ASSOCIATION OF SYSTEMIC INFLAMMATION WITH ARTERIAL STIFFNESS IN HYPERTENSION

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Previous epidemiological studies have demonstrated that arterial stiffness is a significant predictor of an increased risk of stroke, ischemic heart disease, and heart failure, which can result in an increased risk of cardiovascular mortality \cite{1-3}. Arterial stiffening is associated with increased myocardial work and ischemia resulting in a subsequent increase in cardiovascular risk \cite{4}. Pulse wave velocity (PWV) measurements are useful for evaluating arterial stiffness and an independent predictor of mortality in patients with hypertension, diabetes, end-stage renal disease, and even in healthy individuals \cite{5-7}. Recent studies have shown the prognostic importance of identifying arterial stiffness in treated hypertensive patients \cite{8,9}. Although reduction of blood pressure can reduce arterial stiffness in hypertensive patients, there are other important factors involved in the development of arterial stiffness as well \cite{10}. Therefore, treatment of hypertension should not only focus on blood pressure but also on reducing stiffness in large elastic and small muscular arteries \cite{6,8,9}.

High-sensitivity C-reactive protein (hsCRP), a vascular inflammatory biomarker, reflects chronic low-grade vascular inflammation and is a well-known independent predictor of adverse cardiovascular events \cite{11}. In hypertension patients, hsCRP is indicative of atherosclerosis, and a better predictor than systolic blood pressure or pulse pressure \cite{12}. In addition, hsCRP has been reported to be associated with aortic PWV and brachial-to-ankle PWV in both the general population and untreated hypertensive patients \cite{13-15}. A study by Chae et al. demonstrated that in normotensive population, increase in hsCRP is associated with future development of hypertension, suggesting a role for systemic inflammation in the pathogenesis of hypertension \cite{11,13}. Currently, several mechanisms have been proposed to explain the role hsCRP plays in
arterial stiffness in hypertension. One such explanation may be that CRP is associated with endothelial dysfunction, increased cytokine expression, such as monocyte chemoattractant protein-1, and endothelial cell adhesion molecules [16,17]. Endothelial dysfunction and increased expression of pro-inflammatory cytokines may increase vascular inflammation, smooth muscle cell proliferation, impaired endothelial mediated vasodilation, and subsequently increase arterial stiffness [16-18]. Although several studies have demonstrated a significant association of hsCRP with arterial stiffness in hypertensive patients, this was performed in patients who were never treated. Therefore, it is unclear whether chronic vascular inflammation is the precursor to increased arterial stiffness or whether high blood pressure itself initiates inflammation and increased arterial stiffness [13]. Recently, we reported a result from a study in which we sought to determine whether there is a correlation between CRP and arterial stiffness in non-diabetic treated hypertensive patients, independent of cardiovascular risk factor [19]. This study consisted of 424 non-diabetic patients at least 45 years old who were being treated for hypertension. At the time of enrollment, the patients underwent a baseline laboratory assessment of C-reactive protein levels and PWV. The pulse wave velocity was determined by measuring hfPWV as a central stiffness index and baPWV as a central and peripheral stiffness index with a VP-1000 pulse wave unit (Nippon Colin Ltd, Komaki City, Japan) as validated previously [14,20-22].

Briefly, the subjects were categorized into the hsCRP tertiles. Group 1 was patients with 1st tertile of hsCRP level, group 2 was 2nd tertile of hsCRP level, and group 3 was 3rd tertile of hsCRP level. Group 1 consisted of 141 patients (mean age 58 ± 8 years), Group 2 had 142 patients (mean age 60 ± 9 years), and Group 3 had 141 patients (mean age 61 ± 8 years). There were no significant differences in the proportion of patients taking ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and diuretics among the three groups. The patients with higher hsCRP levels tended to be older and have a higher average triglyceride level and body mass index. Fasting blood sugar and serum insulin levels were not significantly different between groups. There were significant differences in the indexes of arterial stiffness between group 1 versus group 3 [hfPWV (p = 0.001) and baPWV (p < 0.001)] and group 2 versus group 3 [hfPWV (p = 0.012) and baPWV (p = 0.025)] (Figure 1).

The hfPWV and baPWV increased significantly along with CRP level. Group 1 had an hfPWV and baPWV of 965 ± 199, 1438 ± 246 cm/sec, respectively, group 2 was 975 ± 174, 1487 ± 258 cm/sec, and group 3 was 1043 ± 215, 1566 ± 252 cm/sec (p < 0.01). The hsCRP level was independently associated with arterial stiffness (hfPWV: R² = 0.273, p < 0.001, baPWV: R² = 0.284, p < 0.005) after controlling for age, body mass index, systolic blood pressure, heart rate, gender, HDL-cholesterol, triglyceride, and glucose levels.

From this study, we demonstrated a significant association of hsCRP with baPWV and hfPWV in treated hypertension patients, after adjustment for confounding factors. Although
administration of antihypertensives are known to decrease PWV and serum CRP [23,24], our study demonstrates that even in patients with relatively well-controlled hypertension, hsCRP is significantly associated with arterial stiffness. These data suggest that chronic, systemic inflammation is an important arterial stiffness determinant in treated hypertension patients. Although reduction of blood pressure with antihypertensive medications results in significant reduction in cardiovascular events, the event reduction in most clinical trials is 20-50%. What can we do about the other 50-80% of cardiac events that occur despite intensive blood pressure reduction? There may be numerous variables that account for the significant cardiovascular events that occur in treated hypertensive patients such as associated cardiovascular risk factors (diabetes mellitus, hyperlipidemia, and smoking). These and other risk factors of cardiovascular disease are known to be associated with increased arterial stiffness and may act in concert to increase vascular inflammation and arterial stiffness. Because increasing arterial stiffness is an independent risk factor for adverse cardiovascular events in hypertensives, efforts to decrease systemic inflammation through modification of risk factors and medications may be needed to reduce arterial stiffness and subsequent reduction of cardiovascular events in hypertensive patients. Weight reduction, sodium restriction, aerobic exercise programs, smoking cessation, and medications such as ACE inhibitors, angiotensin receptor blockers, statins, PPAR gamma agonists are known to reduce systemic inflammation and arterial stiffness. The association of inflammation with arterial stiffness may be an important piece in the complex puzzle of hypertension that will help us in understanding the pathophysiology and treatment of hypertension in the future.

References


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Figure 1. hfPWV and baPWV measurements by hsCRP level in treated hypertension patients. hfPWV, heart to femoral pulse wave velocity; baPWV, brachial to ankle pulse wave velocity; hsCRP, high sensitivity C-reactive protein; Group 1, 1st tertile of CRP level; Group 2, 2nd tertile of CRP level, Group 3, 3rd tertile of CRP level.