Hypertension and Left Ventricular Hypertrophy Are Associated With Impaired Endothelium-Mediated Relaxation in Human Coronary Resistance Vessels

Charles B. Treasure, MD; J. Larry Klein, MD; Joseph A. Vita, MD; Steven V. Manoukian, MD; George H. Renwick; Andrew P. Selwyn, MD; Peter Ganz, MD; and R. Wayne Alexander, MD, PhD

Background. Patients with hypertension and myocardial hypertrophy may have signs and symptoms of myocardial ischemia in the absence of obstructive coronary disease. Prior investigations have demonstrated impaired coronary flow reserve and have led to speculation that microvascular dysfunction might contribute to ischemia in these patients. Experimental studies have shown that the endothelium, an important regulator of microvascular tone, can be damaged by hypertension and is dysfunctional in cardiomyopathy. We hypothesized that endothelium-dependent vasodilation is impaired in the coronary microvasculature of patients with hypertension and ventricular hypertrophy.

Methods and Results. We studied coronary microvascular responses in 10 patients with left ventricular hypertrophy secondary to essential hypertension (HTN) (mean arterial pressure at catheterization, 151/94 mm Hg; mean posterior wall thickness, 1.4±0.1 cm) and nine normal control subjects with no history of hypertension (mean arterial pressure at catheterization, 128/75 mm Hg; mean posterior wall thickness, 1.0±0.02 cm) using the intracoronary Doppler catheter and quantitative angiography to assess changes in coronary blood flow (CBF). All patients had normal left ventricular systolic function. To assess microvascular endothelial function, we infused the endothelium-dependent vasodilator acetylcholine (10⁻⁴–10⁻⁵ M) and the endothelium-independent vasodilator adenosine (10⁻⁴ M) into the left anterior descending coronary artery. In response to acetylcholine, CBF increased only 32±25% in HTN patients, whereas CBF increased 192±39% in normal control subjects (p=0.003). CBF increased 465±93% in HTN patients and 439±41% in normal control subjects in response to adenosine (p=NS). The proportion of coronary flow reserve attributable to endothelium-dependent dilation (obtained from peak acetylcholine/peak adenosine flow response) was 48±9% in normal control subjects but only 7±8% in HTN patients (p=0.008).

Conclusions. Endothelium-dependent vasodilation is markedly impaired in the coronary microvessels of patients with hypertension and ventricular hypertrophy. Loss of this vasodilator mechanism may contribute to disordered coronary flow regulation and the ischemic manifestations of hypertensive heart disease. (Circulation 1993;87:86–93)

Key Words • microvasculature • acetylcholine • adenosine

Patients with hypertension and ventricular hypertrophy frequently have signs and symptoms of myocardial ischemia in the absence of obstructive coronary disease. Contributing factors may include extrinsic vascular compression and inadequate microvascular growth relative to increased left ventricular mass.¹ Factors intrinsic to the coronary microvessel wall may also be important causes of ischemia in these patients. As the ventricle undergoes hypertrophy, the arterial media also thickens. Some investigators suggest that vasoconstrictor responses in these hypertrophied arteries are augmented.² In addition, considerable data exist that are consistent with the notion that dysfunction of the microvascular endothelium may contribute to abnormalities of flow regulation in these patients.³,⁴ Over the last decade, the central importance of the vascular endothelium to cardiovascular homeostasis has been increasingly appreciated. In addition to providing a nonthrombogenic surface for the arterial wall, the endothelium is a major regulator of vascular tone and growth. Furchgott and Zawadski⁵ first demonstrated that endothelial cells release a potent vasodilator, endothelium-derived relaxing factor (EDRF), which produces relaxation of underlying vascular smooth muscle. The endothelium also releases potent vasoconstricting factors (endothelium-derived constricting factors, ED-CFs), although their role in the human circulation remains undefined.⁶,⁷ Injury to the endothelium may
produce alterations in the regulation of vascular tone and growth.

Experimental hypertension is associated with morphological abnormalities of endothelial cells and with impaired endothelium-dependent relaxation to acetylcholine, ADP, and thrombin in large vessels. \textsuperscript{8,9} In the rabbit model, hypertension also impairs microvascular endothelial vasodilator function. \textsuperscript{10} Treatment of hypertension tends to restore normal endothelium-dependent relaxation\textsuperscript{9} and reverse chronic vascular changes. \textsuperscript{11} In humans with essential hypertension, endothelium-mediated relaxation is impaired in the forearm circulation. \textsuperscript{12,13} No studies have evaluated endothelium-mediated relaxation in the coronary microvessels of the hypertensive human. We investigated endothelium-mediated relaxation in the small coronary arteries of patients with hypertension and ventricular hypertrophy by evaluating coronary flow responses to the endothelium-dependent vasodilator acetylcholine and to the smooth muscle dilator adenosine.

**Methods**

**Patient Population**

Coronary microvascular responses were assessed in 10 patients with a history of hypertension (HTN) and compared with nine nonhypertensive control subjects. Patients were studied at Brigham and Women’s Hospital (Boston), Emory University Hospital (Atlanta, Ga.), and Grady Memorial Hospital (Atlanta). One investigator was present for all studies (C.B.T.). Seven of nine control responses have been presented in a previous report.\textsuperscript{14}

The following clinical and laboratory information was collected from all patients: age, sex, history of smoking (defined as cigarette smoking within the 3 months before study), history of hypertension (defined as blood pressure elevation $>140/90$ mm Hg, requiring medication), total cholesterol level (mg/dl) at time of catheterization, family history of myocardial infarction (defined as first-degree relative at age $<60$ years), and history of insulin-dependent diabetes mellitus.

**Protocol**

Written informed consent was obtained from all patients before the diagnostic catheterization, in accordance with guidelines established by the Committee for the Protection of Human Subjects at Brigham and Women’s Hospital and the Human Investigations Committee of Emory University. Vasoactive medications were discontinued 12–24 hours before catheterization.

Diagnostic right and left heart catheterization and coronary angiography were performed by a standard percutaneous femoral approach. After completion of the diagnostic catheterization, 5,000–10,000 units of heparin was given intravenously, and an 8F guiding catheter was positioned in the ostium of the left coronary artery. Each patient then underwent the following study protocol.

A 20-MHz pulsed Doppler crystal mounted on the tip of a 3F infusion catheter (Millar Instruments Inc., Houston, Tex.) was advanced through the guiding catheter into the proximal segment of the left anterior descending coronary artery. The use of this device to assess intracoronary blood flow velocity has been described in detail.\textsuperscript{14,15} The Doppler catheter was connected to a photographic multichannel oscillographic recorder (Electronics for Medicine VR16, Pleasantville, N.Y.) to display phasic and mean velocity waveforms. Before beginning the experimental protocol, the position of the Doppler flow velocity catheter and the range gate control were adjusted to optimize the audio flow velocity signal and the phasic flow velocity waveform. The Doppler catheter position and the range gate control were not changed thereafter.

Serial intracoronary infusions of acetylcholine and adenosine were administered at 0.8 ml/min via the central lumen of the Doppler catheter in the following sequence: 2-minute control infusion (5% dextrose with heparin 1 unit/ml); three 2-minute infusions of acetylcholine to achieve estimated final blood concentrations of $10^{-8}$, $10^{-7}$, and $10^{-6}$ M (based on assumed left anterior descending coronary artery blood flow of 80 ml/min)\textsuperscript{16}; a 4-minute repeat control infusion (0.9% sodium chloride with heparin 1 unit/ml); and three 2-minute infusions of adenosine to achieve estimated final blood concentrations of $10^{-8}$, $10^{-7}$, and $10^{-6}$ M (Sigma Chemical Co., St. Louis, Mo.). With the increase in blood flow observed at higher doses of adenosine, the actual concentrations were proportionately lower. Just before the end of each infusion, coronary arteriography was performed with the use of a power injection of nonionic contrast medium (Omnipaque, Winthrop-Breon, New York). Throughout each infusion the heart rate, arterial pressure, coronary flow velocity, and ECG (lead I) were monitored continuously, and all measurements were recorded in steady-state conditions. All patients received two-dimensional and M-mode echocardiography immediately after cardiac catheterization.

**Quantitative coronary angiography.** Quantitative coronary angiography was performed by a previously validated technique.\textsuperscript{17} Nonionic contrast medium was injected into the left coronary artery at the rate of 5–10 ml/sec to a total of 7–12 ml with the use of a power injector (Medrad, Pittsburgh, Pa.) in order to optimize the quality and reproducibility of the injections.\textsuperscript{18} A biplane system (Pliagnost-C, Philips Medical Systems, Inc., Shelton, Conn.) was used for cineangiography.

**Analysis of arterial dimensions.** Quantitative angiography of the epicardial coronary artery was performed for two reasons: 1) determination of cross-sectional area near the Doppler tip in order to convert flow velocity to an estimate of coronary arterial flow (an arterial segment 2–4 mm distal to the Doppler tip was selected for quantitative analysis in all patients); 2) exclusion of coronary artery flow limitation caused by epicardial coronary artery constriction in response to acetylcholine (flow limitation defined as $>50\%$ diameter constriction in the most constricting segment). Quantitative angiographic analysis was similar to that described in previous studies.\textsuperscript{14} Four digitized cinerecords for each infusion were summed and averaged along the segment profile to give a mean diameter and standard deviation at each point. A single mean and a pooled standard deviation for the segment (at each infusion) were obtained by averaging each of these measures along the segment profile. Suitable segments were required to have a mean standard deviation $<5\%$ of the mean diameter.

**Estimates of coronary blood flow changes.** Relative changes in coronary blood flow were measured by
multiplying changes in mean coronary blood flow velocity (as measured directly by the Doppler catheter; see Figure 1 for representative tracing) by changes in estimated vessel cross-sectional area (determined from the change in vessel diameter 2–4 mm distal to the catheter tip relative to control).

Statistical Analysis

Differences in clinical, hemodynamic, and echocardiographic parameters were compared using a two-sample t test. Microvascular responses to drug infusions were compared using repeated-measures ANOVA. Statistical significance was assumed if the null hypothesis (two-tailed) could be rejected at the 0.05 probability level. All data are expressed as mean±SEM.

Results

Clinical Data

Ten HTN patients were compared with nine nonhypertensive control patients (Table 1). Nine HTN patients and all nonhypertensive control subjects were undergoing diagnostic catheterization for evaluation of chest pain. One HTN patient complained of exertional dyspnea. The mean ages of HTN patients and nonhypertensive control subjects were 49±3 years and 42±3 years, respectively (p=0.08). Four HTN patients and three nonhypertensive control subjects were women. Mean total cholesterol at time of catheterization was 236±23 mg/dl in HTN patients and 207±9 mg/dl in nonhypertensive control subjects (p=0.21). Four HTN patients and three nonhypertensive control subjects had a history of cigarette smoking. Four HTN patients and five nonhypertensive control subjects had a family history of myocardial infarction. One HTN patient had non–insulin-dependent diabetes mellitus. No patient had insulin-dependent diabetes mellitus. Group mean heart rate at time of catheterization was 71±3 beats per minute in HTN patients and 66±4 beats per minute in nonhypertensive control subjects (p=0.5). Group mean blood pressure at time of catheterization was 151/94 mm Hg in HTN patients and 128/75 mm Hg in nonhypertensive control subjects (p=0.03). Left ventricular end-diastolic dimension was 4.7±0.2 cm in HTN patients and 4.6±0.3 cm in nonhypertensive control sub-
TABLE 1. Clinical Data for Hypertensive Patients and Control Subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age</th>
<th>Sex</th>
<th>TOB</th>
<th>FH</th>
<th>CHOL</th>
<th>HR</th>
<th>BP</th>
<th>LVEDD</th>
<th>LVESD</th>
<th>LVPWT</th>
<th>LVEDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>M</td>
<td>N</td>
<td>Y</td>
<td>220</td>
<td>78</td>
<td>75</td>
<td>5.2</td>
<td>3.2</td>
<td>1.0</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>M</td>
<td>N</td>
<td>Y</td>
<td>244</td>
<td>60</td>
<td>108</td>
<td>5.4</td>
<td>3.5</td>
<td>1.0</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>M</td>
<td>Y</td>
<td>N</td>
<td>207</td>
<td>60</td>
<td>111</td>
<td>5.1</td>
<td>3.0</td>
<td>0.9</td>
<td>11*</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>F</td>
<td>N</td>
<td>Y</td>
<td>166</td>
<td>66</td>
<td>67</td>
<td>4.8</td>
<td>2.6</td>
<td>1.0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>M</td>
<td>Y</td>
<td>Y</td>
<td>218</td>
<td>54</td>
<td>81</td>
<td>5.2</td>
<td>3.5</td>
<td>1.0</td>
<td>4*</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>M</td>
<td>Y</td>
<td>N</td>
<td>239</td>
<td>54</td>
<td>91</td>
<td>4.9</td>
<td>3.2</td>
<td>1.0</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>M</td>
<td>N</td>
<td>N</td>
<td>169</td>
<td>72</td>
<td>92</td>
<td>4.6</td>
<td>2.4</td>
<td>1.0</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>F</td>
<td>N</td>
<td>N</td>
<td>203</td>
<td>68</td>
<td>108</td>
<td>3.7</td>
<td>2.7</td>
<td>1.1</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>F</td>
<td>N</td>
<td>Y</td>
<td>200</td>
<td>84</td>
<td>106</td>
<td>2.8</td>
<td>1.6</td>
<td>1.0</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.3</td>
<td>0.2</td>
<td>0.02</td>
<td>2</td>
</tr>
<tr>
<td>Hypertensive patients</td>
<td>59</td>
<td>M</td>
<td>N</td>
<td>N</td>
<td>164</td>
<td>52</td>
<td>113</td>
<td>5.0</td>
<td>3.5</td>
<td>1.3</td>
<td>19</td>
</tr>
<tr>
<td>35</td>
<td>M</td>
<td>N</td>
<td>N</td>
<td>135</td>
<td>60</td>
<td>117</td>
<td>4.5</td>
<td>2.8</td>
<td>1.3</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>F</td>
<td>N</td>
<td>Y</td>
<td>217</td>
<td>78</td>
<td>111</td>
<td>4.8</td>
<td>2.5</td>
<td>1.2</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>M</td>
<td>Y</td>
<td>N</td>
<td>230</td>
<td>80</td>
<td>112</td>
<td>4.5</td>
<td>1.8</td>
<td>1.7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>F</td>
<td>Y</td>
<td>N</td>
<td>245</td>
<td>90</td>
<td>110</td>
<td>3.8</td>
<td>2.5</td>
<td>1.3</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>F</td>
<td>N</td>
<td>Y</td>
<td>382</td>
<td>66</td>
<td>133</td>
<td>4.2</td>
<td>2.3</td>
<td>1.2</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>M</td>
<td>N</td>
<td>Y</td>
<td>215</td>
<td>72</td>
<td>112</td>
<td>3.7</td>
<td>2.2</td>
<td>1.3</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>F</td>
<td>Y</td>
<td>Y</td>
<td>310</td>
<td>72</td>
<td>103</td>
<td>5.4</td>
<td>3.8</td>
<td>1.2</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>M</td>
<td>Y</td>
<td>N</td>
<td>274</td>
<td>68</td>
<td>110</td>
<td>5.2</td>
<td>2.6</td>
<td>1.6</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>M</td>
<td>N</td>
<td>N</td>
<td>187</td>
<td>72</td>
<td>120</td>
<td>5.4</td>
<td>3.3</td>
<td>1.5</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.7</td>
<td>2.7</td>
<td>1.4</td>
<td>18</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.2</td>
<td>0.2</td>
<td>0.1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Pulmonary capillary wedge pressure (mm Hg); TOB, history of smoking within 3 months of study; FH, family history of myocardial infarction before age 60 years; CHOL, total cholesterol level (mg/dl) at time of study; HR, heart rate (beats per minute); BP, mean arterial pressure (mm Hg) at time of study; LVEDD, left ventricular end-diastolic dimension (cm); LVESD, left ventricular end-systolic dimension (cm); LVPWT, left ventricular posterior wall thickness (cm); LVEDP, left ventricular end-diastolic pressure (mm Hg). N, no; Y, yes.

jects (p=0.51). Left ventricular end-systolic dimension was 2.7±0.2 cm in HTN patients and 2.9±0.2 cm in nonhypertensive control subjects (p=0.59). Left ventricular posterior wall thickness was 1.4±0.1 cm in HTN patients and 1.0±0.02 cm in nonhypertensive control subjects (p=0.01). Left ventricular end-diastolic pressure was 18±2 mm Hg in HTN patients and 12±2 mm Hg in nonhypertensive control subjects (p=0.04). All patients had angiographically normal epicardial coronary arteries.

Of the 10 hypertensive patients, five had exercise tolerance tests (four with thallium). All four thallium stress tests showed reversible defects consistent with ischemia. The stress test performed without thallium was nondiagnostic.

**Hemodynamic Responses**

Heart rate and systemic arterial pressure did not vary significantly during evaluation of coronary flow responses in either patient group. In HTN patients, heart rate was 71±3 beats per minute at baseline, 68±4 beats per minute at peak acetylcholine, and 70±3 beats per minute at peak adenosine (all p=NS). In nonhypertensive control subjects, heart rate was 66±4 beats per minute at baseline, 66±4 beats per minute at peak acetylcholine, and 64±4 beats per minute at peak adenosine (all p=NS). In HTN patients, mean systemic arterial pressure was 114±3 mm Hg at baseline, 115±3 mm Hg at peak acetylcholine, and 119±4 mm Hg at peak adenosine (all p=NS). In nonhypertensive control subjects, systemic arterial pressure was 93±5 mm Hg at baseline, 93±7 mm Hg at peak acetylcholine, and 103±8 mm Hg at peak adenosine (all p=NS).

**Coronary Microvascular Flow Responses**

**Acetylcholine.** In HTN patients, coronary flow responses to the endothelium-dependent vasodilator acetylcholine were markedly impaired (Figure 2). In HTN patients, coronary blood flow increased −4±4%, −3±10%, and 32±25% in response to acetylcholine 10-8 M, 10-7 M, and 10-6 M, respectively. In nonhypertensive control subjects, coronary blood flow increased 25±13%, 106±34%, and 192±39% in response to acetylcholine 10-7 M, 10-6 M, and 10-5 M, respectively (p=0.003).

**Adenosine.** Coronary flow responses to the endothelium-independent vasodilator adenosine were similar in HTN patients and nonhypertensive control subjects (Figure 3). In HTN patients, coronary blood flow increased 82±26%, 417±115%, and 465±93% in response to adenosine 10-6 M, 10-5 M, and 10-4 M, respectively. In nonhypertensive control subjects, coronary blood flow increased 170±32%, 286±33%, and 439±41% in response to adenosine 10-6 M, 10-5 M, and 10-4 M, respectively (p=NS).

**Endothelium-dependent flow response.** To examine the endothelium-dependent component of the maximal vasodilator response, each patient's flow response to the endothelium-dependent vasodilator acetylcholine was normalized by his/her maximal flow response to aden-
osine. The endothelium-dependent flow response was markedly impaired in HTN patients (Figure 4). The proportion of coronary flow reserve attributable to endothelium-dependent dilation (obtained from acetylcholine dose/peak adenosine flow response) was $-2\pm1\%$, $-2\pm4\%$, and $7\pm8\%$ to serial doses of acetylcholine in HTN patients. In nonhypertensive control subjects, the proportion of coronary flow reserve attributable to endothelium-dependent dilation was $8\pm5\%$, $28\pm10\%$, and $48\pm9\%$ to serial doses of acetylcholine ($p=0.008$).

**Correlates of the microvascular response to acetylcholine in HTN patients.** To address the relative importance of the effects of hypertension versus ventricular hypertrophy on the coronary microvascular endothelin in HTN patients, we compared the peak response to acetylcholine with left ventricular posterior wall thickness and arterial pressure at time of catheterization (systolic, diastolic, and mean). An important inverse linear relation of the microvascular response to acetylcholine and the mean ($r=0.61$, $p<0.05$) and diastolic blood pressure ($r=0.79$, $p<0.05$) was found (Figure 5). There was no correlation of the microvascular response to acetylcholine with left ventricular posterior wall thickness or systolic blood pressure. The significant relation between blood pressure and the vascular response to acetylcholine was still present when data from one diabetic patient and four patients with serum total cholesterol levels $>240$ mg/dl were excluded.

**Discussion**

This study demonstrates that endothelium-dependent vasodilation is impaired in the coronary microvessels of patients with hypertension and mild ventricular hypertrophy. In this population of patients with essential hypertension and left ventricular hypertrophy, coronary flow responses to intracoronary infusions of adenosine...
were preserved, which probably reflects the mild degree of ventricular hypertrophy.

Endothelium-Derived Relaxing and Constricting Factors

Over the last decade, the endothelium has become recognized as a major regulator of vascular tone and growth. Several landmark studies have led to this appreciation of the importance of the endothelium. Furchgott and Zawadski\(^7\) demonstrated that when appropriately stimulated, endothelial cells release EDRF, a potent vasodilator (later characterized at least in part as nitric oxide\(^{19}\)) that produces relaxation of underlying vascular smooth muscle. This endogenous vasodilator is released in response to many stimuli including acetylcholine, substance P, and bradykinin.\(^20\) Endothelium-dependent relaxation, presumably caused by EDRF, has been demonstrated in both large\(^21\) and small\(^14\) coronary arteries of humans. Recent studies have described a group of at least three EDFCs. EDCF\(_1\) (blocked by calcium channel antagonists)\(^7\) and EDCF\(_2\) (blocked by cyclooxygenase inhibitors)\(^22-23\) have been described in animal models of disease but currently have no known role in the human circulation. Endothelin, a 21-amino acid peptide,\(^6\) is the only EDCF known to be produced in and released from human endothelium.

**Vascular Abnormalities in Hypertension**

Hypertension and myocardial hypertrophy have profound effects on the vasculature. Hypertension accelerates the atherosclerotic process, especially in the presence of concomitant coronary risk factors.\(^24\) Chronic hypertension produces marked intimal hyperplasia and medial thickening of the vessel wall.\(^25\) In humans, early hypertension (without ventricular hypertrophy) is associated with augmented coronary microvascular reactivity to vasoconstrictor stimuli.\(^26\) In the severely hypertrophied heart, the ability of the coronary circulation to allow normal increases in flow in response to intense dilator stimuli is impaired.\(^1,27\) This impaired flow response may be related to increased extracoronary compressive forces and/or inadequate angiogenesis. Abnormalities intrinsic to the coronary microvessels may also contribute. Augmented sensitivity of vascular smooth muscle to vasoconstrictor stimuli, a loss of normal endothelium-mediated vasodilator function, and/or an increased production and release of EDFCs may lead to impaired myocardial perfusion.

**Endothelial Abnormalities in Hypertension: Animal Data**

Experimental studies suggest that endothelial cell structure and function are impaired in hypertension. Hypertension, produced acutely, alters endothelial morphology.\(^28\) Both acute and chronic experimental hypertension are associated with reduced endothelium-dependent relaxation to acetylcholine, ADP, and thrombin in large vessels.\(^5,8\) Treatment of hypertension tends to restore normal endothelium-mediated relaxation in the rat aorta.\(^9,29\) In the microcirculation of the hypertensive rabbit\(^10\) and rat,\(^30\) endothelial vasodilator function is also impaired. Decreased activation of the EDRF-producing pathway may explain this deficit.\(^30\)

Recent animal data suggest that EDFCs may also be important regulators of vascular tone in hypertension. In the aorta of the hypertensive rat, endothelium-dependent contractions occur in response to acetylcholine, an effect that may be mediated by a cyclooxygenase product.\(^22\) In the coronary\(^31\) and mesenteric\(^26\) resistance arteries of hypertensive rats, cyclooxygenase inhibitors normalize endothelial responses to serotonin\(^31\) and acetylcholine.\(^32\) suggesting that a cyclooxygenase-dependent substance may overcome the action of EDRF. This substance may be prostaglandin H\(_2\).\(^33\)

**Endothelial Abnormalities in Hypertension: Human Data**

Human studies support these experimental data. Increases in forearm blood flow during acetylcholine infusion are impaired in patients with essential hypertension when compared with nonhypertensive individuals.\(^12,13\) This impaired response to acetylcholine in the human forearm is related to decreased EDRF release.\(^12\) The present study is the first to demonstrate that coronary microvascular endothelial responses are impaired in patients with hypertension and mild ventricular hypertrophy. Patients with dilated cardiomyopathy (and marked degrees of ventricular hypertrophy) have previously been shown to have impaired endothelium-mediated relaxation of the coronary microvasculature.\(^14\) Although preliminary studies suggest that plasma levels of endothelium-derived vasoconstrictors may be elevated in patients with essential hypertension,\(^34\) little information is known about the role of EDFCs in the hypertensive human.

**Potential Limitations**

Coronary flow reserve was preserved in our hypertensive/hypertrophic patients. Two young HTN patients with minimal left ventricular hypertrophy had supranormal increases in blood flow in response to adenosine (increases in flow of 1,080\% and 906\%). When these two patients are excluded, the responses of the hypertensive group are mildly although not significantly \((p=0.07)\) diminished when compared with control subjects, as one might expect (HTN patients, 333±36\% versus control subjects, 439±41\% for 10\(^{-4}\) M adenosine). The mild degree of ventricular hypertrophy in this hypertensive population coupled with the supranormal responses in these two young HTN patients may explain the observed normal coronary flow responses to adenosine. Duration and severity of hypertension and degree of hypertrophy may have important effects on coronary flow reserve.\(^35\)

Because baseline left anterior descending coronary artery blood flow may be >80 ml/min in patients with hypertension/ventricular hypertrophy, we chose three doses of acetylcholine spanning a range of 2 log units to overshadow any small increases in blood flow that patients with mild left ventricular hypertrophy might have. As the dose–response curves for acetylcholine completely diverge (Figure 2), it is highly unlikely that dilutional differences in drug concentration can explain the observed results.

Since these patients all have essential hypertension and mild ventricular hypertrophy, we cannot associate microvascular endothelial vasodilator dysfunction with either entity exclusively. However, the strong association of coronary microvascular responses to acetylcholine with diastolic arterial pressure (Figure 5) in our
HTN patients coupled with prior observations on hypertension and impairment of endothelium-dependent responsiveness in the human forearm (where organ hypertrophy is not an issue)\(^2,3\) suggest that hypertension alone can impair endothelium-dependent relaxation. Larger numbers of patients would be required to exclude a separate role for ventricular hypertrophy.

Since the mean age of these two patient groups differed slightly, we cannot completely exclude this factor as contributing to the impairment in endothelial vasodilator function seen in the HTN/ hypertrophic patients.

It is also known that diabetes mellitus and hypercholesterolemia can affect endothelium-dependent vaso- motor function in large and resistance coronary vessels. This study has focused on the effects of blood pressure. The data from one diabetic patient and four patients with serum total cholesterol levels >240 mg/dl did not confound these results. Nevertheless, it is likely that these risk factors can interact to alter endothelial regulation of vascular tone.

**Implications**

Patients with hypertension and ventricular hypertrophy frequently have typical angina in the setting of normal epicardial coronary arteries.\(^1\) Considerable evidence supports the presence of microvascular ischemia in these patients.\(^1,2,5\) A dysfunctional endothelium may contribute to this microvascular ischemia. It remains to be determined whether repeated ischemic bouts lead to progressive fibrosis resulting in the severe diastolic and systolic ventricular dysfunction characteristic of end-stage hypertensive heart disease.

**Conclusions**

This study demonstrates that endothelium-mediated relaxation is impaired in the coronary microvessels of patients with hypertension and mild ventricular hypertrophy. These findings may have important implications regarding altered control of myocardial perfusion in hypertensive heart disease.

**Acknowledgments**

We acknowledge the assistance of the technical staffs of Grady Memorial Hospital, Emory University Hospital, and Birmingham and Women’s Hospital Cardiac Catheterization Laboratories for their excellent help in performing these studies.

**References**

32. Diedrich D, Yang Z, Buhrer FR, Luscher TF: Impaired endo- thelium-dependent relaxations in hypertensive resistance arter-


Hypertension and left ventricular hypertrophy are associated with impaired endothelium-mediated relaxation in human coronary resistance vessels. C B Treasure, J L Klein, J A Vita, S V Manoukian, G H Renwick, A P Selwyn, P Ganz and R W Alexander

Circulation. 1993;87:86-93
doi: 10.1161/01.CIR.87.1.86
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/87/1/86

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/