NONINVASIVE EVALUATION OF ARTERIAL ABNORMALITIES IN HYPERTENSIVE PATIENTS

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ASMAR R.G. – Noninvasive evaluation of arterial abnormalities in hypertensive patients.
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SUMMARY : Morbidity and mortality in hypertension are mainly determined by arterial lesions which may occur in different regional circulations: kidney, cerebral, coronary..., causing respectively nephroangiosclerosis, stroke or myocardial infarction... Despite the arteries heterogeneity, structural and functional abnormalities are usually observed at an early stage of hypertension in both large and small arteries. These alterations modify arterial wall physiological and mechanical properties which can be expressed clinically by increasing arterial pulsatility or pulse pressure; they facilitate establishment and progression of atherosclerosis and arteriosclerosis. Since arteries constitute the target, site and common denominator of hypertension cardiovascular complications, several noninvasive techniques may be usefull to assess their haemodynamic: casual and ambulatory blood pressure measurements can evaluate pulse pressure which can be also directly measured in different sites of the arterial tree using the «Tonometer» device; ultrasound techniques can be applied: Doppler signal to assess the arterial flow, video-echo signal to analyse the arterial structure such as intima-media thickness, or echo-tracking systems for direct measurements of arterial wall distension and thickness; pulse wave velocity is widely used as index of arterial distensibility; its assessment, using the Complior® device showed that hypertensive patients present a decrease of arterial distensibility and that antihypertensive treatment do not always reverse this abnormality. Since cardiovascular

(Summary continued on next page)

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RÉSUMÉ : La morbidité et la mortalité liées à l'hypertension sont dues principalement à la constitution de lésions artérielles dans divers lits régionaux. Ainsi, les lésions du rein, de l'encéphale et des coronaires sont respectivement responsables de néphroangiosclérose, d'accidents vasculaires cérébraux et d'infarctus du myocarde. Malgré l'hétérogénéité des artères, des anomalies structurelles et fonctionnelles sont généralement apparentes dès le début de la maladie hypertensive dans les artères de gros comme de petit calibre. Ces lésions altèrent les propriétés physiologiques et mécaniques de la paroi artérielle, ce qui peut se traduire cliniquement par une augmentation de la pulsatilité artérielle réflétée par la pression différentielle ; elles favorisent la constitution puis l'évolution de l'athérosclérose et de l'artériosclérose. Étant donné que les artères constituent la cible, le siège et le dénominateur commun des complications cardio-vasculaires de l'hypertension, divers examens non invasifs peuvent être utiles pour explorer leur hémo-dynamique. Ainsi, la mesure ponctuelle ou ambulatoire de la pression artérielle permet d'évaluer la pression différentielle, qui peut aussi être mesurée directement à divers endroits de l'arbre artériel grâce au « Tonometer ». Diverses techniques échographiques peuvent être utilisées, telles que le signal Doppler pour évaluer le débit artériel, le signal vidéo-écho pour analyser la structure artérielle (notamment l'épaisseur de l'intima et de la média) ou les systèmes d'écho-tracking pour mesurer directement la distension et l'épaisseur de la paroi

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(Summary continued)

morbidity and mortality are due to arterial lesions, it is important to evaluate the effect of cardiovascular prevention on the arterial wall. Large therapeutical trials, including arterial evaluation, are necessary to assess whether this consideration may particularize patients with high cardiovascular risk and contribute to their treatment and prognostic improvement.

KEY-WORDS : Arteries. – Hypertension. – Noninvasive techniques. – Arterial stiffness. – Hemodynamics. – Antihypertensive agents.

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artérielle. La vitesse de propagation de l'onde pulsatile est largement utilisée comme indice de la distensibilité artérielle ; son évaluation grâce à l'appareil Complior® a révélé que la distensibilité artérielle est réduite chez l'hypertendu et que cette anomalie n'est pas constamment corrigée par le traitement anti-hypertenseur. Étant donné que la morbidité et la mortalité cardiovasculaires sont dues aux lésions artérielles, il est important d'évaluer l'effet de la prévention cardiovasculaire sur la paroi artérielle. De larges essais thérapeutiques comportant une évaluation des artères sont nécessaires pour déterminer si l'évaluation de la paroi artérielle permet de repérer des patients à risque cardio-vasculaire élevé et d'améliorer leur traitement et leur pronostic.

MOTS-CLÉS : Artères. – Hypertension. – Techniques non invasives. – Rigidité artérielle. – Hémodynamique. – Antihypertenseurs.

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 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; more recently, on the basis of several observations, the arterial system has been recognized as a complex system and an active participant in cardiovascular function in health and disease [6, 11, 12]. Today, recent progressions in the arterial pathophysiological concepts and technological advancements allow the description of 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]. Thus, central large and elastic arteries present important histomorphometric differences compared to the peripheral small and muscular arteries; incidence and causes of large arterial lesions differ, according to the site of the lesions and their triggered factors. Whether consideration of the arterial hemodynamic in clinical practice may improve the cardiovascular prevention needs to be assessed in large clinical studies [16, 17].

HYPERTENSION AND THE ARTERIAL SYSTEM

Hypertension is a major cardiovascular risk factor which affects all the arterial system, both large and small arteries. It was generally attributed to the rarefaction or the reduction in the caliber 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 blood pressure (BP) and flow fluctuate during the cardiac cycle. More recent and realistic approach is to consider arterial pressure as the summation of a steady component (mean BP) 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 ventricular ejection intermittence and represents the «unproductive» component of external heart work [6, 21]. Hemodynamically, beside the pattern of left ventricular ejection, the determinants of mean BP (and to a less extend of diastolic BP) are primarily the vascular resistance in small peripheral arteries and to a less degree the compliance in large conduit arteries; whereas the determinants of pulse pressure (and of systolic BP) 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 less degree to 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 the neurohumoral conditions [6-8].

In hypertension, structure and function of arteries are important to consider, not only because they may contribute to the definition and mechanisms of hypertension but also because they are obviously involved in the clinical 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 to the decreased coronary reserve due to the vascular remodelling may favour myocardial ischaemia, especially in the subendocardial layer. Moreover, early recognition of arterial changes may identify individuals at high risk for clinical complications of hypertension and atherosclerosis [22-24].

Recent studies using new concept and techniques have reported 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** (*i.e.* internal diameter < 200 μm): arterial remodelling has been described as an adaptive process to the high BP during chronic hypertension. Increased thickness of the arterial wall serves to counteract 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, unchanged or a small increase in cross-sectional area due to the hypertrophy and hyperplasia of the medial smooth muscle cells; the decrease in lumen area and the increase in wall/lumen ratio contribute to the aggravation of hypertension by increasing vascular reactivity to vasoconstrictor agents and peripheral resistances [19, 25, 26]. At the level of **large arteries:** the adaptative process has been described with an increase of wall thickness with unchanged or increased internal diameter and thus an increase of the wall/lumen ratio and cross sectional area. This process has been reported as related to growth process with medial smooth muscle cell hypertrophy and increase in collagen content of the extracellular matrix. Because it is generally postulated that the arterial remodelling induced by hypertension might predispose subjects to the end-organ damage, we may evaluate the effect of the antihypertensive treatment not only on BP 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, that have different and distinct structural and functional features in pathophysiology: a buffering function for larger arteries and a resistance function for the smaller. Since hypertension is usually recognized by arterial pressure measurements obtained at the site of large artery, because hemodynamically the definition and mechanisms of hypertension include determinants related to small and particularily to large arteries, because large arteries constitute the target and the site of cardiovascular complications of hypertension, and finally because the most technical advancements in the recent years are applied to the haemodynamic evaluation of large arteries, only some of the most employed noninvasive methods to evaluate large arteries are summarized and described hereafter.

PULSE PRESSURE MEASUREMENTS

Epidemiologic studies have shown that, in patients over 50 years of age, clinic systolic BP is a stronger cardiovascular risk factor than diastolic BP. Since BP is a pulsatile phenomenon and since hypertension may be considered as a mechanical factor causing arterial wall modifications, another approach is to consider the pulsatile component of BP calculated as the difference between systolic and diastolic BP (pulse pressure = Systolic BP – Diastolic BP). In fact, several reports showed that clinic measurements of brachial pulse pressure is correlated to the target organ damages of hypertension such as the arterial wall alterations and left ventricular hypertrophy; in addition, clinic brachial pulse pressure has been reported to be an independant cardiovascular risk factor in terms of morbidity and mortality [30-35].

Since ambulatory BP recording is more reproducible than casual measurement and since it correlates more strongly than clinic BP with indices of target organ damages of hypertension, several studies showed that it may be applied to evaluate the 24h ambulatory pulse pressure. In fact, whereas some reports reveal large discrepancies between pulse pressure measured in clinic and by ambulatory methods, other studies showed that ambulatory pulse pressure is closely correlated to left ventricular mass and arterial distensibility and that it is more sensitive than the clinic BP measurements to evaluate the consequences of arterial risk factors as smoking, lipid abnormalities and glycemia on the blood pressure level and its variability [30, 36-38]. Moreover, patients with arterial disease showed, by comparison to a control group, an unchanged clinic systolic or pulse pressure whereas ambulatory monitoring demonstrated an elevation of systolic and pulse pressure levels and an increase of their variabilities with perturbation of the circadian pattern [39]. Thus, several reports suggested using systolic and pulse pressure analysis, that ambulatory BP monitoring can be considered as an indirect tool to evaluate arteries, since

it is more sensitive than casual measurement to analyse the relationships between BP and arterial distensibility, the consequences on BP of the arterial risk factors as well as the arterial diseases and their treatment.

APPLANATION TONOMETRY

Considering the relative accuracy of the noninvasive determination of BP according to the Riva-Rocci cuff method, and that pulse pressure increases substantially from central to peripheral arteries due to several factors:

– the progressive decrease in arterial cross-sectional area,

– the progressive increase in arterial rigidity,

– the summation of wave reflections along the arterial tree.

Recently, the accuracy of recording the BP wave contour and measuring the pulse pressure along the arterial tree has been improved by the technique of applanation. This technique employs a pencil-type probe incorporating a high-fidelity strain-gauge transducer (Millar Instruments Inc., Houston Texas). The transducer has a small pressure-sensitive area (0.5 × 1.0 mm) with a frequency response > 2 kHz that is coplanar with a larger area (7 mm diameter) of flat surface that is in contact with the skin overlying the pulse [40].

The instrument uses the principle of applanation tonometry as it is used in ocular tonometry for registration of intraocular pressure. In principle, flattening (applanation) of a curved surface that is subject to internal pressure allows 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, thus 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 modulus or pulse of harmonic components as recorded by the two methods. In subjects undergoing catheterization, Benetos et al. measured blood pressure simultaneously by two methods: invasively, at the site of the aortic arch, and noninvasively, 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, they measured brachial pulse pressure 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].

Because the tonometer transducer is small relative to the size of the artery, the positionning 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 artifacts. 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. 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 was usually minimal. The second characteristic change caused by a further increase in hold-down force is the inversion of the systolic peak. The third source of artifact was caused by the angulation between the probe and vessel. This particularily affects the systolic part of the pressure wave. Ideally, the probe should be kept close to perpendicular to the vessel axis. Intraobserver variability of the measurements is : $4.7 \pm 2.5\%$, and interobserver variability is $6.1 \pm 3.5\%$. Such levels of reproducibility can be achieved after 4-6 weeks use of the probes [41, 42].

This device allows accurate measurements of the pulse pressure at different sites of the arterial tree, the pulse wave contour recording and thus the quantification of the wave reflections (fig. 1). Its clinical application during the last years showed that in clinical hypertension, pulse pressure increased markedly from central to peripheral arteries without substantial change in mean arterial pressure. Moreover, 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 hemodynamic 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].

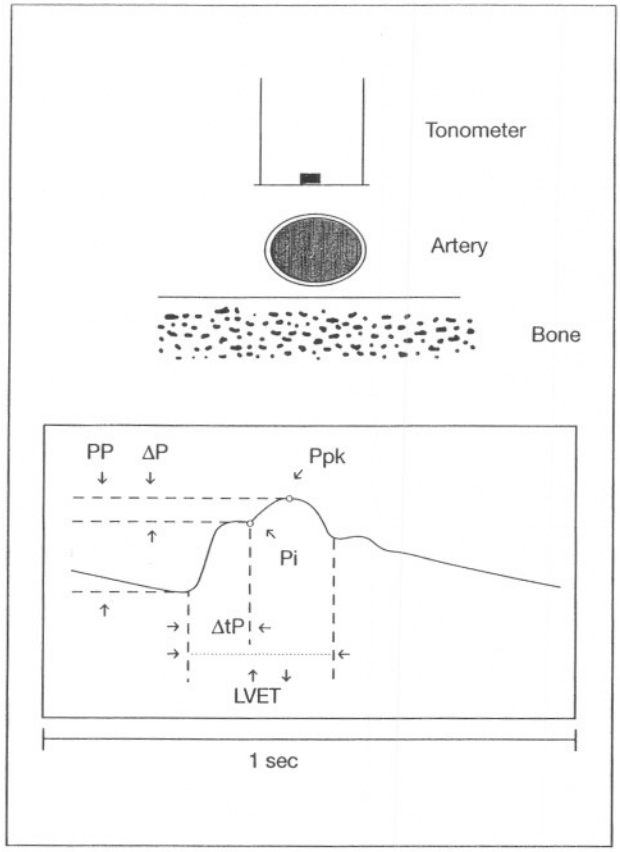


Fig. 1. – Principle of applanation tonometry and analysis of the pulse-pressure waveform. pp = pulse pressure; ΔP = increase in systolic and pulse pressure; Pi = inflection point dividing the pressure wave into an early and late systolic peak; Ppk = peak due to the reflected wave; LVET = left ventricular ejection time; tp = time from the foot to the inflection point.

Fig. 1. – Principe de la tonométrie d'applanation et analyse de la forme de l'onde de pression différentielle. Pp: pression différentielle; ΔP: augmentation de la pression systolique et différentielle; Pi: point d'infléchissement divisant l'onde de pression en un pic systolique précoce et un pic systolique tardif; Ppk: pic produit par l'onde réfléchie; LVET: temps d'éjection ventriculaire gauche; tp: temps séparant le pied de l'onde du point d'infléchissement.

ULTRASOUND TECHNIQUES

In recent years, ultrasound techniques have been developed extensively, allowing one to evaluate the thickness of superficial arteries in humans under completely *in vivo* conditions. Because of the resolution of the various techniques used, the findings can only be analysed in terms of «intima-media 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 the «intima-media thickness» according to the video echo signal

Applications to the carotid artery

B-mode ultrasound has been shown to rely 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 demonstrated 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 intima-media 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 of 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 reports analysed the intra-observer and interobserver reproducibilities of blinded wall thickness measurements; their results showed a good reproducibility coefficient.

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 a number of the critical interfaces is unavailable for interrogation. In fact, 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. Such aspects are important to consider because atherosclerosis is most prominent in the carotid bulb, in contrast to the common carotid artery, 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 the «intima-media thickness» according to 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 and has recently been described and validated successively both for the measurement of radial internal diameter, its systolic-diastolic variations, and for the measurement of radial artery wall thickness in humans. Briefly,

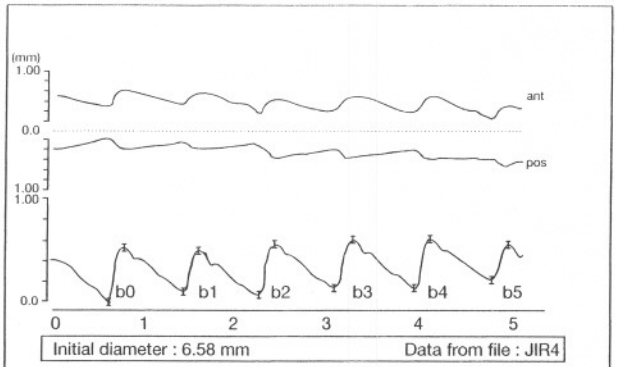
a high-resolution pulse echo-tracking device is used to acquire backscattered radiofrequency data from the radial artery at the wrist. The probe consists of a 10 MHz strongly focused piezoelectric transducer (6 mm diameter, 11 mm focal length) operated in the pulse-echo mode. The –10 dB beam width is 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 center of the artery and the backscaterred echoes both from the anterior and from 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 only visible when the ultrasound beam crosses the axis (center) 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: $\rho L (\pi R_e^2 - R_i^2)$, where ρ is the arterial wall density, L the length of the arterial segment and R_e and R_i the external and internal radii, respectively [47-49].

The ultrasound techniques used to determine the thickness of the carotid and the radial arteries both have their own advantages and disadvantages. However, it is important to recognize that different results may be observed from 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 pricipally 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. In fact, the arterial stiffness of the radial and carotid arteries may be studied under similar transmural conditions in 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 the arterial wall distension or the systolic-diastolic variations of arterial diameter according to the echo-tracking signal

The vessel wall motion of the arteries can be measured using an original pulsed ultrasound echo-tracking system based on Doppler shift. Briefly, this system enables the transcutaneous assessment of the displacement of the arterial wall during the cardiac cycle and hence the time-dependent changes in arterial diameter relative to its initial diameter at the start of the cardiac cycle. The availability of the electrocardiogram (ECG) trigger facilitates the detection of the peak distension of the artery relative to its initial diameter. The lowest and highest values within 300 ms after the occurence of the ECG trigger are taken as the minimum and maximum values of the distension waveform, respectively. Based on the two-dimensional B-mode image, a 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 was developed that allowed the vessel walls to be tracked by the sample volumes. The displacements of the arterial wall are obtained 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 figure 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 coefficient of variation was 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 helped us to understand the large heterogeneity of the arterial modifications observed in hypertension. It showed that high BP affects more the elastic arteries than the muscular arteries. In fact, several reports showed that aorta which is predominantly made up of



Beat	dist. (µm)	diam. (mm)	dist. (%)	RR-int. (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	5.24	-	74
mean	452	6.24	7.26	838	82
stdev	63	0.06	1.07	14	6

Fig. 2. – Recording of pulsatile changes in the common carotid artery diameter obtained with the echo-tracking technique. ANT = anterior wall; POS = posterior wall; dist = systolic-diastolic diameter changes; DIAM = diameter; b0, b1... b5 = beats 0, 1... 5, respectively; RR-INT = RR interval; DAS = data analysis.

Fig. 2. – Enregistrement des modifications pulsatiles du diamètre de la carotide commune réalisé grâce à la technique de l'écho-tracking. ANT : paroi antérieure ; POS : paroi postérieure ; dist : modification du diamètre entre la systole et la diastole ; DIAM : diamètre ; b0, b1... b5 : battements 0, 1... 5, respectivement ; RR-INT, intervalle RR ; DAS : analyse des données.

elastin tissue present an increase of its cross-sectional area and volume with a decrease in distensibility; these hemodynamic changes are highly pressure-dependent. In peripheral arteries, there are little changes in arterial cross-sectional area, volume and distensibility and are less sensitive to changes in BP. In hypertension, this difference in diameter between central aorta and peripheral arteries may contribute to modify the sites of reflection points with age, making them closer to the heart [13, 18, 41].

Assessment of the arterial stiffness using pulse wave velocity measurements (PWV)

The noninvasive methods described here above to evaluate arterial hemodynamic remain reserved to very few clinical research labs. In fact, most of them are complex, expensive, time consuming and need to be performed by high qualified operators. Since the arterial wall constitutes the target and the site of cardiovascular complications of the risk factors, its evaluation using a simple and accurate method in clinical practice is suitable. On the other hand, 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, they renewed interest in aortic pulse wave velocity measurements as a surrogate marker of arterial modifications and diseases. Thus, pulse wave velocity is now widely employed to evaluate the 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 contained 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 incompressible blood. The properties of the arterial wall, its thickness, and the arterial lumen present thus the major factors of pulse wave velocity. The use of pulse wave velocity as an index of arterial elasticity and stiffness, has been largely analyzed. In fact, it has been extensively analyzed from the theoretical and experimental points of view in a number of studies performed on fluid-filled tubes, excised segments of arteries and in intact human subjects. The relationships between pulse wave velocity, pressure, tension, distensibility, and tube volume have been made 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. These physical concepts have been formalized in many mathematical models, where the arterial segment has been considered as a thin-walled tube or as a thick-walled viscoelastic tube. The study of models, taking into account the main features of the human arterial tree, confirmed that pulse wave velocity given by the well-known Moens-Korteweg equation or by the Bramwell-Hill equation presents a good evaluation [6, 17, 54-56].

Moens-Korteweg equation: $PWV^2 = E.h/2r.\rho$, where h is the arterial wall thickness, r is the internal radius, ρ is blood density, and E is the Young modulus of the wall.

Bramwell-Hill equation: $PWV^2 = \Delta P.V/\Delta V\rho$, where ΔP and ΔV are the changes in pressure and volume, V is the baseline volume, and ρ is blood density.

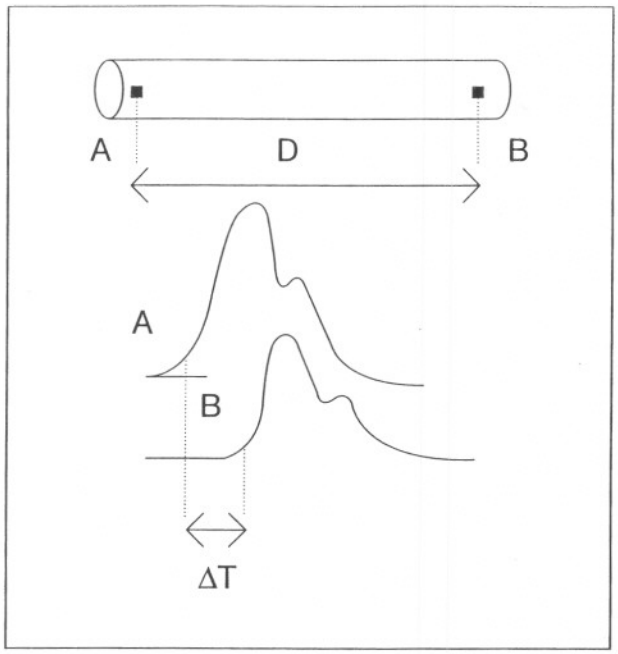


Fig. 3. – Pulse wave velocity measurement. A = wave recorder by the proximal (A) transducer; B = wave recorder by the distal (B) transducer; Δt = time delay between the foot waves; D = distance travelled by the pulse wave.

Fig. 3. – Mesure de la vitesse de propagation de l'onde pulsatile. A : enregistrement de l'onde par le transducteur proximal (A) ; B : enregistrement de l'onde par le transducteur distal (B) ; Δt : retard entre les pieds des ondes ; D : distance parcourue par l'onde pulsatile.

Since volume distensibility = $\Delta V/\Delta P.V$, it can be calculated from the pulse wave velocity using a modification of the Bramwell-Hill equation, distensibility = $D = 1/\rho(PWV)^2$. It can also be expressed on compliance by unit length and the equation becomes: compliance = $\pi.R^2/\rho.(PWV)^2$, where R is the radius and ρ is the blood viscosity.

Measurement of pulse wave velocity (fig. 3)

Two non invasive methods are generally used to measure PWV: the Doppler method or the pressure transducers; the latest is the most commonly employed. Pulse wave is derived from measurements of pulse transit time (t) and the distance (D) covered by the pulse between the two recordings sites, using the formula: PWV (cm/s) = D/t. Transit time is determined from the time delay between the foot of the two corresponding waves: the proximal (A) and the distal (B) pulse waves. The distance (D) covered by the pulse is obtained from superficial measurements of the distance between the two transducers (A and B). PWV is usually calculated on the mean basis of 10 consecutive beats, to cover a complete respiratory cycle.

Pulse wave velocity measurement can be applied on several arteries: 1) upper limb: measurement of the brachial-radial PWV; 2) lower limb: measurement of the femoral-tibial PWV; 3) aorta: measurement of the carotid-femoral PWV.

Automatic measurement of pulse wave velocity

In contrast to the pulse wave recording which is simple and rapidly obtained, the manual determination of the pulse wave foot and the measurement of the time delay between the two waves are tedious and time-consuming. Recently, an automatic device to measure the PWV: the Complior® (Colson; Garges-les-Gonesse, France) has been developed; its program allows an on-line pulse wave recording and an automatic calculation of the PWV. The details of this method have been described elsewhere [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 samples acquisition frequency is for carotid-femoral PWV at 500 Hz. The two pressure waveforms are stored in a memory buffer. A pre processing analyses automatically the gain of each waveform and adjusts it for an equality of the two signals. A maximum of 588 data points per waveform are displayed at any one time, ie the display will cover a time period of from 0.735 to 1.47 seconds. This is sufficient to always capture at least one complete cardiac pressure upstroke. 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 pressure upstrokes is initiated. The first operation performed is to remove 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 differenciated and the time at which peak value occurs is determined. The delay between the two pulse waves is calculated by performing a correlation between the data of 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 amount of data point shift for the best fit calculated. The correlated waveforms are then displayed in their shifted position and the calculated «pulse delay» printed. This procedure is repeated on ten different cardiac cycles and their mean value is considered for the analysis. The reproducibility of this method has been previously described, its intra-observer repeatability coefficient is 0.935 and its inter-observer reproducibility coefficient is 0.890 [57].

Clinical applications

Pulse wave velocity is influenced by a number of factors including age, wall thickness, vessel radius,

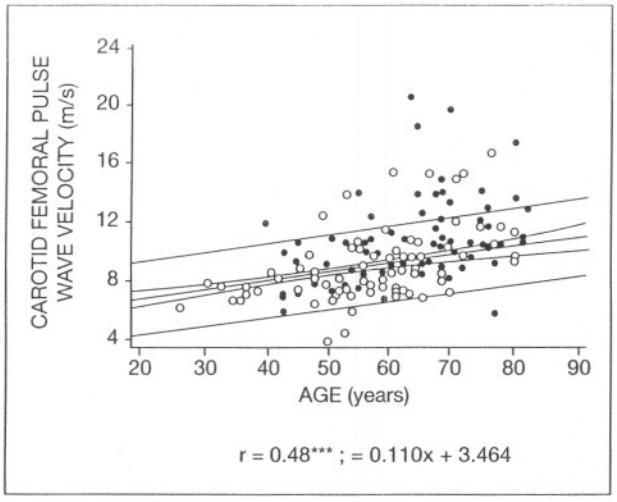


Fig. 4. – Carotid-femoral pulse wave velocity (y): relationship with age (x) in well-controlled hypertensive subjects. Plot with superposition of the normotensive normogram and its individual and mean 95 % confidence limits. ○ = subgroup A, diastolic BP < 90 mmHg and systolic BP < 140 mmHg; ● = subgroup B, diastolic BP < 90 mmHg and systolic BP > 140 mmHg.

Fig. 4. – Vitesse de propagation de l'onde pulsatile entre la carotide et la fémorale (y) : relation avec l'âge (x) chez des malades ayant une hypertension artérielle bien contrôlée. Le nomogramme pour les normotendus est superposé sur le graphique, avec les limites des intervalles de confiance à 95 % individuels et moyen. ○ : sous-groupe A, PA diastolique < 90 mmHg et PA systolique < 140 mmHg; ● : sous-groupe B, PA diastolique < 90 mmHg et PA systolique > 140 mmHg.

blood density, increased vascular tone, velocity of blood flow and blood pressure which may accelerate pulse wave velocity. Alternatively, lumen irregularities, stenosis and vessel tortuousness may retard pulse wave velocity. Apart from the anatomic and physiologic influences, measurement site contributes to modify the pulse wave velocity: the greater the distance from the heart, the higher the pulse wave velocity. Several studies reported that the major two determinants of pulse wave velocity are age and blood pressure level and that arterial distensibility is decreased in hypertensive patients even at the early stage of the disease like in the borderline hypertension. Elsewhere, therapeutical and pharmacological trials have shown that antihypertensive treatments differ by their effect on the arterial distensibility despite their similar antihypertensive effects. Moreover, recent report showed that normalization of high blood pressure by long term antihypertensive treatment is not always associated with a fully reverse of the arterial alterations observed in hypertension (fig. 4) [17, 53, 56, 57].

CONCLUSION

Large artery damage is a major contributing factor to the elevated cardiovascular morbidity and mortality observed in cardiovascular risk factors such as hypertension. Quantitative information on large arteries may be easily obtained by determination of pulse wave velocity. This method enables one to evaluate arterial distensibility and stiffness. Arterial stiffness may be important in the pathophysiology of several cardiovascular diseases; it may also serve as indicator; therefore, the natural history of cardiovascular disease may be more accessible to study and perhaps be better understood. Conceivably, patients who are at 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 in the optimal measurement and reporting of arterial stiffness. Currently, comparisons between cross-sectional studies of arterial stiffness are problematic. Alternative analytic approaches that incorporate blood pressure and the other determinants of arterial stiffness complicate the interpretation but should be developed and employed. 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 the progression of cardiovascular disease are only partially understood and considerable public health benefit may be derived through an enhanced understanding of the relation between arterial stiffness and cardiovascular disease. Several noninvasive methods to measure the arterial stiffness are now available; these measures appear to be amendable to studies in populations. Whether arterial stiffness constitutes an independent cardiovascular risk factor like left ventricular hypertrophy and whether the antihypertensive drugs or other cardiovascular risk factor treatment may improve its prognostic still needs to be clarified by large therapeutic and epidemiologic studies.

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