Role of Inflammation in the Pathogenesis of Arterial Stiffness

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Increased arterial stiffness is an independent predictor of cardiovascular disease independent from blood pressure. Recent studies have shed new light on the importance of inflammation on the pathogenesis of arterial stiffness. Arterial stiffness is associated with the increased activity of angiotensin II, which results in increased NADPH oxidase activity, reduced NO bioavailability and increased production of reactive oxygen species. Angiotensin II signaling activates matrix metalloproteinases (MMPs) which degrade TGFβ precursors to produce active TGFβ, which then results in increased arterial fibrosis. Angiotensin II signaling also activates cytokines, including monocyte chemoattractant protein-1, TNF-α, interleukin-1, interleukin-17 and interleukin-6. There is also ample clinical evidence that demonstrates the association of inflammation with increased arterial stiffness. Recent studies have shown that reductions in inflammation can reduce arterial stiffness. In patients with rheumatoid arthritis, increased aortic pulse wave velocity in patients was significantly reduced by anti-tumor necrosis factor-α therapy. Among the major classes of anti hypertensive drugs, drugs that block the activation of the RAS system may be more effective in reducing the progression of arterial stiffness. Thus, there is rationale for targeting specific inflammatory pathways involved in arterial stiffness in the development of future drugs. Understanding the role of inflammation in the pathogenesis of arterial stiffness is important to understanding the complex puzzle that is the pathophysiology of arterial stiffening and may be important for future development of novel treatments.

Key Words: Arterial stiffness, inflammation, angiotensin II

INTRODUCTION

Increase in arterial stiffness is a consequence of vascular fibrosis and elastic fiber degradation of the large arteries, with resulting in decreased in the arterial compliance. Increased arterial stiffness is the major underlying cause for the increase in systolic blood pressure that is associated with aging. The increase in systolic blood pressure is an important reason for the adverse prognosis associated with increased arterial stiffness. However, arterial stiffness has been demonstrated to be a predictor for increased risk for stroke, coronary artery disease and heart failure independent from blood pressure.1-6 Although increased arterial stiffness is highly correlated with the aging process, it acts in concert with extrinsic factors such as hypertension,
high sodium intake, diabetes, dyslipidemia, obesity, neurohormonal system activation interact with structural elements of the vasculature to accelerate this aging process.5,10 These factors result in endothelial dysfunction, vascular inflammation, vascular smooth muscle cell hyperplasia, increased collagen, and elastin degradation.7,11,12 Recent studies have shed new light on the importance of inflammation in the pathogenesis of arterial stiffness. This review will discuss the role of inflammation in the pathogenesis of arterial stiffness.

MECHANISMS OF ARTERIAL STIFFNESS: CHANGES IN THE STRUCTURAL, CELLULAR COMPONENTS

Arterial stiffness is characterized by thickening of the intima-media, accompanied by an increase in the central arterial lumen,13 endothelial dysfunction, vascular smooth muscle cell hyperplasia, increased collagen, and elastin degradation. The increased fragmentation of elastin molecules that is characteristic of arterial stiffness is mediated by activation of various types of matrix metalloproteinases (MMP) and serine proteinases.7,14 The activity of MMP is increased in intima media of aged aortic tissues and is accompanied by decreased activity of TIMP-2, an endogenous inhibitor of MMP. The relative imbalance between MMP/TIMP-2 activity is important in ECM remodeling and subsequent arterial stiffening.15,16 In addition to elastin degradation, the collagenolytic activity of MMP results in creation of uncoiled, stiffen collagen.7 Also, degradation of basement membrane ECM by activated MMPs and stimulation of chemotaxis may result in increased smooth muscle migration and proliferation in the intima.16,17

The increased MMP activity may be mediated by increased activity of the renin angiotensin system, oxidative stress, endothelial dysfunction, AGE stimulated activation of RAGE, and increased activity of proinflammatory cytokines or cell adhesion molecules.18-20

THE ROLE OF INFLAMMATION IN ARTERIAL STIFFNESS: THE BASIC MECHANISM

Arterial stiffness is associated with increased activity of angiotensin II, which results in increased NADPH oxidase activity, reduced NO bioavailability and increased production of reactive oxygen species.20-22 AngII signaling activates MMPs which degrade the TGFβ precursor to produce active TGFβ. AngII signaling also activates cytokines including monocyte chemoattractant protein-1 (MCP-1), TNF-α, Interleukin-1, Interleukin-17 and interleukin-6.20,23-26 Necropsy studies performed in aged human thoracic aorta demonstrated increased levels of angiotensin converting enzyme, angiotensin II, angiotensin receptor type 1 MMPs and MCP-1, compared to young aorta, suggesting the likelihood for the significant role of inflammation in the pathogenesis of arterial stiffening.20 The activation of the MCP-1/CCR2 pathway, which has been demonstrated to play a significant role in mediating arterial inflammation and remodeling, further stimulates arterial inflammation, increases expression of cell adhesion molecules, increases secretion of MMP, amplifies the activity of other cytokines and increases vascular smooth muscle cell migration.19,27-29 Inflammatory cytokines stimulate the local production of C-reactive protein (CRP) by vascular smooth muscle cells. CRP has an active role in promoting vascular inflammation and reducing endothelial function.20,32 Recent studies have demonstrated a significant association of high-sensitivity (hs) CRP and arterial stiffness.33-35 Although hsCRP is a surrogate marker of vascular inflammation, CRP itself may play an active role in mediating arterial stiffness. For example, CRP may have a direct role in inducing endothelial dysfunction. As a consequence, endothelial dysfunction may result in increased expression of proinflammatory cytokines and cell adhesion molecules. The increased vascular inflammation will increase vascular fibrosis, smooth muscle cell proliferation, and impair endothelial mediated vasodilation, which will subsequently lead to increase in arterial stiffness.32,36,37 Oxidative stress appears to play a role in the pathogenesis of arterial stiffness, as oxidative injury may result in increased vascular inflammation and increased cellular proliferation, which may subsequently lead to impaired arterial elasticity.38

CLINICAL EVIDENCE OF THE ASSOCIATION OF INFLAMMATION AND ARTERIAL STIFFNESS

hsCRP is an inflammatory biomarker that is widely used to determine the degree of low grade systemic inflammation. Numerous studies have demonstrated that hsCRP is an inde-
dependent predictor of adverse cardiovascular events. A study done in a normotensive population demonstrated that increase in systemic inflammation, as demonstrated by increase in hsCRP, is an independent predictor of future development of hypertension in normotensive population. The results demonstrate that systemic inflammation may have a role in the pathogenesis of vascular remodeling that leads to the development of hypertension. In individuals without any traditional cardiovascular risk factors, high cysteine level, which is a marker of increased extracellular oxidative stress, was associated with pulse wave velocity (PWV) and augmentation index, independent of age, gender, arterial pressure, height, weight, heart rate and CRP. A 20-year follow-up from the Caerphilly Prospective Study, a predominantly Caucasian cohort of 825 men who underwent baseline and follow-up PWV measurement, demonstrated that the only independent predictors of the PWV at follow-up was pulse pressure, CRP, glucose and waist circumference. Among the clinical variables, cumulative exposure to CRP was the variable with the strongest association, demonstrating the importance of chronic low grade inflammation in the progression of arterial stiffness.

Recent studies have shown that reduction of inflammation can reduce arterial stiffness. In patients with rheumatoid arthritis, increased aortic pulse wave velocity in patients was significantly reduced by anti tumor necrosis factor-α therapy. Drugs that block the activation of the RAS system may also effectively reduce progression of arterial stiffness. In one study, hypertensive males over 65 years of age received either angiotensin receptor blocker (Valsartan), ACE inhibitor (Tenocapril), L,N type calcium channel blocker (cilnidipine) or L type calcium channel blocker (nifedipine CR) for 3 months and were assessed for baseline and follow-up brachial ankle PWV (baPWV). Angiotensin receptor blockers yielded the largest reduction in baPWV followed by ACE inhibitors, whereas L type calcium channel blockers showed no significant improvement. A similar study in patients with essential hypertension randomized to either valsartan or nifedipine demonstrated the superiority of Valsartan in reducing PWV, despite a similar reduction in blood pressure. Thus, there is rationale for targeting specific inflammatory pathways involved in arterial stiffness in the development of future drugs.

CONCLUSION

The importance of inflammation in the pathogenesis of arterial stiffness has been amply demonstrated. Understanding the role of inflammation in the pathogenesis of arterial stiffness is important in understanding the complex puzzle that is the pathophysiology of arterial stiffening and is important for future development of novel treatments.

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