Non-invasive evaluation of arterial abnormalities in hypertensive patients

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Arterial abnormalities in hypertension **Morbidity and mortality in hypertension are mainly determined by arterial lesions which may occur in different regional circulations (e.g. kidney, cerebral, coronary circulations, causing nephroangiosclerosis, stroke or myocardial infarction, respectively). Despite arterial heterogeneity, structural and functional abnormalities are usually observed at an early stage of hypertension in both large and small arteries. These alterations modify physiological and mechanical properties of the arterial wall, which may become clinically evident by increasing arterial pulsatility or pulse pressure; the alterations facilitate the establishment and progression of atherosclerosis and arteriosclerosis.**

Methods of assessing arterial abnormalities **Several non-invasive techniques can be used to assess haemodynamic properties of arteries: (1) casual and ambulatory blood pressure measurements can be used to evaluate pulse pressure; (2) pulse pressure can be measured directly in different sites of the arterial tree using the Tonometer device; (3) ultrasound techniques can be applied, including Doppler signals to assess the arterial flow, video-echo signals to analyse the arterial structure such as the intimal–medial thickness and echo-tracking systems for direct measurements of arterial wall distension and thickness; (4) pulse wave velocity is widely used as an index of arterial distensibility; this parameter, assessed by the Complior device, has shown that hypertensive patients have decreased arterial distensibility and that antihypertensive treatment does not always reverse this abnormality.**

Treatment **It is important to evaluate the effect of cardiovascular risk-reduction measures on the arterial wall. Large therapeutic trials are necessary to show whether an evaluation of arterial abnormalities can identify patients with a high cardiovascular risk and contribute to their treatment and prognostic improvement.**

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Introduction

Cardiovascular disease is the leading cause of mortality in most industrialized populations. Arterial pathology is a major contributor to cardiovascular disease, morbidity and mortality. Arterial wall alterations are usually associated with a number of cardiovascular risk factors, including age, smoking, lipoprotein abnormalities, diabetes and hypertension [1–3]. These arterial wall changes are observed at an early stage of the diseases with structural and functional modifications in both large and small arteries [4–7]; they modify the physiological and mechanical properties of the arterial wall and have been proposed as a possible mechanism in the initiation and progression of atherosclerosis [8–10].

Historically, arteries were considered to be passive conduits of blood. Now the arterial system is recognized as a complex and active regulator of cardiovascular function in health and disease [6,11,12]. Recent progress in arterial pathophysiology and technological advances have made it possible to describe the arterial system as a complex and heterogeneous system with major differences in the structure and functions of various arteries of the arterial tree [13–15]. Not only do central large and elastic arteries differ from peripheral small and muscular arteries in important histomorphometric respects, but the incidence and causes of large arterial lesions differ according to the site of the lesions and their triggered factors. Therefore, clinical consideration of arterial haemodynamics may make it possible to improve cardiovascular prevention; this issue needs to be assessed in large clinical studies [16,17].

Hypertension and the arterial system

Hypertension is a major cardiovascular risk factor which affects the whole arterial system, both large and small arteries. The mechanism of risk has generally been attributed to rarefaction, that is, a reduction in the calibre of small arteries or arterioles, with a resulting increase in peripheral resistance and mean blood pressure [1,18–20]. This definition refers to steady phenomena and ignores that the fact that blood pressure and flow fluctuate during the cardiac cycle. A more recent and realistic approach to arterial haemodynamics is to

consider arterial pressure as the sum of a steady component (mean blood pressure) and a pulsatile component (pulse pressure). The former is the pressure for the distribution of steady flow to the tissues and represents the useful component of external heart work; the latter is the consequence of intermittent ventricular ejection and represents the 'unproductive' component of external heart work [6,21]. Haemodynamically, beside the pattern of left ventricular ejection, the determinants of mean blood pressure (and to a lesser extent diastolic blood pressure) are primarily the vascular resistance in small peripheral arteries, and to a lesser degree the compliance in large conduit arteries, whereas the determinants of pulse pressure (and systolic blood pressure) are primarily the compliance and elastic properties of large arteries, the timing and intensity of arterial wave reflections inside the arterial tree and to a lesser degree the resistance in small peripheral arteries. These functions of small and large arteries are related to the structure and geometry of the arterial wall and are influenced by neurohumoral conditions [6–8].

In hypertension, the structure and function of arteries are important not only because they may contribute to the definition and mechanisms of hypertension but also because they are obviously involved in the end-organ damage of untreated hypertension, and therefore in the effectiveness of antihypertensive therapy. In fact, most of the complications of hypertension are related to arterial wall changes. In the cerebral circulation, structural alterations within the vasculature predispose subjects to medial necrosis, inflammatory cell infiltration and eventual microaneurysm formation; in the coronary circulation, capillary rarefaction associated with the decreased coronary reserve caused by vascular remodelling may favour myocardial ischaemia, especially in the subendocardial layer. Moreover, early recognition of arterial changes may identify patients with a high risk of clinical complications of hypertension and atherosclerosis [22–24].

Recent studies using new concepts and techniques have emphasized the heterogeneity of the various arteries in the arterial tree and described the arterial changes observed in hypertensive patients. At the level of small arteries (internal diameter <200 μm), arterial remodelling has been described as an adaptive process to high blood pressure during chronic hypertension. An increased thickness of the arterial wall serves to counter the rise in wall tension; this is achieved by changes in cellular mass and connective tissue content. It is associated with a decrease in internal diameter and with no change or a small increase in cross-sectional area due to hypertrophy and hyperplasia of the medial smooth muscle cells; the decrease in lumen area and the increase in the wall : lumen ratio contribute to the aggravation of hypertension by increasing vascular reactivity to vasoconstrictor agents and peripheral resistance [19,25,26].

At the level of large arteries the adaptive process has been described as an increase in wall thickness with an unchanged or increased internal diameter and thus an increase in the wall : lumen ratio and cross-sectional area. This process has been attributed to growth processes, with medial smooth muscle cell hypertrophy and an increase in the collagen content of the extracellular matrix. Because it is generally postulated that the arterial remodelling induced by hypertension might predispose subjects to end-organ damage, antihypertensive treatment may be evaluated not only for its effects on blood pressure reduction but also by its ability to reverse arterial abnormalities [27–29].

Methodological aspects

Large and small arteries constitute two major compartments of the arterial system which have different and distinct structural and functional features in pathophysiology: a buffering function for larger arteries and a resistance function for the smaller. However, hypertension is usually recognized by arterial pressure measurements obtained at the site of a large artery for several reasons: first, because haemodynamically, the definition and mechanisms of hypertension include determinants related to small but more particularly to large arteries; second, because large arteries constitute the target and the site of the cardiovascular complications associated with hypertension; and finally, because most technical advances in recent years affect the haemodynamic evaluation of large arteries. In this brief review, some of the non-invasive methods used most often to evaluate large arteries are described.

Pulse pressure measurements

Epidemiological studies have shown that in patients aged over 50 years, clinic systolic blood pressure is a stronger cardiovascular risk factor than diastolic blood pressure. Since blood pressure is a pulsatile phenomenon and since hypertension may be considered as a mechanical factor causing arterial wall modifications, another approach is to assess the pulsatile component of blood pressure, which is calculated as the difference between systolic and diastolic blood pressure. A number of reports have shown that clinic measurements of brachial pulse pressure are correlated with the end-organ damage associated with hypertension, such as arterial wall alterations and left ventricular hypertrophy; in addition, clinic brachial pulse pressure has been reported to be an independent cardiovascular risk factor for morbidity and mortality [30–35].

Since ambulatory blood pressure recording is more reproducible than casual measurements and since it is correlated more strongly than clinic blood pressure with indices of hypertensive target-organ damage, this technique has been applied to evaluate 24-h ambulatory pulse pressure. Whereas some reports have shown large discrepancies between pulse pressure measured in the clinic and by ambulatory methods, other studies have shown that ambulatory pulse pressure is closely correlated with left ventricular mass and arterial distensibility and that it is more sensitive than clinic blood pressure measurements in evaluating the consequences of arterial risk factors as smoking, lipid abnormalities and glycaemia on blood pressure and its variability [30,36–38]. Moreover, in comparison with a control group, patients with arterial disease had

unchanged clinic systolic or pulse pressures, whereas ambulatory monitoring demonstrated an elevation in systolic and pulse pressure levels and an increase in pressure variability with changes in the diurnal pattern [39]. Several reports have suggested that analysis of systolic and pulse pressures obtained by ambulatory blood pressure monitoring can be used as an indirect measure of arterial function, since ambulatory pressures are more sensitive than casual measurements to the relationships between blood pressure and arterial distensibility, to the blood pressure consequences of arterial risk factors and to arterial diseases and their treatment.

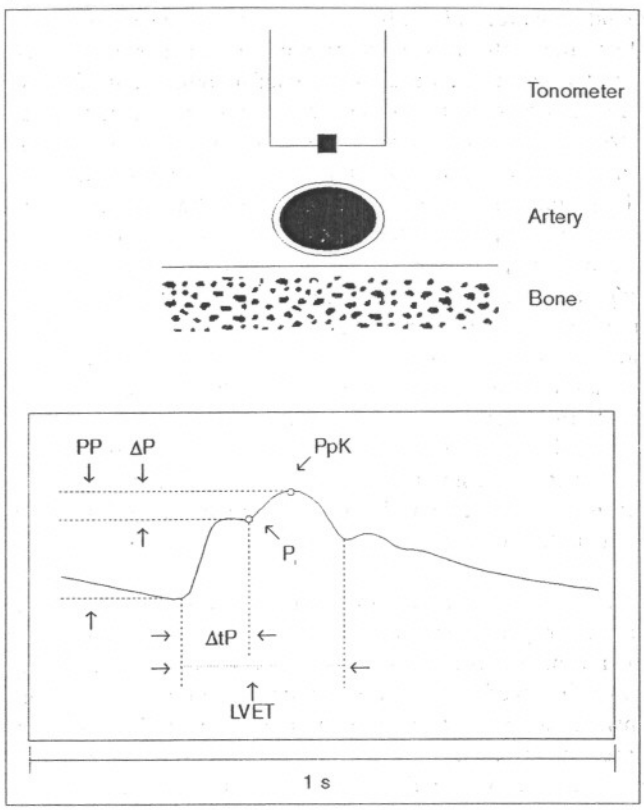
Applanation tonometry

Non-invasive determination of blood pressure according to the Riva-Rocci cuff method is relatively accurate. Pulse pressure increases substantially from central to peripheral arteries due to several factors: (1) a progressive decrease in arterial cross-sectional area, (2) a progressive increase in arterial rigidity and (3) the summation of wave reflections along the arterial tree. Recently, the accuracy of recording the blood pressure wave contour and measuring the pulse pressure along the arterial tree has been improved by the technique of applanation. This technique uses a pencil-type probe incorporating a high-fidelity strain-gauge transducer (Millar Instruments Inc., Houston, Texas, USA). The transducer has a small pressure-sensitive area (0.5 × 1.0 mm) with a frequency response of >2 kHz that is coplanar with a larger area (7 mm diameter) of flat surface in contact with the skin overlying the pulse [40].

The instrument uses the principle of applanation tonometry as used in ocular tonometry for registration of intraocular pressure. In principle, flattening (applanation) of a curved surface that is subject to internal pressure allows a direct measurement of the pressure within the structure. The wall flattening is important, since the force vectors from the intra-arterial pressure must be evenly distributed to the force-sensing area without distortion from the circumferential stresses inherent in a curved wall. With applanation achieved, the circumferential forces are rendered normal to the direction of the probe and hence balanced. An applanated artery supported on a rigid bony structure thus provides a contact force between the skin and the sensor area equal to the intra-arterial pressure. The contact force is converted to an electrical signal by the transducer, providing a continuous beat-to-beat recording (Fig. 1).

The use and accuracy of this tonometer were tested on the exposed canine femoral artery and percutaneously on the human radial artery. There was no significant difference in the modulus or pulse of harmonic components as recorded by the two methods. In subjects undergoing catheterization, Benetos *et al.* [13,41] measured blood pressure simultaneously by two methods: invasively, at the site of the aortic arch, and non-invasively, at the site of the common carotid artery. A significant positive correlation ($r = 0.92$; $P < 0.0001$) was observed, with a slope equal to 1.05 and an intercept that was not significantly different from zero (0.4 mmHg). In another study, brachial pulse pressure was measured by conventional sphygmomanometry and radial pulse pressure by applanation tonometry. The two parameters were strongly correlated ($r = 0.97$; slope, 0.98; intercept, 1.4 mmHg) [13,41].

Fig. 1



Principle of applanation tonometry and analysis of pulse-pressure waveform. PP, pulse pressure; ΔP, increase in systolic and pulse pressure; P_i, inflection point dividing the pressure wave into an early and late systolic peak; Ppk, peak due to the reflected wave, LVET, left ventricular ejection time; Δtp, time from the foot to the inflection point.

Because the tonometer transducer is small relative to the size of the artery, the positioning of the transducer over the site of the artery was found to be an important consideration in clinical investigation. First, movement of the transducer introduced by the operator's hand or movement of the subject may cause artefacts. This can easily be prevented by the use of a stereotaxic system to fix the probe and by the operator's being relaxed and comfortable. Second, the hold-down force should be just enough to achieve adequate applanation. Excessive force leads to two characteristic changes. First, it is initially accompanied by a gradual increase in the pressure levels recorded in late diastole with a distortion of the diastolic part of the wave shape, often seen as a sharp negative deflection before the succeeding systolic upstroke. The change in the value of systolic pressure recorded at this stage is usually minimal. The second characteristic change caused

by an increase in hold-down force is inversion of the systolic peak. Another source of artefacts lies in the angulation between the probe and vessel. This particularly affects the systolic part of the pressure wave. Ideally, the probe should be kept perpendicular to the vessel axis as nearly as possible. The intra-observer variability of these measurements has been assessed at 4.7 ± 2.5% and the interobserver variability as 6.1 ± 3.5%. These levels of reproducibility can be achieved after 4–6 weeks' use of the probes [41,42].

This device allows accurate measurements of pulse pressure at different sites of the arterial tree, of the pulse wave contour recording and thus a quantification of the wave reflections (Fig. 1). Clinical experience with the device in recent years has shown that in clinical hypertension, pulse pressure increases markedly from central to peripheral arteries without a substantial change in mean arterial pressure. This pulse pressure gradient disappears with age because of concomitant changes in the amplitude and timing of arterial pressure wave reflections within the ascending aorta. Since these alterations in pulse pressure are due chiefly to an increase of systolic pressure, this haemodynamic pattern has several important implications. First, in any given patient, it is not possible to describe a single blood pressure curve for the totality of the arterial tree. Second, systolic and pulse pressure measured within the ascending aorta may be significantly reduced by drug treatment, whereas brachial systolic and pulse pressure may remain poorly modified. Third, pulse pressure changes may also have important implications in cardiovascular pharmacology, because pulsatile pressure can attenuate both peripheral and central components of baroreflex adaptation [4,7].

Ultrasound techniques

In recent years, ultrasound techniques have been developed extensively, so that the thickness of superficial arteries in humans can now be measured under fully *in vivo* conditions. Because of the resolution of the various techniques used, the findings can be analysed only in terms of intimal–medial thickness. In addition, only the superficial and straight arteries can be investigated adequately, making the carotid artery, the brachial and the radial arteries the most widely used models.

Measurement of intimal–medial thickness by the video-echo signal

Applications to the carotid artery

B-mode ultrasound relies on acoustic characteristics of tissues to generate a cross-sectional image of the near and far walls of the carotid artery. The validity of the B-mode method for wall thickness measurement has been established by comparison with tissue specimens. Studies using arterial tissue *in vitro* showed that the normal arterial wall produces a double-line pattern. Dissection of the arterial specimen showed that one line was created by the media–adventitia interface and the second by the lumen–intima interface. The distance between the two lines correlates well with the intimal–medial thickness [43,44].

Early studies that focused on individual arterial lesions were frustrated by the poor reproducibility of the method. Subsequently, methodology improved greatly. Ultrasound equipment has been improved to provide axial resolution in the order of 300 μm. In addition, videotape quality has been improved to reproduce images more reliably and sonographers have become more aware of the investigation procedure so that reliable observations may be made. Several groups have analysed the intra-observer and interobserver reproducibilities of blinded wall thickness measurements, and have obtained a good reproducibility coefficient [45–47].

Although the reliability of individual measurements is excellent, it is becoming increasingly evident that the B-mode technique is not able to measure certain sites consistently because one or more of the critical interfaces is unavailable for interrogation. Inconsistent visualization of the far wall of the internal carotid artery might occur in 18% of patients; for the near and far walls of the bifurcation, in 10 and 8% of patients, respectively; and for the near and far walls of the common carotid artery in 4 and 2% of patients, respectively. These problems are important because atherosclerosis is most prominent in the carotid bulb, in contrast to the common carotid artery, an area in which it is easier to obtain more reproducible scans; therefore, it might be difficult, in carotid measurements, to evaluate and differentiate lesions related to hypertension from those related to atherosclerosis [45–47].

Measurement of intimal–medial thickness by the echo-tracking signal

Applications to the radial artery

The ultrasound system used for the radial artery is different from that for the carotid artery; it has recently been validated successively for the measurement of radial internal diameter, its systolodiastolic variations, and for the measurement of radial artery wall thickness in humans. Briefly, a high-resolution pulse echo-tracking device is used to acquire backscattered radiofrequency data from the radial artery at the wrist. The probe consists of a 10-MHz strongly focused piezoelectric transducer (6 mm diameter, 11 mm focal length) operated in the pulse-echo mode. The –10 dB beam width is 0.3 mm at the focal point and the depth of field at –10 dB is 5 mm. A stereostatic arm permits motion of the transducer in three directions with micrometric steps in order to place the probe perpendicularly to the arterial axis, in its largest cross-sectional dimension. The transducer is positioned so that its focal zone is located at the centre of the artery and the backscattered echoes from the anterior and posterior walls can be visualized. A typical radiofrequency signal is then displayed on a computer monitor interfaced with the transducer system. Arterial diameter and posterior wall thickness are measured when a double-peak radiofrequency ultrasound signal of the anterior and the posterior wall is obtained. These signals are visible only when the ultrasound beam crosses the axis (centre) of the vessel. Their movements are electronically tracked for 60 s, sampled at 100 MHz over 8 bits and stored at a 50-Hz repetition frequency on a hard disk for further data processing. The

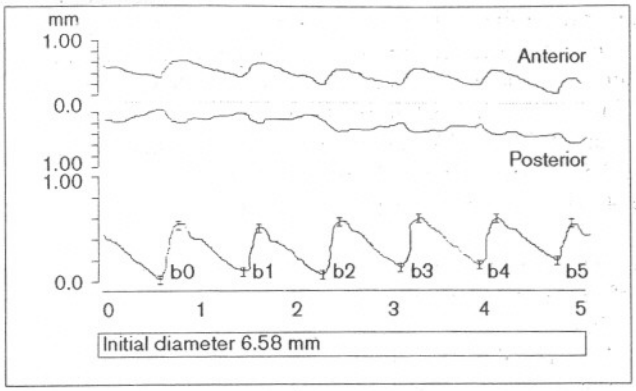
pulse length of this 10-MHz ultrasound system is 0.1 μs at 6 dB, corresponding to a practical axial resolution of 0.16 mm for absolute internal diameter or wall thickness measurements. Because of the characteristics of the device and because the radial artery is straight, superficial and cylindrical, the degree of reproducibility of the measurement is very high. This method can be applied to measure the radial artery mass according to the formula, $\rho L (\pi R_e^2 - \pi R_i^2)$, where ρ is the arterial wall density, L the length of the arterial segment and R_e and R_i are the external and internal radii [47–49].

The ultrasound techniques used to determine the thickness of the carotid and the radial arteries have both advantages and disadvantages. However, it is important to recognize that different results may be observed in the carotid and the radial arteries because the carotid artery is a rather elastic artery, with high amounts of elastin and collagen and great sensitivity to age and atherosclerosis, whereas the radial artery is composed principally of arterial smooth muscle. This artery is not sensitive to the atherosclerotic process and is poorly modified with ageing. These methodological advances have steadily modified our understanding of arterial stiffening in hypertension. The arterial stiffness of the radial and carotid arteries can now be studied under similar transmural conditions in both normotensive and hypertensive subjects using pulsatile and not static pressure–volume relations. The factors governing static and pulsatile compliance conditions are markedly different; static compliance is dependent mainly on smooth muscle tone and on the structural characteristics of the arterial wall; pulsatile compliance is frequency dependent and is importantly modified by changes in arterial viscosity, a factor related to the smooth muscle connections and extracellular matrix.

Measurement of arterial wall distension or systolodiastolic variations of arterial diameter by the echo-tracking signal

The motion of the arterial wall can be measured using an original pulsed ultrasound echo-tracking system based on Doppler shift. Briefly, this system allows transcutaneous assessment of the displacement of the arterial wall during the cardiac cycle, and hence of the time-dependent changes in arterial diameter relative to the initial diameter at the start of the cardiac cycle. The availability of the electrocardiogram trigger facilitates detection of the peak distension of the artery relative to the initial diameter. The lowest and highest values within 300 ms after the occurrence of the electrocardiogram trigger are taken as the minimum and maximum values of the distension waveform, respectively. Based on the two-dimensional B-mode image, a time–mutation (TM) line perpendicular to the artery has to be selected. The radiofrequency signal of three to eight cardiac cycles can be recorded, digitized and temporarily stored in a large memory. Two sample volumes, selected under cursor control, are positioned on the anterior and posterior arterial walls. To overcome the possibility that nearby structures generating prominent echoes may have temporarily entered the selected sample volumes, thus obscuring the vessel wall signal, a Doppler tracking system

Fig. 2



Beat no.	Dist (μm)	Diameter (mm)	Dist (%)	RR interval (ms)	Rise–time (ms)
0	527	6.15	8.57	837	86
1	404	6.23	6.48	825	75
2	503	6.18	8.14	837	87
3	467	6.26	7.46	862	84
4	455	6.27	7.26	830	83
5	356	6.32	5.64	–	74
Mean	452	6.24	7.26	838	82
SD	63	0.06	1.07	14	6

Recording of pulsatile changes in the common carotid artery diameter (mm) obtained with the echo-tracking technique. b0, b1, b2, b3, b4, b5, beats 0, 1, 2, 3, 4, 5, respectively; Dist, systolic–diastolic diameter changes.

was developed to allow the vessel walls to be tracked by the sample volumes. Displacements of the arterial wall are visualized by processing the Doppler signals originating from the two selected sample volumes. A typical displacement waveform of the anterior and posterior walls of the common carotid artery is shown in Fig. 2: the successive values of the stroke change in diameter during systole (Ds – Dd), the end-diastolic diameter (Dd) and the relative stroke change in diameter [(Ds – Dd)/Dd] are computed from the recording [50,51]. The repeatability of the carotid artery measurement was assessed using the recording of three to eight successive cardiac cycles. The mean ± SEM coefficients of variation determined under these conditions were 1.0 ± 0.3, 6.0 ± 0.1 and 6.0 ± 0.1% for Dd, (Ds – Dd) and (Ds – Dd)/Dd, respectively; the mean intra-observer coefficients of variation were 3.0 ± 0.1%, 8.0 ± 0.1% and 10.0 ± 0.1% for Dd, (Ds – Dd) and (Ds – Dd)/Dd, respectively [13,41].

Application of this technique to clinical hypertension has allowed a better understanding of the heterogeneity of the arterial modifications observed in hypertension. The evidence showed that high blood pressure has more effect on the elastic arteries than the muscular arteries. The aorta, which is predominantly made up of elastin tissue, undergoes an increase in cross-sectional area and volume with a decrease in distensibility; these haemodynamic changes are highly pressure-dependent. In peripheral arteries, there is little change in arterial cross-sectional area, volume and distensibility. In hypertension, this difference in diameter between the cen-

tral aorta and peripheral arteries may modify the sites of reflection points with age, making them closer to the heart [13,18,41].

Assessment of arterial stiffnéss using pulse wave velocity measurements

The non-invasive methods described here for evaluating arterial haemodynamics are accessible to only a very few clinical research laboratories. Most are complex, expensive, time-consuming procedures needing highly qualified operators. A simple and accurate clinical method of evaluating arterial wall function is important. Since researchers realized that vascular changes lead to a change in the stiffness of the artery and that this, in turn, changes the rate at which the arterial pulse wave moves along the vessel, there has been renewed interest in aortic pulse wave velocity measurements as a surrogate marker of arterial modifications and diseases. This measurment is now used widely to evaluate arterial distensibility as an index of arterial stiffness [52,53].

Principles

The contraction of the left ventricular myocardium and the ejection of blood into the ascending aorta dilate the aortic wall and generate a pulse wave which is propagated throughout the arterial tree at a finite speed. This propagation velocity constitutes an index of arterial distensibility and stiffness. Higher velocity corresponds to higher arterial rigidity and thus to lower distensibility. This speed is determined by the elastic and geometric properties of the arterial wall and the characteristics (density) of the fluid (blood). Since blood is an incompressible fluid and is contained in elastic conduits (arteries), the energy propagation occurs predominantly along the walls of the arteries and not through the blood. The properties of the arterial wall, its thickness and the arterial lumen are thus the major factors influencing pulse wave velocity.

The use of pulse wave velocity as an index of arterial elasticity and stiffness has been extensively analysed from theoretical and experimental viewpoints in a number of studies performed on fluid-filled tubes, excised segments of arteries and intact human subjects. The relationships between pulse wave velocity, pressure, tension, distensibility and tube volume have been investigated by Bramwell, Downing and Hill on segments of excised carotid artery and by Hamilton, Remington and Dow on mercury-filled Gooch tubing and on cadaver aortas [52,54]. These physical concepts have been formalized in many mathematical models, with the arterial segment represented as a thin-walled tube or as a thick-walled viscoelastic tube. Studies with these models, taking into account the main features of the human arterial tree, have confirmed that the pulse wave velocity (PWV) given either by the Moens–Korteweg equation (1) or by the Bramwell–Hill equation (2) is a good approximattion [6,17,54–56]:

$$PWV^2 = E \times h/2r \times \rho \quad (1)$$

$$PWV^2 = \Delta P \times V/\Delta V \times \rho \quad (2)$$

where E is the Young modulus of the wall, h is arterial wall thickness, r is internal radius, ρ is blood density, ΔP and ΔV are changes in pressure and volume, respectively, and V is baseline volume.

A modification of the Bramwell–Hill equation (2) can be used to calculate distensibility (D) from pulse wave velocity and compliance (C). Since volume distensibility is $DV/DP \cdot V$:

$$D = 1/\rho \times (PWV)^2$$

$$C = \pi \times R^2/\rho \times (PWV)^2$$

where R is radius.

Measurement of pulse wave velocity

Two non-invasive methods are generally used to measure pulse wave velocity, the Doppler method and the pressure transducer method (Fig. 3). The later method is the most commonly used. The pulse wave is derived from measurements of pulse transit time (t) and the distance (L) covered by the pulse between the two recordings sites, using the formula:

$$PWV\ (cm/s) = L/t$$

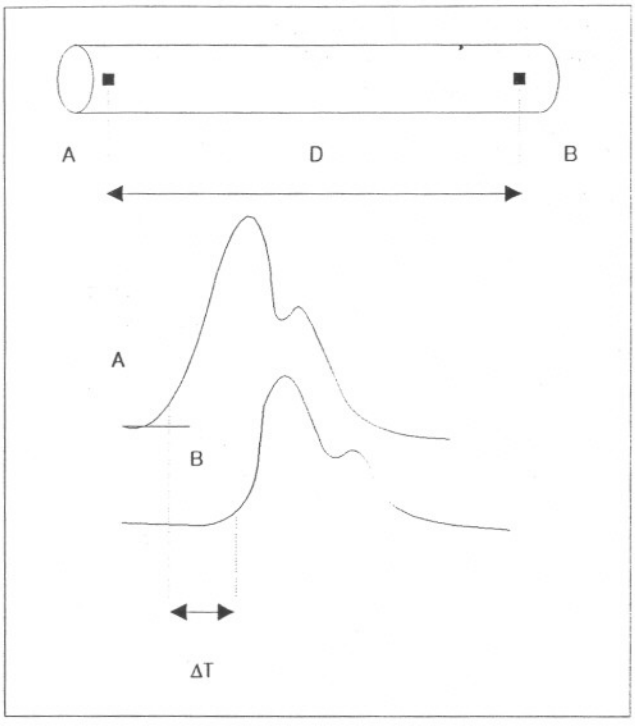
Transit time is determined from the time delay between the foot of the two corresponding waves, proximal (A) and distal (B). The distance (L) covered by the pulse is obtained from superficial measurements of the distance between the two transducers (A and B). Pulse wave velocity is usually calculated on the mean basis of 10 consecutive beats, to cover a complete respiratory cycle.

Pulse wave velocity measurements can be taken in several arteries: (1) upper limb, measurement of the brachial–radial pulse wave velocity; (2) lower limb, measurement of the femoral–tibial pulse wave velocity; and (3) aorta, measurement of the carotid–femoral pulse wave velocity.

Automatic measurement of pulse wave velocity

In contrast to the pulse wave recording, which is simple and rapidly obtained, manual determinations of the pulse wave foot and measurements of the time delay between the two waves are tedious and time-consuming (Fig. 4). Recently, an automatic device to measure the pulse wave velocity, the Complior (Colson, Garges-les-Gonesse, France) has been developed; the program allows an on-line pulse wave recording and automatic calculation of the pulse wave velocity [57]. Briefly, the pulse wave is recorded using a TY-306-Fukuda pressure-sensitive transducer (Fukuda, Tokyo, Japan). The pressure waveforms are digitized at different rates according to the distance between the recording sites; the sample acquisition frequency for carotid–femoral pulse wave velocity is set at 500 Hz. The two pressure waveforms are stored in a memory buffer. A preprocessing system automatically analyses the gain in each waveform and adjusts it for equality of the two signals. A maximum of 588 datapoints per waveform are displayed at any one time, so that the display will cover a time period of 0.735–1.47 s. This is sufficient to capture at least one complete cardiac pressure upstroke for each time interval. When the operator observes a pulse waveform of sufficient quality on the computer screen, digitization is suspended and calculation of the time delay between the two

Fig. 3



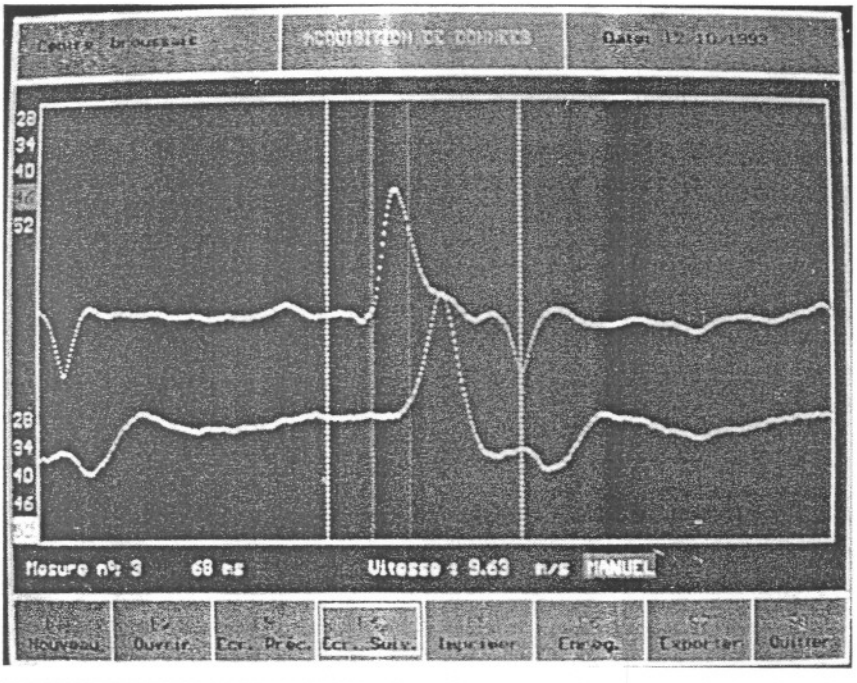
Pulse wave velocity measurement. A, wave recorder by the proximal (A) transducer; B, wave recorder by the distal (B) transducer; ΔT, time delay between the foot waves; D, distance travelled by the pulse wave.

pressure upstrokes is initiated. The first analysis removes spikes that may be present in the pulse waveform, as these will interfere with later processing; this is done by using a moving average digital filter algorithm. The leading pulse waveform is then digitally differentiated and the time at which the peak value occurs is determined. The delay between the two pulse waves is calculated by performing a correlation between the data for the two waveforms. The distal pressure upstroke is then time-shifted by subtracting one sample period and the correlation coefficient is again calculated; the procedure is repeated until the datapoint shift for the best fit has been calculated. The correlated waveforms are then displayed in their shifted positions and the calculated pulse delay is printed. This procedure is repeated over 10 different cardiac cycles and the mean is used in the final analysis. The reproducibility of this method has been determined, with an intraobserver repeatability coefficient of 0.935 and an interobserver reproducibility coefficient of 0.890 [57].

Clinical applications

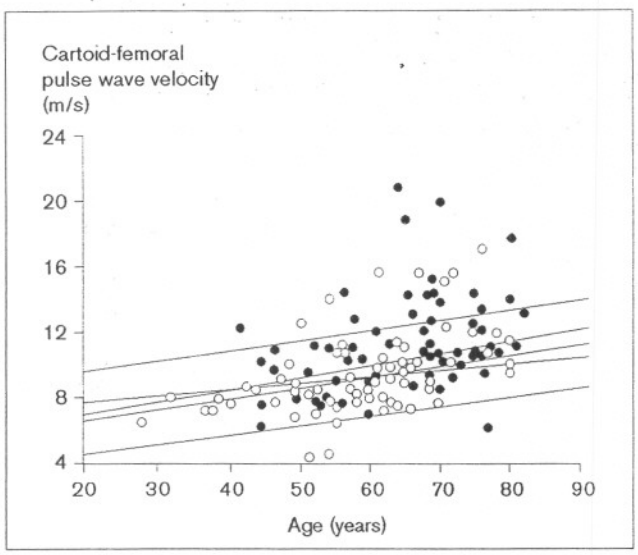
Pulse wave velocity is influenced by a number of factors, including age, wall thickness, vessel radius, blood density, increased vascular tone, velocity of blood flow and blood pressure, all of which may accelerate pulse wave velocity. Alternatively, lumen irregularities, stenosis and vessel tortuousness may retard pulse wave velocity. Apart from anatomic and physiologic influences, measurement site also affects the measured pulse wave velocity: the greater the distance from the heart, the higher the pulse velocity. A number of studies

Fig. 4



Complior traces show automatic measurements of pulse wave velocity. The upper wave is obtained from the proximal recording site (carotid) and the lower from the distal site (femoral). Vertical discontinuous lines indicate the calculation interval, and vertical continuous lines indicate the possibility of manual and visual control.

Fig. 5



Carotid–femoral pulse wave velocity (y) in relation to age (x) in well-controlled hypertensive subjects. A normotensive normogram is superimposed, with individual and mean 95% confidence limits. Open circles, diastolic blood pressure <90 mmHg and systolic blood pressure <140 mmHg; closed circles, diastolic blood pressure <90 mmHg and systolic blood pressure >140mmHg.

have shown that the two most important determinants of pulse wave velocity are age and blood pressure level, and that arterial distensibility is decreased in hypertensive patients even at an early stage of the disease such as borderline hypertension.

Moreover, therapeutic and pharmacological trials have shown that different antihypertensive treatments have different effects on arterial distensibility despite similar antihypertensive effects. A recent report has shown that normalization of high blood pressure by long-term antihypertensive treatment is not always associated with full reversal of the arterial alterations observed in hypertension (Fig. 5) [17,53,56].

Conclusion

Large artery damage is a major contributing factor to the elevated cardiovascular morbidity and mortality observed in the presence of cardiovascular risk factors such as hypertension. Quantitative information on large arteries may be easily obtained by a determination of pulse wave velocity. This method also allows an evaluation of arterial distensibility and stiffness. The latter may be important in the pathophysiology of several cardiovascular diseases, and it may also serve as an indicator; therefore, the natural history of cardiovascular disease may now become more accessible to study and perhaps be better understood. Conceivably, patients with a high risk could be identified before clinical cardiovascular complications develop. Ultimately, the range of options for appropriate primary intervention at the individual level and in populations could be expanded.

To progress in this field, there is a need for consensus concerning the optimal measurement and reporting of arterial stiffness. Currently, comparisons between cross-sectional studies of arterial stiffness are problematic. Alternative analytic approaches that incorporate measurements of blood pressure and the other determinants of arterial stiffness complicate interpretations but need to be developed. Prospective analyses will assist in the determination of whether alterations in arterial stiffness precede the development of hypertension and atherosclerosis or vice versa. Although the initiation and progression of cardiovascular disease are still only partly understood, considerable public health benefit may be derived through a better understanding of the relationship between arterial stiffness and cardiovascular disease. Several noninvasive methods that are now available for measuring arterial stiffness appear to be suitable for population studies. Whether arterial stiffness constitutes an independent cardiovascular risk factor, like left ventricular hypertrophy, and whether treatment for hypertension or for other cardiovascular risk factors can improve prognosis still needs to be clarified by large therapeutic and epidemiologic studies.

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