

The pathogenesis of arterial stiffness and its prognostic value in essential hypertension and cardiovascular diseases

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Abstract

The elasticity of a given arterial segment of the aorta and of big elastic arteries is not constant but depends on its distending pressure. As distending pressure increases, there is greater recruitment of inelastic collagen fibers and thereby a reduction in elasticity. It also depends on structural changes in the medial layer of the elastic arteries (mainly aorta and major arterial conduits), and is largely the result of progressive elastic fibre degeneration.

Aortic Pulse Wave Velocity (PWV), is the most robust marker of arterial stiffness, however additional useful information can also be provided by the Central Augmentation Index (AIx C), and pulse pressure. The presence of systemic inflammation in cardiovascular disease and in particular in essential hypertension affects arterial stiffness and increases PWV. Some pharmacological and non-pharmacological interventions may improve arterial stiffness and thereby decrease PWV. Hippokratia 2009; 13 (2): 70-75

Key words: pulse wave velocity, arterial stiffness, augmentation index, pulse pressure

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Arterial stiffness

Arteries are conduits that deliver blood at high pressure to peripheral vascular beds. They are separated into two anatomic regions with distinct functions: (1) Large elastic arteries (e.g. aorta, carotid, iliac), which store the blood during systole and expel it to the peripheral circulation during diastole, so that the capillaries receive a steady blood flow through the whole cardiac cycle. (2) Muscular arteries, especially those in the lower body (e.g. femoral, popliteal, posterior tibial), which alter their tone and thus can modify the speed of travel of the pressure wave along their length, thereby determining the extent to which and timing at which, the reflected wave arrives back at the heart¹.

The arterial wall consists of three layers: intima, media, and adventitia. The intima consists of a single layer of endothelial cells, supported by smooth muscle cells and is separated from the media by the internal elastic lamina, which is composed largely of elastic fibres. The medial layer represents the main determinant of the mechanical properties of the elastic arteries, and comprises of elastic laminae in concentric layers interspersed with collagen and smooth muscle cells. The third layer is the adventitia, consisting mainly of fibroblasts and collagen. The elasticity of the large arteries is the result of the high elastin to collagen ratio in their walls, which progressively declines toward the periphery². Moreover, the elasticity of a given arterial segment is not constant but depends also on its distending pressure. As distending pressure increases, there is greater recruitment of inelastic collagen fibers and thereby a reduction in elasticity.

Increased arterial stiffness parallels structural chang-

es in the medial layer of the elastic arteries (mainly aorta and major arterial conduits), and is largely the result of progressive elastic fiber degeneration. An increase in stiffness related to arterial wall composition occurs with aging, and is accelerated in patients with hypertension^{3,4}. It is also seen in patients with end-stage renal disease and diabetes^{5,6}. Recently, increased arterial stiffness has been reported in women but not in men with type II diabetes mellitus⁷. With ageing, the orderly structure of the elastic lamina becomes deranged due to its thinning and fracturing. Furthermore, there is secondary accumulation of collagen in the arterial wall and increased collagen cross-linking. The most obvious clinical consequences of arterial stiffening are increased pulse pressure (PP), caused by higher SBP and lower DBP, with a resulting increase in left ventricular afterload and reduction in coronary perfusion⁸.

Measurement of wave reflections

Applanation tonometry is used to record the pulse pressure waveform in the radial artery. This waveform can be then analysed by applying a transfer function⁹, and the central pulse pressure waveform in the aorta can be inferred. However, in a recent study it was shown that transfer function, although required to determine central SBP from the radial artery, is not necessary and that similar information about the central pressure wave can be derived directly from the radial pulse¹⁰.

The pulse pressure (PP) wave is formed by the combination of the incident wave and waves reflected back from the periphery. The incident wave is generated by the left ventricle during systole and travels along the

arterial system towards the periphery through a low resistance pathway which keeps the mean pressure almost unchanged. However, close to capillaries, mean pressure falls in a short distance within the high resistance arterioles. At the junction between high-conductance arteries and high-resistance arterioles, wave reflection occurs. Under normal circumstances, almost 80% of the incident wave is reflected from arterioles¹¹. The PP wave is a combination of incident and reflected waves at any point along the arterial system. When the large elastic arteries are compliant, the incident wave travelling from the heart to the periphery is responsible for peak SBP. The wave velocity is slow and therefore the reflected pressure wave arrives from the periphery in diastole augmenting the DBP and preserving coronary perfusion. As large elastic arteries stiffen the wave velocity is increased and the reflected wave returns earlier and merges with the systolic part of the incident wave¹. As a consequence, an increase in systolic and a decrease in diastolic BP occurs, thereby increasing PP and decreasing coronary perfusion¹². The shape of PP waveform varies throughout the arterial tree due to differences in elastic qualities and wave reflection. In young healthy subjects, the SBP and PP are amplified in the peripheral circulation, whereas at older ages this amplification is reduced, as a result of both the increase in pulse wave velocity (PWV) with age, and the earlier return of the reflected wave due to the involvement of reflection sites closer to the heart. PP waveform is different in health and disease, with characteristic shapes in elderly or hypertensive patients. Characteristic PP waveforms from the radial artery and the central aorta, from a younger (20 years old, A) and from an older (64 years old, B) healthy man, are shown for comparison in Figure 1.

Augmentation index (Aix) is calculated as the increment in pressure from the first shoulder in the ascending aortic pressure wave to the peak of this wave, expressed as a percentage of the peak ascending aortic pressure wave (Figure 2). Aix depends on the duration of the cardiac cycle (and consequently on heart rate), on the velocity of the pulse wave, and on the amplitude of the reflected pulse wave. Therefore DBP and height may influence Aix as they may influence the reflection sites¹². In healthy elastic arteries, Aix is related mainly to the magnitude of the reflected wave rather than to its velocity, whereas in stiff arteries the relationship between PWV and Aix is stronger¹³. By the measurement of the pulse wave one can obtain information about central systolic pressure and PP, and also central Aix (Aix C). However, Aix C is not considered a direct index of arterial stiffness and needs to be combined with the measurement of PWV. In a recent study performed in 4,001 healthy subjects, it was shown that both Aix C and PWV increase with age but Aix C increases more in young individuals and PWV increases more in older ones, suggesting that the former is a more sensitive marker of arterial stiffness in young and the latter is more sensitive in older subjects¹⁴.

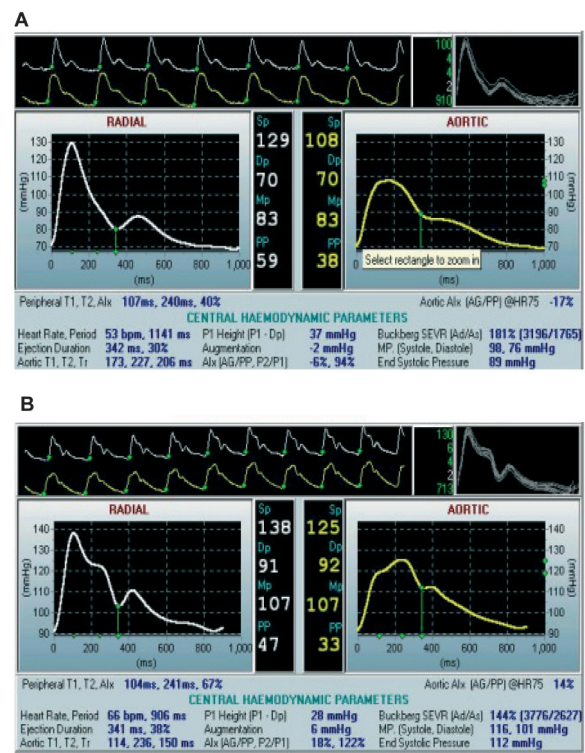


Figure 1: Pulse pressure waveforms from the radial artery and the derived waveform in the central aorta. Peripheral and central pressure waveforms, acquired with the Sphygmocor device, in a young (A) and an older (B) healthy man.

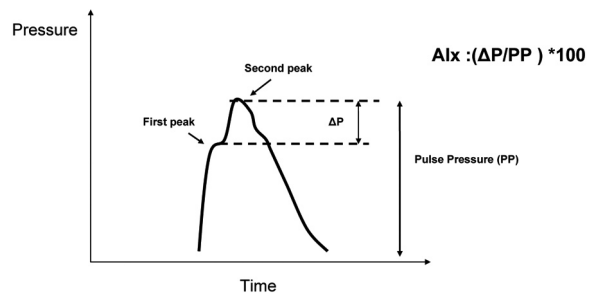


Figure 2: Illustration of a central aortic pressure waveform in a middle-aged subject. The second systolic peak becomes more prominent with age or as arteries stiffen, and is caused by wave reflection. The Aix C is defined as the difference between the second and first systolic peaks (ΔP) expressed as a percentage of the PP.

Measurement of pulse wave velocity

The aortic PWV is the “gold standard” marker for measuring arterial stiffness, and is widely used to estimate vascular stiffness and “vascular health”. The velocity of the arterial wave is predicted by the Moens-Korteweg equation, $PWV = \sqrt{(Eh/2\rho R)}$, where E is Young’s modulus of the arterial wall, h is wall thickness, R is arterial radius at the end of diastole, and ρ is blood density¹. The veloc-

ity of the wave is measured between two predefined sites of the arterial system. The arterial pulse wave is recorded at a proximal artery such as the common carotid, as well as at a distal artery such as the femoral. These two arteries are the most widely used, because they are superficial and the recording of the pulse waveforms can be done non-invasively using tonometry. Furthermore, between those two sites, the pulse wave has to travel through most of the aorta, an artery particularly prone to atherosclerosis. The distance travelled by the pulse wave is measured over the body surface. The time delay of the arrival of the foot of the pulse wave at these two sites is obtained by gating to the R wave of the ECG¹² (Figure 3).

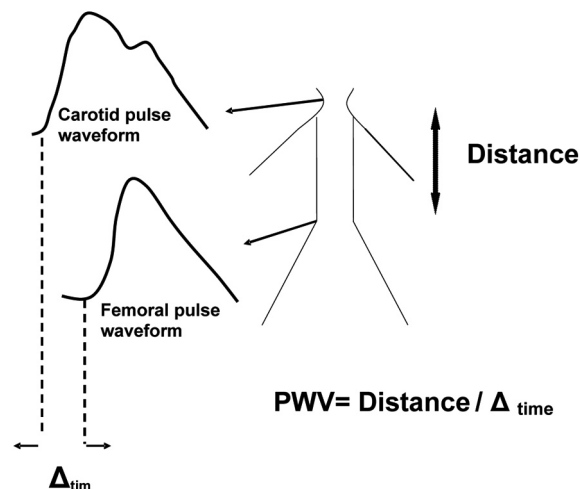


Figure 3: Measurement of aortic PWV. The time delay (Δ_{time}) is measured between the foot of the wave at the two arterial sites, and the distance is measured over the body surface. PWV is calculated as $\text{Distance}/\Delta_{\text{time}}$.

The measurement of aortic PWV has been recognized as the most simple and reproducible for estimating arterial stiffness¹². Therefore it has been widely used in a variety of patient groups and has been established as a strong marker of cardiovascular events. Data from the Framingham study showed that men have slightly higher PWV compared to women and, although significant, this difference is small¹⁵.

Heart rate has been reported to influence PWV^{16,17} but this has been attributed to methodological considerations¹⁵. Recently a study was performed comparing the effects of increased heart rate, induced either by pacing or by infusing a β_2 -adrenergic agonist, and measuring PWV using two different devices (SphygmoCor and Complior); it was shown that there is indeed a true increase in PWV with heart rate, and that this is not attributable to changes in BP or to different algorithms used by the two devices¹⁸. However, the authors concluded that the influence of heart rate on PWV is likely to vary according to age, sex and degree of arterial stiffening. Indeed, another study demonstrated an increase in aortic PWV after

an increase in heart rate in males but not in females¹⁹. However, Zambanini and colleagues have proposed that, because the heart-pacing rates which were used in most of these studies may increase central mean and diastolic pressure, it is likely that this contributes to the increase in PWV rather than the increase of the heart rate itself²⁰.

The role of NO in regulating arterial elasticity has been controversial. By investigating the effect of L-NMMA (N^G -monomethyl-L-arginine, a non-specific inhibitor of Nitric Oxide Synthase) on the elastic properties of different arteries (e.g. radial and brachial), the results from studies have been conflicting. Some researchers showed that infusion of L-NMMA decreases the elastic properties of the brachial artery²¹, while others showed no effect on radial artery stiffness²². Similarly the effect of endothelium-derived NO on aortic PWV is also controversial. PWV measured in the ovine iliac artery, a more muscular artery than the aorta, was found to be significantly increased after infusion of L-NMMA²³. These investigators applied the same technique to humans, and showed that L-NMMA increased and GTN (glyceryl trinitrate, an exogenous Nitric Oxide donor) reduced iliac arterial stiffness, when infused locally into the artery, without any change in the mean arterial pressure²⁴. In contrast to these studies, Stewart et al showed that systemic infusion of L-NMMA increased mean arterial pressure and carotid-femoral PWV in humans; however, they found that this effect was similar to that produced by two other vasoactive drugs (norepinephrine and dobutamine) used as controls²⁵. In accordance with this, a previous study from the same group showed that systemic infusion of GTN, in the absence of a change in BP, has no effect on aortic stiffness¹³. The authors suggested that mean arterial pressure is the most important determinant of short-term changes in carotid-femoral PWV²⁵.

Arterial stiffness and inflammatory markers

Arterial stiffness is largely dependent on the structural properties of the large artery wall. Elastin, as the main component of the large artery wall, is susceptible to degradation by enzymes such as metalloproteinases (MMP), mainly MMP-9 and MMP-2, and also by serum elastase. Increased activity of the above enzymes has been related to atherosclerosis and also to generation of aneurysms in humans through destruction of elastic laminae^{26,27}. Recently, it has been demonstrated that individuals with isolated systolic hypertension have increased activity of MMP-9, MMP-2 and serum elastase. MMP-9 was also correlated linearly to aortic PWV in hypertensives, and both MMP-9 and serum elastase activity levels were linearly correlated to PWV in young healthy individuals²⁸. Levels of MMP-9 were associated with C-reactive protein (CRP) levels also in young individuals, indicating a possible link between inflammation and increase in arterial stiffness²⁸. Indeed it has been shown that inflammation is associated with increased arterial stiffness, and PWV is independently correlated to CRP levels in patients with inflammatory diseases such as systemic vasculitis²⁹ and rheumatoid

arthritis³⁰. Treatment of the inflammatory disease may result in significant reduction of PWV³⁰. Furthermore acute systemic inflammation, after *Salmonella typhi* vaccination, leads to increase in aortic stiffness³¹. A strong correlation between CRP levels and PWV was also found in healthy individuals, suggesting a role of inflammation in the process of arterial stiffening even in health³². In essential hypertension, the contribution of systemic inflammation to arterial stiffening was investigated by Mahmud and colleagues. They showed that levels of CRP, tumor necrosis factor (TNF- α) and interleukin-6 (IL-6) were independently correlated to PWV and to AIX C³³. Other investigators also have shown independent correlations between CRP and PWV in essential hypertension³⁴. Apart from the relation between inflammation and arterial stiffening, evidence also exists for a genetic contribution. It has been shown that polymorphisms of the MMP-9 gene may affect arterial stiffening and levels of elastase activity in healthy individuals³⁵.

The usefulness of measuring AIX and PWV in cardiovascular diseases, including essential hypertension

AIX C and central PP are independent predictors of cardiovascular and all-cause mortality in patients with end-stage renal disease^{36,37}, and of cardiovascular events in hypertensive patients³⁸. In the latter study patients that were on antihypertensive treatment with amlodipine/perindopril had lower central aortic pressure and PP compared with patients taking atenolol/thiazide, despite similar brachial SBP and no difference in PWV. Central PP was significantly associated with total cardiovascular events and procedures and with the development of renal impairment in this cohort of hypertensive patients. This was attributed mainly to the prolonged systolic ejection time in the atenolol/thiazide group, which delayed the outgoing pressure wave and increased the possibility that the reflected wave will augment it during systole. An earlier return of the wave reflection due to relative vasoconstriction in the atenolol/thiazide group may also have contributed to the findings³⁸. This study was the first powered sufficiently to investigate if different antihypertensive drug treatments may have differential effects on central aortic pressure and if this is associated with cardiovascular outcomes. It provides also a reasonable explanation why β -blockers (and specifically atenolol), according to a recent meta-analysis of the early BP trials, were not found to be better than placebo in preventing cardiovascular events³⁹. These findings imply that brachial BP may not always be the best measure of severity of hypertension, and that in future the measurement of central aortic BP may provide more useful information about prognosis and the effectiveness of treatment.

Aortic PWV has been found to be a strong predictor of cardiovascular mortality in healthy subjects older than 70 years old⁴⁰, in end-stage renal disease⁵, diabetes⁶, and hypertension⁴¹. Aortic PWV is an independent predictor of cardiovascular and all-cause mortality⁴², of coronary

events⁴³, and of fatal strokes⁴⁴ in patients with essential hypertension. It also correlates strongly with coronary atherosclerosis⁴⁵, and predicts coronary heart disease and stroke in a population of older individuals without a previous history of either⁴⁶.

Since aortic stiffness predicts cardiovascular events, it is important to investigate factors that may worsen or improve it. For example, it has been shown that caffeine, smoking, black tea and acute mental stress all have detrimental effects on arterial stiffness⁴⁷⁻⁵⁰. Non-pharmacological measures such as exercise⁵¹ and dietary changes, in particular weight loss⁵², low salt diet⁵³ and moderate alcohol consumption⁵⁴, can all reduce arterial stiffness. Pharmacological studies in hypertensive populations have shown improvement of arterial stiffness after initiation of antihypertensive treatment. These studies include treatment with diuretics⁵⁵, ACE inhibitors^{55,56}, ARBs⁵⁷, Ca²⁺-blockers⁵⁸, and aldosterone antagonists⁵⁹. Other pharmacological interventions that decrease arterial stiffening are hormone replacement therapy⁶⁰, antidiabetic agents⁶¹, and advanced glycation end product breakers⁶², and anti-tumor necrosis factor-alpha (anti-TNF α) treatment³⁰ and statin therapy⁶³ in patients with rheumatoid arthritis

Conclusion

In summary, measurement of AIX C, PP, and PWV are useful markers for estimating vascular function in patients with cardiovascular diseases and in particular essential hypertension. The "gold standard" marker of arterial stiffness remains PWV, however in the light of the most recent studies additional important information may be obtained also by measuring AIX C and PP.

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Retraction

This retracts the article: Votsi E, Roussos D, Katsikis I, Karkanaki A, Kita M, Panidis D. Kisspeptins: a multifunctional peptide system with a role in reproduction, cancer and the cardiovascular system. *Hippokratia* 2008; 12: 205-210

The Editorial Board of Hippokratia journal regrets to inform its readership that plagiarism was documented in the above named paper. A letter dated 17.12.08 was received from Prof D. Panidis, corresponding author of the above article. In his letter Prof Panidis is asking for the retraction of the article because as he states "the title as well as some paragraphs of the text have been copied verbatim from an earlier review article with the same title in *The British Journal of Pharmacology*, 2007; 151: 1143-1153".

In addition to his letter, all authors have signed a statement agreeing to the retraction of this article, which is on file at Hippokratia Journal.

The Editors