well known that age-relating changes in the arterial structure reflect general aging on the whole body. In order to totally understand the process leading to the loss of elasticity of large elastic arteries, just think of the physiological loss of elasticity of the skin in the elderly. Try and pinch the skin on a forearm of elderly people: the skin will tend to remain in the pinched position and it will take a long time to return to normal. On the contrary, what a different reaction in the skin of children or young adults! The elasticity of these cutaneous tissues allows the skin to go back to its normal position quickly. As the skin loses its original elasticity in the elderly, so the aorta and large arteries tend to lose their elasticity and become stiffer with aging (arteriosclerosis process).

Arterial hypertension is characterized by an increase in transmural pressure, and arteries are at risk for breaking. Thus, a greater biosynthesis of collagen in arterial wall occurs in order to counterbalance the increase in transmural pressure. Although it is accumulated, the relative quantity of elastin remains unchanged, and further changes of the elastin and collagen ratio are found. This process can be associated with functional alterations, with muscle hypertonia, and with the phenomenon of "remodeling" of the arterial wall, with hypertrophia and hyperplasia of smooth muscle cells and alterations in the endothelial function. These structural alterations in the arterial wall, caused by a steady increase in blood pressure values, will remain even when normal blood pressure values are restored after an effective antihypertensive treatment. Only after years of therapy with drugs that have proven to be effective on the arterial wall there may be an improvement in arterial distensibility.

Structural alterations have been described even in *metabolic diseases* such as diabetes, kidney failure, liver failure, and alterations in calcium metabolism. Some metabolic disorders can be accompanied by an increase in oxidative stress, by areas of parietal calcifications and by inflammation of the arterial wall. *Inflammation* causes both arterial stiffening and endothelial dysfunction.

On the contrary, there is no change in arterial distensibility related to *gender* (some gender differences being highlighted only in infancy and adolescence).

Genetic disorders characterized by synthesis of an abnormal fibrillin-1 (FBN1), which plays an important role in structural proteins of the arterial wall, lead to changes in the elastic properties of the arteries. Patients affected by Marfan syndrome and Ehler–Danlos syndrome present a significant greater rigidity of the arterial wall and particularly of the aorta. Studies carried out on mouse model of Marfan syndrome (mgR/mgR mouse) suggested that a fragmentation of the medial elastic network occurs later in life in Marfan patients when lamellar structure is already established. This elastic fiber fragmentation leads to increased wall arterial stiffening, causing the progressive dilatation of the aorta, potentially leading to aortic dissection and death. Actually, preliminary data show that an increase in PWV values is an important marker of aortic dissection risk in patient with Marfan syndrome.

It is important to stress that the phenomenon of arterial stiffness has nothing to do with atherosclerosis, although the two events can easily coexist, as they share major risk factors (aging, diabetes, and hypertension).

One should emphasize that arterial stiffness is not synonymous with atherosclerosis.

Widespread phenomena of atherosclerosis can also cause a certain degree of arterial stiffness, most of all in the presence of extended calcifications. However, the concepts of atherosclerosis (arterial thrombotic phenomena, at prevailing endoluminar expression) and of arterial wall stiffness need to be separated.

2.2.2.2 Functional Factors

We have seen that PWV is a marker of distensibility of large elastic arteries. In other words, PWV measures the elasticity of the arterial wall generated by pulse wave transmission. It is important to stress that the term "distensibility" does not have to be taken in the sense of a virtual potentiality, that is to say as an intrinsic and unchangeable characteristic of the arterial wall. Actually, all the structural or functional factors affecting arterial distensibility may modify PWV. Therefore, the viscoelastic properties of the arterial wall are not only defined by its structural characteristics. Aortic PWV is also increased by all the other factors able to decrease the elasticity of an artery.

Although functional changes are less important than structural changes, their role is in fact very complex, and their changes are transitory and transient. The main functional factors that determine transient and variable changes in vascular distensibility include mean arterial pressure, arterial smooth muscle tone (related mainly to adrenergic activity), left ventricular systolic ejection function, and heart rate (Fig. 2.20). The relationship between PWV and these functional factors could affect the reproducibility of PWV and the reliability of between-subjects comparison of PWV values.

Mean arterial pressure values can affect PWV values for the functional fraction represented by the change in smooth muscle tone (as to average caliber arteries) or by increased tension of an elastic vessel (aorta) due to high blood pressure values, which may occur. Its wall could reach its maximum extension and, therefore, be in the "rigid" phase of its elastic modulus. The role of blood pressure at test time is greater in young people, where functional components prevail, linked to the activation of the sympathetic system. On the contrary, it is weak in adults or elderly people, where structural components prevail. This is the reason why it is advisable to adjust data collected for mean arterial pressure in the course of statistical analysis for clinical research.

The *sympathetic nervous system* is considered to be one of the major elements involved in the regulation of mean arterial pressure and in the activity of the cardiovascular system.

The activation of the sympathetic nervous system increases heart rate, ventricular contractility, and causes peripheral vasoconstriction, which can selectively or diffusely increase peripheral vascular resistance, leading to an increase in mean arterial pressure. As for the arterial system, the control of the sympathetic nervous system is carried out through the modulation of the activity of the smooth muscle cell of the arterial wall.

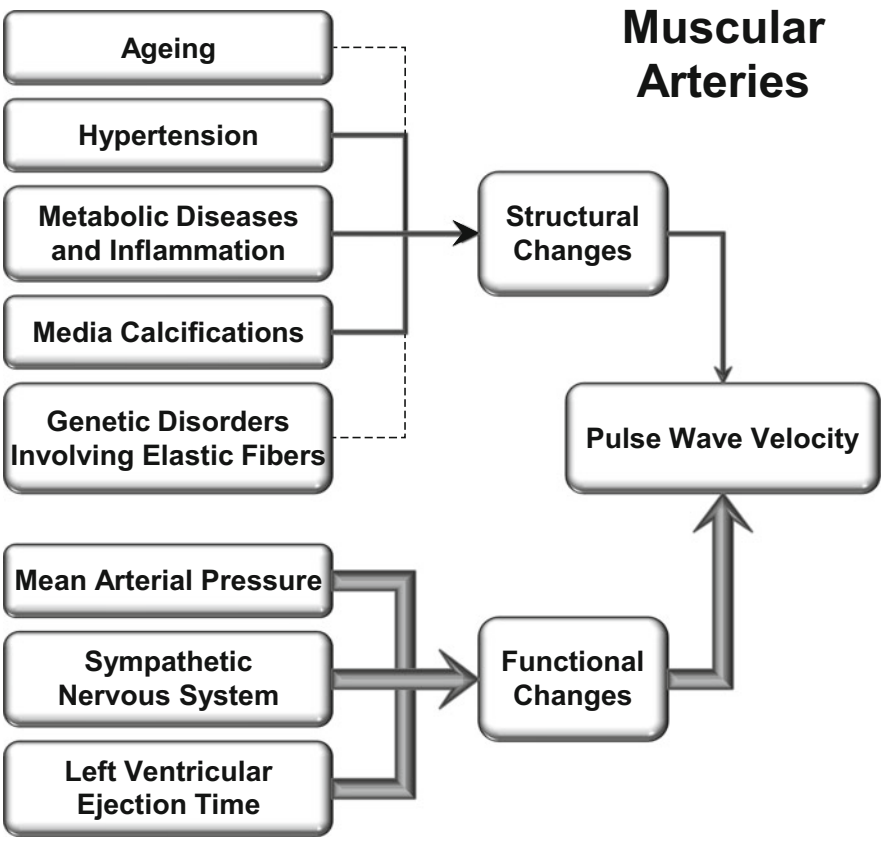

Fig. 2.20 Structural and functional factors affecting pulse wave velocity in muscular arteries. The thickness of the *arrow* shows how much every single factor affects pulse wave velocity

Yet, the role of the sympathetic nervous system is different as for the various arterial districts and the different types of arteries.

Two types of arteries may be identified in relation to the prevalence of elastic fibers or smooth muscle cells in their walls:

1. The large elastic arteries, including the vessels emerging from the heart ventricles, such as aorta, pulmonary artery, anonymous trunk, common carotid, and subclavian arteries
2. The muscular arteries, including the main branches of the arterial tree, like brachio-radial, femoral, and cerebral arteries

The shift between these types of arterial vessels is gradual. The amount of elastic tissue decreases from the center to the periphery of the arterial tree, on the contrary, the smooth muscle component assumes gradually more and more prominence in the

peripheral arteries. Through the controlled variation in the diameter of the peripheral arteries, these arteries distribute blood flow to different parts of the body according to regional needs.

The Sympathetic Nervous System and Muscular Arteries

The sympathetic nervous system exerts a pronounced restraint on distensibility of medium size and large muscular arteries. Procedures or situations that acutely increase sympathetic activity are associated with reduction in distensibility of muscular arteries, such as brachial, radial, or femoral arteries.

The Sympathetic Nervous System and Elastic Arteries

The activity of the sympathetic nervous system on viscoelastic properties of central arteries remains still widely unknown. Actually, some studies showed that the mechanical properties of the human aorta remain unaltered during sympathetic stimulation, and the role of sympathetic nervous system on aortic distensibility properties is really weak.

However, we should not conclude that the sympathetic nervous system has not any effect on pulse pressure. Actually, high sympathetic activity may also affect pulse pressure by increasing systemic vascular resistance, thus, modifying amplitude and distribution of reflected pressure waves. An increase in backward pressure waves can increase central systolic blood pressure and reduce blood pressure amplification in the periphery even without change in aortic distensibility.

Reduced *left ventricular ejection time* (LVET) is accompanied by a decrease in aortic distensibility and by a secondary increase in PWV [11]. The opposite association of PWV with LVET appears to be stronger than the one with heart rate in all age groups (Fig. 2.21). At least two mechanisms could justify the strong link we observed between PWV and LVET.

Firstly, the relationship between LVET and PWV can be explained by a simple energetic model. At a given heart rate, if there is a reduction in systolic ejection time, the mechanical work of the left ventricle is carried out in shorter time, but

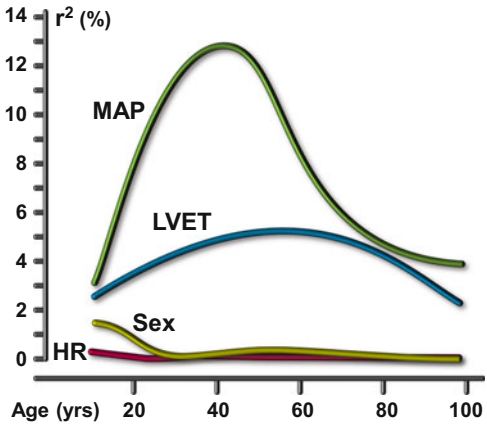

Fig. 2.21 Relative weight of major determinants of pulse wave velocity by age. Data are the result of subdividing a population of more than 3000 patients for class of age and weighing up the r^2 increment in stepwise regression analysis into each class of age [11]. *MAP* mean arterial pressure, *LVET* left ventricular ejection time, *HR* heart rate

with greater power. Power (P) represents the work (W) of blood pressure on arterial wall during a given time interval (t) (i.e., $P = dW/dt$). Given that power is proportional to mean arterial pressure and to the velocity of traveling waves, an increase in power corresponds to an increase in PWV. Thus, for a given value of heart rate, a reduction in LVET determines an increase in PWV. This power concept probably relates to time-dependent mechanisms associated with arterial stiffness such as wall viscoelasticity.

Secondly, aortic PWV may also significantly affect left ventricular performance and hemodynamic status. Because LVET depends on the capability of the left ventricle to eject blood and, thus, on left ventricular inotropic function and loading conditions, an alteration in any of these variables may influence LVET.

Thus, taking into account these two plausible mechanisms, the relationship between LVET and PWV should not only be considered as the result of a direct modulation of arterial distensibility induced by heart rate changes but also as the result of a mutual interaction between left ventricular ejection function and aortic and large artery distensibility. It can be hypothesized that with advancing age, when age progressively becomes the most powerful predictor of PWV, the inverse relationship between LVET and PWV may be an epiphenomenon of an age-related increase in large artery stiffness contributing to an increased aortic impedance that ultimately tends to limit ejection duration. On the contrary, in the youngest subjects with distensible arteries, PWV shows a prevalent association with mean arterial pressure and LVET, suggesting a stronger dependence of PWV on left ventricular performance (Fig. 2.22).

The determinants of PWV are different at different ages [11]. As clearly shown in Fig. 2.21, the role of LVET is constant and homogeneous throughout life. Indeed, both in very young and in very old subjects, mean blood pressure and left ventricular ejection time, reflecting left ventricular performance and peripheral resistance, are both less powerful determinants of pulse wave speed along the arterial tree.

However, as the clinical significance of the assessment of PWV is closely related to the study of structural alterations of the arterial wall, in clinical studies and research, it is strongly recommended the adjustment of PWV values for the following factors: age, mean arterial pressure, and left ventricular ejection time.

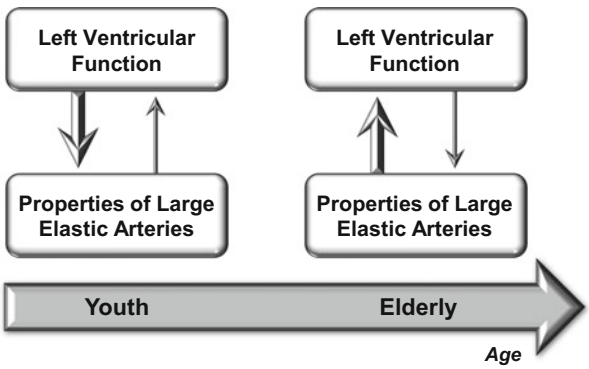

Fig. 2.22 Differences in the mutual relationship between left ventricular function and properties of of large arteries at different ages. In young people, the effects of left ventricular function on properties of of large arteries prevail, whereas in the elderly, the effects of arterial properties (increased stiffness) on heart function are more pronounced

2.2.3 Reference Values of Aortic Pulse Wave Velocity

One of the main problems in assessing PWV is the heterogeneity of the data supplied by the different devices being used. This is not only due to the different methods of measuring the distance between the recording sites of pulse waves but also to the different algorithms which are used for assessing the time delay in the femoral pulse wave with respect to the carotid pulse wave.

The data reported in Figs. 2.23 and 2.24 refer to the reference values of carotid–femoral PWV, obtained by means of the PulsePen using the "subtractive" method

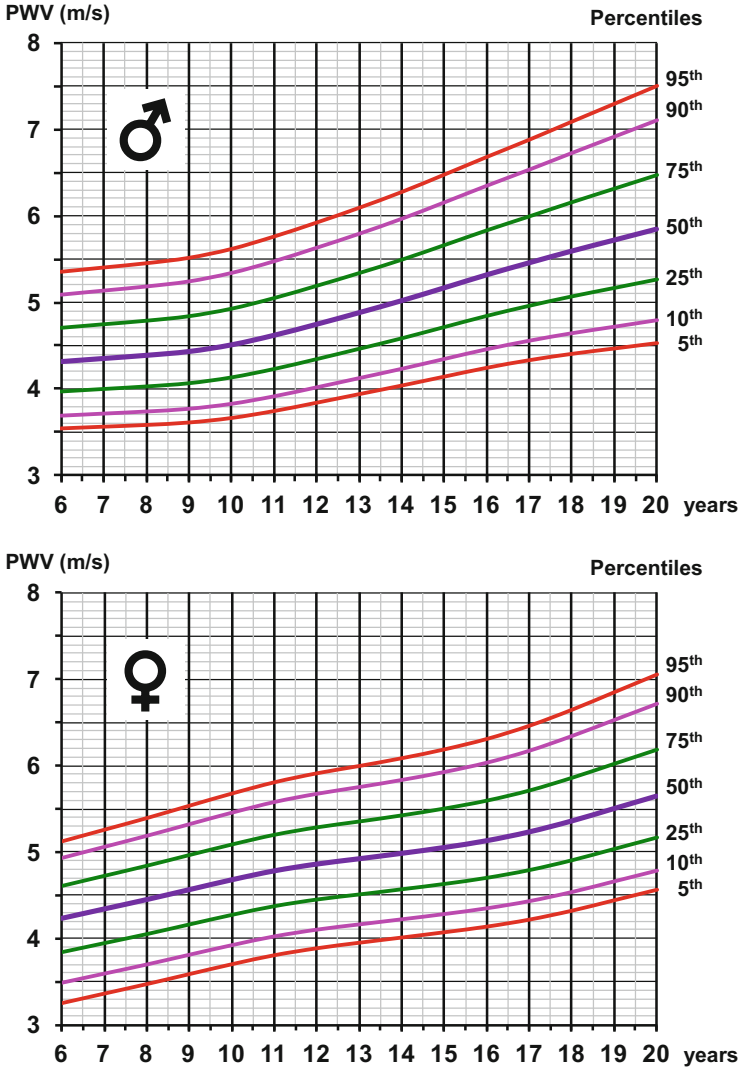

Fig. 2.23 Aortic pulse wave velocity reference values: percentile curves according to age (range 6–20 years) in male (*upper panel*) and female subjects (*lower panel*). Distance measured using the "subtractive" method [12]

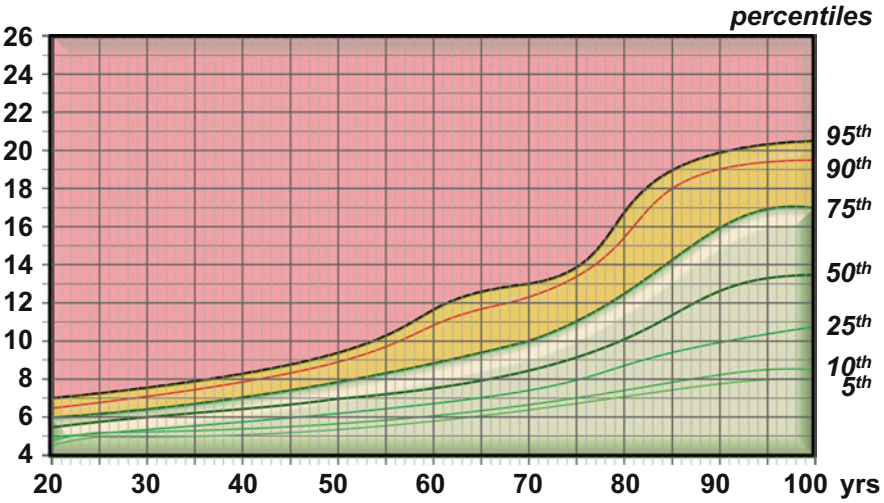

Fig. 2.24 Aortic pulse wave velocity reference values: percentile curves in adults according to age. Data observed in healthy population, free from overt cardiovascular diseases and cardiovascular risk factors, using the PulsePen® tonometer. Distance measured using the "subtractive" method

to measure distance [(suprasternal notch to femoral artery) − (suprasternal notch to carotid)]. These reference values were obtained in more than 1000 children and teenagers (Fig. 2.23) [12], and in 3208 apparently healthy adults, with no cardiovascular risk factors and without manifest cardiovascular diseases (Fig. 2.24). In Fig. 2.25, the reference values were obtained in the same subjects using the "direct" method to measure distance [carotid to femoral artery] × 0.8, as suggested by a recent expert consensus document on the measurement of aortic stiffness [9].

The data shown in the graphics can be interpreted as follows:

- The values below the 75th percentile may be considered as "normal values"
- Between the 75th and 95th percentile: "border-line values". It is advisable to repeat the test periodically and to try to identify the causes of increased arterial stiffness
- Above the 95th percentile: evidence for "arterial stiffness". High risk for cardiovascular disease

The Complior Analyse®, the PulsePen®, and the SphygmoCor® use similar algorithm systems for measuring the time delay of the femoral pulse wave with respect to the carotid pulse wave, and their outcomes are superimposable. Therefore, these reference values can be applied, in clinical application and research, when these devices are used.

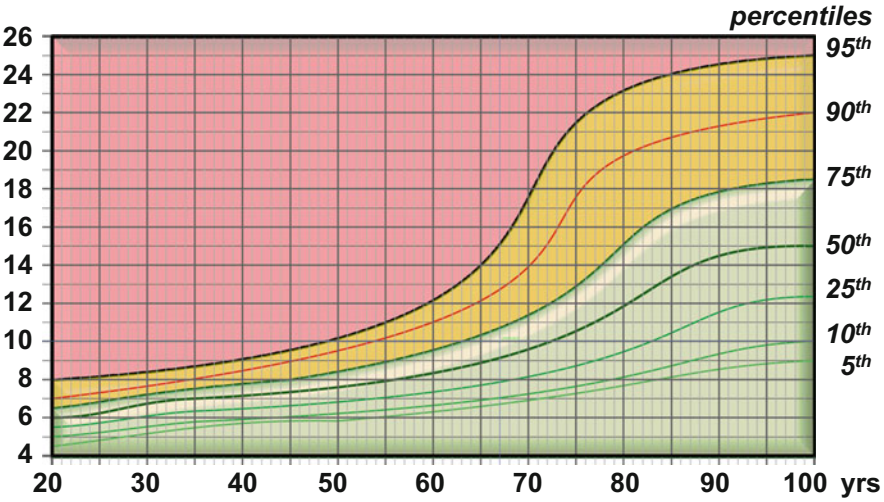

Fig. 2.25 Aortic pulse wave velocity reference values: percentile curves in adults according to age. Data observed in healthy population, free from overt cardiovascular diseases and cardiovascular risk factors, using the PulsePen® tonometer. Distance measured using the "direct" method (carotid-to-femoral distance) × 0.8

2.3 Pulse Wave Velocity in Other Arterial Districts

Carotid–femoral PWV is an index of aortic stiffness, but PWV can also be assessed in other arterial districts.

2.3.1 Upper Limb and Lower Limb Pulse Wave Velocity

Carotid–radial and carotid–brachial PWV assess the mechanical properties of the upper limb arteries. In these cases, the distal transducer records pulse wave in the radial artery and in the brachial artery, respectively. However, several studies have confirmed that this measurement has neither prognostic nor clinical significance. Moreover, while carotid–femoral PWV increases significantly with aging, carotid–radial and carotid–brachial pulse wave velocities do not change with age (Figs. 2.26 and 2.27).

Most likely, upper limb PWV reflects the functional condition of the arterial tree, which is closely related to the activation of the sympathetic system. This explains the presence of high values under particular stress conditions, such as altitude or hypoxia. It is no surprise that carotid–radial PWV changes significantly when diastolic blood pressure, mean arterial pressure, and heart rate change.

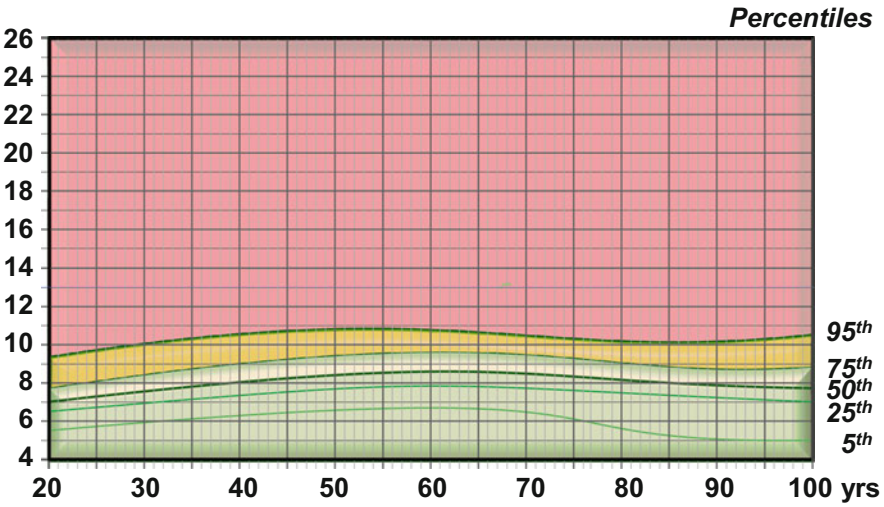

Fig. 2.26 Upper limb (carotid–radial) pulse wave velocity reference values: percentile curves in adults according to age. Data observed in healthy population, free from overt cardiovascular diseases and cardiovascular risk factors, using the PulsePen® tonometer. Distance measured using the "subtractive" method

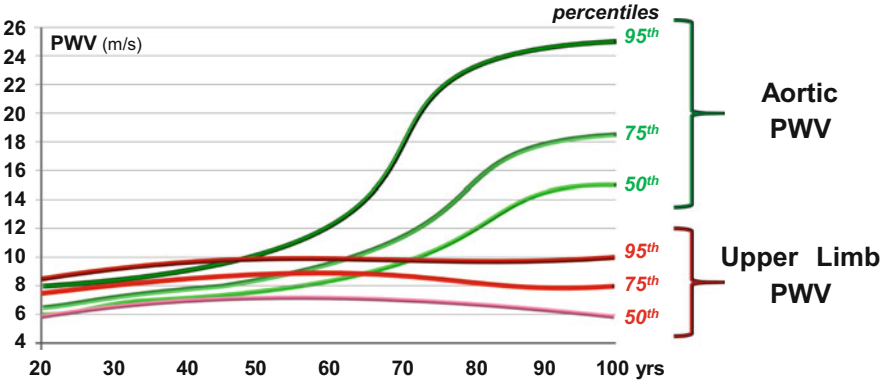

Fig. 2.27 Carotid–femoral (*green lines*) and carotid–radial (*red lines*) pulse wave velocity (PWV) changes with aging. Data expressed in percentiles according to age

Further studies should clarify the particular arterial condition of the axillo-brachial axis, characterized by little tendency to thrombotic phenomena and little tendency to structural alterations of the arterial wall.

Femoro-tibial PWV assesses the viscoelastic properties of the arterial system in the lower limb. The proximal transducer records the pulse wave in the femoral artery, while the distal transducer records the pulse wave in the posterior tibial or dorsalis pedis artery. This method can supply useful information about the

functional state of the peripheral blood circulation but it has neither prognostic nor clinical importance for general cardiovascular risk.

Studies targeted at comparison between different arterial districts have confirmed that only aortic PWV (i.e., carotid–femoral PWV) has independent prognostic significance for cardiovascular disease. On the contrary, neither the axillo-brachial axis nor the lower limb arteries has prognostic significance (Fig. 2.28). Upper limb PWV and lower limb PWV have sensitivity and specificity greatly inferior to carotid–femoral PWV (Fig. 2.29).

2.3.2 Brachial–Ankle Pulse Wave Velocity

Several methods, most of all used in Asian Far East, measure aortic PWV by assessing the time delay in the pulse waveform recorded in the tibial (or femoral) artery with respect to the brachial pulse waveform. These methods record the pulse wave transit time using an oscillometric technique and cuffs that are similar to those used in normal digital or mercury sphygmomanometers, placed at the arm and at the ankle (or thigh). These are simple, operator-independent methods. However, owing to the different degree of arterial stiffness in the aorta and in the muscular arterial districts, they should be considered unreliable and unsuitable for the study of aortic distensibility or evaluation of cardiovascular risk.

At present, the carotid–femoral PWV is considered to be the gold-standard measurement for aortic stiffness, whereas brachial–ankle PWV measures a hazy arterial distensibility including also upper and lower limb muscular arteries. As we have already mentioned above, PWV presents different characteristics in muscular arteries and in elastic arteries (Table 2.1):

- Aortic PWV may be considered a reliable parameter representing vascular aging, whereas PWV in muscular arteries is relatively unchanged with age, i.e., it does not suffer vascular aging effects.
- Aortic PWV is relatively insensitive to sympathetic system activation, whereas PWV in muscular arteries is deeply affected by sympathetic system activity; carotid–femoral PWV reflects the mechanical properties (distensibility) of the aorta, i.e., the elastic and collagenous fibers ratio in the aortic wall. Changes in carotid–femoral PWV need organic changes in aortic wall. Thus, PWV values are relatively stable with time and the follow-up of patients is possible. On the contrary, PWV in muscular arteries (like lower limb arteries) easily changes in relationship with changes in functional factors; since sympathetic activity changes, the reliability of the longitudinal studies are questionable, particularly in adolescents and in young adults, where sympathetic activity is marked.
- In the elderly, arterial disease is frequent in lower limbs, and PWV may change according to the severity of the atheromatous process.

As PWV in muscular arteries does not change with age and it is relatively constant in healthy adults, it is not surprising that some studies have shown a

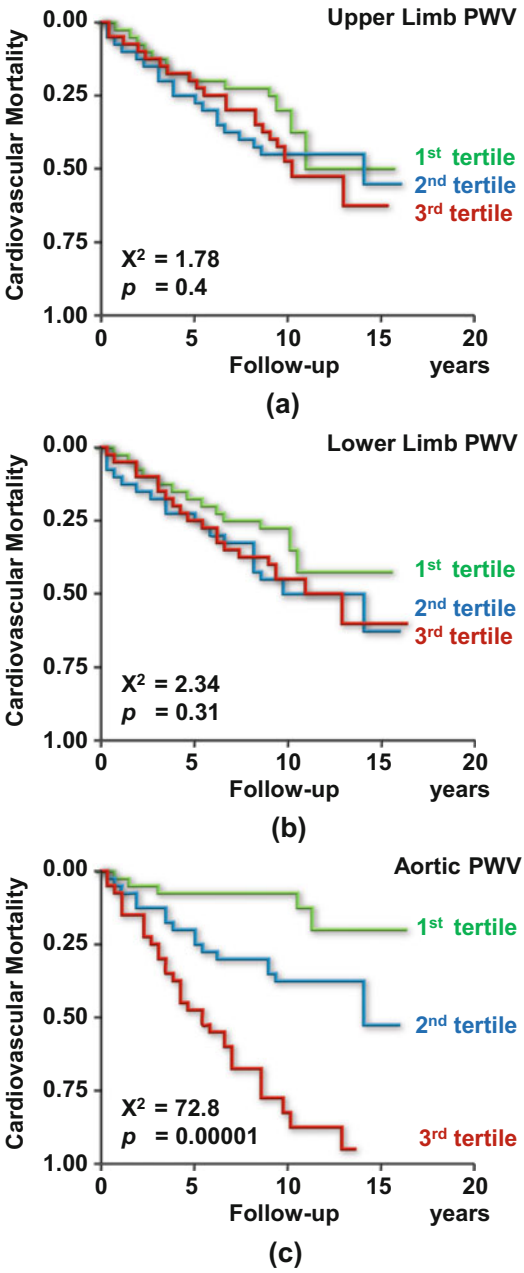

Fig. 2.28 Cardiovascular mortality in patients with end-stage renal disease: predictive value of carotid–radial (**a**), femoro-tibial (**b**), and carotid–femoral (**c**) pulse wave velocity. In each subfigure, the analysis is carried out in tertiles of pulse wave velocity pressure values: the first tertile, *green line*; the second tertile, *blue line*; the third tertile, *red line* [13]

significant association between carotid–femoral and brachial–ankle PWV values (i.e., if "$A = B + C$", obviously "A" is closely associated with "B", when "C" is a relatively stable parameter).

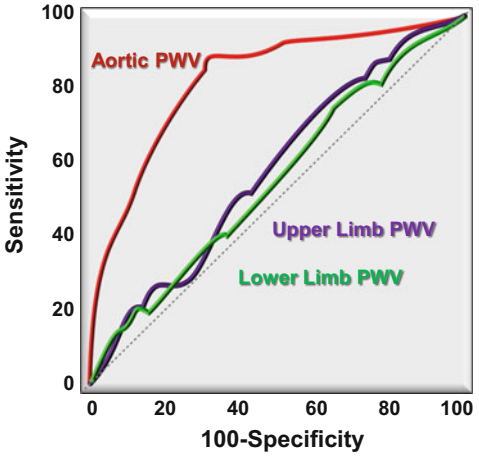

Fig. 2.29 Sensitivity and specificity of carotid–femoral (aortic PWV), carotid–radial (upper limb PWV), and femoro-tibial (lower limb PWV) pulse wave velocity in relation to cardiovascular mortality in patients with end-stage renal disease: receiver operating characteristic (ROC) curves of cardiovascular death [13]

Table 2.1 Main differences between pulse wave velocity (PWV) in muscular and elastic arteries

PWV in the aorta	PWV in muscular arteries
Carotid–femoral PWV increases with age	Carotid–radial PWV does not change with age
Carotid–femoral PWV may be considered an index of biological age of the vascular system	Carotid–radial PWV does not provide information about the vascular aging
An increase in carotid–femoral PWV is an independent risk factor for cardiovascular risk	An increase in carotid–radial PWV or femoral–tibial PWV is not related to cardiovascular risk
PWV in the aorta is not affected by sympathetic system activity	PWV in muscular arteries is affected by sympathetic system activity
The stiffening of elastic arteries is related to structural changes in the arterial wall (elastin and collagen ratio in media layer, inflammation, media calcifications, etc.)	The stiffening of muscular arteries is mostly related to functional changes in the arterial wall

As far as the brachial–ankle PWV is concerned, the main questions are: what does the brachial–ankle PWV measure? Why should brachial–ankle PWV be measured? This method does not provide reliable information either about arterial and aortic stiffness or biological vascular aging. Why should the measurement of brachial–ankle PWV be preferred to carotid–femoral PWV then? Moreover, the carotid–femoral PWV acquisition by arterial tonometers is often easier and faster than brachial–ankle PWV. Cultural and ethical reasons are also unjustified, since at present we can use very sensitive tonometers (such as the PulsePen® tonometer)

able to record blood pressure wave on femoral artery, which do not require the patient to undress. In conclusion, there are no justifiable reasons for the assessment of brachial–ankle PWV in daily clinical practice or in clinical research.

2.4 Instruments for the Assessment of PWV

Over the last few years, a lot of new instruments measuring pulse wave velocity have been launched onto the market. Although many are in daily clinical use, they do not necessarily provide identical information. In 2010, the ARTERY Society provided guidelines for a standard methodology for validating devices that measure PWV. This document fixed reference standards to measure true aortic velocity and carotid–femoral pulse wave velocity and provided guidelines for the process of validating new devices.

Actually, it seems that the main aim of some manufactures of the latest devices is to supply operator-independent devices, which can perform faster, whereas the accuracy of the measurement or the scientific soundness of the algorithms used is of secondary importance. This research on simplification may lead to the design of fanciful instruments, which are extremely easy to use but not scientific devices.

The following sections provide the reference standard for the true aortic PWV and carotid–femoral PWV, as they have been fixed by the ARTERY Society; subsequently, the properties of the main devices on the market are described (ARTERY Society guidelines for validation of noninvasive hemodynamic measurement devices [14].

2.4.1 Reference Standards for the Assessment of the PWV

2.4.1.1 Reference Standards for True Aortic PWV Assessment Obtained Using Invasive Methods

Recommended reference:

Simultaneous pressure waveforms recorded invasively with high-fidelity pressure sensors from just above the aortic valve and just above the aortic bifurcation.

Alternative reference:

Sequential ECG-gated recordings from just above the aortic valve and just above the aortic bifurcation. In this case, it is important to ensure that there is no significant variation in heart rate or blood pressure during the recordings.

The following characteristics are recommended for recording and analysis:

– Sampling rate: $\geq$1 kHz

– Recording time: ≥10 cardiac cycles;
– Transit time determined from the feet of the pulse waveforms
– Path length determined from radiographic images obtained during the procedure or from the catheters themselves

2.4.1.2 Reference Standards for Carotid–Femoral PWV Assessment

Recommended reference:

Simultaneous carotid and femoral artery tonometry.

Alternative reference:

Sequential ECG-gated carotid and femoral artery tonometry. In this case, it is important to ensure that there is no significant variation in heart rate or blood pressure during the recordings.

The following characteristics are recommended for recording and analysis (Table 2.2):

– Sampling rate: ≥1 kHz
– Recording time: ≥10 cardiac cycles
– Transit time determined from the feet of the pulse waveforms

2.4.2 Devices on the market

The main properties of the devices on the market are described in Table 2.3 (data provided by the manufacturers). Instruments that aim at measuring pulse wave velocity by recording pulse wave at the arm and ankle (or thigh) simultaneously to

Table 2.2 Characteristics of the reference standard devices for the assessment of aortic pulse wave velocity

Device	Recommended reference	Alternative reference
Aortic PWV assessment	Carotid–femoral PWV	Carotid–femoral PWV
Method based on transit time delay assessment	Simultaneous carotid and femoral artery recordings	Sequential ECG-referenced carotid and femoral artery recordings
Probes	Two tonometers	One tonometer
Transit time delay	Foot-to-foot method	Foot-to-foot method
Sample rate	≥1 kHz	≥1 kHz
Recording time	≥10 cardiac cycles	≥10 cardiac cycles

ARTERY Society guidelines for validation of noninvasive hemodynamic measurement devices [14]

Table 2.3 Characteristics of the devices on the market for the assessment of PWV, in relation to the reference standards set by the ARTERY Society [14]

Device	PulsePen® WPP-ETT	PulsePen® WPP-ET	Complior Analyse®
Manufacturer	DiaTecne srl	DiaTecne srl	Alam Medical
Made in	Italy	Italy	France
URL	www.pulsepen.com	www.pulsepen.com	www.complior.com
Aortic PWV assessment	Carotid–femoral PWV	Carotid–femoral PWV	Carotid–femoral PWV
Method based on transit time delay assessment	Simultaneous carotid and femoral artery recordings	Sequential ECG-referenced carotid and femoral artery recordings	Simultaneous carotid and femoral artery recording
Probes	Two tonometers	One tonometer	Two piezoelectric sensors
Transit time delay	Foot-to-foot method	Foot-to-foot method	Foot-to-foot method
	interpolating intersecting	interpolating intersecting	
Sample rate	1 kHz	1 kHz	1 kHz
Recording time	10 cardiac cycles	10 cardiac cycles	Two options: –up to 30 s –10 cardiac cycles
Options to record extended period	Up to 24 h [LP-WPP software]	Up to 24 h [LP-WPP software]	No
Agreement with reference standards	☺ ☺ ☺	☺ ☺ ☺	☺ ☺

Device	SphygmoCor®	SphygmoCor® XCEL PWV system	Vicorder® Arterial Stiffness
Manufacturer	AtCor Medical Pty Ltd	AtCor Medical Pty Ltd	Skidmore Medical Ltd
Made in	Australia	Australia	United Kingdom
URL	www.atcormedical.com	www.atcormedical.com	www.skidmoremedical.com
Aortic PWV assessment	Carotid–femoral PWV	Carotid–femoral PWV	Carotid–femoral PWV Optional: brachial–femoral and brachial–ankle PWV
Method based on transit time delay assessment	Sequential ECG-referenced carotid and femoral artery recordings	Simultaneous carotid and femoral artery recording	Simultaneous arteries recording
Probes	One tonometer	One tonometer + 1 oscillometric system (cuff on lower limb)	Oscillometric system (2 cuffs)
Transit time delay	Four options: Foot-to-foot method Maximum of second derivative Maximum dP/dT Pulse height percent	Foot-to-foot method	
Sample rate	128 Hz	256 Hz	556 Hz
Recording time	10 s	5, 10, or 20 s	3.5 s
Options to record extended period	Up to 30 s	No	14 s
Agreement with reference standards	☺ ☺	☺	☺

(continued)

Table 2.3 (continued)

Device	BPLab Vasotens®	Mobil-O-Graph® 24-h PWA monitor	Arteriograph®
Manufacturer	BPLab	I.E.M. GmbH	TensioMed
Made in	Russia	Germany	Hungary
URL	www.bplab.com	www.iem.de	www.tensiomed.com
Aortic PWV assessment	By analysis of the oscillometric pressure curves registered on the upper arm	By analysis of the oscillometric pressure curves registered on the upper arm	By analysis of the oscillometric pressure curves registered on the upper arm
Method based on transit time delay assessment			
Probes	Oscillometric system (1 cuff on upper arm)	Oscillometric system (1 cuff on upper arm)	Oscillometric system (1 cuff on upper arm)
Transit time delay	By analysis of the oscillometric pressure curves registered on the upper arm	By analysis of the oscillometric pressure curves registered on the upper arm	By analysis of the oscillometric pressure curves registered on the upper arm
Sample rate	100 Hz	100 Hz	200 Hz
Recording time	4–8 cardiac cycles	10 s	8 s
Options to record extended period	24-h (ABPM)	24-h (ABPM)	
Agreement with reference standards	☹	☹	☹

Device	pOpmètre®	VaSera® VS-1500 and VS-2000
Manufacturer	Axelife sas	Fukuda Denshi
Made in	France	Japan
URL	www.axelife.fr/en/index.php	http://www.fukuda.co.jp/english
Aortic PWV assessment	Finger–toe PWV	Cardio-ankle vascular index [CAVI]
Method based on transit time delay assessment	Simultaneous recording of the pulse wave at finger and toe	Simultaneous recording at brachial and ankle artery by 4 cuffs with phonocardiogram and ECG recordings
Probes	Oxymetric clip Customized	Oscillometric system (4 cuffs) phonocardiogram
Transit time delay	Second derivative	
Sample rate	1 kHz	1 kHz
Recording time	10 cardiac cycles	5 cardiac cycles or 5 s
Options to record extended period	30 s	16 s [VS-2000]
Agreement with reference standards	☹ ☹	☹ ☹

obtain the so-called brachial–ankle PWV are not considered. Since the arterial system is very complex, even if these are operator-independent and easy-to-perform methods, their measurements are unable to provide accurate evaluation of aortic stiffness Fig. 2.30–2.39.

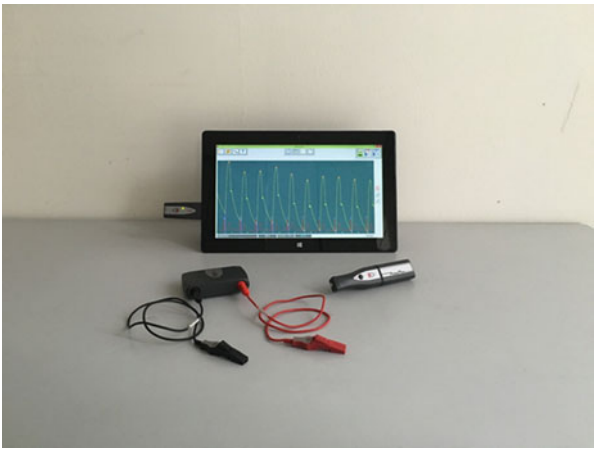

Fig. 2.30 The PulsePen® WPP-ET (DiaTecne srl, Italy)—DiaTecne aims at developing scientific research in the vascular hemodynamic field. It creates innovative, reliable instruments at affordable prices so that diagnostic methods can be widely used and applied in everyday clinical practices [15]. The PulsePen® is a pocket-size and really reliable wireless system composed of a receiver, an optional table-PC, a tonometer, and a small electrocardiograph. This is a valid and reliable instrument for the assessment of pulse wave velocity in accordance with all the recommendations from the authoritative ARTERY Society concerning the reference standards for the assessment of carotid–femoral pulse wave velocity. This model of PulsePen® (WPP-ET) measures carotid–femoral pulse wave velocity at two times by using one tonometer combined with electrocardiographic tracing. The central pressure waveform and central pressure values are recorded directly, starting from the carotid pulse wave analysis. Central pressure values assessed with the PulsePen® device are reliable and widely validated. The sampling rate of the PulsePen® is 1 kHz (i.e., it records a signal every ms), with definition of the pressure waveform at 16 bits. The probe is shockproof. The recorded data can be directly exported to Excel® files. Moreover, waveforms can be recorded and exported to ASCII format. This allows the PulsePen® to be inserted in a polygraphic recording together with other physiological parameters. The relationship between quality and price is particularly favorable for PulsePen®. Despite the high-technology precision system and high-quality parts, PulsePen® is low cost. All the same, the low price of the PulsePen® is also its weakest point: "*. . . if the PulsePen® is cheaper than the other devices, it means that it is less reliable and less accurate, and that it has less than desirable technical support* . . .". Following this reasoning, physicians (nine out of ten) usually decide that they will buy other devices, which are usually more expensive, less reliable and poorly performing

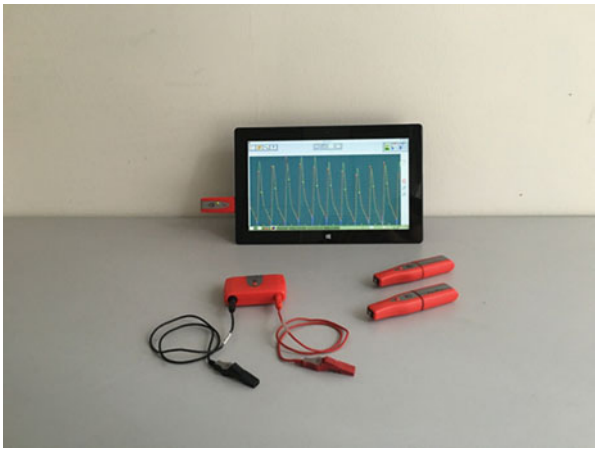

Fig. 2.31 The PulsePen® WPP-ETT (DiaTecne srl, Italy)—This model of PulsePen® (WPP-ETT) measures carotid–femoral PWV at one time by using two high-fidelity tonometers [15]. The proximal tonometer is placed on the common carotid artery and the second tonometer records the pulse wave curve simultaneously in the peripheral artery. It is a pocket-size wireless sympathetic system composed of a receiver, an optional table-PC, two tonometers, and an electrocardiograph. The recording of the ECC tracing allows the measurement of carotid–femoral pulse wave velocity also at two times by using one tonometer combined with electrocardiographic tracing. This method is suitable when the test is carried out only by one operator, namely when the recording of the two arterial signals could be difficult. High-fidelity tonometers are very sensitive and pressure waveforms are generally acquired easily; femoral pressure waveforms can be recorded by placing the probe on clothing (even on blue jeans), and patients do not need to undress in most cases. The whole test usually lasts from 4 to 8 min. At the end of it, an automatic report can be printed for the patient. The PulsePen® is available in anthracite gray and Ferrari red, symbol of Italian technology and design. The recording of pulse wave velocity and central arterial pressure is a real fun!

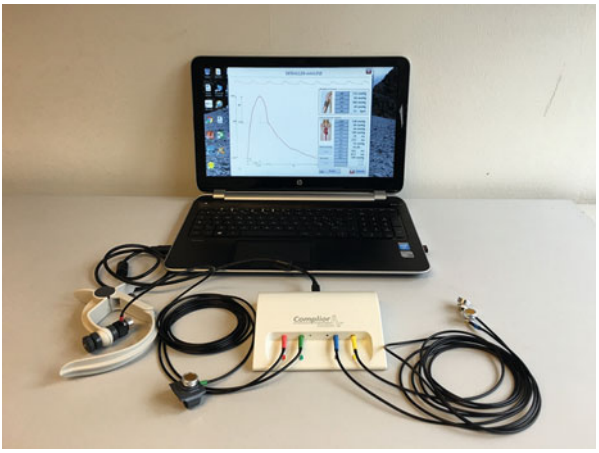

Fig. 2.32 The Complior Analyse® (Alam Medical, France)—Complior® SP was the first instrument launched on the market for the measurement of pulse wave velocity. The Complior Analyse®, which is the latest model offered by Alam Medical, uses two piezoelectric sensors, to be placed on the carotid and femoral arteries, which are able to record the curves of arterial diameter variations secondary to changes in blood pressure. The Complior® takes advantage of its "famous" name; thanks to studies carried out with this device that measured pulse wave velocity value has been confirmed as an independent prognostic factor for cardiovascular disease. The main advantage of this device is the simultaneous recording of the central and peripheral signal. The probe assessing the carotid waveform can be fixed through practical pincers; the curve is purpose-drawn and less linked to involuntary movements of the operator. Central arterial pressure is directly defined starting from the carotid pressure waveform without using a questionable "transfer function"

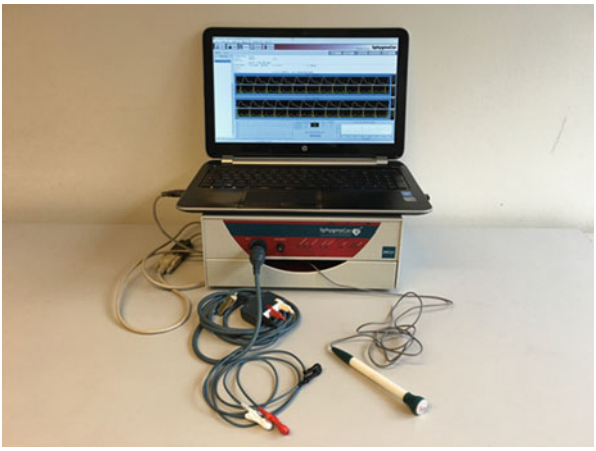

Fig. 2.33 The SphygmoCor® (AtCor Medical Pty Ltd, Australia)—The SphygmoCor® CPV is perhaps the best-selling instrument in the world for the assessment of pulse wave velocity. This system is composed of a tonometer and an electrocardiograph; the measurement of pulse wave velocity occurs at two times, using the R wave of the QRS complex of the ECG as reference point. This device uses a Millar tonometer, and the algorithm used for the assessment of pulse wave velocity is similar to the one implemented in the PulsePen®. Central pressure waveform and the ascending aorta pressure values are defined by means of a transfer function, starting from the radial pulse wave. The radial pulse waveform is calibrated using blood pressure values measured by traditional method on the brachial artery. The discovery of a significant difference between blood pressure values in radial and brachial arteries has cast serious doubts on the reliability of this calibration system. The sampling rate of the SphygmoCor® is 128 Hz (i.e., it records a signal every 7.8 ms). It is important to stress that, with a low sampling rate, the calculation of the pulse wave traveling time is inaccurate, but thanks to an interpolation process the waveform will be very clear. Over the last few years, the SphygmoCor® XCEL has been launched on the market by the AtcCor Medical, where the recording of the femoral pressure waveform occurs by placing a cuff around the thigh, which replaces the traditional tonometer. The sampling rate of the SphygmoCor® XCEL is 256 Hz (i.e., it records a signal every 3.9 ms)

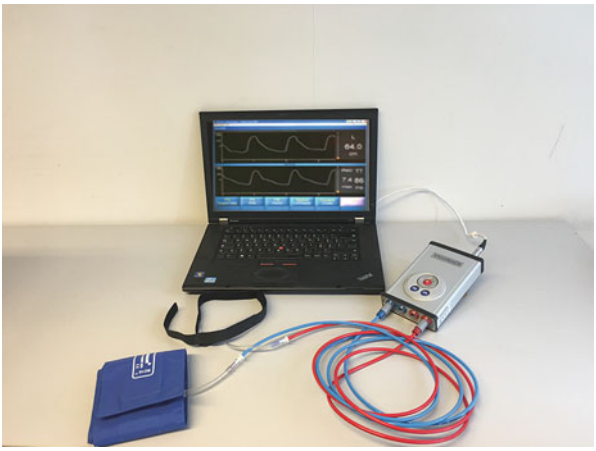

Fig. 2.34 The Vicorder® PWV system (Skidmore Medical Ltd, UK)—The Vicorder® offers an original system for the assessment of the carotid–femoral pulse wave velocity. It is composed of two elements: a neck pad sensor placed at the level of the carotid artery and a blood pressure cuff placed at the root of the thigh to measure the femoral pulse. Both cuffs are automatically inflated to 65 mmHg and the corresponding oscillometric signal from each cuff is digitally analyzed. Thus, the pulse wave transit time is determined using an in-built cross-correlation algorithm centered around the peak of the second derivative of pressure. Path length was defined as the distance from the suprasternal notch to the top of the thigh cuff as indicated by the manufacturer. The system is interesting, but both the methods used to measure distance and the relationship between the pulse wave velocity values recorded with this system and the ones recorded with other devices, which use codified and validated methods and algorithms, are not clear. Vicorder® not only allows the measurement of aortic PWV but also the assessment of central blood pressure values through the recording of pulse wave in brachial artery acquired by means of oscillometric method and application of a global transfer function

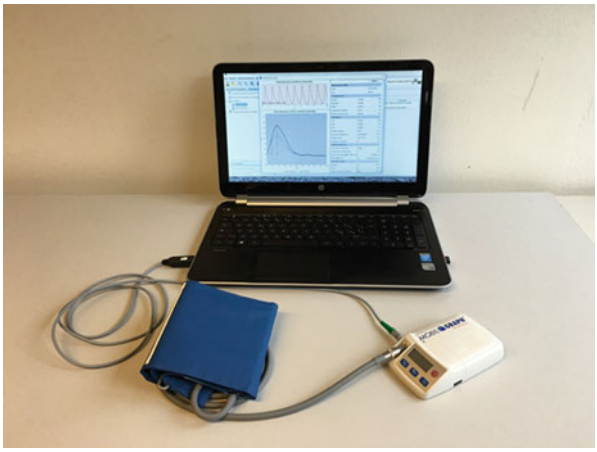

Fig. 2.35 The Mobil-O-Graph® (I.E.M. GmbH, Germany)—Il Mobil-O-Graph® is not only an excellent instrument for the 24-h ambulatory blood pressure monitoring, but it is also used for the dynamic monitoring of central arterial pressure and the determination of aortic pulse wave velocity. The method used by Mobil-O-Graph® for the assessment of central blood pressure and pulse wave velocity is based on the acquisition of arterial pressure in the brachial artery using an oscillometric method by means of the cuff used for measuring blood pressure. Pulse wave in brachial artery is recorded by a MPX5050 pressure sensor (Freescale Inc., Tempe, AZ, USA). Aortic pressure wave is analyzed using a transfer function. The system used by Mobil-O-Graph® is based on rather unconvincing physiological hypotheses and the algorithm used in the evaluation of pulse wave velocity bewilders. In fact, this seems to be based more on the patient's personal data rather than on a real analysis of the pressure waveform. Actually, the pulse wave velocity values supplied by the Mobil-O-Graph® drastically change if we change the patient's birthdate. If age is what defines pulse wave velocity, why should one waste time and money by using the Mobil-O-Graph® then? It would be wiser to ask how old the patient is

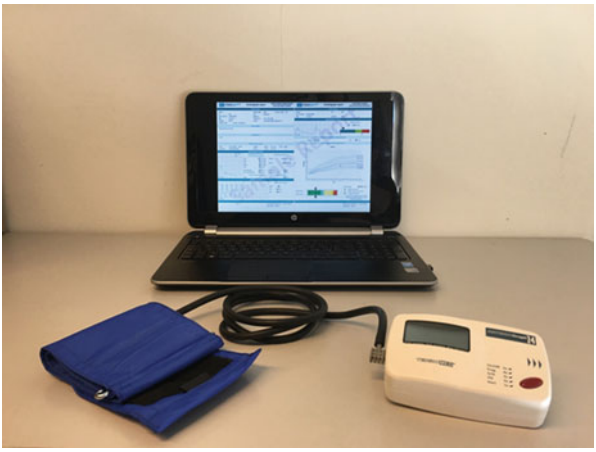

Fig. 2.36 The Arteriograph® (Tensiomed, Hungary)—This instrument aims at assessing central blood pressure and aortic pulse wave velocity by analyzing the blood pressure curve recorded in the upper arm with a simple upper arm cuff, using an oscillometric method. Further validation studies are required here as well, as the Arteriograph method is based on imaginative and weak physiological bases. Moreover, comparative studies on the different methods that are currently being used have provided very conflicting data so far

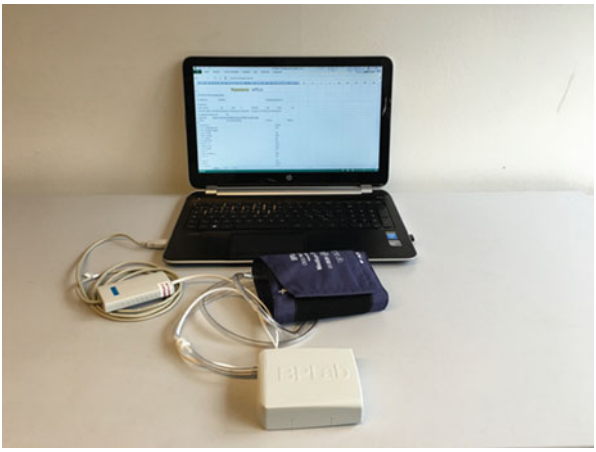

Fig. 2.37 The BPLab Vasotens® (BPLab, Russia)—BPLab Standard is a 24-h ambulatory blood pressure monitor. BPLab Vasotens® is also able to measure central blood pressure and define aortic pulse wave velocity. BPLab® uses an inexpensive oscillometric method for the estimation of arterial stiffness, central, and peripheral hemodynamics parameters. A regular cuff acts as a sensitive transducer. The measurements with a cuff should be faster and operator-independent even theoretically, but the assessments of the hemodynamic parameters are not always easily performed so that the operator is forced to repeat the test several times before reliable data are recorded. Moreover, the bizarre hypothesis claiming that the aortic pulse wave velocity can be recorded on the basis of the recording of an oscillometric signal recorded at the brachial artery is still questionable

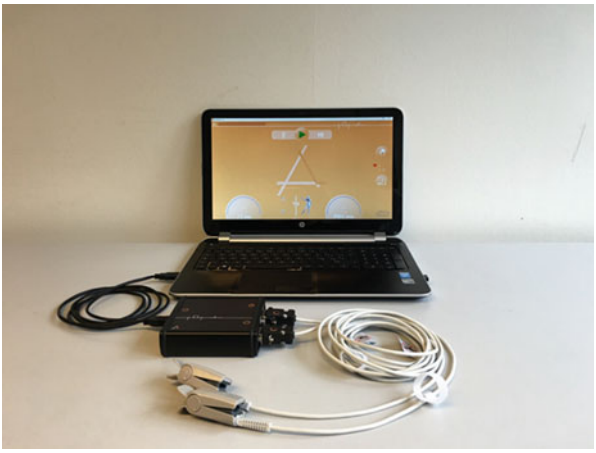

Fig. 2.38 The pOpmètre® (Axelife sas, France)—The pOpmètre® explores arterial stiffness by measuring the finger–toe pulse wave velocity. In the pOpmètre® system, two photodiode sensors are placed on the finger and on the toe, next to the pulp artery. The positioning of the toe sensor must be accurate so that the pulp can be in contact with the photodiode. Pulse waves are recorded continuously for 20 s, and the difference between the toe and the finger pulse wave transit time is calculated. The travel distance is based on the subject's height. Theoretically, this system proposed by Axelife seems to be very simple, rapid and does not need special training to be used. Actually, the measurement of pulse wave velocity is not sometimes possible even when all the recommendations of the producer are observed such as the right position of the sensors, the immobility of the patient, the temperature, and the amount of light in the room. The acquisition of the signal is seldom validated the first time and several attempts must be done before a recording considered to be reliable by the system is obtained. As a result, long execution times are needed and the operator must be very patient. The measurement of the finger–toe pulse wave velocity by the pOpmètre® is three times longer than the traditional acquisition of the carotid–femoral pulse wave velocity with a tonometer. Moreover, it is important to know the clinical significance of the finger–toe pulse wave velocity. As a matter of fact, this method not only assesses the aorta but also pressure wave velocity along the upper and lower limbs, including elastic and muscular arteries

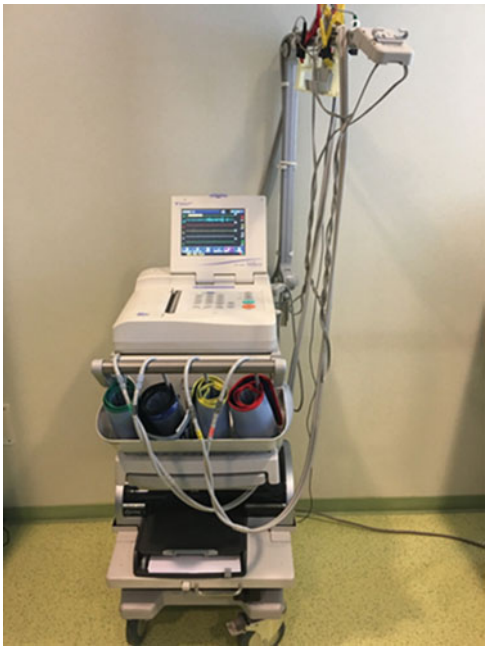

Fig. 2.39 VaSera® VS-1500 and VS-2000 (Fukuda Denshi, Japan)—Fukuda suggests cardio-ankle vascular index (CAVI) as an index for the measurement of arterial stiffness. Unlike the instruments using the brachial–ankle pulse wave velocity system, the VaSera® uses the recording of cardiac tones as a central reference point for the assessment of pulse wave velocity. As for peripheral recording, a cuff is placed at the ankle, which records pulse wave using an oscillometric method. Therefore, this system records the distensibility of the whole aorto-iliac, femoral–tibial segment. This system, as well as the brachial–ankle pulse wave velocity systems, considers both the aorta and the peripheral arterial axis of the lower limb, but this can lead to incorrect definition of aortic distensibility

2.5 Non-propagative Models to Define Vascular Distensibility

Propagative models (PWV) and non-propagative models have been suggested for assessing distensibility in the large arteries. The latter, owing to technical requirements and high costs, are usually reserved for research in few scientific centers.

The mechanical properties of arteries can be measured starting from the volume and pressure ratio of an isolated arterial segment. Therefore, from a general point of view, the mechanical properties of a blood vessel are not linear, that is to say, they depend on the pressure they are subjected to and at which they are measured.

Different parameters are used for assessing the mechanical properties of large arteries and for supplying indications about their viscoelastic properties. The main parameters used in the literature are listed below.

Compliance

Compliance represents the change in diameter (or in section) of the artery in absolute values, at a given pressure level, for a given arterial length. In other words, compliance is the ratio between change in volume and change in pressure.

In situations of good arterial elasticity, small changes in pressure result in significant changes in volume. On the contrary, under arterial stiffness conditions, significant changes in pressure result in small changes in volume:

$$\text{Compliance}\ (\text{cm}/\text{mmHg}) = \frac{(D_\text{s} - D_\text{d})}{(P_\text{s} - P_\text{d})} = \frac{\Delta D}{\Delta P}$$

where ($D_\text{s} - D_\text{d}$, systolic diameter – diastolic diameter) represents the change in diameter (ΔD) and ($P_\text{s} - P_\text{d}$, systolic blood pressure – diastolic blood pressure) the change in pressure (ΔP).

Distensibility

Distensibility defines the value of arterial compliance in relation to the initial diameter of the artery. Distensibility is defined as the relative change in diameter (or in section) in relation to the change in pressure (i.e., the inverse of the elastic modulus).

$$\text{Distensibility}\ \left(\text{mmHg}^{-1}\right) = \frac{(D_\text{s} - D_\text{d})}{(P_\text{s} - P_\text{d}) - D_\text{d}} = \frac{\Delta D}{\Delta P - D_\text{d}}$$

where ($D_\text{s} - D_\text{d}$, systolic diameter – diastolic diameter) represents the change in diameter (ΔD), ($P_\text{s} - P_\text{d}$, systolic blood pressure – diastolic blood pressure) the change in pressure (ΔP), and D_d the diastolic diameter.

Compliance Coefficient

The compliance coefficient (CC) is defined as the compliance per unit length, which is the change in cross-sectional area per unit of pressure:

$$\mathrm{CC} = \frac{(\Delta V/L)}{\Delta P} = \frac{\Delta A}{\Delta P} = \frac{\pi D \Delta D}{2\Delta P}$$

where D represents the diameter, ΔD the change in diameter, ΔA the change in cross-sectional area, and ΔP the change in pressure.

Distensibility Coefficient

The distensibility coefficient (DC) is defined as the relative change in cross-sectional area per unit of pressure:

$$\mathrm{DC} = \frac{(\Delta A/A)}{\Delta P} = \frac{2(\Delta D/D_\mathrm{d})}{\Delta P}$$

where ΔA represents the change in cross-sectional area, ΔD represents the change in diameter, ΔP the change in pressure, and D_d the diastolic diameter.

Local arterial (carotid) PWV (in m/s) may be calculated using the Bramwell–Hill equation:

$$\text{local arterial PWV} = \sqrt{1(\rho \mathrm{DC})}$$

where ρ represents the density of blood. This parameter, when it is not really calculated, may be assumed to be 1050 kg/m^3.

Peterson's Elastic Modulus

The elastic modulus is the pressure change required for a (theoretical) 100 % increase in resting diameter:

$$\text{Elastic Modulus (mmHg)} = \frac{\Delta P\, D_\mathrm{d}}{\Delta D}$$

where ΔP represents the change in pressure, D_d the diastolic diameter, and ΔD the change in diameter.

Young's Elastic Modulus

Young's elastic modulus represents the elastic modulus per unit of area and is defined as the (theoretical) pressure increase, per cm^2, required for 100 % stretch from resting length:

$$\text{Youngs Modulus (mmHg/cm)} = \frac{\Delta P\, D_\mathrm{d}}{(\Delta D h)}$$

where ΔP represents the change in pressure, D_d the diastolic diameter, ΔD the change in diameter, and h the arterial wall thickness.

Stiffness Index

The Stiffness Index (β) is defined as the logarithm of the ratio between systolic blood pressure and diastolic blood pressure ($P_\mathrm{s}/P_\mathrm{d}$) and the relative change in arterial diameter:

$$\text{Stiffness Index } (\beta) = \frac{\ln (P_s/P_d)}{[\Delta D/D_d]}$$

where ΔD represents the change in diameter and D_d the diastolic diameter.

Some ultrasound devices have been integrated with analysis systems for arterial wall motion, so that the curve representing the relative change in arterial diameter during the cardiac cycle is provided. These systems define the systo-diastolic arterial diameter change by using radiofrequency systems. Recently, other systems have also been suggested, using cine magnetic resonance imaging (MRI). Although they have very high costs, they allow the analysis of large deep arterial trunks.

2.5.1 Wall Track System

One of the first instruments used for recording the diameter change curve was the Wall Track System (WTS; Pie Medical, Maastricht). This device assesses arterial diameter change, during a cardiac cycle, using a radiofrequency signal integrated with ultrasound scanning (Fig. 2.40).

An echo-Doppler test of the carotid axis with *B-mode* ultrasound is carried out, and after excluding plaques or segmental arterial thickening, the common carotid segment to be analyzed is defined, and the depth of the artery evaluated. In this way, the anterior and posterior walls of the artery to analyze are easier to identify. Then an *M-line*, perpendicular to the artery, is selected; the signal is sent to a personal computer and analyzed. On the screen, the line of the radiofrequency analysis is displayed and the operator can select the peaks which correspond to interface. After that, the exact motion relative to each selected peak is estimated by means of an interpolation technique. At the end of the analysis procedure, the curves representing the systo-diastolic motion of the anterior and posterior wall are displayed on the screen, and under these, the arterial diameter change curve, resulting from the sum of the two previous ones, is displayed as well.

This system was taken over by Esaote and is an integral part of some ultrasound machines offered by this company. A similar system has also been developed, and integrated into some of its ultrasound machines, by Aloka.

2.5.2 Arterial Compliance

We have seen that arterial compliance is given by the ratio between the change in diameter and the change in arterial pressure. Therefore, to be able to obtain an arterial compliance curve, simultaneous recording of pressure and arterial diameter change curves is needed.

The recording of the diameter change curve may be performed by means of the Wall Track System, while the pressure curve may be recorded by means of a transcutaneous high-fidelity arterial tonometer, like the PulsePen® device. Blood pressure and arterial diameter are simultaneously recorded and synchronization of

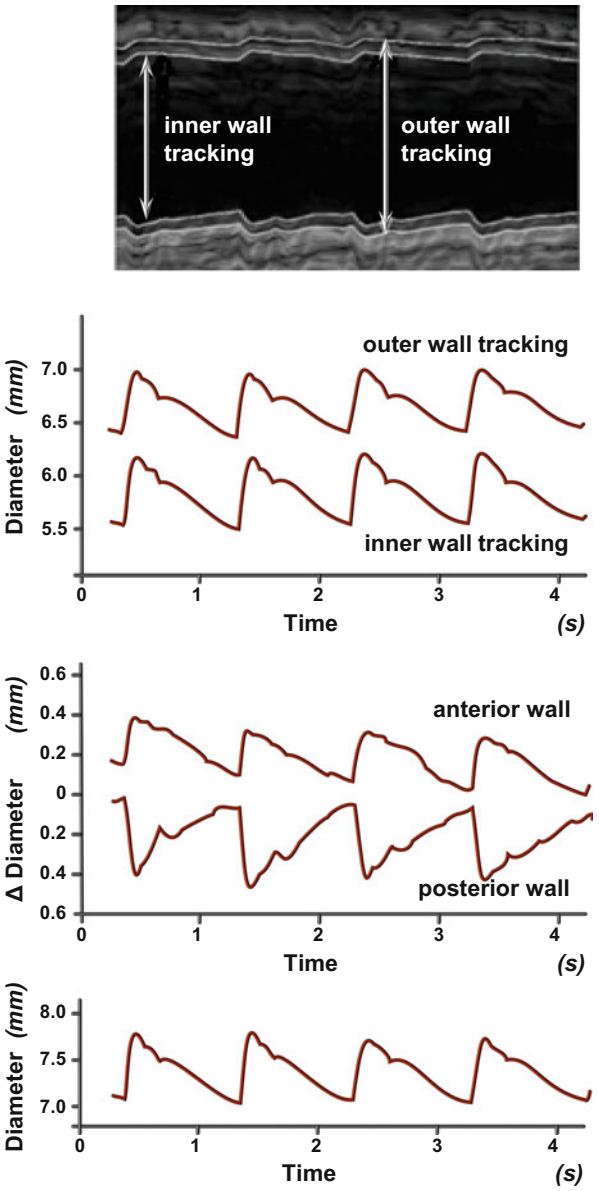

Fig. 2.40 Wall Track System: assessment of the arterial diameter change during a cardiac cycle by means of an ultrasound device

the two tracings (diameter and pressure) is achieved by superimposition of their respective ECG tracings. The great variability in the R′–R′ interval guarantees accuracy in this process. Obviously, the diameter/pressure curves, recorded in young subjects, are different from the ones in elderly subjects (Figs. 2.41, 2.42, and 2.43).

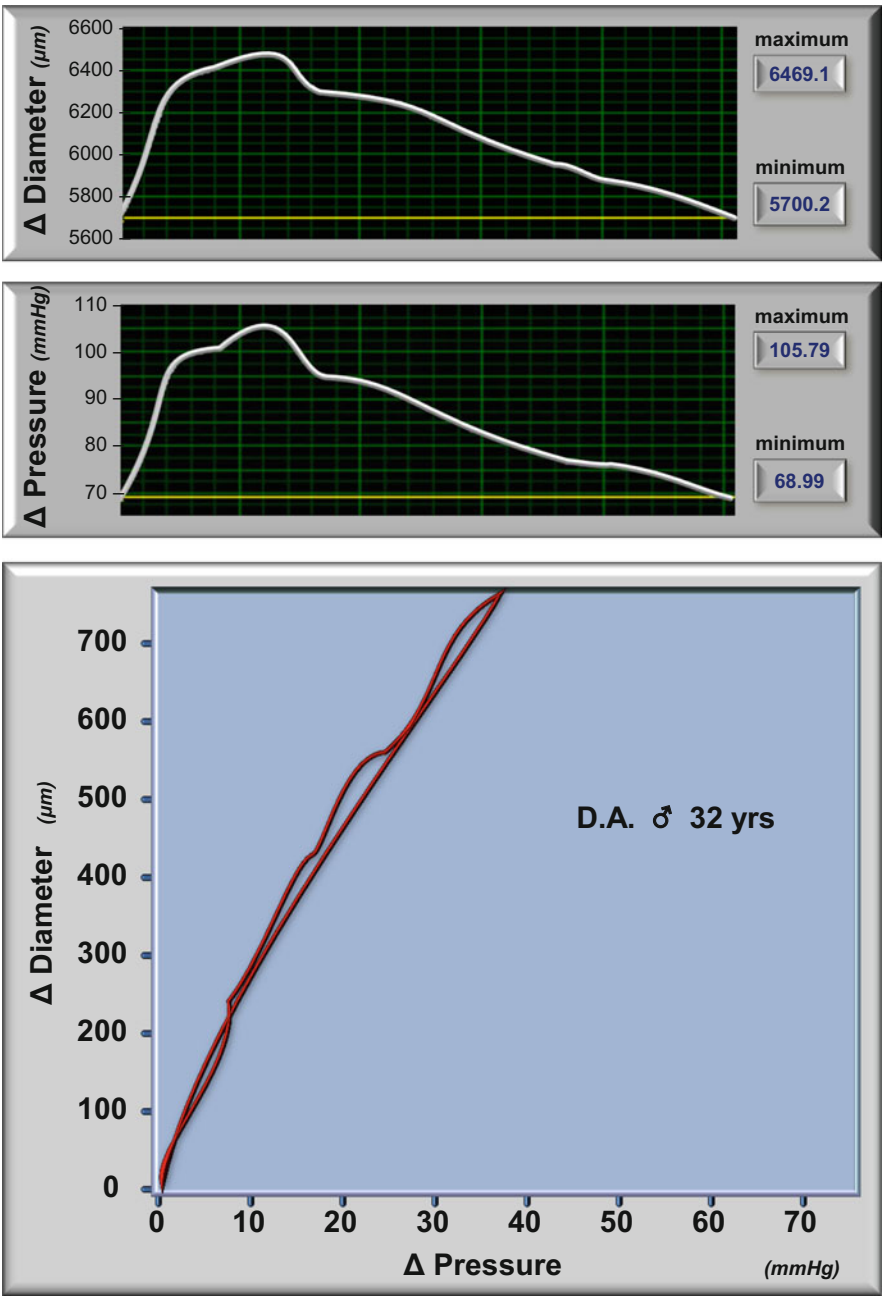

Fig. 2.41 Simultaneous recording in common carotid artery of diameter and pressure change in a 32-year-old subject and correlation curve between diameter and pressure during a cardiac cycle. The slope of the curve in the *lower panel* defines the arterial compliance

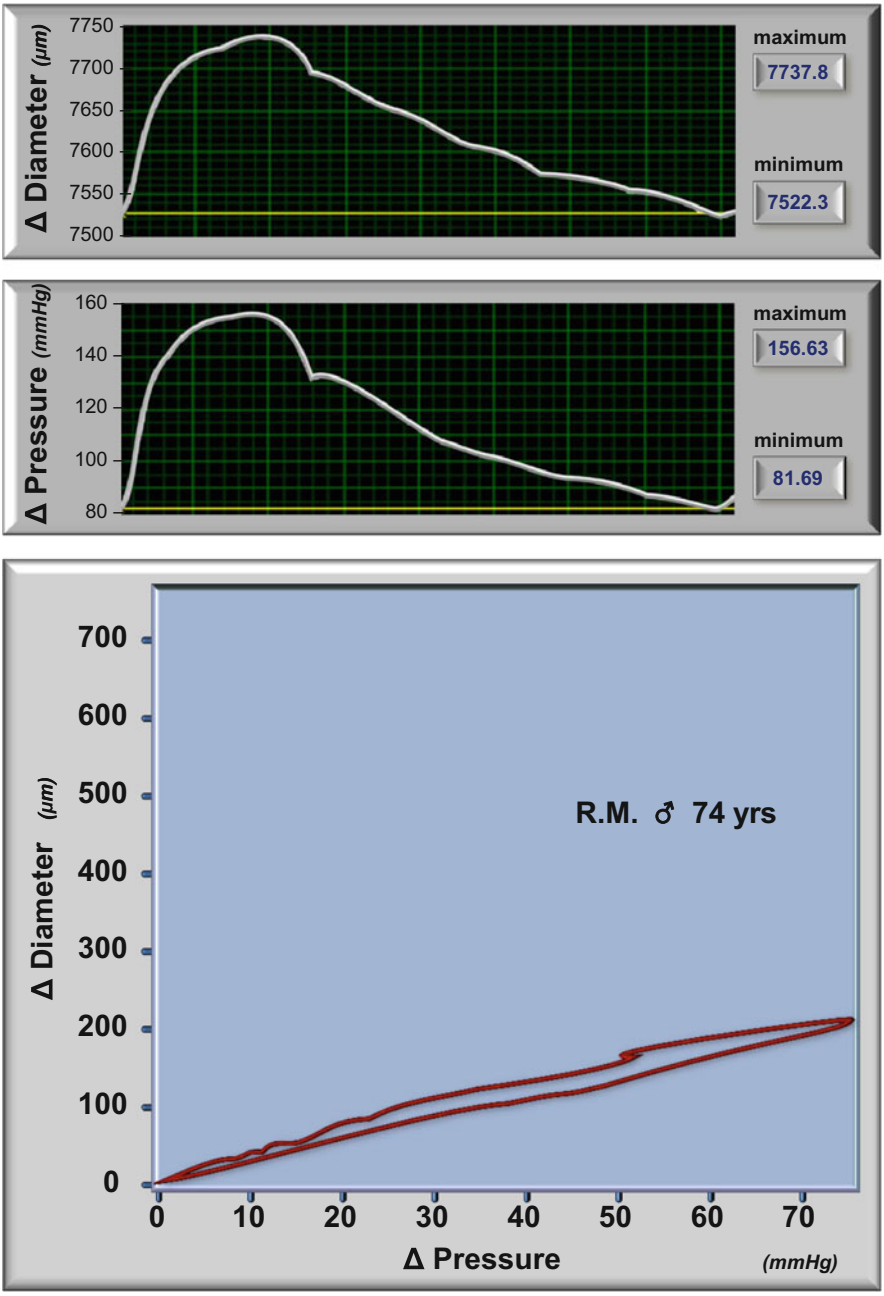

Fig. 2.42 Simultaneous recording in common carotid artery of diameter and pressure change in a 74-year-old subject and correlation curve between diameter and pressure during a cardiac cycle. The slope of the curve in the *lower panel* defines the arterial compliance

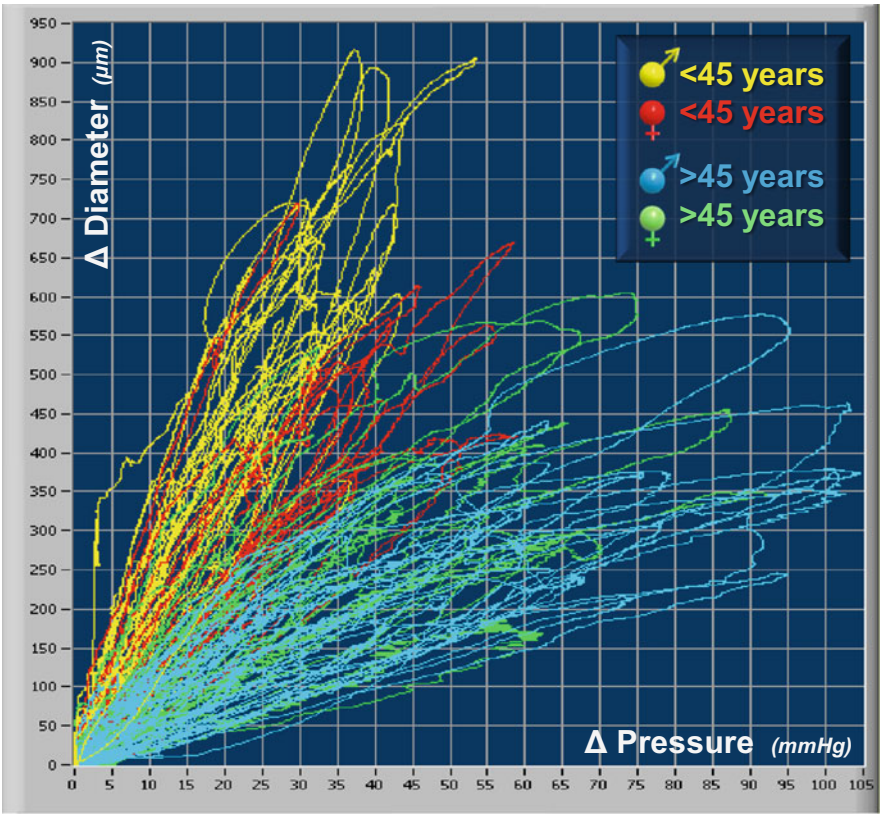

Fig. 2.43 Relationship between change in diameter and blood pressure during the cardiac cycle assessed in 80 subjects: 29 subjects younger than 45 years of age (males, *yellow line* and females, *red line*) and 51 subjects older than 45 years of age (males, *blue line* and females, *green line*). Diameter and pressure change curves were recorded simultaneously in the common carotid artery. The slope of the curve defines arterial compliance

The slope of the diameter and pressure ratio is defined for each segment; the higher the diameter and pressure ratio (index of arterial compliance), the higher the slope. For every cardiac cycle, it is possible to define:

- The slope of the entire systo-diastolic cycle of the diameter-pressure ratio
- The area defined by the curve of the diameter-pressure ratio of the entire systo-diastolic cycle
- The slope of the ascending and descending phases of the diameter-pressure ratio, which correspond to the compliance of the systolic and diastolic phases, respectively

Pills for Growing

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Arterial Stiffness and Blood Pressure Variability

3

3.1 Blood Pressure Variability

"Blood pressure variability" refers to the spontaneous instability of arterial blood pressure values over short- and long-term periods of time. The easiest way to evaluate blood pressure changes is to assess the size of the standard deviation relative to a set of data. Consequently, the standard deviations of systolic, diastolic, mean arterial blood pressure, and pulse pressure values can be analyzed separately.

Blood pressure variability consists of different components, which can be assessed over time intervals of different widths and with different methods:

1. *Long-term visit-to-visit blood pressure variability*, assessed with repeated office blood pressure measurements or home blood pressure monitoring
2. *Mid-term blood pressure variability*, assessed day-by-day using home blood pressure monitoring
3. *Short-term blood pressure variability* (assessed over a 24-hour period), using a 24-hour ambulatory blood pressure monitoring (ABPM)

   The standard deviation of the mean of the values obtained by multiple measurements over 24 hours reflects short-lasting blood pressure changes. It is also strongly influenced by the amount of day–night blood pressure changes. This is the reason why additional more specific indices of short-term blood pressure variability, able to avoid the contribution to overall variance of nocturnal blood pressure fall, may be computed. They may refer to:
   (a) The standard deviation of daytime blood pressure
   (b) The standard deviation of nighttime blood pressure
   (c) "Weighted" 24-hour blood pressure standard deviation, defined as the mean of daytime and nighttime blood pressure standard deviation weighted by the duration (in number of hours) of each time period
   (d) Average real variability (ARV) of 24-hour blood pressure, defined as the average of the absolute differences of consecutive measurements. ARV better predicts cardiovascular risk in hypertensive patients in comparison

P. Salvi, *Pulse Waves*, DOI 10.1007/978-3-319-40501-8_3

with the traditional standard deviation of short-term blood pressure variability
4. *Very short-term blood pressure variability*, assessed by means of continuous beat-to-beat blood pressure recordings.

Each of these blood pressure variability components has been related to the development or the progression of hypertensive target organ damage and to an increased risk for cardiovascular events and mortality.

3.2 Blood Pressure Variability and Cardiovascular Risk

Hypertension is considered to be the major risk factor for cardiovascular events and mortality. We have already seen that blood pressure has two distinct but interdependent components:

1. Mean arterial pressure, depending on cardiac output and systemic vascular resistance, and
2. Pulse pressure, depending mainly on the viscoelastic properties of large elastic arteries, which represents the fluctuation in pressure values around the mean value of blood pressure.

We can consider blood pressure variability as a third component characterizing blood pressure properties (Fig. 3.1).

These three components of blood pressure must be considered in the clinical assessment of patients. None of them must be overlooked. Let us try to better understand the importance of them. Suppose you live in Venice (Table 3.1). Venice is a wonderful Italian city, which is built on water and is situated on the Adriatic Sea. The streets of Venice are made of canals, and cars are, therefore, replaced by boats and motor-boats. Residents in Venice have always had a very close relationship with the sea and when sea level rises, life is difficult there.

If you live in Venice, you must, therefore, be aware of tides, i.e., the average sea-level, and you cannot ignore either wave motion, i.e., the vivacity and width of the waves traveling to town, or the waves produced by motorboats, steamboats, or cruising ships. Similarly, in the clinical assessment of our patients, we cannot only take into account mean arterial pressure value (tide), but we must also consider the dynamic variation in blood pressure values with respect to mean arterial pressure value (wave motion) and daily changes in mean and pulse pressures (wave motion created by motorboats).

Actually, cardiovascular risk is not only related to an increase in arterial pressure values but also to a degree of short-term blood pressure variability, unrelated to average values of systolic or diastolic blood pressure. The extent of fluctuations of blood pressure over time may provide additional, independent prognostic information compared with both isolated office readings and average ambulatory blood pressure levels, respectively. Prospective studies have clearly demonstrated that

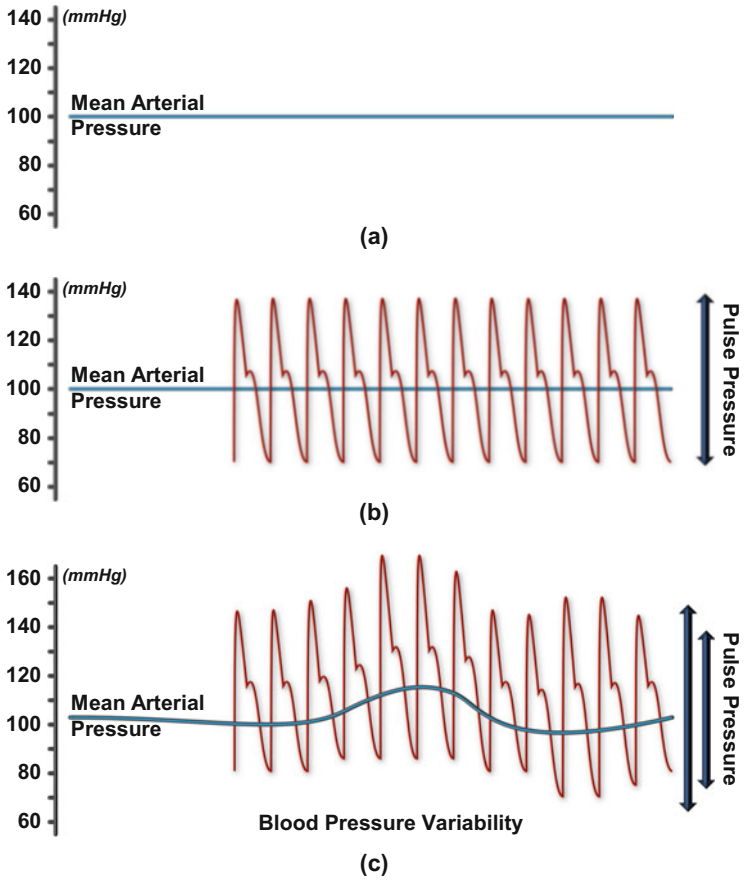

Fig. 3.1 The three components characterizing blood pressure properties. (**a**) Mean arterial pressure, the steady component. (**b**) Pulse pressure represents the fluctuation in pressure values around the mean value of blood pressure. (**c**) Blood pressure variability represents spontaneous oscillations of mean arterial pressure and pulse pressures over short-term and long-term periods

Table 3.1 Similarities between the factors affecting blood pressure values and those affecting sea level in Venice

	Sea	Blood pressure
Steady condition	Tide	Mean arterial pressure
Dynamic condition	Wave motion	Pulse pressure
Variable dynamic condition	Change in the width of waves coming from boats	Blood pressure variability

short-term blood pressure variability is an independent predictor of the progression of subclinical organ damage, cardiovascular events, and cardiovascular mortality [1–3]. These clinical studies support the concept that the adverse cardiovascular

consequences of high blood pressure depend not only on mean blood pressure values but also on fluctuation of blood pressure values.

3.3 Baroreflex Sensitivity and Arterial Stiffness

Blood pressure variability is a physiologic expression of spontaneous cardiovascular regulation and reflects sympathetic activation, the effectiveness of cardiovascular baroreflex modulation, as well as the effects of other intrinsic and environmental factors including physical exercise and emotional stress [4]. The baroreflex modulation of cardiovascular homeostasis affects changes in sympathetic activity, causing reflex changes of arterial tone and modifications of cardiac output (including vagally mediated changes in heart rate). The arterial baroreflex buffers blood pressure fluctuations, mainly by controlling peripheral resistance.

The baroreflex is the most important mechanism for short-term control of blood pressure. This reflex system consists of baroreceptor stretch receptors located in the wall of the aortic arch and in the carotid sinus, at the origin of the internal carotid artery (Fig. 3.2). Afferent influences originating from the stretch receptors in the carotid sinus ascend to the medulla (nucleus tractus solitarius) via the glossopharyngeal nerve (cranial nerve IX), whereas afferent influences originating from the aortic receptors ascend via the vagus nerve (cranial nerve X).

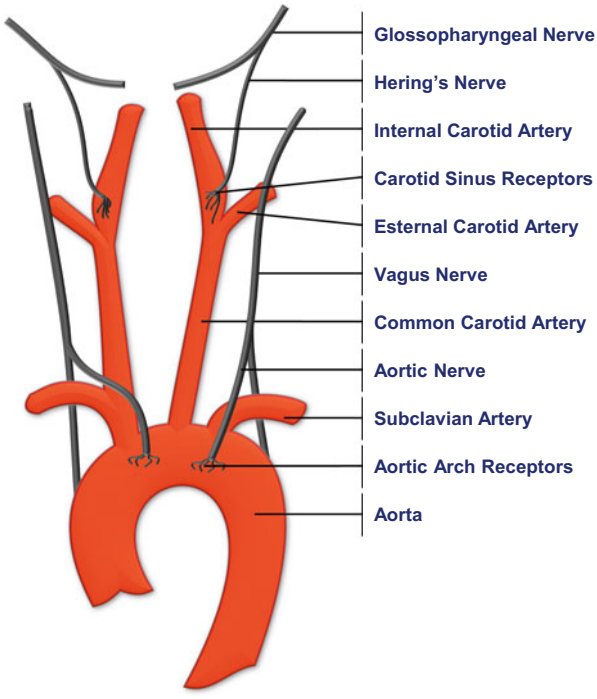

Fig. 3.2 Location and innervations of arterial baroreceptors

The efferent pathways of the baroreflex involve the parasympathetic and sympathetic nervous systems. A reduction in arterial blood pressure reduces afferent input to the medulla, which leads to increased sympathetic and reduced parasympathetic output.

By adjusting systemic vascular resistance, these efferent pathways cause an increase in blood pressure. On the contrary, a rise in arterial blood pressure increases afferent input to the medulla, decreases sympathetic and increases parasympathetic output, causing a decrease in blood pressure. This blood pressure buffering mechanism reduces blood pressure excursions; the buffering action may well be considered the primary function of the arterial baroreflex.

Actually, the aortic arch and carotid arteries are prevalently elastic vessels, particularly responsible for arterial stiffness (arteriosclerosis phenomena). It is important to highlight that arterial baroreceptors respond to the extent of stretching/relaxation of carotid/aortic arterial walls, rather than directly to changes in blood pressure values themselves. Thus, in subjects with increased arterial stiffness, whose vessels distend less than more elastic vessels in response to blood pressure changes, baroreflex responsiveness will be reduced. This means that the arterial baroreflex function is significantly affected by the degree of distensibility/stiffness of arterial walls, which in turn determines the degree of stretching/relaxation of carotid/aortic walls triggered by blood pressure fluctuations (Fig. 3.3).

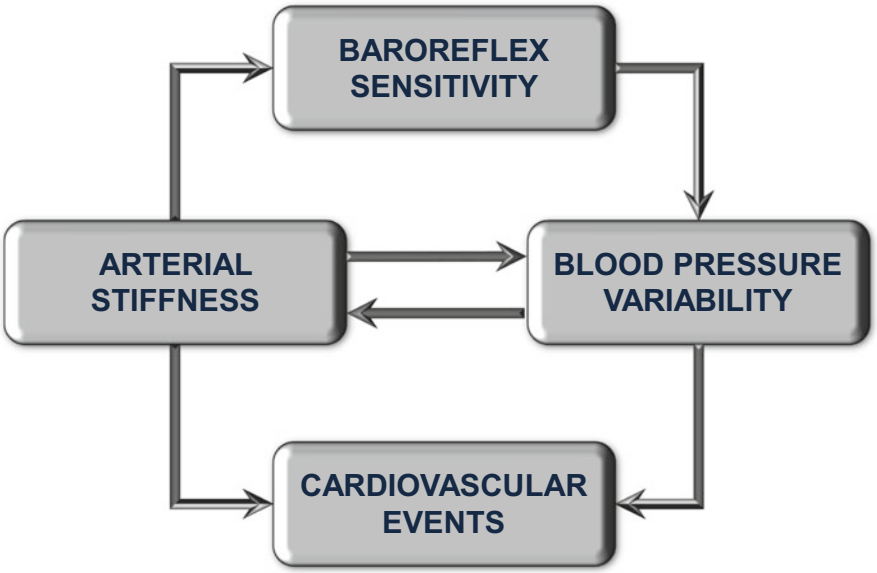

Fig. 3.3 Relationship between arterial stiffness, blood pressure variability, and baroreflex sensitivity

This reasonable pathophysiological hypothesis was supported by studies showing that, in humans, increased local carotid stiffness may be associated with reduced cardiovagal baroreflex sensitivity. A rigid carotid and aortic wall was found to be responsible for a reduced stimulation of arterial baroreceptors located in these vascular areas by pulsatile blood pressure, with a consequent reduced sensitivity of the baroreflex and its resulting reduced efficacy in buffering blood pressure fluctuations.

The development of noninvasive techniques for the study of arterial viscoelastic properties has made it possible to investigate more in depth the relationship between arterial wall stiffness and baroreflex function. A significant inverse correlation between sympathetic baroreflex sensitivity and the degree of carotid stiffness has been clearly demonstrated, as well as between sympathetic baroreflex sensitivity and aortic stiffness, as assessed by carotid–femoral pulse wave velocity.

Apart from the baroreflex control of blood pressure, to some extent blood pressure variability may be directly influenced by large artery mechanics. The passive effects of arterial mechanical properties clearly influence blood pressure pulsatile behavior, so that in a stiff arterial system, an increase in blood pressure produces wider blood pressure fluctuations, compared to what occurs in an elastic arterial system. This phenomenon can be understood by considering the *windkessel* properties of the large arteries. In a stiffer model, stroke volume cannot be properly cushioned, and an increase in systolic blood pressure is accompanied by a reduction in diastolic blood pressure, resulting in a wider pulse pressure. Considering the physiological variations in stroke volume over the 24 hours, short-term systolic blood pressure variability will be, therefore, amplified in the presence of increased large arteries stiffness.

Relevant determinants of short-term blood pressure variability are, therefore, both the active mechanisms involved in the reflex closed-loop control of blood pressure (i.e., the arterial baroreflex) and the passive mechanical elastic properties of large conduit arteries. These mechanisms are inextricably intertwined each other and with other factors, influencing blood pressure variations in vivo, such as mechanical (e.g., ventilation), neurohumoral, and psychological factors, and may contribute to modify blood pressure variability in a complex manner in response to environmental stimulations.

The relationship between short-term 24-hour blood pressure variability and arterial stiffness, assessed as carotid–femoral pulse wave velocity, has been clearly demonstrated and confirmed after excluding multiple confounding factors and survived after accounting for differences in average blood pressure levels, thus, demonstrating the independence of this association from office and 24-hour average blood pressure [5]. As it is possible to define blood pressure variability in different ways, various measures of blood pressure variability were explored. The stronger association with carotid–femoral pulse wave velocity was found with measures of blood pressure variability focusing on short-term changes of systolic blood pressure, such as average real variability (i.e., the average difference between successive blood pressure measurements over 24 hours) and weighted 24-hours standard deviation (i.e., the average of daytime and nighttime standard deviation separately

considered and weighted for the different duration of daytime and nighttime, a calculation which, therefore, excludes the influence exerted on 24 hour standard deviation by day–night blood pressure changes). Indeed, both these measures of short-term blood pressure variability are free from any influence by the degree of day–night blood pressure changes. Several studies showed that no measure of diastolic blood pressure variability is associated with arterial stiffness, which is not surprising if we consider that, with large-artery stiffening, diastolic blood pressure is progressively lower and less modulated.

3.4 Age, Mean Blood Pressure, and Blood Pressure Variability

As it is difficult, in vivo, to separate the active and passive mechanisms involved in the control of blood pressure, the effect of large artery mechanics on blood pressure variability has been studied by the research group directed by Alberto Avolio [6] in a simulated model of systemic circulation. This model has also allowed us to explore the blood pressure dependency of arterial properties as the stiffness of large arteries increases with an increase in distending pressure. This pressure-dependency property of arterial stiffness is lost with advancing age (Fig. 3.4). Simulations performed in such a model showed that systolic blood pressure variability is dependent on the degree of pressure dependency of arterial stiffness. Interestingly, in this model, the relationship between mean blood pressure and systolic blood pressure variability seems to be U-shaped, with an optimal mean arterial pressure for minimal systolic blood pressure variability. This optimal mean blood pressure increases with advancing age (Fig. 3.5). The findings of this modeling study suggest that the hemodynamic effect of age-related increases in large artery stiffness is an increase in blood

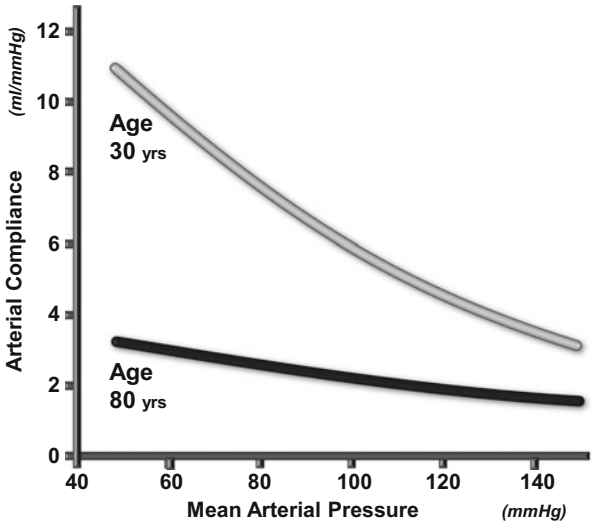

Fig. 3.4 Exponential relation between aortic compliance and mean blood pressure for people aged 30 (*gray line*) and 80 (*black line*) [7]

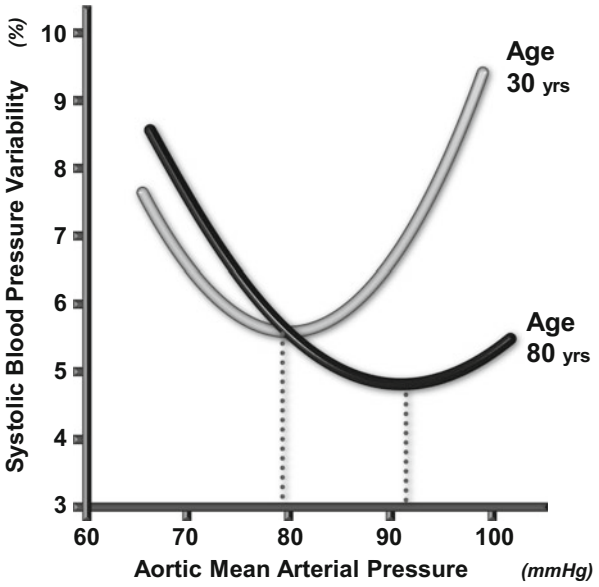

Fig. 3.5 Simulation of systolic blood pressure variability as a function of mean blood pressure with change in pressure dependency on arterial compliance. The *dot lines* show the critical mean pressure for minimal systolic blood pressure variability for people aged 30 (*gray line*) and 80 (*black line*): with aging, the critical pressure, where blood pressure variability is minimal, is higher [6]

pressure variability in the elderly as compared to the youth, when exposed to the same blood pressure levels.

Potentially, this effect may have important implications in hypertension treatment as excessive pressure drop could paradoxically increase blood pressure variability, particularly in the elderly. In the light of these considerations, it remains to be shown whether it may be appropriate to set blood pressure targets based on age or on arterial stiffness parameters.

Finally, it is clear that arterial stiffness and short-term blood pressure variability are closely interrelated phenomena. A reduced baroreflex sensitivity, which is a characteristic feature of autonomic cardiac modulation in hypertension, might be one of the factors, together with the accompanying increase in arterial stiffness, responsible not only for the increased blood pressure variability typical of hypertensive subjects but also for the higher speed of changes in beat-to-beat systolic blood pressure fluctuations reported to occur in hypertensive patients as compared with normotensive individuals. The effects of changes in baroreflex sensitivity on blood pressure variability should be considered in the context of the complex interaction among different mechanisms involved in cardiovascular regulation, including, among them, chemoreflex influences, which may play a major role in conditions of hypoxia exposure.

In conclusion, the increasing evidence for a significant association between short-term blood pressure variability and arterial stiffness emphasizes the importance of changes in arterial wall properties, in relation to the effectiveness of cardiovascular control mechanisms and to the degree of hemodynamic fluctuations (Fig. 3.6). These findings may suggest that paying attention to mean blood pressure

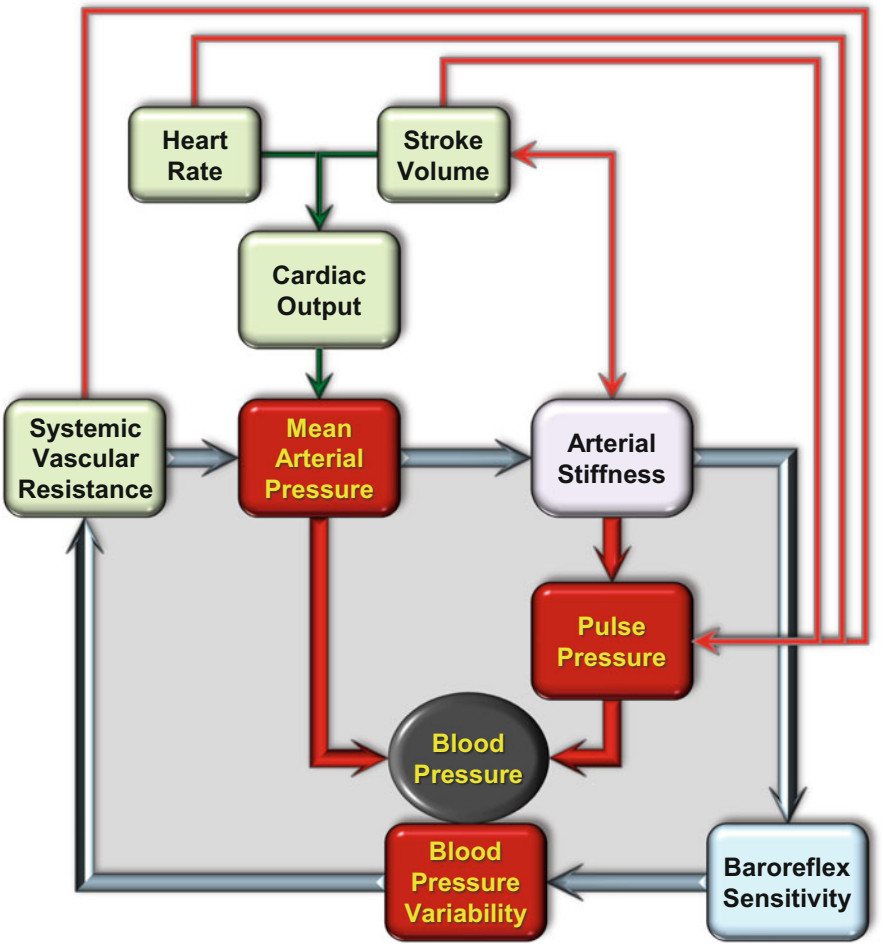

Fig. 3.6 Factors defining blood pressure. The three main components are mean arterial pressure, pulse pressure, and blood pressure variability. The diagram stresses the role of blood pressure variability

levels in the management of patients with arterial hypertension may not be enough to achieve cardiovascular protection. To this aim, an additional assessment of the degree of blood pressure variability and, at the same time, of the degree of arterial stiffness appears to be clinically relevant.

Pills for growing

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Central Blood Pressure: Part 1, Pathophysiology

4

"Central arterial blood pressure" is the term commonly used to describe blood pressure in the ascending aorta, on leaving the left ventricle.

At the beginning of the new millennium, some studies had already pointed out the importance of central systolic blood pressure and of central pulse pressure (central systolic blood pressure—diastolic blood pressure) as cardiovascular prognostic factors, much more significant than peripheral blood pressure values measured in the brachial artery by means of traditional sphygmomanometers.

However, it was only after the Conduit Artery Functional Evaluation (CAFE) study published its outcomes that central systolic blood pressure started to be in the spotlight.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) had stressed a greater reduction in cardiovascular events in patients treated with calcium channel blockers (amlodipine) compared with patients treated with β-blocker (atenolol), without any difference being noted in the reduction of brachial systolic blood pressure values between the groups treated. The CAFE study, a branch of the ASCOT study, supplied reasonable arguments to explain this more marked reduction in cardiovascular events in subjects treated with vasodilators (Fig. 4.1) [1]. More than 2000 subjects, taking part in the ASCOT study, were measured for central blood pressure. The CAFE study showed that the decrease in central systolic blood pressure and in central pulse pressure was greater in subjects taking some vasodilators with respect to those treated with non-vasodilator drugs (diuretic or β-blocker), despite similar brachial systolic blood pressures (Fig. 4.1). On the basis of the same brachial blood pressure, in the group treated with amlodipine, central systolic blood pressure was much lower compared with the group treated with atenolol. Therefore, the authors concluded that the greater reduction in cardiovascular events in the group treated with vasodilators could be caused by a greater effect of these drugs in lowering central systolic blood pressure, with respect to β-blockers. In conclusion, it is reasonable to infer, from the outcomes of the CAFE study, that peripheral blood pressure is not always the best method to assess the effects of drugs on blood pressure and that central systolic blood pressure and

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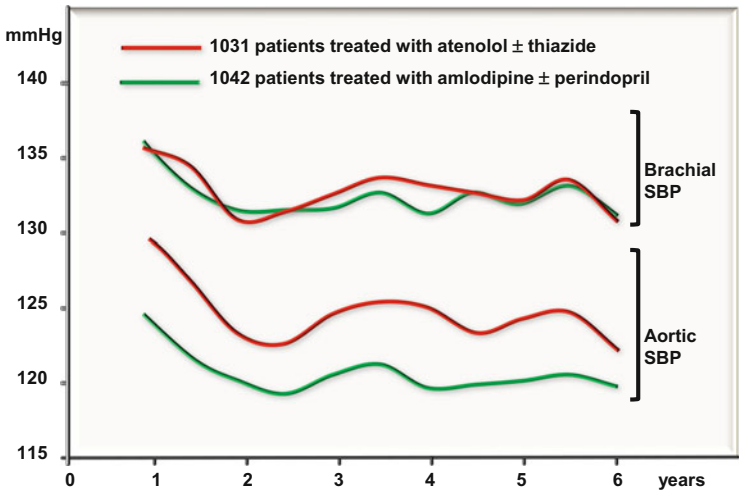

Fig. 4.1 Outcomes of the CAFE study [1]. The two *upper lines* refer to systolic blood pressure values recorded in the brachial artery; the two *lower lines* refer to central systolic blood pressure values

central pulse pressure are able to evaluate the real load imposed on the left ventricle much better than peripheral systolic blood pressure and peripheral pulse pressure.

Assessment of central arterial pressure values is important because of the difference between peripheral and central blood pressure values. It is well known that mean arterial pressure is characterized by relative "steadiness" in the arterial tree. In other words, it tends to remain constant along the arterial system, from the ascending aorta to peripheral arteries. Diastolic blood pressure behaves in the same way: the difference between central and peripheral diastolic blood pressure values is insignificant (usually below 1 mmHg in the brachial artery in relation to the ascending aorta). On the contrary, peripheral systolic blood pressure values (in the radial, brachial, and femoral arteries) are higher than the ones measured in the ascending aorta. In fact, the difference between blood pressure in the aorta and in the brachial artery is, on average, about 15 mmHg, but even higher differences can be recorded, up to 40–50 mmHg in young adults. This is called the "amplification phenomenon of arterial pressure".

However, don't you think that this phenomenon is rather weird? Do you think it is normal that a hydraulic circuit, like the hemodynamic circuit, has blood pressure values lower just after the pump (on leaving the left ventricle) with respect to the periphery? Don't you consider all this to be strange? Tell me in what mechanical system conceived by human beings, the magnitude of the force at the periphery of the system is greater than the one near the engine. Let us consider an ordinary grass watering system made up of a pump and a hosepipe. It is obvious that the pressure exerted by the water gradually decreases as we leave the pump. Well, do you think it is normal that, in the cardiovascular system, on the contrary, the pressure in the

peripheral arteries is higher than near the cardiac pump? How can this phenomenon be explained?

The study of the role of wave reflections can help to explain this amplification phenomenon of arterial pressure.

4.1 Reflected Waves

In the first part of this book, we have seen that blood pressure is changed and modulated by the viscoelastic properties of the aorta and large arteries.

Then, we investigated the clinical significance of arterial stiffness and the evolution of the pressure waveform resulting from the interaction between the heart and large arteries.

However, the relationship between the left ventricle and the aorta cannot explain, in itself, all the phenomena defining blood pressure values and the blood pressure waveform. Therefore, let us now introduce the second parameter characterizing pulse pressure: wave reflections.

The existence of reflected waves is typical of any hydrodynamic system but with different expressions. The concept of wave reflection can be easier to understand if we consider what happens when we drop a stone into the center of a basin full of water (Fig. 4.2). From the point where the stone impacts, a concentric wave is created and travels towards the edges of the container. Here, the wave does not stop, but when it hits the external edges, it creates a wave, which moves back towards the center of the basin. This is a "reflected wave".

Now, if we drop a series of stones, at regular intervals of one second, into the center of our basin, we can see that the backward waves to the center superimpose on the centrifugal waves generated directly by the next stone falling into the basin, generating much larger waves (Fig. 4.3). Therefore, the amplitude of the resultant wave will be defined by the sum of the amplitude of the forward wave and the backward wave.

Let us consider another example that can help explain the idea of wave reflections. Think about ocean waves breaking on the rocks and then going back seawards. These waves add to the next ones, generating higher and higher waves, which are the result of the sum of the waves coming from the ocean and the backward waves coming from the rocks.

The arterial system behaves like any other hydrodynamic circuit in this regard, where the wave generated by the activity of an intermittent pump (heart) travels down a pipe (the aorta, arteries, arterioles, capillaries, etc.). At reflection sites, reflected waves are generated and travel towards the center of the system.

However, in the arterial system, reflected waves arise and travel in a very particular way. The circulatory system has three features: (a) it is a closed circuit, (b) it is small sized, and (c) pressure waves travel quickly, on the order of 4–30 m/s, as we have already seen in the chapter on pulse wave velocity (Chap. 2). This is the reason why wave reflection does not affect the next wave (as is the case for the stone in the basin, or the wave on the rocks), but rather the backward wave superimposes

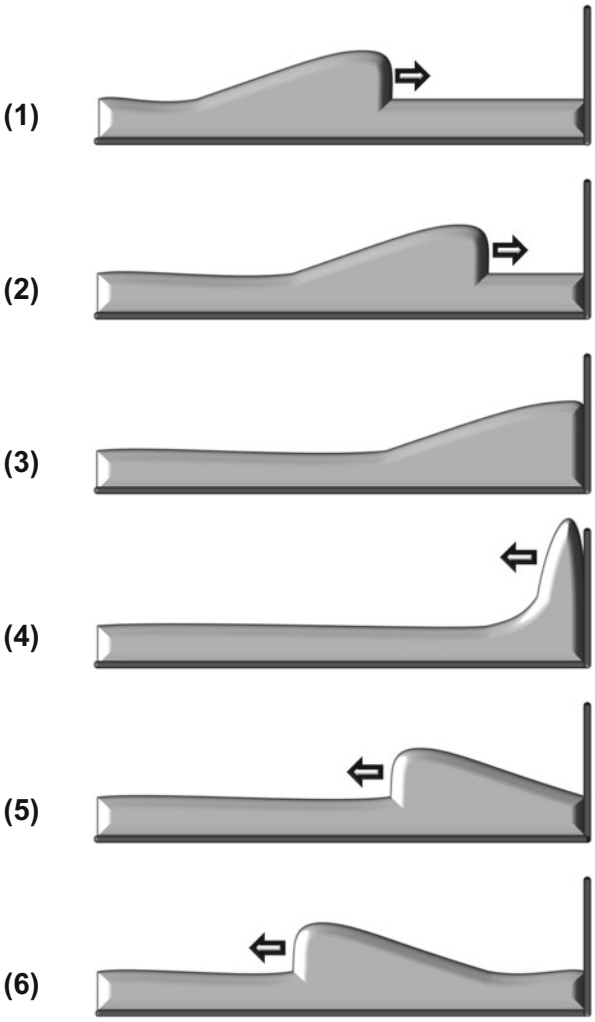

Fig. 4.2 Generation of a single reflected wave

on the same forward wave generating it, therefore, having repercussions for the whole pressure waveform. Figure 4.4 helps us have a better understanding of these important features on the hemodynamics of the cardiovascular system. As a consequence, arterial blood pressure results from the sum of a forward (centrifugal) pressure wave and backward (centripetal) pressure waves.

$$\text{Blood pressure wave} = \text{Forward pressure wave} + \text{Backward pressure wave}.$$

Wave reflection is very important and must be taken into consideration, as it is a proven fact that the magnitude of the reflected wave may be until 80–90 % that of the forward wave.

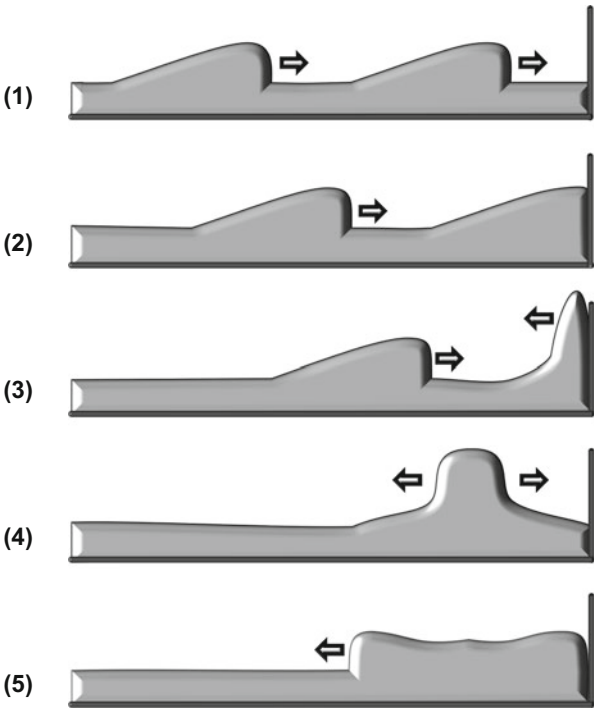

Fig. 4.3 Backward waves arising and superimposition of forward and backward waves

4.2 Reflection Sites

In the cardiovascular system, there are some well-defined sites from which reflected waves arise:

1. Arterial bifurcations
2. Atherosclerotic plaques, causing arterial narrowing or obstruction
3. Terminal arterioles, which define the systemic vascular resistance

4.2.1 Arterial Bifurcations

Important reflection sites are arterial bifurcations (Fig. 4.5). In the presence of a bifurcation, not only does the forward wave (FW) divide into two single centrifugal waves (FW_a and FW_b), but it also generates a centripetal backward wave (BW). The amplitude of these waves is related to the angle of bifurcation and to the caliber of the secondary branches, which arise from the main artery.

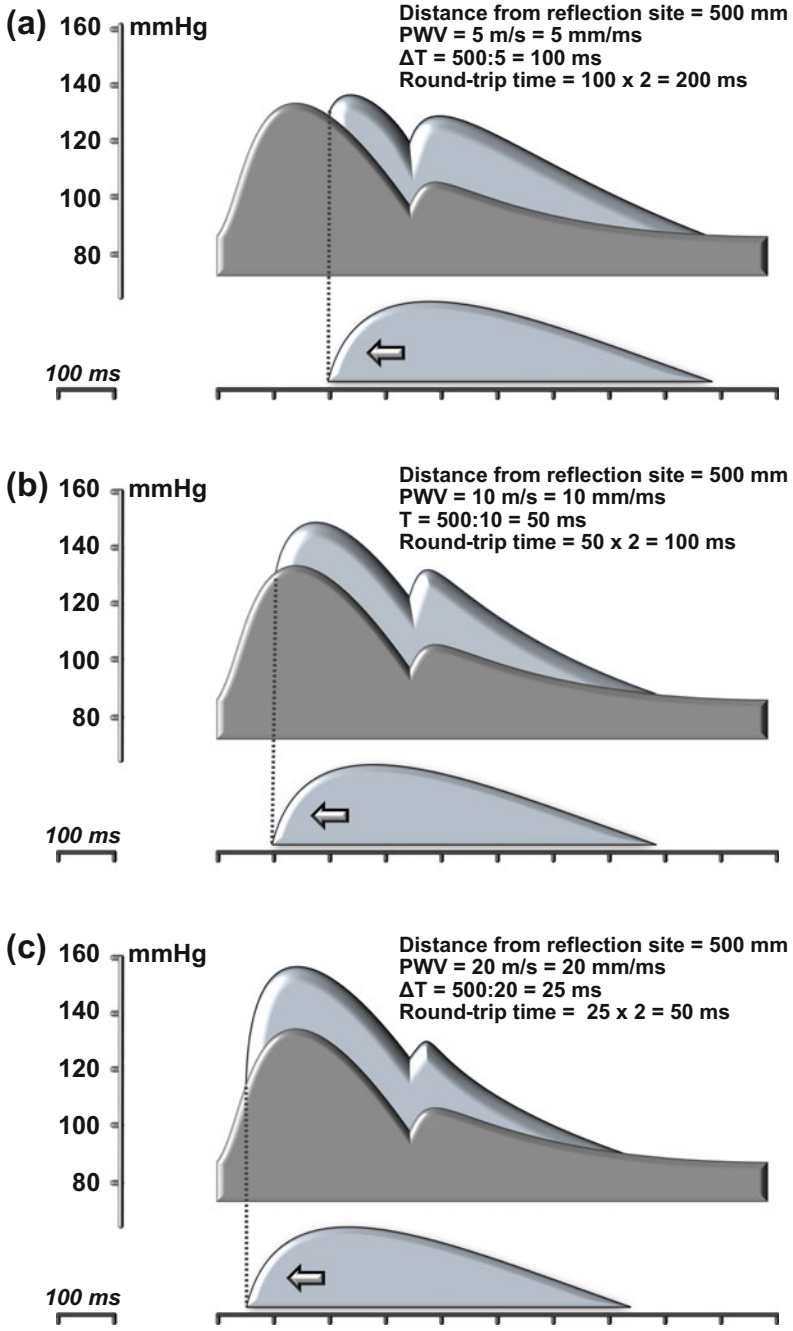

Fig. 4.4 Superimposition of backward waves on the forward pressure wave in the ascending aorta: illustrative models. Each figure shows the forward (*centrifugal*) pressure wave (*dark gray*), the backward (*centripetal*) pressure wave (*light gray*, at the *bottom* of each picture), and the

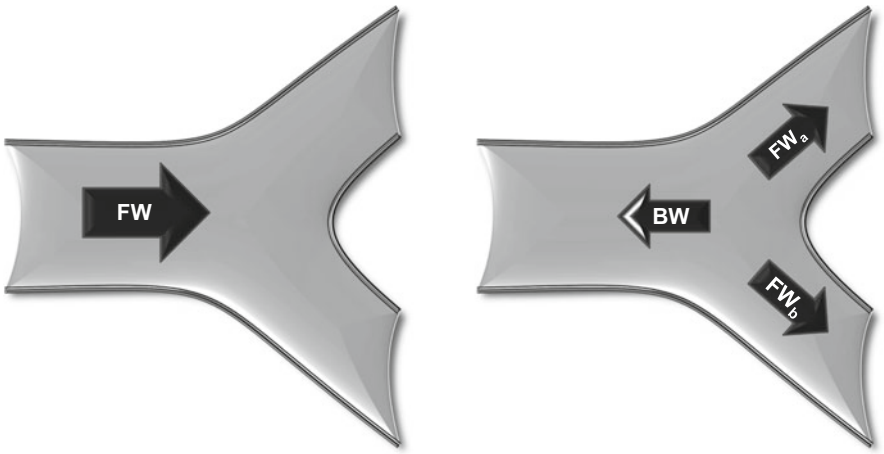

Fig. 4.5 Reflected wave generated by arterial bifurcation

4.2.2 Atherosclerotic Plaques

Atherosclerotic plaques, causing arterial narrowing or obstruction and segmental alterations of the viscoelastic properties of arteries, are another reflection site (Fig. 4.6), relevant under hemodynamically significant stenosis and multifocal atherosclerotic vascular disease.

The forward wave (FW), next to an atheroma and vascular stenosis, divides into two components: a forward component, which continues its journey through the arterial system in a centrifugal way, and a component which, on the contrary, is sent back to the heart (BW) by the endoluminar obstruction.

Fig. 4.4 (continued) superimposition of both the forward and backward waves. In fact, it is well known that there are a number of reflection sites, but, in this scheme, given for illustrative purpose, only one reflection site has been considered and it is placed at 500 mm from the registration point. The heart rate is 60 beats/min (cardiac cycle = 1000 ms). The backward wave delay time has been considered under different arterial stiffness conditions. (**a**) In normal viscoelastic properties of the aorta, with a pulse wave velocity (PWV) of 5 m/s, the backward wave goes back to the ascending aorta 200 ms after the beginning of left ventricular ejection. The superimposition with the forward wave occurs in the meso-telesystolic phase and lasts almost for the whole diastolic phase. (**b**) With a PWV of 10 m/s, the forward and backward waves meet 100 ms after the beginning of the cardiac cycle. (**c**) In the presence of aortic stiffness, with a PWV of 20 m/s, the two waves meet very early (after 50 ms), and the superimposition with the forward wave occurs in the protomesosystolic phase and lasts almost for the whole systolic phase. The resulting shape of the pulse wave depends on the earliness of the superimposition onto the forward and backward waves

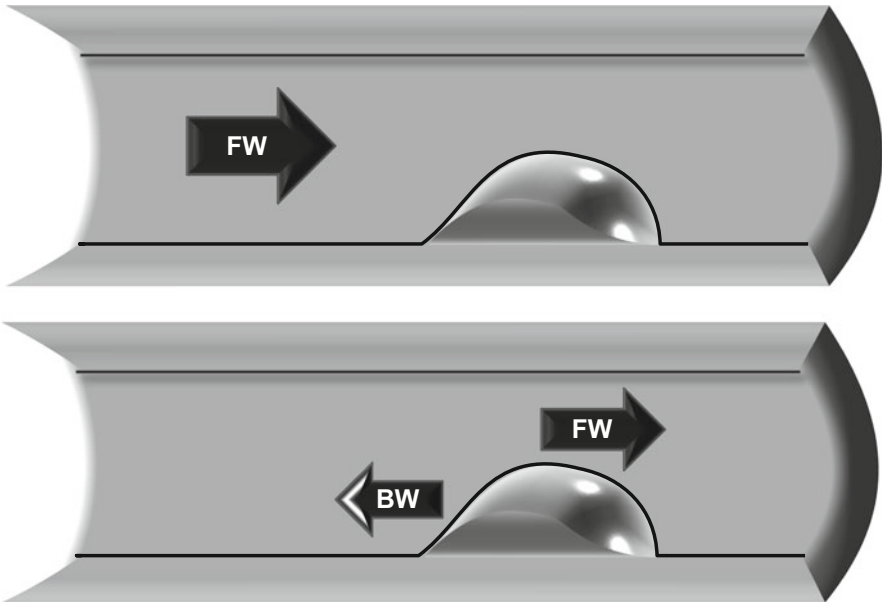

Fig. 4.6 Stenosis and arterial thrombotic phenomena generate reflected wave

4.2.3 Systemic Vascular Resistance

It is well known that resistance is directly proportional to viscosity (η) and inversely proportional to the fourth power of the radius (Hagen–Poiseuille law):

$$\text{Resistance} = \frac{8\eta l}{\pi r^4}$$

Therefore, the resistive properties in the large arteries are insignificant whereas vascular resistance is concentrated at the level of the precapillary arterioles (diameter < 150 μm). The arteriolar system represents a sort of narrowing of the arterial system, and, at this level, a sharp fall in blood pressure values occurs (Fig. 4.7).

The forward pressure wave, generated by the interaction between the heart and large arteries, travels through the arterial tree and, at the periphery of the cardiovascular system, breaks against the "wall" made up by peripheral vascular resistance. Here, a backward wave is generated, going to the heart and superimposing on the centrifugal (forward) wave.

It is likely that peripheral resistance is the major reflection site, and its importance is also linked to the possibility of changing and modulating reflected waves arising here, by means of pharmacological therapy.

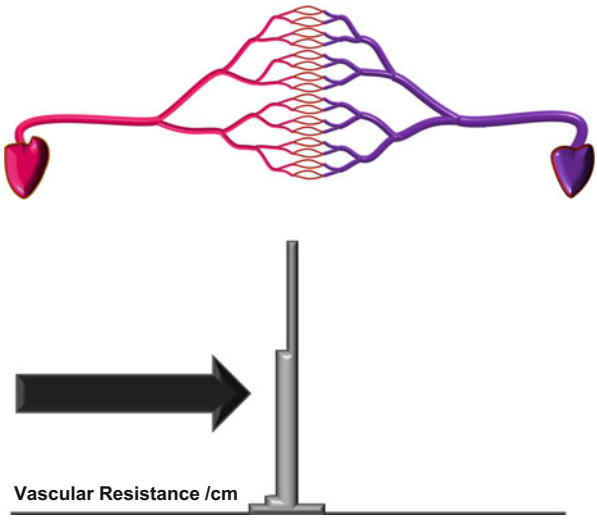

Fig. 4.7 Schematization of the cardiovascular system (*top*). Rapid increase of systemic vascular resistance in precapillary small-diameter arterioles (*bottom*)

4.3 Reflected Waves and Peripheral Blood Pressure

The superimposition of the forward pressure wave and backward waves is particularly important in the peripheral arteries, following the first bifurcations of the aorta, such as the femoral, brachial and radial arteries, i.e., those arteries where we usually measure blood pressure with traditional sphygmomanometers.

Peripheral arteries are close to the main sites of wave reflection (we are near the rocks on which the waves break), so that the superimposition of the forward and backward waves occurs very early during the systolic phase (Fig. 4.8).

As a consequence, the pressure peak will be strongly affected by backward waves, and the reflected component will strongly affect systolic blood pressure values. Therefore, systolic blood pressure in the peripheral arteries is mainly defined by the presence of wave reflection.

4.4 Reflected Waves and Central Blood Pressure

The pressure waveform always depends on the temporal relationship between the encounter and superimposition of the forward (centrifugal) pressure wave and backward (centripetal) pressure waves.

From the periphery of the arterial system, the backward wave "travels" centripetally towards the heart. In the ascending aorta, its encounter with the forward wave occurs at the end of the systolic phase, and the superimposition of the two waves lasts the whole diastolic phase (Fig. 4.9).

This occurs when the viscoelastic properties of large arteries are undamaged. Thus, the central blood pressure waveform shows the following consequences:

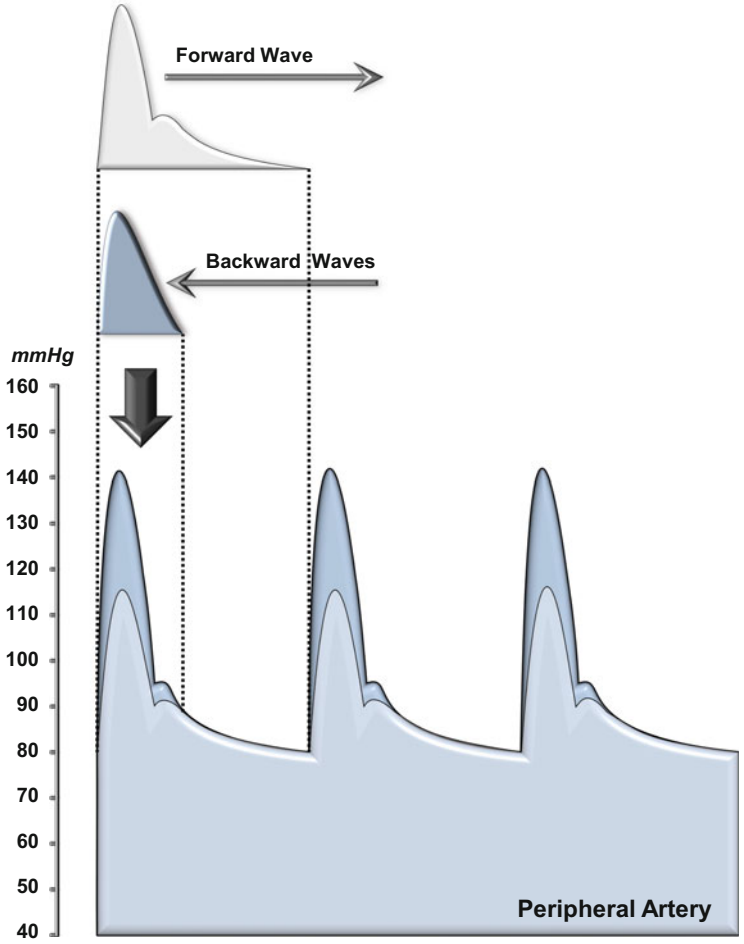

Fig. 4.8 Pressure waveform recorded in peripheral artery in a subject with undamaged viscoelastic properties of the arterial wall. Early superimposition of backward and forward pressure waves

- The peak systolic blood pressure is not affected by the backward waves, and the backward waves do not change systolic blood pressure values. Therefore, systolic blood pressure is only defined by the forward wave, i.e., by the heart–aorta interaction.
- Backward waves affect the diastolic phase of the cardiac cycle, so that the central pulse waveform, in diastolic phase, will appear full and convex.

To sum up, under normal physiological conditions, reflected waves play a positive role and have advantageous effects as they do not increase the left-ventricular afterload, maintaining high blood pressure values during the diastolic phase and supplying good coronary blood flow.

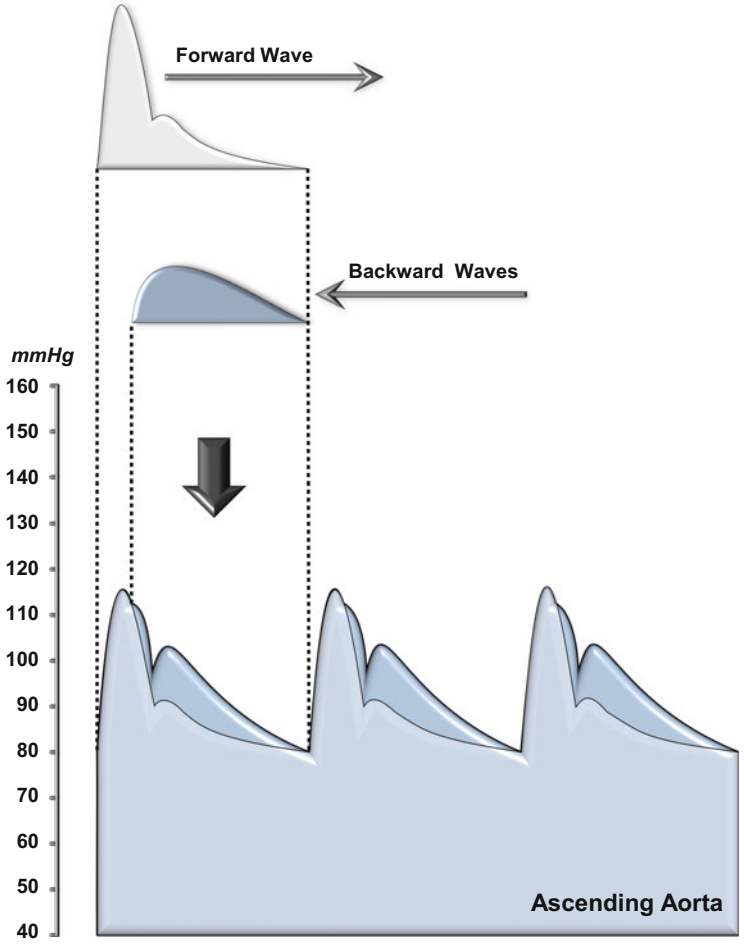

Fig. 4.9 Pressure wave recorded in the ascending aorta in a subject with undamaged viscoelastic properties of the arterial wall. The encounter between backward and forward waves occurs at the end of the systole, and the superimposition of the two waves lasts the whole diastole

4.4.1 Blood Pressure and Flow Velocity Waveforms

In the absence of the phenomenon of wave reflection, the behaviors of blood flow and pressure are closely connected: a given blood pressure corresponds to a given flow velocity, with a linear relationship. Let us imagine watering the grass of our garden; the stronger the water pressure, the faster the water flow coming out from the pump: this relationship is clearly linear.

In arteries, blood flow velocity and pulse waveforms are superimposable in the early systolic phase, but when reflected waves arise, this relationship tends to change and the close pressure-flow coupling is broken.

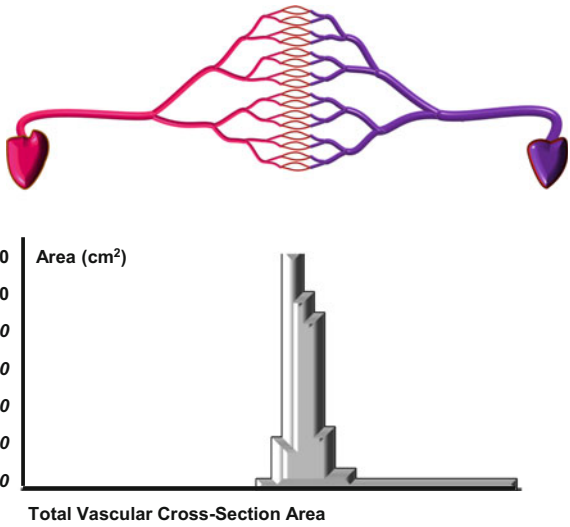

Fig. 4.10 Schematization of the cardiovascular system (*top*). Rapid capillary and precapillary increase of the cross-sectional area of all blood vessels (*bottom*)

The relationship of pressure and flow waves with respect to reflected waves is the exact opposite. It is well known that, in the capillary network, the total cross-sectional area becomes almost 600 times greater than the area in the large arteries, and blood flow velocity exhibits a clear fall (Fig. 4.10). The pressure wave has a totally opposite effect, it breaks against the wall of peripheral vascular resistance and generates reflected waves. The backward wave of flow, going back to the center, takes on a negative and symmetrical waveform in relation to the backward pressure wave, and when it superimposes on the forward wave, it creates a blood flow velocity waveform resulting from the subtraction of the backward wave from the forward wave.

In order to understand the different relationship of blood pressure and blood flow velocity in relation to reflected waves, close your eyes for a few minutes (after reading this paragraph, of course) and imagine that we are scuba diving. First we are swimming underwater, near a rocky coast where the sea is rough. Then we are offshore, chasing a shoal of multicolored fish. Then, we have to go back ashore. Waves are breaking on the rocks, generating reflected waves going offshore. We start swimming faster and faster. At every stroke, we advance, but when the force of the stroke created by the waves reflected from the rocks prevails, we are inevitably driven offshore. The stronger these reflected waves, the stronger our strokes, but we are driven offshore again at the end of each stroke. Now you can open your eyes and think. This is exactly what happens in our arteries: our strong stroke (systolic output) generates a forward motion of our body (both pressure and flow waves have the same steep and positive slope waveform) until we meet reflected waves from the rocks (at which point the pressure and flow waves diverge). We are driven offshore and we lose ground (the negative phase of the blood flow waveform curve), in spite of our effort. In short, we can consider blood flow velocity as the

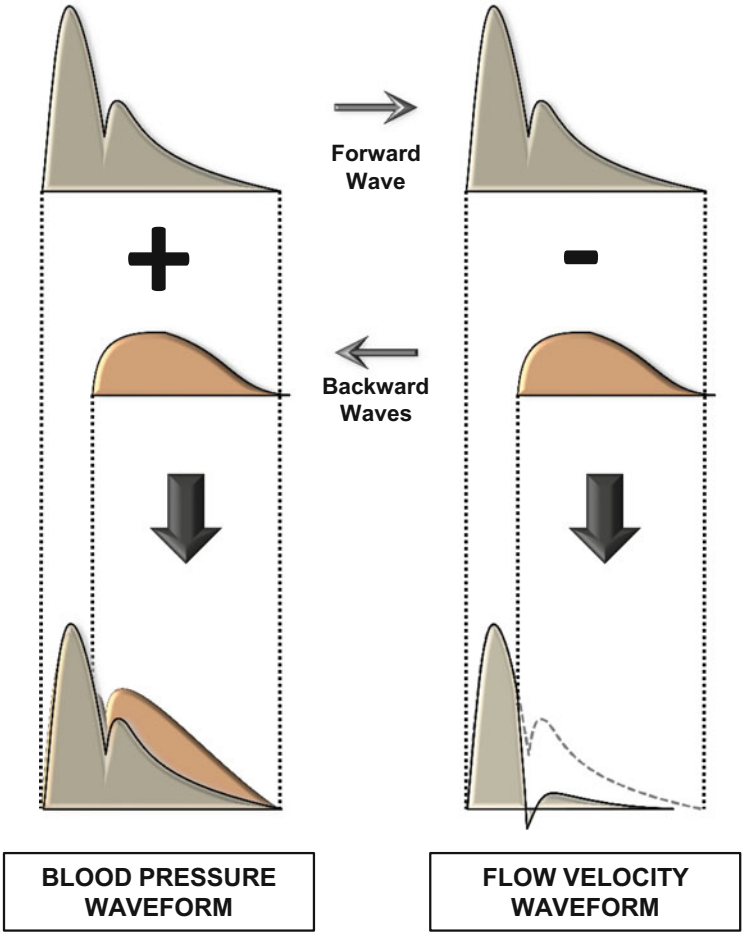

Fig. 4.11 Different pressure waveforms in the ascending aorta (=forward wave + backward wave, *left*) and blood flow velocity waveform (=forward wave − backward wave, *right*)

result of the subtraction of reflected waves from the stroke generated by the heart-aorta interaction.

In the arterial system, pressure and flow reflected waves are, therefore, generated with opposite direction. The pressure waveform, recorded in the large arteries, is the result of the sum of the forward wave and the backward wave (Fig. 4.11, left). On the contrary, the flow velocity waveform results from the subtraction of the backward wave from the forward wave (Fig. 4.11, right).

$$\text{Blood pressure wave} = \text{Forward pressure wave} + \text{Backward pressure waves},$$

$$\text{Flow velocity wave} = \text{Forward flow wave} - \text{Backward flow waves}.$$

This explains the difference between the pressure waveform and flow velocity waveform in the same arterial segment.

Let us now briefly introduce the concept of *impedance*. Impedance represents the opposition to pulsatile as well as steady flow in a given hydraulic system. A system will have low impedance if, for similar pressure, the flow is high. Going back to the example of the previous paragraph, when we are swimming underwater and we make a stroke, if we move fast, our impedance will be low. On the contrary, if, for the same stroke, we find it hard to move forward, then our impedance is high.

The ratio between blood pressure and flow, in the initial phase of the cardiac cycle when both these parameters are not affected by reflected waves, defines the *characteristic impedance* (Z) of the system.

$$Z = \frac{\text{Pressure}}{\text{Flow}}$$

4.5 Amplification Phenomenon of Arterial Pressure

If we now compare the pulse waveform recorded in the peripheral artery with the pulse waveform recorded in the aorta, we immediately realize that systolic blood pressure values in the aorta are clearly lower in relation to the periphery (Fig. 4.12). This is the mechanism underlying the amplification phenomenon of arterial pressure.

What makes the two pulse waves different is the earlier occurrence of backward waves in the periphery in relation to the center. Peripheral peak systolic blood pressure is defined by forward pressure wave + backward pressure wave, while central systolic blood pressure is defined just by the forward wave, because of the time delay in the backward wave.

The amplification phenomenon is surprising in its cleverness. Just the fact that, in a mechanical, hydraulic circuit such as the cardiovascular system, blood pressure is higher at the periphery rather than at the center is astonishing in itself. The aim of any mechanical system created by human beings is usually to reduce kinetic energy dissipation as much as possible as we move towards the periphery of the system. On the contrary, in the case of the cardiovascular system, peripheral blood pressure is higher in relation to the blood pressure at the level of the pump (heart).

We have to bear in mind that the pump (heart) needs to function in a continuous and uninterrupted way, for very long periods of time, even more than 100 years. This is the reason why the system makes use of all the phenomena that can allow the heart to work as little as possible.

The aim of the cardiovascular system is to transfer and distribute oxygen and nutritional substrates to peripheral tissues. Therefore, the ratio between cardiac work and peripheral perfusion must be kept as low as possible, and it is important to obtain a proper stroke with the least cardiac effort. The amplification phenomenon

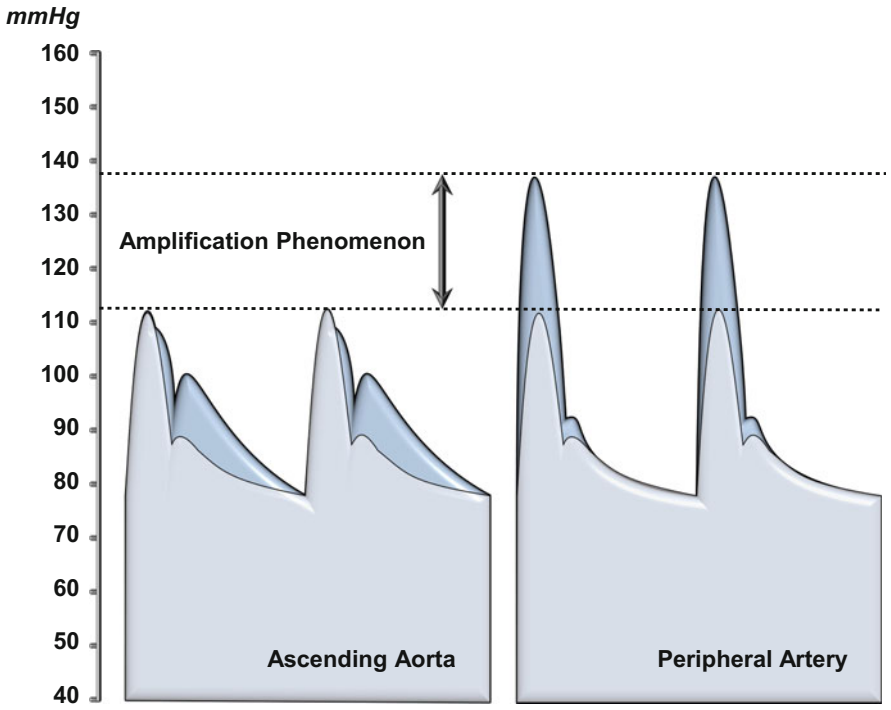

Fig. 4.12 The amplification phenomenon of arterial pressure in a subject with undamaged viscoelastic properties of the aorta

is suitable for this: for similar peripheral blood pressure, high amplification is associated with lower central blood pressure values, with lower afterload and reduced cardiac work.

4.5.1 Factors Affecting Central Blood Pressure and the Amplification Phenomenon

The main factors affecting central blood pressure and, therefore, the pressure amplification phenomenon are:

- The viscoelastic properties of the aorta and large arteries
- Magnitude and variability in reflected waves, mainly in relation to systemic vascular resistances
- The length of the aorta (i.e., the subject's height)
- Heart rate
- The attenuation phenomenon of pressure waves.

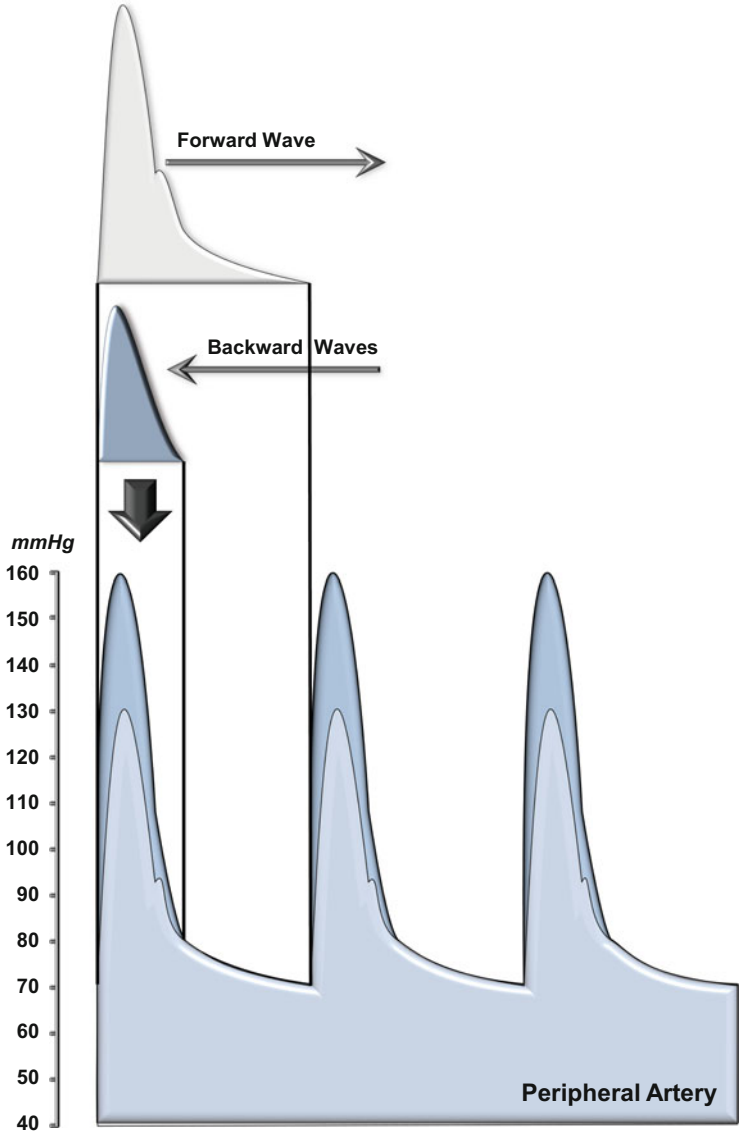

Fig. 4.13 Pressure waveform recorded in peripheral artery in a subject with marked arterial stiffness. Early superimposition of backward waves onto a forward pressure wave already characterized by an increase in systolic blood pressure values and by a decrease in diastolic blood pressure values

4.5.1.1 Arterial Stiffness

In the previous chapters, we have shown that an alteration in the mechanical properties of large arteries causes an increase in systolic blood pressure and a

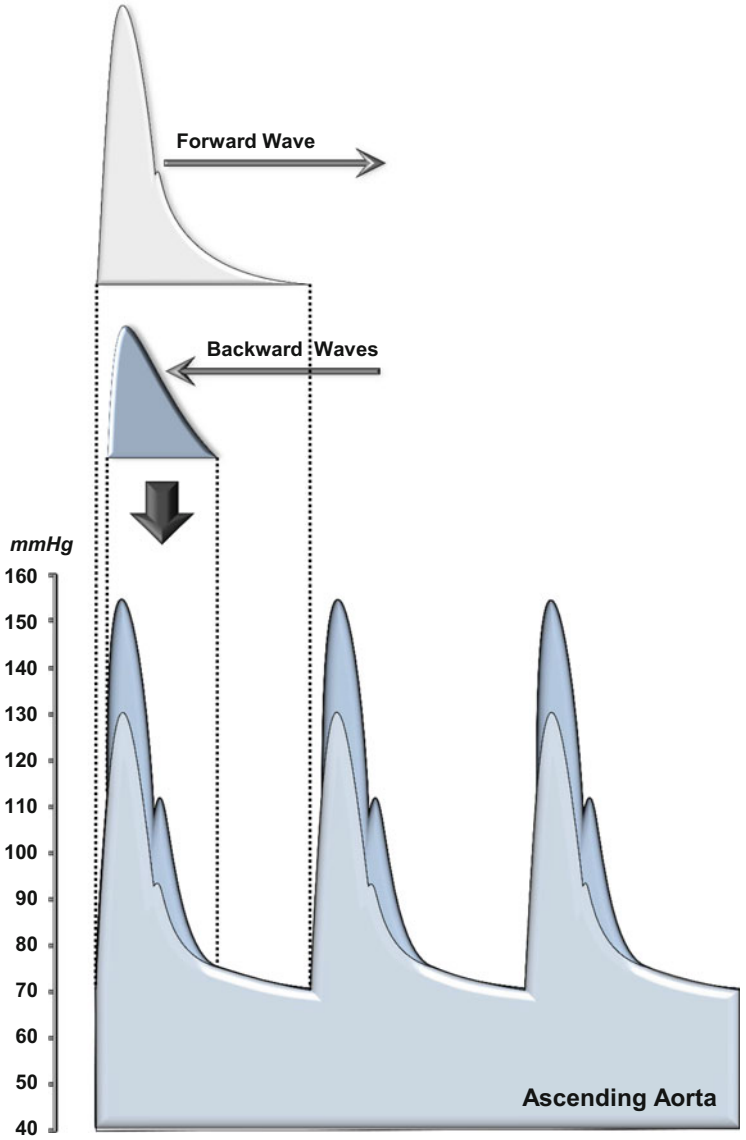

Fig. 4.14 Pressure wave recorded in the ascending aorta in a subject with marked arterial stiffness. The superimposition of backward waves onto the forward pressure wave occurs in early systole and the superposition of the two waves lasts the whole systolic phase

decrease in diastolic blood pressure and, as a consequence, an increase in pulse pressure (PP = systolic − diastolic blood pressure).

At the periphery of the arterial system, this difference between diastolic and systolic blood pressure becomes more marked, owing to the early superimposition of the reflected wave (Fig. 4.13).

The increase in pulse wave velocity in the large arteries is the main sign of alteration in the viscoelastic properties of the wall of the large arteries. Therefore, if the forward (centrifugal) pressure wave travels faster owing to arterial stiffness, similarly, the backward (centripetal) pressure wave goes back to the center faster (Fig. 4.4). To sum up, under reduced vascular elasticity, the two waves meet very early, in the protomesosystolic phase, and their superimposition lasts almost the whole systolic phase (Fig. 4.14).

Under arterial stiffness conditions, two clear consequences on central blood pressure are to be noted:

- The systolic peak is strongly affected by the backward waves. Systolic blood pressure increases still further, not only owing to the earliness of backward waves, but also to the heart–aorta interaction (the latter already compromised because of the alteration in viscoelastic properties of the aorta). It is important to stress, once again, that backward waves superimpose, in systole, onto a forward wave which, under arterial stiffness conditions, already has high systolic blood pressure values due to the alteration in the "buffer" function of the aorta.
- The diastolic phase remains depleted, because of the limited superposition of reflected waves, and it is only defined by the heart–aorta interaction, so that the pulse waveform, in the diastolic phase of the cardiac cycle, will appear to be empty and concave.

To sum up, under arterial stiffness conditions, such as aging process, hypertension, vascular calcifications, etc., early backward waves cause further increase in systolic blood pressure values and in pulse pressure and, therefore, in afterload, creating difficulties for the left ventricular pump function and leaving the diastolic phase increasingly depleted, also causing problems for coronary blood flow.

Let us now compare the pulse wave recorded in the peripheral artery with the pulse wave recorded in the aorta (Fig. 4.15). In both, a similar condition occurs: the backward wave superimposes onto the forward wave in early systole, meaning that there is a slight difference between central and peripheral systolic blood pressure values.

The amplification phenomenon is, therefore, inversely related to the pulse wave velocity (Fig. 4.16); the faster the backward waves to the center, the earlier their superimposition onto the forward wave, creating a slight difference between peripheral systolic blood pressure and systolic blood pressure in the ascending aorta.

4.5.1.2 Length of the Aorta

Another factor affecting the timing of backward waves and, as a consequence, pulse waveform and the relationship between central and peripheral systolic blood pressure, is the distance between the reflection sites and the ascending aorta. This

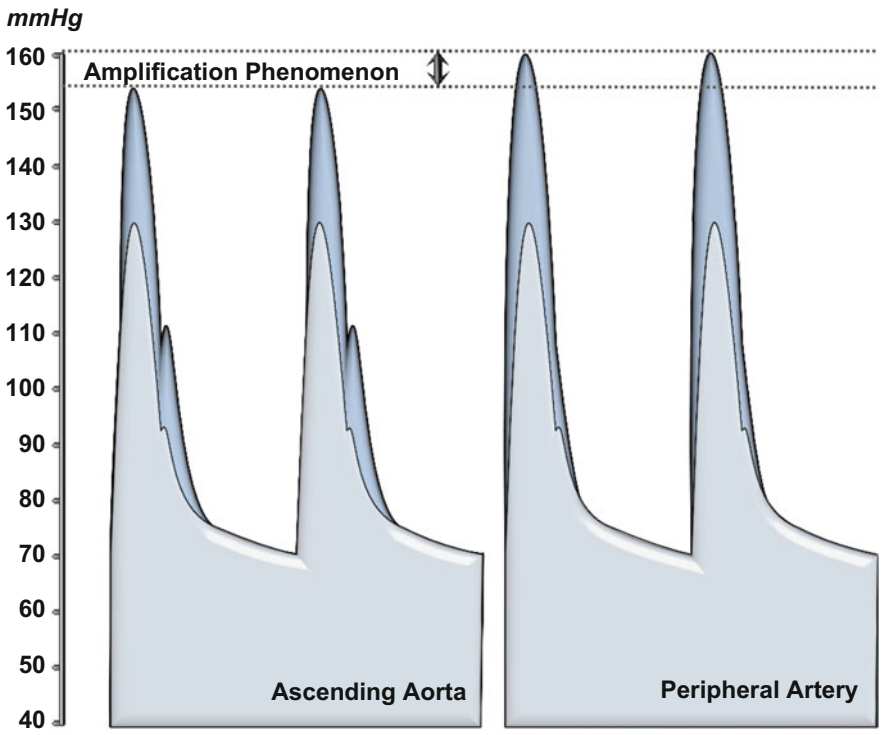

Fig. 4.15 Reduced amplification phenomenon of arterial pressure in a subject with marked arterial stiffness

seems to be rather obvious: with similar arterial stiffness (that is to say, with similar pulse wave velocity), the nearer the reflection sites are to the center, the earlier the reflected wave reaches the ascending aorta. As a result, the amplification phenomenon of arterial pressure reduces.

The subject's height is the parameter best correlated with the length of the aorta and the distance to reflection sites. Therefore, we can guess what may happen under extreme conditions:

- Short subjects, with reduced aortic length and reflection sites nearer the center: in this case, the centrifugal waves reach reflection sites in a short time; the backward waves superimpose onto the forward wave in the ascending aorta very early. As a result, the amplification phenomenon of arterial pressure is reduced.
- Tall subjects, with long aortic length and reflection sites further from the center: in this case, the centrifugal waves reach reflection sites with delay; the timing of backward waves is delayed, and they superimpose onto the forward wave in the ascending aorta very late. As a result, the amplification phenomenon of arterial pressure is higher.

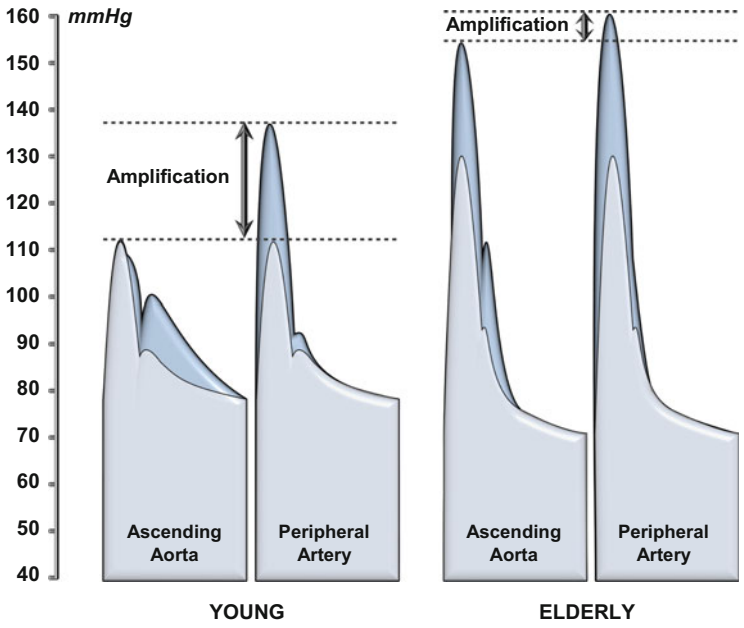

Fig. 4.16 The amplification phenomenon of blood pressure. On the *left panel*, in young people, the delayed superposition of reflected waves (*dark gray areas*) on forward waves (*light gray areas*) in the ascending aorta causes a considerable difference in systolic blood pressure between peripheral and central arteries; this difference in systolic blood pressure is known as "amplification phenomenon". On the *right panel*, in the elderly, reflected waves return earlier in the ascending aorta because of arterial stiffness. As a result, there is a precocious superposition of backward waves on forward waves and a reduced amplification phenomenon

In other words, for similar arterial stiffness and, therefore, similar pulse wave velocity, if the length of the aorta and the large arteries is greater (tall subjects), reflected waves will take a long time to reach the ascending aorta, causing an increase in the amplification phenomenon of arterial pressure and so a decrease in afterload.

This effect could be considered as a brilliant compensation. In fact, if we consider, once again, the activity of the left ventricle and the need to reduce cardiac work to the very least, and the general population, we could speculate that short subjects are luckier as they need less cardiac activity to maintain arterial perfusion over a small area. Actually, in short subjects, the cardiovascular system must perfuse smaller and closer areas, and, therefore, cardiac work should be lower than in tall subjects. Again, we could speculate that short subjects might live longer, but this is not true because of the amplification phenomenon of arterial pressure, which helps tall subjects; so, for similar peripheral blood pressure, central blood pressure is lower in tall subjects. Thanks to these compensation and balancing phenomena, we can conclude that cardiac work is not overly affected by subject's height.

4.5.1.3 Variability in Reflected Waves

The forward (centrifugal) wave has a well-defined waveform, as it results from the left ventricle–aorta interaction. It is generated by the systolic stroke and changes in relation to the viscoelastic properties of large arteries. The backward (centripetal) wave, on the contrary, is the combined expression of thousands of individual reflection sites and has a very irregular and variable waveform. Therefore, wave reflection is not to be considered as a unique, well-defined hemodynamic element, as it comes from multiple wave reflections.

At this point, we can speculate that, in subjects with similar viscoelastic properties of the arterial wall, we may find totally different waves, in relation to the way in which reflected waves arise and develop.

Figure 4.17 shows central blood pressure waveforms recorded in a hypertensive patient. Because of a marked arterial stiffness, the forward and backward waves superimpose at the beginning of the systolic phase. Giving the patient an antihypertensive therapy based on peripheral vasodilator drugs decreases the size of reflected waves and modulates their way back to the ascending aorta (Fig. 4.17b). As a result, blood pressure values are brought down into the normal range, left ventricle afterload is reduced, and subendocardial perfusion is improved. This example shows that the properties of reflected waves affect arterial blood pressure values significantly.

The ability to modulate the intensity of reflected waves together with changing their timing can be two important aspects of arterial hypertension pharmacological therapy.

4.5.1.4 Heart Rate

The ways in which heart rate affects pulse wave analysis and the forward–backward wave relationship are complex and conflicting.

First of all, heart rate affects pulse wave velocity; an increase in heart rate, or better a decrease in left ventricular ejection time, is accompanied by an increase in pulse wave velocity. As a consequence, an increase in both heart rate and pulse wave velocity should cause a (theoretical) decrease in the amplification phenomenon. However, there is a predominant action of heart rate, which is not due to the early arrival of reflected wave but rather to the complex relationship between the forward waveform and the timing of the backward wave (Fig. 4.18).

An increase in heart rate is accompanied by a relative decrease in diastolic time of the cardiac cycle and a small change in systolic time. The main consequence of the decrease in diastolic time, therefore, will be a decrease in left ventricular diastolic filling time. This changes the pulse wave morphology, characterized by a quick systolic peak followed by a sharp fall in blood pressure values. When the backward wave travels to the center, it will tend to superimpose onto the forward wave in its "descending phase". Thanks to this process and to the high heart rate, the reflected wave does not participate much in defining aortic systolic blood pressure values. As a consequence, there will be an increase in the difference between central and peripheral systolic blood pressures (Fig. 4.18b).

On the contrary, for low heart rate, the decrease in pulse wave velocity, and, therefore, the delay in reflected wave, is counterbalanced by the complete superimposition of the backward wave at the systolic peak of the forward wave.

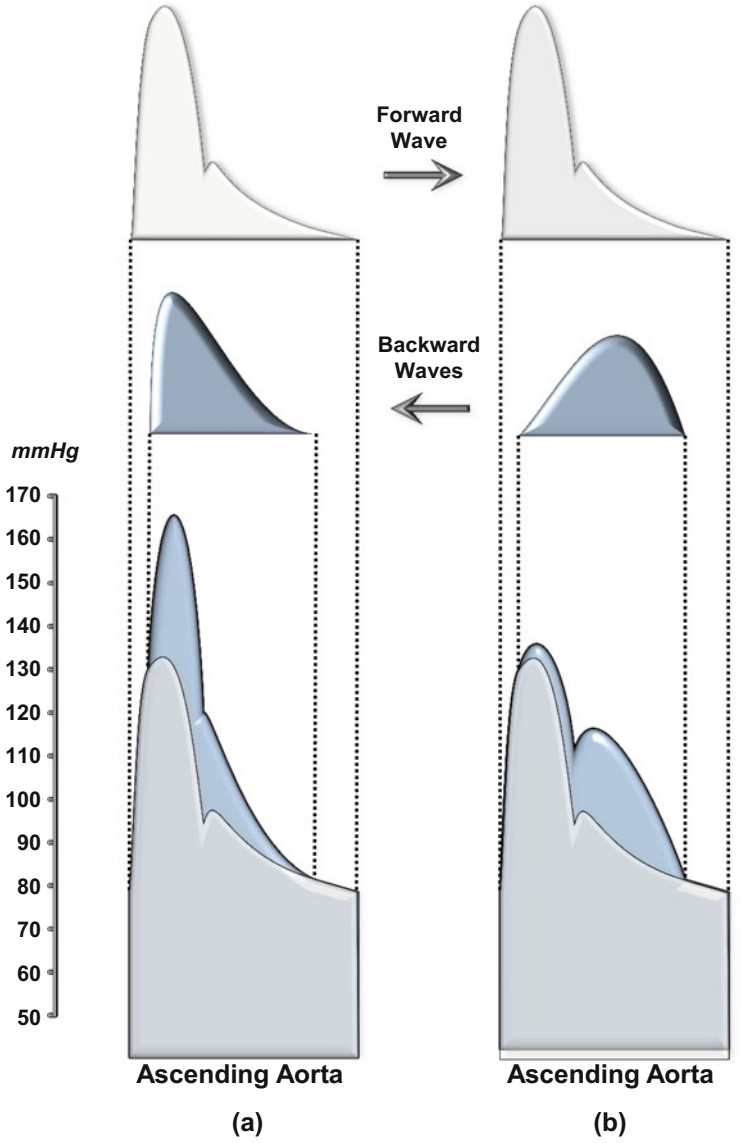

Fig. 4.17 Central blood pressure waveform recorded in a patient with marked arterial stiffness, before (**a**) and after (**b**) treatment with vasodilators. The forward wave is unique, being generated by the left ventricle–aorta interaction (*top*) whereas the reflected waves, generated by bifurcations and vessel resistance, are, therefore, variable and significantly change after treatment (*center*). The pressure waves resulting from the superimposition of the forward and backward waves will, therefore, exhibit different waveforms (*bottom*)

As a result, there is a decrease in the amplification of arterial pressure at low heart rates (Fig. 4.18a). This decrease in the difference between central and peripheral arterial pressures, which occurs with low heart rate, is considered to be the main

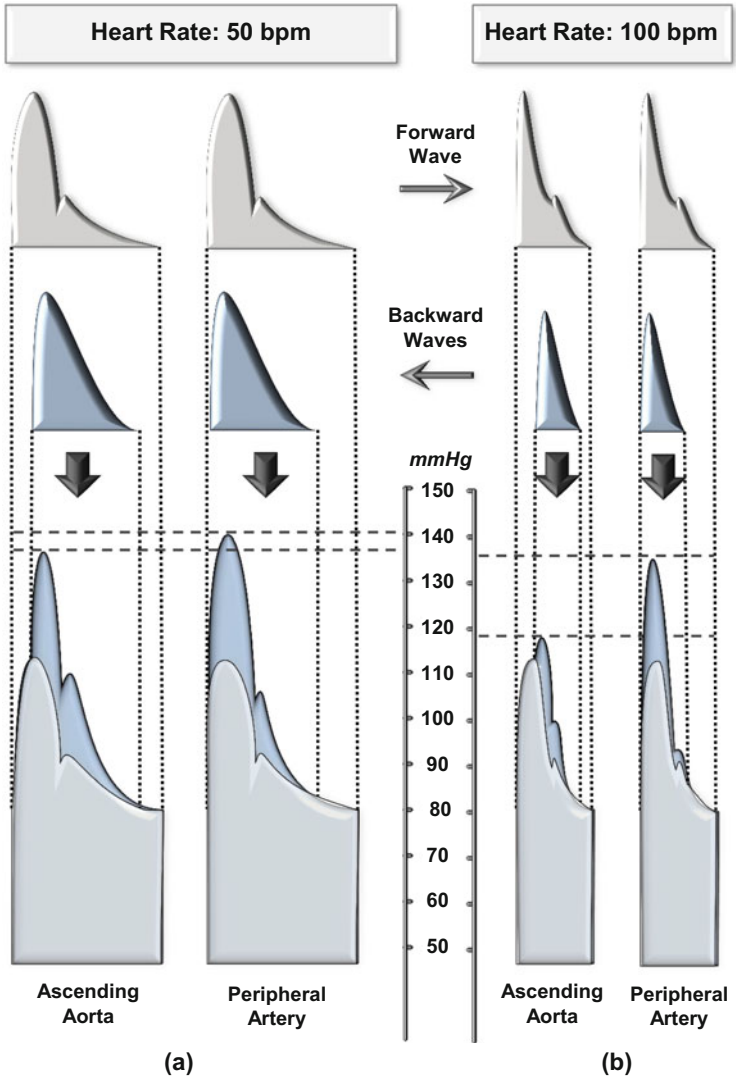

Fig. 4.18 Change in the amplification phenomenon in the same subject when heart rate changes: (**a**) decrease in amplification with low heart rate and (**b**) increase in amplification with high heart rate [2]

(but not the only) cause of the lower decrease in central arterial pressure with β-blocker treatment.

However, we must bear in mind that the decrease in heart rate is likely to be the main event able to reduce heart work and to improve coronary blood perfusion.

Therefore, amplification phenomenon and heart rate should be considered together in the general context in the evaluation of global cardiac work.

We often run the risk of taking blood pressure values as something objective, external, almost unrelated to the global physiology of the body, to which the good or poor functioning of the human "machine" is referred. They are considered as numbers to be inserted into a database, to be assessed in terms of mortality and morbidity and to be managed even in association with other numbers (heart rate, cholesterol, glycemia, etc.). "*Tell me your blood pressure values, and I will tell you your cardiovascular risk*". Substantial financial resources have been invested in frantic research into blood pressure values able to better account for "life-support curves": diastolic blood pressure, mean arterial pressure, pulse pressure, pulse wave analysis, and last but not least, amplification of pulse pressure.

Sometimes, this scientific approach is questioned by clinical trial outcomes themselves. A paradigmatic example is represented by the heart rate/pressure amplification dilemma. First, clinical studies showed that low heart rate is a favorable element in cardiovascular risk; then, when they showed that low pulse rate is accompanied by a decrease in amplification of pulse pressure, this was questioned, to the extent that β-blockers were considered as second-rate drugs, accused of not being able to reduce central arterial pressure properly. There is the bitter feeling that physiologists and clinicians have given into statistics and that human intuition and cleverness have surrendered to calculation systems and data processing.

It is important to think things over and reconsider people in their essence as indivisible physiological entities. We need to reflect upon physiological and pathophysiological events again and to have a preference for tools that enable us to investigate these events deeply.

4.5.1.5 Attenuation of Pressure Wave

According to what we have seen so far regarding the amplification phenomenon, it seems that there is a close relationship between amplification and arterial distensibility and between amplification and the viscoelastic properties of the arterial wall. In this case, we would then expect a progressive decrease in amplification with aging and particularly high values in infancy and adolescence.

On the contrary, in clinical practice, the amplification phenomenon is often absent in very young subjects, where excellent arterial elasticity is assumed. Moreover, it is not uncommon to find situations where peripheral systolic blood pressure values are lower than aortic blood pressure values. A similar situation occurs even in small laboratory animals. These are characterized by marked arterial distensibility and by pulse wave velocity values around 4–5 m/s. Also, in the study of blood pressure values with dual sensor catheter (in femoral artery and ascending aorta), higher blood pressure values are usually found in the aorta with respect to the periphery.

Once again, we have to consider the cardiovascular system as a hydraulic circuit. The pressure wave, which is generated by the heart–aorta interaction (forward wave), loses energy along its way. This energy dissipation is insignificant under

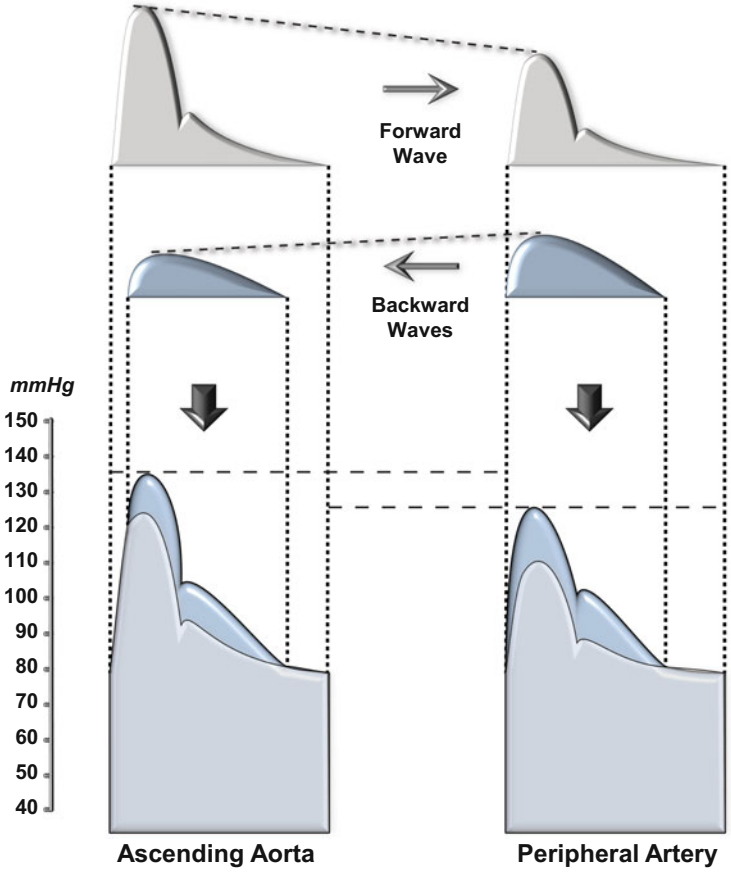

Fig. 4.19 Damping phenomenon of pressure wave. With elevated arterial distensibility, the pressure waveform amplitude dampens from the center to the periphery (*top*), therefore, generating weaker reflected waves, which travel towards the center (*middle*). The result will be a clear-cut decrease in the amplification of arterial pressure (*bottom*), until higher blood pressure values are reached in the ascending aorta rather than at the periphery of the system, as in the case shown in the figure

arterial stiffness conditions or with normal viscoelastic properties of the arterial wall whereas it is significant under marked arterial distensibility conditions (Fig. 4.19). The forward wave, being small on its arrival at the periphery, generates small-sized reflected waves as well, which will travel back to the center. According to this process, it is possible to have peripheral systolic blood pressure lower than aortic blood pressure, with the amplification phenomenon being absent.

This process is easier to understand if we think about an electrical system (Fig. 4.20): if we consider aortic distensibility as a capacitor inserted into the system, the higher its capacity, the greater the energy accumulated.

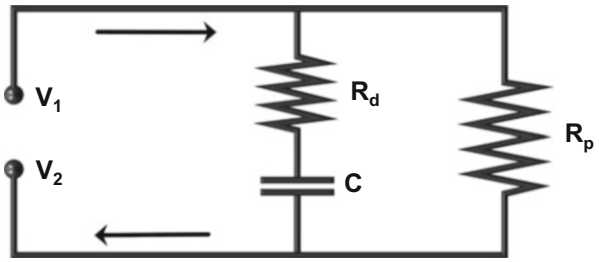

Fig. 4.20 Electrical model corresponding to the cardiovascular system. The model consists of a resistor (Rp), which represents systemic vascular resistance, in parallel with a complex made up of a resistor (Rd) in series with a capacitor (C), which represents static compliance

4.6 Interaction Between Hemodynamic Parameters in Determining Blood Pressure

In the first part of this book, we have analyzed the two components of blood arterial pressure: mean arterial pressure, which represents the "steady" part of blood arterial pressure, and the pulsatile one, which represents the "dynamic" component of blood arterial pressure.

In this chapter, we have dealt with the role of the mechanical properties of the aorta and large arteries as main factor that determines pulse pressure, affecting both the forward traveling wave originating from the interaction between the left ventricle and the aorta and the backward traveling waves, reflected from the periphery of the cardiovascular system towards the left ventricle.

Nevertheless, it stands to reason that the interactions between the factors defining mean arterial pressure and the ones defining pulse pressure are indeed a considerable number (Fig. 4.21).

- First of all, several clinical studies have pointed out that mean arterial pressure affects the distensibility of the aorta and large arteries. Actually, an increase in mean arterial pressure results in an increase in the arterial wall tension and in a reduction in the elastic properties of the aorta.
- We have also highlighted that the centrifugal traveling wave comes from the mutual interaction between left ventricular function (systolic pump) and the viscoelastic properties of the aorta (diastolic pump).
- Finally, pulse pressure analysis has also to take into account the role of heart rate and peripheral vascular resistance on conditioning reflected traveling waves.

To sum up, numerous factors must be considered in defining arterial blood pressure on the basis of mutual influence.

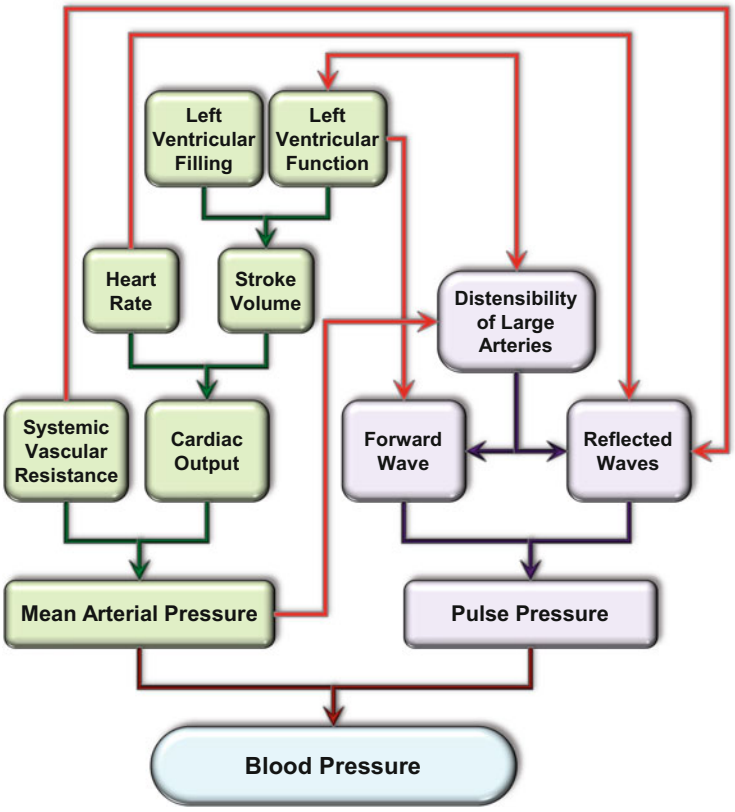

Fig. 4.21 Strong interaction exists between the factors defining mean arterial pressure and those defining pulse pressure

4.7 The So-Called Spurious Systolic Hypertension of Youth

The recent 2013 European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension [3] claim that, on the assessment of hypertensive patients, more investigation is needed before recommending the measurement of central blood pressure for routine clinical use.

> *The only exception may be isolated systolic hypertension in the young: in some of these individuals increased systolic blood pressure at the brachial level may be due to high amplification of the central pressure wave, while central blood pressure is normal [3].*

Actually, high systolic blood pressure values in young subjects is quite common finding in clinical practice (about 3–4 % of teenagers), sometimes in healthy, male, tall, and thin subjects, who exercise regularly. Blood pressure values in these subjects usually tend to be very changeable. In some cases, the study of central

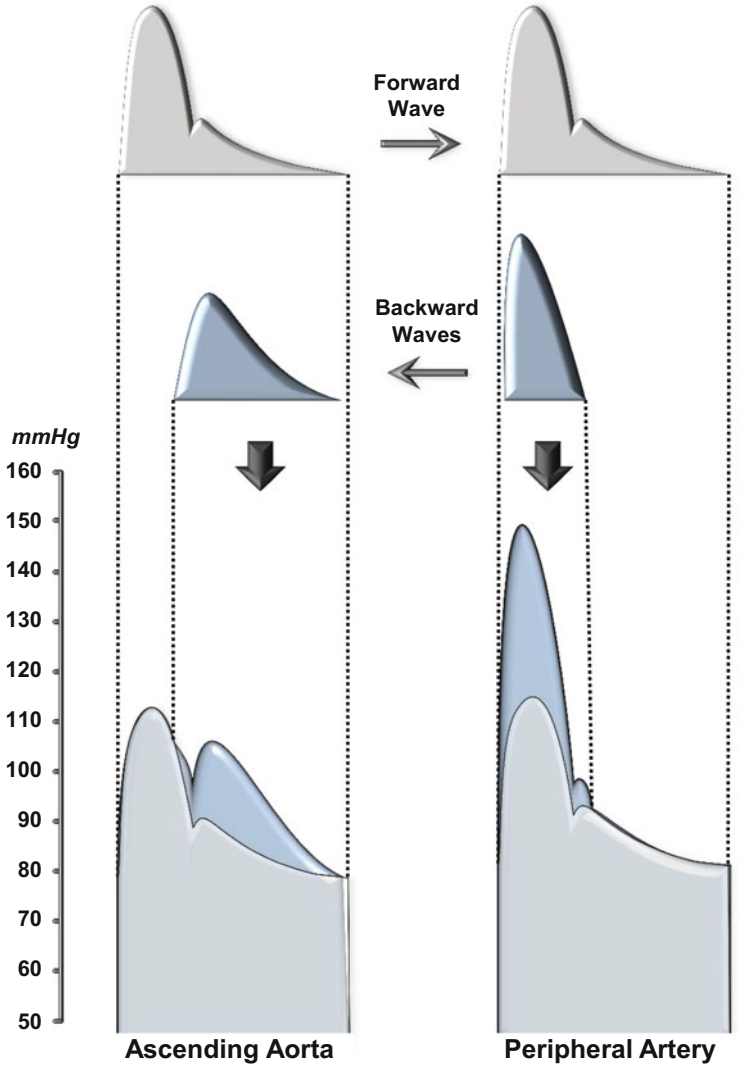

Fig. 4.22 Hemodynamic mechanism underlying spurious systolic hypertension in youth: strong cardiac output and early backward waves at the periphery of the arterial system cause high peripheral systolic blood pressure whereas in the ascending aorta, systolic blood pressure values are lower, owing to the slow backward waves to the center, due to good arterial distensibility

arterial pressure has shown normal systolic blood pressure values even in the presence of high systolic brachial pressure [4].

After the first cases were indicated, there has been the tendency to consider as spurious systolic hypertension all those cases where high systolic blood pressure values are found in young subjects, neglecting the appropriate clinical tests. This

attitude, which generalizes the concept of spurious systolic hypertension, runs the risk of becoming dangerous, as it does not allow us to isolate and deeply investigate the real cases of youth hypertension. Probably, this is the reason why some authoritative hypertensiologists think that the definition of spurious systolic hypertension in youth is wrong and misleading and suggest that the terms "spurious" or "pseudo-" systolic hypertension should be absolutely avoided with regard to young hypertensive subjects [5].

In conclusion, the diagnosis of "spurious systolic hypertension" should be limited to cases with the following features (Fig. 4.22):

- An increase in systolic blood pressure values completely due to a peripheral pressure waveform, characterized by an early systolic peak
- Normal diastolic blood pressure values in the brachial artery
- Normal mean arterial blood pressure values defined by the integral of the brachial pulse wave
- Normal carotid pulse waveform and amplitude according to age

Pills for Growing

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Central Blood Pressure: Part 2, Pulse Wave Analysis

5

We have already dealt with the importance of central blood pressure values and we have seen that pulse wave analysis can provide clear indications of the interpretation of blood pressure values. But how can we measure, noninvasively, central blood pressure values and record aortic pressure wave?

5.1 How to Measure Blood Pressure: Work in Progress

Reverend Stephen Hales (1677–1761), an English naturalist, was the first to quantitatively measure blood pressure. Figure 5.1 describes the experiment as it was published. However, he did not continue with his blood pressure experiments for long, as his studies on animal vivisection were greatly criticized. One of his best friends, the poet Alexander Pope, used to say about him: "*He is a very good man, only he has his hands imbrued with blood*".

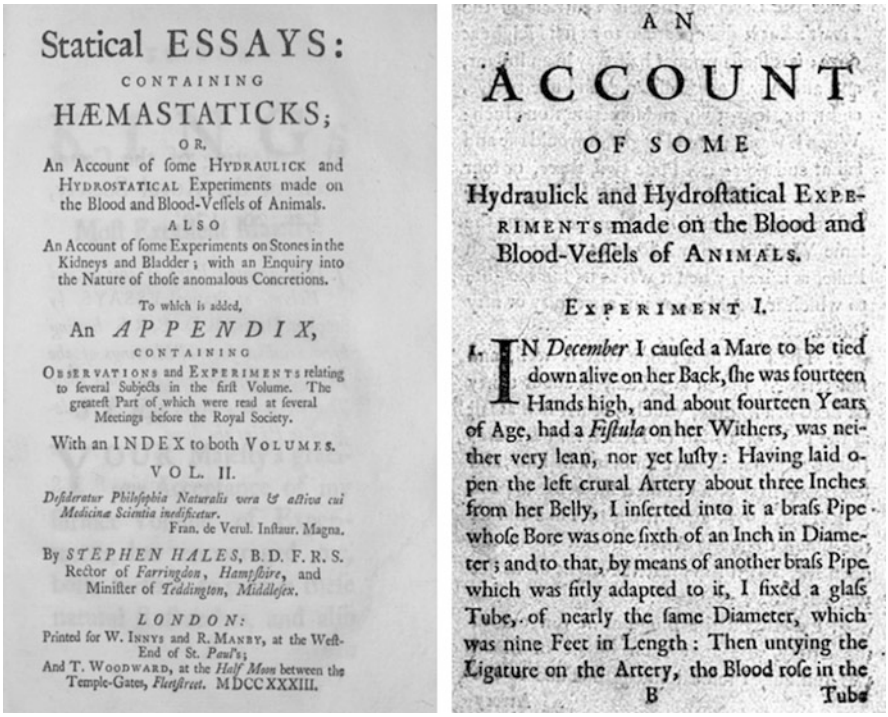
Thus, it was not until a century later that the accurate study of blood pressure was taken up again. At first, invasive methods, such as hemautography, were used (Fig. 5.2). With this test, large-sized animals were stung on a large artery, and the spurt of their blood would trace out a curve on a moving strip of paper.

Finally, in the second half of the 19th century, some physiologists, realizing that arterial blood pressure played a large role in cardiovascular diseases, raised the question of noninvasive recording of arterial pressure waveform and assessment of blood pressure values.

5.1.1 Primitive Recordings of Arterial Pulse Wave in Humans

The sphygmograph, developed by Karl von Vierordt (1818–1884) in 1854, was the first noninvasive device used to estimate blood pressure. Von Vierordt's sphygmometer was a system of levers and weights placed to determine the amount of external pressure needed to stop blood flow in the radial artery (Fig. 5.3).

P. Salvi, *Pulse Waves*, DOI 10.1007/978-3-319-40501-8_5



Statical ESSAYS:
CONTAINING
HÆMASTATICKS;
OR,
An Account of some HYDRAULICK and HYDROSTATICAL Experiments made on the Blood and Blood-Vessels of Animals.
ALSO
An Account of some Experiments on Stones in the Kidneys and Bladder; with an Enquiry into the Nature of those anomalous Concretions.
To which is added,
An *APPENDIX*,
CONTAINING
OBSERVATIONS and EXPERIMENTS relating to several Subjects in the first Volume. The greatest Part of which were read at several Meetings before the Royal Society.
With an INDEX to both VOLUMES.
VOL. II.
Desideratur Philosophia Naturalis vera & activa cui Medicinæ Scientia inædificetur.
Fran. de Verul. Instaur. Magna.
By *STEPHEN HALES*, B. D. F. R. S. Rector of *Farringdon*, *Hampshire*, and Minister of *Teddington*, *Middlesex*.
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And T. WOODWARD, at the *Half Moon* between the Temple-Gates, *Fleetstreet*. MDCCXXXIII.

A N
ACCOUNT
OF SOME
Hydraulick and Hydroſtatical EXPERIMENTS made on the Blood and Blood-Veſſels of ANIMALS.
EXPERIMENT I.
I. IN *December* I cauſed a Mare to be tied down alive on her Back, ſhe was fourteen Hands high, and about fourteen Years of Age, had a *Fiſtula* on her Withers, was neither very lean, nor yet luſty: Having laid open the left crural Artery about three Inches from her Belly, I inſerted into it a braſs Pipe whoſe Bore was one ſixth of an Inch in Diameter; and to that, by means of another braſs Pipe which was fitly adapted to it, I fixed a glaſs Tube, of nearly the ſame Diameter, which was nine Feet in Length: Then untying the Ligature on the Artery, the Blood roſe in the
B Tube

Fig. 5.1 Stephen Hales described his first attempts to measure the values of blood pressure in *Volume II of Statical Essays* (1733) as follows: "*In December I caused a mare to be tied down alive on her back; she was 14 hands high* [142 cm], *and about 14 years of age, had a fistula on her withers, was neither very lean, nor very lusty: having laid open the left crural artery about 3 inches* [7.62 cm] *from her belly, I inserted into it a brass pipe whose bore was 1/6 of an inch in diameter* [0.42 cm] *and to that by means of another brass pipe which was fitly adapted to it, I fixed a glass tube of nearly the same diameter which was 9 feet in length* [274 cm]. *Then untying the ligature on the artery, the blood rose in the tube to 8 feet in length* [244 cm; 244 cm H_2O = about 180 mmHg], *3 inches* [7.6 cm] *perpendicular above the level of the left ventricle of the heart*"

However, the result was a bulky and rudimentary device, providing inaccurate measurements.

Étienne Jules Marey (1830–1904) improved von Vierordt's sphygmograph by making it portable and available in clinical practice (Fig. 5.4). He placed, above the radial artery, a specialized instrument able to magnify arterial pulse waves and record them on paper with an attached pen (Fig. 5.5). In addition to being a capable physiologist, Marey was also a physicist of genius. He had a dynamic outlook on life, and this attitude dominated all his studies in the field of physics, anatomy, and physiology.

Photography had just developed in those years, but Marey was not satisfied with giving just a photographic likeness of reality. After all, a photograph was nothing more than a painting, even though a perfect one. He was looking for a more

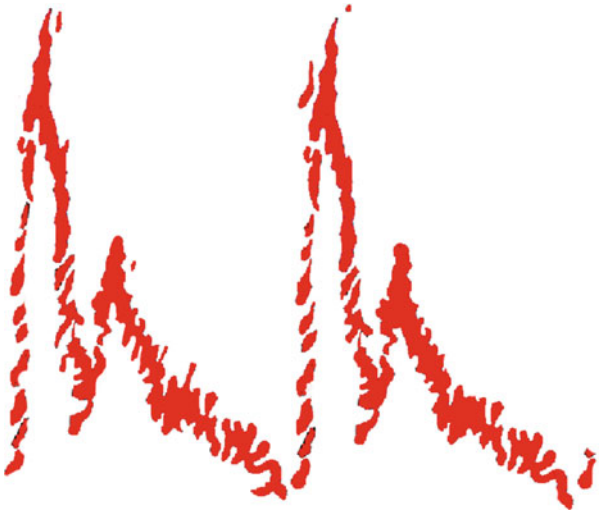


Fig. 5.2 Hemautographic tracing of the posterior tibial artery of a large dog (Leonard Landois, *Lehrbuch der Physiologie des Menschen*. Wien, 1881)

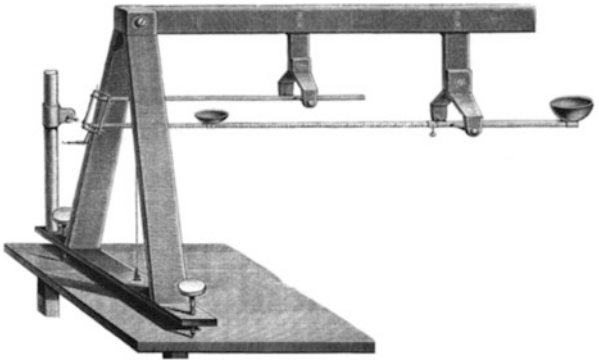


Fig. 5.3 The first sphygmograph was proposed by Karl von Vierordt (1818–1884) in 1854. This apparatus estimated arterial blood pressure using a mechanical balance and weights, exploiting the principle that blood pressure could be determined by measuring the counter pressure that would suppress the pulse

revolutionary invention. His interest in capturing instant of movement and dynamism of things led him to deal with this spirit photography.

Actually, Marey was also the inventor of the first portable camera, called "chronophotographic gun", in 1882 (Figs. 5.6 and 5.7). This "chronophotographic gun" was equipped with photographic plates, circular or octagonal, placed in a small dark room. The barrel was used as a viewfinder, and the lens were placed inside it. The gun recorded 12 frames/s on the same picture, resulting in a single

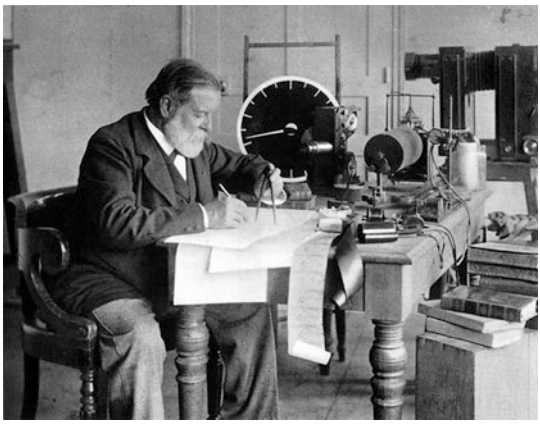


Fig. 5.4 Étienne-Jules Marey (1830–1904) working in his laboratory in Paris

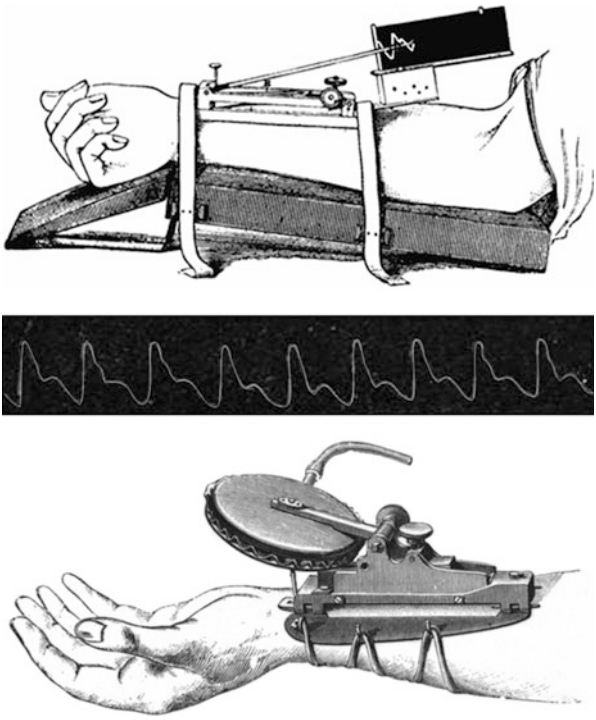


Fig. 5.5 Two sphygmographs built by Étienne-Jules Marey in 1860

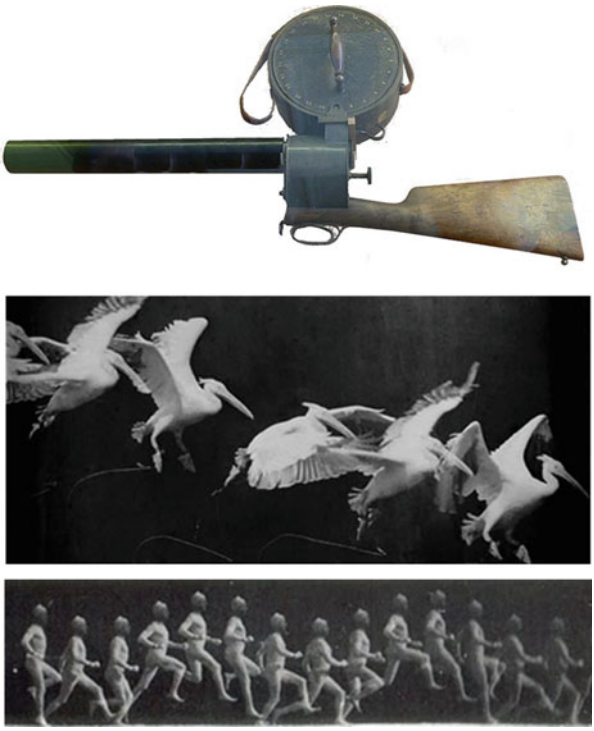


Fig. 5.6 The "chronophotographic gun" built by Étienne-Jules Marey (1881) was able to record 12 frames/s on the same picture. In this way, it was possible to study several phases of the subject's movement, elusive to the human eye

Fig. 5.7 A ballet dancer's movement recorded with the Marey's chronophotographic gun. Chronophotography affected Futurism, the artistic movement. Most of Giacomo Balla's pieces allude to the wonder of dynamic movement (as in *Girl Running on Balcony*, 1912 or in *Dynamism of a Dog on a Leash*, 1912), as well as in Marcel Duchamp's painting (*Nude Descending a Staircase*, 1912)

picture that captured several phases of the subject's movement. In this way, Marey studied the movements of humans, horses, birds, and other animals, shooting tight movements, elusive to the human eye. In 1888, Marey built a new chronophotographic device able to shoot 60 images/s and of excellent image quality. Thus, Marey is considered to be one of the forerunners of modern cinematography nowadays.

Marey's sphygmograph paved the way for many other devices for measuring and recording arterial pressure waveforms from the brachial or radial artery. The sphygmographs proposed by scientists and physiologists, such as F.H.H.A. Mahomed (1849–1884), J. Jaquet, R.E. Dudgeon (1820–1904), and L. Landois (1837–1902), were used to record pulse waves and, indirectly, to study blood pressure and cardiac function in clinical research and clinical practice in the last decades of the 19th century (Figs. 5.8, 5.9, 5.10, 5.11, 5.12, and 5.13).

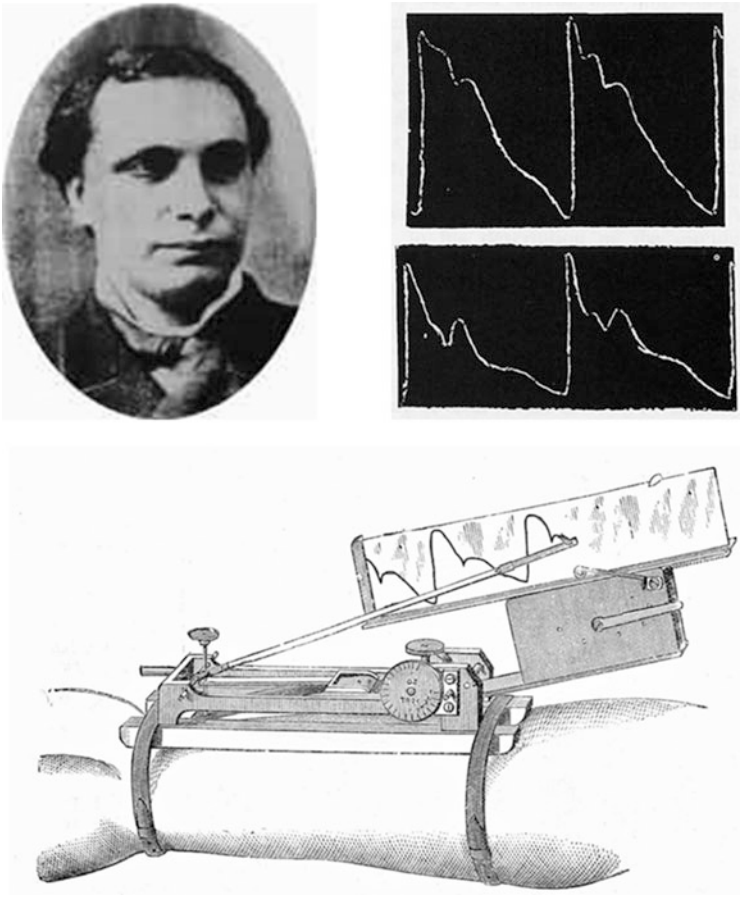


Fig. 5.8 Frederick Henry Horatio Akbar Mahomed (1849–1884); his sphygmograph was built in 1872. Pulse wave was recorded with this device

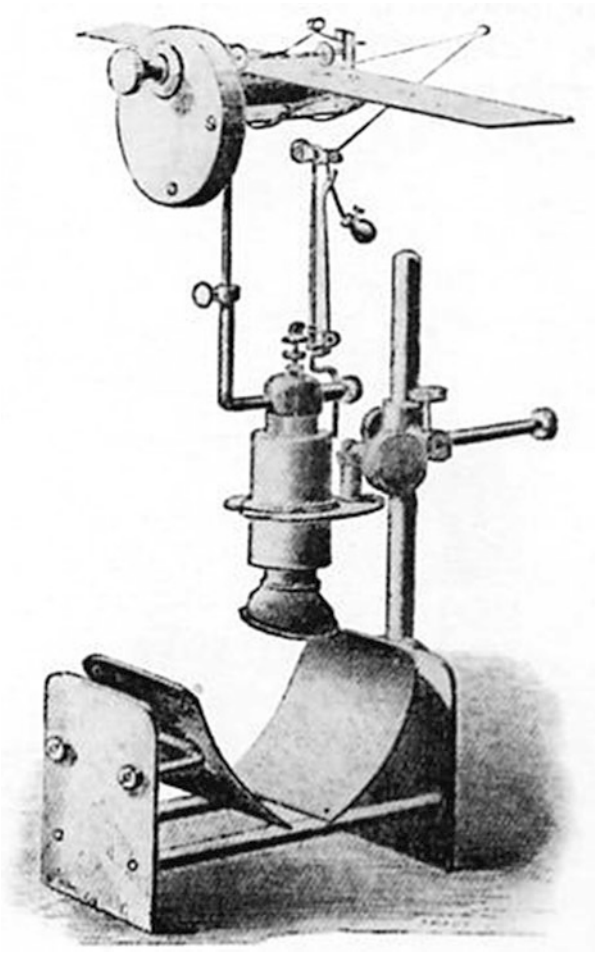


Fig. 5.9 Erasmus A. Pond's sphygmograph (1879). With the base to lay wrist in on supports, the sphygmograph adjusts downward to create pressure and a smoked paper recording is made by a clockwork mounted at the *top*

Fig. 5.10 Traces recorded with Leonard Landois' sphygmograph and relative pulse wave analysis (1881)

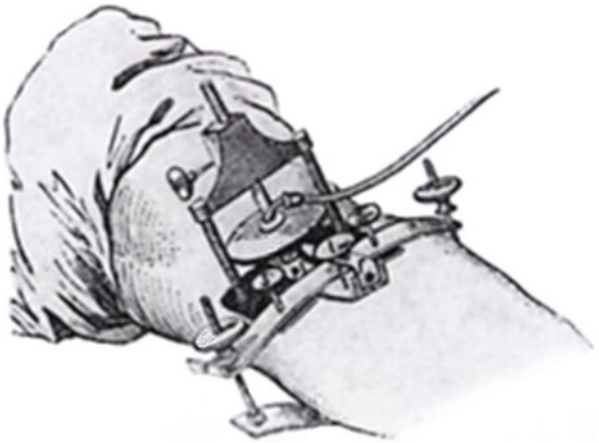


Fig. 5.11 Meurisse and Mathieu's sphygmograph, a replica improved by Crumach (1882)

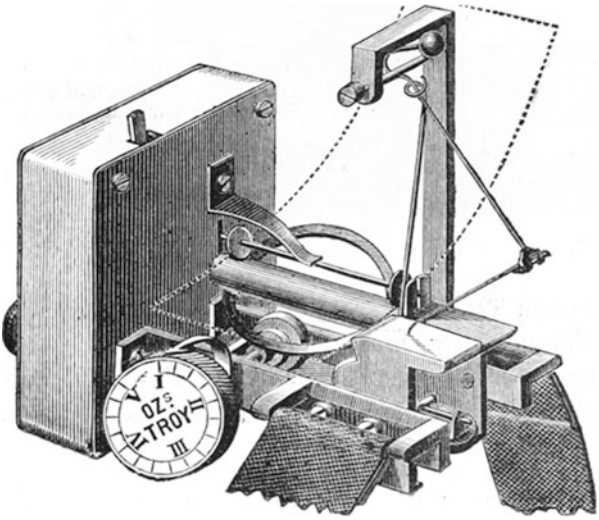
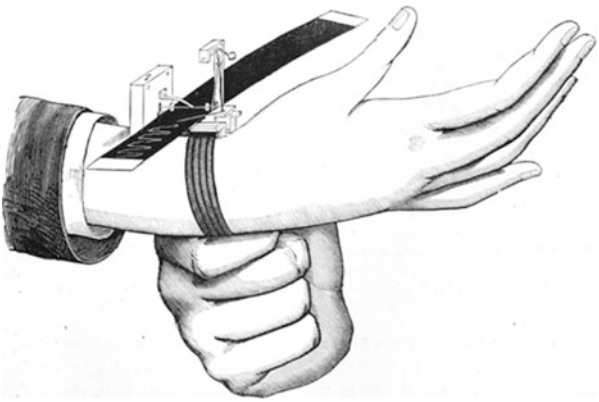


Fig. 5.12 Marey's sphygmograph was made more practical by Robert Ellis Dudgeon (1880) with the help of a young watchmaker



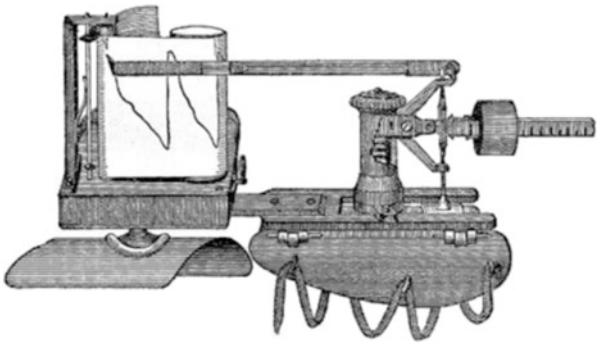


Fig. 5.13 Philadelphien's sphygmograph (1897)

Since then, radial pulse wave recording has been commonly used in classic cardiovascular semiological examinations.

In 1860, Marey was able to measure blood pressure by enclosing an arm in a water-filled glass chamber; water pressure would increase until it stopped the arterial circulation. This point of pressure was identified as systolic blood pressure.

5.1.2 Appearance of the Sphygmomanometer

Improving upon these methods, in 1881, Samuel Siegfried Karl Ritter von Basch (1837–1905) built the first sphygmomanometer (Fig. 5.14). He placed a rubber bag around a manometer bulb and filled the bag with water to restrict blood flow in the artery. Then he connected the bulb to a mercury column, which was able to translate the pressure required to completely obscure the pulse into millimeters of mercury; that peak of pressure was called systolic pressure.

The true inventor of the modern sphygmomanometer (Fig. 5.15) was Scipione Riva-Rocci (1863–1937). He placed an air cuff around the arm's circumference. Thanks to the uniform distribution of the compression around the arm, it was possible to avoid common errors related to blood pressure measurements, which previous devices used to do. He also led to the measurement of arterial blood pressure at the level of the brachial artery, which was more accurate than the radial artery. The pressure in the cuff would increase until the radial pulse was no longer present. At this point, the pressure in the cuff was released. The pressure at which the radial pulse reappeared was recorded as systolic pressure. Riva-Rocci published the results of his studies in the Gazzetta Medica Torinese in 1896. However, the assessment of diastolic blood pressure remained elusive with the Riva-Rocci's sphygmomanometer. The ability to measure diastolic pressure was first achieved in 1905 with the auscultatory method, proposed by Nikolai Korotkoff (1874–1920), using a sphygmomanometer and a stethoscope.

> *The cuff of Riva-Rocci is placed on the middle third of the upper arm; the pressure within the cuff is quickly raised up to complete cessation of circulation below the cuff. Then, letting the mercury of the manometer fall one listens to the artery just below the cuff with a*

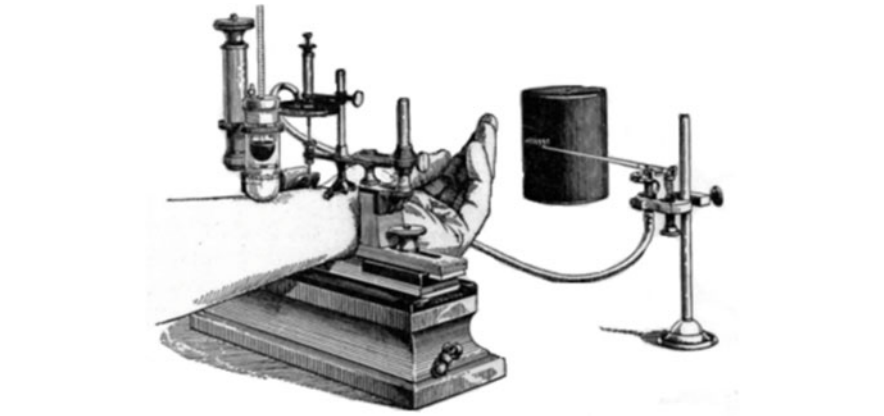


Fig. 5.14 Von Basch's sphygmomanometer (1881)

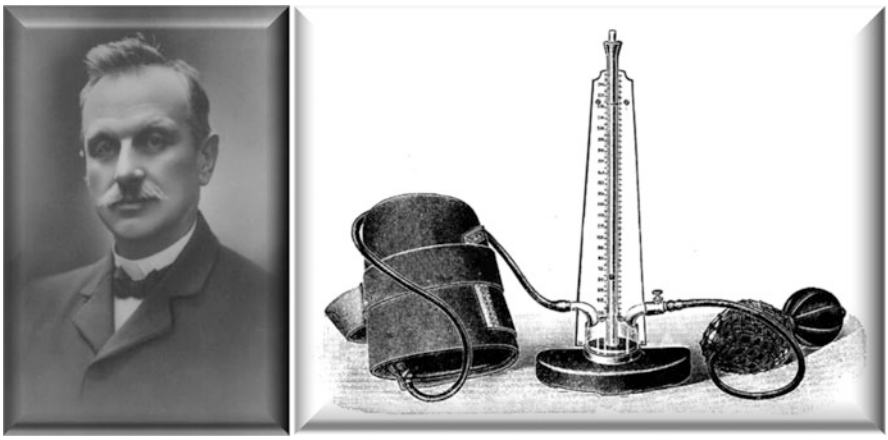


Fig. 5.15 Scipione Riva-Rocci and his sphygmomanometer

children's stethoscope. At first no sounds are heard. With the falling of the mercury in the manometer down to a certain height, the first short tones appear; their appearance indicates the passage of part of the pulse wave under the cuff. It follows that the manometric figure at which the first tone appears corresponds to the maximal pressure. With the further fall of the mercury in the manometer one hears the systolic compression murmurs, which pass again into tones (second). Finally, all sounds disappear. The time of the cessation of sounds indicates the free passage of the pulse wave; in other words, at the moment of the disappearance of the sounds the minimal blood pressure within the artery predominates over the pressure in the cuff. It follows that the manometric figures at this time correspond to the minimal blood pressure.

(Nikolai Korotkoff. 1905. Reports of the Imperial Military Medical Academy of St Petersburg)

However, the use of arterial pressure measurement in clinical practice was not universally accepted until much later. An editorial, published in 1905 in the British Medical Journal, argued that "*by such methods (sphygmomanometry) we pauperize our senses and weaken clinical acuity*". In this regard, a wise judgment is attributed to Arthur Schopenhauer (1788–1860): "*All truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident*".

As a matter of fact, the introduction of the cuff sphygmomanometer caused an interruption in the study of pulse wave recording and analysis. Besides, the possibility of measuring systolic and diastolic blood pressure, i.e., the zenith and the nadir, respectively, of the pulse pressure wave, made pulse wave recording outdated, under the belief that these measurements could provide a full explanation of vascular hemodynamics, throughout the 20th century.

5.1.3 The Revival of Pulse Wave Analysis

In the second half of the 20th century, blood pressure values became an object of increasing clinical interest and a target for therapeutic intervention. The operational model being used was simplified and reduced to a pump working against a peripheral vascular resistance. Although certainly oversimplified, it cannot be denied that this model helped to effectively antagonize high blood pressure, which is the most important risk factor for cardiovascular disease, achieving one of the greatest medical success of the past century, with a significant reduction in cardiovascular mortality.

When the registration of pulse waves was technically possible using invasive catheterization, pressure wave morphology was brought to the forefront once again, and physiologists and interventional cardiologists were mostly interested in aortic blood pressure measurement and pulse wave recording.

Over the past 20 years, there has been a radical change in scientific knowledge, thanks to clinical research, and this has dramatically changed the approach to the hypertensive patient. The single acquisition of blood pressure values was considered to be inadequate to rightly and entirely study patients with high blood pressure values.

Marey's intuition regarding a dynamic outlook of blood pressure and all physical phenomena was taken up again.

5.2 Non-invasive Central Blood Pressure Assessment

"*Why on earth, in ophthalmology, is it possible to measure intraocular pressure non-invasively, using external devices, while arterial pressure has to be measured invasively, by cardiac catheter?*" It is likely that, in the early 1960s, researchers such as R.S. Mackay and E. Marg tried to provide an answer to this question too, when they took up the first research on tonometry application from ophthalmology, in the evaluation of intra-arterial pressure.

Arterial tonometry is based on the principle of applanation tonometry (Fig. 5.16). Arterial applanation tonometry is a noninvasive, reproducible, well tolerated, and fast test [1]. A few studies have shown that arterial pressure waveforms recorded

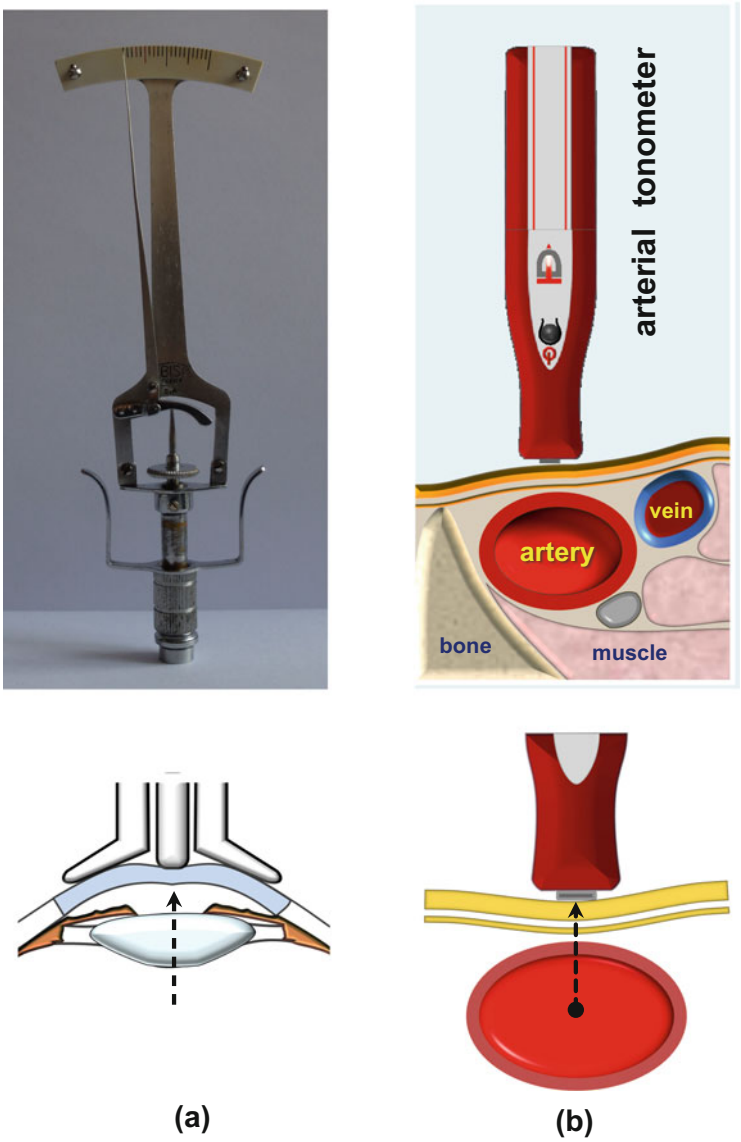


Fig. 5.16 Applanation tonometry. Left panels (**a**): ophthalmic Schiotz tonometer (Sbisà, Florence, Italy). Right panels (**b**): transcutaneous arterial tonometer. Applanation tonometry principle: a circular structure with a given pressure inside (eyeball or artery) is flattened; in this way, circumferential pressures are equalized and the sensor records the pressure within the structure to be analyzed accurately. As far as arterial recording is concerned, a strain gauge sensor, the size of a fountain pen, is placed on a superficial artery, after having located the point of maximal arterial pulsation; pressing down lightly, the arterial area against the underlying bone structures flattens, and the arterial pressure wave is recorded

noninvasively by transcutaneous tonometry are largely superimposable onto those recorded invasively, by means of an intra-arterial catheter. Moreover, the test is very easy to carry out, and it enables evaluation of those arterial districts where the artery runs superficially and where its compression against underlying structures occurs, i.e., at the level of the carotid (Fig. 5.17), brachial, radial, femoral, posterior tibial, dorsalis pedis and superficial temporal arteries.

The availability of transcutaneous tonometers able to measure pressure waveform noninvasively led to in-depth studies of the role of the mechanics of large arteries in pathophysiology of arterial hypertension.

The outcomes of several epidemiological clinical trials pointed out some peculiar aspects of vascular hemodynamics, showing aortic stiffness as an independent predictor of cardiovascular mortality, stressing the importance of pulse wave velocity measurement [2, 3]. Moreover, some studies had already highlighted the importance of central systolic blood pressure and central pulse pressure as cardiovascular prognostic factors, more significant than peripheral blood pressure values measured in the brachial artery by means of traditional sphygmomanometers [4–6]. Actually, peripheral blood pressure is not always the best method to assess the effects of drugs on blood pressure and central systolic blood pressure and central pulse pressure are able to evaluate the real load imposed on the left ventricle much better than peripheral systolic blood pressure and peripheral pulse pressure [7, 8].

Even if transcutaneous arterial tonometry is not currently considered to be one of the diagnostic tests recommended for arterial hypertension, sometimes it represents a significant diagnostic in-depth analysis. In particular, it is useful for the assessment of particular diseases characterized by increasing blood pressure values or in conditions where an accurate assessment of the central pulse wave analysis is requested for an indirect study of the myocardial function or heart work. Therefore, it is very important that central blood pressure values recorded with this method are reliable and that the parameters relative to the central arterial pressure waveform correspond to the ones recorded in ascending aorta.

There has been an ever-growing technological development in noninvasive techniques of recording arterial pressure waveform over the last 20 years, and wireless, pocket-sized tonometers have been launched on the market. These instruments can be easily used in clinical practice such as the latest PulsePen tonometer (Fig. 5.18).

Let us now analyze noninvasive methods able to record the central arterial pressure wave corresponding to the ascending aortic pressure wave.

There are two well validated and reliable methods to record the central pressure wave with arterial tonometry: a “direct method” and an “indirect method”.

I am not going to mention the methods measuring central blood pressure in the peripheral districts, which usually use oscillometric systems. In fact, over the last few years, devices which are simple to operate and require little or no training, have been commercialized but they lack scientific and methodological rigor. Unfortunately, these often represent business deals based on models and algorithms without solid scientific basis, whose scientific justification goes through a series of adjustments and algorithm such as “A” is related to “B”, “B” is similar to “C”, “C” is indicative of “D”, therefore, “D” is able to define “A”, which cannot be accepted from a scientific point of view.

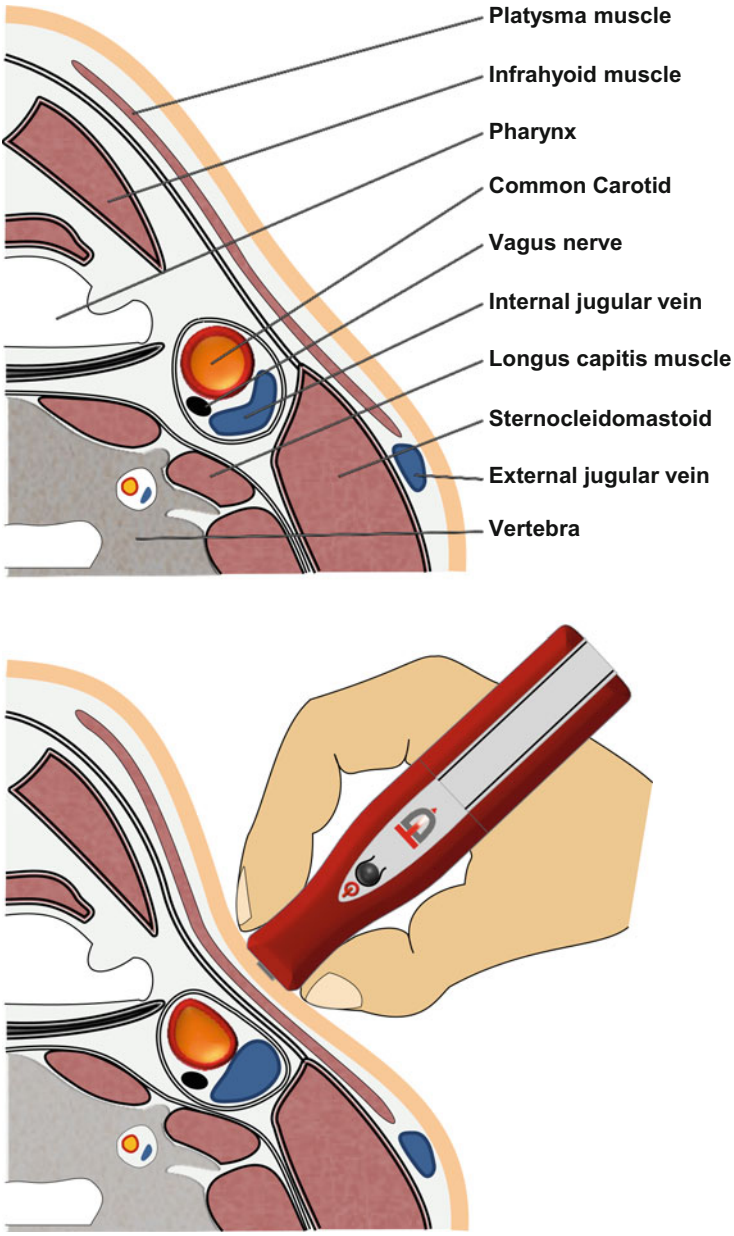


Fig. 5.17 Applanation tonometry at the level of the carotid artery. The carotid artery can be easily pressed down against the underlying stiff structures: pharynx, paravertebral muscles, and sternocleidomastoid muscle

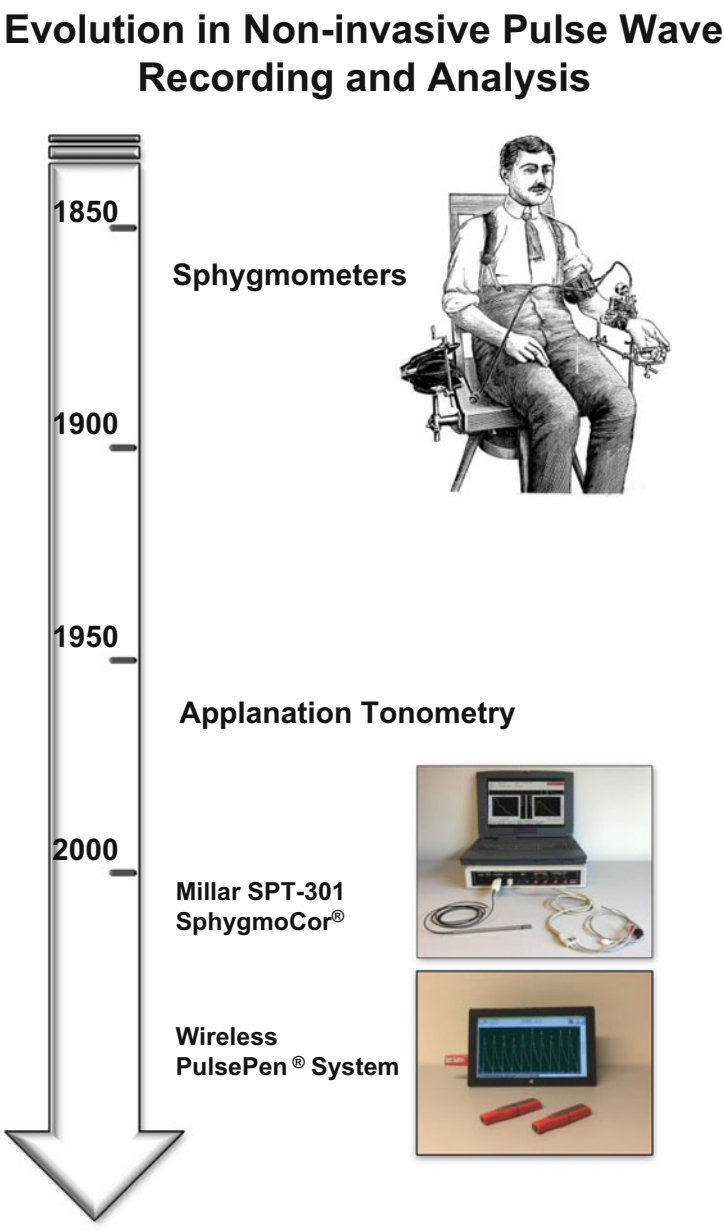


Fig. 5.18 Evolution in non-invasive recording and analysis of pulse wave. From the sphygmometers used in the second half of the 20th century, to the latest, easy-to-use, wireless pocket-sized PulsePen device

5.2.1 Direct Method: Recording of Central Blood Pressure in Carotid Artery

The "direct method" records pulse wave in common carotid artery; it is a surrogate for ascending aortic pressure because these arterial sites are in close proximity.

It has been widely tested that the shape of the pressure wave in the ascending aorta is similar to the one recorded in the common carotid artery, so that direct application of tonometry in the carotid artery seems to be an easy and reproducible approach to record central blood pressure. Moreover, the carotid artery is generally well accessible and superficial (Figs. 5.17 and 5.19), and good quality carotid waveforms can be easily obtained even in obese patients. This technique is reliable for routine high-throughput screening of central pressure.

This is the method used by the PulsePen® (DiaTecne srl, Milan, Italy) and the Complior Analyse® (Alam Medical, Vincennes, France).

The validity of transcutaneous tonometry in measuring the aortic central pressure wave is based on two principles, both widely validated and tested.

1. First of all, the sphygmic waves recorded from transcutaneous tonometry are superimposable onto those recorded by means of catheterization.

   During some hemodynamic sessions, while a catheter, inserted into the origin of the common carotid artery, was recording the pressure wave, carotid transcutaneous tonometry was performed simultaneously; the two pressure waves were absolutely superimposable (Fig. 5.20).

   However, the most accurate method to compare two periodic pressure waves is by analyzing the first harmonics of the arterial pressure wave. It is well known that the analysis of the first six harmonics accurately defines the pressure waveform. Moreover, the analysis of each harmonic has confirmed that the two pressure waves, recorded both noninvasively and invasively, are perfectly superimposable (Fig. 5.21).

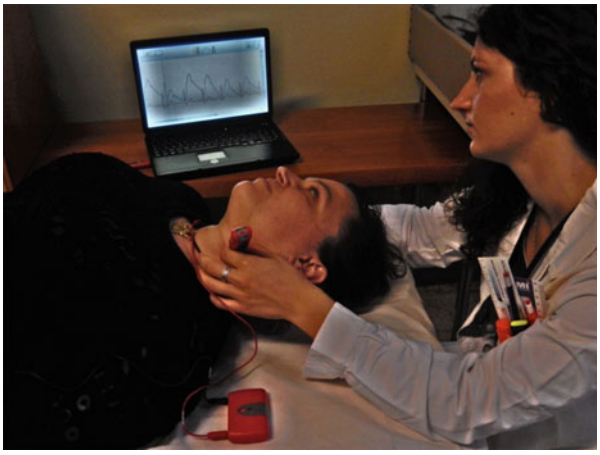


Fig. 5.19 Arterial tonometry performed at the level of the carotid artery using a PulsePen® tonometer

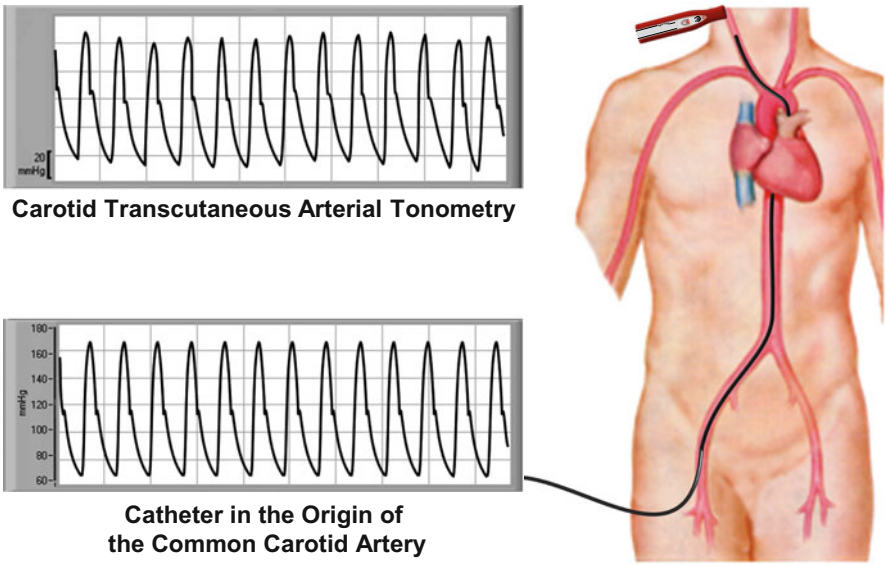


Fig. 5.20 Comparison between the pressure signal recorded in the carotid artery by transcutaneous tonometer and the pressure signal at the origin of the common carotid artery recorded invasively [9]

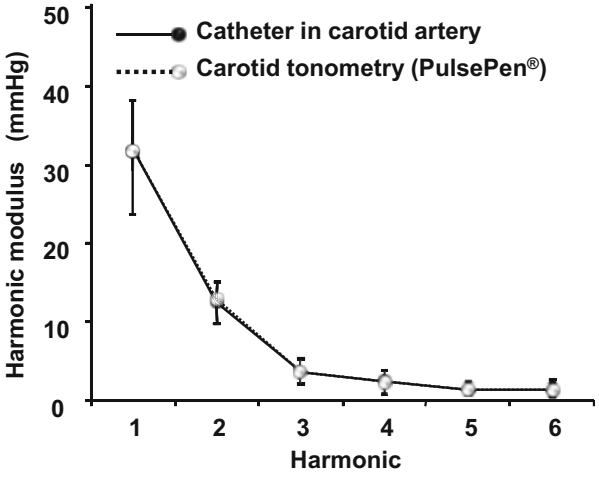


Fig. 5.21 Outcome of Fourier analysis on the first six harmonics of the pressure waveform recorded in the carotid artery by transcutaneous tonometer and the pressure waveform at the origin of the common carotid recorded invasively [9]

2. It is important to note that the sphygmic waves recorded in the carotid artery are similar to the ones recorded in the ascending aorta. While a catheter, placed in the ascending aorta, was recording the pressure wave, carotid transcutaneous

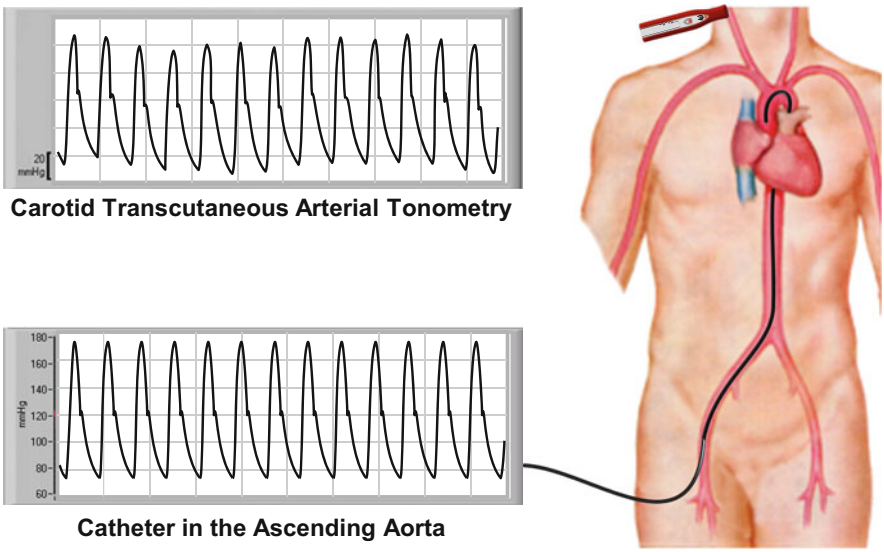


Fig. 5.22 Comparison between the pressure signal recorded in the carotid artery by transcutaneous tonometer and the pressure signal in the ascending aorta recorded invasively [9]

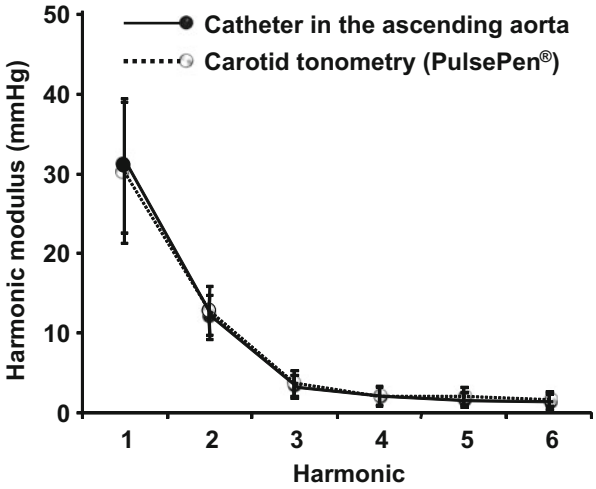


Fig. 5.23 Outcome of Fourier analysis on the first six harmonics of the pressure waveform recorded in the carotid artery by transcutaneous tonometry and the pressure waveform in the ascending aorta recorded invasively [9]

tonometry was performed simultaneously: the two pressure waves were nearly superimposable (Fig. 5.22). The analysis of the first six harmonics showed only a slight, and insignificant difference in the first harmonic of the pressure wave too (Fig. 5.23). The difference between the two pressure wave values was <5 mmHg.

5.2.1.1 Methodological Aspects

The tonometer is easy to use but it is an extremely sensitive instrument, not only to the pressure exerted on the artery to be explored but also to the involuntary movements made both by the operator and by the patient. These movements make the recording of the pressure waveform importantly affected by "noise", which can make the correct identification of both the foot of the blood pressure wave and of transit time a difficult task. It is, therefore, very important to reduce the presence of these "noise" factors to a minimum [10]. Some practical advice to remove the "noise" coming from these undesirable movements is shown in Fig. 5.24.

A good recording, without any artifactual movement, is essential to obtain valid central pulse waveforms and valid PWV values. On the contrary, a pulse pressure waveform, which is incorrectly recorded or affected by artifactual movements, could easily lead to unreliable central blood pressure and PWV values. When recording blood pressure waveforms by means of tonometry, therefore, priority must be given to the quality of the tracing being recorded. In fact, whenever the tonometric test is accurately carried out, the variability in results associated with the operator performance can be reduced to a minimum. Based on these considerations, it is easy to understand that in spite of the general recommendation to use the right carotid artery for PWV assessment, a left-handed operator should carry out the test on the left carotid artery, as the approach to the left side of the neck is easier and characterized by a better performance in such a case.

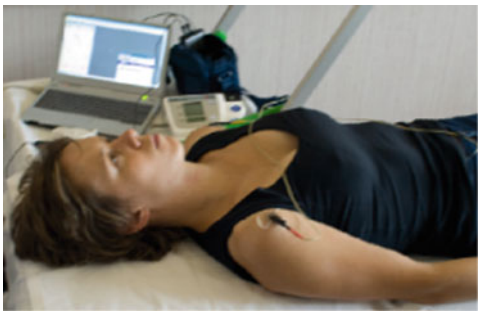
5.2.2 Indirect Method: Transfer Function

With the "indirect method", applanation tonometry is performed in the radial artery (Fig. 5.25); using a generalized transfer function, the central pressure waveform is rebuilt, starting from the waveform recorded in the radial artery calibrated to the blood pressure values measured in brachial artery [11] (Fig. 5.26).

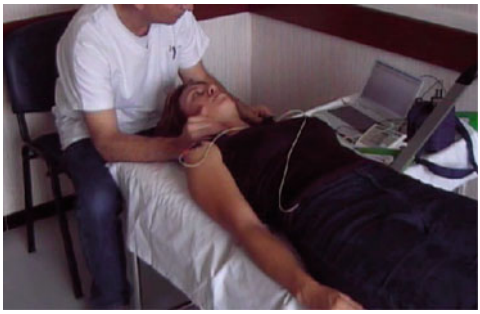
The indirect method is used by the SphygmoCor® (AtCor Medical Pty. Ltd., Sydney, Australia). A similar method is used by the Omron HEM-9000AI® (Omron Healthcare Co. Ltd., Kyoto, Japan), which uses peripheral pressure waveforms recorded by tonometry at the site of the radial artery in order to calculate central systolic blood pressure via a regression equation employing the second systolic peak as an independent variable.

Several researchers are skeptical about this indirect system, most of all in the extreme phases of life or under particular hemodynamic conditions. One wonders why people make things more difficult and analyze the radial arterial pressure waveform, when, in most cases, access to the carotid artery is much easier (measurement of central pressure wave with direct method).

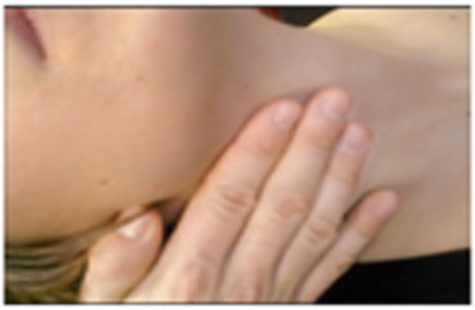
The results of the Asklepios Study [12] showed the occurrence of significant differences between pulse pressure (and systolic blood pressure) values assessed in brachial artery and those obtained in radial artery, differences which were much greater than the differences between central arterial pressure and brachial arterial pressure values (Fig. 5.27). In other words, pulse pressure amplification is more



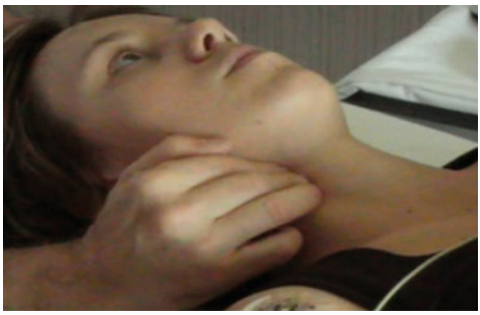
The patient should lie relaxed, in a comfortable position.
The patient should neither hyperextend nor rotate the head.
The absence of the pillow is preferable.



A correct position of the operator with respect to the patient is very important.
The operator should comfortably sit behind the head of the patient.

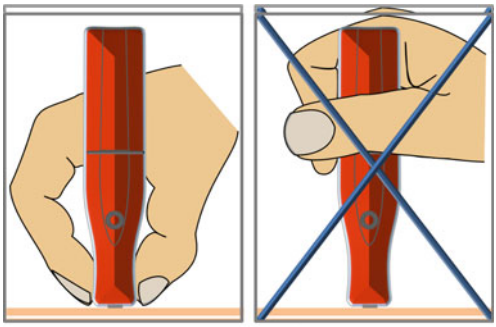


The operator places all the fingers of the flat hand on the neck and locates the position of the carotid artery.
With the tip of the index and middle finger, the operator locates the widest pulsation point on the artery

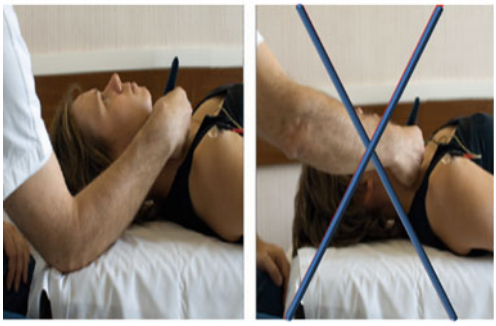


By applying a light pressure on the artery with the fingers, the operator finds the optimal angle where the probe can be applied on the artery.
Only after having 'mentally recorded' the arterial pressure curve sense with fingers, the operator should start using the probe.

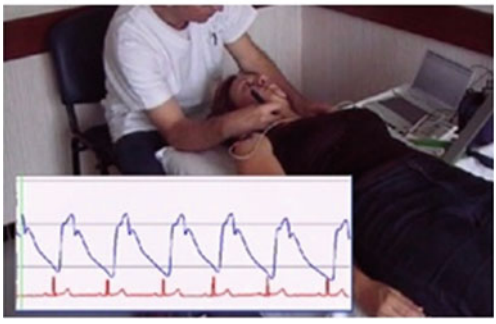
Fig. 5.24 Practical recommendations for the assessment of carotid pulse wave by means of applanation tonometry [10]



To avoid any undesirable movement, the probe should be immobilized at its base between the thumb and the index. With these fingers, the probe should be firmly pressed on the skin



The probe must be considered as an extension of the operator's body, the elbow leaning on the bed, so that the movements connected to involuntary tremors and the instability of the position of the elbow could be minimized.



Both the operator and the patient should be in a natural position, avoiding any active contraction of muscles, which could cause involuntary muscle tremors. Once a good signal is obtained, the operator should hold his/her breath throughout the recording, so that any involuntary hand movement is avoided, which could otherwise affect the tonometric tracing.

Fig. 5.24 (continued)

marked in the brachio-radial arterial segment than in the aortic-axillo-brachial one. If a peripheral waveform is calibrated to brachial systolic and diastolic cuff pressure values, given the abovementioned differences between blood pressure parameters derived from different arterial segments, such procedure might introduce relevant errors in the estimation of central blood pressure. Thus, as a general consideration, caution is needed whenever using algorithms for central pressure estimation based on the measurement of pressure values in brachial artery to calibrate a pressure wave recorded in radial artery.

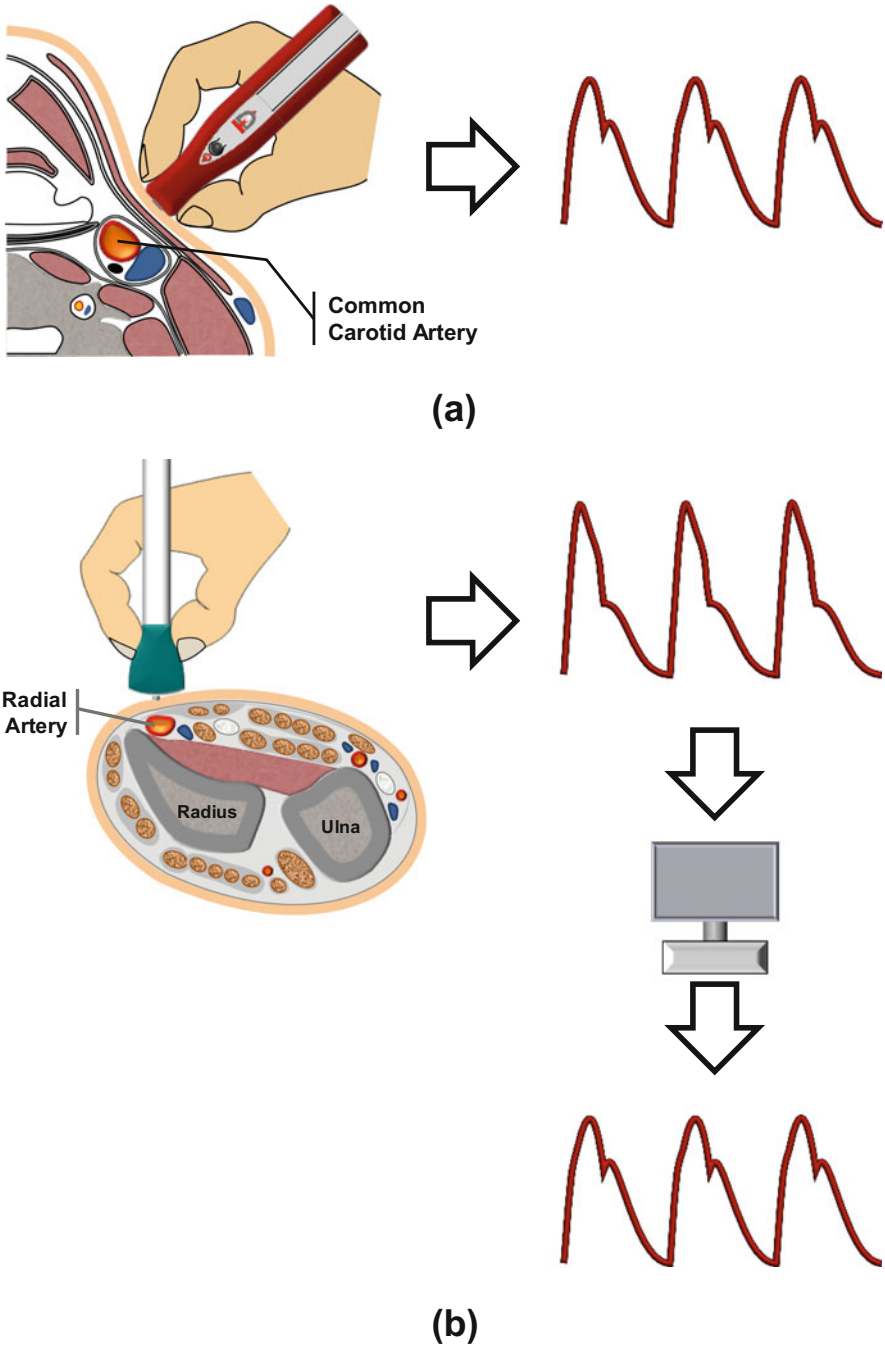


Fig. 5.25 Methods for assessing central blood pressure and pulse wave analysis with arterial tonometry. *Upper panel* (**a**): central blood pressure waveform is recorded at the carotid artery level ("direct method"). *Lower panel* (**b**): arterial pulse wave is recorded at the radial artery level and afterwards software rebuilds the corresponding central pulse waveform and provides central blood pressure values ("indirect method")

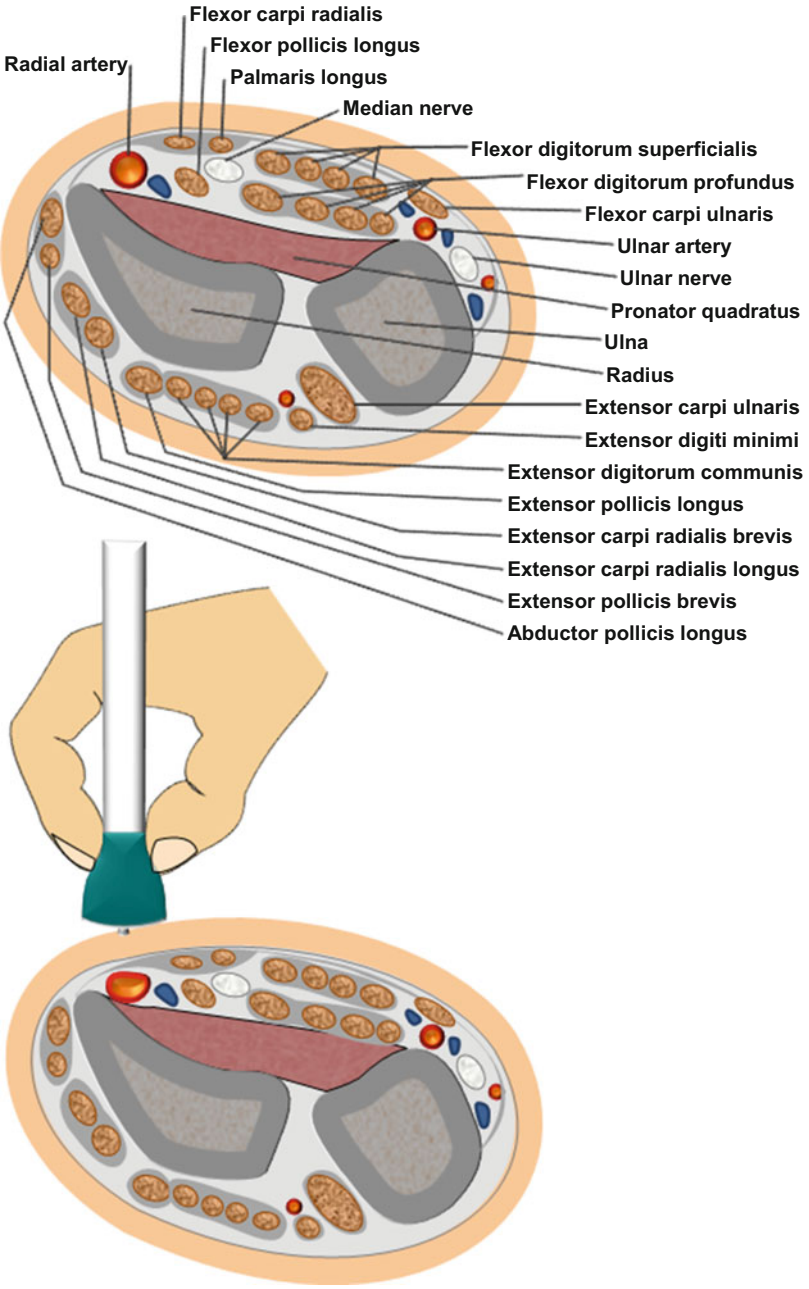


Fig. 5.26 Applanation tonometry at the level of the radial artery. The artery can be easily pressed down against the underlying stiff structures: radius, tendons, and muscular structures

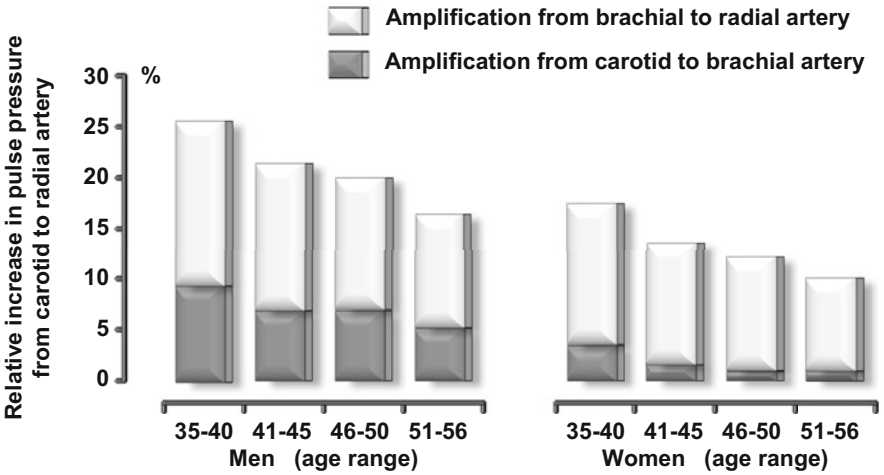


Fig. 5.27 Pulse pressure amplification between carotid and brachial arteries (*dark stippled*) and between brachial and radial arteries (*light stippled*). The *dark* and *light stippled columns* together define the pulse pressure amplification between carotid and radial arteries. The data are for male (on the *left*) and female subjects (on the *right*). Outcomes by Asklepios Study [12]

5.2.3 Calibration of Tonometric Pressure Signal

The main limitation of applanation tonometry is that it cannot provide absolute values of arterial pressure.

A tonometer is able to define pulse pressure values, but it is unable to provide accurate values of diastolic and systolic blood pressure. These are gathered starting from the concept, clearly shown by now, that mean arterial pressure remains constant from the aorta to the peripheral arteries, as does diastolic blood pressure (which tends to decrease, albeit insignificantly, i.e., by <1 mmHg, from the center to the periphery). To sum up, a calibration of tonometric pressure wave using brachial arterial pressure values is always required, in particular when central blood pressure is estimated through the analysis of more or less peripheral pulse waves.

How then are effective values of arterial pressure on the central pressure wave obtained?

Simultaneously, with the recording of transcutaneous tonometry, the value of arterial blood pressure in the brachial artery is measured by a traditional, validated sphygmomanometer. Then mean arterial pressure is calculated from diastolic and systolic blood pressure values. As mean arterial and diastolic pressures are equal in the center and at the periphery, the difference between mean and diastolic pressures will be constant as well. Subsequently, the mean blood pressure value of the central sphygmic wave is defined by the integral of the pressure waveform (Fig. 5.28).

Now, we have the value in mmHg of the difference between mean and diastolic blood pressures and the bits corresponding to this value. At this point, all we have to do is to solve the equation to find the value in mmHg of central systolic arterial pressure:

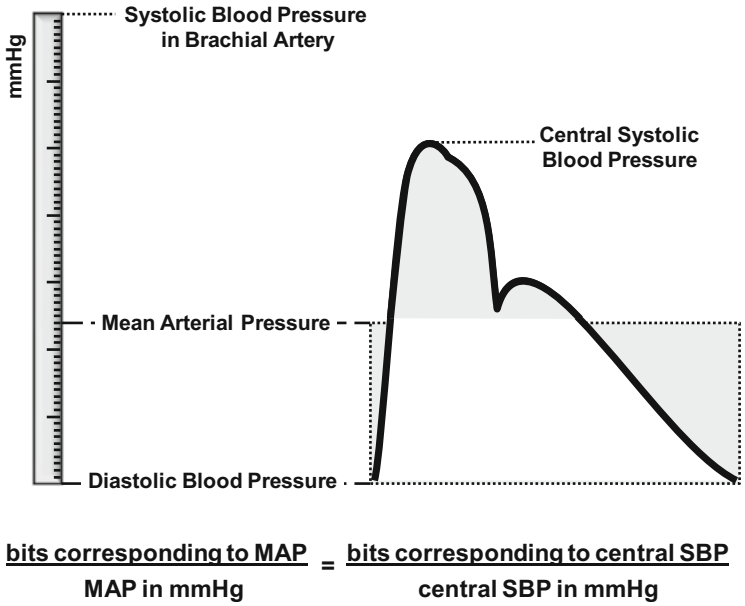


Fig. 5.28 Calibration of pulse wave starting from the pressure values recorded in brachial artery (*column* on the *left*). Mean arterial pressure is defined by the integral of pulse wave analysis (on the *right*)

$$\frac{bits\,corresponding\,to\,Mean\,Arterial\,Pressure}{Mean\,Arterial\,Pressure\,in\,mmHg} = \frac{bits\,corresponding\,to\,Central\,Systolic\,BP}{Central\,Systolic\,BP\,in\,mmHg}$$

The calibration of pulse wave analysis assures that arterial tonometry is performed accurately, as it makes tonometry free from all the variables which could alter the test, such as the pressure exerted by the operator with the probe on the skin when the pressure signal is recorded, and anatomical factors such as the depth of the artery.

Moreover, the examination of the pulse pressure waveform and the definition of pressure values occurs by analyzing the pulse pressure waveform beat to beat; in this way, all variables related to instability in the signal offset secondary to respiratory movements of the patient are removed.

To obviate the problem linked to the choice of the algorithm to define mean arterial pressure starting from the brachial artery, the PulsePen® tonometer provides the possibility of defining the real value of mean arterial pressure starting from the integral of the tonometric pressure wave recorded in the brachial artery. Theoretically, the most reliable method to derive calibrated central blood pressure values from analysis of radial or carotid waveforms should be based on brachial pulse waveform recordings, calibrated by systolic and diastolic blood pressure measured through a validated sphygmomanometer at the same brachial artery level. Subsequently, the mean arterial pressure so calculated from the integral of the brachial

pressure waveform can be used, together with the corresponding diastolic blood pressure, to calibrate pulse waveforms recorded elsewhere. Actually, with a standard procedure, the inter- and intraobserver reproducibility of pulse waveforms recorded at brachial site is weak because the brachial artery lies beneath the stiff bicipital aponeurosis; it is not supported by bone and, thus, cannot be reliably flattened under the sensor. However, the reliability of brachial pulse wave recordings may significantly increase by placing the index and middle fingers against the lateral wall of the brachial artery aimed at preventing its displacement by the probe and at allowing the adequate recording of pulse waveforms (Fig. 5.29).

5.3 Pulse Wave Analysis

Since the information which the pulse affords is of so great importance, and so often consulted, surely it must be to our advantage to appreciate fully all it tells us, and to draw from it every detail that it is capable of imparting

(Frederick Akbar Oratio Mahomed, 1872 [13])

F.A.O. Mahomed was a man of genius of the end of the 19th century, and he is considered to be a pioneer of pulse wave analysis. After the first enthusiasm regarding pulse wave analysis, it fell into disuse, because of the introduction of the Riva-Rocci sphygmomanometer in clinical practice. Since then, for almost the whole of the 20th century, the possibility of assessing and analyzing pulse wave globally has become obsolete, owing to the use of two values: systolic and diastolic blood pressure values.

The ability to measure the blood pressure values has actually led to unquestionable advantages in daily clinical practice. High blood pressure values have been recognized as the main risk factor for cardiovascular mortality and morbidity, and the reduction in blood pressure, measured with sphygmomanometer, has significantly reduced cardiovascular mortality in Western countries.

However, the suitability and accuracy of traditional blood pressure measurements for cardiovascular risk staging is now a matter of lively debate. Over recent years, pulse waveform analyses have experienced somewhat of a revival. Indeed, the technique of pulse wave analysis, using non-invasive high-fidelity arterial tonometers, has recently become increasingly popular. This method can provide not only quantitative, although indirect, information concerning the levels of central blood pressure but also qualitative data on the ascending aortic waveform. Analysis of such waveforms can, in fact, define the elastic properties of the arterial wall and can estimate the importance and the transmission speed of reflected waves.

The tables and figures which follow present the main parameters defined by the pulse wave that are used in central pulse wave analysis (Tables 5.1 and 5.2; Figs. 5.30 and 5.31).

The most important element, which characterizes the systolic phase of the pulse waveform, is the inflection point (P_i), which represents the point where forward and

Fig. 5.29 Applanation tonometry at brachial site. Brachial artery is not supported by bone and, thus, cannot be reliably flattened under the sensor of the tonometer probe (*upper panel*). By placing index and middle fingers at one side of the brachial artery, it is possible to prevent its displacement by the tonometer probe and, thus, to allow an accurate recording of pulse waveforms (*medium* and *lower panels*)

Table 5.1 Parameters used in central pulse wave analysis (part I)

Parameter	Acronym	Meaning
Central systolic blood pressure	${}_{c}SBP$	The maximum blood pressure value in systole
Diastolic blood pressure	DBP	The blood pressure value in end-diastole
Central pulse pressure	${}_{c}PP = {}_{c}SBP - DBP$	The pulse pressure, i.e., the systo-diastolic change in arterial pressure
End-systolic blood pressure	ESBP	The blood pressure value at the end of systole
Travel time of the reflected wave	Ti	The time delay of the backward waveform, corresponding to P_i
Blood pressure at inflection point	P_i	The blood pressure value corresponding to the point where the backward wave starts superimposing onto the forward wave
Augmented pressure	$AP = {}_{c}SBP - P_i$	The increase in blood pressure due to the earliness of the backward wave
Augmentation index	$AIx = \frac{AP}{{}_{c}PP}$	The percentage increase in blood pressure due to the earliness in the backward wave with regard to the pulse pressure

backward waves meet. When it appears on the pulse wave, it is "shoulder shaped". The time delay in backward wave is defined by T_i.

5.3.1 Augmentation Index

Augmentation index (AIx) is a parameter which provides an indication of the incidence of reflected waves on the total pulse pressure. The "weight" of the backward wave is related to both its early superimposition onto the forward wave and the magnitude and distribution of reflected waves. AIx is calculated as the ratio between the augmented pressure (AP) due to reflected waves and the pulse pressure (PP = systolic − diastolic blood pressure):

$$\mathrm{AIx} = \frac{\mathrm{AP}}{\mathrm{PP}}$$

In the previous chapters, we have seen, from the previous chapter, that, under marked arterial stiffness conditions, there is early superimposition of backward waves onto the forward wave, causing an increase in systolic blood pressure. AIx is a useful parameter to quantify the role of wave reflection in high systolic blood pressure values.

By convention, this ratio assumes a negative value when the inflection point P_i (which represents the point where forward and backward waves meet) is after the peak systolic pressure; on the contrary, AIx is positive if P_i is before the peak systolic pressure (Fig. 5.32). This convention allows us to have a "continuum" of AIx values in relation to the timing of reflected waves.

Table 5.2 Parameters used in pulse wave analysis (part II)

Parameter	Acronym	Meaning
Mean arterial pressure	MAP	Mean arterial blood pressure values, set by the integral of the pressure curve
Mean pulse pressure	MPP = MAP – DBP	Mean pulse pressure values (mean arterial pressure – diastolic blood pressure)
Mean systolic blood pressure	MSBP	Mean arterial blood pressure values during the systolic phase of the cardiac cycle
Mean systolic blood pressure	MDBP	Mean arterial blood pressure values during the diastolic phase of the cardiac cycle
Left ventricular ejection time	LVET	Duration of the systolic phase of the cardiac cycle
Diastolic time	DT	Duration of the diastolic phase of the cardiac cycle
Heart period	HP	Duration of the cardiac cycle, corresponding to the R'–R' interval of ECG
Diastolic time fraction	$\mathrm{DTF} = \frac{\mathrm{DT}}{\mathrm{HP}}$	Diastolic time as a fraction of the heart period
Systolic pressure–time index (tension–time index)	SPTI (TTI) = MSBP · LVET	Area subtending the systolic phase; it represents the myocardial oxygen demand
Diastolic pressure–time index	DPTI = (MDBP – LVDP) DT	Area included between pulse wave in ascending aorta and pressure wave in left ventricle in diastole (LVDP); it represents the myocardial oxygen supply
Subendocardial viability ratio	$\mathrm{SEVR} = \frac{\mathrm{DPTI}}{\mathrm{SPTI}}$	This index represents the balance between subendocardial oxygen supply and demand
Amplification phenomenon	Ampl. $= {}_{\mathrm{p}}\mathrm{SBP} - {}_{\mathrm{c}}\mathrm{SBP}$	Difference between systolic blood pressure values measured in the brachial artery ($_{\mathrm{p}}$SBP) with respect to systolic blood pressure values in the ascending aorta (cSBP)
Pulse pressure amplification (%)	$\mathrm{PPA} = \frac{\left({}_{\mathrm{p}}\mathrm{PP} - {}_{\mathrm{c}}\mathrm{PP}\right)}{{}_{\mathrm{c}}\mathrm{PP}}$	Percentage increase in pulse pressure values measured in the brachial artery ($_{\mathrm{p}}$PP) with respect to pulse pressure values measured in the ascending aorta (cPP)
Form factor	$\mathrm{FF} = \frac{\mathrm{MPP}}{{}_{\mathrm{c}}\mathrm{PP}}$	Ratio between mean pulse pressure and pulse pressure; it is an attempt to "quantify" pulse waveform

The inflection point (P_i) is generally easily recognizable in pulse waveform analysis. All the same, when pulse waves are recorded with a low sampling rate (<500 Hz), the detection of P_i may be difficult and the assessment of AIx unreliable.

It has to be acknowledged that several factors may affect AIx (Fig. 5.33):

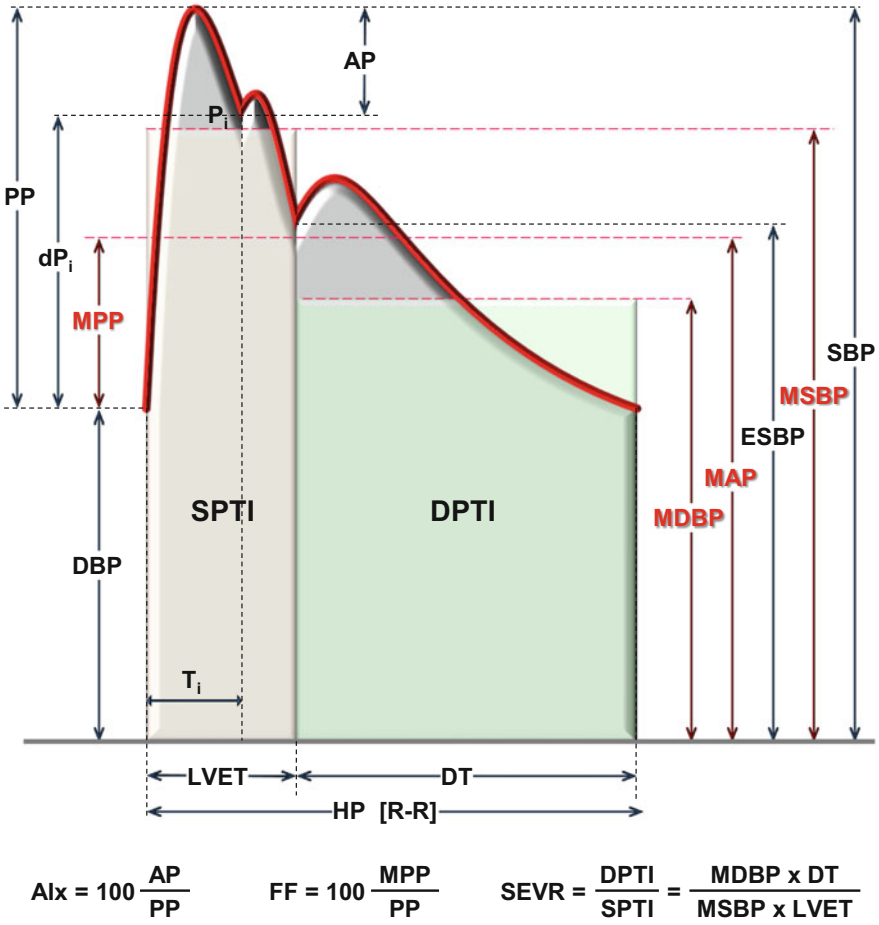


Fig. 5.30 Parameters defined in pulse wave analysis in young people: *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PP* pulse pressure, *ESBP* end-systolic blood pressure, *AP* augmented pressure, defined by wave reflection; P_i inflection point, T_i timing of reflected wave, dP_i pulse pressure at T_i, *MAP* mean arterial pressure, *MPP* mean pulse pressure, *MSBP* mean systolic blood pressure, *MDBP* mean diastolic blood pressure, *SPTI* systolic pressure–time index, *DPTI* diastolic pressure–time index, *HP [R–R]* heart period [R–R interval], *AIx* augmentation index, *FF* form factor, *SEVR* subendocardial viability ratio

– Arterial stiffening. As we have shown in the previous chapter, the value of AIx is mainly determined by the viscoelastic properties of the aorta and large arteries, therefore by measurement pulse wave transit time in the aorta
– The magnitude and variability of reflected waves, mainly in relation to systemic vascular resistance

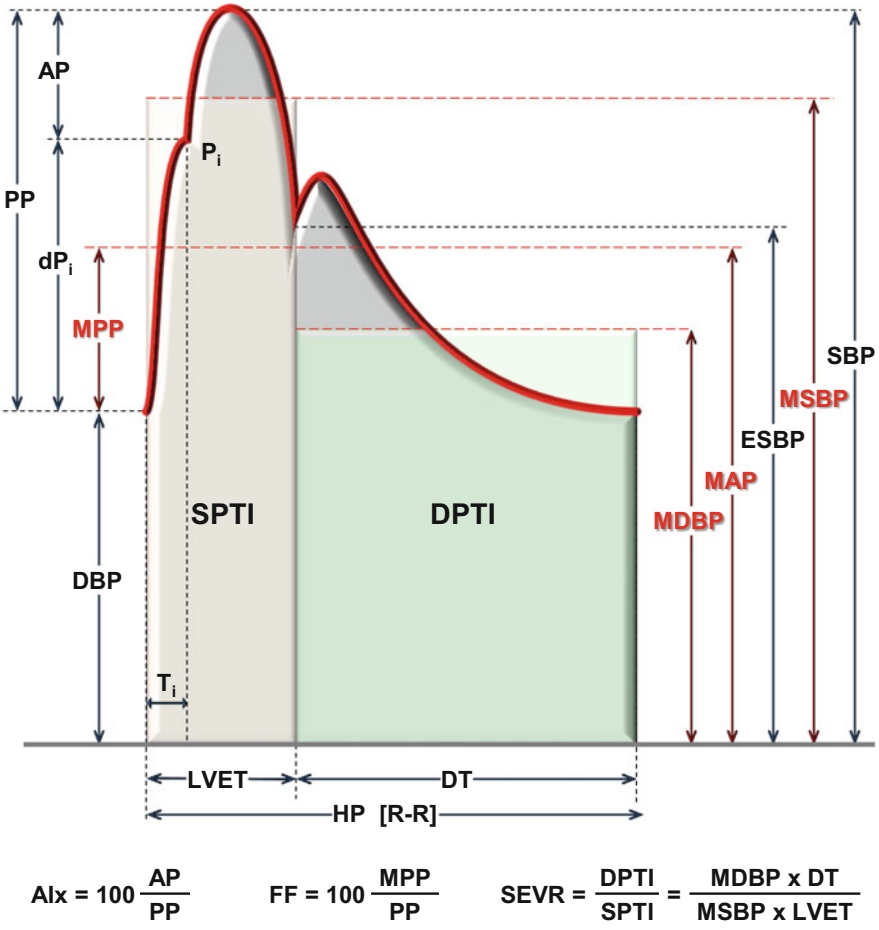


Fig. 5.31 Parameters defined in pulse wave analysis in elderly people: *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PP* pulse pressure, *ESBP* end-systolic blood pressure, *AP* augmented pressure, defined by wave reflection; P_i inflection point, T_i timing of reflected wave, dP_i pulse pressure at T_i, *MAP* mean arterial pressure, *MPP* mean pulse pressure, *MSBP* mean systolic blood pressure, *MDBP* mean diastolic blood pressure, *SPTI* systolic pressure–time index, *DPTI* diastolic pressure–time index, *HP [R–R]* heart period [R–R interval], *AIx* augmentation index, *FF* form factor, *SEVR* subendocardial viability ratio

- The length of the aorta (related to an individual's height), because at any given level of arterial distensibility, the nearer the reflection sites are to the ascending aorta, the shorter is the time needed for the reflected wave to reach it
- The possible presence of vascular prostheses
- The patient's heart rate; an increase in heart rate being accompanied not only by an increase in pulse wave velocity but also by a decrease in augmented pressure, i.e., in AIx

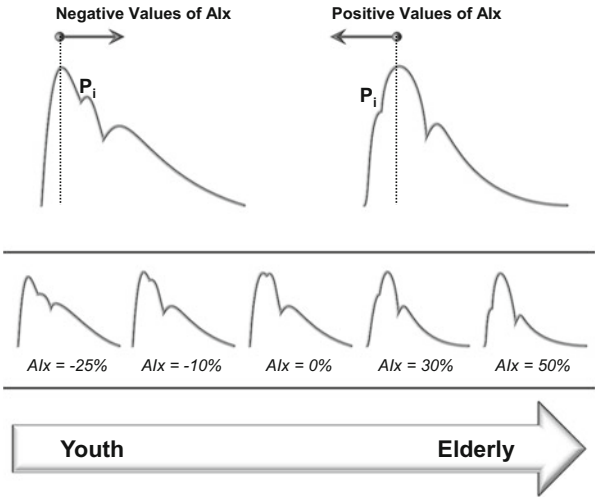


Fig. 5.32 Augmentation index (AIx) values are negative if the point of encounter between forward and backward waves (P_i) is after the peak systolic pressure; values are positive if P_i is before the peak systolic pressure. At the *bottom* of the picture, some examples with growing values of AIx are shown

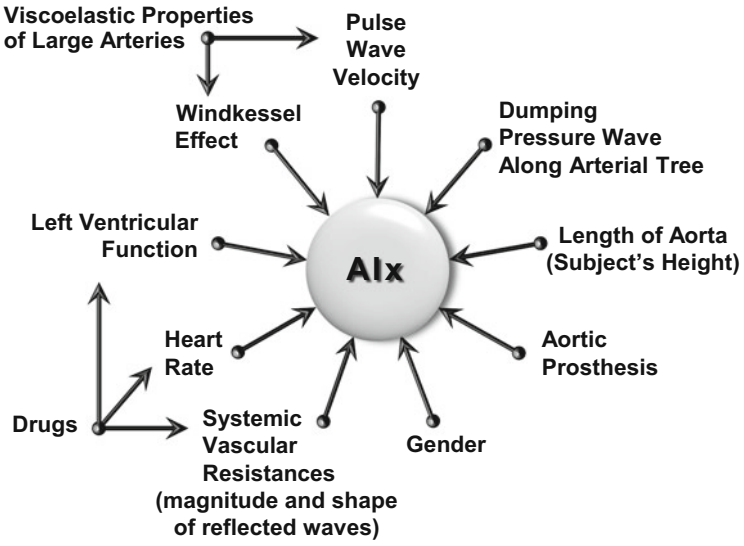


Fig. 5.33 Several factors affecting augmentation index (AIx)

– The phenomenon of pressure wave attenuation while traveling along the arterial tree
– The role of gender; several studies having shown significantly higher values of AIx in females than in males of comparable height

Thus, given the contribution of several factors to AIx magnitude, the use of this parameter as a specific index of the viscoelastic properties of large arteries is incorrect and may lead to inaccurate estimates [14]. In fact, in clinical practice, it is not uncommon to find a marked discrepancy between pulse wave velocity (considered as the gold-standard marker of arterial distensibility) and AIx values, which may indeed be due to the multiple factors involved in determining the latter parameter.

Heart rate (HR) is one of the main parameters affecting AIx values, and it has been calculated that an increase in heart rate of 10 beats per minute (bpm) causes a decrease in AIx of 3.9 %. Therefore, to avoid the effect of heart rate, it is possible to normalize the data of AIx for standard heart rate.

To normalize data for heart rate of 75 bpm ($AIx_{@75}$), the formula is:

$$AIx@75 = AIx - 0.39(75 - HR).$$

For instance:

for an AIx of 20 and a HR of 90 bpm: $AIx_{@75} = 20 - 0.39\ (75 - 90) = 25.85\ \%$
for an AIx of 20 and a HR of 50 bpm: $AIx_{@75} = 20 - 0.39\ (75 - 50) = 10.25\ \%$

However, there are some doubts related to this formula. Actually, this formula was obtained by a study which used the SphygmoCor transfer function, in a well-defined population and under particular conditions. Therefore, it would not be correct to extend it to different situations, where subjects of different ages and conditions and with different devices are studied. A valid and advisable alternative could be the incorporation of heart rate covariates into statistical models. In this way, AIx values are normalized for heart rate values.

Now, let us take a break and look at some pictures of some central blood pressure waves corresponding to subjects of different ages (Figs. 5.34, 5.35, 5.36, 5.37, 5.38, 5.39, 5.40, 5.41, and 5.42).

I would like you to pay attention, most of all, to two elements which change dramatically with aging:

1. The inflection corresponding to the beginning of the superimposition of backward waves (P_i), which becomes increasingly earlier with aging:
   (a) In young people, the inflection (P_i) occurs after peak systolic pressure: this causes negative values of AIx; in this case, systolic blood pressure values are not affected by backward waves at all
   (b) In adults, there is a camel's hump-shaped waveform, and the values of AIx are around zero. In these cases, the influence of backward waves on systolic blood pressure is insignificant as well
   (c) With further aging, the values of AIx become absolutely positive, so that systolic blood pressure is mainly defined by the early superimposition of backward waves onto the forward wave

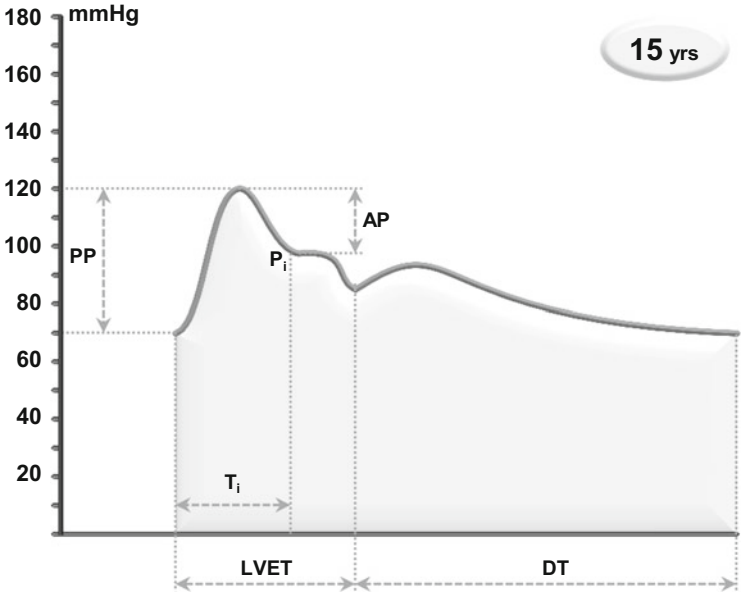


Fig. 5.34 15-year-old subject, AIx: −43 %

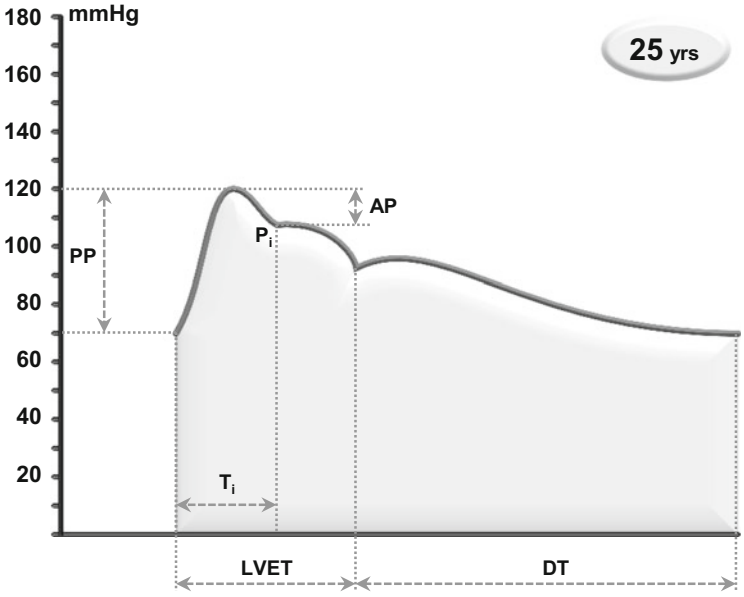


Fig. 5.35 25-year-old subject, AIx: −24 %

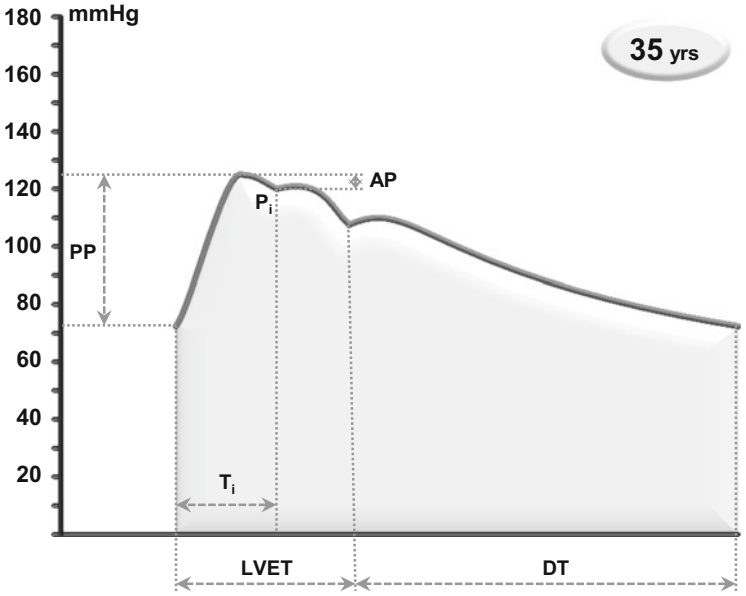


Fig. 5.36 35-year-old subject, AIx: −5 %

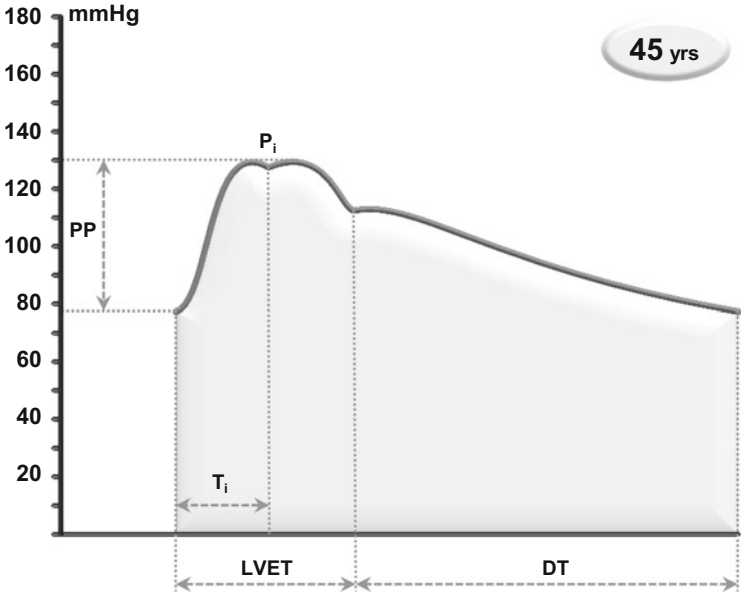


Fig. 5.37 45-year-old subject, AIx: +3 %

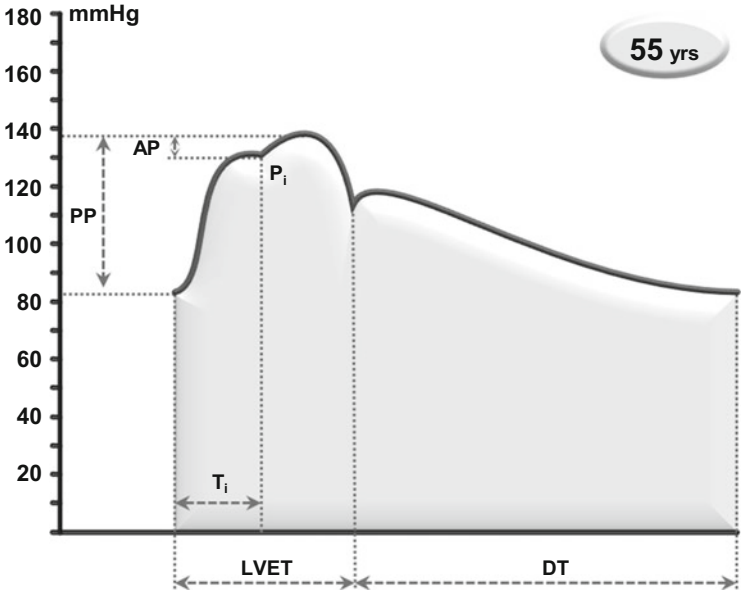


Fig. 5.38 55-year-old subject, AIx: +14 %

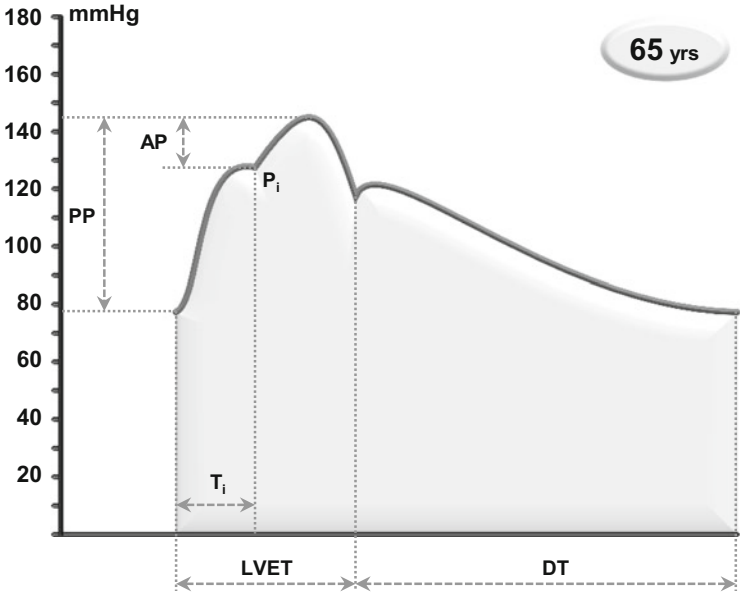


Fig. 5.39 65-year-old subject, AIx: +24 %

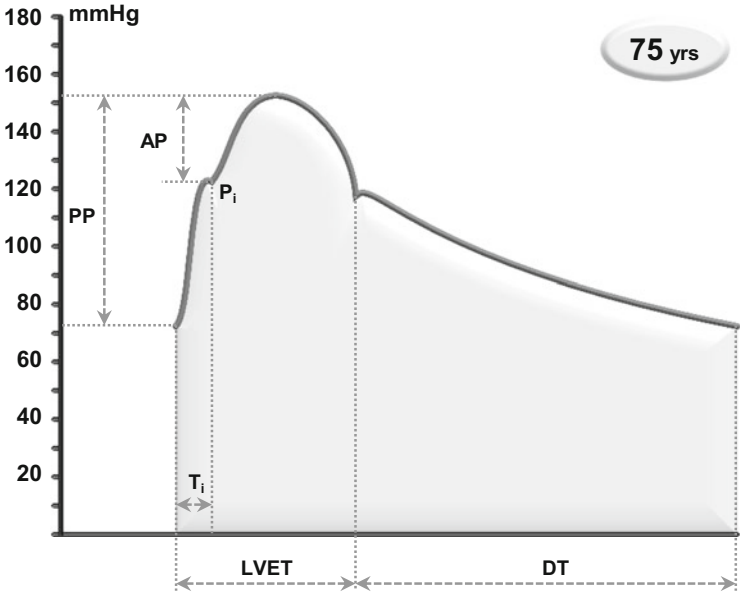


Fig. 5.40 75-year-old subject, AIx: +36 %

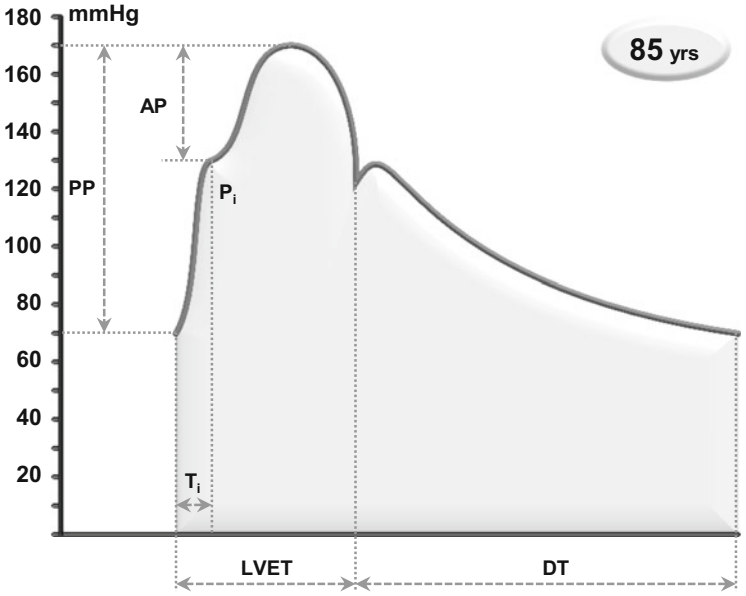


Fig. 5.41 85-year-old subject, AIx: +42 %

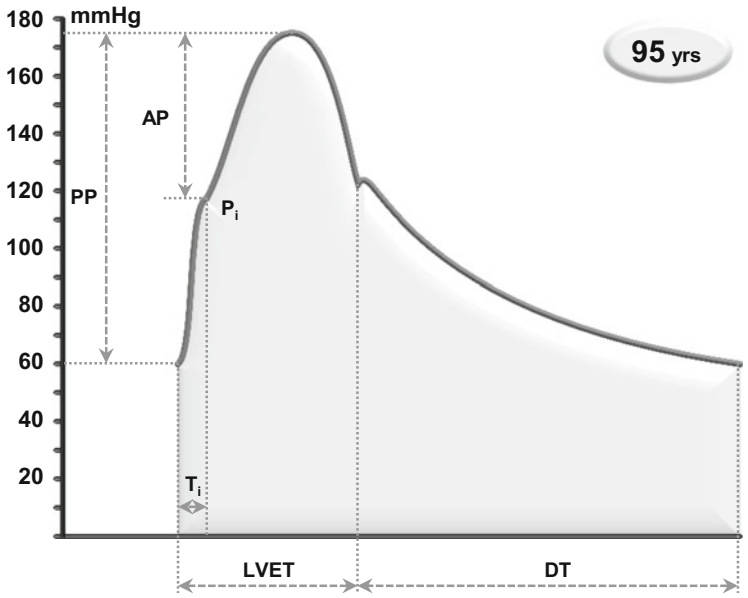


Fig. 5.42 95-year-old subject, AIx: +50 %

Table 5.3 Classification of central pulse waveform (Murgo–Nichols)

	AIx (%)	Timing of reflected waves	Age (years)	Diastolic waveform
Type A	>12	Protosystole	>40, <65	Concave
Type B	>0, <12	Mesosystole	>30, <40	Convex
Type C	<0	End-systole	<30	Convex
Type D	>>12	Early protosystole	>65	Concave

2. In diastolic phase of the cardiac cycle, the waveform becomes progressively emptied out and depleted with age, being a convex hill in young people and a concave crater in the elderly.

According to the classification suggested by Murgo (1980) and later modified by Nichols (1992), it is possible to distinguish four types of pulse waveforms on the basis of the earliness of backward waves (Table 5.3 and Fig. 5.43).

5.3.2 Form Factor

The form factor (FF) is a parameter created in an attempt to "quantify" the different pulse waveforms. It is defined as the ratio between mean pulse pressure (MPP, i.e.,

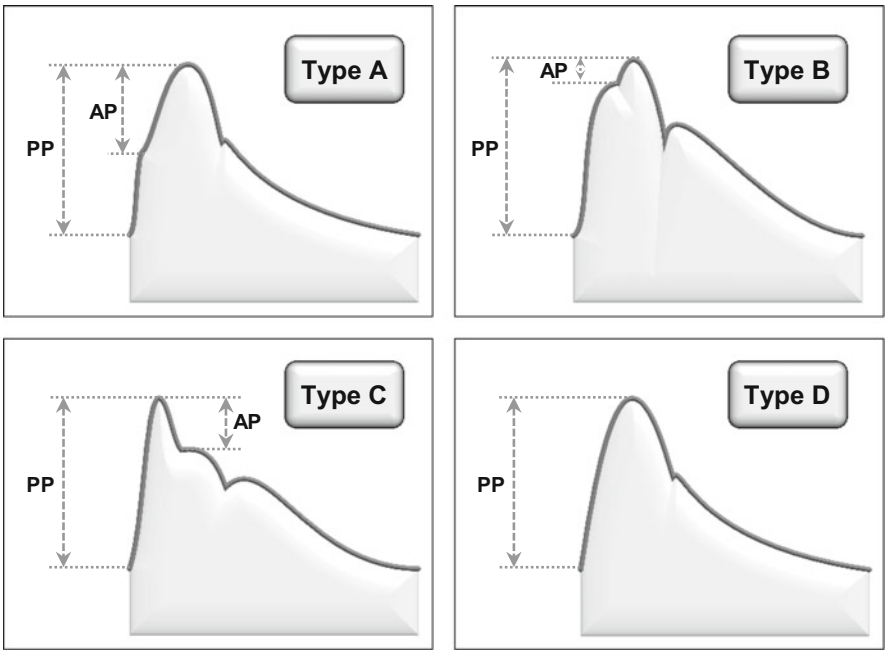


Fig. 5.43 Classification of central pulse waveforms by Murgo–Nichols: *PP* pulse pressure, *AP* augmented pressure due to backward waves

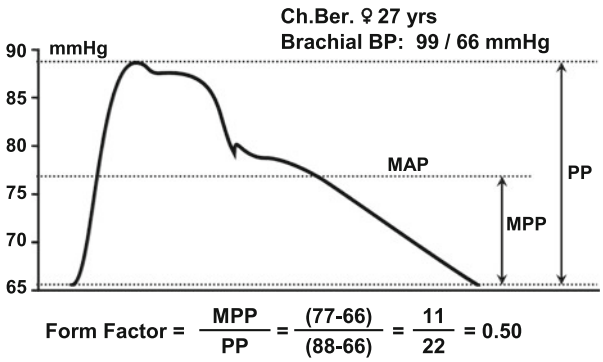


Fig. 5.44 Form factor in a 27-year-old subject. *MAP* mean arterial pressure, *MPP* mean pulse pressure, *PP* pulse pressure

mean arterial pressure from which diastolic blood pressure is subtracted) and pulse pressure (PP = systolic blood pressure − diastolic blood pressure).

The form factor measurement is particularly important in central blood pressure wave analysis. Let us now consider three examples regarding the form factor calculation, corresponding to the carotid pulse waveform in a 27-year-old woman (Fig. 5.44), a healthy 51-year-old man (Fig. 5.45), and an 84-year-old man with hypertension (Fig. 5.46).

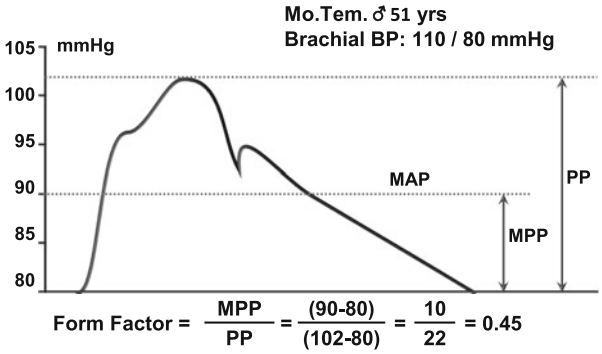


Fig. 5.45 Form factor in a 51-year-old subject. *MAP* mean arterial pressure, *MPP* mean pulse pressure, *PP* pulse pressure

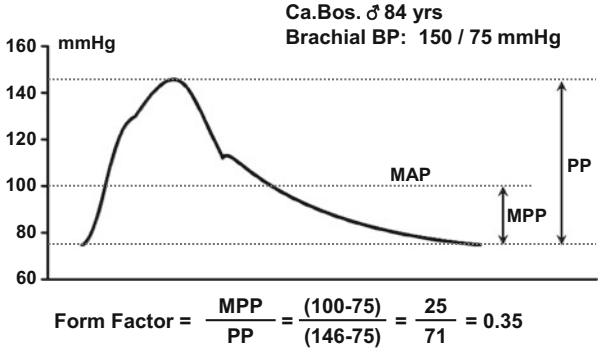


Fig. 5.46 Form factor in an 84-year-old subject. *MAP* mean arterial pressure, *MPP* mean pulse pressure, *PP* pulse pressure

5.3.3 Pulse Pressure Amplification

Amplification of pulse pressure is defined by the increase in blood pressure values from the center (the ascending aorta) towards the periphery of the cardiovascular system (Fig. 5.47). We have already seen in Chap. 4 that the amplification phenomenon can be justified by the presence of blood pressure reflected waves. Under undamaged viscoelastic properties of the arterial wall, backward waves superimpose onto forward waves, during systolic phase, only in the peripheral arteries, near reflection sites. As they move centripetally, backward waves arrive late in the ascending aorta, during end-systolic phase, and superimpose onto the forward wave, most of all during diastolic phase. In this way, pulse pressure values in the ascending aorta are not affected by the presence of backward waves. This mechanism explains the observation that arterial pressure is higher in the peripheral arteries (radial, brachial, femoral, arteries, etc.) than in the ascending aorta.

Some studies have shown that the reduction or the absence of pulse pressure amplification is a significant predictor of cardiovascular mortality [15, 16]. The PARTAGE study, which involved more than 1100 nursing-home residents over the age of 80 years, showed that reduced pulse pressure amplification values are related

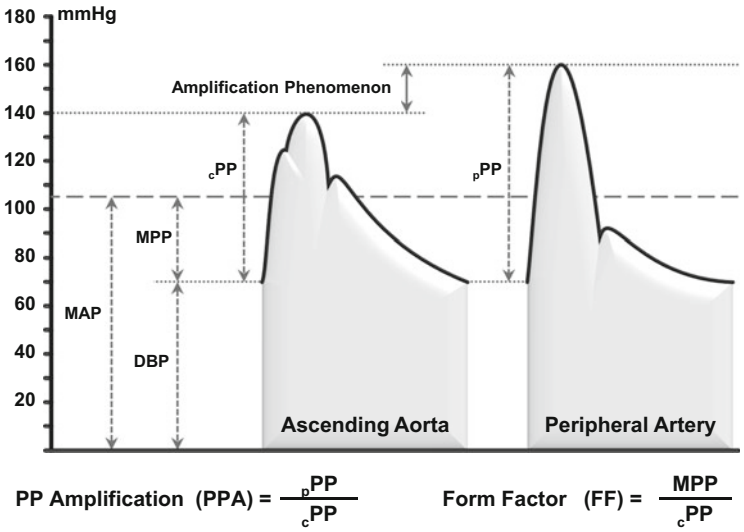


Fig. 5.47 Definition of pulse pressure amplification (PPA) and form factor (FF). *MAP* mean arterial pressure, *MPP* mean pulse pressure, *DBP* diastolic blood pressure, $_cPP$ central pulse pressure, $_pPP$ peripheral pulse pressure

to marked prevalence of cardiovascular disease [17] (Fig. 5.48) and are real predictors of total mortality [18] (Fig. 5.49).

Different parameters have been suggested for quantification of blood pressure amplification:

1. The simplest parameter is measurement of the difference (in absolute values) between systolic blood pressure values measured with traditional method at the arm ($_pSBP$) and central blood pressure values ($_cSBP$) measured with arterial tonometry:

$$\text{Amplification} = {}_pSBP - {}_cSBP \ (\text{in mmHg}).$$

2. Another parameter, the amplification ratio (AR), is defined as the ratio between pulse pressure values (systolic blood pressure – diastolic blood pressure) measured from the brachial artery ($_pPP$) with traditional method and central pulse pressure ($_cPP$) measured with arterial tonometry:

$$AR = \frac{{}_pPP}{{}_cPP}$$

If, for instance, this ratio is 1.30, it means that the amplitude of pulse pressure values in brachial artery is 30% higher than pulse pressure values in the ascending aorta.

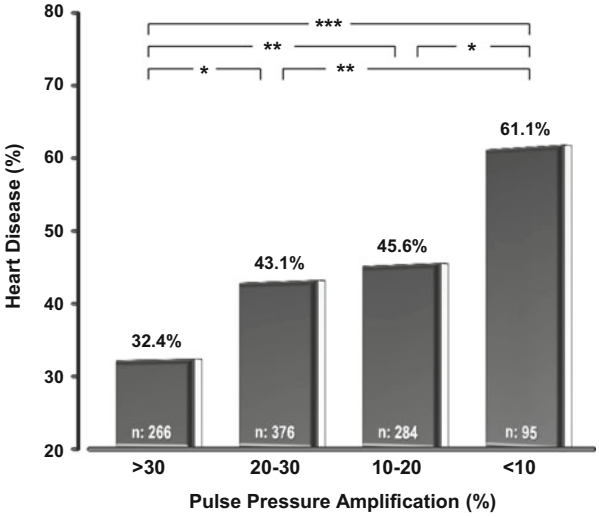


Fig. 5.48 Prevalence of cardiovascular diseases in relation to pulse pressure amplification. Data adjusted according to age, gender, mean arterial pressure, and heart rate. $*p < 0.01$, $**p < 0.005$, $***p < 0.001$. Outcomes of the PARTAGE Study [...]

3. Likewise, pulse pressure amplification (PPA) defines the percentage increase in pulse pressure values measured from the brachial artery ($_{p}$PP) by traditional method, with respect to central pulse pressure values ($_{c}$PP) measured with arterial tonometry:

$$\mathrm{PPA} = 100\,\frac{\left({}_{p}\mathrm{PP} - {}_{c}\mathrm{PP}\right)}{{}_{c}\mathrm{PP}}\,(\%).$$

   This parameter is better than the previous ones as it is more intuitive and easier to understand.
4. Actually, pulse pressure amplification has uncertain clinical relevance as there is no unequivocal method to measure this phenomenon. The problem arises because of the need to calibrate central pressure wave, recorded with tonometry, using diastolic and mean arterial pressure values measured from brachial artery with traditional sphygmomanometers.

5.3.3.1 Form Factor Displaying Pulse Pressure Amplification

Actually, by analyzing the central pulse wave, it is possible to define the pulse pressure amplification regardless of peripheral arterial pressure values. The form factor in central artery (recorded from the common carotid or with transfer function from radial artery) is a parameter defining the magnitude of pulse pressure amplification, regardless of peripheral arterial pressure values.

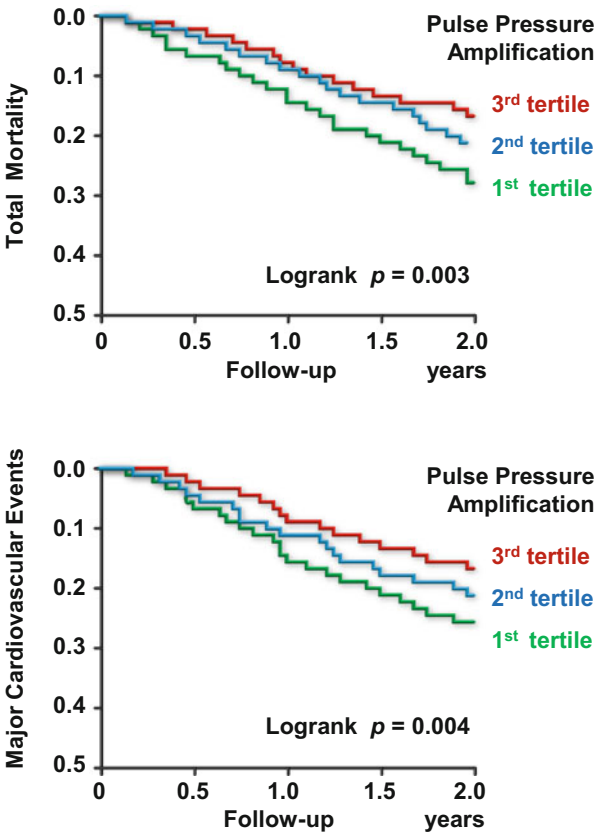


Fig. 5.49 Survival curves (log-rank analyses) for total mortality and major cardiovascular events in 1126 subjects according to the tertiles of pulse pressure amplification (1st: 0–18.8 %; 2nd: 18.9–28.0 %; 3rd: 28.1–58.7 %). Outcomes of the PARTAGE Study [...]

Pulse pressure amplification ratio (AR) can be expressed as the ratio between brachial pulse pressure ($_{p}$PP) and aortic pulse pressure ($_{c}$PP), i.e., AR = $_{p}$PP/$_{c}$PP. In clinical practice, pulse waveforms can be recorded, noninvasively, by transcutaneous arterial tonometers. These devices can record pulse waveform and measure pulse pressure values, but they are unable to set the corresponding real value of systolic and diastolic blood pressures. This is the reason why a process of calibration of pulse waveform, using mean and diastolic blood pressure values, is required. At present, in fact, calibration of the central pulse waveform is based on the observation that mean arterial pressure is constant in the aorta and at the periphery of the arterial system and that diastolic blood pressure changes are insignificant (<1 mmHg). Until a few years ago, mean arterial pressure was calculated by adding one-third of peripheral pulse pressure values to diastolic blood pressure values (MAP = DBP + $_{p}$PP/3). From this formula, therefore, the clear inference is that peripheral pulse pressure is three times the difference between arterial mean

pressure (MAP) and diastolic blood pressure (DBP), i.e., three times the mean pulse pressure (MPP):

$$_{\mathrm{p}}\mathrm{PP} = 3(\mathrm{PAM} - \mathrm{PAD}) = 3\mathrm{MPP}.$$

It has recently been shown that mean arterial pressure, at the brachial artery, is underestimated by this formula and that it would be more correct to add 40 % of peripheral pulse pressure to diastolic blood pressure values ($\mathrm{PAM} = \mathrm{DBP} + {}_{\mathrm{p}}\mathrm{PP}/2.5$). In this case, peripheral pulse pressure will be 2.5 times the difference between mean arterial pressure (PAM) and diastolic blood pressure (DBP), i.e., 2.5 times the mean pulse pressure (MPP):

$$_{\mathrm{p}}\mathrm{PP} = 2.5(\mathrm{PAM} - \mathrm{PAD}) = 2.5\mathrm{MPP}.$$

The difficulty in describing mean arterial pressure values accurately, and, therefore, in the calibration of the pulse waveform, places doubt over the accuracy of the determination of pulse pressure amplification, as the amplification values change depending on the algorithm used to define mean arterial pressure. However, it is possible to define the amplification phenomenon regardless of peripheral arterial pressure values, by analyzing central pulse waveform alone.

In fact, if $\mathrm{AR} = {}_{\mathrm{p}}\mathrm{PP}/{}_{\mathrm{c}}\mathrm{PP}$ and ${}_{\mathrm{p}}\mathrm{PP}$ is mean pulse pressure value (MPP = mean arterial pressure − diastolic blood pressure) multiplied by a constant k (whose value can be 3 or 2.5, according to the algorithm used), we will have, therefore:

$$\mathrm{AR} = k\,\frac{\mathrm{MPP}}{{}_{\mathrm{c}}\mathrm{PP}} = k\,\mathrm{Form\,Factor}.$$

This $\mathrm{MPP}/{}_{\mathrm{c}}\mathrm{PP}$ ratio (Form Factor) is easily calculated in pulse wave analysis without absolute pressure values.

To sum up, Form Factor measured in central pulse waveform may be considered as a reliable index of arterial pressure amplification. This confirms what is usually shown for closed hydrodynamic circuits, i.e., the central arterial pressure feels the effects of the periphery of the system, just as in an electrical circuit, where the parameters of a generator are always affected by the load (resistors, capacitors, and inductors).

5.3.4 SubEndocardial Viability Ratio

A non-invasive assessment of the degree of myocardial perfusion relative to left-ventricular workload can be obtained through the quantification of subendocardial viability ratio (SEVR). This parameter is computed as the ratio between diastolic pressure–time index (DPTI, an estimate of myocardial oxygen supply based on both coronary driving pressure in diastole and diastolic time) and systolic pressure–time

index (SPTI, an estimate of myocardial consumption of oxygen). SEVR and its clinical relevance will be analyzed in Chap. 6: "Aortic Stiffness and Myocardial Ischemia".

5.3.5 Wave Separation Analysis

One of the main aims of arterial hemodynamic research is to define the decomposition of the central pulse wave into its forward and backward components.

Several research groups have made an attempt to analyze, noninvasively, these two components of the pulse wave separately. One of the most interesting attempts is perhaps the so-called Avolio's triangle (Fig. 5.50).

As already discussed in the previous chapter, while the pulse wave recorded in the aorta is the result of the sum of forward and backward waves ($P = P_f + P_b$), whereas blood flow velocity is the result of the subtraction of the centripetal blood flow velocity wave derived from reflection sites from the centrifugal blood flow velocity wave ($F = F_f - F_b$).

In the absence of simultaneous recording of flow and pulse waveform (which would allow easy decomposition of the two components of the pulse wave), it has been suggested to use a simulation of the blood flow velocity waveform with a triangle whose base is the horizontal line connecting the feet of the pulse wave to the end-diastolic point and whose vertex is the encounter point between the forward and backward waves (the P_i point). The area of this triangle corresponds, roughly, to the area subtended by the blood flow velocity waveform in the aorta (Fig. 5.50a). Therefore, the reflected wave is defined by half the area included between the side of this triangle and the contour of the pulse wave recorded.

An evolution of this system for discovering reflected waves has recently been implemented by the PulsePen® (DiaTecne, Milan, Italy) tonometer (Fig. 5.51). The Wave Separation Analysis (WSA) implemented by the PulsePen® tonometer is able to calculate the following parameters:

- The forward wave amplitude (P_f)
- The backward wave amplitude (P_b)
- The global reflection coefficient (GRC), i.e., the backward wave amplitude divided by forward wave amplitude $GRC = P_b/P_f$
- As backward wave amplitude divided by forward wave amplitude
- The ratio between backward wave area and total pulse wave area
- The distribution area of forward and backward waves during the systolic and diastolic phase of the cardiac cycle

Figure 5.51 shows the Wave Separation Analysis performed by PulsePen® tonometer in a young healthy adult (Fig. 5.51a) and in an old hypertensive patient (Fig. 5.51b).

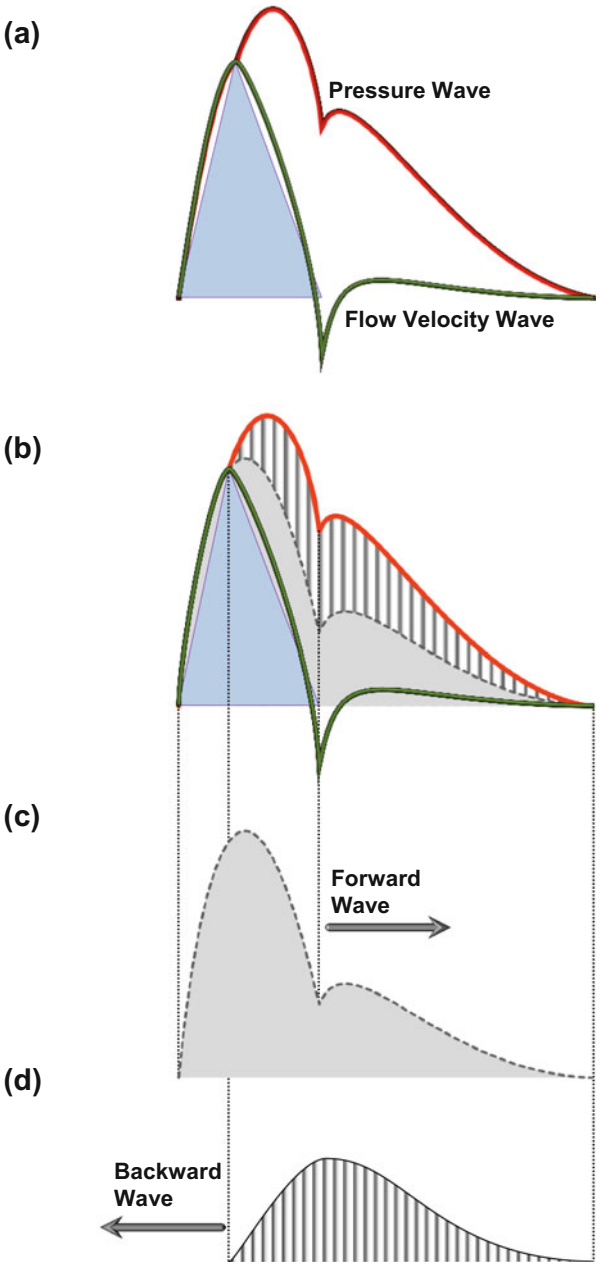
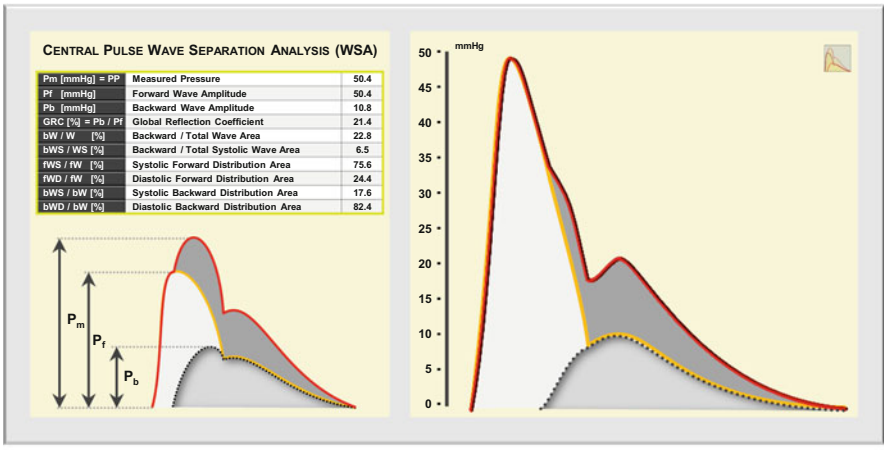
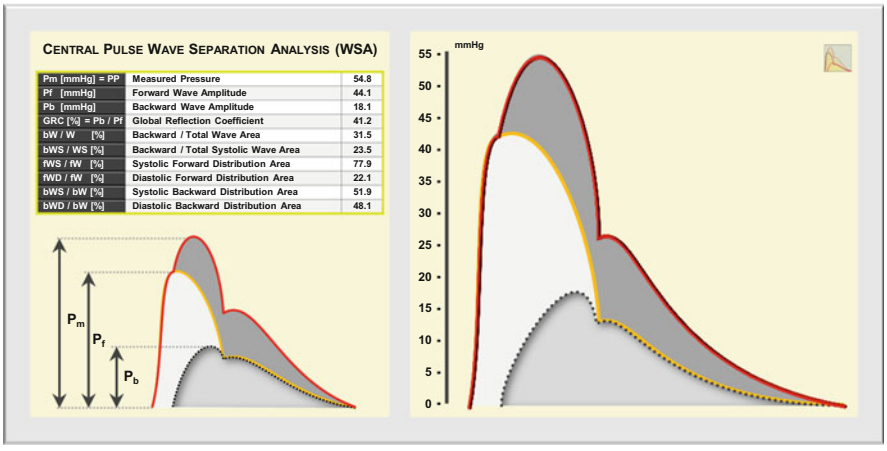


Fig. 5.50 Decomposition of pulse wave into forward and backward waves according to the "triangle" method



(a) Young



(b) Old

Fig. 5.51 Wave Separation Analysis (WSA) in a young healthy adult (**a**) and in an old hypertensive patient (**b**). WSA allows the decomposition of the central pulse wave into its forward (P_f) and backward (P_b) components

5.4 Pulse Waves

This section provides some examples of pulse waveforms recorded by applanation tonometry in the common carotid artery (Figs. 5.52, 5.53, 5.54, 5.55, 5.56, 5.57, 5.58, 5.59, 5.60, 5.61, 5.62, 5.63, 5.64, 5.65, 5.66, 5.67, 5.68, 5.69, 5.70, 5.71, 5.72, 5.73, 5.74, 5.75, 5.76, 5.77, 5.78, 5.79, 5.80, and 5.81). Careful examination of these waveforms can be very useful to understand the great variability in central pulse waveforms. For each pulse waveforms, the corresponding value for

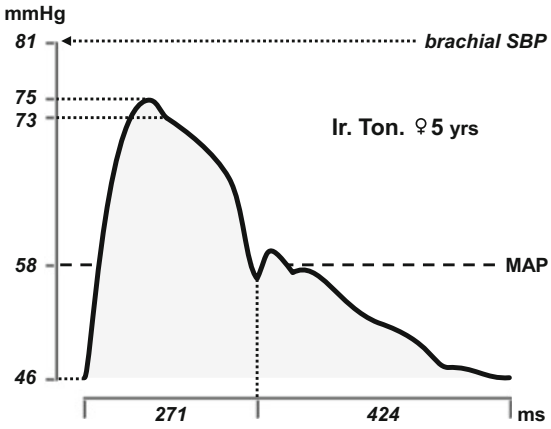


Fig. 5.52 Pulse waveform no. 1: Ir. Ton., 5-year-old girl; brachial blood pressure: 81/46 mmHg; AIx = −7 %; PPA = 21 %; FF = 40 %

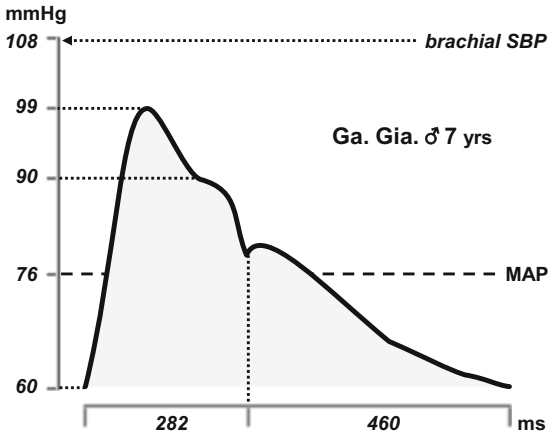


Fig. 5.53 Pulse waveform no. 2: Ga. Gia., 7-year-old boy; brachial blood pressure: 108/60 mmHg; AIx = −23 %; PPA = 23 %; FF = 41 %

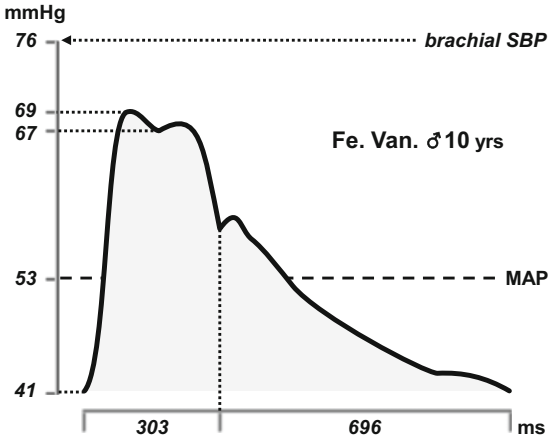


Fig. 5.54 Pulse waveform no. 3: Fe. Van., 10-year-old boy; brachial blood pressure: 76/41 mmHg; AIx = −7 %; PPA = 25 %; FF = 42 %

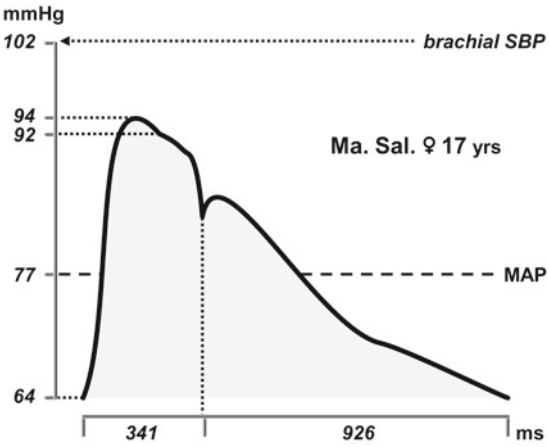


Fig. 5.55 Pulse waveform no. 4: Ma. Sal., 17-year-old girl; brachial blood pressure: 102/64 mmHg; AIx = −7 %; PPA = 27 %; FF = 42 %

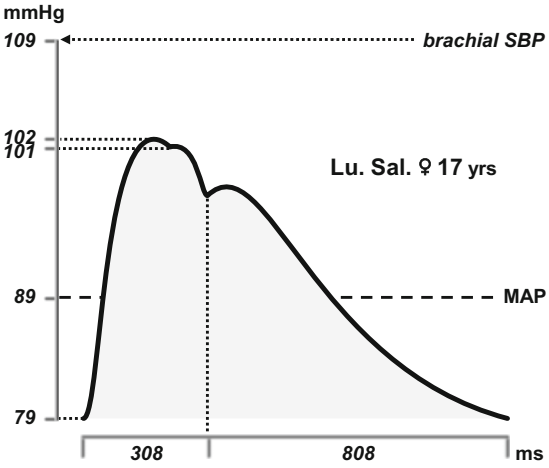


Fig. 5.56 Pulse waveform no. 5: Lu. Sal., 17-year-old girl; brachial blood pressure: 109/79 mmHg; AIx = −4 %; PPA = 30 %; FF = 43 %

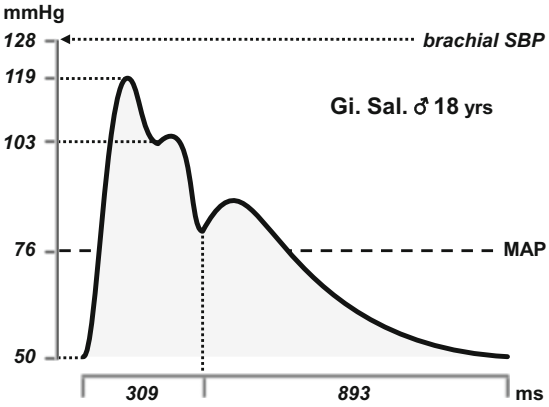


Fig. 5.57 Pulse waveform no. 6: Gi. Sal., 18-year-old boy; brachial blood pressure: 128/50 mmHg; AIx = −23 %; PPA = 13 %; FF = 38 %

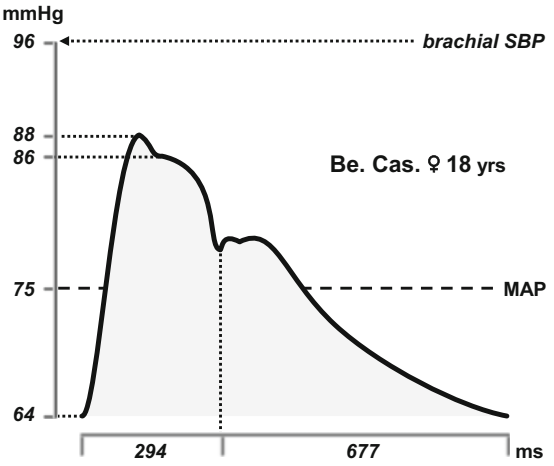


Fig. 5.58 Pulse waveform no. 7: Be. Cas., 18-year-old girl; brachial blood pressure: 96/64 mmHg; AIx = −8 %; PPA = 33 %; FF = 44 %

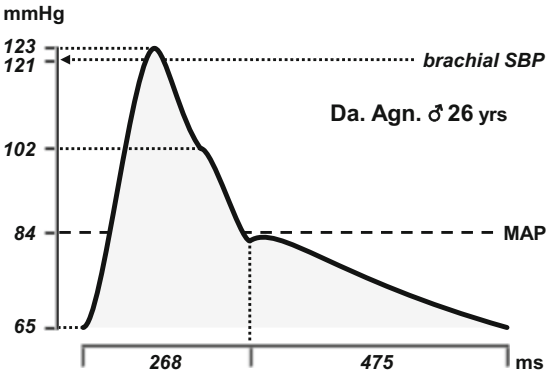


Fig. 5.59 Pulse waveform no. 8: Da. Agn., 26-year-old man; brachial blood pressure: 121/65 mmHg; AIx = −36 %; PPA = −3 %; FF = 32 %

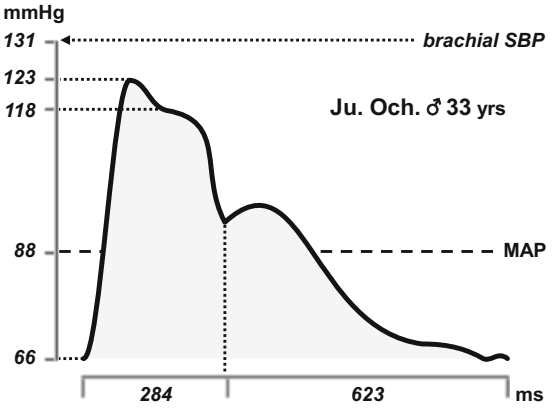


Fig. 5.60 Pulse waveform no. 9: Ju. Och., 33-year-old man; brachial blood pressure: 131/66 mmHg; AIx = −9 %; PPA = 14 %; FF = 38 %

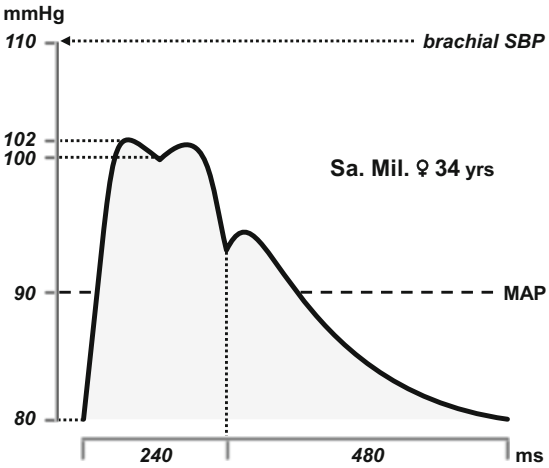


Fig. 5.61 Pulse waveform no. 10: Sa. Mil., 34-year-old woman; brachial blood pressure: 110/80 mmHg; AIx = −9 %; PPA = 36 %; FF = 45 %

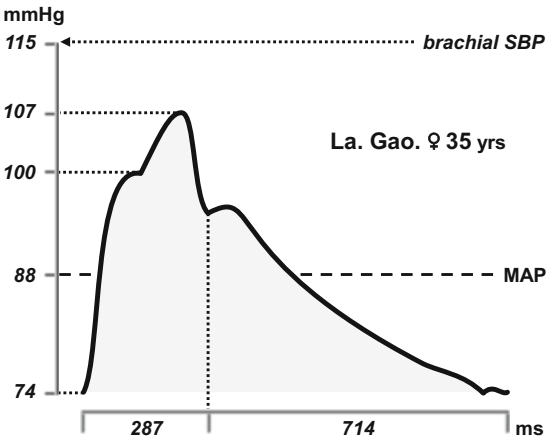


Fig. 5.62 Pulse waveform no. 11: La. Gao., 35-year-old woman; brachial blood pressure: 115/74 mmHg; AIx = +21 %; PPA = 24 %; FF = 41 %

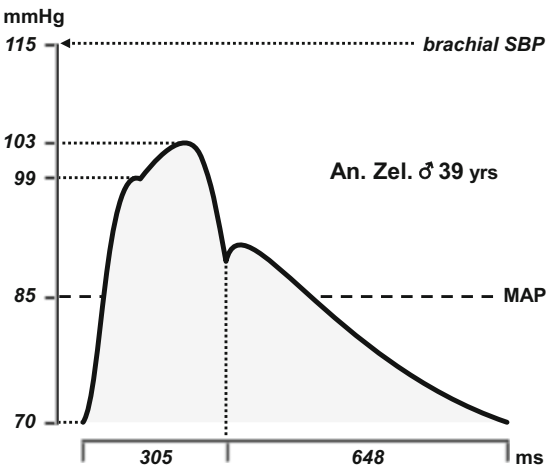


Fig. 5.63 Pulse waveform no. 12: An. Zel., 39-year-old man; brachial blood pressure: 115/70 mmHg; AIx = +12 %; PPA = 36 %; FF = 45 %

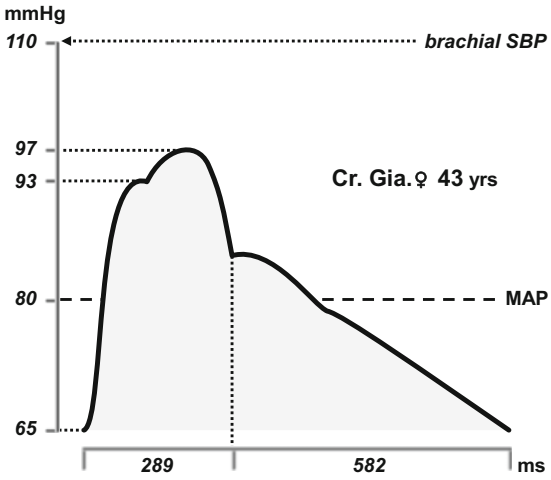


Fig. 5.64 Pulse waveform no. 13: Cr. Gia., 43-year-old woman; brachial blood pressure: 110/65 mmHg; AIx = +13 %; PPA = 41 %; FF = 47 %

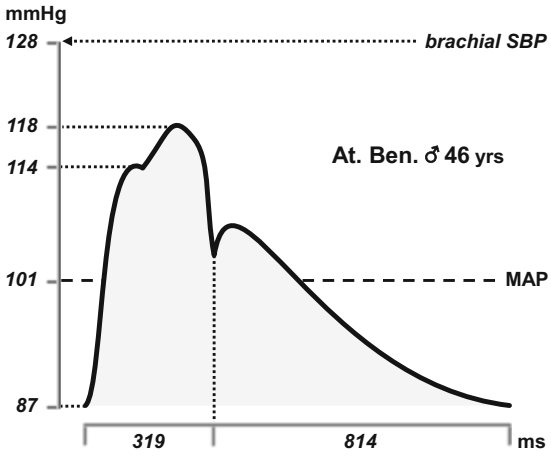


Fig. 5.65 Pulse waveform no. 14: At. Ben., 46-year-old man; brachial blood pressure: 128/87 mmHg; AIx = +13 %; PPA = 32 %; FF = 44 %

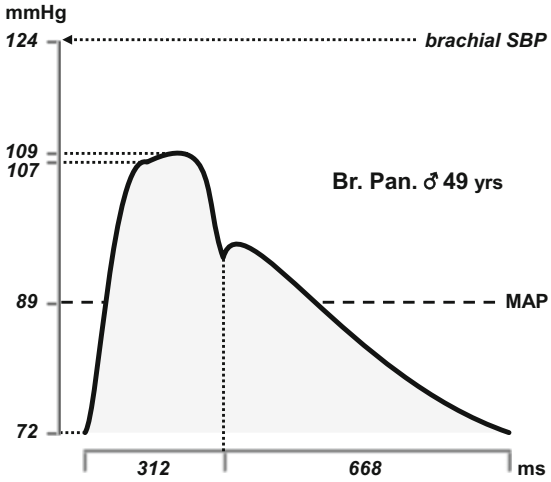


Fig. 5.66 Pulse waveform no. 15: Br. Pan., 49-year-old man; brachial blood pressure: 124/72 mmHg; AIx = +5 %; PPA = 41 %; FF = 47 %

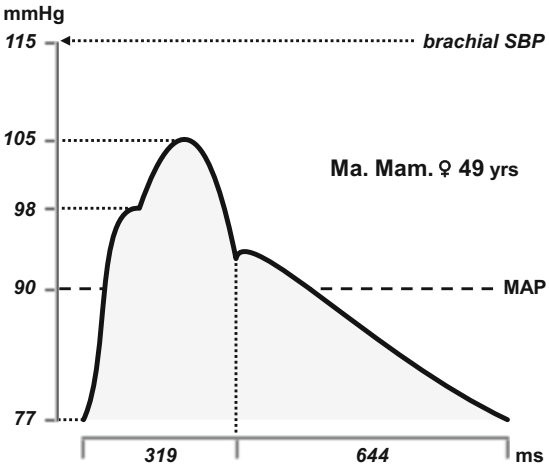


Fig. 5.67 Pulse waveform no. 16: Ma. Mam., 49-year-old woman; brachial blood pressure: 115/77 mmHg; AIx = +25 %; PPA = 36 %; FF = 45 %

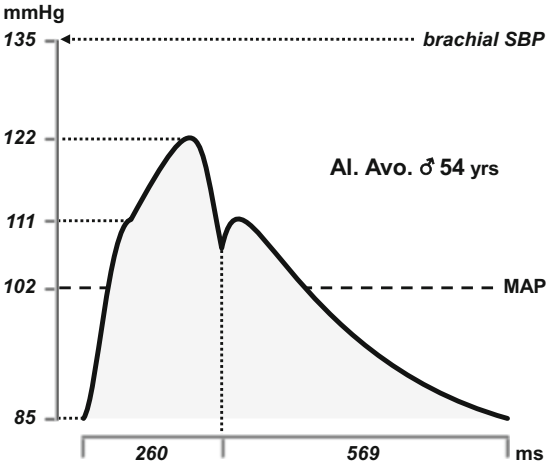


Fig. 5.68 Pulse waveform no. 17: Al. Avo., 54-year-old man; brachial blood pressure: 135/85 mmHg; AIx = +30 %; PPA = 35 %; FF = 45 %

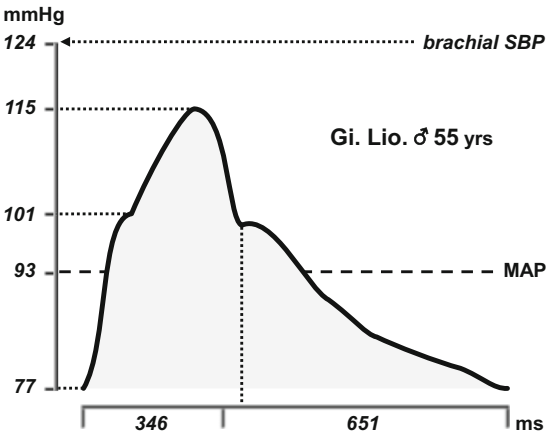


Fig. 5.69 Pulse waveform no. 18: Gi. Lio., 55-year-old man; brachial blood pressure: 124/77 mmHg; AIx = +37 %; PPA = 24 %; FF = 41 %

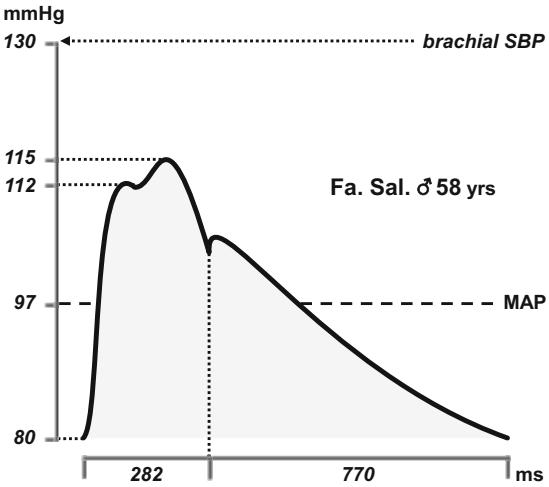


Fig. 5.70 Pulse waveform no. 19: Fa. Sal., 58-year-old man; brachial blood pressure: 130/80 mmHg; AIx = +9 %; PPA = 43 %; FF = 48 %

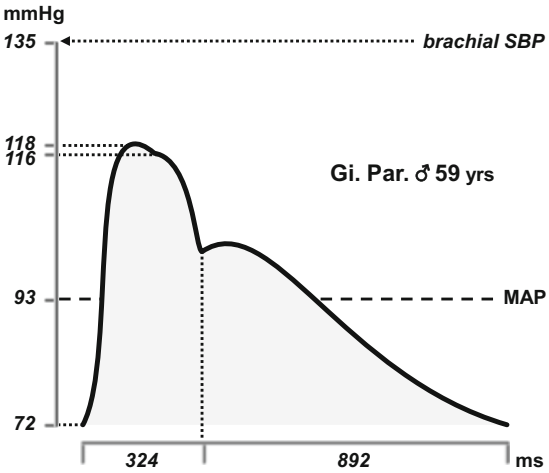


Fig. 5.71 Pulse waveform no. 20: Gi. Par., 59-year-old man; brachial blood pressure: 135/72 mmHg; AIx = −4 %; PPA = 37 %; FF = 46 %

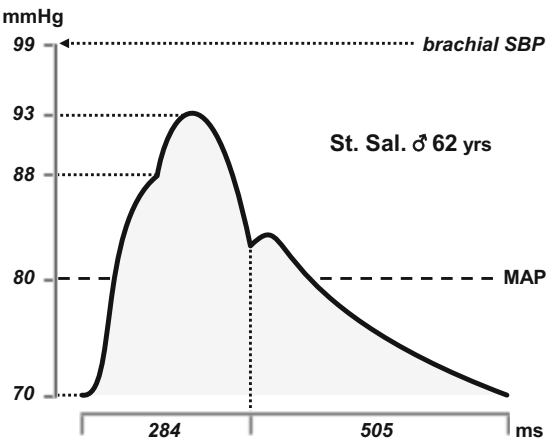


Fig. 5.72 Pulse waveform no. 21: St. Sal., 62-year-old man; brachial blood pressure: 99/70 mmHg; AIx = +22 %; PPA = 26 %; FF = 42 %

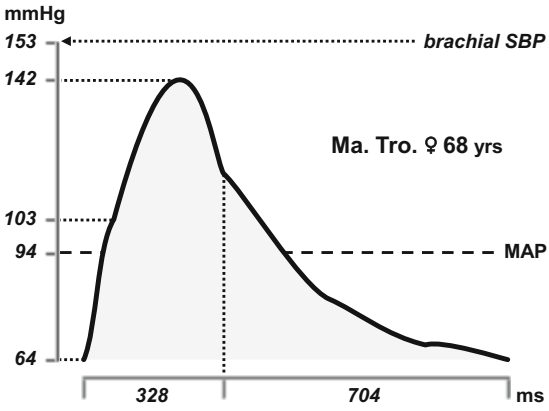


Fig. 5.73 Pulse waveform no. 22: Ma. Tro., 68-year-old woman; brachial blood pressure: 153/64 mmHg; AIx = +50 %; PPA = 14 %; FF = 38 %

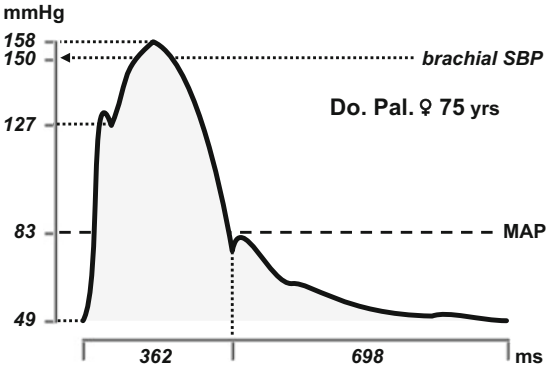


Fig. 5.74 Pulse waveform no. 23: Do. Pal., 75-year-old woman; brachial blood pressure: 150/49 mmHg; AIx = +28 %; PPA = −7 %; FF = 31 %

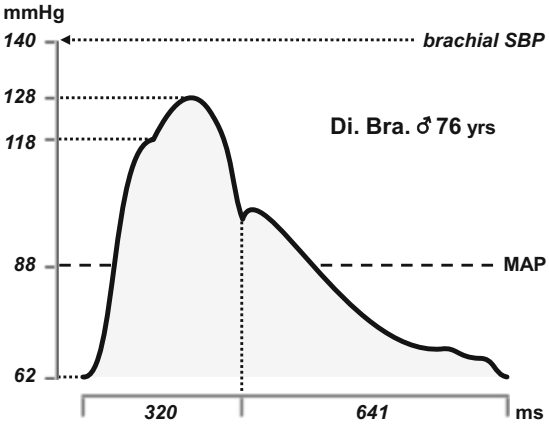


Fig. 5.75 Pulse waveform no. 24: Di. Bra., 76-year-old man; brachial blood pressure: 140/62 mmHg; AIx = +15 %; PPA = 18 %; FF = 39 %

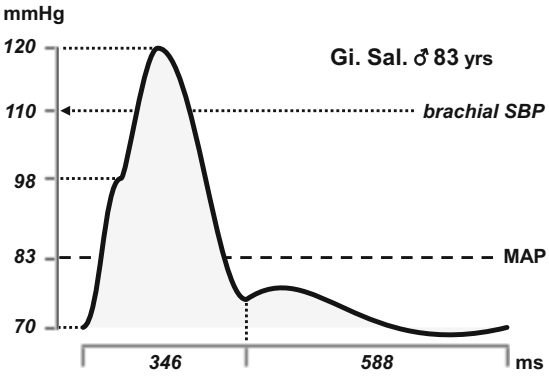


Fig. 5.76 Pulse waveform no. 25: Gi. Sal., 83-year-old man; brachial blood pressure: 120/70 mmHg; AIx = +30 %; PPA = 25 %; FF = 42 %

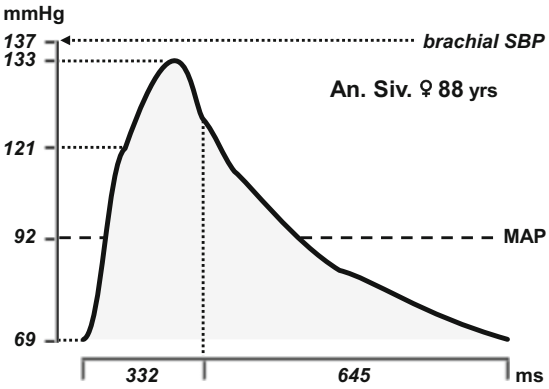


Fig. 5.77 Pulse waveform no. 26: An. Siv., 88-year-old woman; brachial blood pressure: 137/69 mmHg; AIx = +31 %; PPA = 6 %; FF = 35 %

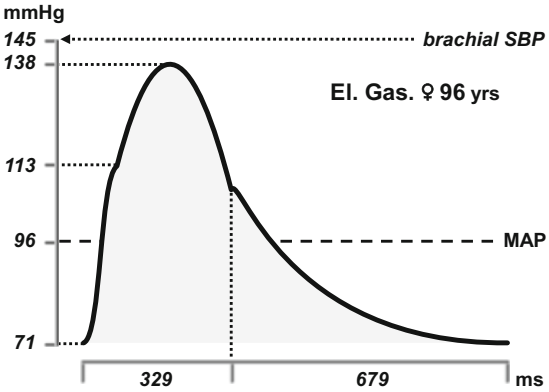


Fig. 5.78 Pulse waveform no. 27: El. Gas., 96-year-old woman; brachial blood pressure: 145/71 mmHg; AIx = +37 %; PPA = 10 %; FF = 37 %

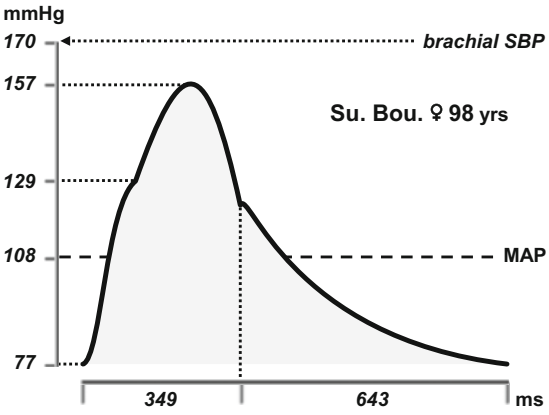


Fig. 5.79 Pulse waveform no. 28: Su. Bou., 98-year-old woman; brachial blood pressure: 170/77 mmHg; AIx = +35 %; PPA = 16 %; FF = 39 %

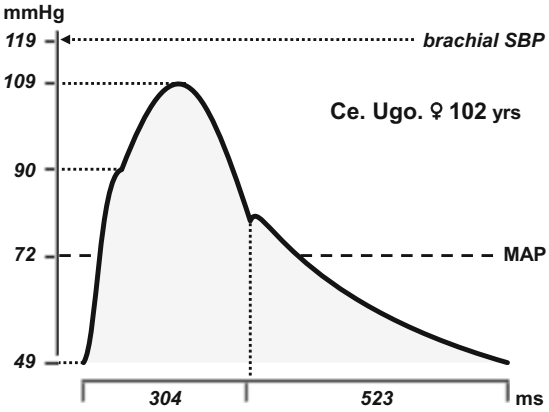


Fig. 5.80 Pulse waveform no. 29: Ce. Ugo., 102-year-old woman; brachial blood pressure: 119/49 mmHg; AIx = +32 %; PPA = 17 %; FF = 39 %

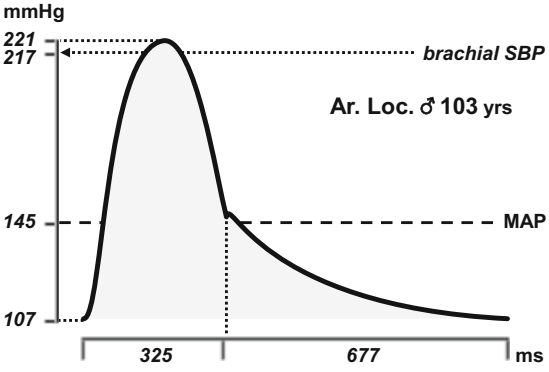


Fig. 5.81 Pulse waveform no. 30: Ar. Loc., 103-year-old man; brachial blood pressure: 221/107 mmHg; AIx = n.d.; PPA = −4 %; FF = 35 %

augmentation index (AIx), pulse pressure amplification (PPA) and form factor has been calculated.

5.5 Instruments for the Assessment of Central Blood Pressure and Pulse Wave Analysis

Over the last decade, several devices for the non-invasive assessment of central blood pressure and indices of arterial function derived from peripheral pulse wave analysis have become commercially available.

Although most of these devices have been celebrated for their ability to provide automated measurements of different hemodynamic parameters in a relatively fast and operator-independent manner, the evidence supporting their ability to properly acquire aortic waveform and accurately calculate central aortic pressure is less clear. Issues related to the algorithms used for transfer function that have been implemented in some of these devices—which in some instances have raised important questions regarding their accuracy and validity in estimating central aortic pressure based on the analysis of brachial or radial pulse waveforms—are also unclear.

5.5.1 Devices on the Market

The main properties of the devices on the market are described in Table 5.4 (data provided by the manufacturers).

5.5.2 The "Tale" of Validation

The ability of validation studies to determine the actual accuracy of devices for the non-invasive assessment of central aortic pressure (reconstructing central blood pressure from peripheral blood pressure measurements) against invasive standard procedures should be questioned.

From a mathematical perspective, the average difference between systolic blood pressure values acquired at the brachial artery level by means of a standard sphygmomanometer and central systolic blood pressure values is approximately 10–15 mmHg. This difference may significantly change due to heart rate values and as a consequence of the blood pressure measurement technique employed. Moreover, the degree of variability between peripheral and central blood pressure levels may be significantly affected by age: although in elderly patients the blood pressure amplification phenomenon is almost absent, in youths the difference between central and peripheral blood pressure levels may exceed 25 mmHg. However, when assessed in a general population including subjects of different ages, the average interindividual difference between central and peripheral blood pressure levels may be significantly reduced to a few mmHg. If we account for this difference in an algorithm for transfer function (regardless of its complexity), it

Table 5.4 Characteristics of the devices for the assessment of central blood pressure and pulse wave analysis on the market

Device	PulsePen	Complior analyse	OMRON HEM-9000AI
Manufacturer	DiaTecne s.r.l.	Alam Medical	OMRON Healthcare
Made in	Italy	France	Japan
URL	www.pulsepen.com	www.complior.com	www.omron.com
Where pulse pressure is recorded (to assess central blood pressure)	Carotid artery	Carotid artery	Radial artery
Method for assessing central blood pressure	Applanation arterial tonometry	Pressure wave recorded by a piezoelectric sensor	Applanation arterial tonometry
	Direct method without transfer function	Direct method without transfer function	Indirect method [second systolic peak detection]
Calibration	Calibration from diastolic BP and mean arterial pressure measured at brachial artery	Calibration from diastolic BP and mean arterial pressure measured at brachial artery	Calibration from systolic and diastolic BP measured at brachial artery
Sample rate	1 kHz	1 kHz	
Recording time	10 cardiac cycles	Two options: –Up to 30 s –10 cardiac cycles	
Options to record extended period	Up to 24 h [LP-WPP software]	No	
Quality control	Monitoring of the quality control during recording	No quality control	Monitoring of the quality control during recording
Device	SphygmoCor	SphygmoCor XCEL PWV system	Oscar 2 with SphygmoCor inside
Manufacturer	AtCor Medical Pty Ltd	AtCor Medical Pty Ltd	AtCor Medical Pty Limited + SunTech Medical Inc
Made in	Australia	Australia	Australia, USA
URL	www.atcormedical.com	www.atcormedical.com	www.atcormedical.com
Where pulse pressure is recorded (to assess central blood pressure)	Two options: –Carotid artery –Radial artery	Brachial artery	Brachial artery
Method for assessing central blood pressure	Applanation arterial tonometry	Brachial oscillometric blood pressure cuff-based method	Brachial oscillometric blood pressure cuff-based method

(continued)

Table 5.4 (continued)

Device	SphygmoCor	SphygmoCor XCEL PWV system	Oscar 2 with SphygmoCor inside
	Two options: –Direct method –Indirect method [generalized transfer function]		
Calibration	Two options for calibration: –From diastolic and mean BP measured at brachial artery –From systolic and diastolic BP measured at brachial artery	Calibration from systolic and diastolic BP measured at brachial artery	Calibration from systolic and diastolic BP measured at brachial artery
Sample rate	128 Hz	256 Hz	
Recording time	10 s	5, 10, or 20 s	
Options to record extended period	Up to 30 s	No	
Quality control	The result of the quality control appears once the recording is finished	The result of the quality control appears once the recording is finished	The result of the quality control appears once the recording is finished
Device	Mobil-O-Graph 24-h PWA monitor	BPLab	Arteriograph
Manufacturer	I.E.M. GmbH	BPLab	TensioMed Ltd
Made in	Germany	Russia	Hungary
URL	www.iem.de	www.bplab.com	www.tensiomed.com
Where pulse pressure is recorded (to assess central blood pressure)	Brachial artery	Brachial artery	Brachial artery
Method for assessing central blood pressure	Brachial oscillometric blood pressure cuff-based method	Brachial oscillometric blood pressure cuff-based method	Brachial oscillometric blood pressure cuff-based method
Calibration	Two options for calibration: –From diastolic and mean BP measured at brachial artery –From systolic and diastolic BP measured at brachial artery	Calibration from systolic and diastolic BP measured at brachial artery	Calibration from mean and diastolic BP measured at brachial artery
Sample rate	100 Hz	100 Hz	200 Hz
Recording time	10 s	4–8 cardiac cycles	8 s
Options to record extended period	24 h (ABPM)	24 h (ABPM)	24 h (ABPM)

(continued)

Table 5.4 (continued)

Device	Mobil-O-Graph 24-h PWA monitor	BPLab	Arteriograph
Quality control	The result of the quality control appears once the recording is finished	The result of the quality control appears once the recording is finished	The result of the quality control appears during recording

Device	Vicorder Arterial Stiffness	BPro + A-Pulse CASP System A-Pulse CASPro A-Pulse CASPal
Manufacturer	Skidmore Medical Ltd	HealthSTATS International
Made in	United Kingdom	Singapore
URL	www.skidmoremedical.com	www.healthstats.com
Where pulse pressure is recorded (to assess central blood pressure)	Brachial artery	Radial artery
Method for assessing central blood pressure	Brachial oscillometric blood pressure cuff-based method	Applanation arterial tonometry
		Indirect method [*N*-point moving average]
Calibration	Calibration from diastolic BP and mean arterial pressure measured at brachial artery	Calibration from systolic and diastolic BP measured at brachial artery
Sample rate	556 Hz	
Recording time	3.5 s	
Options to record extended period	14 s	
Quality control	Monitoring of the quality control during recording	Monitoring of the quality control during recording

might be accurate for the estimation of central blood pressure levels from peripheral blood pressure measurements in the context of a validation study.

Our data, coming from the analysis of more than 3000 subjects, show this (Fig. 5.82) [19]. The central blood pressure levels of these subjects were assessed with a validated and reliable device and their peripheral blood pressure levels were simultaneously recorded with a standard validated sphygmomanometer at the level of the brachial artery. To assess central systolic blood pressure from peripheral blood pressure levels, 10 mmHg was subtracted from the brachial systolic blood pressure values. When correlation analyses were performed, there was a strong and significant linear relationship between central blood pressure levels determined by the two methods ($r^2 = 0.94$; $r = 0.97$), with a mean difference of 0.30 ± 4.74 mmHg (mean + 2 Standard Deviation = 9.78 mmHg; mean − 2SD = −9.17 mmHg) in the Bland–Altman analysis. The correlation between central blood pressure levels obtained by tonometry and central blood pressure levels derived from peripheral blood pressure measures was further improved ($r^2 = 0.97$) when heart

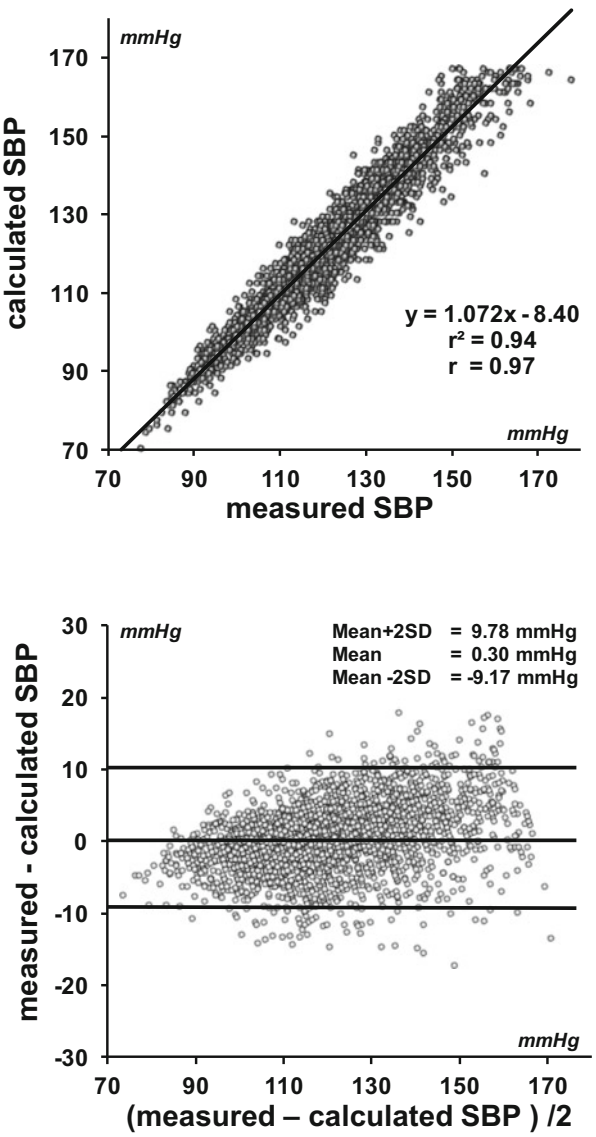


Fig. 5.82 Correlation between central systolic blood pressure values, calculated according to a mathematical formula using brachial pressure values and central systolic blood pressure values, measured directly with a non-invasive validated method. *Upper panel*: linear regression; *lower panel*: Bland–Altman analysis. *SBP* systolic blood pressure

rate values were also considered. Starting from 75 beats/min, adding or subtracting 1 mmHg to peripheral blood pressure for each 10 bpm increases or decreases the heart rate, respectively; the difference between the two methods assessing central systolic blood pressure was 0.75 ± 4.47 mmHg (mean + 2SD = 9.69 mmHg; mean − 2SD = −8.17 Hg) in the Bland–Altman analysis. In addition, when central systolic blood pressure values estimated by subtracting 10 mmHg from the brachial systolic blood pressure were compared with the central systolic blood pressure

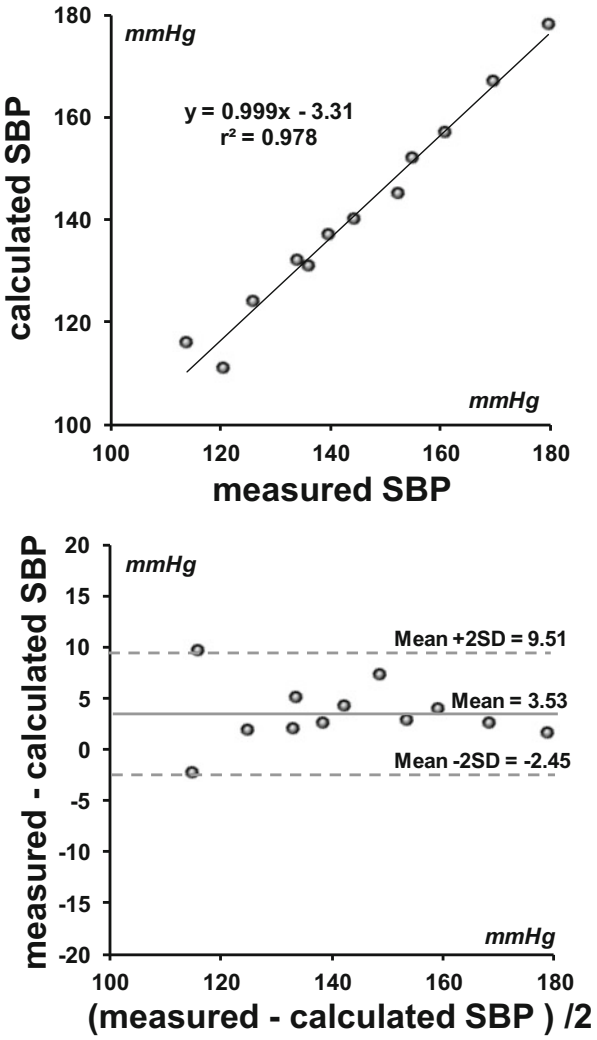


Fig. 5.83 Correlations between central systolic blood pressure values, calculated according to a mathematical formula using brachial pressure values and central systolic blood pressure values recorded invasively in the ascending aorta. *Upper panel*: linear regression; *lower panel*: Bland–Altman analysis. *SBP* systolic blood pressure

directly measured in the ascending aorta with a standard invasive method, a significant and close correlation was observed between the two methods (Fig. 5.83).

These data indicate that even the application of a simple mathematical formula to estimate central blood pressure values from peripheral measurements might be sufficient to obtain a good correlation with non-invasive (i.e., obtained with a reference tonometric method) and invasive measures of central blood pressure.

The example illustrated above clearly shows that any device for assessing central blood pressure on the market can easily obtain a formal validation. Instruments with no scientific basis may be validated, even if they have undergone rigorous testing protocols in important and authoritative research centers. Consequently, if

validation studies concerning instruments for assessing central blood pressure consider the outcome alone (i.e., central systolic blood pressure value), it is likely that they either provide misleading results or certify devices with no scientific basis. Thus, validation studies should concentrate on validation of the method employed for non-invasive hemodynamic assessment rather than considering only quantitative variables (i.e., central blood pressure levels). In brief, validation studies should consider important issues regarding the physical and physiological validity of the method employed by devices to record central blood pressure and central pressure waveforms.

Only after such an assessment, which must be accurate and prove the reliability of the method, we can finally validate the non-invasive device against a reference gold-standard invasive method, comparing the blood pressure values and the first harmonics of the waveforms recorded both invasively and noninvasively.

Some instruments often come with a set of wide validation or comparative studies against other instruments, which have already been validated. It is strongly recommended to reconsider the accuracy of these studies.

Rather than performing pseudovalidations, by comparing different methods based on the blood pressure values obtained, it would be better to verify the physical and physiological scientific validity of the systems used for the measurement of central blood pressure (same for PWV).

I would like to stress that these studies can often lead to "pseudovalidation" outcomes of the instruments analyzed. Now I will tell you a story.

One day, Mister Ming-Lu goes into his nearest chemist's and buys a very simple arterial pressure gauge, which has been validated and costs about 80 US dollars. Mister Ming-Lu is a very good electronics engineer, and cheaply changes the display of the sphygmomanometer so that it can show, not only the usual brachial pressure values, but also central blood pressure values. He also makes secondary changes such as a change in the cuff, with the setting of false sensors.

Then he gives his instrument a set of instructions to make it display central blood pressure values according to a formula which takes only brachial systolic blood pressure and heart rate into account, according to an algorithm derived from linear regression formulas measured in studies about the relationship between pressure amplification and heart rate. Mister Ming-Lu knows very well that heart rate is one of the parameters which mainly affects pressure amplification, and therefore the difference between brachial systolic blood pressure values and central systolic pressure values.

After that, he calls one of the most famous international research center and asks for a validation study, comparing the blood pressure values provided using his instrument with the blood pressure values measured by intra-arterial catheterization.

The validation study can only confirm the strict correlation between systolic blood pressure obtained by Ming-Lu's algorithm and the pressure measured with the gold-standard method.

Finally, Mister Ming-Lu puts his instrument on the market, at a very competitive price of 10,000 US dollars, accompanied with all the scientific documentation certifying that it is a reliable device, validated by one of the most important research centers.

Of course, this is a story, which does not refer to real situations or characters, but I think that, nowadays, there are all the conditions to let this story become true.

Unfortunately, even the best validation protocol may be unable to unmask such fake scientific instruments. We can no longer accept validation of instruments which define central blood pressure by taking into account the outcome alone (in this case, the central systolic blood pressure value). Businesses sell for profit and sometimes without scruples. Only after assessing, accurately and without a shadow of doubt, the reliability of the method, we can move onto validations versus the gold-standard system. Moreover, validation of instruments able to assess central blood pressure should focus on pulse wave analysis, comparing the first harmonics of the waveforms recorded both invasively and noninvasively.

Pulse wave analysis and evaluation of central blood pressure values are currently considered as complementary diagnostic tests for hypertensive patients. Pulse wave analysis may also provide useful information for an indirect study of the myocardial function and cardiac work. Moreover, assessment of central blood pressure waveform, aortic distensibility and central blood pressure values may provide significant insight into the pathophysiological mechanisms involved in the pathogenesis of hypertension and other cardiovascular diseases. This knowledge might lead to a more personalized diagnostic and therapeutic approach to hypertensive and cardiovascular patients, increasing blood pressure control rates, preventing unnecessary treatment and drug side effects, and improving patient compliance to therapy.

Therefore, it is very important that central blood pressure waveform, aortic distensibility and central blood pressure values recorded noninvasively are reliable and that the parameters relative to the central arterial pressure waveform accurately reproduce those recorded in the ascending aorta.

Pills for Growing

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Aortic Stiffness and Myocardial Ischemia

6

All too often, myocardial ischemia is considered synonymous with coronary artery disease, as if coronary atherosclerotic phenomena were the only responsible mechanism for myocardial ischemia. On the contrary, a more correct approach to ischemic heart disease would need to consider all the factors potentially responsible for an ischemic myocardial injury, besides atherosclerotic coronary stenosis. Among them, we should consider myocardial oxygen needs, myocardial (subendocardial) flow supply and the arterial oxygen content. In order to better understand the link between arterial stiffness and myocardial ischemia, it is, thus, necessary to consider ischemic heart disease through a very broad perspective, namely, as the complex balance between subendocardial oxygen supply and demand.

In this chapter, we will analyze the role that central blood pressure plays in the ischemic heart disease, namely, the relationship between aortic stiffness and myocardial ischemia. Firstly, it is important to clarify whether the association between myocardial ischemia and aortic stiffness is secondary to an independent action of aortic stiffness on myocardial supply–demand ratio, or rather whether this association depends on the presence of any factors able to affect both coronary flow and arterial wall properties. The question is, thus, how a stiff aorta might affect myocardial supply flow.

Watanabe et al. [1] described clear signs of regional myocardial dysfunction and a reduction in coronary reserve flow following a mechanical increase in aortic stiffness. These researchers reduced aortic distensibility in dogs by banding the thoracic aorta with adjustable plastic rings and studied the changes in coronary flow. Even in the absence of coronary stenosis, decreased aortic compliance was shown to be associated with inadequate subendocardial oxygenation, which could obviously be further impaired in the presence of coronary stenosis [2].

Indeed, the aorta and large arteries play a major role in the regulation of blood pressure and peripheral blood flow. It is well known that large arteries not only have a passive function in relation to the transfer of oxygenated blood from the heart to the periphery but also exert an important buffering function, as they are able to

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"cushion" left ventricular stroke volume thanks to their viscoelastic properties. In fact, each cardiac cycle includes a left ventricular contraction phase, in which a given amount of blood is forcibly pushed into the arterial system (systole) and a relaxation phase (diastole), in which ventricular filling occurs. Large arteries, therefore, have the task of damping the pulsatile output of the left ventricle and translating the rhythmic, intermittent, and discontinuous activity of the cardiac pump into continuous blood flow. After ejection of stroke volume and closure of the aortic valves, a great quantity of blood remains "stored" in the aorta and large arteries. The potential energy stored in the walls of the aorta in systole then turns into kinetic energy in diastole, pushing the stored blood into the bloodstream (so-called "*Windkessel* phenomenon"). Thus, the aorta behaves like a sort of "diastolic pump". ensuring the achievement of a proper blood pressure level during the diastolic phase of the cardiac cycle to guarantee adequate flow to the periphery.

A number of conditions such as aging, hypertension, inflammation, media calcifications, and metabolic alterations can change the anatomical, structural, and functional properties of large arteries, thereby degrading their mechanical properties. The resulting alterations in the viscoelastic properties of the arterial system cause a stiffening in the arterial wall and reduced elasticity in the aorta and large arteries. Under these conditions, the amount of stroke volume that is stored by the aorta during the systolic ejection time decreases, even drastically whereas most of the blood ejected at each systole is "pushed" directly towards the periphery of the vascular system. As a consequence, aortic systolic blood pressure increases and aortic diastolic blood pressure decreases (Fig. 6.1).

The reduction in diastolic blood pressure in the aorta may cause a reduction in subendocardial blood flow supply [3]. Actually, subendocardial perfusion occurs during diastole because of the development of extravascular compressive forces through the systolic phase of the cardiac cycle. When the left ventricle contracts, the blood vessels going through the myocardial wall are compressed. The compressive force exerted on coronary blood vessels is higher in the subendocardium, where it is similar to the pressure within the left ventricle. Thus, blood flow in subendocardium is virtually withdrawn, even though subepicardial layers remain normally perfused. During the diastolic phase, the whole cardiac muscle is normally perfused again. As a consequence, the subendocardial blood flow is almost exclusively diastolic. In the absence of coronary hemodynamically significant stenosis, the diastolic pressure in coronary arteries is equal to diastolic pressure in the ascending aorta. Thus, not only does subendocardial coronary flow depend on diastolic time but also on aortic diastolic pressure and on the pressure gradient in diastole between coronary arteries intravascular pressure and left ventricular pressure.

Blood pressure in the ascending aorta represents the pressure against which the left ventricle has to pump during systolic contraction. If the mean arterial pressure during the systolic phase in ascending aorta is high, the left ventricle must contract more energetically to maintain adequate stroke volume. Thus, an increase in systolic blood pressure related to an increase in left ventricular afterload leads to

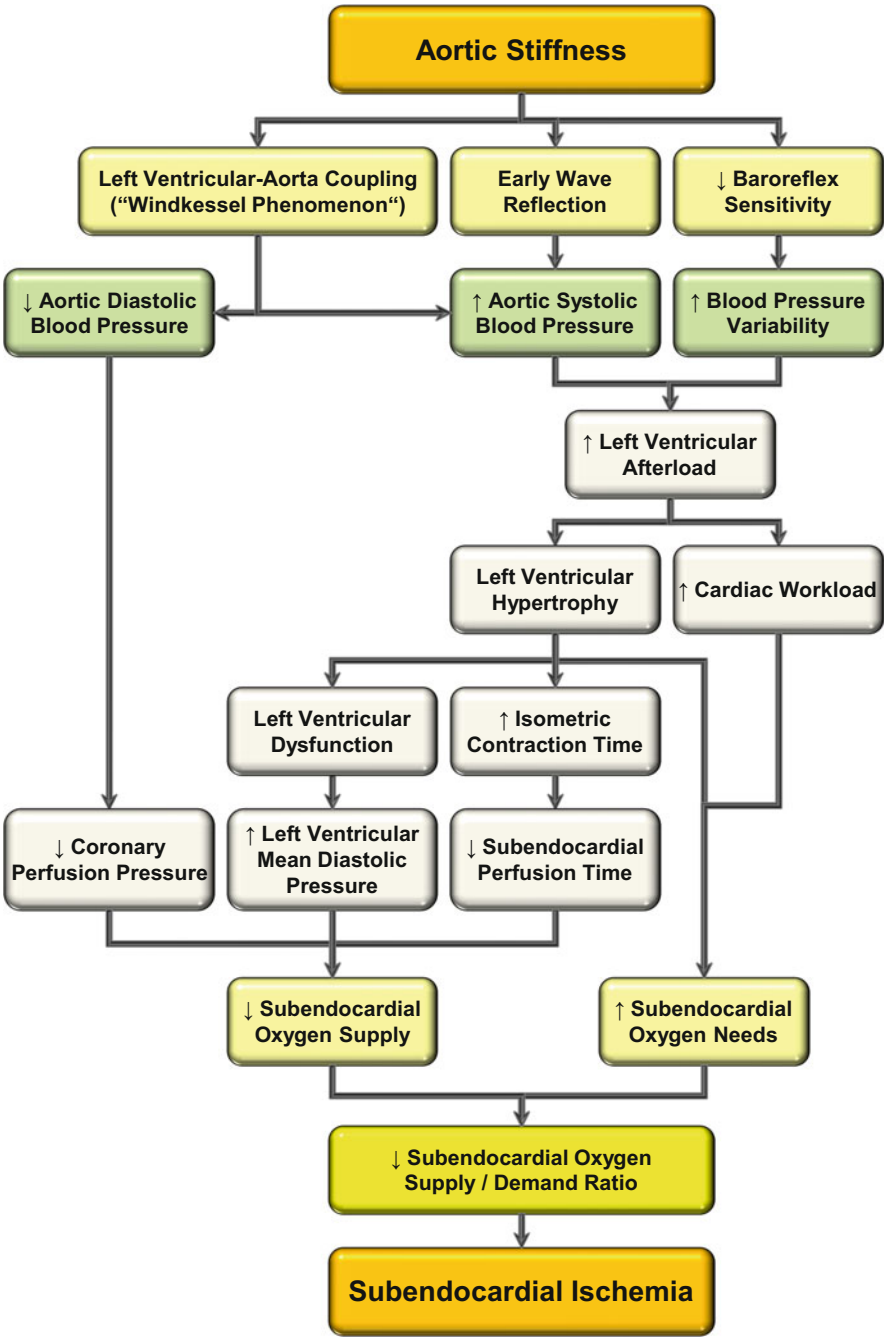

Fig. 6.1 From aortic stiffness to myocardial ischemia

a rise in cardiac work and consequently to an increase in left ventricular mass and myocardial oxygen needs. The development of left ventricular hypertrophy and progression towards the resulting left ventricular failure predispose to an increase in left ventricular diastolic pressure and to a prolongation in isometric contraction time, further reducing the diastolic subendocardial pressure gradient and perfusion time. The result of all these processes is a decrease in subendocardial oxygen supply.

Moreover, arterial stiffness causes an increased pulse wave velocity through the arterial system. Therefore, if the forward (centrifugal) pressure wave travels faster owing to increased arterial stiffness, similarly, the backward (centripetal) pressure wave goes back to the center at a higher speed. Thus, under reduced arterial viscoelasticity, the earlier superimposition of the two waves, in the protomesosystolic phase of the cardiac cycle, produces a further increase in systolic blood pressure and pulse pressure values.

Another factor affected by arterial stiffness must be considered besides the increase in pulse pressure, i.e., the increase in short-term blood pressure variability. Large studies showed a link between increased arterial stiffness and an increase in short-term blood pressure variability. Among other mechanisms, such an association may be partly due to a reduced sensitivity of the arterial baroreflex, i.e., of the most important mechanism for short-term control of blood pressure. This reflex system consists of stretch receptors located in the wall of the aortic arch and in the carotid sinus, at the origin of the internal carotid artery, connected through afferent fibers to neurons in the brain stem, from which efferent influences guarantee reflex sympathetic and parasympathetic modulation of cardiac and vascular targets. Arterial baroreceptors respond to the extent of stretching/relaxation of carotid/aortic arterial walls, rather than directly to changes in blood pressure values themselves. Thus, baroreflex responsiveness will be reduced in individuals with increased arterial stiffness, whose vessels distend less than more elastic vessels in response to blood pressure changes. This means that the arterial baroreflex function is significantly affected by the degree of distensibility/stiffness of arterial walls, which in turn determines the degree of stretching/relaxation of carotid/aortic walls in response to blood pressure fluctuations.

As a result of the pathophysiological changes mentioned above, aortic stiffness may cause an ischemic heart injury through a reduction in subendocardial oxygen supply and/or an increase in subendocardial oxygen demand (Fig. 6.1). Aortic stiffness indeed appears to be an important factor affecting subendocardial oxygen supply–demand balance, and thus, it should be considered more than just an independent risk factor for coronary artery disease. On the other hand, ischemic heart disease should then be considered not only to be the result of a vascular atherosclerotic process affecting coronary arteries, but rather the result of a complex interaction among local coronary atherosclerotic damage, changes in vascular hemodynamics, oxygen arterial content, and the oxygen requirements of myocardial cells (Fig. 6.2). This suggests that assessment of aortic distensibility (either through magnetic resonance imaging or more simply by measuring carotid–femoral pulse wave velocity) should therefore be included among the tests

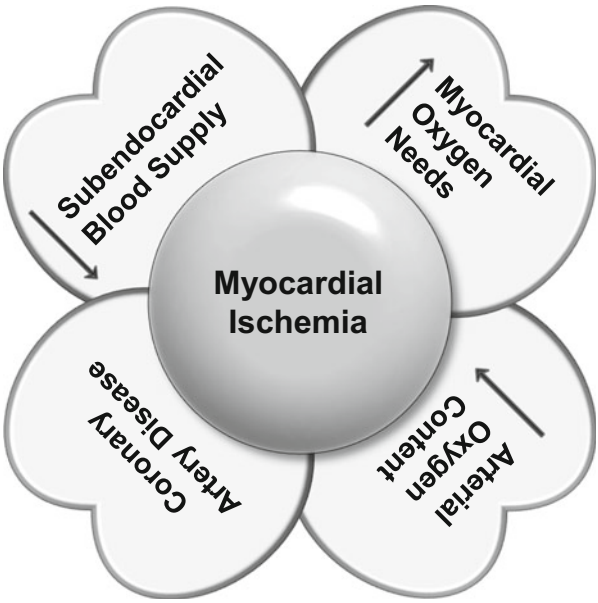

Fig. 6.2 Factors responsible for myocardial ischemia

recommended to screen for the risk of heart disease in daily clinical practice. In particular, on the background of these considerations, an imbalance between myocardial flow supply and demand should be always considered in the evaluation of patients with chronic myocardial ischemia.

6.1 SubEndocardial Viability Ratio

A useful index in the assessment of cardiac ischemic risk was introduced by Gerald David Buckberg and Julien I.E. Hoffman at the beginning of the 1970s and named SubEndocardial Viability Ratio (SEVR), also known as Buckberg's index or DPTI: SPTI ratio [4, 5]. This index reflects the subendocardial oxygen supply–demand ratio and can be defined by analyzing left ventricular and aortic pressure curves (Fig. 6.3).

The area under the left ventricular (or aortic) pressure waveform in systole (SPTI, systolic pressure–time index), from the onset of ventricular systole to the dicrotic notch, represents the left ventricular afterload and defines cardiac work. If the mean arterial pressure during the systolic phase in the ascending aorta is high, the left ventricle must contract more energetically to maintain adequate stroke volume. Thus, SPTI directly correlates with myocardial oxygen needs and mainly depends on left ventricular ejection time, ejection pressure, and myocardial contractility.

The area between the aortic and left ventricular pressure curves in diastole represents the pressure that affects the coronary blood flow and maintains adequate

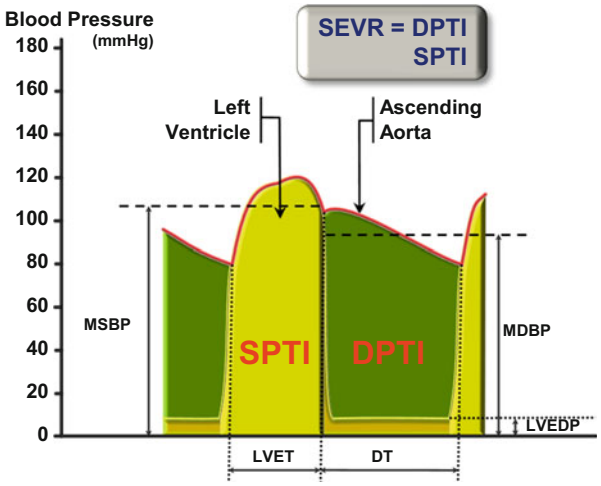

Fig. 6.3 Parameters characterizing subendocardial viability ratio (SEVR). SPTI (systolic pressure–time index) reflects the cardiac workload; DPTI (diastolic pressure–time index) reflects the subendocardial flow supply. Thus, DPTI:SPTI ratio represents the subendocardial oxygen supply–demand ratio. DT, diastolic time; *LVEDP* left ventricular end diastolic pressure, *LVET* left ventricular ejection time, *MDBP* mean diastolic blood pressure, *MSBP* mean systolic blood pressure

subendocardial blood supply in the diastolic phase of the cardiac cycle (DPTI, diastolic pressure–time index). During the systolic phase, blood supply to the subendocardial layers is not allowed, owing to the presence of two extravascular compressive forces: (1) the first force is left ventricular intracavitary pressure, which is fully transmitted to the subendocardial layers, but which falls off to almost zero at the epicardium and (2) the second one is the force developed during left ventricular contraction itself leading to coronary vascular occlusion. The overall compressive force exerted on coronary blood vessels is higher in the subendocardium, whereas it is similar to the pressure within the left ventricle. Thus, blood flow to subendocardial fiber layers is virtually absent in systole, even though subepicardial layers remain normally perfused. Along this line, experimental studies clearly showed that a reduction in aortic distensibility alters the transmural myocardial blood flow distribution of the left ventricle and decreases the subendocardial–subepicardial flow ratio. During the diastolic phase, the degree of myocardial perfusion largely depends on DPTI, which, in turn, is a function of the coronary arterial diastolic pressure, the pressure gradient in diastole between coronary arteries and left ventricular pressure, and the duration of diastole. DPTI is obtained by subtracting the area relative to left ventricular mean diastolic blood pressure (LVDP) from the area, in diastole, of the aortic pressure curve. LVDP can be, substantially and successfully, replaced by an estimate of the left ventricular (or atrial) end-diastolic pressure, which is more easily assessed, noninvasively, by echocardiography.

A very easy method for the numerical calculation of left ventricular end-diastolic pressure (LVEDP) based on the estimation of mean arterial pressure (MAP) and ejection fraction (EF) has been proposed by Abd-El-Aziz:

$$\mathrm{LVEDP} = 0.54\ \mathrm{MAP}\ (1 - \mathrm{EF}) - 2.23$$

Therefore, the subendocardial viability ratio can be calculated using the following formula:

$$\mathrm{SEVR} = \frac{\mathrm{DPTI}}{\mathrm{SPTI}}$$

The diastolic pressure–time index (DPTI) is given by the area between the aortic and left ventricular pressure curves in diastole:

$$\mathrm{DPTI} = (\mathrm{AoMDBP} - \mathrm{LVEDP})\ \mathrm{DT},$$

where AoMDBP represents the aortic mean blood pressure in diastolic phase, while LVDP represents the left ventricular mean diastolic pressure and DT represents the diastolic time.

Systolic pressure–time index (SPTI) represents the area under the aortic pressure curve in systole:

$$\mathrm{SPTI} = \mathrm{AoMSBP} \times \mathrm{LVET},$$

where AoMSBP represents the aortic (=left ventricular) mean systolic blood pressure and LVET represents the left ventricular ejection time, so:

$$\mathrm{SEVR} = \frac{(\mathrm{MDBP} - \mathrm{LVEDP})\ \mathrm{DT}}{\mathrm{MSBP} \times \mathrm{LVET}}$$

where MDBP and MSBP represent the mean value of central (aortic, carotid) blood pressure during the diastolic and systolic phase of the cardiac cycle respectively. The left ventricular end-diastolic pressure (LVEDP) can be defined by means of echocardiography.

To sum up, the subendocardial viability ratio describes the relationship between supply and demand, i.e., between the myocardial blood supply and myocardial oxygen requirement.

The DPTI:SPTI ratio represents, thus, the balance between oxygen subendocardial supply and demand. In the elderly and in the presence of aortic stiffness, these two parameters significantly change (SPTI increases and DPTI decreases) and the subendocardial oxygen supply–demand ratio (DPTI:SPTI ratio) is greatly reduced, as clearly shown in Fig. 6.4, a finding which highlights the possible usefulness of subendocardial oxygen supply–demand ratio assessment in clinical practice. However, in the past, an invasive arterial catheterization was

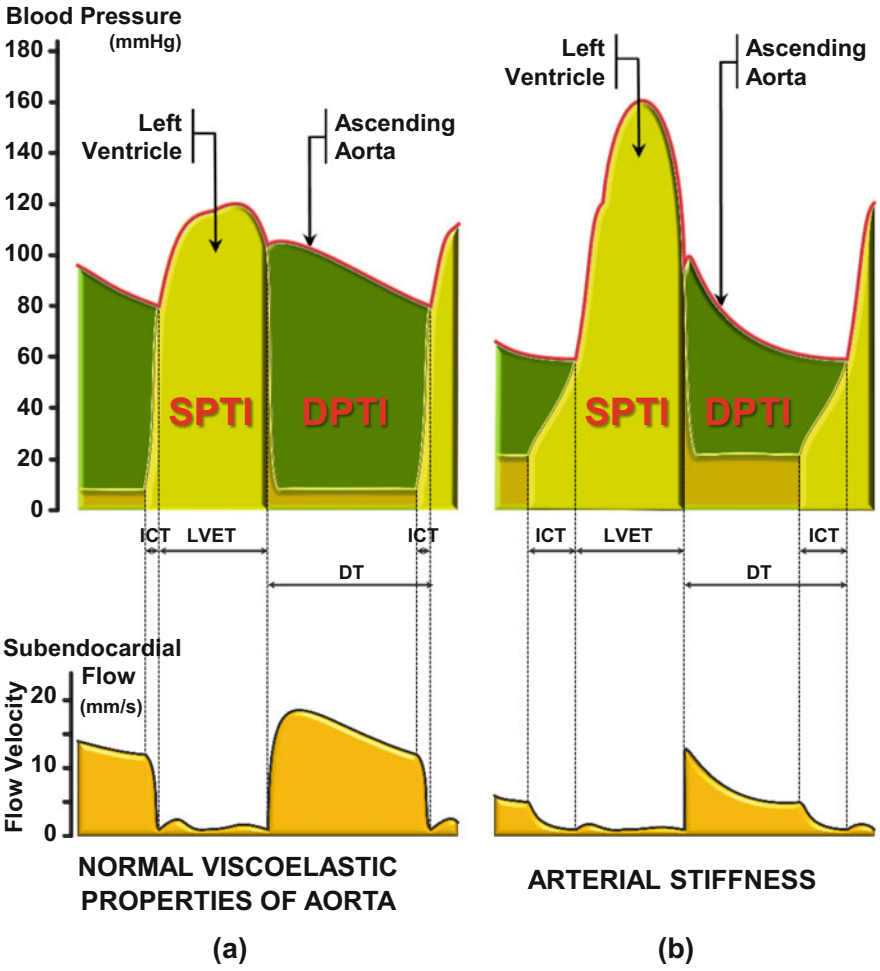

Fig. 6.4 Systolic pressure–time index (SPTI) and diastolic pressure–time index (DPTI) (**a**) in a young healthy adult with normal viscoelastic properties of aorta and (**b**) in an old hypertensive patient with heart failure and increased aortic stiffness. SPTI reflects the cardiac workload; DPTI reflects the subendocardial flow supply. Thus, DPTI:SPTI ratio represents the subendocardial oxygen supply–demand ratio. *Lower panels* show the corresponding subendocardial flow velocity in both the conditions. Several studies have stressed the similarity between the morphology of the diastolic central pressure waveform and the morphology of the coronary blood flow curve. *DT* diastolic time, *LVET* left ventricular ejection time, *ICT* isovolumic contraction time

needed to assess it, which was its major limitation for it to be applied in a clinical setting.

The Rotterdam Study demonstrated that an increase in pulse wave velocity (PWV) is accompanied by an increase in SPTI and by a decrease in DPTI, and, therefore, by a significant reduction in SEVR. The boost in oxygen consumption,

generated by the increase in afterload owing to arterial stiffness, and the reduction in oxygen supply to the myocardium are elements which can help us understand the association between aortic stiffness (as shown by PWV) and cardiovascular mortality and morbidity.

6.1.1 Reference Values for SEVR

Are there any normal values for SEVR? What are the reference values for this parameter?

A "critical" value has been proved for SEVR; it corresponds to 0.45, below which the ratio between subendocardial flow and subepicardial flow, per gram, is reduced in the left ventricle as a signal of insufficient subendocardial vascularization [6]. However, even thanks to the coronary autoregulation, over this critical value, a linear relationship between SEVR and coronary blood flow does not exist.

In other words, for values greater than 0.45, the degree of subendocardial vascularization remains almost constant (Fig. 6.5a) and the ratio between subendocardial flow and subepicardial flow, per gram, remains within the reference range.

Actually, oxygen supply to the subendocardium depends not only on coronary blood flow but also on the arterial oxygen content [7, 8]. It is worth considering in this regard that, for the same coronary blood flow, the oxygen supply to the subendocardium can decrease significantly in the presence of anemia or hypoxemia (e.g., with respiratory insufficiency or at high altitude).

Under these conditions, it is advisable to adapt the formula defining the subendocardial viability ratio (SEVR) by multiplying DPTI by the arterial oxygen content (CaO_2).

The arterial oxygen content can be estimated using the following formula:

$$CaO_2 = 1.34\ Hb \times O_2Sat + 0.003\ pO_2,$$

where Hb represents hemoglobin (g/dl), O_2Sat is the arterial oxygen saturation (%), and pO_2 the arterial pressure of oxygen (mmHg).

According to this formula, the "critical" value for SEVR corresponds to 9. Reduced subendocardial blood flow and oxygen supply are likely to be associated with values below this critical level (Fig. 6.5b). When the supply–demand ratio is over 9, adequate oxygen delivery to the left ventricle is maintained. With ratios below 9, subendocardial oxygen delivery reduces respect to the needs, flow becomes inhomogeneously distributed, and electrocardiographic and clinical signs of ischemia appear [6].

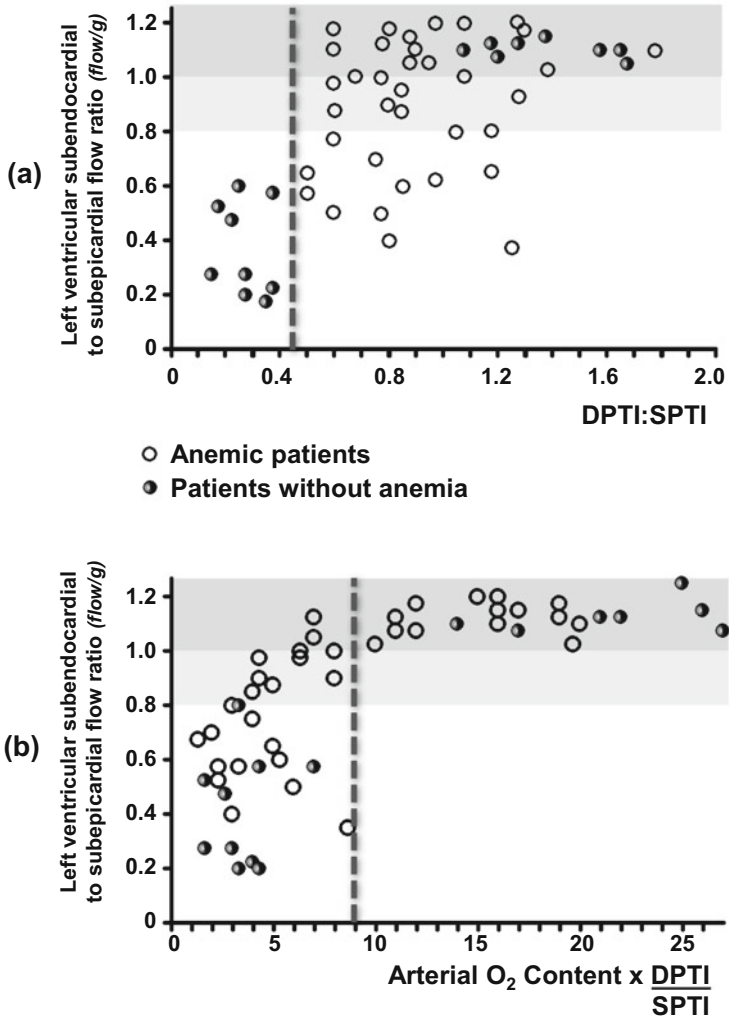

Fig. 6.5 (**a**) Flow ratio per gram of left ventricular subendocardial to subepicardial muscle with respect to subendocardial viability ratio (SEVR = DPTI:SPTI). The *white dots* indicate patients with anemia; *dark dots* indicate control subjects or patients without anemia. (**b**) Flow ratio per gram of left ventricular subendocardial to subepicardial muscle with respect to subendocardial viability index corrected for oxygen content [8]. The figure highlights that oxygen content should be taken into account in the assessment of subendocardial viability. *DPTI* diastolic pressure–time index, *SPTI* systolic pressure–time index. Normally, flow per gram per minute is about 1–1.2 times higher in the subendocardium than in the subepicardium. Subendocardial muscle becomes ischemic when the proportion of total coronary blood flow delivered to the subendocardial region becomes reduced (subendocardial/subepicardial flow ratio <0.8). Flow ratios below 0.8 always occurs whenever DPTI/SPTI is less than 0.45 or $CaO_2 \times$ DPTI/SPTI is less than 9

6.2 Unreliable Assessment of SEVR by Arterial Tonometry

The introduction of transcutaneous arterial tonometry has provided a new approach to noninvasive assessment of the subendocardial oxygen supply–demand ratio through a simple and easily implementable test. Actually, applanation tonometry is, at present, considered the reference method for noninvasive estimation of central blood pressure and for central pulse wave analysis. The devices using this method, which are currently available, provide values of Buckberg's index on the basis of the morphological analysis of the central arterial pressure wave recorded by the tonometer itself. In the context of DPTI:SPTI ratio assessment by transcutaneous tonometry, DPTI represents the area under the diastolic portion of the blood pressure wave and is obtained by multiplying the mean value of blood pressure during the diastolic phase of cardiac cycle by the diastolic time. Conversely, SPTI represents the area under the systolic portion of the pressure wave, obtained by multiplying the mean value of blood pressure during the systolic phase of cardiac cycle by the left ventricular ejection time (Fig. 6.6). So,

$$\text{Traditional Unreliable SEVR by Arterial Tonometry} = \frac{\text{DPTI}}{\text{SPTI}} = \frac{\text{MDBP}}{\text{MSBP}} \times \frac{\text{DT}}{\text{LVET}}$$

emerging as the result of the ratio between two pressures (MDBP and MSBP) and two time measures (DT and LVET). At present, this method for the assessment of SEVR is carried out by the SphygmoCor® System and the most common systems for the analysis of the curve of central pressure wave.

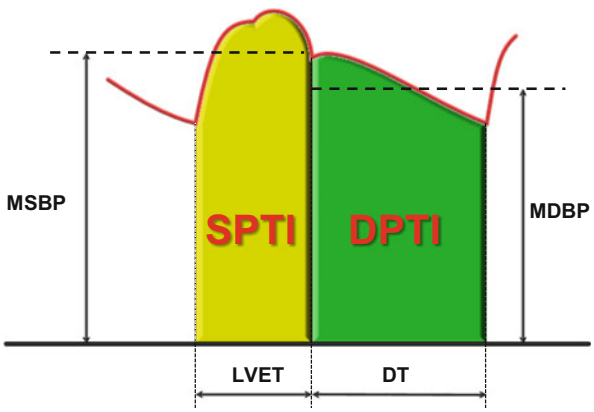

Fig. 6.6 Parameters characterizing the traditional, unreliable method for assessing subendocardial viability ratio (SEVR) by arterial tonometry. SPTI (systolic pressure–time index) reflects the cardiac workload; DPTI (diastolic pressure–time index) reflects the subendocardial flow supply. *DT* diastolic time, *LVET* left ventricular ejection time, *MDBP* mean diastolic blood pressure, *MSBP* mean systolic blood pressure

6.2.1 Limitation of SEVR Usually Assessed by Arterial Tonometry

At present, the assessment of DPTI:SPTI ratio is only based on pulse waveforms recorded by arterial tonometers in daily clinical practice and is, therefore, affected by a number of important limitations:

1. Firstly, only left ventricular ejection time is taken into account when analyzing tonometric pulse waveforms to calculate this ratio, whereas left ventricular isovolumic contraction time is not considered in the determination of systolic left ventricular function, with a consequent underestimation of SPTI (Fig. 6.7). On the other hand, left ventricular isovolumic contraction time is considered in DPTI determination, even though this parameter should actually be considered as a component of cardiac workload and not as an oxygen supply time, with the consequent result of an overestimation of DPTI. Since the isovolumic contraction time/ejection time ratio increases significantly in the elderly and in heart failure, the tonometry method may overestimate the DPTI:SPTI ratio in these patients by even 80–100 % with regard to its real value, as shown in Fig. 6.7.
2. Secondly, left ventricular diastolic pressure is not taken into account by this approach. In subjects with heart failure or with cardiac valve disease, characterized by increase in left ventricular diastolic pressure, this limitation leads to overestimate the DPTI value when only focusing on tonometry data.
3. Finally, a correct estimation of the oxygen demand by the myocardium cannot ignore the muscle mass or contractility. Actually, an increase in muscular mass, such as in left ventricular hypertrophy, increases the oxygen needs. Thus, in order to improve the estimation of SPTI, recently, Hoffmann and Buckberg suggested multiplying SPTI by the relative left ventricular mass as determined by echocardiography [6].

These methodological aspects may have affected the studies performed so far on SEVR. Despite SEVR being calculated in all epidemiological studies estimating arterial stiffness by arterial tonometry, there are indeed very few papers reporting data on the relationship between SEVR and cardiovascular disease. This may be partly due to the above-reported inaccuracies affecting the measurement of DPTI:SPTI ratio.

Overall, in light of the fact that the estimation of Buckberg's index is only based on arterial tonometry data, the current approach seems to provide a relatively unreliable surrogate assessment of the real subendocardial oxygen supply–demand ratio.

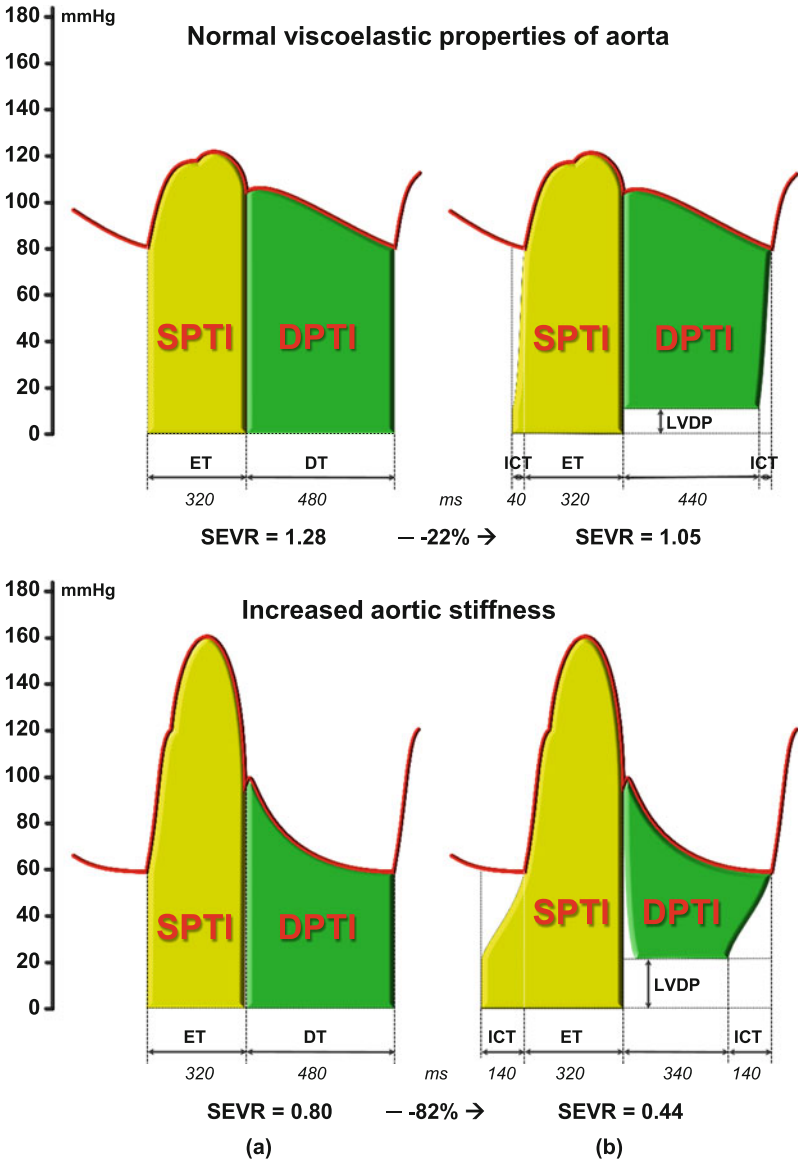

Fig. 6.7 Systolic pressure–time index (SPTI) and diastolic pressure–time index (DPTI) in a young healthy adult with normal viscoelastic properties of aorta (*upper panels*) and in an old hypertensive patient with heart failure and increased aortic stiffness (*lower panels*). SPTI reflects the cardiac workload; DPTI reflects the subendocardial flow supply. Thus, DPTI:SPTI ratio represents the subendocardial oxygen supply–demand ratio. (**a**) The *panels* on the *left* show SPTI and DPTI as calculated only by arterial tonometry whereas (**b**) the panels on the right show the real area corresponding to SPTI and DPTI. In young healthy adults, tonometry overestimates DPTI:SPTI ratio by 22 %, whereas in old patients the overestimation is 82 %. *DT* diastolic time; *ET* left ventricular ejection time, *ICT* isovolumic contraction time, *LVDP* left ventricular diastolic pressure, *SEVR* subendocardial viability ratio

6.3 New Reliable Assessment of SEVR by Arterial Tonometry

Clinical and hemodynamic studies have been recently performed in order to improve the non-invasive approach to the detection of critical reductions in subendocardial oxygen supply–demand ratio. A polycentric study, involving research centers in Milan, Trieste, Sidney, and Beijing, showed that left ventricular isovolumic contraction time can be easily evaluated by analyzing the pulse waveform recorded at common carotid artery by arterial tonometry. The time delay between the ascending aorta and the carotid artery was measured taking into account the aortic pulse wave velocity and the distance between carotid artery and aortic valve.

Moreover, the assessment of the isovolumic contraction time allows an indirect estimation of the left ventricular end-diastolic pressure (LVEDP).

Actually, the reverse relationship between the ICT/LVET ratio (isovolumic contraction time/left ventricular ejection time) and the ejection fraction is common knowledge. An increase in isovolumic contraction time in relation to ejection time is, therefore, associated with a reduced left ventricular ejection fraction.

We have seen in the above paragraphs that left ventricular end-diastolic pressure may be indirectly but reliably obtained by assessing mean arterial pressure and left ventricular ejection fraction.

To sum up, the assessment of the isovolumic contraction time significantly improves the accuracy of SEVR. Figure 6.8 shows (a) the evaluation of SEVR using invasive methods by Buckberg in 1972 [4], (b) the unreliable assessment of SEVR by arterial tonometry as it is still offered by the SphygmoCor® and other manufacturers of instruments able to perform central pulse wave analysis, and (c) the new reliable assessment of SEVR by arterial tonometry, which is currently available only in the PulsePen® device (Fig. 6.9).

The great difference between these two non-invasive methods for the assessment of SEVR can be explained by analyzing the data concerning a population of more than 1000 subjects older than 80, who participated in the PARTAGE studio. In this population, the average value of SEVR (±standard deviation) assessed using the traditional method is 1.47 ± 0.30, whereas the average value of SEVR drops to 0.74 ± 0.18 with the new method. This new method for the assessment of SEVR is almost superimposable to the invasive methods carried out by Buckberg and Hoffman in the 1970s.

An accurate assessment of the myocardial oxygen supply:demand index would require a double correction: at the numerator, the DPTI would always be adjusted for the arterial content of O_2 (CaO_2), whereas at the denominator, the SPTI would also consider the relative left ventricular mass (LVM), according to the following formula [6]:

$$\text{Myocardial Oxygen Supply:Demand Index} = \frac{\text{DPTI} \times \text{CaO}_2}{\text{SPTI} \times \text{Relative LVM}}$$

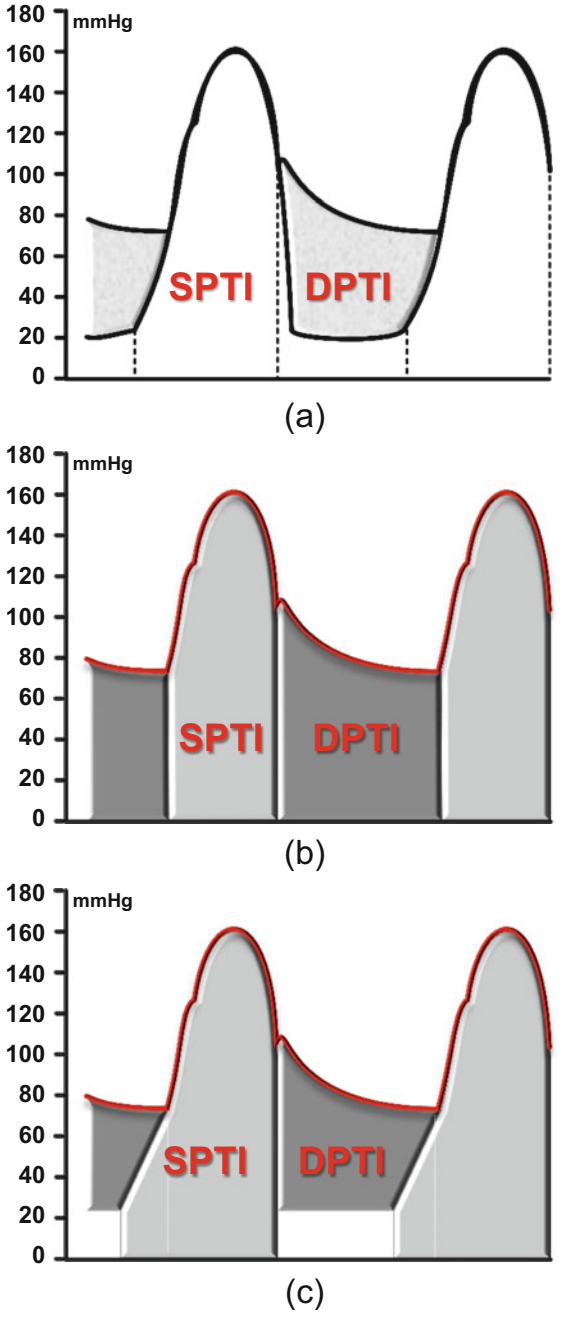

Fig. 6.8 (**a**) Parameters used to assess SEVR using an invasive method [4]; (**b**) traditional, unreliable assessment of SEVR by arterial tonometry; (**c**) new reliable assessment of SEVR by arterial tonometry [9]. *SPTI* systolic pressure–time index, *DPTI* diastolic pressure–time index

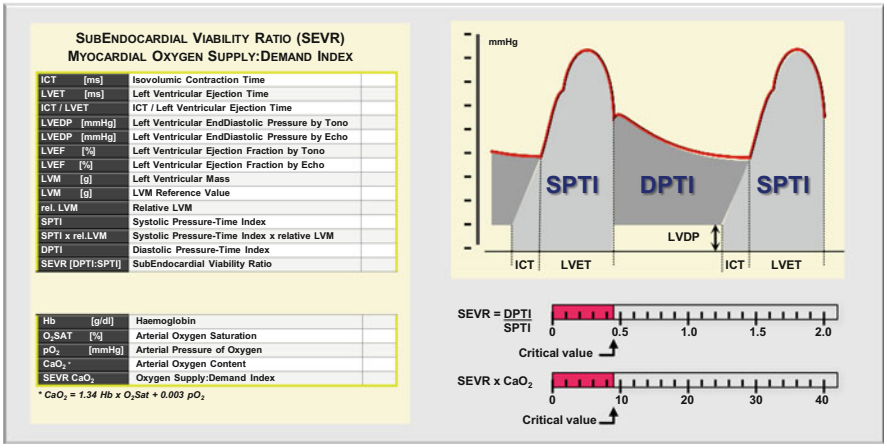

Fig. 6.9 A new reliable assessment of SEVR by arterial tonometry as it is assessed with the PulsePen® device. This instrument allows the manual clinical data of the patient to be inserted in order to optimize the assessment of the myocardial oxygen supply:demand index by adjusting SEVR for the arterial content of oxygen and the relative left ventricular mass

The PulsePen® device offers a complete assessment of the myocardial oxygen supply:demand index allowing the parameters relative to the arterial content of oxygen and left ventricular mass to be inserted in the calculation of this index.

6.3.1 Clinical Cases

Now let us consider some conditions where SEVR has been estimated.

Clinical Case No. 1
The subject is a healthy young adult woman. SEVR was calculated using the traditional unreliable formula:

$$\text{Traditional SEVR} = \frac{\text{MDBP} \times \text{DT}}{\text{MSBP} \times \text{LVET}} = \frac{81 \times 701}{97 \times 287} = 2.04$$

The area under the diastolic portion of the pressure curve (DPTI) is, therefore, 104 % wider than the area under the systolic portion of the pressure curve (SPTI).

In this subject, left ventricular end-diastolic pressure (LVEDP) was 9 mmHg and isovolumic contraction time (ICT) was 85 ms; therefore, the true SEVR (Fig. 6.10), which was evaluated taking into account both of these parameters, is 1.53.

As you can see, the traditional old method for assessing SEVR, in this case, supplies values exceeding the true SEVR by 33 %.

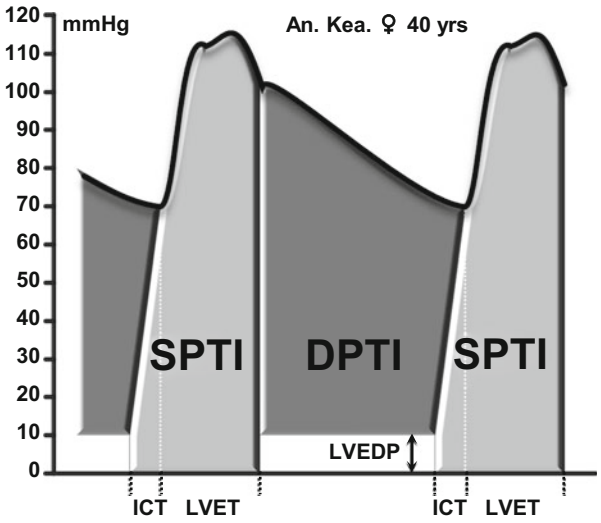

Fig. 6.10 Clinical case no. 1: a 40-year-old, apparently healthy woman. *SPTI* systolic pressure–time index, *DPTI* diastolic pressure–time index, *LVET* left ventricular ejection time, *ICT* isovolumic contraction time, *LVEDP* left ventricular end-diastolic pressure

Clinical Case No. 2

The second subject is a diabetic elderly woman with history of coronary disease. SEVR was calculated using the traditional unreliable formula:

$$\text{Traditional SEVR} = \frac{\text{MDBP} \times \text{DT}}{\text{MSBP} \times \text{LVET}} = \frac{77 \times 637}{116 \times 350} = 1.21$$

The area under the diastolic portion of the pressure curve (DPTI) is, therefore, 21 % wider than the area under the systolic portion of the pressure curve (SPTI).

In this subject, left ventricular end-diastolic pressure (LVEDP) was 19 mmHg and isovolumic contraction time (ICT) was 53 ms; therefore, the true SEVR (Fig. 6.11), which was evaluated taking into account both of these parameters, is 0.84.

We can notice, in this case where higher ventricular diastolic pressure is present, that the traditional old method supplies values exceeding the true SEVR by 44 %.

Clinical Case No. 3

Particular environmental conditions, such as hypobaric hypoxia at high altitude, can cause a decrease in the DPTI/SPTI ratio as well, which could even create severe difficulties in labile myocardial compensation [10, 11]. This case was recorded during a scientific expedition, at high altitude. The subject is a healthy 59-year-old man without any history of cardiovascular disease. After undergoing arterial tonometry in Milan (122 m above sea level), Monte Rosa was reached, ascending on foot, with overnight stay at Gnifetti Hut (3647 m a.s.l.), with repetition of the test about 5 h after arrival at Margherita Hut (4559 m a.s.l.). During the stay at high altitude, several ventricular arrhythmias were recorded. Let us now assess this subject's traditional SEVR:

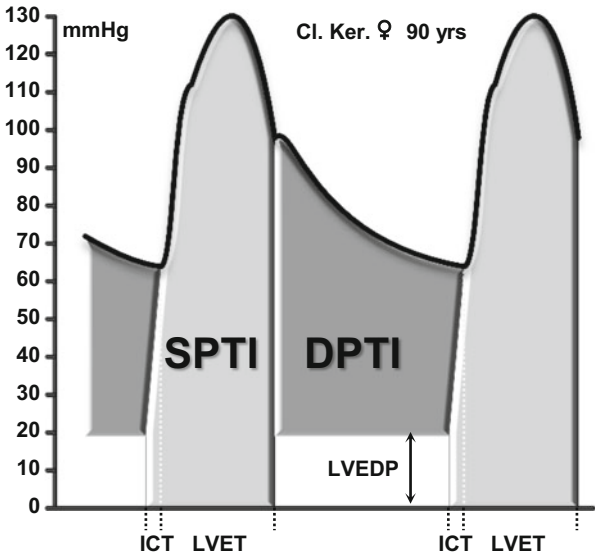

Fig. 6.11 Clinical case no. 2: a 90-year-old, diabetic woman with history of coronary artery disease. *SPTI* systolic pressure–time index, *DPTI* diastolic pressure–time index, *LVET* left ventricular ejection time, *ICT* isovolumic contraction time, *LVEDP* left ventricular end-diastolic pressure

$$\text{Traditional SEVR at sea level} = \frac{\text{MDBP} \times \text{DT}}{\text{MSBP} \times \text{LVET}} = \frac{87 \times 892}{110 \times 324} = 2.18$$

$$\text{Traditional SEVR at high altitude} = \frac{\text{MDBP} \times \text{DT}}{\text{MSBP} \times \text{LVET}} = \frac{82 \times 425}{98 \times 249} = 1.43$$

Left ventricular end-diastolic pressure, measured by ultrasound scanning, was 13.8 mmHg at sea level and 13.5 mmHg at high altitude, and isovolumic contraction time (ICT) was 77 ms at sea level and 121 ms at high altitude; therefore, the true SEVR (Fig. 6.12), which was evaluated taking into account both of these parameters, was 1.62 at sea level and 0.86 at high altitude.

In this case, the traditional old method supplies values exceeding the true SEVR by 35 % at sea level and 66 % at high altitude.

Therefore, at high altitude, myocardial oxygen requirement rises whereas diastolic coronary blood flow falls. SEVR decreases by 47 %, from 1.62 to 0.86.

However, under such hypoxic condition, caused by high altitude, we must correct SEVR for the arterial oxygen content (SEVR-CaO_2). Since Hb was 14.1 g under basal conditions, oxygen saturation was 98 % and pO_2 was 100 mmHg, the calculation of SEVR × CaO_2 will be:

$$\begin{aligned}\text{SEVR-CaO}_2 \text{ at sea level} &= 1.62\,[(1.34\text{Hb}) \times (\text{O}_2\text{Sat}) + (0.003\ \text{pO}_2)] \\ &= 1.62\,[(1.34 \times 14.1) \times (0.98) + (0.003 \times 97)] \\ &= 1.62 \times 18.8 = 30.4\end{aligned}$$

On the contrary, at high altitude (4559 m a.s.l), Hb was 14.1 g/dl, O_2 saturation was 65 %, and pO_2 was 34 mmHg, therefore, the calculation of SEVR-CaO_2 will be:

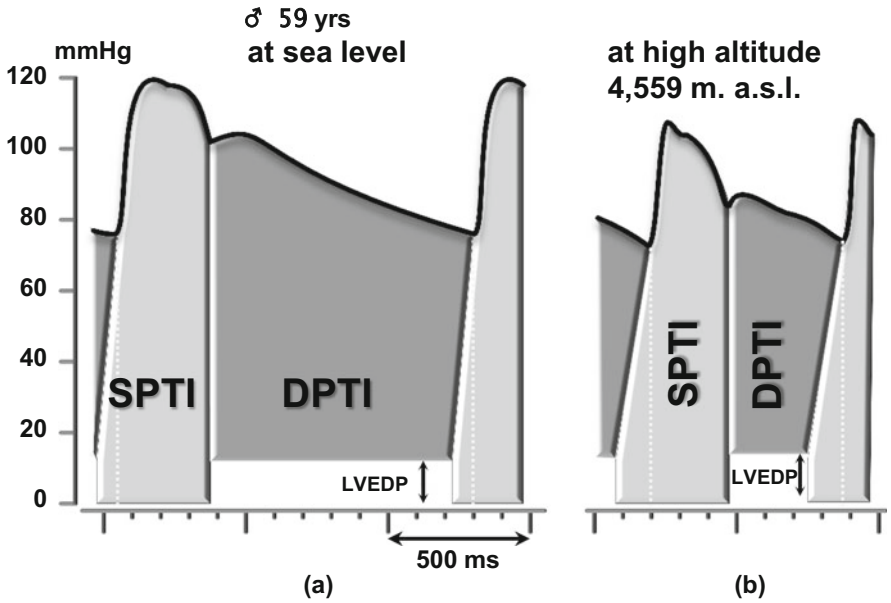

Fig. 6.12 Clinical case no. 3: 59-year-old, apparently healthy man, without any history of heart disease. Significant decrease in myocardial oxygen supply:demand index induced by acute exposure at very high altitude. (**a**) Pressure wave at sea level; (**b**) pressure wave at high altitude (4559 m a.s.l.). *SPTI* systolic pressure–time index, *DPTI* diastolic pressure–time index, *LVEDP* left ventricular end-diastolic pressure

$$\begin{aligned}\text{SEVR-CaO}_2 \text{ at high altitude} &= 0.86\,[(1.34 \times 14.1) \times (0.65) + (0.003 \times 34)] \\ &= 0.86 \times 12.4 = 10.8\end{aligned}$$

The calculation of SEVR × CaO_2, therefore, highlights a clear fall in the subendocardial vascularization index, which is near to "critical" values, arousing suspicion that the cardiac symptomatology reported by the subject could be related to the clear fall in SEVR, all the more so because any possible further falls in oxygen saturation, at nighttime, cause critical values for SEVR (an O_2 saturation of 54 % corresponds to SEVR × CaO_2 of 9.0).

6.4 The Dilemma of the "J-Shaped Curve"

The relationship between a decrease in pressure values and the risk of cardiovascular mortality and morbidity is described by a J-shaped curve (Fig. 6.13); the risk is greater for high arterial pressure values and reduces in parallel with a fall in blood pressure, until a nadir is reached, beyond which further reduction in blood pressure causes an increase in cardiovascular risk.

Several trials have shown that such a J-curve mainly exists between diastolic blood pressure values and coronary disease, most of all in the frailest patients.

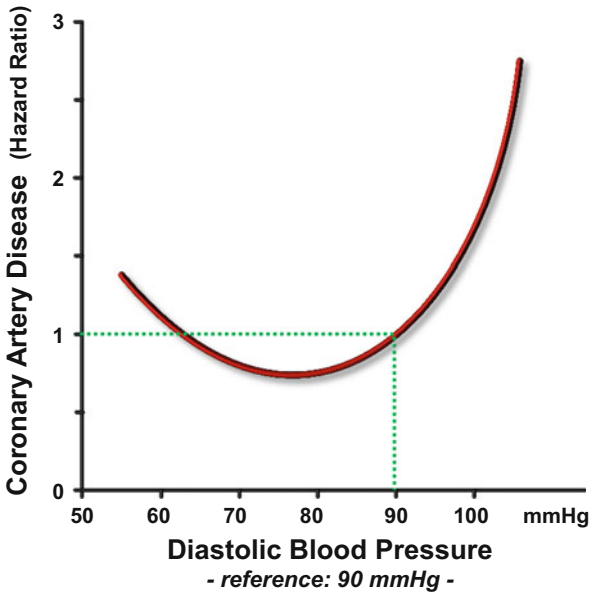

Fig. 6.13 Relationship between coronary artery disease and diastolic blood pressure values, expressed by a J-shaped curve

The J morphology of the relationship between arterial pressure and cardiovascular risk, therefore, casts doubt on the traditional saying about a decrease in blood pressure values in course of therapy: "*the lower the better*".

Early in 2011, a provocative article appeared in the Journal of Hypertension; it was entitled "Blood pressure regulation during the aging process: the end of the 'hypertension era'?". This has thrown new light on the importance of the J-shaped curve, suggesting a revolutionary therapeutic approach to the hypertensive patient [12].

A decrease in blood pressure values following antihypertensive treatment, by at least 6–7 mmHg, is considered of clinical relevance, as it is able to cause significant reduction in cardiovascular complications. However, according to the discussion above, a different clinical and therapeutic approach to the patient with high blood pressure values is required. In fact, we should consider as clinically relevant only reductions in pressure values which are the consequence of an improvement in arterial function or of a redistribution of wave reflection.

Clinical Case No. 1

A 63-year-old diabetic subject with 160/85 mmHg blood pressure and history of coronary disease.

This patient starts antihypertensive therapy (Fig. 6.14):

- The treatment causes both a significant improvement at the level of microcirculation and a reduction in peripheral vascular resistances. Moreover, the viscoelastic properties of large arteries are improved as well.

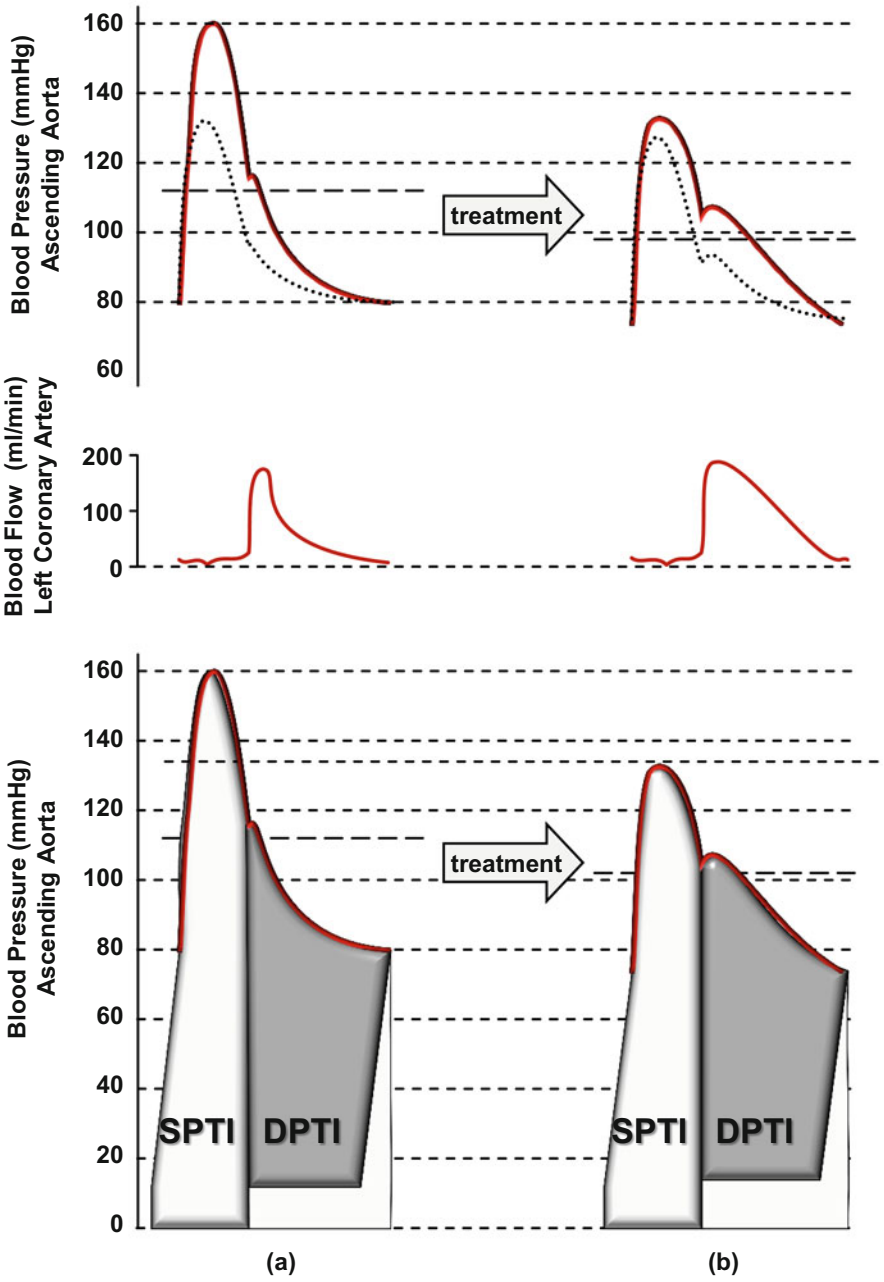

Fig. 6.14 Clinical case no. 1. *Upper panel*, the curve of arterial pressure (*the dotted line* highlights the forward blood pressure wave); *medium panel*, the curve of flow in the left coronary artery; *lower panel*, systolic (SPTI) and diastolic (DPTI) pressure–time index. (**a**) On the *left*, pretreatment situation; (**b**) on the *right*, after antihypertensive therapy

- Both attenuation of direct wave propagation and delay in wave reflection occur, which, partly, superimpose onto the direct wave in diastole.
- Systolic blood pressure decreases (140 mmHg), with moderate reduction in diastolic blood pressure (74 mmHg). Moreover, the central pressure wave curve alters as well, and the morphology of the curve in diastole seems to be "convex" now.
- Therefore, we can speculate that the coronary perfusion flow is greatly improved.

In this case, the permanent reduction in arterial pressure can also be considered of clinical relevance, with positive effects on coronary circulation.

Clinical Case No. 2

A 74-year-old diabetic subject, with 165/70 mmHg blood pressure and history of coronary artery disease. This subject also presents increased arterial stiffness, as proved by a high pulse wave velocity (PWV, 19 m/s) and an early return of wave reflection, while the morphology, in diastole, of the central pressure wave seems to be "concave". We can speculate that the coronary perfusion flow is at "critical" levels, following the morphology of pressure in diastole.

This patient starts antihypertensive therapy (Fig. 6.15):

- Vascular elasticity is greatly damaged, and the antihypertensive treatment is not able to improve the viscoelastic properties of large arteries.
- No hemodynamic change occurs in the propagation of direct waves and reflected waves.
- Mean arterial pressure decreases as well as systolic blood pressure (150 mmHg) and diastolic blood pressure (55 mmHg). The central blood pressure waveform does not change much, but the pressure values in diastole seem to be lower.
- Therefore, we can speculate that the coronary perfusion flow is under a further critical condition, with the serious possibility of outbreak of clinical manifestations related to an acute coronary syndrome.

In this second case, treatment precipitated a labile compensation condition, with worsening of the clinical condition.

These two clinical cases show that further diagnostic methods are needed to assess arterial hypertension and personalize treatment. Under a hypertension condition, characterized by good viscoelastic properties of large arteries, antihypertensive treatment can, therefore, cause a decrease in systolic blood pressure without any significant alteration in diastolic blood pressure, due to the redistribution of reflected waves in diastole. Under these conditions, a decrease in blood pressure can improve coronary blood perfusion. On the contrary, in the presence of marked arterial stiffness, antihypertensive treatment can lower diastolic blood pressure too much, contributing to a reduction in coronary blood flow.

This approach is, clearly, more complex than the traditional approach of "*Tell me a number and I will tell you your cardiovascular risk*". Nevertheless, it is

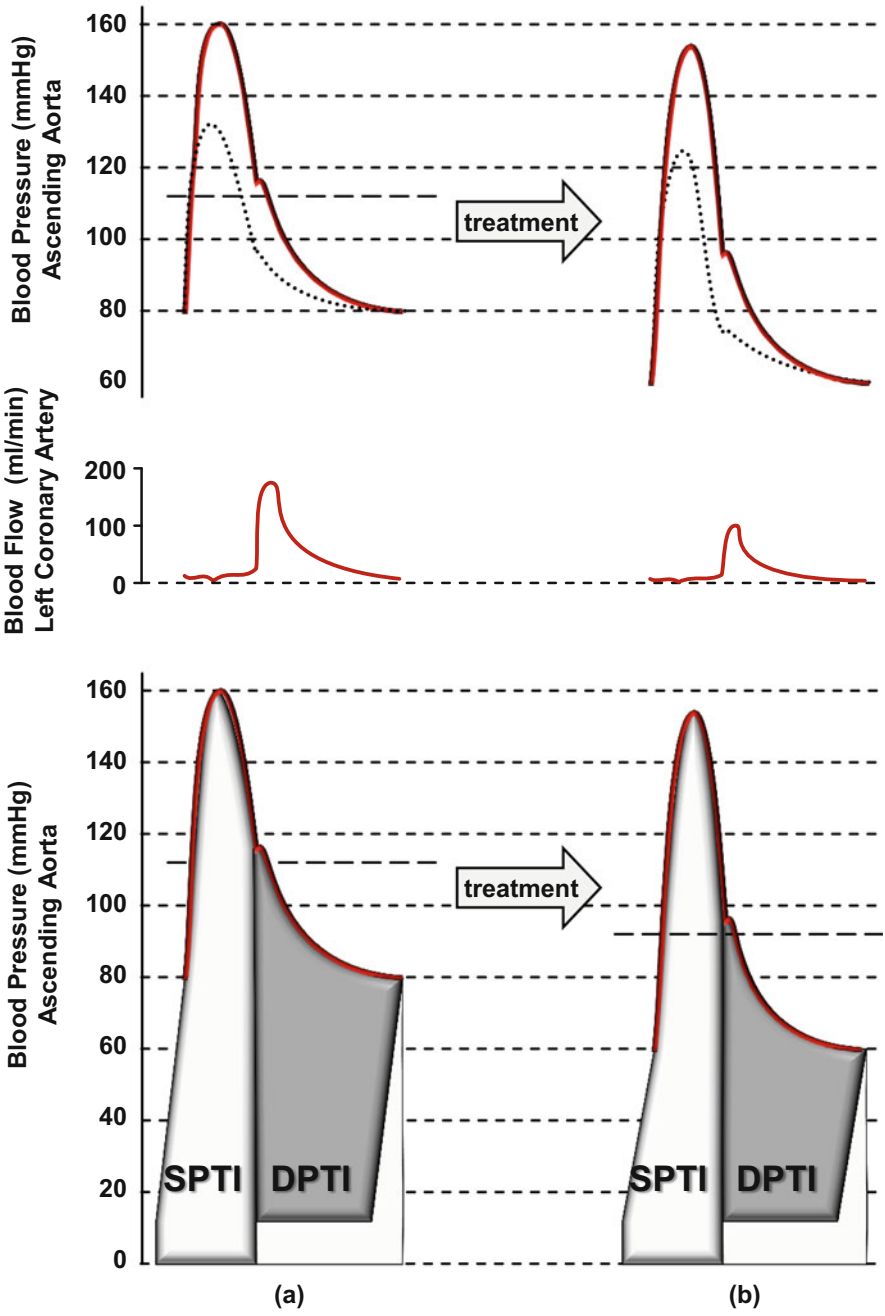

Fig. 6.15 Clinical case no. 2. *Upper panel*, the curve of arterial pressure (*the dotted line* highlights the forward blood pressure wave); *medium panel*, the curve of flow in the left coronary artery; *lower panel*, systolic (SPTI) and diastolic (DPTI) pressure–time index. (**a**) *Left*, pretreatment situation; (**b**) *right*, after antihypertensive therapy

probably the only real opportunity to settle the issue of the J-shaped curve and its clinical relevance.

Pills for Growing

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Arterial Stiffness in Chronic Kidney Disease 7

Life expectancy in patients with Chronic Kidney Disease (CKD) appears to be substantially reduced compared to the general population. As a matter of fact, it is well known that the high incidence of cardiovascular events heavily affects the prognosis in patients with renal disease. There is a close relationship between aortic stiffness and Chronic Kidney Disease, which is supported by a number of studies.

7.1 Vascular Calcifications and Arterial Stiffness

Several biological processes are involved in the progression of atherosclerosis and arteriosclerosis in patients with Chronic Kidney Disease. This disease is associated with accelerated vascular aging; activation of the renin–angiotensin system, aortic inflammation, and vascular metalloproteinase activity lead to changes in the extracellular matrix and to endothelial dysfunction, paving the way to arterial stiffening. Indeed, increased arterial stiffness is observed even in the early stages of Chronic Kidney Disease, suggesting that arterial remodeling occurs early in the course of the disease.

It is worth noting that arterial calcifications occur in Chronic Kidney Disease, and it is associated with increased morbidity and mortality. An inverse relationship between arterial calcifications and bone density has been documented in uremic patients. Disturbances of calcium and phosphate metabolism in Chronic Kidney Disease are associated with PTH secretion and uremic bone disease. Actually, in patients with Chronic Kidney Disease and end-stage renal disease (ESRD), the association between bone and vascular calcifications concerns both aspects of bone disorders: secondary hyperparathyroidism, characterized by high bone turnover, and low bone activity (adynamic bone disease). Even if in secondary hyperparathyroidism the increased bone resorption associated with endogenous release of phosphate and calcium could play a critical role in the induction of vascular calcification, all the same, in these patients, arterial calcifications are more frequently observed in patients with adynamic bone disease (ABD), characterized by a

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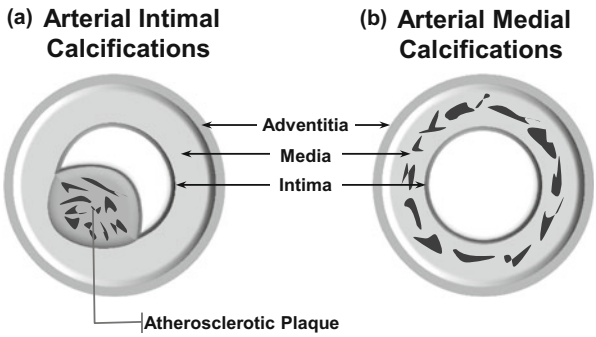

Fig. 7.1 Arterial calcifications. (**a**) Atherosclerotic intimal calcifications: intimal calcification is associated with the development of plaques and occlusive lesions. (**b**) Arterial medial calcifications: calcifications involving the arterial medial layer cause alterations of the arterial wall viscoelastic properties but not a reduction in the arterial lumen

low-bone turnover without osteoid accumulation [1, 2]. The clinical link between mineral bone disorder (MBD) and vascular disease arising from primary perturbations in calcium phosphate homeostasis is clearly recognized. So that KGIDO (international group on Kidney Disease: Improving Global Outcomes) codified the clinical entity CKD-MBD, the mineral and bone disorder of Chronic Kidney Disease that encompasses the vascular calcification of Chronic Kidney Disease.

The presence and extent of arterial calcifications are independently predictive of subsequent cardiovascular disease and mortality beyond established conventional risk factors. Calcification develops in two distinct sites [3]: the intima and media layers of the arterial wall (Fig. 7.1).

7.1.1 Arterial Intimal Calcification (AIC)

Atherosclerotic intimal calcification is associated with the development of plaques and occlusive lesions. It is also associated with inflammatory process and with cholesterol depositions and usually contributes to stenotic lesions and occlusion of the artery. Intimal calcification is mainly found in the elderly and in patients with diabetes, who have a clinical history of atherosclerotic complications and is associated with lower serum albumin, elevated phosphate, and higher calcium carbonate intake.

7.1.2 Arterial Medial Calcification (AMC)

Medial calcification (Mönckeberg medial calcific sclerosis) is characterized by concentric mineral deposits within the arterial middle layer (tunica media),

initiating along mural elastin fibers. Calcifications in the arterial medial layer are frequently observed with aging in the general population; however, it is significantly more pronounced in patients with metabolic disorders, such as diabetes or Chronic Kidney Disease. Vascular calcification is often triggered by active processes involving inflammatory cytokines and metalloproteinases in the absence of atherosclerotic plaques. Actually, hyperparathyroidism and disordered calcium and phosphate metabolism, which are common features of advanced Chronic Kidney Disease, contribute to it.

Calcifications may be observed in the medial layer of the aorta and large elastic arteries, in medium-sized visceral and kidney arteries, as well as in coronary and other transitional arteries with diameter of at least 0.5 mm. A systemic distribution of vascular medial calcification appears to be uncommon.

While arterial intimal calcification appears to be associated with generalized atherosclerosis, which is not specifically attributable to hemodialysis, arterial medial calcification seems to be much more closely associated with hemodialysis treatment and its duration.

Until the late twentieth century, only intimal calcifications, associated with atherosclerosis, were considered at high risk for cardiovascular diseases. As a matter of fact, the cardiovascular risk was considered to be secondary to the reduction in the arterial lumen due to the atherothrombotic process. Vascular calcifications were considered to be a cardiovascular risk since they revealed the presence of atherosclerosis plaques. From a prognostic point of view, on the contrary, medial calcifications were considered less important. Actually, these were wrongly considered to be a low risk factor for cardiovascular disease, as their presence did not alter the size of the vascular lumen. However, epidemiological studies have shown that vascular calcifications, either intimal or medial, are associated with high cardiovascular mortality and morbidity. Therefore, the increase in the cardiovascular risk is not only associated with the degree of the reduction affecting the vascular lumen but also with increases in arterial stiffness. Medial calcification processes in the aorta and large arteries determine an alteration in arterial viscoelastic properties, causing arterial stiffness (Fig. 7.2).

Arterial stiffness can also influence the beat-to-beat and short-term variability of pressure and flow. Through both a reduction in baroreflex sensitivity and the passive effect of the loss of arterial wall elastic properties, arterial stiffness increases blood pressure variability, which, in turn, might contribute to the development and progression of renal damage.

7.2 Arterial Stiffness and Cardiovascular Risk in CKD

When considered as a marker of vascular damage, both arterial stiffness and the indices of aortic calcification show their greatest predictive value for cardiovascular events in patients with end-stage renal disease (Fig. 7.3). The predictive value of aortic pulse wave velocity and calcification score are considerably higher than

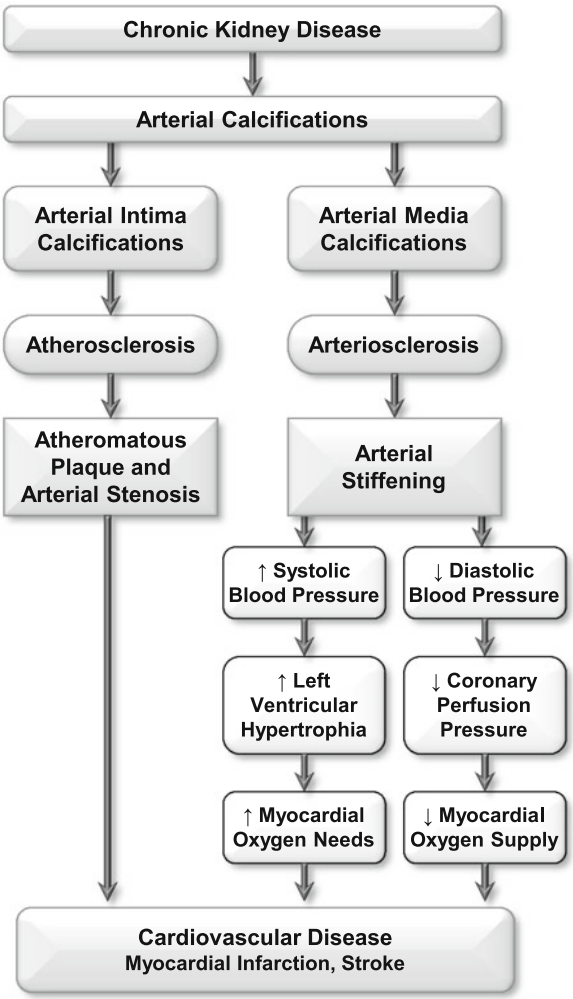

Fig. 7.2 Both intimal and medial arterial calcifications are associated with high cardiovascular mortality and morbidity

"classic" parameters involved in the cardiovascular risk (age, pulse pressure, left ventricular mass, intima media thickness) [4].

Carotid–femoral pulse wave velocity (aortic PWV) reflects the viscoelastic properties of the aorta and is considered to be the gold-standard method for arterial stiffness assessment.

Aortic PWV is considered to be an independent predictor of cardiovascular mortality, and several studies have shown that an increase in aortic PWV is associated with an increase in cardiovascular events.

Here, you will find the outcome of a particularly significant longitudinal study, carried out in patients with end-stage renal disease (Fig. 7.4) [5]. A total of 241 subjects, subdivided into tertiles according to pulse wave velocity reference

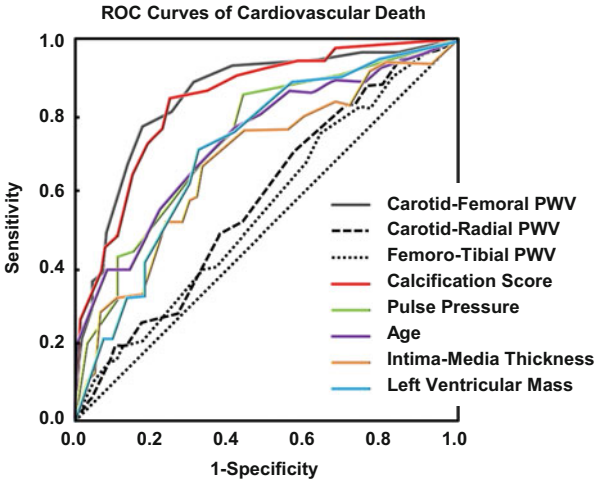

Fig. 7.3 Sensibility and specificity of age, pulse pressure, intima-media thickness, left ventricular mass, calcification score, carotid–femoral, carotid–radial, and femoro-tibial pulse wave velocity (PWV) in relation to cardiovascular mortality in end-stage renal disease patients: receiver operating characteristic (ROC) curves of cardiovascular death [4]

values, were studied. In the figure, you can see that, after 140 months of follow-up, among the subjects with low values of aortic PWV (first tertile) "only" 6 out of 81 died (7 %) whereas, among the subjects with high values of aortic PWV (third tertile), 51 out of 80 died (64 %). This is really shocking. The incidence of cardiovascular events had similar outcomes (Fig. 7.5).

7.3 Arterial Stiffness and Renal Microcirculatory Damage

The link between arterial stiffness and renal function is undoubtedly complex, and it is not a one-way relationship.

Although small vessels in the systemic circulation are generally protected from increased blood pressure load by upstream arterial vasoconstriction activity, the renal vascular bed is characterized by low resistance and low impedance. The kidneys are, therefore, continually and passively perfused through systole and diastole by a high-volume pulsatile flow. The flow displays characteristics that make renal parenchyma particularly vulnerable to an increase in the amplitude of pulse pressure and to the wide variation in systolic and diastolic flow caused by large artery stiffness [6].

A stiff aorta increases the delivery of pulsatile energy into the kidney circulation. Thus, the hemodynamic impact of this pulsatile flow is transferred to the vulnerable renal microvasculature because of its low impedance and can lead to the constriction of resistance vessels and subsequently to structural damage. It can, therefore, be assumed that there is a pathogenetic link between aortic stiffness and renal damage through the transfer of a highly pulsatile flow into the renal microvasculature [7]. On the other hand, a high pulse pressure secondary to aortic stiffening without an accompanying increase in flow pulsatility did not increase the transmission of pulsatile power into the vascular bed and did not result in microvascular

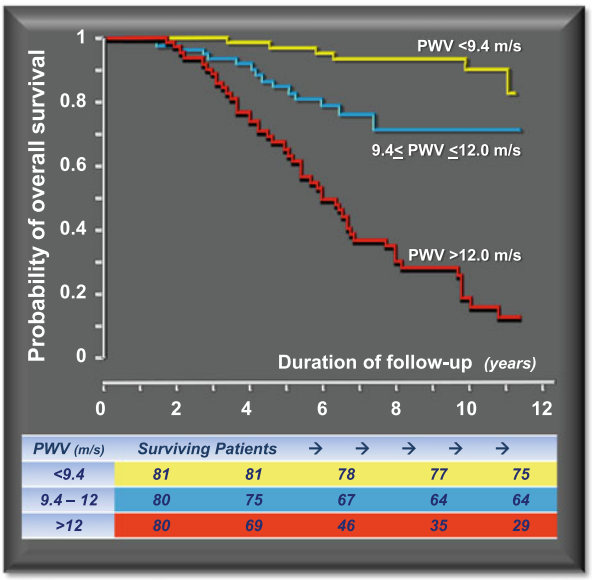

Fig. 7.4 Probabilities of overall survival in end-stage renal disease according to the level of pulse wave velocity (PWV) divided into tertiles. Comparisons between survival curves were highly significant ($\chi^2 = 67.23$, $P < 0.0001$). In the lower chart, the number of patients who survived at each point according to the tertile of PWV [5]

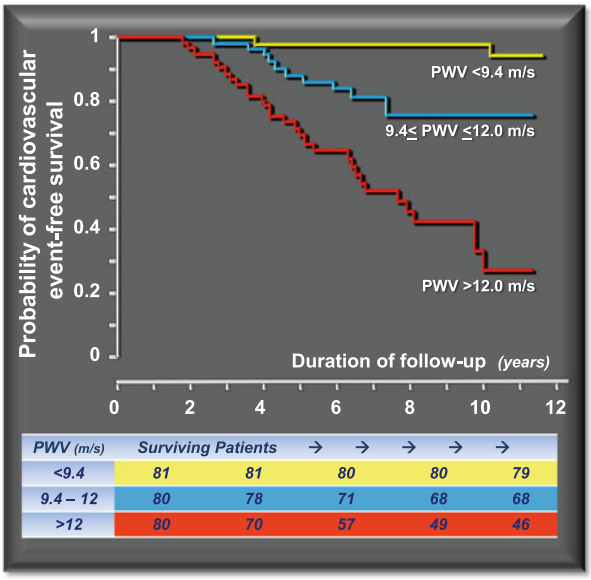

Fig. 7.5 Probabilities of event-free survival (cardiovascular mortality) in end-stage renal disease according to the level of pulse wave velocity (PWV) divided into tertiles. Comparisons between survival curves were highly significant ($\chi^2 = 47.04$, $P < 0.0001$). In the lower chart, the number of patients who survived at each point according to the tertile of PWV [5]

damage either. It is important to stress that, although mainly determined by arterial pulse pressure, pulsatility index in the kidney circulation can be affected by other factors, such as renal vascular resistance, renal reflected waves, local arterial viscoelastic properties, renal artery stenosis, heart rate, and blood pressure variability (Fig. 7.6).

A reduction in pulsatility index might protect the kidney microcirculation against damage generated by high-pressure pulsatility. In the setting of hypertension, characterized by high pulse pressure, drugs that reduce pulsatility index and renal vascular resistance (such as RAS blockers) should, therefore, be preferred. The importance of vascular calcifications as determinants of arterial stiffness suggests that treatment strategies aimed at suppressing or inhibiting their formation, such as supplementation with Vitamin K, magnesium salts, and possibly pyrophosphate, may be highly effective in maintaining arterial function, reducing cardiovascular risk, and interrupting the vicious cycle between arterial stiffness and kidney microvascular damage.

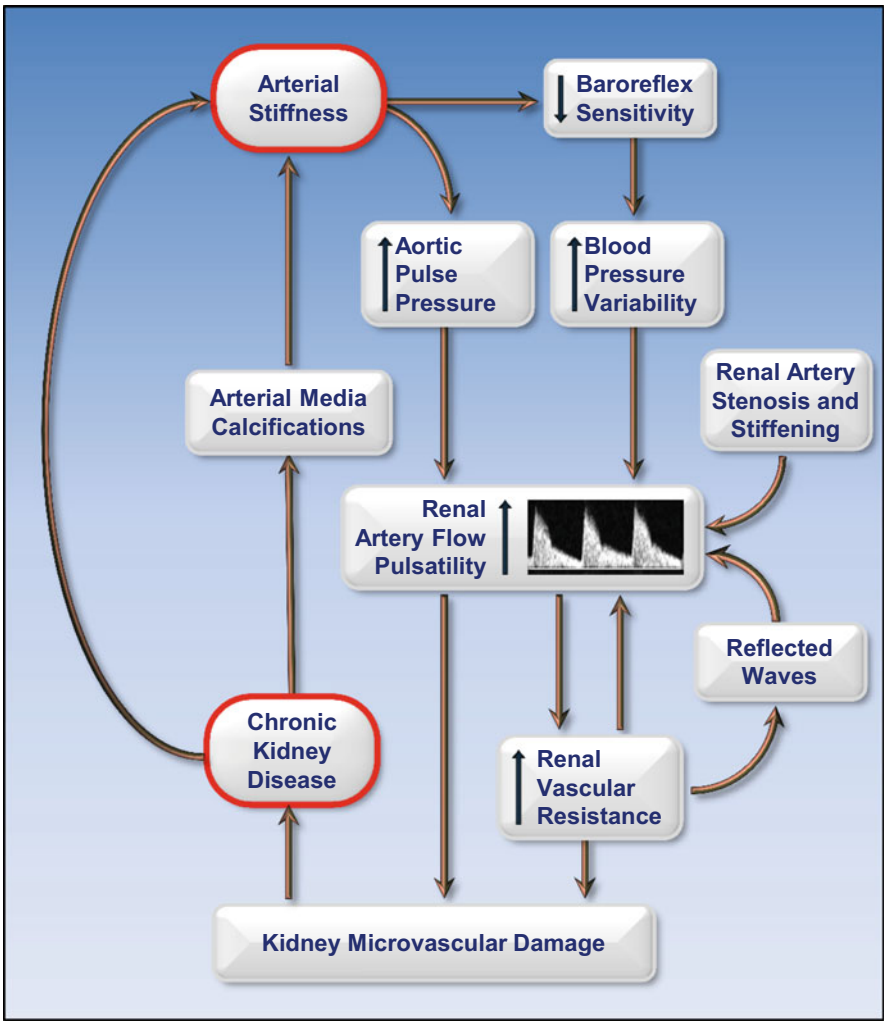

Fig. 7.6 The complex relationship between arterial stiffness and Chronic Kidney Disease [7]

New drugs, able to reduce arterial stiffness and to buffer increased blood pressure variability, are likely to further improve the current approach to the treatment of arterial hypertension.

Pills for Growing

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Pulse Wave Velocity and Pulse Wave Analysis in Experimental Animals

8

8.1 Invasive Methods

Until a few years ago, pulse wave velocity, in little experimental animals (mice, rats, rabbits, etc.), could only be measured by invasive methods. The carotid and femoral arteries were surgically isolated and catheterized to assess intra-arterial pressure (Fig. 8.1).

A pressure micro-transducer was inserted via the carotid artery into the aortic arch for the clinical recording of the intravascular central arterial pressure wave. Another catheter was inserted into the peripheral end of the abdominal aorta and placed just above the aortic bifurcation through the femoral artery. The carotid and femoral signals were recorded simultaneously. The signals were digitized and stored using a data acquisition system, and the delays between proximal and distal pressure waveforms were evaluated by a specifically designed software. After the recordings were completed, the animals were euthanized and the full length of the aorta was exposed. The distance between the proximal and distal pressure transducers was determined by measuring the length of a damp cotton thread stuck onto the aorta between the tips of the two pressure transducers and marked.

However, this operation would cause the death of the small laboratory animal, which was then dissected to measure the distance between the two catheters. Pulse wave velocity was calculated in this way. The biggest problem with this procedure is the impossibility of carrying out longitudinal studies for the evaluation of arterial distensibility. Actually, longitudinal studies in small laboratory animals are particularly interesting because, as their life is so brief, a few months correspond to decades of life in human beings. This is the reason why even follow-up over a few weeks (i.e., after a predetermined diet or after taking some drugs) can show significant thrombogenic action or change in the viscoelastic properties of arteries. It is also important to note that particular rat strains simulate specific pathological conditions of human beings; for example, spontaneous hypertensive rats (SHRs) are very useful for the evaluation of cardiovascular risk and for the evaluation of

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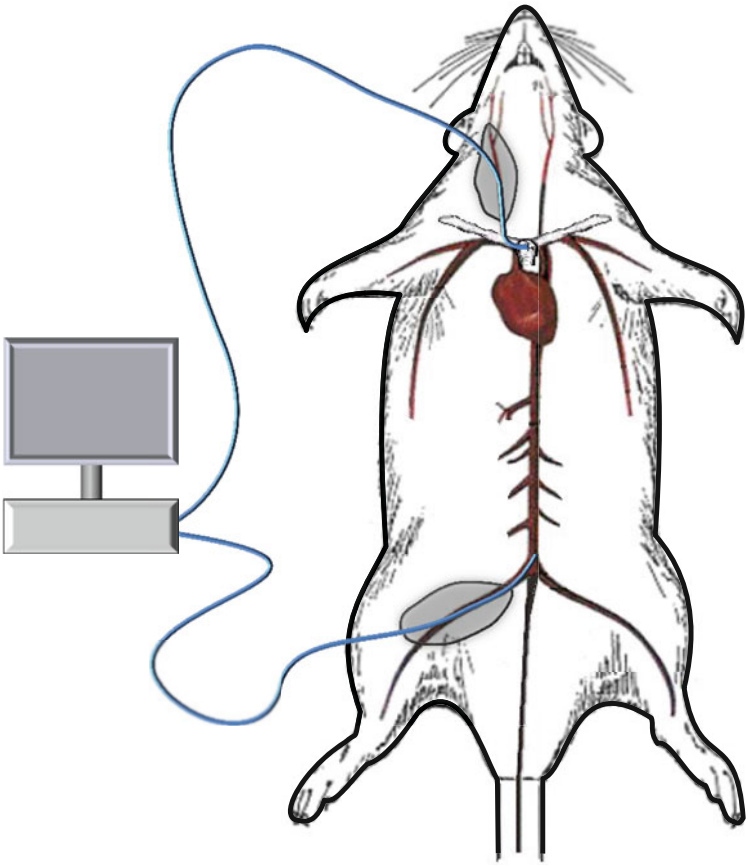

Fig. 8.1 Invasive assessment of carotid–femoral pulse wave velocity in rats. Carotid and femoral arteries are surgically isolated. A pressure micro-transducer is inserted via the carotid artery into the aortic arch, and a second catheter is placed just above the aortic bifurcation through the femoral artery. Both carotid and femoral signals are recorded simultaneously and then analyzed by a specifically designed software

antihypertensive drugs and obese Zucker rats simulate a condition which is similar to severe metabolic syndrome.

8.2 Non-invasive Methods

Non-invasive approaches to assess pulse wave velocity have already been discussed; nevertheless, these methods are not suitable for large and longitudinal studies. At present, magnetic resonance imaging and Doppler ultrasound-based

transit time approaches have been considered to estimate local arterial PWV at different sites in mice and rats.

PulsePenLab® (DiaTecne s.r.l., Milan) has recently been validated. It is an instrument derived from the PulsePen® tonometer (widely used in clinical practice for human beings), specifically designed for the study of central blood pressure and acquisition of pulse wave velocity in small laboratory animals. In the light of the high heart rate in rats (average 350–400 beats/min), the sampling rate of the tonometer was increased up to 1000 Hz (1 kHz), therefore, improving the definition of the signal (16 bits). The transducer was changed as well; its contact area was reduced, with a significant increase in sensitivity. The PulsePen® uses two tonometers, able to record carotid and femoral (or tail) pulse waves simultaneously.

To sum up, a non-invasive measurement of aortic pulse wave velocity and pulse wave analysis in rats and little animals can be possible today, using a very efficient device called PulsePenLab®. Longitudinal studies for assessing the action of drugs or diet on aortic distensibility are now easily and quickly feasible in small laboratory animals. PulsePenLab® tonometers are currently used in studies involving several groups of rats: spontaneous hypertensive rats (SHRs), Wistar, lean Zucker Fa/Fa rats, fatty insulin-resistant Zucker fa/fa rats, Sprague–Dawley, etc.

8.2.1 Aortic PWV in Little Experimental Animals

Aortic PWV may be described as the time taken by the blood pressure wave to propagate from the common carotid artery, considered as central artery, to the peripheral artery. PWV is defined as the ratio of the distance between the two locations on which blood pressure wave was measured as the time delay of the peripheral pulse wave in relation to the carotid pulse wave. Aortic PWV can be assessed in two ways:

- Carotid–femoral PWV (Fig. 8.2). This method requires simultaneous recording of pulse waves by placing one probe on common carotid artery and one probe on femoral artery.
- Carotid–tail PWV (Fig. 8.3), where pressure waves are recorded simultaneously at the level of the carotid artery and of ventral tail artery, at the beginning of the tail.

Before starting, the body weight of an experimental rat should be measured by using a precision electronic scale and linear body measurement (from the tip of the nose to end of the tail) obtained by precision digital calipers. Its body temperature should be maintained at about 37 °C by placing the rat on a thermostatically regulated heating board. It is advisable to shave the area at the level of the carotid and femoral arteries to optimize the signal quality and strength according to a standard procedure. The two probes should be positioned and fixed on the arteries by means of mechanical arms, equipped with micro-regulators. After that, pressure signals are transmitted to a computer by means of an optical fiber that ensures the electromagnetic isolation for the animal undergoing the test (Figs. 8.4 and 8.5).

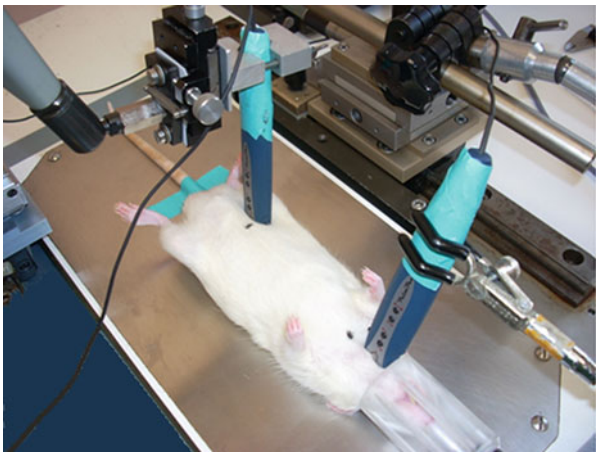

Fig. 8.2 Non-invasive assessment of carotid–femoral pulse wave velocity in a spontaneous hypertensive rat. Arterial pressure waves are simultaneously recorded in carotid and femoral arteries with PulsePenLab® arterial tonometer

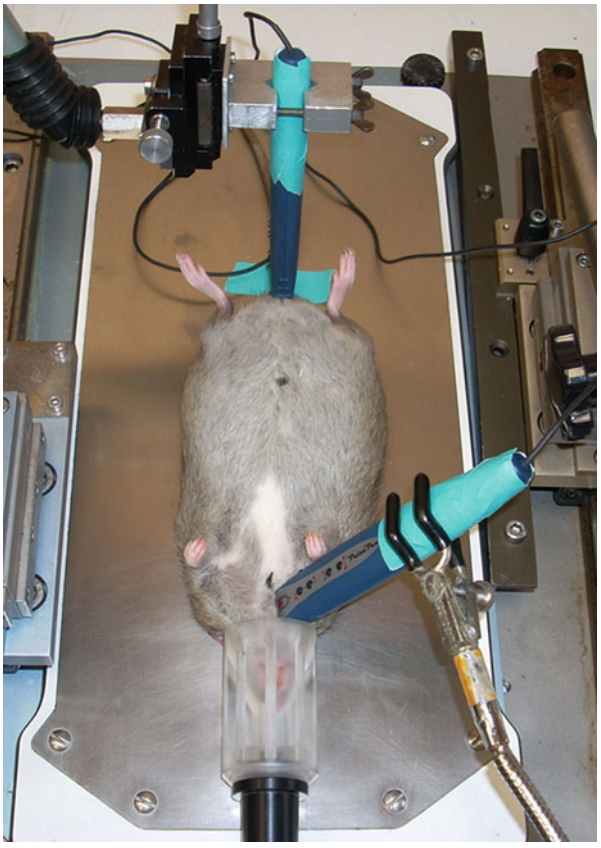

Fig. 8.3 Non-invasive assessment of carotid–tail pulse wave velocity in a fatty insulin-resistant Zucker fa/fa rat. Arterial pressure waves are simultaneously recorded in carotid and tail arteries with PulsePenLab® arterial tonometer

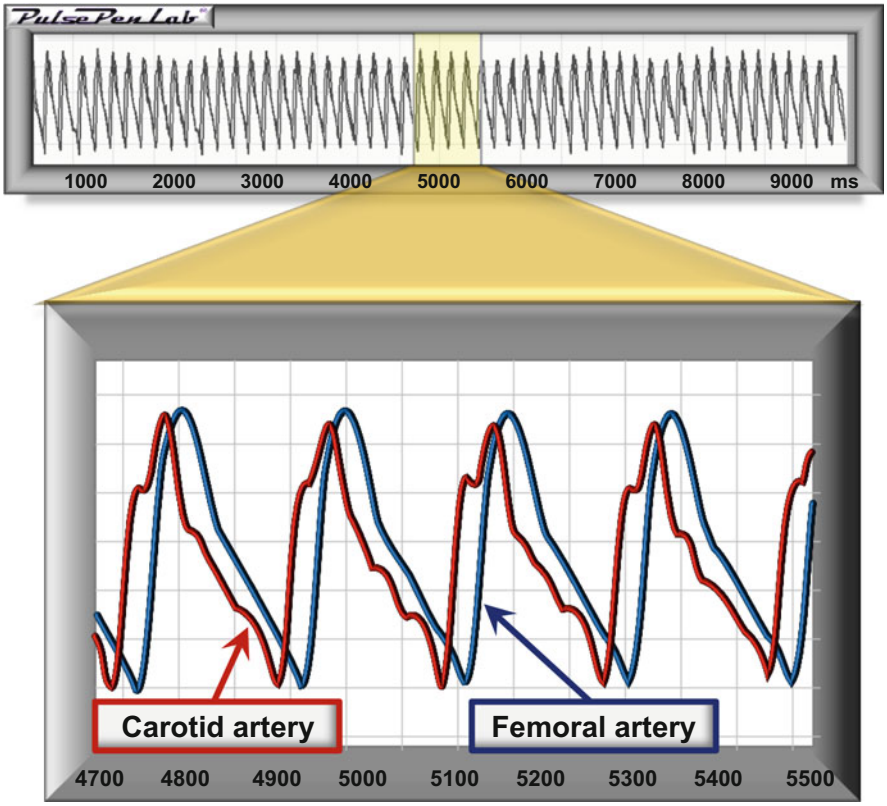

Fig. 8.4 Non-invasive simultaneous recording of carotid and femoral arterial pressure waves in rat using PulsePenLab® arterial tonometer

PWV is calculated as the distance between the two recording sites divided by the time delay between the two arterial waveforms at each site.

8.2.1.1 Measuring Distances

The measurement of the distance between the pulse wave recording sites is a basic parameter for the calculation of pulse wave velocity. This is a ticklish question especially in small-sized animals, where accurate measurement of distance is required.

After the tonometric pulse wave acquisition, the sites where probes have been placed are marked on the skin with an indelible felt-tip.

The direct distance from the carotid point of tonometer application and the peripheral point of application of the tonometric probe (femoral artery or tail artery) is measured with a high precision digital caliper (Fig. 8.6).

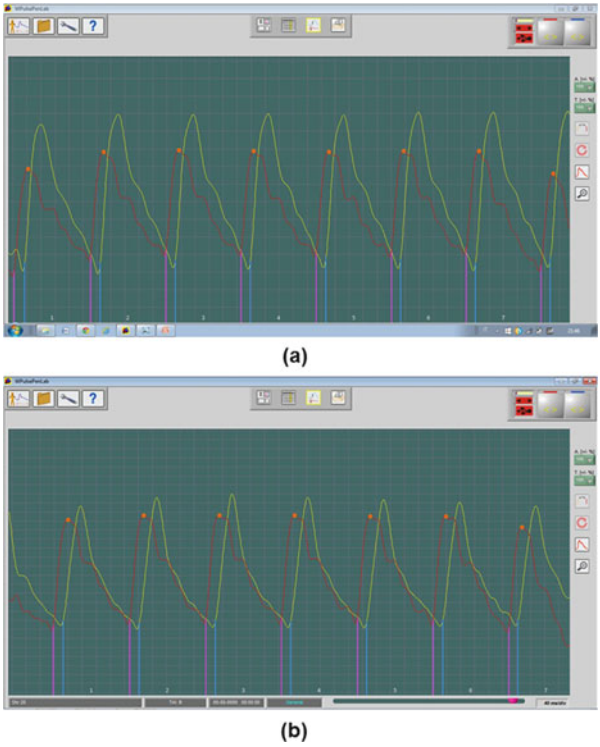

Fig. 8.5 Pulse waves recorded with PulsePenLab® tonometer at carotid and femoral arteries (**a**) and carotid and tail arteries (**b**) analyzed by a specifically designed software. Pulse wave transit time is calculated in order to assess the carotid–femoral pulse wave velocity

As far as carotid–femoral PWV is concerned, the direct carotid to femoral artery distance multiplied for 0.8 appears to be the best method, i.e., the 80 % of the direct carotid–femoral distance, which is very close to the real distance covered by the pulse waves. As to carotid–tail PWV, the direct carotid to tail artery distance has to be multiplied by 0.77, i.e., the 77 % of the direct carotid–tail distance.

8.2.1.2 Adjustment of Pulse Wave Transit Time for Heart Rate

As recommended by international guidelines, the time delay between femoral and carotid pulse waves is determined using a foot-to-foot method.

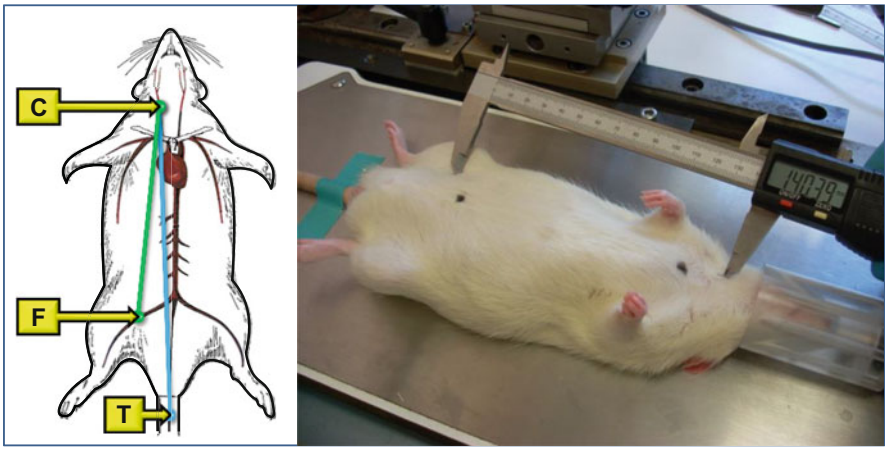

Fig. 8.6 Pulse wave recording sites (*left panel*) (*C* carotid, *F* femoral, *T* tail); measurement of the distance between carotid and tail arteries, with precision electronic sliding calipers, to determine pulse wave velocity (*right panel*)

Heart rate may be an important confounding factor that should be taken into account when performing analysis based on PWV measurements in rats. A direct, close relationship between pulse wave transit time delay from carotid to peripheral artery and heart period (R–R interval) was shown in several studies. Thus, pulse wave transit time delay (PWTT) should be normalized for a theoretical heart rate of 375 beats/min, corresponding to a heart period (HP), i.e., R–R interval of 160 ms.

Thus, pulse wave transit time (PWTT), resulting from this normalization, can be shown as $PWTT_{@375}$ and PWV values as $PWV_{@375}$. It is advised that the following formula is used to calculate $PWTT_{@375}$:

$$PWTT_{@375} = PWTT + [0.131 \cdot (160 - HP)]$$

where HP is the heart period (=60,000/HR). Thus, the formula used to calculate $PWV_{@375}$ is:

$$PWV_{@375} = \frac{\text{Distance}}{PWTT_{@375}} = \frac{(\text{mm})}{(\text{ms})}$$

i.e.,:

$$PWV_{@375} = \frac{\text{direct distance between carotid and femoral artery} \times 0.8}{\text{carotid to femoral PWTT} + [0.131(160 - HP)]}$$

and

$$\mathrm{PWV}_{@375} = \frac{\text{direct distance between carotid and tail artery} \times 0.77}{\text{carotid to tail artery PWTT} + [0.131(160 - \mathrm{HP})]}$$

8.2.2 Pulse Wave Analysis in Little Experimental Animals

As widely shown in Chap. 5, pulse wave in common carotid artery, recorded by arterial applanation tonometer, is a reliable surrogate for aortic pressure. Actually, it has been widely tested that the shape of the pressure wave in the ascending aorta is similar to the one recorded in the common carotid artery, so that direct application of tonometry in the carotid artery is an easy and reproducible approach to record central blood pressure.

Pulse waveform analyses provide quantitative and qualitative data on the ascending aortic blood pressure and supply further elements concerning the elastic properties of the arterial wall, estimating the importance and the transmission speed of reflected waves.

All parameters derived from the analysis of pulse waveform in humans, like augmentation index, amplification phenomenon, form factor, and so on, can be estimated also in little animals (Fig. 8.7).

An accurate algorithm has recently been implemented by the PulsePenLab® in order to make a distinction between forward and backward waves.

The wave separation analysis (WSA) implemented by the PulsePenLab® is able to calculate the following parameters:

- The forward wave amplitude (Pf)
- The backward wave amplitude (Pb)
- The global reflection coefficient (GRC), i.e., the backward wave amplitude divided by forward wave amplitude; GRC = Pb/Pf

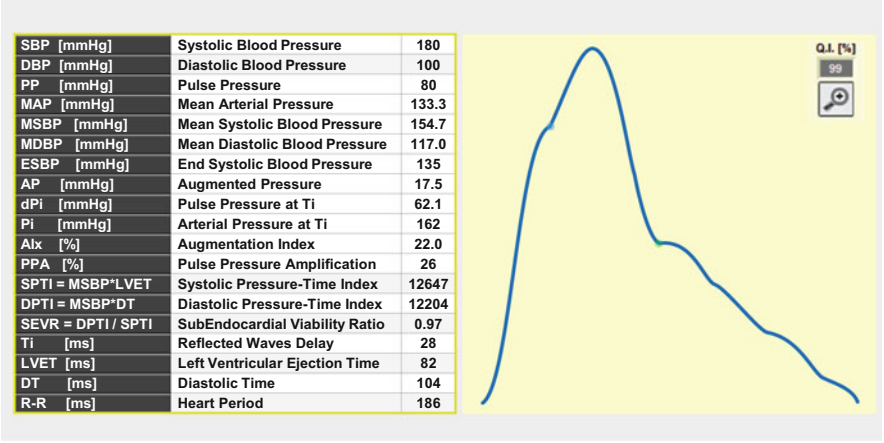

Fig. 8.7 Parameters defined by pulse wave analysis in a spontaneous hypertensive rat (SHR). Data acquired by PulsePenLab® tonometer

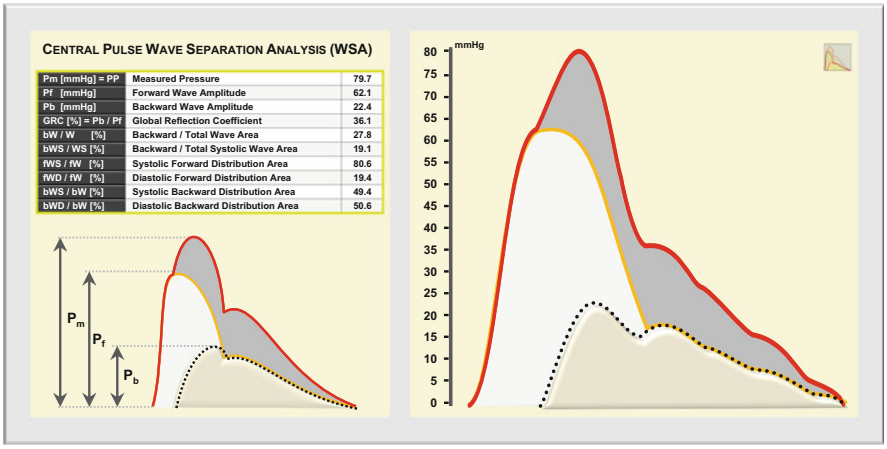

Fig. 8.8 Wave separation analysis (WSA) in a spontaneous hypertensive rat (SHR). WSA allows the decomposition of the central pulse wave into its forward (Pf) and backward (Pb) components. Data acquired by PulsePenLab® tonometer

- As backward wave amplitude divided by forward wave amplitude
- The ratio between backward wave area and total pulse wave area
- The distribution area of forward and backward waves during the systolic and diastolic phase of the cardiac cycle

Figure 8.8 shows the wave separation analysis performed by PulsePenLab® in a spontaneous hypertensive rat (SHR).

Disclosures

The author of this book (Paolo Salvi, MD, PhD) is a specialist in Internal Medicine and in Cardiology, Associate Professor in the Department of Internal Medicine and Geriatrics at the University of Nancy (France) from 2007 to 2010. Currently, he is a researcher of the Istituto Auxologico Italiano, Milan, Italy.

For more than 30 years, he has dealt with arterial hypertension and vascular problems, in clinical and research activity, at first, developing subjects related to microcirculation, then devoting himself to the study of the role of large arteries in affecting arterial pressure as well. The author participated in several clinical research trials and studies which would confirm the prognostic relevance of the indices connected to arterial stiffness and the importance of an everyday clinical application of the instruments for the study of the mechanics of large arteries.

However, owing to the high cost of the devices on the market, instruments would run the risk of being confined to few university research centers.

This is the reason why, together with his engineer friend Giuseppe Lio, the author has developed a tonometer with two basic features. First of all, great reliability, corresponding to the principles of physics and physiology; made with high-quality, high-tech components; validated with invasive methods and verified by a laboratory; using precision instruments. Second, low selling price, which could allow it to be used in public or private outpatient clinics, in industrialized, developing or third-world countries.

In 2002, the patent of the new tonometer, called PulsePen, was obtained, and in 2004, the DiaTecne s.r.l. was established to manufacture and market the tonometer. Over the last few years, the author has collaborated, with enthusiasm, to develop and diffuse this instrument, checking that the initial aims, of absolute reliability, are maintained daily.

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