Arterial functions: how to interpret the complex physiology

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Abstract

Arterial pressure is a cyclic phenomenon characterized by a pressure wave oscillating around the mean blood pressure, from diastolic to systolic blood pressure, defining the pulse pressure. Aortic input impedance is a measure of the opposition of the circulation to an oscillatory flow input (stroke volume generated by heart work). Aortic input impedance integrates factors opposing LV ejection, such as peripheral resistance, viscoelastic properties and dimensions of the large central arteries, and the intensity and timing of the pressure wave reflections, associated with the opposition to LV ejection influenced by inertial forces. The two most frequently used methods of arterial stiffness are measurement of PWV and central (aortic or common carotid artery) pulse wave analysis, recorded directly at the carotid artery or indirectly in the ascending aorta from radial artery pressure curve. The arterial system is heterogeneous and characterized by the existence of a stiffness gradient with progressive stiffness increase (PWV) from ascending aorta and large elastic proximal arteries to the peripheral muscular conduit arteries. Analysis of aortic or carotid pressure waveform and amplitude concerns the effect of reflected waves on pressure shape and amplitude, estimated in absolute terms, augmented pressure in millimeter of mercury, or, in relative terms, ‘augmentation index’ (Aix in percentage of pulse pressure). Finally, if the aortic PWV has the highest predictive value for prognosis, the aortic or central artery pressure waveform should be recorded and analysed in parallel with the measure of PWV to allow a deeper analysis of arterial haemodynamics.

Epidemiological studies have emphasized the close relationship between blood pressure (BP) and the incidence of cardiovascular diseases with mean BP (MBP) being considered as a major factor of left ventricular (LV) afterload. This interpretation resulted from the view that MBP was the product of cardiac (cardiac output, CO) and vascular factors (peripheral resistance, PR) reflected by the equation MBP = CO × PR. Peripheral resistance as a determinant of mean BP sets the general level at which the pressure wave will fluctuate, and represents the opposition to steady component of blood flow, i.e. cardiac output. Peripheral resistance is mainly determined by vasomotor tone and the number of perfused arterioles and blood viscosity. This model has however several limitations, the principal being that blood pressure and blood flow are considered as constant over time, and the second that it does not take the arterial factors opposing left ventricular ejection into consideration. Arterial pressure is a cyclic phenomenon characterized by a pressure wave oscillating around the mean BP. The limits of these oscillations are the systolic and diastolic pressures whose determinants are different from those of mean BP, and who play also important roles as determinants of LV afterload and coronary perfusion. Initially, the stroke volume is accommodated in the proximal aorta where the rise in pressure creates a pressure gradient from aorta towards peripheral arteries, initiating blood movement/flow. The relationships between these cyclic flow and pressure changes are best characterized by aortic input impedance [1]. Aortic input impedance is a measure of the opposition of the circulation to an oscillatory flow input (i.e. stroke volume). Aortic input impedance integrates factors opposing LV ejection, i.e. (i) peripheral resistance; (ii) viscoelastic properties and dimensions of the aorta and large central arteries; (iii) and the intensity and timing of the pressure wave reflections. Finally, the opposition to LV ejection is also influenced by inertial forces represented by the mass of blood in the aorta and LV that must be mobilized during cardiac cycle [1].

The arterial wall has both elastic and viscous properties. The difference is related to the time-dependent response to stress–strain relationship (pressure change–diameter change). In a purely elastic artery, this relationship is time-independent, and after removal of stress, the arterial diameter dimensions would return to initial dimensions. In the presence of wall viscosity, the arterial wall retains part of the deformation. The arterial viscous properties are responsible for part of the LV energy dissipation characterized by hysteresis of the pressure–diameter loop [2] (Figure 1). Difficult to measure and to evaluate in humans, the role of arterial ‘viscosity’ has not been evaluated as extensively as the ‘elastic’ properties of arteries expressed as compliance, distensibility, stiffness or elastic modulus.

Prospective epidemiologic studies have drawn the attention to the arterial elastic properties as independent and strong cardiovascular risk factor and predictor of all-cause and cardiovascular death [3–5]. Several different para-
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The arterial system has two intimately interrelated haemodynamic functions: (i) they behave as pipes to deliver an adequate blood supply from the heart to peripheral tissues, as dictated by metabolic activity—‘the conduit function’; and (ii) they also behave as a ‘windkessel’ (hydraulic filter) to dampen blood flow and pressure oscillations caused by the intermittent character of the LV ejection ensuring peripheral organ perfusion at steady flow and pressure—‘cushioning or dampening function’ [6].

The efficiency of the conduit function is the consequence of the width of the arterial diameters and the very low resistance of large arteries offered to flow (under normal conditions, the MBP drops between the ascending aorta and arteries in the forearm or leg by not more than 2–4 mmHg in supine position). Atherosclerosis, characterized by the presence of plaques and arterial narrowing, is the most common occlusive vascular disease that disturbs the conduit function.

The second role of arteries is to dampen the pressure oscillations and to ensure an almost steady flow of the peripheral tissues and organs. Owing to the peripheral resistance to flow, only part of the stroke volume is forwarded directly to the peripheral tissues. About 50% of stroke volume would be momentarily stored in the aorta and large elastic arteries stretching the arterial walls and raising the blood pressure (Figure 2). In normal conditions, ~10% of the energy produced by the heart is diverted for the distension of arteries and is ‘accumulated’ in the vessel walls. During diastole, the ‘accumulated’ energy recoils the aorta, squeezing the stored blood forward into the peripheral tissues, ensuring a continuous flow (Figure 2). When the arterial system is rigid and cannot be stretched, the entire stroke volume will flow through the arterial system and peripheral tissues only during systole. For the dampening function to be efficient, it is essential that the energy necessary for arterial distension and recoil be as low as possible, i.e. for a given stroke volume, the pulse pressure should be as low as possible. The efficiency of this function depends on the elastic properties of the arterial walls and the geometry of the arteries, including their diameter and length. The ability of arteries to accommodate the volume ejected by the LV instantaneously can be described in terms of ‘compliance’, ‘distensibility’, or ‘stiffness’ of the aorta, an individual artery or the systemic arterial system (systemic compliance). These terms express the contained volume of the vasculature (total or segmental) as a function of the pulse pressure range. Compliance (C) is a term that describes the absolute change in volume (ΔV, strain) due to a change in pressure (ΔP, stress): $C = \frac{\Delta V}{\Delta P}$. The reciprocal value of compliance is elastance ($E = \frac{\Delta P}{\Delta V}$), or stiffness. To facilitate comparisons of elastic properties of structures with different initial dimensions, compliance can be expressed relative to the initial volume as a coefficient of distensibility $D_i$, defined as $D_i = \frac{\Delta V}{\Delta P V_i}$ where $\Delta V/\Delta P$ is compliance and $V$ is the initial volume. In contrast to compliance or elastance/stiffness which provides information about the ‘elasticity’ of the artery as a hollow structure, the elastic incremental modulus ($E_{inc}$, Young’s modulus) provides direct information on the intrinsic elastic properties of the materials that compose the arterial wall independent of vessel geometry. The pressure–volume relationship is non-linear; at low distending pressure, the tension is borne by elastin-distensible fibres, whereas at a high distending pressure, the tension is predominantly transferred to and borne by less extensible collagen fibres, and the arterial wall becomes stiffer [6]. Thus, the stiffness can only be defined in terms of a given pressure since stiffness increases with...
increases in BP. Arterial stiffness can be measured with several methods depending on the clinical use or experimental situation. In clinical practice, arterial stiffness can be non-invasively estimated by three principal methodologies: (i) pulse transit time for evaluation of the pulse wave velocity (PWV), (ii) the analysis of the arterial pressure wave contour, and (iii) the direct stiffness estimation using measurements of diameter or arterial luminal cross-sectional area and distending pressure measured at the site of diameter changes (Figure 1) [7–9]. The two most frequently used methods are measurement of PWV and central (aortic or common carotid artery) pulse wave analysis, recorded directly at the carotid artery or indirectly in the ascending aorta, and computed from the radial artery pulse wave using a transfer function [9]. PWV is an assessment of stiffness of an artery as a hollow structure, and it depends on the geometry of the artery (thickness, h, and radius, r) as well as the intrinsic elastic properties of the arterial wall (i.e. elastic incremental modulus, $E$) and the blood density ($\rho$). According to the Moens and Korteweg formula, $PWV^2 = Eh/2\pi r \rho$ [6].

The assessment of PWV involves measurement of two parameters: transit time of the arterial pulse along the analysed arterial segment ($t$), and distance between recording sites ($D$) measured over the body surface: $PWV = D/t$. The measurement of carotid–femoral (‘aortic’) PWV is considered the gold standard [8]. PWV is measured along the aortic and aorto-iliac pathway. PWV can also be measured at the level of peripheral arteries, but ‘aortic’ PWV is the most relevant because the aorta is the principal ‘cushioning’ artery and is responsible for the pathophysiological effects of arterial stiffening and its association with cardiovascular events (Figure 3) [10]. The arterial system is heterogeneous and characterized by the existence of a stiffness gradient with progressive stiffness (PWV) increase from ascending aorta and large elastic arteries towards the peripheral muscular conduit arteries [10,11] (Figure 4).

PWV must not be confounded with blood velocity. PWV varies according to age and pressure between 4 and 12 m/s, while blood velocity is in order of centimetres/second. PWV relates to transmission of energy through the arterial wall, while blood velocity relates to displacement of mass through the incompressible blood column. This difference in speed propagation is physiologically advantageous for the LV and the arterial flow. When the left ventricle starts to eject incompressible blood, it is faced with a blood column occupying the aorta and the arterial tree. During the first milliseconds, the ejected blood has to find space, and this is done partly by distending the proximal aorta and pushing forward the blood column already present. All these changes are confined to a short segment of the proximal aorta. These local alterations are to be transmitted downstream since the incompressible blood displaced from the proximal aorta must also find place in downstream segments. Relying only on the ‘pushing’ force of blood entering the proximal aorta, the movement of all the arterial blood would necessitate a very high cardiac energy expenditure due to the high inertial forces of the blood column. In parallel to the blood entering the aorta, the proximal aortic pressure starts to rise creating a local small pressure gradient with pressures higher in the proximal part than in the downstream segments. This pressure gradient is moving downstream to distal arterial segments at a high speed (PWV in metres/second) propagating rapidly the pressure gradient from segment to segment, i.e. displacing blood in these segments downstream (Figure 4). As PWV increases from the aorta towards the peripheral arteries, this rapidly propagated ‘shunting effect’ along the arterial...
Fig. 3. Probability of cardiovascular survival of ESRD patients according to the levels of aortic, brachial and femoral PWVs [10].

Fig. 4. Schematic illustration of the pressure wave transmission along the arterial system. Vertical thick arrows indicate the position of the pulse pressure 'head'. Dotted filling represent the 'local' blood column movement. Pulse pressure travels along the arterial tree in 0.3 sec., while blood ejected from the left ventricle only 20 cm per beat (small arrow) (adapted from [13]).
tree results in almost immediate (in milliseconds) downstream mobilization of blood in the arterial system [12]. This occurs still during the ventricular ejection time, and the downstream displacement of arterial blood ‘liberates’ space for the stroke volume. At the end of LV ejection, the stroke volume now occupies the blood column whose length (stroke distance) is in centimetres—mean velocity of blood (Figure 4) [12]. The fact that PWV exceeds largely the blood velocity in the aorta is important; otherwise, the peak aortic flow velocity exceeding PWV would create conditions for generation of longitudinal shock waves (like those generated by an airplane passing the speed of sound) potentially provoking arterial injury [6].

Aortic stiffness together with stroke volume and ejection velocity is a determinant of arterial pressure wave amplitude, influencing systolic, diastolic and pulse pressures in the aorta (PP). Analysis of aortic or carotid pressure waveform and amplitude is another frequently used method to assess large artery properties and eventually arterial stiffness. The principal ‘stiffness’ parameter assessed concerns the effect of reflected waves on pressure shape and amplitude, estimated in absolute terms, i.e. augmented pressure in millimeter of mercury (mmHg), or in relative terms, i.e. ‘augmentation index’ (Aix in percentage of PP) [9,13] (Figures 5 and 6). Considered to be a stiffness index, relationships of Aix with arterial stiffness are more complex, depending on the overlap between forward and reflected pressure waves. The overlap is influenced by the relationships between transit time of pressure waves from the aorta to reflecting sites and back (Figure 7A) (Tr, depending on PWV and travelling distance—body size) (Figure 7B), and duration of LV ejection (heart rate) [6,13,14] (Figure 7C).

Arterial stiffening determines the arterial pressure shape and amplitude by two mechanisms. The first, which is a ‘direct mechanism’, involves the generation of a higher pressure wave by the left ventricle ejecting into a stiff arterial system. This direct mechanism is complemented by a second, which is an ‘indirect mechanism’ via the influence of increased arterial stiffness on increased PWV and the timing of forward and reflected pressure waves. Indeed, the pressure wave generated in the aorta (forward or incident wave) is propagated to arteries throughout the body.

**Fig. 5.** (A) Recorded aortic pulse pressure waveform and its composing waves. PP, pulse pressure; Aix, augmentation index (effect of reflected wave expressed in percentage of PP); Tr, travelling time of pressure wave from the aorta to reflecting sites and back (milliseconds); LVET, left ventricular ejection time (milliseconds). (B) Representation of wave propagation using the model of a rope with fixed end.

**Fig. 6.** (A) Schematic representation of arterial pressure waves travelling from the aorta towards the periphery and back. In the peripheral arteries, the reflected wave occurs at the impact of forward wave—the waves are in phase (Tr = 0) and summed up. Reflected wave returns towards the aorta with a delay corresponding to Tr. The forward and reflected waves are not in phase—aortic PP and systolic pressures are lower than in periphery (B).
The progressive increase of arterial stiffnesses, together with changes in aortic geometry (tapering), local arterial branchings and lumen narrowing, creates an impedance mismatch causing partial reflections (‘echo’) of forward progressing incident pressure waves, i.e. a reflected wave, travelling back to the central aorta, and participating to changes in the amplitude of systolic and pulse pressure along the arterial tree [6,9,13–16] (Figure 6).

Forward and reflected pressure waves are overlapping and are summed up in the measured pressure wave (Figures 5 and 6). The final amplitude and shape of the measured pulse pressure wave are determined by the phase relationship (the timing) between the component waves, i.e. the overlap between the two waves which depends on the site of pressure recording in the arterial tree. Peripheral arteries are close to reflection sites, and the reflected wave occurs immediately at the impact of forward wave, i.e. the waves are in phase (Tr = 0, where Tr is transit time of pressure wave from the aorta to reflecting sites and back), producing an additive effect (Figure 6). The ascending aorta and central arteries are distant from reflecting sites, and the return of the reflected wave is variably delayed. In central arteries (aorta and carotid), the forward and reflected waves are not in phase, and the shape and amplitude of pressure wave depend on the overlap between forward wave and reflected wave. The overlap between forward and reflected pressure waves depends on the PWV and travelling distance of pressure waves to reflection sites (determinants of Tr) and the left ventricular ejection time (LVET) duration as a determinant of the overlap possibility. In subjects with low PWV (low stiffness), the Tr is long, and reflected waves impact on central arteries during diastole, after ventricular ejection has ceased (Figure 8A), increasing the aortic pressure in early diastole and not during systole. This is physiologically advantageous since the increase in early diastolic pressure has a boosting effect on the coronary perfusion without increasing the left ventricular afterload. This decreased overlap between component pressure waves results in lower aortic systolic and pulse pressures compared with peripheral arteries (central-to-peripheral systolic and PP amplification) (Figure 6). The higher peripheral pressure is not only due to a high overlap between incident and reflected wave but also due to higher stiffness of the peripheral arteries, i.e. the higher local pressure effect of the displaced blood column [6].

The desirable timing is disrupted by an increased PWV due to arterial stiffening. With increased PWV, the reflected waves return earlier impacting on the central arteries during systole rather than diastole, amplifying aortic and ventricular pressures during systole and reducing aortic pressure during diastole (Figure 8B). With ageing or in the presence of high PWV, the Tr is very short, and even in the aorta, the forward and reflected waves are almost in phase, the central aortic pressure is close to the peripheral pressure and the amplification tends to disappear or to be attenuated. The overlap (timing) between forward and reflected wave depends also on the LVET. In the presence of tachycardia, the duration of LVET could be too short for the ‘reception’ of the reflected wave, and the latter will impact on the diastole and not on the systole (Figure 8C and D ). Short LVET is associated with increased central-to-peripheral pressure amplification. In contrast, long LVET is favourable for ‘reception’ of the reflected wave still during generation of the forward wave, increasing the overlap between these pressure waves and reducing the central-to-peripheral systolic and pulse pressure amplification (Figure 8C).

Finally, the partial reflection of the forward wave depends on the existence of impedance mismatches of the successive arterial segments [11,15,16]. The impedance mismatch is pronounced in young subjects characterized by a low aortic PWV and higher PWV of the peripheral arteries. The impedance mismatch of successive arterial
segments originates local partial reflections which are distant from the peripheral vascular bed and limiting the transmission of pulsatile energy to microcirculation and capillaries. As it is coupled with low aortic PWV, the reflected wave still returns in diastole (Figure 9, upper panel). With ageing, the aortic stiffness (PWV) increases to a far greater extent than the peripheral artery stiffnesses, dissipating progressively the stiffness gradient [11,15,16]. This limits and progressively decreases the partial reflection, increasing the transmission of the pulsatile energy into the peripheral microcirculation [16] (Figure 9, lower panel). This ‘non-protection’ is especially pronounced in the brain and the kidney, two organs highly perfused with low resistance. At the systemic level, the impedance mismatch depends on the relationships between the characteristic impedance (depending on ascending aortic diameter and stiffness) and peripheral resistances, and will determine the systemic reflection coefficient [1,2].

Local arterial stiffness, e.g. aortic, carotid, brachial or radial artery, can be determined by local PP changes (aortic, carotid, radial or brachial) coupled with local changes in arterial diameter or luminal cross-sectional area (ultrasound echo-tracking, MRI) (Figure 1). As PP and systolic BP are amplified from the aorta towards peripheral arteries, only local PP can be used to measure local stiffness. Local PP changes can be recorded non-invasively by applanation tonometry [9]. A major advantage of local stiffness is that it is derived directly from pressure–diameter changes without using any model of the circulation. The ultrasound technique has the advantages of allowing simultaneous measurements of intima–media thickness and is the only method able to determine non-invasively the elastic properties of the arterial wall material (Young’s elastic modulus).

**Arterial stiffness interpretation**

All studies dealing with arterial stiffness should consider the two principal factors influencing stiffness and necessitating careful matching when comparing different populations. These factors are age and ‘operating’ BP. It was already mentioned that stiffness is pressure-dependent and increases with higher BP. Decrease of stiffness in the presence of decreased BP cannot be interpreted only as an improvement of arterial wall properties, while increased stiffness in the presence of decreased or unchanged BP could be interpreted as a worsening condition [17].

The second factor is age. With ageing, the arterial wall thickens, and the arteries become stiffer. The principal changes occur in the media and intima, where the orderly arrangement of elastic laminae disappears, being replaced by thinning, splitting and fragmentation of the elastic fibres [6]. The degeneration of the elastic fibres is associated with an increase in collagen fibres and ground substance, and deposition of calcium. The loss of distensibility is partly compensated by dilatation of the arteries. A major manifestation of these changes is the rise in systolic and pulse pressures, an increase in aortic PWV, and the disappearance of pressure amplification between the aorta and peripheral arteries due to the earlier return wave reflections [11,16].

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Fig. 8. (A, B) Influence of PWV on aortic pulse pressure shape and Tr. (A) Low PWV reflected wave impacts during late systole and diastole (long Tr), and Aix is negative. (B) High PWV reflected wave impacts during systole (shorter Tr), and Aix is positive. (C, D) Influence of left ventricular ejection time (LVET) on aortic pulse pressure shape and Aix. With long LVET, reflected wave gets back during systole (C); when LVET shortens (tachycardia), reflected wave is more likely to impact during diastole (in conditions of unchanged PWV) (D).
Arterial stiffening is typically observed in several pathological conditions, including isolated systolic hypertension, atherosclerosis, diabetes and chronic kidney disease. Several studies demonstrated that arterial stiffening (increased aortic PWV) and increased wave reflections are per se independent predictors of all-cause and cardiovascular death in ESRD and diabetic patients as well as in the general population [3–5,10]. For clinical or epidemiological studies, the aortic PWV is the most useful measurement of stiffness, and in comparison with other surrogate markers of cardiovascular risk, the aortic PWV has the highest predictive value (Figure 3). The aortic or central artery pressure waveform should be recorded and analysed in parallel with the measure of PWV. This allows a deeper analysis of the pathogenesis and significance of arterial pressure waves and arterial haemodynamics.

Conflict of interest statement. None declared.

References
Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guidelines: a European Renal Best Practice (ERBP) commentary statement

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Abstract

Under the auspices of the European Renal Best Practice, a group of European nephrologists, not serving on the Kidney Disease Improving Global Outcomes (KDIGO) working group, but with significant clinical and research interests and expertise in these areas, was invited to examine and critique the Chronic Kidney Disease–Mineral and Bone Disorder KDIGO document published in August 2009 in the Lancet. This commentary statement presents the ERBP’s endorsement of the KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) guidelines, highlighting key points and areas for further discussion.