REVIEW

Arterial Stiffness

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With advancing age, all organ systems undergo anatomical and functional changes. Vasculature suffers generalized stiffening as a hallmark of this process. Although this phenomenon has been described long ago, only in recent years has the clinical significance of the stiffening of the large arteries been widely understood and its correlation with hypertension, coronary heart disease, stroke, heart failure and atrial fibrillation has been recognized. It has also been accepted that it mediates the vascular effects of diabetes mellitus, atherosclerosis and renal disease. [1-5]

The arterial systems consists of two functional components with different structural characteristics: a) the large *elastic* arteries (aorta, carotid and iliac arteries) which store part of the blood ejected during systole and expel it to the periphery during diastole to provide the tissues with a relatively steady flow through the entire cardiac cycle and b) the *muscular* arteries (arteries below the axillary and femoral ones) which regulate the vascular tone and hence determine the peripheral resistance. The former have a thick tunica media in which the elastic fibers dominate and form numerous concentric layers. The later possess a tunica media characterized mainly by smooth muscle cells and the elastic component is confined to the thin internal and external elastic laminae. The different mechanical properties of the arterial tree along its course and the varying diameter of the arterial branches, gives rise to the reflected waves which are produced when the pulse wave encounters sites with different impedance. A part of these secondary waves amplifies the forward moving wave and another part moves backward to enhance the pressure of the central aorta. Normally it reaches its target in late systole or early diastole and it contributes to the diastolic flow towards the coronary arteries and the periphery (**Fig**. 1).[6-10]

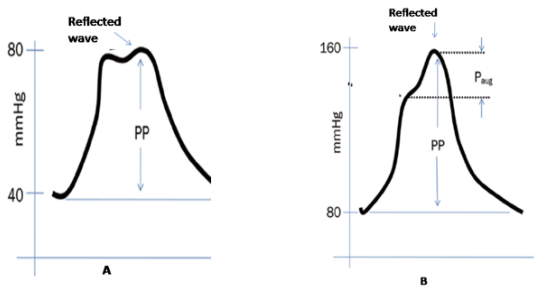

Figure 1. Reflected waves and their contribution in systolic & diastolic aortic pressure. **A**: young, healthy adult. **B**: elderly, hypertensive patient. PP = pulse pressure

With increasing age and the influence of cardiovascular risk factors (hypertension, diabetes, salt intake) and genetic factors (gene polymorphisms in ACE, angiotensin receptors, endothelin receptors, collagen and other connective tissue components) the great elastic vessels undergo elastin depletion and fragmentation and collagen deposition resulting in thickening of the intima. Infiltration of the vessel wall by macrophages, mononuclear cells, smooth muscle cells and increased presence of matrix metalloproteases, TGF-β and adhesion molecules also occurs. [11-16] These structural changes lead to the stiffening of the vessel and a rise in the velocity of the propagating and reflected pulse wave. As a consequence the retrograde directed wave arrives in the central aorta during early systole, augmenting the systolic pressure rather than the diastolic one. Moreover, the endothelial dysfunction which arises under these circumstances promotes arterial stiffening and is accentuated by it, completing a vicious circle of NOS reduction and vascular dysfunction. [17] The reduced vascular compliance is clinically reflected in increased systolic arterial pressure and pulse pressure (the difference between systolic and diastolic pressure), and it correlates with cardiovascular and cerebrovascular episodes, heart failure. [18- 20]

Several methods to measure aortic stiffness have been described. Direct measurements are obviously impractical because of the difficulty to access the vessel lumen. Thus, techniques of indirect measurement have been developed, which estimate either the central or peripheral vessel compliance. The simplest way to assess aortic stiffness is to measure pulse pressure (PP), which depends on cardiac output, elastic arteries stiffness and wave reflection. As age progresses, systolic pressure rises and diastolic pressure remains relatively constant between 50-60 years of age and declines thereafter. Thus, in older individuals PP increases and represents a good surrogate measurement for central arterial stiffness. Pulse pressure values have been shown to predict cardiovascular events both in healthy persons and patients with hypertension or diabetes mellitus. [21-28] However, the researcher needs to keep in mind that PP depends on other factors beyond aortic stiffness as well, it cannot be conclusive in cases of aortic insufficiency or arteriovenous malformations and that the measurement of PP is based on the measurement of peripheral arterial systolic and diastolic pressures, which can be substantially different from central ones. [29] Furthermore, in large conduit vessels, PP is related to the mean arterial pressure since the pressure-volume relationship is non-linear. A drop in blood pressure could therefore decrease PP without exerting a direct effect on the arterial wall. For that reason the index stroke volume

/pulse pressure (SV/PP) has been developed to compensate for the influence of volume changes during systole on blood pressure. This index has been evaluated in the general population and in hypertensive patients and is considered a predictor of cardiovascular events. [30, 31]

The method considered the "gold standard" to assess arterial stiffness is the measurement of pulse wave velocity (PWV). It is recommended as an index of asymptomatic organ damage in hypertensive patients by the recent guidelines published by the European Society of Hypertension (ESH). [32] According to the Moens-Korteweg equqtion [Co= √(Eh/2Rρ)] [33], PWV depends on wall thickness (h), vessel radius (r), density of the fluid that flows in the lumen (ρ) and vessel distensibility as expressed by Young's modulus (E). PWV is determined by simultaneously recording the pulse in the carotid and femoral arteries and dividing the distance between them, which is measured over the body surface using a tape, by the time interval between fiduciary points on the pressure waveform of the proximal and distal recording sites. Some devices calculate the time difference from a certain point of the electrocardiogram (ECG) to the pulse wave between the two sites of interest. A value exceeding 12m/sec was considered abnormal, until recently when the cutoff point has dropped to 10m/sec. [32]

Both distance and time measurement are prone to errors. Regarding distance, differences in body shape are not taken into consideration and an assumption that the aorta is straight is made. The time variable presents a difficulty in identifying the start of the pulse cycle in the recorder waveform. The same point in both waveforms must be used to ensure proper timing; however this can be challenging because of the different pulse waveform contour in the central and peripheral recording.

PWV varies from vessel to vessel. It is reported that typical velocities in ascending the ascending aorta would be around 4 m/sec, in the abdominal aorta and carotid arteries 5 m/sec, in the brachial artery 7 m/sec and in the iliac arteries 8 m/sec. [34] The measurement of PWV along the aorta or aorto-iliac axis is considered the most clinically relevant and compared to PWV in other locations it has been better correlated with progressing age and other cardiovascular risk factors. [35, 36] Increased aortic stiffness as assessed by PWV is associated with mortality in renal failure, diabetes mellitus and hypertension [37- 39] and can predict cardiovascular and coronary events. [40] It is also related to rheumatoid arthritis, systemic lupus erythematosus, Takayasu's arteritis, elevated homocysteine, hypothyreoidism, metabolic syndrome and cognitive dysfunction. [41-46]

Pressure recordings are feasibly obtained in central and large peripheral vessels but cannot be acquired in small arteries. However, small vessel mechanical properties are reflected in large vessel behaviour and frequently they are the very first site affected by the pathological vascular processes. [47, 48] Moreover, pulse waveform derived from large arteries can provide information about the characteristics of small vessels. This technique, called pulse waveform analysis, requires a more sophisticated pressure recording (applanation tonometry) and evaluates the magnitude and timing of reflected waves by analyzing the diastolic pressure decay part of the waveform. [49] The computerized analysis of diastolic phase with the employment of mathematical models can provide an assessement of large and small artery compliance. [50]

Unfortunately, aorta, which is the most important vessel to determine arterial stiffness, is not available to application of applanation tonometry techniques, because invasive access is required. However, it is possible to predict the pressure waveform in the central aorta by mathematically processing the waveform recorded in peripheral sites (e.g. radial artery). The mathematical functions ("transfer functions") used take into account the mechanical properties of the vascular bed that lies between the sites of interest and recording, but their reliability has been put to the question.[51,52] In fact, transfer function are derived in healthy individuals and their applicability in diseased vascular beds is doubted. [53] Furthermore, the tonometry procedure itself is prone to several errors of technical nature, and the results differ significantly with regard to the tonometer calibration method, using as standard the invasive versus non-invasive blood pressure measurement. [54]

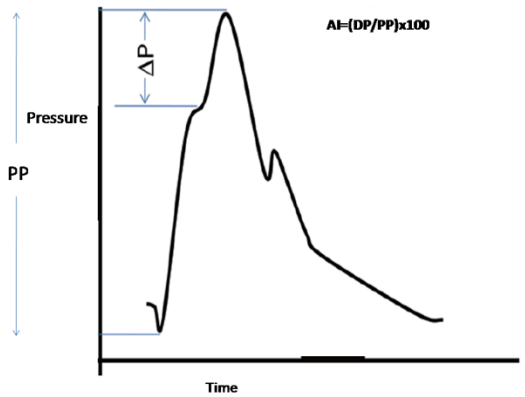

Figure 2. Calculation of augmentation index. PP:pulse pressure

The start of the reflected wave is usually visible in the pressure waveform as an inflection point. The increment of pressure from this point up to the peak aortic pressure calculated as a percentage of pulse pressure, is called augmentation index (AI) (**Fig**. 2). Augmentation index has a correlation with PWV and it is elevated in cases of

diabetes mellitus, smoking, hupercholesterolaemia, and raised hsCRP, while it is inversely related to endothelial function as assessed by flow-mediated dilatation in the brachial artery. [55-59] AI increases with age and it may be a more sensitive tool to assess arterial stiffness than PWV in young (<50 years old) individuals. [59] It is also reported to correlate with prognosis in end-stage renal failure. [60] AI measurement is significantly influenced by heart rate (increases in heart rate lead to reductions in AI) and ejection fraction (in heart failure the results are unreliable), and it must be calculated from waveforms recorded in central arteries. [61,62]

Direct calculation of arterial compliance can be achieved by simultaneously measuring the vessel diameter and pressure. The former variable can be determined by ultrasound or MRI; the later would require an intravascular catheter which apart from the technical difficulties and complication risks, it can also affect local blood flow. Intravascular ultrasound devices with pressure transducer have been used. [63, 64] However this method can potentially obtain an accurate measurement but confined in a small portion of the artery, the mechanical properties of which may be substantially different along its length.

Lately, genetic studies have revealed an influence of heritability in the development of arterial stiffness. Heritability estimates are repoted between 0.18 and 0.37 for augmentation index, 0.13 and 0.54 for pulse pressure and around 0.4 for PWV. [65-71] Several candidate genes have been recognized which encode either for proteins involved in cell proliferation and vascular hypertrophy, or for molecules regulating blood pressure, vascular tone (renin-angiotensin system, NO synthase, adrenergic receptors, endothelin etc) and structural properties of the arteries (collagen, elastin, fibrillin) as reviewed by Yasmin and Kevin O' Shaughnessy. [71] Furthermore, the role if inflammation has emerged, as activation of matrix metalloproteinases and numerous cytokines takes place in the diseased vessel wall. [72]

Arterial stiffness has not yet been targeted by specific therapeutic maneuvers. There are scarse evidence that statins, β-blockers and renin-angiotensin system inhibitors can improve the elastic properties of the arteries. [73-76] Advanced glycosylation end-products (AGE) have been given a pathophysiological role in arterial stiffening and specific drugs which inhibit AGE formation such as pimagedine have been tested in diabetic patients with hardly encouraging results. ACTION I trial failed to achieve its primary end-point (time to doubling of serum creatinine equal in both groups) but the drug reducer proteinuria and decelerated retinopathy progression. ACTION II was prematurely stopped due to drug toxicity.[77,78] Drugs that disorganize AGE crosslinks have also been developed but studies in humans are still few. Alagebrium (ALT-711) has improved endothelial function and arterial stiffness indices.[79] The addition of sodium nitrite (a derivative of nitrates contained in fruits and vegetables) and curcumin (an ingredient of Indian diet) in the diet has provided some encouraging evidence although still confined to animal models. [81-82] However, more trials are needed so that the novel therapeutic approaches can find their place in everyday clinical practice. Until then, the control of classical risk factors will play a cardinal role in preserving good health, quality & function of blood vessels.

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