Επίκαιρο Άρθρο

Arterial stiffness in physiology: role of ageing and hypertension

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ABSTRACT

The characteristic of hypertension is the progressive alteration in the blood pressure curve as function of age, with a progressively higher systolic (SBP) and a lower diastolic BP. Systolic hypertension is the most frequent form of essential hypertension over the age of 65 years. The ability of arteries to accommodate the changes in blood volume related to cardiac contraction and stroke volume are described in terms of compliance, or arterial stiffness/rigidity. Arterial stiffness and wave reflections are the most important factors determining these pressures. Age-associated vascular changes are associated with numerous deleterious changes in the structure and function of the vascular system. Increased vascular ageing (Early Vascular Aging – EVA syndrome) is an acceleration of arterial stiffness inappropriate for the given chronological age. Furthermore the association of arterial stiffening and inflammation in essential hypertension was clearly demonstrated. The contribution of the arterial stiffness and stiffness gradient to the properties of systemic arterial wave propagation and reflections and macrovascular-microvascular interactions are presented here. Stiffening of arteries is associated with increased cardiovascular mortality and morbidity. The age-stiffness correlation could be influenced by therapeutic intervention. Early and prolonged antihypertensive treatment could slow-down aortic early vascular aging.

Introduction

Arterial hypertension is a major cardiovascular risk. The arbitrary thresholds of 140 and/or 90 mm Hg of systolic and diastolic BP are the most widely adapted criterions of hypertensive diagnosis. The characteristic of hypertension is the progressive alteration in the blood pressure curve as function of age, with a progressively higher systolic (SBP) and a lower diastolic BP. Systolic hypertension is the most frequent form of essential hypertension over the age of 65 years[1]. In the presence of cardiac, cerebral or renal complications, systolic BP is considered the principal risk predictor. Nevertheless, at any given systolic level, this risk is accentuated when diastolic level is further reduced leading to an increased pulse pressure. Mean pulse pressure (PP - the difference between SBP and DBP), increases markedly with age and is considered as a major cardiovascular risk factor. Recognizing that increased systolic pressure is the most challenging form of hypertension today and that pulse pressure as an independent cardiovascular risk factor has focused attention on arterial stiffness and wave reflections as the most important factors determining these pressures. In recent years, many studies emphasized the role of arterial rigidity in the development of cardiovascular diseases, and it was shown that stiffening of arteries is associated with increased cardiovascular mortality and morbidity[2].

Arterial stiffness in physiology

The ability of arteries to accommodate the changes in blood volume related to cardiac contraction and stroke volume are described in terms of *compliance,*

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or *arterial stiffness/rigidity.* These terms express the relationships between changes in the volume of the vasculature and transmural pressure. Compliance (C) describes the volume change (DV = strain) due to a pressure change (D*P* = stress): $C = DV/DP$. Compliance could be expressed relative to baseline volume (V) as Distensibility $Di = DV/V \times DP$. The reciprocal value of compliance is elastance or stiffness ($E = DP/DV$). The compliance or stiffness, provides information about the "elasticity" of the artery as a hollow structure including vessel dimensions, the elastic incremental modulus (E_{inc}, Young's modulus) characterizes the intrinsic elastic properties of the biomaterials constituting the arterial wall independent of vessel geometry[3]. The arterial stiffening is characterized by a steep pressure-volume relationship, i.e; increased systolic pressure during ventricular ejection and decreased diastolic pressure during diastolic runoff, resulting in high pulse pressure. The pressure-volume relationship is non-linear. At the beginning of left ventricular contraction the arterial wall distension is applied on elastic (distensible) elements with limited pressure effect, with increased distension the stress is transferred to collagen elements more "resistant" to distension limiting arterial blood pooling and increased blood pressure effect. The basic physiological role of stiffness/compliance is to dampen the systolic-diastolic pressure oscillations and to transform these pressure oscillations and cyclic blood flow in the aorta into a continuous capillary flow and pressure. During ventricular contraction, part of the stroke volume is forwarded directly to peripheral tissues, and part of the energy produced by the heart is diverted for the distension of arteries and is "stored" in the vessel walls. During diastole, the "stored" energy recoils the aorta, propelling the accumulated blood forward into the peripheral tissues, ensuring continuous flow. To limit the cardiac work required during ventricular ejection, the energy necessary for arterial distension and recoil should be low, i.e., for a given stroke volume, the pressure rise should be as small as possible, i.e. the stiffness should be low[3]. In addition to the "resistance to distension", arterial stiffness determines the propagation velocity of the pressure wave from the proximal aorta towards peripheral vessels; i.e., pulse wave velocity (PWV). PWV is a convenient way to measure arterial stiffness. Briefly, the speed of pressure-wave propagation in a solid is proportional to its rigidity. PWV assesses the stiffness of an artery as a hollow structure and according to the Moens and Korteweg's formula: $PWV^2 = E_{inc} \times h/2r \times r$. It depends on artery geometry (wall thickness, *h*; radius, *r; young's modulus* $E_{inc;}$ and density r). PWV must not be confounded with blood velocity. Indeed, while PWV is in orders of m/s, blood velocity is in the order of cm/s. PWV represents the transmission of energy through the arterial wall, while blood velocity represents the displacement of mass through the incompressible blood column. This difference in speed propagation is physiologically advantageous for left ventricular work and arterial blood flow. During ventricular ejection, the incompressible blood faces a blood column occupying the aorta and arterial tree, and the ejected blood has to find space. Concomitant to blood entering the aorta, the proximal aortic pressure rises, creates a pressure wave with higher pressures in a short segment of the proximal aorta than in distal arteries (pressure gradient). These local alterations are transmitted downstream, because the incompressible blood displaced from the proximal aorta must also find its place in downstream segments. The pressure wave moves downstream to distal arterial segments, propelling the pressure gradient along the arterial tree, resulting in a rapid downstream mobilization of blood in the arterial system. This transmission occurs during ventricular ejection, and the downstream displacement of arterial blood "frees-up" space for the stroke volume. Relying only on the "thrusting" force of blood volume entering the proximal aorta, the movement of all arterial blood would require very high cardiac energy expenditure to counter the high inertial forces of the blood column. At the end of ventricular ejection, the stroke volume is now occupying the blood column whose length (stroke distance) is measured in centimeters, i.e., mean blood velocity in cm/s. The fact that PWV largely exceeds blood velocity in the aorta is important; otherwise, peak aortic flow velocity exceeding PWV would create conditions for the generation of longitudinal shock waves (like those generated by an airplane passing the speed of sound), potentially provoking arterial injury[4-6].

The arterial system is heterogenous, with PWV increasing progressively from the ascending aorta to

the peripheral muscular conduit arteries, generating a stiffness gradient that is important for the regulation of cardiac work and pulsatile pressure transmission to the microcirculation.

Partial pressure-wave reflections are generated along the stiffness gradient limiting pulsatile energy transmission downstream to the microcirculation. 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[7,8].

Arterial stiffening can be associated with modified E_{inc} (collagen accumulation and cross-links, broken elastin fibers, vascular smooth-muscle–cell apoptosis, calcifications, inflammation and fibrosis, endothelial dysfunction) and arterial remodeling (changes in wall thickness and/or radius). The inflammation plays a dominant role in many conditions including aging and hypertension. The association of arterial stiffening and inflammation in essential hypertension was demonstrated through the relationships between arterial stiffness and either tumor necrosis factor-alpha (TNFα), interleukin-6 or highly sensitive CRP (hs-CRP). Interleukin-6 and TNFα are also independent risk factors for high blood pressure in apparently healthy subjects. In untreated patients with essential hypertension, aortic stiffness, assessed through carotid-to-femoral PWV, was significantly associated with hs-CRP and interleukin-6[9].

Arterial stiffness and vascular aging

All epidemiological studies have clearly shown that aging is the most determinant risk factor for development of cardiovascular complications, and age-related alterations in the vasculature play an important role. The age-related alterations could be observed in the absence of classical and conventional CV risk factors. The pathophysiological roles of cellular and molecular mechanisms of aging are complex and multifactorial, including oxidative stress, mitochondrial dysfunction, cellular senescence with chronic low-grade inflammation, genomic instability, epigenetic alterations, and other factors[9-11]. Age-associated vascular changes are associated with numerous deleterious changes in the structure and function of the vascular system. These change concern all segments of vasculature from large elastic conduit arteries to peripheral muscular conduit arteries, and microcirculation. The principal vascular changes observed with aging are an enlargement and lengthening (tortuousness) of arterial tree, principally of the aorta and central elastic type arteries. Increased arterial radius is followed by the vessel wall thickening and higher wall-to-lumen ratio maintaining circumferential tensile stress. Aging incurs aortic stiffening and dilation, but these changes are less pronounced in peripheral arteries. These structural changes are associated by wall stiffening predominantly due to arterial media alterations (fragmentation of elastic laminae and fibers, collagen accumulation and cross-links, vascular smooth muscle apoptosis, fibrosis and inflammation, calcifications)[12]. Young subjects are characterized by significantly lower aortic than peripheral stiffness and thus by a significant “stiffness gradient”. With aging and pathologies, aortic rigidity increases much more than hardening in peripheral arteries. This leads to progressive equalization of aortic and peripheral arteries rigidity with decreased or inversed stiffness gradient and impedance gradient influencing progression of the forward and reflected pressure waves propagation. The “effective” reflection sites are now closer to the microcirculation, increasing pulsatile energy transmission into the peripheral microcirculation. The decreased stiffness gradient associated with high aortic PWV could account for the inverse relationships observed between aortic PWV and impaired kidney and brain function[13-15]. Autoregulation which is an important protective mechanism limiting the pressure transmission. Decreased autoregulation, largely associated with endothelial dysfunction, is observed in several conditions, e.g., aging, diabetes, hypertension and chronic nephropathies favors the pulsatile pressure transmission associated with decreased stiffness gradient[16,17]. Increased vascular ageing (Early Vascular Aging – EVA syndrome) is an acceleration of arterial stiffness inappropriate for the given chronological age. This could be observed in various disease states such as hypertension, diabetes, inflammatory diseases, and chronic and end-stage renal disease[17]. In untreated essential hypertension, the early vascular ageing is principally characterized by an upward reset of the age-aortic stiffness relationship (Figure 1). Nevertheless, the age-stiffness correlation could be influenced by therapeutic intervention. Figure 2 in-

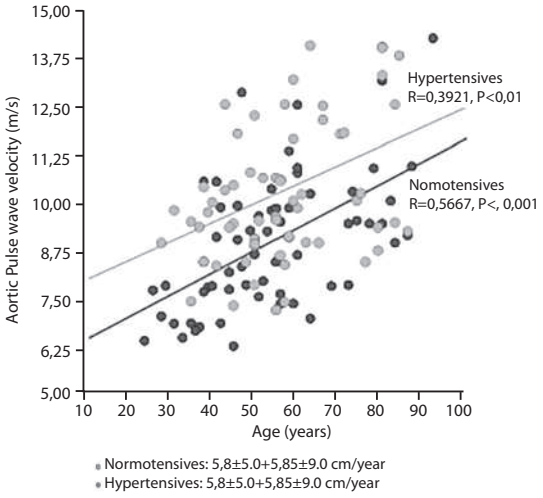


Figure 1. *Correlation between age and aortic pulse wave velocity (PWV) in normotensive (black circles) and hypertensive subjects (gray circle). An upward non-significant (P=0.112) reset of the correlation is observed in hypertension.*

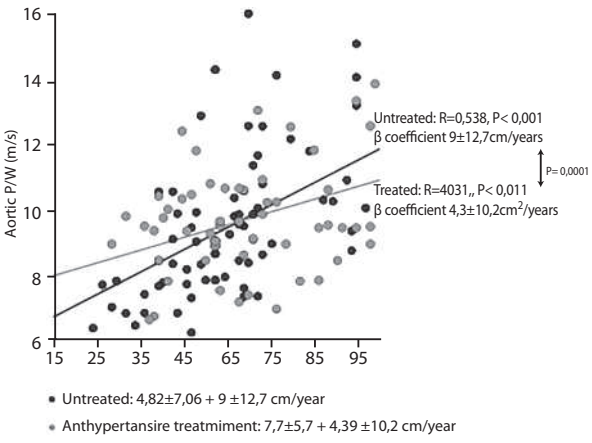
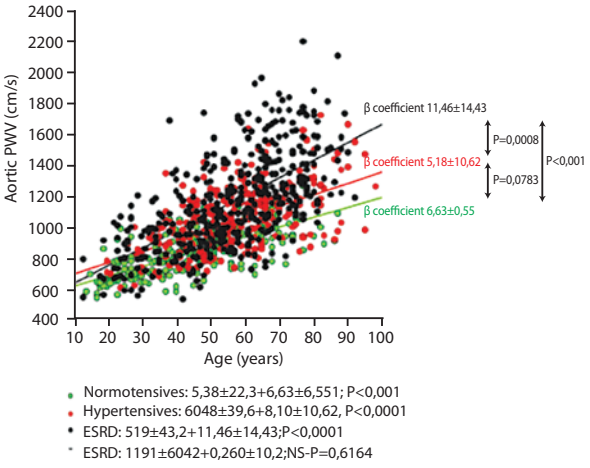
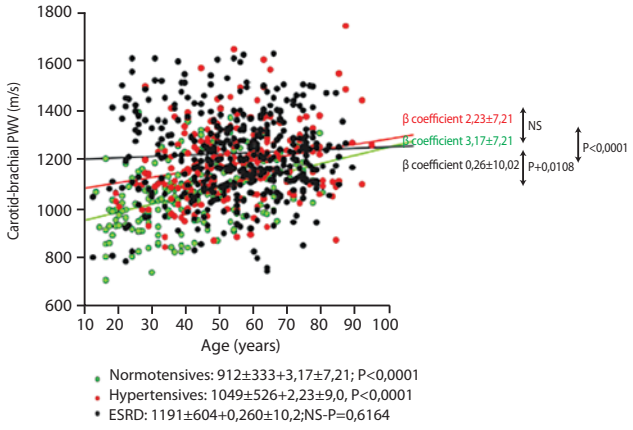


Figure 2. *Correlation between age and aortic pulse wave velocity in untreated hypertensive subjects, and patients treated for more than 36 months. The slope (b coefficient) is significantly steeper in untreated patients independently from blood pressure level.*

dicates that the slope of age-PWV correlation is significantly steeper in untreated hypertensives subjects than in those on long-term antihypertensive treatment. This could be interpreted as a slow-down of accelerated ageing under efficient antihypertensive treatment. The slope of the correlation (beta coefficient) between age and arterial stiffness indices is usually not increased as observed in other conditions such as advanced renal disease (Figure 3).

In conclusion, recent reports have drawn attention to the contribution of the arterial stiffness and stiffness gradient to the properties of systemic arte-





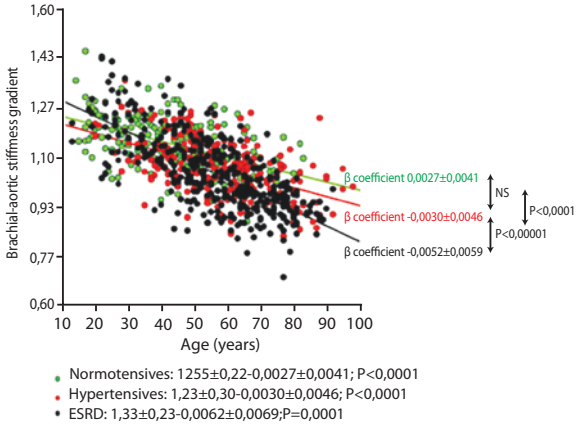


Figure 3. *The slope of the correlation (beta coefficient) between age and arterial stiffness indices is usually not increased as observed in other conditions such as advanced renal disease.*

rial wave propagation and reflections and macrovascular-microvascular interactions. A stable stiffness gradient exerts a protective effect against pulsatile microvascular pressure transmission. Stiffness gradient decreases with age, principally in relation age-related more pronounced stiffening of the aorta than peripheral vasculature. It seems that early and prolonged antihypertensive treatment could slow-down aortic early vascular aging, but firther controlled studies are needed.

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