Hypertension

Effects of Normal Blood Pressure, Prehypertension, and Hypertension on Coronary Microvascular Function

Dogan Erdogan, MD; Ibrahim Yildirim, MD; Ozgur Ciftci, MD; Ismail Ozer, MD; Mustafa Caliskan, MD; Hakan Gullu, MD; Haldun Muderrisoglu, MD, FESC

Background—The assessment of coronary flow reserve (CFR) by transthoracic Doppler echocardiography has recently been introduced into clinical practice, and reduced CFR has been suggested to be a sensitive indicator of hypertensive end-organ damage; however, to date, this methodology has not been used to evaluate CFR in subjects with prehypertension. Accordingly, the present study was designed to evaluate CFR in subjects with prehypertension.

Methods and Results—We measured CFR of 40 subjects with prehypertension, 60 patients with hypertension, and 50 normotensive healthy volunteers using transthoracic Doppler echocardiography. None of the subjects had any systemic disease. Age, gender, body mass index, heart rate, lipid profiles, fasting glucose levels, and hemoglobin were similar among the 3 groups. CFR was significantly lower in the hypertension group than in the prehypertension and control groups; in addition, it was significantly lower in subjects with prehypertension than in control subjects (2.23±0.47, 2.54±0.48, and 2.91±0.53, respectively). Furthermore, we found that prehypertension (β=−0.31, P<0.01) and hypertension (β=−0.57, P<0.01) were significant predictors of lower CFR in a multivariable model that adjusted for other variables. CFR was significantly and inversely correlated with age (r=−0.20, P=0.01), systolic blood pressure (r=−0.51, P<0.01), diastolic blood pressure (r=−0.47, P<0.01), high-sensitivity C-reactive protein levels (r=−0.21, P=0.01), left atrium diameter (r=−0.22, P<0.01), mitral E deceleration time (r=−0.19, P=0.02), and mitral A velocity (r=−0.27, P<0.01), whereas mitral E/A ratio was significantly and positively correlated with CFR (r=0.26, P<0.01).

Conclusions—CFR is impaired in subjects with prehypertension, but this impairment is not as severe as that in hypertension. (Circulation. 2007;115:593-599.)

Key Words: blood pressure ■ echocardiography ■ blood flow ■ hypertension

Prehypertension, formerly defined as high-normal and above-optimal blood pressure (BP),1 is defined in a normotensive person as systolic BP 120 to 139 mm Hg and/or diastolic BP 80 to 89 mm Hg based on ≥2 properly measured, seated BP readings on each of 2 or more office visits.2 Compared with normal BP, prehypertension is associated with an increase in cardiovascular morbidity and mortality.3,4 The mechanism of excess risk from prehypertension is presumed to be the same as that from hypertension. It has also been shown that prehypertension is associated with subclinical atherosclerosis, including increased coronary atherosclerosis, and target-organ damage.5-7

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The mechanism involved in microvascular dysfunction leading to myocardial ischemia and angina in patients with hypertension without coronary artery disease is not yet clear. Left ventricular hypertrophy in subjects with elevated BP is a well-known factor responsible for impairment of coronary vasodilator capacity8,9; however, angina and impairment of coronary vasodilating capacity may occur in some hypertensive individuals in the absence of left ventricular hypertrophy.10,11 Abnormalities in coronary reactivity may also exist in asymptomatic hypertensive individuals.12 To date, the mechanisms that may be involved in the alteration of coronary flow reserve (CFR) in hypertension have not been studied extensively in humans because of the complex and invasive techniques used to evaluate CFR. Pharmacological stress transthoracic Doppler echocardiography (TTDE) is a relatively recent, useful, and highly reproducible tool to evaluate CFR, and its feasibility has been validated in several studies.13 Furthermore, it has recently been shown that CFR measured by TTDE has an excellent correlation with CFR measured by positron emission tomography, which has been validated as the “gold standard” for CFR measurement.14 Although substantial evidence supports the contention that prehypertension is associated with atherosclerosis and target-organ damage, to date there has been no study that investi-
gated CFR in these patients with TTDE. In the present study, we measured CFR in normotensive subjects, in subjects with prehypertension, and in newly diagnosed and never-treated patients with established hypertension without excessive left ventricular hypertrophy using TTDE.

**Methods**

**Study Population**

The overall study population consisted of 150 subjects: 40 subjects with prehypertension (group I), 60 patients with hypertension (group II), and 50 healthy volunteers with normal BP (group III). Their demographic and clinical data are shown in Table 1. The inclusion criterion was age 18 to 55 years. All subjects, including those with prehypertension and hypertension, were asymptomatic and free of coronary artery disease. Exclusion criteria were presence of any systemic disease, such as hemolytic, hepatic, and renal diseases, or any disease that could cause CFR impairment (eg, diabetes mellitus: fasting plasma glucose after a 75-g oral glucose challenge >126 mg/dL [7.0 mmol/L] or impaired oral glucose tolerance test; or fasting plasma glucose level measured on 3 separate days in 1 week >30 kg/m², % Metabolic syndrome, % Current smoker, % Systolic BP, mm Hg Diastolic BP, mm Hg Total cholesterol, mg/dL LDL cholesterol, mg/dL Non-HDL cholesterol, mg/dL Triglyceride, mg/dL Hemoglobin, g/dL Non-HDL cholesterol, mg/dL Triglyceride/HDL cholesterol hsCRP, mg/L Glucose, mg/dL

<table>
<thead>
<tr>
<th></th>
<th>Group 1: Prehypertension (n=40)</th>
<th>Group 2: Hypertension (n=60)</th>
<th>Group 3: Normotensive Controls (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.6±5.9</td>
<td>44.2±7.3</td>
<td>44.0±6.0</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>17/23</td>
<td>28/32</td>
<td>23/27</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.8±4.1</td>
<td>29.0±4.6</td>
<td>28.3±2.8</td>
</tr>
<tr>
<td>Body mass index ≥30 kg/m², %</td>
<td>53†‡</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>Metabolic syndrome, %</td>
<td>35*</td>
<td>40*</td>
<td>14</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>10</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>133.2±4.3†‡</td>
<td>150.1±7.5†§</td>
<td>111.8±5.6</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>86.7±2.4††</td>
<td>96.5±5.3†§</td>
<td>72.3±5.0</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>73.1±5.4</td>
<td>72.2±9.5</td>
<td>74.4±9.0</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>195.1±29.4</td>
<td>194.8±33.2</td>
<td>189.1±27.9</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>42.7±8.2‡</td>
<td>48.2±11.3</td>
<td>45.8±12.0</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>123.7±23.6</td>
<td>119.1±27.5</td>
<td>116.0±23.3</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>130.8±46.1</td>
<td>134.5±65.8</td>
<td>145.0±75.9</td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>14.3±1.2</td>
<td>14.2±1.1</td>
<td>14.4±1.2</td>
</tr>
<tr>
<td>Ratio total/HDL cholesterol</td>
<td>4.83±1.95</td>
<td>4.18±0.88</td>
<td>4.37±1.19</td>
</tr>
<tr>
<td>Ratio triglyceride/HDL cholesterol</td>
<td>3.29±1.66</td>
<td>2.96±1.60</td>
<td>3.46±2.15</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>2.8±1.6</td>
<td>3.3±2.6*</td>
<td>2.0±1.5</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>95.5±8.2</td>
<td>95.2±7.4</td>
<td>93.4±7.7</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and hsCRP, high-sensitivity C-reactive protein. *P<0.01 vs group 3; †P<0.0001 vs group 3; ‡P<0.05 vs group 2; §P<0.0001 vs group 1.

**Blood Pressure Measurement**

In accordance with American Heart Association guidelines, BP was measured with a mercury sphygmomanometer in an office setting; the first and fifth phases of Korotkoff sounds were used for systolic and diastolic BP. Appropriate cuff sizes were chosen for each subject’s arm circumference. BP was measured 3 times by skilled, trained physicians after subjects had rested for 15 minutes in the sitting position, and the average of the measurements was recorded. Physical examination included measurement of height (centimeters) and weight (kilograms), and a resting 12-lead ECG was recorded.

**Diagnosis of Prehypertension, Hypertension, and Normotension**

In each subject, BP was measured on at least 3 separate days after a 15-minute period of comfortable, seated rest, and these measurements were averaged. On the basis of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, prehypertension was defined as systolic BP between 120 and 139 mm Hg and/or diastolic BP between 80 and 89 mm Hg. Individuals who had systolic BP ≥140 mm Hg and/or a diastolic BP ≥90 mm Hg were diagnosed as hypertensive. Control subjects who had systolic BP <120 mm Hg and diastolic BP <80 mm Hg were diagnosed as normotensive controls.

**Echocardiographic Examination**

Each subject was examined with an Acuson Sequoia C256 echocardiography system equipped with 3V2c and 5V2c broadband transducers with second harmonic capability (Acuson Corp, Mountain View, Calif). Two-dimensional, M-mode, and subsequent transthoracic Doppler harmonic echocardiography examinations were performed on each subject.

**Left Ventricular Mass Determination**

Left ventricular mass was calculated from M-mode records taken on parasternal long-axis images according to the formula below (corrected American Society of Echocardiography cube method)15,16.

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where LVM is left ventricular mass, IVSd is interventricular septum thickness at diastole, PWd is posterior wall thickness at diastole, and LVDD is left ventricular diastolic diameter. To take into account differences in body size that might influence heart size, left ventricular mass was divided by height to create a left ventricular mass index.

**CFR Measurement**

Visualization of the distal left anterior descending coronary artery (LAD) was performed with a modified, foreshortened, 2-chamber view obtained by sliding the transducer on the upper part and medially from an apical 2-chamber view. Coronary flow in the distal LAD was examined by color Doppler flow mapping over the epicardial part of the anterior wall, with the color Doppler velocity range set in the range of 8.9 to 24.0 cm/s. The left ventricle was imaged on the long-axis cross section, and the ultrasound beam was then inclined laterally. Next, coronary blood flow in the LAD (middle to distal) was searched by color Doppler flow mapping (Figure 1). All subjects had Doppler recordings of the LAD with a dipyridamole infusion at a rate of 0.56 mg/kg over 4 minutes. By placing the sample volume on the color signal, spectral Doppler of the LAD showed the characteristic biphasic flow pattern, with larger diastolic and smaller systolic components (Figure 1). Coronary diastolic peak velocities were measured at baseline and after dipyridamole by averaging the highest 3 Doppler signals for each measurement. CFR was defined as the ratio of hyperemic to baseline diastolic peak velocities. CFR $\geq 2.0$ was considered normal.$^{8,9,13,17}$ CFR measurement was achieved in 150 (98.6%) of the 152 subjects. To test the reproducibility of CFR measurement, in 20 subjects assigned randomly, the measurement was repeated 2 days later. Intraobserver intraclass correlation coefficients for coronary flow measurements were 0.862 and 0.822 (baseline and hyperemic diastolic peak velocities, respectively), and for CFR value, the coefficient was 0.878.

**Statistical Analyses**

The analyses were performed with SPSS 9.0 (SPSS for Windows 9.0, Chicago, Ill). Data are expressed as mean±SD. Groups were compared with $\chi^2$ test with regard to categorical variables. One-way ANOVA followed by Tukey’s test or Kruskal-Wallis test (comparison of a characteristic across the 3 study groups if that characteristic did not have a normal distribution, such as high-sensitivity C-reactive protein and triglycerides) was used to compare continuous variables. Pearson’s correlation test was used to test the associations between coronary flow measurements and the study variables. Multivariable analysis was used to assess associations of CFR with potential confounders via a multivariate linear regression model. A probability value $<0.05$ was considered significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Clinical Characteristics of the Study Population**

The general characteristics and risk factors for coronary artery disease of the study population are presented in Table 1. Age, gender, heart rate, lipid profiles, fasting glucose
levels, and hemoglobin were similar among the 3 groups. Although the mean value of body mass index was similar within the groups, the percentage of obesity (body mass index ≥30 kg/m²) was significantly higher in the prehypertension group than in the other 2 study groups. The frequency of metabolic syndrome was significantly lower in the control group than in the other 2 groups. The serum high-sensitivity C-reactive protein level did not differ significantly between the prehypertension and control groups or between the prehypertension and hypertension groups; however, it was significantly higher in the hypertension group than in the control group. Other left ventricular diastolic parameters were slightly different between the hypertension and control groups, but these differences did not reach statistical significance (Table 2).

### Analysis of CFR Measurements
Baseline and peak heart rates were similar among the 3 groups. Peak systolic and diastolic BP were significantly higher in patients with hypertension than in those with prehypertension or control subjects. In addition, peak systolic and diastolic BP were significantly higher in the prehypertension group than in the control group (Table 2). Baseline diastolic peak flow velocity of the LAD was similar between the prehypertension and control groups and between the prehypertension and hypertension groups; however, it was slightly higher in the hypertension group than in the control group (P=0.06). Compared with the control group, hyperemic diastolic peak flow velocity was significantly lower in the hypertension group and slightly lower in the prehypertension group (Table 2). Accordingly, CFR was significantly lower in the hypertension and prehypertension groups than in the control group. In addition, hyperemic diastolic peak flow...
velocity was slightly different and CFR was significantly different between the prehypertension and hypertension groups (CFR: 2.23 ± 0.47, 2.54 ± 0.48, and 2.91 ± 0.53 in the hypertension, prehypertension, and control groups, respectively; Figure 2). None of the control subjects had abnormal CFR (<2); however, 7 subjects with prehypertension (18%) and 21 patients with hypertension (35%) had abnormal CFR (Table 2). Furthermore, in multivariable analysis in which CFR was taken as a dependent variable and the classification status of the subjects (prehypertension, hypertension, or control), age, body mass index, lipids, and other confounders, including left ventricular mass index, diastolic function parameters, and high-sensitivity C-reactive protein, were taken as independent variables, we found that the presence of prehypertension (β = −0.31, P < 0.01) and hypertension (β = −0.57, P < 0.01) were significant predictors of lower CFR.

Correlation Analyses
CFR was significantly and inversely correlated with age (r = −0.197, P = 0.01), systolic BP (r = −0.507, P < 0.0001), diastolic BP (r = −0.472, P < 0.0001), high-sensitivity C-reactive protein levels (r = −0.205, P = 0.01), left atrium diameter (r = −0.223, P = 0.006), mitral E deceleration time (r = −0.185, P = 0.02), and mitral A velocity (r = −0.273, P = 0.001), whereas the mitral E/A ratio was significantly and positively correlated with CFR (r = 0.263, P = 0.001). In addition, total cholesterol and low-density lipoprotein cholesterol trended toward a negative correlation and HDL cholesterol toward a positive correlation with CFR.

Discussion
Coronary artery disease and stroke are the most common forms of target-organ damage and the most common causes of mortality associated with hypertension. Although substantial evidence supports the premise that hypertension impairs CFR, no prior data exist regarding the impact of hypertension, prehypertension, and normal BP on CFR in subjects without any clinical evidence of coronary artery disease. In the present study, we aimed to evaluate CFR and thus coronary microvascular function in subjects with prehypertension, in patients with established hypertension, and in normotensive healthy controls using TTDE. We found that CFR was significantly impaired in patients with prehypertension compared with normotensive subjects; however, in subjects with prehypertension, impairment of CFR was not as severe as in those with hypertension.

It has been suggested that impairment of CFR may occur very early in hypertension, before hypertrophy is apparent, and thus may cause subsequent ischemia and fibrosis. Reduced CFR is largely the result of changes in minimal coronary resistance that are independent of vascular tone. Therefore, structural changes in the coronary vasculature are most likely to be the major contributors to impaired CFR. These structural changes may be qualitatively similar to the well-described effects of hypertension on the peripheral circulation. Furthermore, quantitative histological studies performed on septal biopsy tissue showed that reduced coronary dilatory capacity was associated with increased arteriolar media area and perivascular and interstitial fibrosis in patients with arterial hypertension and angina pectoris in the absence of relevant coronary artery stenosis. These conditions are sensitive indicators of hypertensive target-organ damage. The presence of subclinical hypertensive target-organ damage signals a condition of increased risk for cardiovascular and renal morbidity and mortality. Therefore, the search for impaired CFR may add valuable information to the cardiovascular risk assessment of hypertensive patients.

Recently, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure provided guidelines for the new category of BP levels between normal BP (systolic BP <120 mm Hg and diastolic BP <80 mm Hg) and established hypertension (systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg). This new category between normal BP and established hypertension, prehypertension, includes a population at high risk for developing hypertension and in whom lifestyle modifications are recommended. However, the absolute reduction in the incidence of new-onset hypertension with the most successful lifestyle modification was only 8% in the Trials of Hypertension Prevention. The most important epidemiological data on high-normal and above-normal BP (ie, prehypertension) come from 2 analyses of the Framingham Heart Study data. The first one included 9745 subjects. Compared with the optimal BP group (<120/80 mm Hg), the subjects with above-normal BP (systolic BP between 120 and 129 mm Hg or diastolic BP between 80 and 84 mm Hg) or high-normal BP (systolic BP between 130 and 139 mm Hg or diastolic BP between 85 and 89 mm Hg), who were combined into the prehypertension category under the guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, had a markedly increased risk.
of developing hypertension within 4 years (relative risk 11.6 for subjects 35 to 64 years of age and 5.5 for subjects ≥65 years of age). The second analysis from the Framingham Heart Study population included 6859 subjects followed up for 10 years, and this analysis showed that compared with optimal BP, high-normal BP was associated with a risk factor–adjusted hazard ratio for cardiovascular disease of 2.5 (95% confidence interval [CI] 1.6 to 4.1) in women and 1.6 (95% CI 1.1 to 2.2) in men.25

Although prehypertension (formerly high-normal and above-optimal BP) has been widely studied in the past, it remains a matter of controversy, especially with regard to its treatment. Its prognostic importance and risk profile for target-organ damage have not yet been clearly established, and the term “prehypertension” has yet to be widely adopted. Several previous studies have demonstrated that subjects with prehypertension are at increased cardiovascular risk and may already have evidence of target-organ damage, such as impairment of ventricular relaxation or microalbuminuria caused by greater left ventricular wall stress.11,27 Second, the maximal coronary flow response to physiological or pharmacological stimuli may be limited by a reduction in the tone of coronary resistance vessels that result from higher BP and extravascular compression in the presence of left ventricular hypertrophy caused by greater left ventricular wall stress.11,27

In line with the suggestions mentioned above, we found that, compared with normotensive control subjects, patients with prehypertension had impaired CFR, which is a surrogate marker of hypertensive target-organ damage. Several possible mechanisms could explain the reduction in CFR in hypertensive patients. First, baseline coronary flow may be increased because of increments in the tone of coronary resistance vessels that result from higher BP and extravascular compression in the presence of left ventricular hypertrophy.26 Increases in the wall stress induced by greater left ventricular wall stress impair nutrient blood flow predominantly occurs during diastole, an impairment in left ventricular diastolic function may also play an important role in CFR impairment in hypertension.30 In line with these suggestions, we found that there was an association between left ventricular diastolic function parameters and CFR. In conclusion, these data provide evidence of impaired CFR, or impaired coronary microvascular function, in subjects with prehypertension. Our results are consistent with the idea that the presence of mildly elevated BP is associated with an abnormal coronary flow response.

Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Substantial evidence suggests that hypertension impairs coronary flow reserve (CFR), which suggests that coronary microvascular function and impairment of the CFR may occur very early in hypertension, before hypertrophy is apparent. Structural changes in the coronary vasculature are most likely to be the major contributors to impaired CFR. Therefore, evaluation of CFR may add valuable information to the cardiovascular risk assessment of hypertensive patients. Pharmacological stress transthoracic Doppler echocardiography is a useful and highly reproducible tool for evaluation of CFR, and it has been shown that CFR measured by transthoracic Doppler echocardiography has an excellent correlation with CFR measured by positron emission tomography, which has been validated as a “gold standard” for CFR measurement. Growing evidence shows that prehypertension (systolic blood pressure 120 to 139 mm Hg and/or diastolic blood pressure 80 to 89 mm Hg) is associated with target-organ damage, and prehypertensive subjects are at high risk for developing hypertension. The present study, by assessing CFR in prehypertensive, hypertensive, and normotensive individuals, provides novel information on the potential impact of prehypertension on target-organ damage.
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