Blood Pressure and Inflammation in Apparently Healthy Men

Claudia U. Chae, Richard T. Lee, Nader Rifai, Paul M. Ridker

Abstract—Inflammation plays an important role in the development of atherosclerosis, but the specific stimuli governing cytokine release in atherogenesis are unknown. We examined the hypothesis that hypertension may increase the risk of atherosclerosis via proinflammatory effects. In a cross-sectional study involving 508 apparently healthy men, we studied the association between blood pressure and baseline plasma concentrations of 2 inflammatory markers, intercellular adhesion molecule-1 (sICAM-1) and interleukin-6 (IL-6). Increase in systolic blood pressure (SBP) (P=0.003), pulse pressure (PP) (P=0.019), and mean arterial pressure (P=0.014) was significantly associated with levels of sICAM-1. All of these measures of blood pressure, as well as diastolic blood pressure (DBP), were significantly associated with levels of IL-6 (all, P≤0.001). In multiple linear regression models controlled for age and other cardiac risk factors, SBP (7.6 ng/mL per 10 mm Hg, P=0.016) and PP (8.13 ng/mL per 10 mm Hg, P=0.038) were significantly associated with sICAM-1 levels, whereas SBP (0.11 pg/mL per 10 mm Hg, P<0.001), DBP (0.11 pg/mL per 10 mm Hg, P=0.008), PP (0.10 pg/mL per 10 mm Hg, P=0.009), and mean arterial pressure (0.15 pg/mL per 10 mm Hg, P<0.001) had similar strong relationships with log-transformed IL-6 levels. Therefore, in apparently healthy men, we observed significant graded relationships between blood pressure and levels of sICAM-1 as well as IL-6. These data suggest that increased blood pressure may be a stimulus for inflammation and that this is a possible mechanism underlying the well-established role of hypertension as a risk factor for atherosclerotic disease. (Hypertension. 2001;38:399-403.)

Key Words: blood pressure ◦ cell adhesion molecules ◦ inflammation ◦ interleukins ◦ risk factors

Hypertension is a well-known risk factor for cardiovascular disease, but the pathologic and molecular mechanisms by which elevated blood pressure leads to vascular disease are uncertain. There is some experimental evidence, however, to suggest that hypertension may promote endothelial expression of cytokines1,2 and stimulate inflammation.3,4 These data are particularly intriguing given the growing evidence that inflammation plays a critical role in the pathogenesis of atherosclerosis.5 Elevated levels of interleukin-6 (IL-6),6,7 a primary stimulant of the acute phase response, and of intercellular adhesion molecule-1 (sICAM-1),7,8 which mediates the attachment and migration of leukocytes across the endothelial surface, are associated with future risk of myocardial infarction (MI) and cardiovascular death. The specific stimuli that promote cytokine release in atherogenesis, however, have not been fully elucidated.

To explore the hypothesis that hypertension may increase the risk of atherosclerosis via proinflammatory effects, we conducted a cross-sectional study examining the relationship between blood pressure and levels of sICAM-1 and IL-6 in apparently healthy men.

Methods
Study participants were apparently healthy middle-aged men enrolled in the Physicians’ Health Study (PHS),9 a randomized, double-blind, placebo-controlled, 2×2 factorial-design trial of aspirin and beta-carotene in the primary prevention of cardiovascular disease and cancer. All participants were free of prior MI, stroke, transient ischemic attack, and cancer at study entry. Before enrollment, blood collection kits were sent to each participant. Blood was drawn into tubes containing EDTA, which were then centrifuged and returned (accompanied by a cold pack) by overnight courier. Plasma specimens were divided into aliquots and stored at −80°C. Of the 22 071 men enrolled in the PHS, 14 916 (67.6%) provided baseline blood samples. Participants also reported baseline age, height, weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP), current drug treatment for hypertension, smoking status, history of hypercholesterolemia, diabetes, parental history of MI before age 60, frequency of vigorous physical activity, and alcohol use.

In 2 prior nested case-control analyses from this cohort, we have demonstrated that baseline levels of sICAM-1 and IL-6 predict risk of MI. The cases were selected from the PHS participants with baseline plasma samples who had a confirmed MI during follow-up, and they were matched with 1 control. Controls had baseline plasma samples, had no reported vascular disease during follow-up, and were randomly selected from the PHS participants who met the matching criteria of age (+/− 1 year), length of study follow-up

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(6-month intervals), and smoking status (never, past, current). Stored plasma was thawed and assayed for sICAM-1 and IL-6 in 508 of these participants by commercially available ELISAs (R&D Systems), with methods described elsewhere.

One-way ANOVA was used to examine differences in sICAM-1 and IL-6 levels between categories of SBP (<120, 120 to 129, 130 to 139, and ≥140 mm Hg), DBP (<80, 80 to 89, and ≥90 mm Hg), and mean arterial pressure (MAP) (<90, ≥90 to 95, ≥95 to 100, and ≥100 mm Hg), and between tertiles of pulse pressure (PP) (<45, 45 to 50, and ≥50 mm Hg). MAP was calculated as (SBP + 2DBP)/3. PP was calculated as SBP – DBP. Crude linear regression models were performed to evaluate the relationship between SBP, DBP, MAP, PP and sICAM-1 and IL-6 levels after adjusting for age and case-control status. IL-6 has a skewed distribution and therefore was log-normalized for these analyses. These models were then repeated with additional control for history of diabetes, high cholesterol, alcohol use (rare/never, monthly, weekly, daily), parental history of MI, aspirin use, smoking status (current, past, never), vigorous physical activity (less than or at least once per week), and body mass index (kg/m²). Finally, the models were repeated with additional control for use of antihypertensive medications. Forward-selection multiple-regression analyses were used to identify those variables with the greatest influence on levels of sICAM-1 and IL-6. All probability values were 2-tailed.

**Results**

The study population was middle-aged (mean age ± SD, 59.2 ± 8.9 years), with mean SBP and DBP of 128.0 ± 12.6 and 80.0 ± 7.71 mm Hg, respectively. There was a relatively low prevalence at baseline of cardiac risk factors such as history of diabetes (3.6%), high cholesterol (13.4%), or parental history of MI before age 60 (13.5%). Current smokers, past smokers, and those who had never smoked comprised 14.8%, 40.9%, and 44.3% of the population, respectively. Over two-thirds (69.3%) reported vigorous exertion at least once per week. The majority used alcohol weekly (46.5%) or daily (24.2%). Mean body mass index was 25.30 ± 3.18 kg/m².

As shown in Figure 1, increasing levels of SBP (P < 0.01), PP (P < 0.01), and MAP (P < 0.05) were significantly associated with increased levels of sICAM-1. DBP, however, was not (P > 0.10). All blood pressure parameters were significantly associated with increasing levels of IL-6 (all, P < 0.001) (Figure 2).

In multiple linear regression models controlling for age, case-control status, and other cardiac risk factors, SBP was independently associated with increased levels of sICAM-1 and IL-6 (Table). After multivariate adjustment, for every 10-mm Hg increment in SBP, sICAM-1 levels increased by 7.55 ng/mL (95% confidence interval [CI], 1.44 to 13.66, P = 0.016), and log-transformed IL-6 levels increased by 0.11 pg/mL (95% CI, 0.06 to 0.17, P < 0.001). PP (8.13 ng/mL per 10-mm Hg increment, 95% CI 0.49 to 15.77, P = 0.038) also predicted sICAM-1 levels after multivariate adjustment. DBP
did not have a statistically significant association with levels of sICAM-1 (multivariate adjusted \( P = 0.27 \)) but was an independent predictor of IL-6 levels, with each 10-mm Hg increment in DBP associated with an increase in log-IL-6 levels of 0.11 pg/mL (95% CI, 0.03–0.19, \( P = 0.008 \)). PP (0.10 pg/mL per 10 mm Hg, 95% CI 0.03 to 0.17, \( P = 0.009 \)) and MAP (0.15 pg/mL per 10 mm Hg, 95% CI 0.07 to 0.23, \( P < 0.001 \)) had similar strong relationships with log-transformed IL-6 levels. Additional control for use of antihypertensive medications somewhat attenuated the relationship between sICAM-1 and SBP (\( P = 0.049 \)) and PP (\( P = 0.086 \)), but had no substantive impact on the association between blood pressure and IL-6 levels.

In forward-selection multiple regression models, SBP (\( F = 10.50, P = 0.001 \)) was outweighed only by current smoking (\( F = 15.94, P < 0.001 \)) as a determinant of sICAM-1 levels. Log-transformed IL-6 levels were determined most strongly by SBP (\( F = 33.98, P < 0.001 \)).

**Discussion**

In these data in apparently healthy men, we observed significant linear relationships between all blood pressure measures and ICAM-1 and IL-6 levels.
and levels of the inflammatory markers sICAM-1 and IL-6, with the exception of DBP and sICAM-1. After controlling for other traditional cardiac risk factors, SBP and PP were significantly associated with levels of sICAM-1, and all blood pressure measures remained strong independent predictors of IL-6 levels. Both sICAM-1 and IL-6, in turn, have been shown to predict future risk of MI and cardiovascular death in the same cohort.6,8 These data suggest that increased blood pressure may be a stimulus for inflammation and that this may be a possible mechanism underlying the well-established role of hypertension as a risk factor for atherosclerotic disease. To the best of our knowledge, this is the first large study to address the possible relationship between hypertension and cytokine levels.

Several plausible mechanisms may explain the relationship between blood pressure and inflammation. Increased blood pressure may promote atherogenesis by modulation of the biomechanical stimuli from pulsatile blood flow, such as increased hydrostatic pressure or cyclic strain, which in turn affects endothelial cell gene expression and function.10 Cyclic strain has been shown to increase sICAM-1 expression in a time- and strain-dependent manner, resulting in greater monocyte adhesion to endothelial cells.11 Increased cyclic stretch also upregulates mRNA expression and secretion of monocyte chemotactic protein-1 (MCP-1) in a dose-dependent fashion;12,13 MCP-1 plays a key role in monocyte recruitment and inflammation in atherosclerosis.14 These data suggest mechanisms by which the increase in pulsatile load and cyclic wall stress imposed on the vasculature in hypertension may contribute to atherogenesis. Correspondingly, in our data, we found a dose-response relationship between PP and sICAM-1 levels, which was significantly stronger than that between DBP and sICAM-1.

In vitro1 and in vivo2 studies have also demonstrated increased sICAM-1 expression and greater monocyte adhesion in spontaneously hypertensive rats compared with normotensive rats, further suggesting that chronic hypertension may result in enhanced endothelial responsiveness to factors promoting monocyte adhesion, and perhaps subsequent atherosclerosis. Others, however, found no upregulation of sICAM-1 in spontaneously hypertensive rats compared with wild-type rats in vivo.15 Few prior studies in humans have addressed the possible relationship between hypertension and endothelial cell adhesiveness. In a study of 11 hypertensive men and 10 controls, men with hypertension had significantly higher sICAM-1 levels; SBP (r = 0.25) and age were the primary determinants of sICAM-1 levels.16 As in our study, SBP was more strongly associated than DBP with sICAM-1 levels.

We also found that increased blood pressure was independently associated with levels of IL-6. The presence of elevated circulating levels of cytokines such as IL-6 many years before a first MI6,7 suggests a possible role in early lesion development. Stimulation of human vascular smooth muscle cells by angiotensin (Ang) II, a key regulator of blood pressure, results in inflammatory activation with dose-dependent increases in expression and release of IL-6.3,4 IL-6 also promotes vascular smooth muscle cell proliferation, a hallmark of the early stages of hypertension and of atherosclerosis.17 These mechanisms may in part explain the association we observed between increasing blood pressure and IL-6 levels, which have been demonstrated to predict risk of MI in the same cohort.6

Other mechanisms involving Ang II may also help explain the link between increased blood pressure, inflammation, and atherogenesis suggested by our data. Hypertension may also have a proinflammatory effect on the arterial wall because of increased oxidative stress.18 In animal models of Ang II–induced hypertension, direct generation of superoxide anions in the vasculature was observed,19 as well as a marked inflammatory response with aortic infiltration by monocytes and macrophages.20 Ang II may play other key roles via blood pressure–dependent and –independent mechanisms. In addition to its effects on IL-6 expression,3,4 Ang II also stimulates increased sICAM-1 expression and vascular infiltration by monocytes and macrophages, which is reversible by ACE inhibitors and Ang type 1 receptor blockade.21 It is possible that the antiatherosclerotic effect of ACE inhibitors in patients with cardiac risk factors or coronary artery disease22 may in part be due to anti-inflammatory effects mediated by Ang II suppression.3

Limitations of our study include its cross-sectional design, which limits our ability to infer a causal relationship between increased blood pressure and elevated levels of sICAM-1 and IL-6. In addition, although we controlled for other major cardiac risk factors, including potential confounders such as diabetes, hypercholesterolemia, body mass index, and smoking, the existence of unrecognized confounding variables is always possible. Our analyses are based on single measurements of blood pressure and of inflammatory markers, which may not reflect these relationships over time. Our assays were performed on plasma samples that had been stored at −80°C for up to 12 years, raising the possibility of protein degradation over time. However, the distributions of sICAM-1 and IL-6 were similar to those reported in studies using fresh plasma.6,8 Blood pressures were self-reported, increasing the possibility of measurement error and of imprecision in the reported values. In validation studies of physicians’ self-reported blood pressure, however, measured SBP (r = 0.72, P < 0.0001) and DBP (r = 0.60, P = 0.0001) were strongly correlated with self-reported values.23

Our findings may have important clinical implications. Despite the unequivocal increase in risk of cardiovascular disease conferred by hypertension, the precise underlying mechanisms remain unknown. Our data suggest that increased blood pressure may contribute to atherogenesis by promoting inflammatory activation of the arterial wall. Recent cross-sectional data from the Framingham Offspring Study24 suggest that hypertension may also be associated with impaired fibrinolysis, with linear increases in plasminogen activator inhibitor-1 and tissue plasminogen activator antigen levels seen with increasing SBP and DBP. The observed linear relationships between blood pressure and atherogenic factors such as cytokine levels and thrombotic factors are in concordance with the increased risk of cardiovascular events seen even in those with “high normal” blood pressure.25 These data add to our growing understanding of a continuum of cardiovascular risk as blood pressure rises, which is not
confined only to those with overt hypertension. Whether targeting the potential inflammatory sequelae of elevated blood pressure for treatment will confer additional benefits in reducing cardiovascular risk, in addition to that seen with blood pressure reduction with current antihypertensive treatment, requires further study. In conclusion, we found that increased blood pressure was significantly associated with elevated levels of circulating sICAM-1 and IL-6 in apparently healthy men. These findings support a possible role of hypertension as a proinflammatory stimulus contributing to atherogenesis and increased risk of future cardiovascular events.

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