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Arterial Stiffness and Coronary Artery Disease

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Abstract

Atherosclerosis is a chronic inflammatory response involving lipid accumulation, smooth cell proliferation, cellular apoptosis, necrosis, fibrosis and local inflammation. It is a leading cause of death in adults. Arterial stiffness results from a degenerative process affecting the extracellular matrix of elastic arteries under the effect of age and cardiovascular risk factors (such as diabetes, hypertension, smoking and sedentary lifestyle). Cardiovascular risk factors are associated with both the atherosclerotic process and arterial stiffness; these conditions have an age-related progression and develop at similar sites of the arterial tree. Assessment of arterial stiffness has emerged as a key tissue biomarker for cardiovascular risk stratification and estimation of biological age. This review study aimed to describe the pathophysiology of arterial stiffness, indirect measurement methods and clinical implications for the management of atherosclerotic disease [1-4].

Keywords: Arterial stiffness; Coronary artery; Hypertension; Chronic inflammatory

Abbreviations: BP: Blood Pressure; CAD: Coronary Artery Disease; PWV: Pulse Wave Velocity; CAFE: Conduit Artery Functional Endpoint; ASCOT: Anglo-Scandinavian Cardiovascular Outcomes Trial; CCTA: Coronary Computed Tomography Angiography; CAVI: Cardio-Ankle Vascular Index; PWV: Pulse Wave Velocity; AIx: Augmentation Index; AP: Augmentation Pressure

Aortic Stiffness

Increased aortic stiffness is an established vascular condition that occurs through the normal biological evolution. Recent evidence shows it may be associated with atherosclerotic disease when arterial beds such as aortic arch and its branches are affected at an earlier stage [5].

The arterial network, primarily large vessels, is a compliant system that expands and contracts in response to pressure changes [6] to accommodate the blood during cardiac systole and keep the blood flow at the periphery during diastole [5].

In addition to aging, aortic stiffening may be accelerated in the presence of several conditions including systemic arterial hypertension, insulin resistance and diabetes mellitus, smoking, atherosclerosis and chronic kidney disease [7-11].

Reduced aortic compliance has also been associated with other factors such as genetic predisposition, inflammation and infection [12] (Figure 1). A decrease in arterial compliance plays a role in the dysfunction and exposure of endothelial and smooth muscle cells [13]. This is a complex process that causes the initial pathophysiological changes of vascular damage involving cellular and other extracellular matrix elements of the vascular wall [14].

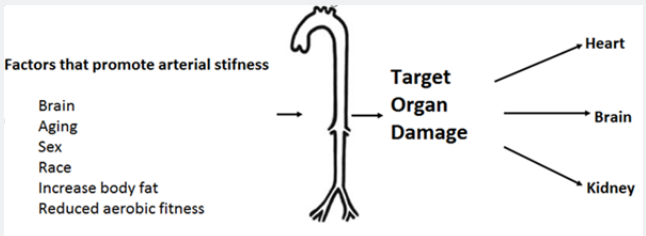

Figure 1: Epidemioogical contributors to arterial with potential implications for target organ damage. Adapted from Fleenor and Berrones [46].

Arterial stiffness is associated with increased collagen turnover and metalloproteinase activity [15-17] as well as a reduction in elastin with increased collagen deposition in the arterial wall that lead to middle layer thickening and formation of the atherosclerotic plaque [14].

Infection and inflammatory mechanisms are also involved with increasing circulating levels of phospholipase A2 [18], interleukin 1b [19] and *Chlamydia pneumoniae* [20]. Neurohormonal and inflammatory markers including renin-angiotensin-aldosterone system, C-reactive protein, platelet activation and apolipoprotein E deficiency [21,22] have also been implicated.

Pulse wave

When the normal heart contracts during systole, it generates a pulse wave that is transmitted along the arteries. This wave is reflected by each bifurcation or other irregularities that it encounters and is then reflected back to its starting point- the heart [23].

In a system with preserved compliance, this wave is reflected back to the heart during diastole resulting in a rise in coronary perfusion pressure and a decrease in systolic blood pressure (BP) [23]. When aortic stiffness is increased, the pulse wave propagates backward prematurely in the cardiac cycle during systole and consequently leads to increased post-load, prolonged ventricular ejection, reduced oxygen delivery to the tissues and increased metabolic ventricular demand [24-26].

Arterial stiffness and coronary artery disease

Arterial stiffness is a manifestation of the atherosclerotic process and usually precedes the formation of obstructive plaques. It is thus an early marker of coronary artery disease (CAD) (Figure 2). Assessment of the arteries using non-invasive measurements including pulse wave velocity (PWV) has allowed to identify patients at higher cardiovascular risk. The Conduit Artery Functional Endpoint (CAFE) sub study [27] of the Anglo-Scandinavian Cardiovascular Outcomes Trial (ASCOT) [28] reported that hypertensive patients with lower central BP (measured by radial artery applanation tonometry and PWV) showed fewer cardiovascular outcomes than those with apparently controlled BP in peripheral measurements but with high central BP levels.

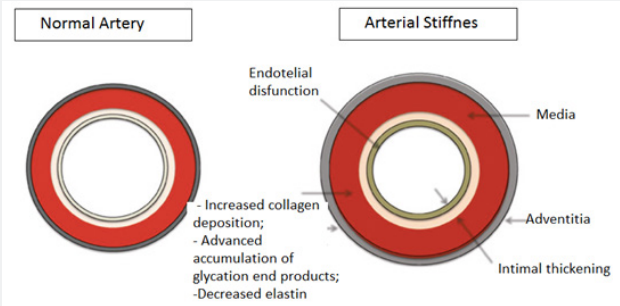

Figure 2: Multiple causes of arterial stiffness with aging and disease. Adapted from Fleenor and Berrones [46].

Other authors have investigated the correlation between CAD and aortic stiffness assessed by PWV and augmentation index (AIx). The Framingham Heart Study assessed PWV, pulse wave reflection (AIx, brachial pressure amplification) and central pulse pressure in 2,232 patients and correlated these measures with major cardiovascular outcomes including myocardial infarction, stroke, unstable angina and heart failure. The multivariate analysis showed that patients with higher PWV values had 48% higher risk of cardiovascular events regardless of other risk factors associated (p=0.002). The other aortic stiffness measurements assessed did not show to be as valuable [29].

A cohort study from China (2011) [30] evaluated 706 asymptomatic patients for the association between aortic stiffness measurements as assessed by ankle brachial PWV and coronary atherosclerosis as assessed by coronary computed tomography angiography (CCTA). The multivariate logistic regression analysis revealed that the cut-off PWV value at 14–18 m/s had an odds ratio (OR) of 3.16 for the association with coronary atherosclerosis (p<0.001).

Several other studies have demonstrated the association of different arterial stiffness measurements with CAD. Weber et al. [31] evaluated a cohort of 465 Austrian men with CAD undergoing coronary angiography and its correlation with aortic stiffness measurements (PWV, AIx and augmentation pressure). They found a positive associated between high AIx and CAD (OR 4.06) [27]. Byung-Hee Oh et al. [32] assessed the association of the cardio-ankle vascular index (CAVI) and the presence of calcification and coronary stenosis detected by CCTA. They reported an association between CAVI and >50% coronary stenosis (OR 2.8; p=0.032) [31].

To support the use of arterial stiffness measurements as markers for primary prevention in target populations, two studies examined these measurements in elderly patients and patients with type 2 diabetes mellitus (DM2). Gaszner et al. conducted a case-control study to assess PWV and AIx in two different groups of cardiovascular patients: DM2 and CHD. After stratification by gender and age, BP and heart rate, they found a significant association of CAD with PWV (p<0.01) and AIx (p<0.5). Interestingly, after they compared the results of patients with DM2 with healthy controls, only increased PWV values remained significant (p<0.05), which may suggest different outcomes depending on the methodology used to assess arterial stiffness [32]. Similarly, in a case-control study, Po-Chang Wang et al. [33] found a relationship of aortic stiffness with CAD and aging (elderly individuals over 65 years). They assessed brachial-ankle PWV measurements and found a significant relationship between PWV and the presence of CAD in elderly patients (OR 1.097; p=0.026) [34].

The use of arterial stiffness measurements as indicators for secondary prevention as an additional risk stratification approach has gained increasing ground in recent research. For more effective non-invasive risk stratification of patients with suspected or established CHD, several studies have investigated the correlation between aortic stiffness measures and severity of CAD.

Yoshikawa et al. [35] demonstrated a relationship between aortic stiffness and coronary reserve flow in patients with CAD. They found a significant correlation of increasing PWV measurements and number of damaged coronary vessels [35]. Xiong et al. [36] examined in a cohort of 321 patients with suspected CAD the relationship between brachial-ankle PWV and severity of CAD as assessed by the SYNTAX score and found a

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significant positive relationship with PWV and corrected measures by the SYNTAX score (OR 4.13; p<0.001) [36]. Moreover, Chung et al. [37] evaluated the relationship between aortic stiffness and the SYNTAX score. In their study, brachial-ankle PWV was a major predictor of CAD (OR 1.05) and correlated with the severity of CAD as assessed by the SYNTAX score [37].

To explore an association with severity of CAD, Duman et al. [38] assessed arterial stiffness by measuring carotid-femoral PWV and its relation with the extent of CAD (as assessed by Gensini scores). There was a significant positive relationship with the variables studied (p<0.001); and the PWV cut-off of 7.3 m/s showed a sensitivity of 83% and a specificity of 86% for CAD diagnosis [38].

Regarding patients with coronary stenosis undergoing angioplasty, Mahfouz et al. [39] reported a positive correlation between arterial stiffness measures and intra-stent restenosis within one year of follow-up after angioplasty [39]. In contrast, in a more recent retrospective observational study, Do-Sun Lim et al. did not find any correlation between aortic stiffness measures (aortic-ankle stiffness and AIx) and CAD among patients with prior angioplasty [40]. The (Table 1) summarizes the studies assessing arterial stiffness and CAD [41-46].

Table 1: Arterial stiffness and coronary artery disease.

Ss Author	Journal	Study Design	Method	Outcome
Weber et al. [32]	Circulation	Coorte	VOP, Alx e AP	Relationship with CAD
Sharma et al. [40]	Indian Heart Journal	Case-Control	Alx e AP	Relationship with CAD
Liu et al. [30]	Atherosclerosis and Thrombosis	Coorte	PWV ankle-brachial	Association with coronary stenosis
Xiong et al. [35]	Journal of Atherosclerosis and Thrombosis	Coorte	PWV ankle-brachial	Association with CAD severity
Park et al. [32]	Journal of Atherosclerosis and Thrombosis	Coorte	Ankle-brachial vascular index (CAVI)	Relationship with CAD
Lenkey et al. [33]	Physiological Research	Case-control	PWV e Alx	Relationship with CAD
Fukuda et al. [34]	Heart Journal	Coorte	PWV ankle-brachial	Association with CAD severity
Zhang et al. [41]	Chinese Medical Journal	Case-control	PWV	Relationship with CAD
Chung et al. [36]	The American Journal of Medical Science	Cross sectional	PWV ankle-brachial	Relationship with CAD and CAD severity
Chung et al. [42]	Clinical Interventions Aging	Cross sectional	PWV ankle-brachial	Association with CAD severity
Joo et al. [39]	BMC Cardiovascular Disorders	Cross sectional	PWV ankle brachial, Alx	Relationship with CAD
Mahfouz et al. [38]	Echocardiography	Coorte	strain, distensibility and aortic stifness	Relationship with CAD and re stenosis intra stent
Duman et al. [37]	Acta Cardiologica	Coorte	PWV	Relationship with CAD and disease severity
Watanabe et al. [43]	Clinical and experimental Hypertension	Coorte	Alx	Association with coronary calcification
Vlachopoulos et al. [44]	Atherosclerosis	Review		
Whelton et al. [45]	Hypertension	Review		

PWV: Pulse Wave Velocity; AIx: Augmentation Index; AP: Augmentation Pressure.

In conclusion, arterial stiffness can be understood as a pathophysiologic aging process of arteries that is strongly correlated with known major cardiovascular risk factors. Arterial stiffness measurements may have important clinical implications as evidence supports their usefulness for identifying patients at higher risk for major cardiovascular events. Recent studies have also pointed to a relationship of these measurements and established coronary disease, and it may thus help identifying patients with high risk of cardiovascular events or more extensive disease requiring more aggressive clinical management. Arterial stiffness assessments should be interpreted carefully in view of different measurement approaches and devices used in studies designed to validate their usefulness in research and clinical practice.

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