REVIEW ARTICLE

Arterial Stiffness: Pathophysiological and Genetic Aspects

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Abstract

Cardiovascular diseases (CVD) are the main cause of mortality and it represents a significant percentage of hospitalizations. In the scenario of minimization of costs of the health system, methods that identify subclinical CVD would be important. Some guidelines include the measures of aortic stiffness and intima-media thickness of the carotid artery as methods to identify subclinical CVD in hypertensive patients. The pulse wave velocity (PWV) is the gold standard for the evaluation of arterial stiffness. In this review, we report the pathophysiology, the determinants of arterial stiffness, and justify its inclusion in the assessment of hypertensive patient due its direct association with cardiovascular risk, as show in the I Diretriz Brasileira de Prevenção Cardiovascular. In addition, we raised the main genetic studies of this phenotype, due to its complexity, can be modulated by dozens of genes. However, a better understanding of the relationship genetic-arterial stiffness and, even an intervention based on genotypes, should be achieved in future studies.

Introduction

Circulation, "Cardiovascular Health in Brazil - Trends and Perspectives", addressed an issue of aging and an increasing prevalence of obesity, hypertension and diabetes in the Brazilian population. Despite the 24% reduction in mortality rates for CVD, on the period from 2000 to 2011, since CVD is a major public health problem in the country, it is a leading cause of death and represents a significant percentage of expenditures on health with hospital admissions.[1]

The VII Brazilian Guideline of Hypertension includes the measurement of arterial stiffness and the intima-media thickness of the carotid artery as methods to assess the additional risk in the hypertensive patient. The PWV measurement constitutes the gold standard for the evaluation of arterial stiffness, due to the reproducibility and reliability of the method, as well as the demonstration of its association with cardiovascular risk in different populations.[2,3]

In this narrative review, we address the pathophysiology and determinants of arterial stiffness. Still, we raised the main genetic studies for this phenotype.

Keywords

Vascular stiffness; polymorphism; heritability; pathophysiology.

Aspects of arterial stiffness

Pathophysiology

Increased arterial stiffness is a complex phenomenon characterized by decreased complacency (distensibility) of the large arteries. The phenomenon occurs with aging[4] and in the presence of diseases associated with the cardiovascular system, such as: diabetes[5], atherosclerosis[6] and chronic kidney disease[7]. Clinically, increased arterial stiffness may be manifested by increased pulse pressure (PP) and isolated systolic hypertension.[8,9] Aortic stiffening results in elevated systolic blood pressure (SBP) and decreased diastolic blood pressure (DBP). Thus, arterial stiffness is associated with increased post-load of the left ventricle and decrease in mean coronary perfusion pressure[10], which occurs mainly in the diastole. These changes result in hypertrophy of the left ventricle[11], worsening of coronary ischemia[12] and increased stress in the vascular wall[13] which, in turn, may facilitate the rupture of atherosclerotic plaques.[14]

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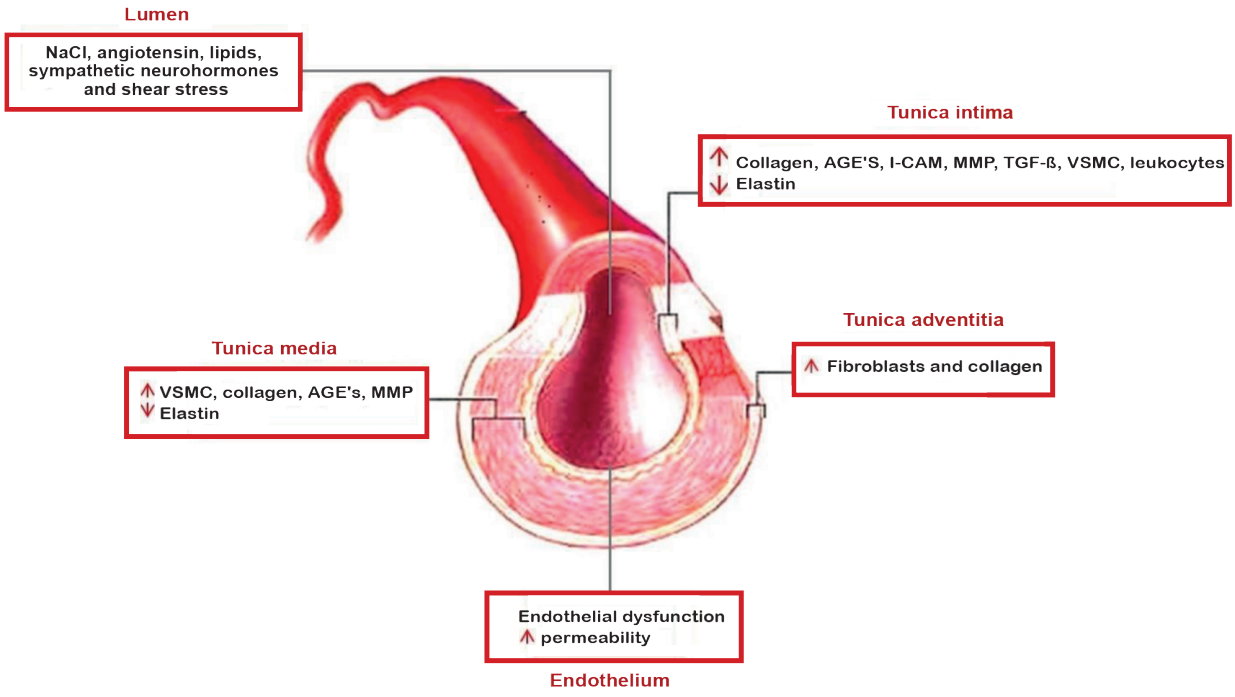

Figure 1 – *Diagram of the main effectors involved in the regulation of arterial stiffness.*
NaCl: sodium chloride; VSMC: vascular smooth muscle cell; AGE's: advanced glycation end product; MMP: matrix metalloproteinases; I-CAM: intercellular adhesion molecule; TGF-β: transforming growth factor-beta.

Arterial stiffening occurs through a complex interaction between dynamic and stable adaptations involving cellular elements and the extracellular matrix of the vascular wall. These changes are influenced by hemodynamic forces[15,16] and extrinsic factors, such as hormones[17] and inflammatory mediators[18], which may be related to sodium and glucose balance.[19] Arterial rigidity is modulated by means of a fine balance between production and degradation of elastin and collagen. The loss or disorganization of elastin and its replacement by collagen determines the increase in wall stiffness. Therefore, imbalance of this system, which may be caused by pro-inflammatory substances, alterations in the inhibition or activation of metalloproteinases and pressure overload may lead to collagen overproduction and/or reduction of elastin, thus contributing to a decrease in vascular distensibility,[20] as shown in Figure 1.

Evaluation of arterial stiffness and cardiometabolic phenotypes

The evaluation of arterial stiffness can be performed by invasive and non-invasive methods. In the clinic, non-invasive methods are increasingly applicable and three techniques can be used: assessment of distensibility (given by simultaneous measurement of intravascular volume and pressure),[21] arterial pulse waveform analysis (arterial tonometry),[22] and measurement of PWV. The latter, according to consensus, is the gold standard method for measuring arterial stiffness.[23]

The consolidation of the PWV measure in the evaluation of arterial stiffness led several studies to demonstrate the association of this phenotype with several pathological conditions. Blacher et al.[24], studying individuals with atherosclerosis, showed that PWV is associated not only with the presence but also with the extension of the atherosclerotic process. In another study, London et al.[25] showed higher PWV values in patients with chronic kidney disease compared to healthy controls. Toto-Moukouo et al.[26], evaluating the properties of large arteries of obese and non-obese individuals with essential hypertension, observed that PWV was higher in obese subjects. In addition, epidemiological studies have reported the role of arterial stiffness in predicting morbidity and mortality, independently of

other cardiovascular risk factors. Recently, Vlachopoulos et al.[27], in a meta-analysis with 17 studies, reported that elevated PWV (≥ 12 m / s) predicted a 102% increase in the risk of mortality from cardiovascular events. In addition, they showed that the 1 m/s increase in PWV corresponded to a 15% increase in cardiovascular risk. These data led to the inclusion of carotid-femoral PWV as part of the evaluation of cardiovascular risk in primary and secondary care.

Determinants of arterial stiffness

The main biological factor associated with increased arterial stiffness is the progression of age.[4] Hypertension,[28] diabetes,[5] dyslipidemia[29] and obesity[30] are pointed out as potential promoters of increased arterial stiffness. Some studies have argued that African ancestry would be associated with greater arterial stiffness.[31] Of all the above factors, age and high blood pressure are the most relevant.[32]

Data from the *Framingham Heart Study* show that, up to 50 years of age, the proportion of individuals with high PWV (≥ 12 m / s) is relatively low (only 5-10%). This proportion increases rapidly from this age, so that, in the age group over 70 years, the prevalence is greater than 60%.[33] In recent years, studies have shown that the increase in PWV with aging is not uniform throughout the aorta.[34,35] Hickson et al.[34] reported that much of the vascular stiffening occurs in the abdominal aorta and presents an increase rate of 0.9 m/s per decade. Recent studies have shown that increased arterial stiffness associated with aging is closely related to increased sympathetic nerve activity[36] and, consequently, exacerbation of the inflammatory process.[37] It is important to note that the chronic diseases most associated with increased PWV (diabetes, hypertension and obesity itself) have an underlying inflammatory component. Thus, the PWV measurement could represent the clinical sentinel monitoring the chronic inflammatory process in these conditions.

The association between arterial hypertension and increased arterial stiffness is well established. Increased pressure causes increased pulsatile stress in the vascular wall resulting in more rapid degradation of elastin fibers.[38] However, the cause/effect relationship between hypertension and elevated arterial stiffness has been much discussed in the last decade. Studies indicate that high blood stiffness in normotensive individuals is associated with the progression of blood pressure levels and an increased risk of hypertension,[39,40] suggesting that stiffness could also be a cause and not a consequence of pressure increase. The most probable is the existence of a biunivocal relationship between these two variables. Only long-term longitudinal studies can delimit the contribution of pressure increase to increase stiffness or, conversely, increase stiffness (which raises the afterload) by determining adaptive pressure rise response.

Increased arterial stiffness associated with diabetes has been widely reported in recent years.[41,42] Alvim et al.,[5] studying individuals from the Brazilian general population, showed that diabetics had higher PWV values compared to non-diabetics. The presence of diabetes represented a 127% greater risk for increased arterial stiffness when compared to the group of individuals without diabetes. Experimental studies have demonstrated that elevated glycemic levels may intensify the inflammatory process, increase advanced glycation products, and reduce NO bioavailability in vessels.[43,44] Despite the data presented, the association between diabetes and increased arterial stiffness has been contested. A systematic review, published in the journal Hypertension,[45] indicated that only 52% of the studies suggested an association between these variables.

The inadequate lipid profile is recognized as an important cardiovascular risk factor. In the last decades, numerous studies have demonstrated the relationship between LDL-c, HDL-c, triglycerides and total cholesterol concentrations and the progression of atherosclerotic disease.[46,47] Part of these results can be explained by the vascular dysfunction generated by the inflammatory process increase, increase of the oxidative process, and oxidation of the particles of LDL-c.[48,49] However, despite the strong correlation between atherosclerosis and vascular dysfunction, the results of the studies associating the lipid profile with arterial stiffness phenotypes are controversial.[50,51] Part of these contradictions can be justified, however, or by the differences between the populations investigated or by the different methods used in the determination of arterial stiffness.

The increased incidence of diabetes, metabolic syndrome and systemic arterial hypertension is strongly related to the obesity epidemic.[52] In addition, obesity is known to significantly increase CVD mortality.[53] Recently, it has been suggested that vascular dysfunction, Including increased arterial stiffness, may be the link between obesity and CVD.[54] Some studies have shown that adults[55,56] and obese children[57] have increased

arterial stiffness compared to their eutrophic pairs. However, inverse association,[58] or absence of association after adjustment for blood pressure[59] between PWV and visceral obesity were also reported in other studies, indicating the need for additional investigations to detect the causal link between these phenotypes.

The more robust studies show that age and blood pressure are the main determinants of arterial stiffness. However, it is possible that other variables, such as diabetes, dyslipidemias and obesity, are important actors in this complex scenario.

Treatment

Due to the proven impact of increased arterial stiffness on the risk of cardiovascular morbidity and mortality, one issue that arises is the possibility of treatment. Considering that the structural degeneration of the elastic components of the great arteries is little reversible with current pharmacological therapies,[60] it is extremely important to evaluate the impact of preventive interventions, that is, to reduce the impact of aging on increasing stiffness. The factors proposed so far include sodium restriction in diet,[61] regular physical exercise,[62] elimination of smoking[63] and reduction of alcohol consumption,[64] use of fish oils[65], and consumption of foods rich in isoflavonoids[66]. There are controversies about the contribution of drugs in reducing arterial stiffness. Some studies have identified positive results using antihypertensives[67,68] and hypolipidemic agents.[69,70] The effect of antihypertensives, however, is due to the reduction of blood pressure. Thus, pharmacological treatment for other diseases, associated with the measures mentioned above, which may attenuate the loss of elastic fibers in the arteries, may have an additional effect on the control of arterial stiffness.

Genetic aspects of arterial stiffness

Heritability of arterial stiffness

Several studies have shown the influence of genetic factors in the modulation of phenotypes related to arterial stiffness.[71,72] Concomitantly, numerous investigations with families have shown moderate heritability (21-66%) for traits associated with arterial stiffness.[73,74]

In a study of 1480 individuals belonging to 817 nuclei of the *Framingham Study Offspring Cohort*, Mitchell et al.[75] demonstrated that the heritability of PWV was 40%. In another study involving pairs of dizygotic and monozygotic twins living in Hungary and the United States, Tarnoki et al.[76] observed 51%, adjusted for age, gender and country of origin. A study of 930 individuals in the family of the *Erasmus Rucphen Family Study* (Sayed-Tabatabaei et al.[77]) found that the heritability of PWV was 26%, adjusted for several risk factors (gender, age, mean arterial pressure, LDL-c , heart rate, and fasting glycemia). Alvim et al.[78] studying 1675 individuals from a Brazilian population (*Baependi Heart Study*), observed a moderate heritability of PWV (26%), after adjusting for several confounding factors.

Thus, these studies indicate a significant variation in the heritability values of PWV. Much of this discrepancy could be explained by differences related to the study design (twins or family nuclei), population differences (ethnicity), and types of adjustments used in statistical analyzes.

Genetic markers and arterial stiffness

The number of genetic studies involving vascular phenotypes has grown exponentially in recent years. Investigations using genome scanning methods have pointed out that the arterial stiffness phenotype can be modulated by different chromosomal regions.[75,79] Despite the increasing investment in more sophisticated methods of genetic evaluation, the association studies with candidate genes remain the most abundant in literature. Considering the arterial stiffness phenotype, the most investigated polymorphisms come from systems that directly or indirectly interact in the vascular enhancer pathophysiology, such as the *renin-angiotensin-aldosterone system* (RAAS), proteins of the structure Vascular, effectors related to endothelial function and pro-inflammatory agents (Table 1).

RAAS, in addition to its important function in the regulation of blood pressure, is prominent in the vascular remodeling process. Therefore, it is evident that genetic variants capable of affecting the activity of its effectors (angiotensin, angiotensin-converting enzyme, angiotensinogen and renin) could significantly influence vascular pathophysiology. In this sense, several studies have observed an association between some polymorphisms in RAAS genes with arterial stiffness phenotypes. Benetos et al.,[80] studying healthy and hypertensive individuals, demonstrated that the presence of the I allele I/D polymorphism of *angiotensin-converting enzyme* (ACE) was associated with increased arterial stiffness in both groups.

Table 1 – Genetic variants associated with arterial stiffness

Gene	Polymorphism	Association with arterial stiffness phenotypes
Angiotensin converting enzyme (ECA), chromosome 17; Location 17q23.3	rs4340: I/D (Instron insertion 16)	Allele I: increase of PWV[73]
Angiotensinogen (AGT), chromosome 1: location 1q42-q43	rs699: c.704T>C (Exon 2, p.Met235Thr)	Allele T: reduction of carotid distensibility[74]
Endothelial nitric oxide synthase (eNOS), chromosome 7; Location 7q36	rs1799983: c.894G>T (exon 7, p.Glu298Asp)	Genotype GG: high central PP[76]
Endothelin β receptor (ETBR), chromosome 13; Location 12q22	rs5351: c.831A>G (exon 5, p.Leu277Leu)	Allele G: increase in PWV, only in women[77]
P22phox subunit of NADPH oxidase (p22phox or CYBA), chromosome 16; Location 16p2	rs4673: c.242C>T (exon 3, p.Tyr72His)	TT genotype: increased PWV, increased risk of increased arterial stiffness[79]
Thioredoxin interacting protein (TXNIP), chromosome 1; Location 1p13	rs7212: 1035C>G 3'UTR (Untranslated region)	Allele G: increase of PWV[78]
Tumor necrosis factor alpha (TNF-α), chromosome 6; Location 6p21.3	rs1800629: -308A>G (Promoter region)	Allele A: increased carotid stiffness index in patients with Kawasaki disease[81]
C-reactive protein (CRP), chromosome 1; Location 1q22-q25	rs1130864: 1444C>T 3'UTR (Untranslated region)	T allele: increased carotid stiffness index in patients with Kawasaki disease[81]
Vascular cell adhesion molecule (VCAM-1), chromosome 1; Location 1p32-p31	rs3176878: c.2079T>C (exon 9, p.Asp693Asp)	CC genotype: increase in PWV[82]
Metalloproteinase 9 from the matrix (MMP-9), chromosome 20; Location 20q11.2-q13.1	rs17576: c.855A>G (exon 6, p.Arg279Gln)	Allele G: increase in PWV[84]
Elastin (ELN), Chromosome 7; Location 7q11.23	3'UTR - / A (untranslated region)	Allele A: increase in PWV[83]

PWV: pulse wave velocity.

Bozec et al.,[81] studying hypertensive patients, demonstrated that the presence of the TT genotype of the p.Met235Thr polymorphism of *angiotensinogen* (AGT) was associated with lower compliance and greater carotid artery wall stiffness.

Endothelium, which also plays a key role in vascular physiology, mainly acts in the control of vascular tone and flow through the release of nitric oxide and other vasoactive peptides.[82] The importance of endothelial integrity and function in vascular function is proven. Evaluated the impact of genetic variants linked to endothelial physiology with arterial stiffness phenotypes. Mitchell et al.,[83] studying the *Framingham Heart Study* population, demonstrated that the GG genotype of the endothelial nitric oxide synthase (eNOS) enzyme p.Glu298Asp polymorphism was associated with high central PP, especially in women. However, the data were not reproduced, as expected, for VWP. Lajemi et al.,[84] studying untreated hypertensive patients, demonstrated the association of the G allele of the c-30G> A polymorphism of the endothelin β receptor (ETBR) with higher levels of PWV in women. In addition, two studies with the Brazilian general population observed associations of polymorphisms in the *p22phox* and TXNIP genes with PWV.[85,86] The first showed that individuals with TT genotype for *p22phox* c.242C>T polymorphism had a higher mean of PWV and greater risk for increased arterial stiffness compared to individuals with CC or CT genotypes.[86] The second one identified individuals with CG or GG genotypes for the TXNIP rs7212 polymorphism had a higher mean of PWV, compared to individuals with genotype CC.[85]

The remodeling of the vascular wall results from the interaction of several mechanisms, among them, the inflammatory process. Numerous studies have demonstrated the role of inflammatory agents

in endothelial dysfunction and atherosclerosis.[87] Thus, researchers investigated the possible impact of genetic polymorphisms on proinflammatory genes on arterial stiffness phenotypes. Cheung et al.,[88] studying patients with a history of Kawasaki disease, demonstrated the synergistic effect of the A-allele's 308 A> G polymorphism of *tumor necrosis factor alpha* (TNF-α) and the T allele of the 1444 C> T polymorphism Of the *C-reactive protein* (CRP) with the high arterial stiffness index in the carotid artery. Moreover, considering the pathophysiological role of adhesion molecules, Zhu et al.[89] demonstrated in young and healthy individuals the association of the CC genotype of the p.Asp693Asp polymorphism in the VCAM-1 gene (*vascular cell adhesion molecules*) with higher levels of PWV.

In addition to the endocrine, inflammatory and vasoactive endothelium-derived components, the structural components of the vessel wall are also protagonists in the vascular stiffening process, since imbalance in the synthesis of collagen and/or elastin contributes to the decrease of vascular distensibility.[20] Iwai et al.,[90] evaluating individuals from the Japanese population, demonstrated the association of allele A of the 3'-UTR *elastin polymorphism* (ELN) with higher values of PWV. The influence of polymorphisms on genes of some metalloproteinases was also investigated. Yasmin et al.,[91] studying healthy subjects, demonstrated the association of the G-allele of the c.855A> G *polymorphism of matrix metalloproteinase-9* (MMP-9) with increased values of PWV.

The above studies reinforce the hypothesis that genetic variants, located in different genes, contribute to the modulation of the arterial stiffness phenotype. Within this theme, larger studies that evaluate the use of genetic markers in the prevention, diagnosis, treatment and prognosis of the patient are still necessary.

Conclusion

Knowing the physiopathological aspects, as well as the determinants of arterial stiffness, it is plausible that PWV is included as one of the components in CVD prevention efforts, at least in hypertensive patients, as indicated in the VII Brazilian Hypertension Guideline and in the I Brazilian Guideline on Cardiovascular Prevention. The assessment of arterial stiffness can be done by the measurement of PWV or other previously validated methods. Genetic data indicate that dozens of genes can modulate this complex phenotype. However, a better understanding of the genetic-arterial rigidity relationship, and even a genotype-based intervention, should constitute goals to be achieved in future studies.

Author contributions

Conception and design of the research: Alvim RO, Santos PCJL. Acquisition of data: Alvim RO, Santos PCJL. Analysis and interpretation of the data: Alvim RO. Writing of the manuscript: Alvim RO, Santos PCJL, Mill JG, Pereira AC. Critical revision of the manuscript for intellectual content: Alvim RO, Bortolotto LA, Mill JG, Pereira AC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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