Journal of the American College of Cardiology
© 2005 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 46, No. 10, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.07.050

The Relationship Between Blood Pressure and C-Reactive Protein in the Multi-Ethnic Study of Atherosclerosis (MESA)

Susan G. Lakoski, MD, MS,* Mary Cushman, MD, MSc,‡ Walter Palmas, MD, MS,§
Roger Blumenthal, MD, FACC,‖ Ralph B. D'Agostino, Jr, PhD,†
David M. Herrington, MD, MHS, FACC*

Winston-Salem, North Carolina; Burlington, Vermont; New York, New York; and Baltimore, Maryland

OBJECTIVES The goal of this study was to determine the relationship between resting blood pressure (BP) and C-reactive protein (CRP) in a multi-ethnic cohort of men and women from the Multi-Ethnic Study of Atherosclerosis (MESA).

BACKGROUND Several investigators have observed elevated levels of CRP in individuals with hypertension. Hypertension prevalence varies considerably across ethnic groups. Important questions remain regarding whether the relationship between hypertension and CRP is similar across ethnic and gender subgroups.

METHODS The MESA participants had CRP levels determined at the baseline clinical examination (N = 6,814). Hypertension, treated as a dichotomous variable (yes/no), was defined as a systolic or diastolic BP ≥140/90 mm Hg or a self-reported history of hypertension and use of antihypertensive medications.

RESULTS The geometric mean CRP in hypertensive participants was 2.3 ± 0.07 mg/l compared with 1.6 ± 0.07 mg/l among normotensive participants ($p < 0.0001$). The relative difference in CRP levels in hypertensives compared with normotensives was similar regardless of gender (13% in men and 13% in women). Ethnic comparisons showed that Chinese participants had the lowest CRP concentration but the largest difference in CRP by hypertension status (24%). Caucasians and African Americans had 10% to 15% higher CRP levels with hypertension, whereas Hispanics had no significant difference in CRP by hypertension status.

CONCLUSIONS This study confirms the existence of an independent association between hypertension and inflammation in both men and women. Ethnic group differences were evident, with the strongest association observed in Chinese participants and no difference in CRP levels by hypertension status in Hispanics. (J Am Coll Cardiol 2005;46:1869–74) © 2005 by the American College of Cardiology Foundation

Hypertension is an important modifiable risk factor contributing to an increased risk of myocardial infarction (MI) worldwide (1). Despite the longstanding recognition of an association between hypertension and MI, the precise mechanisms that account for this relationship remain unclear. Multiple substudies of large clinical trials have found that higher C-reactive protein (CRP) concentrations are associated with worse outcomes in patients with unstable coronary disease (2–4). Recently, several investigators have observed higher CRP concentrations in individuals with hypertension (5–7). This raises the possibility that higher CRP, or subclinical inflammation as indicated by CRP, may be one of the causal mechanisms contributing to an increased risk for MI in hypertensive patients.

Although there have been several large studies looking at the association between hypertension and CRP, most participants have been Caucasian, potentially limiting the generalizability of results (5,6,8). Hypertension varies considerably across ethnic groups, with the highest rates among African-American women (9). In addition, CRP levels differ by ethnicity (10,11). It is not known whether the relationship between CRP and hypertension is present across multiple ethnic groups. A consistent pattern across ethnicity would provide additional evidence that the observed association reflects a fundamental feature of human biology and is not simply attributable to confounding by unmeasured factors that are common in Caucasian individuals.

In the present study, our primary goal was to determine whether there was an association between hypertension and CRP among a multi-ethnic group of men and women ages 45 to 84 years old enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). A secondary goal was to ascertain whether gender and ethnicity modify the relationship between hypertension and CRP.

METHODS

The MESA study was initiated in July 2000 to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease in individuals without known cardio-

From the Departments of *Internal Medicine/Cardiology and †Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina; ‡Departments of Medicine and Pathology, University of Vermont, Burlington, Vermont; §Department of Medicine, Columbia University, New York, New York; and the ‖Ciccarone Preventive Cardiology Center, Johns Hopkins University School of Medicine, Baltimore, Maryland. Supported by National Heart, Lung, and Blood Institute (NHLBI) contracts N01-HC-95159 through N01-HC-95166 and NHLBI research training grant 1 T32 HL076132-01.

Manuscript received May 6, 2005; revised manuscript received July 11, 2005, accepted July 18, 2005.

JACC Vol. 46, No. 10, 2005
November 15, 2005:1869–74

Abbreviations and Acronyms

BP = blood pressure
CRP = C-reactive protein
HTN = hypertension
JNC 7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
MESA = Multi-Ethnic Study of Atherosclerosis
MI = myocardial infarction

vascular disease (12). The cohort consisted of 6,814 men and women ages 45 to 84 years old recruited in six U.S. communities. There are 47% men with an ethnic representation of 38% white, 28% African-American, 22% Hispanic, and 12% Asian (of Chinese descent) individuals.

History, measurements, and laboratory data for the present analysis were taken from the first examination of the MESA cohort beginning in July 2000. Information about age, gender, ethnicity, medical history, and alcohol consumption was obtained by questionnaires. A history of hypertension and the use of blood pressure (BP) medications for hypertension were obtained from medical history. Resting BP was taken three times in the seated position after a five-minute rest using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida) (13) with the average of the last two measurements recorded and verified. Diabetes was defined as normal, impaired fasting glucose, or diabetes based on 1997 American Diabetes Association guidelines (14). Smoking was defined as never, current, or former. Body mass index was derived from the equation weight (kg)/height (m^2). Physical activity was defined as total of all light, moderate, and vigorous activities (min/week) multiplied by individual metabolic equivalent values. The CRP was measured using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, Illinois) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, Vermont). Analytical intra-assay coefficient of variations ranged from 2.3% to 4.4%, and inter-assay coefficient of variation ranged from 2.1% to 5.7%.

Statistical analysis. Hypertension, treated as a dichotomous variable (yes/no), was defined as a systolic or diastolic BP ≥140/90 mm Hg or a self-reported history of hypertension and current use of antihypertensive medications. In secondary analyses, systolic BP, diastolic BP, and pulse pressure were modeled as continuous variables. In addition, categories of BP defined by Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines (<120/<80 mm Hg, 120 to 139/80 to 89 mm Hg, ≥140/90 mm Hg) (15) were also used when analyzing the relationship between BP and CRP. The CRP as a continuous variable was log-transformed to more closely reflect a normal distribution for the statistical analysis. The geometric mean of CRP and its geometric mean standard error were used for tabular and graphical presentation. The standard error of CRP values was estimated for the back-transformed data using a delta method approximation.

Differences in baseline characteristics by hypertension status were determined by chi-square and *t* tests. Linear regression modeling was used to determine the relationship between the outcome variable, CRP, and hypertension (HTN) in univariable and multivariable models and after stratifying by gender and ethnicity. The multivariable analysis included the following covariates: age, ethnicity, gender, clinic site, body mass index, low-density lipoprotein and high-density lipoprotein cholesterol, diabetes, smoking, alcohol consumption, use of HMG-CoA reductase inhibitors, estrogen therapy, and aspirin. Similar linear models were used to determine the relationship between CRP and systolic BP, diastolic BP, or categories of BP by JNC 7 criteria after adjustment for the same covariates. For these models, participants on BP medications were excluded. The interaction terms, gender × HTN and ethnicity × HTN were tested separately in the full model. Logistic regression modeling was used to determine the relative odds of hypertension by category of CRP (<1 mg/l, 1 to 3 mg/l, >3 mg/l) after stratifying by ethnicity in both an unadjusted and an adjusted analysis. The Zhang-Yu method was used to estimate the relative risk of hypertension from the calculated odds ratio given the outcome, hypertension, was common (16). Statistical analyses were performed using SAS 9.0 software (SAS Institute Inc., Cary, North Carolina).

RESULTS

The cohort consisted of 6,814 individuals with an average age of 63 years. Table 1 shows differences in baseline characteristics stratified by the presence of hypertension. Participants with hypertension were different from normotensive individuals in every category listed in Table 1 except for levels of high-density lipoprotein cholesterol. Adjustments in the statistical models were made to account for these differences.

The geometric mean of CRP in hypertensive individuals was 2.3 ± 0.07 mg/l, compared with 1.6 ± 0.07 mg/l among normotensive individuals ($p < 0.0001$). After adjustment for potential confounders, this difference remained statistically significant (2.5 ± 0.1 mg/l vs. 2.2 ± 0.1 mg/l, $p < 0.0001$). In 4,225 participants not taking BP medications, systolic BP and pulse pressure, but not diastolic pressure, were associated with CRP in univariable ($p = 0.0001$, 0.0001, and 0.5, respectively) and multivariable models ($p = 0.003$, 0.002, and 0.2, respectively). When treating CRP as a categorical variable, mean systolic BP was 2 mm Hg higher in those with CRP values >3 mg/l compared with <1 mg/l (124.2 ± 0.8 mm Hg vs. 121.7 ± 0.8 mm Hg, $p < 0.0001$) after multivariable adjustment. When resting BP was categorized by JNC 7 criteria, individuals with BPs of