The coronary vasculature is lined by an endothelial cell monolayer, which plays an important role in regulation of coronary blood flow through release of vasoactive substances and modulation of vasomotor stimuli (1–4). Although anatomically similar in morphology, conduit and resistance coronary vessels differ importantly in size, function and local environment and appear to be differentially affected in certain disease processes, such as atherosclerosis and hypertension. However, little is known about the effect of hypertension on conduit and resistance coronary vessels in humans.

**Methods.** Changes in coronary blood flow (a measure of resistance vessel reactivity) and coronary artery diameter (a measure of conduit vessel reactivity) were investigated in response to graded infusion of the endothelium-dependent agonist acetylcholine (ACh) in 98 patients with normal coronary arteries.

**Results.** In 31 normotensive, euglycemic patients, conduit and resistance coronary artery responses to intracoronary infusion of ACh were significantly correlated ($r = 0.73, p = 1 \times 10^{-6}$), although eight patients (26%) had constriction of conduit but dilation of resistance arteries at peak effect. In 28 hypertensive patients without left ventricular hypertrophy (LVH), conduit and resistance artery responses to ACh remained significantly correlated ($r = 0.5, p = 0.006$), although 12 patients (43%) had discordant findings. Finally, in 39 hypertensive patients with LVH, conduit and resistance artery responses to ACh displayed the lowest correlation ($r = 0.38, p = 0.02$), with 22 patients (56%) demonstrating conduit artery constriction and resistance artery dilation.

**Conclusions.** Despite angiographically normal coronary arteries, heterogeneous vasomotor responses (dilation and constriction) were demonstrated in contiguous conduit and resistance arteries in normotensive and hypertensive patients referred for cardiac catheterization because of chest pain. In addition to more severe endothelial dysfunction among conduit and resistance arteries, a greater frequency of discordant conduit and resistance artery responses and resistance vessel constriction was found with increasing severity of hypertension. Our study suggests differing mechanisms of endothelial responsiveness to ACh among conduit and resistance coronary arteries.

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**Heterogeneous Vasomotor Responses of Coronary Conduit and Resistance Vessels in Hypertension**

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**Objectives.** The purpose of our study was to investigate the relation between conductance and resistance coronary vasomotor responsiveness in hypertensive patients without atherosclerosis.

**Background.** Although similar in morphology, conduit and resistance coronary vessels differ importantly in size, function and local environment and appear to be differentially affected in certain disease processes, such as atherosclerosis and hypertension. However, little is known about the effect of hypertension on coronary conduit and resistance vessels in humans.

**Methods.** Changes in coronary blood flow (a measure of resistance vessel reactivity) and coronary artery diameter (a measure of conduit vessel reactivity) were investigated in response to graded infusion of the endothelium-dependent agonist acetylcholine (ACh) in 98 patients with normal coronary arteries.

**Results.** In 31 normotensive, euglycemic patients, conduit and resistance coronary artery responses to intracoronary infusion of ACh were significantly correlated ($r = 0.73, p = 1 \times 10^{-6}$), although eight patients (26%) had constriction of conduit but dilation of resistance arteries at peak effect. In 28 hypertensive patients without left ventricular hypertrophy (LVH), conduit and resistance artery responses to ACh remained significantly correlated ($r = 0.5, p = 0.006$), although 12 patients (43%) had discordant findings. Finally, in 39 hypertensive patients with LVH, conduit and resistance artery responses to ACh displayed the lowest correlation ($r = 0.38, p = 0.02$), with 22 patients (56%) demonstrating conduit artery constriction and resistance artery dilation.

**Conclusions.** Despite angiographically normal coronary arteries, heterogeneous vasomotor responses (dilation and constriction) were demonstrated in contiguous conduit and resistance arteries in normotensive and hypertensive patients referred for cardiac catheterization because of chest pain. In addition to more severe endothelial dysfunction among conduit and resistance arteries, a greater frequency of discordant conduit and resistance artery responses and resistance vessel constriction was found with increasing severity of hypertension. Our study suggests differing mechanisms of endothelial responsiveness to ACh among conduit and resistance coronary arteries.

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is part of a larger study whose purpose is to examine the effects of hypertension, LVH, hemodynamically insignificant atherosclerosis, gender and ethnicity on coronary artery and arteriolar relaxation. Thirty-one normotensive and 49 hypertensive subjects from the present study were previously included in a report that described the relation between ethnicity and coronary vasoreactivity (21). Enrolled patients had normal epicardial coronary arteries documented during coronary arteriography. Patients were excluded from the study because of coronary artery disease, significant valvular heart disease or other serious medical disorders. Patients fasted for a minimum of 8 h before the study. Current smokers were instructed to refrain from smoking for a minimum of 8 h.

Patients were grouped by the presence of hypertension and left ventricular mass hypertrophy. Hypertension was defined as reproducible blood pressure measurements $\geq 140/90$ mm Hg or self-reported taking of antihypertensive medication. Left ventricular hypertrophy was defined as left ventricular mass (calculated from M-mode echocardiographic measurements) indexed by body surface area (BSA) in excess of gender-specific normal values established by the Framingham Heart Study ($\geq 131 \, \text{g/m}^2$ for men and $\geq 100 \, \text{g/m}^2$ for women) (22). Diabetes mellitus was diagnosed by a self-reported history or by a fasting serum glucose level $> 140$ mg/dl. Twenty-eight patients had hypertension without LVH and 39 had hypertension with LVH. A comparison group of 31 normotensive, euglycemic subjects was studied using similar methodology. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood was obtained in the fasting state for measurement of total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, lipoprotein a and glucose.

All patients were referred for cardiac catheterization for evaluation of chest pain or an anginal equivalent. Chest pain was classified as angina pectoris, atypical angina or noncardiac chest pain. Angina pectoris was defined in the classic manner as substernal chest discomfort (heaviness or pressure) brought on by exertion and relieved by rest or nitroglycerin, or a prolonged episode of anginal pain at rest requiring hospital admission. Atypical angina was defined as chest pain with some features of classic angina but with other characteristics not generally associated with angina pectoris such as sharp or pleuritic character or an intermittent relation to exercise. Noncardiac chest pain had no features of angina pectoris other than substernal location of chest pain. An anginal equivalent was defined as symptoms or findings commonly associated with ischemia in the absence of chest pain, such as dyspnea or heart

failure. Of normotensive patients, 19 (61%) were judged to have angina pectoris, 9 (29%) atypical angina, 2 (7%) an anginal equivalent and 1 (3%) noncardiac chest pain. Of 28 hypertensive patients without LVH, 12 (43%) had angina pectoris, 14 (50%) atypical angina, 1 (3.5%) an anginal equivalent and 1 (3.5%) noncardiac chest pain. Finally, of 39 hypertensive patients with LVH, 20 (51%) had angina pectoris, 9 (23%) atypical angina; 8 (21%) an anginal equivalent and 2 (5%) noncardiac chest pain.

Of the 31 normotensive patients, 11 (35%) were taking potentially vasoactive medications for treatment of chest pain. These included 10 patients receiving drugs with coronary vasodilating properties, such as nitroglycerin or a calcium channel blocker, and one patient receiving both a calcium channel blocker and a beta-blocker. In only one patient was a vasoactive medication (nitroglycerin paste) used within 12 h of cardiac catheterization.

Of the 28 hypertensive patients without LVH, 24 (86%) were taking potentially vasoactive medications for treatment of chest pain or hypertension. These included 10 patients receiving coronary vasodilator drugs alone, 4 patients receiving a beta-blocker alone, 5 patients receiving both a vasodilator and a beta-blocker and 4 patients receiving an angiotensin-converting enzyme (ACE) inhibitor or alpha-adrenergic blocking drug together with other drugs. In only two patients were vasoactive medications used within 12 h of cardiac catheterization (beta-blocker in one patient and calcium channel blocker in another).

Of the 39 hypertensive patients with LVH, 31 (79%) were taking potentially vasoactive medications for treatment of chest pain or hypertension. These included 13 patients receiving coronary vasodilating drugs alone, 2 receiving beta-blockers alone, 9 receiving both vasodilator and beta-blockers and 7 receiving an ACE inhibitor or alpha-adrenergic blocker together with other drugs. In nine of these patients, vasoactive medications were used within 12 h of cardiac catheterization. These included coronary vasodilator drugs in six patients, calcium channel blockers and beta-blockers in two patients and an ACE inhibitor in one patient.

Although only 12% of the study patients were taking vasoactive medications within 12 h, 7 normotensive patients, 16 hypertensive patients without LVH and 25 hypertensive patients with LVH (49%) were taking long-acting calcium channel antagonists or ACE inhibitors within 24 h of the study. A separate analysis revealed that there were no significant differences in peak responses to the endothelium-dependent and -independent agonists among these patients when compared with the larger group.

**Left ventricular mass measurements.** Left ventricular mass was calculated using M-mode echocardiographic measurements made in accordance with the Penn convention and corrected to agree with necropsy data as follows (23, 24):

$$
LV \, \text{mass} \, (g) = 1.04 \times (IVS \, + \, LVID \, + \, PWT)^{3} - (LVID)^{3} - 13.7,
$$

where IVS = interventricular septal thickness (cm); LV = left ventricular; LVID = left ventricular internal dimension at
end-diastole (cm); and PWT = left ventricular posterior wall thickness (cm). Analyses were performed using the calculated value of left ventricular mass indexed by BSA in meters squared. Partition values for LVH were taken from the Framingham Heart Study. Using BSA for indexing, normal meant $<131$ g/m$^2$ for men and $<100$ g/m$^2$ for women (22). Comparisons were made among normotensive subjects and hypertensive patients with and without LVH using the partitioning system described.

**Invasive coronary artery testing.** After diagnostic cardiac catheterization was performed, 7,000 U of intravenous heparin was administered and a 0.018-in. (0.045-cm) Cardiometrics Flo-Wire Doppler-tipped guide wire was advanced through a 7F or 8F coronary artery guiding catheter into the proximal to mid portion of the left anterior descending coronary artery in 64 patients, the left circumflex artery in 29 patients and the distal portion of the left main coronary artery in 5 patients. The placement of this device was optimized according to Doppler signal quality. At least 15 min elapsed between the end of the diagnostic study and baseline coronary velocity measurements. Coronary flow velocity signals were sampled at a preset fixed distance of 5.2 mm from the device tip to minimize the effect of turbulence caused by the presence of the measuring device. After stable measurements of baseline coronary flow velocity were obtained, drugs were infused in the left main coronary artery to test the capacity for vascular relaxation by endothelium-dependent and -independent mechanisms. Coronary flow velocity was continuously recorded on super VHS tapes during drug infusions so that peak drug effect could be identified during processing of data performed at a later date. Coronary angiograms were obtained under baseline conditions and at the end of each graded infusion of ACh.

**Intracoronary drug infusion protocols.** The following protocol was used to study endothelium-independent coronary vascular relaxation. Incremental doses of adenosine were used because of the potential for a dilutional effect of hypertension and LVH in some patients, due to increased coronary blood flow. Therefore, adenosine, 8 $\mu$g, was first administered by bolus infusion through the guiding catheter into the left main coronary artery. After return to the baseline values of coronary flow velocity, blood pressure and heart rate, adenosine, 16 $\mu$g, then 20 $\mu$g, was similarly administered. Typically, 60 s elapsed between each bolus infusion of adenosine. The next protocol was used to study graded responses during endothelium-dependent coronary vascular relaxation. An infusion monorail catheter was advanced over the Doppler wire device and placed near the tip, but still within the guiding catheter so that ACh was infused into the left main coronary artery (assumed blood flow 150 ml/min). After verification of stable velocity tracings, 3 ml of ACh was infused over 2 min through the infusion catheter at a rate of 0.15 $\mu$g/min ($10^{-8}$ mol/liter) using a Medfusion (Harvard) syringe pump. A coronary angiogram was obtained, and after return to the baseline values of coronary flow velocity, blood pressure and heart rate, 3 ml of ACh was infused over 2 min at a rate of 1.5 $\mu$g/min ($10^{-7}$ mol/liter); a third infusion was similarly administered at a rate of 15 $\mu$g/min ($10^{-6}$ mol/liter). In the same manner, a final infusion at a rate of 30 $\mu$g/min ($2 \times 10^{-6}$ mol/liter) was performed in 49% of the patients. Typically, 60 s elapsed between the end of one infusion and the onset of the next.

**Quantitative coronary angiography.** Baseline angiography of the coronary vessel undergoing study was performed in an optimal right anterior oblique or anteroposterior projection so that overlapping of branches and foreshortening of the region of interest were minimized. Angiography was repeated in the identical view after each infusion of ACh. Angiography was not repeated after each bolus of adenosine, because it was assumed that epicardial coronary diameter changes were minimal in response to this drug (25). An optimal end-diastolic cineangiographic frame was selected and coronary artery diameter measurements were performed at the site of Doppler velocity measurements at baseline and after each infusion of ACh. Measurements were performed using electronic digital calipers (Sandhill Scientific). Area was calculated assuming a circular cross-sectional profile. Percent change in coronary vessel diameter above baseline was calculated in response to each infusion of ACh. The contrast agent, iohexol, was used in all studies. Digital caliper measurements were later performed by a single investigator (J.L.H.) who had no knowledge of the clinical and echocardiographic findings. Measurements were repeated at least 1 year later in 27 patients randomly selected from the study cohort. Linear regression analysis of intraobserver variability for measurement of coronary artery diameter showed good reproducibility ($r = 0.92$, SEE = 0.26, $p < 0.001$).

**Coronary artery blood flow measurements.** Coronary artery blood flow was calculated as the product of mean coronary blood flow velocity and coronary artery cross-sectional area at the site of Doppler wire velocity measurements. Baseline values were calculated before infusion of the predominantly endothelium-independent agent, adenosine, and before infusion of the endothelium-dependent agent, ACh. Percent change in coronary blood flow above baseline was calculated in response to each infusion of adenosine and ACh.

**Statistical analysis.** Summary clinical data and outcomes of the research studies (percent change in coronary blood flow and in coronary diameter measurements in response to endothelium-dependent and -independent agonists) are expressed as the mean value ± SE. The unpaired Student t test (for continuous variables) and the chi-square test or Fisher exact test (for categoric variables) were used to assess statistical significance of group differences, where $p < 0.05$ was considered significant. Using linear regression analysis, correlations between percent change in coronary blood flow after ACh (a measure of resistance artery dilation) and percent change in coronary artery diameter after ACh (a measure of conduit artery dilation or constriction) were performed for 31 normotensive subjects, 28 hypertensive patients without LVH and 39 hypertensive patients with LVH. Repeated measures analysis of variance was used to test for differences found in coronary blood flow and coronary artery diameter responses to graded infusion of ACh, with the Bonferroni adjustment of probability values for multiple comparisons.
Table 1. Characteristics of 31 Normotensive Subjects, 28 Hypertensive Subjects Without Left Ventricular Hypertrophy and 39 Hypertensive Subjects With Left Ventricular Hypertrophy

<table>
<thead>
<tr>
<th></th>
<th>Normotensive (n = 31)</th>
<th>HTN Without LVH (n = 28)</th>
<th>HTN With LVH (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46 ± 2</td>
<td>48 ± 2</td>
<td>53 ± 2*</td>
</tr>
<tr>
<td>Female gender</td>
<td>13 (42%)</td>
<td>12 (43%)</td>
<td>27 (70%)*</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>15 (48%)</td>
<td>10 (36%)</td>
<td>19 (50%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>10 (26%)</td>
</tr>
<tr>
<td>LVM/BSA (g/m²)</td>
<td>101 ± 3</td>
<td>98 ± 3</td>
<td>149 ± 5*</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>135 ± 6</td>
<td>132 ± 7</td>
<td>131 ± 6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 1</td>
<td>32.5 ± 1.7*</td>
<td>33 ± 1*</td>
</tr>
<tr>
<td>EF (%)</td>
<td>62 ± 2</td>
<td>66 ± 2</td>
<td>64 ± 2</td>
</tr>
</tbody>
</table>

*p < 0.05 for significant difference. Data presented are mean value ± SE or number (%) of patients. BMI = body mass index; BSA = body surface area; EF = ejection fraction; HTN = hypertension; LDL = low density lipoprotein; LVM = left ventricular hypertrophy; LVH = left ventricular hypertrophy; LV = left ventricular mass.

Results

Patients. Ninety-eight subjects underwent invasive testing of coronary artery and arteriolar relaxation. None of the subjects had angiographic evidence of coronary artery disease. Sixty-one patients (62%) were white and 37 (38%) were African American. We have previously shown, in a cohort of black and white patients referred for coronary arteriography because of chest pain, that African American race is not associated with excess intrinsic or acquired depression in coronary vascular relaxation during peak effect of the endothelium-dependent and -independent agonists, ACh and adenosine, after adjustment for the presence of LVH (21). Fifty-two subjects (53%) were women and 46 (47%) were men. Thirty-one subjects were normotensive; 28 had hypertension without LVH; and 39 had hypertension with LVH based on the Framingham partitioning system described in the Methods section. Other characteristics are shown in Table 1. This reveals no significant differences in tobacco use, low density lipoprotein cholesterol and left ventricular ejection fraction among normotensive subjects, hypertensive patients without LVH and hypertensive patients with LVH. Those with hypertension were slightly older, more likely to be women and more likely to be obese when compared with normotensive subjects.

Endothelium-independent coronary microvascular relaxation. The response of the coronary microcirculation to the endothelium-independent agent, adenosine, was evaluated in 31 normotensive subjects, 28 hypertensive patients without LVH and 39 hypertensive patients with LVH. After adenosine, percent increase in coronary blood flow above baseline was similar among normotensive subjects and hypertensive patients without LVH (234 ± 10% vs. 232 ± 16%), but markedly depressed in patients with LVH (169 ± 14%, p < 0.004).

Of the three incremental doses of adenosine, the peak response occurred in the normotensive group after 8 µg in 7 (23%), after 16 µg in 15 (48%) and after 20 µg in 9 (29%). In hypertensive patients without LVH, the peak response occurred after 8 µg in 7 (25%), after 16 µg in 10 (36%) and after 20 µg in 11 (39%). Finally, in hypertensive patients with LVH, the peak response occurred after 8 µg in 5 (13%), after 16 µg in 12 (31%) and after 20 µg in 22 (56%).

Endothelium-dependent coronary microvascular and epicardial relaxation. Figure 1 demonstrates the response of the coronary microcirculation to the endothelium-dependent agent, ACh. Similarly, Figure 2 demonstrates the response of coronary epicardial vessels to ACh. After ACh, peak percent increase in coronary blood flow was similar among normotensive subjects and hypertensive patients without LVH, although slightly reduced in the latter group (213 ± 22% vs. 184 ± 28%). Similarly, responses of epicardial vessels (percent diameter increase above baseline) were not significantly different among normotensive subjects and hypertensive patients without LVH, although the responses were qualitatively different with dilation among normotensive subjects and mild constriction occurring among hypertensive patients (2.9 ± 2.1% vs. −1.1 ± 2.7%). However, significant depression in microcirculatory vasodilation (87 ± 10%, p < 0.0005) and frank constriction of epicardial vessels (−7.5 ± 1.9%, p < 0.05) were found in hypertensive patients with LVH.

Although the average response of conduit coronary arteries in normotensive subjects was dilation in response to ACh,
there was a range of findings, from a 31% increase to a 22% decrease in coronary diameter. Eight of 31 normotensive subjects (26%) demonstrated vasoconstriction after ACh. In hypertensive patients without LVH, the average response of conduit coronary arteries to ACh was mild constriction, with a range of findings from a 41% increase to a 29% decrease in coronary diameter. Twelve of 28 such patients (43%) demonstrated vasoconstriction after ACh. Finally, in hypertensive patients with LVH, the average response of conduit coronary arteries to ACh was constriction, with findings ranging from a 9% increase to a 41% decrease in coronary diameter. Twenty-two of 39 such patients (56%) demonstrated vasoconstriction after ACh.

In our study, the nearly universal response of coronary resistance vessels to ACh at peak effect was dilation. Although normotensive patients demonstrated an average increase in coronary blood flow of >200%, the range was 15% to 500%. Similarly, although hypertensive patients without LVH demonstrated an average increase in coronary blood flow of 184%, the range was 37% to 737%. Finally, hypertensive patients with LVH demonstrated an average increase in coronary blood flow of 87%, with a range of 3% to 238%. Although there was variation in the response of resistance vessels within each grouping, normotensive subjects and hypertensive patients without LVH both had markedly greater blood flow responses than did hypertensive patients with LVH (excess increase [95% confidence intervals]: 126% [73% to 179%] for normotensive subjects and 97% [42% to 152%] for hypertensive patients without hypertrophy).

Correlation between microcirculatory and conduit responses in normotensive subjects. Figure 3 shows the relation between microcirculatory and conduit vessel responses at peak effect of intracoronary infusion of ACh in 31 normotensive subjects. A significant correlation was found between the two variables ($y = 191 + 7.8x$, $r = 0.73$, $p = 10^{-6}$). For the most part, congruence was found among vasomotor responses of the microvasculature and conduit vessels with absence of vasoconstriction in 23 (74%) of 31 subjects. In the 8 subjects with conduit artery constriction, percent increase in microcirculation blood flow was significantly lower than in the 23 subjects with no change or dilation of conduit vessels (99 ± 28% vs. 253 ± 24%, $p = 0.001$). Other causes of endothelial dysfunction, such as increased age, hypercholesterolemia, male gender, tobacco usage and diabetes mellitus, were not disproportionately present among these eight subjects. Vasoconstriction of the microcirculation occurred in only one normotensive subject at ≥10^{-6} mol/liter of ACh, but in three patients at ≥10^{-7} mol/liter of ACh. The single subject demonstrating resistance vessel constriction during maximal and submaximal ACh infusion also demonstrated diffuse conduit vessel constriction at high and low infusion rates. Resistance vessel constriction occurring in two subjects during submaximal ACh infusion was transient and not associated with conduit vessel constriction.

Figure 2. Percent increase (negative numbers indicate constriction) in coronary artery diameter above baseline in response to graded intracoronary infusion of the endothelium-dependent agent ACh in 31 normotensive patients, 28 hypertensive patients without LVH and 39 hypertensive patients with LVH. Data are expressed as mean value ± SE. Abbreviations as in Figure 1.

Figure 3. Peak increase in coronary blood flow above baseline (percent) versus peak change in coronary artery diameter compared with baseline (percent) after intracoronary infusion of ACh in 31 normotensive patients. A significant correlation was found between the two variables ($y = 191 + 7.8x$, $r = 0.73$, $p = 10^{-6}$).
Correlation between microcirculatory and conduit responses in hypertensive patients without LVH. Figure 4 shows the relation between microcirculatory and conduit vessel responses at peak effect of intracoronary infusion of ACh in 28 hypertensive patients without LVH. A significant correlation was found between the two variables (y = 190 + 5x, r = 0.50, p = 0.006).

Correlation between microcirculatory and conduit responses in hypertensive patients with LVH. Figure 5 shows the relation between microcirculatory and conduit vessel responses at peak effect of intracoronary infusion of ACh in 39 hypertensive patients with LVH. A significant correlation was found between the two variables (y = 102 + 2x, r = 0.38, p = 0.02).

Discussion

The focus of our study was investigation of endothelial function among contiguous conduit and resistance coronary arteries in similar normotensive subjects and hypertensive patients referred for cardiac catheterization because of chest pain. Using the endothelium-dependent agonist, ACh, our study shows that endothelium-mediated responses of conduit and resistance coronary arteries are correlated most strongly among normotensive subjects (r = 0.73), less strongly among hypertensive patients without LVH (r = 0.50) and least strongly among hypertensive patients with LVH (r = 0.38). In response to graded infusion of ACh, endothelium-dependent vasodilation of coronary resistance vessels was slightly depressed in hypertensive patients without LVH and markedly depressed in hypertensive patients with LVH when compared with normotensive subjects. Similarly, conduit vessels dilated in normotensive subjects after ACh, constricted slightly in hypertensive patients without LVH and constricted significantly in hypertensive patients with LVH. Greater frequency of discordant conduit and resistance artery responses and transient constric-
tion of resistance arteries during submaximal infusion of ACh were found with increasing severity of hypertension. As a point of reference, vasomotor responsiveness of the microcirculation to the endothelium-independent agonist, adenosine, was nearly identical among normotensive subjects and hypertensive patients without LVH. However, hypertensive patients with LVH demonstrated significantly depressed vasomotor responses to adenosine. In our study, hypertensive patients with and without LVH required a higher adenosine bolus than did normotensive patients to elicit the greatest response.

Conduit vessel responses. In response to peak effect of ACh, the average response of conduit coronary arteries was dilation in normotensive subjects, mild constriction in hypertensive patients without LVH and significant constriction in hypertensive patients with LVH. A range of findings from dilation to constriction was present in all three groups, but was shifted toward dilation in normotensive subjects and toward constriction in hypertensive patients with LVH. As a group, hypertensive patients with and without LVH demonstrated the most heterogeneity of conduit artery responses. In all three groups, conduit vessel constriction was, overall, associated with resistance vessel dysfunction, although there were exceptions found among hypertensive patients without LVH. Increasing severity of hypertension was associated with an increasing tendency for conduit artery constriction and associated resistance vessel dysfunction.

Resistance vessel responses. Although conduit vessels displayed a range of findings from dilation to constriction, the usual response of resistance vessels to ACh was progressive relaxation. Relaxation was greatest among normotensive subjects, followed closely by hypertensive patients without LVH, but then trailed distantly by hypertensive patients with LVH.

Correlation between conduit and resistance artery responses. When present, depression in endothelial function was usually, but not always, manifested in both conduit and resistance vessels. Thus, epicardial coronary artery constriction predicted depression in microcirculatory function in normotensive subjects and hypertensive patients without overt coronary atherosclerosis in our study. As a group, however, more dispersion of responses was found among hypertensive patients without LVH, which may, in part, be related to varying duration of disease and to the clinical heterogeneity of mild to moderate hypertension. Although maximal ACh infusion (≥10−6 mol/liter) resulted in epicardial vasocstriction in 43% of patients, microcirculatory vasocstriction (as evidenced by decreased coronary blood flow when compared with baseline) occurred in only two patients (2%) during maximal infusion of ACh. Both of these subjects demonstrated conduit artery constriction. However, transient vasocstriction of the microcirculation occurred in 23 patients in response to submaximal infusion of ACh (≤10−7 mol/liter), with conversion to dilation in all 23 at greater infusion rates of ACh. Sixteen of these 23 patients demonstrated conduit vessel constriction.

Explanations for a heterogeneous effect of ACh on conduit and resistance vessels include the following possibilities: differing contractile sensitivity of conduit and resistance vessel smooth muscle and differing release or efficacy of endothelium-derived relaxing or constricting factors in response to ACh. The latter possibility includes differences not only in type but also in quantity of vasoactive substances released by the endothelium. Some studies have suggested that, unlike conduit arteries where nitric oxide is the principal endothelium-derived relaxing factor released by the endothelium, resistance artery endothelium releases predominantly endothelium-derived hyperpolarizing factor in response to ACh (7,8,26,27). Because specific blockers of endothelium-derived relaxing factors were not administered during our study, the exact mechanisms cannot be identified. Release of both endothelium-derived relaxing and constricting factors after exposure to ACh was previously demonstrated in aortic rings from the spontaneously hypertensive rat, resulting in depression of relaxation at higher concentrations of the muscarinic agonist (10−6 to 10−5 mol/liter) (28). Just as the predominant type of relaxing factor released by the endothelium may differ between conduit and resistance coronary vessels, so too may the predominant form of endothelium-derived constricting factor differ.

Although the vascular wall is morphologically similar among coronary conduit and resistance vessels, certain differences exist. Like other vascular beds, the conduit vessels are exposed to systemic arterial pressures, but a large pressure drop occurs across smaller coronary arteries, leading to markedly lower perfusion pressures in the resistance arteries (29,30). Unlike other vascular beds, the intramyocardial resistance coronary arteries are exposed to the throttling effect of left ventricular contraction during each systole. Thus, coronary perfusion is governed not only by the driving pressure and resistance vessel tone, but also by the parenchymal resistance encountered during each systole. Because of these special characteristics, coronary blood flow occurs predominantly in diastole in the left coronary artery (31). In hypertension, blood pressure elevation usually precedes development of LVH. Thus, the earliest adverse findings are expected in conduit coronary vessels that are exposed to the ambient systemic pressure. Later in the course of hypertension, development of LVH contributes to increased parenchymal resistance and is associated with resistance vessel endothelial dysfunction (10). Our study suggests that coronary conduit vessels are affected, on average, earlier and more prominently than resistance vessels in the course of hypertensive disease. In addition, we have shown that LVH appears to be a marker for resistance coronary artery endothelial dysfunction.

Clinical implications. Endothelial dysfunction of the coronary arteries is found across a broad spectrum of conditions in patients who are free of angiographic evidence of coronary atherosclerosis (9,10,32–38). These conditions include increased age, systemic hypertension, LVH, cardiomyopathy, hyperlipidemia, diabetes mellitus, chronic tobacco use and estrogen deficiency. Not coincidentally, most of these conditions are risk factors for development of coronary artery atherosclerosis (39). Endothelial function studies, performed in the human forearm circulation, have contributed impor-
stantly to the understanding of endothelial dysfunction in hypertension. These studies have demonstrated that peripheral conduit and resistance artery responses to several endothelium-dependent vasodilator agonists (including ACh, bradykinin, substance P and flow mediators) are significantly blunted in hypertension (13–15). Several studies have also shown that endothelial dysfunction begins early even before evidence of atherosclerotic plaques and is present among asymptomatic children and young adults at high risk for future development of atherosclerosis because of unfavorable risk factor profiles (12,14).

Our study concentrates on one risk factor, systemic hypertension, and the associated adverse effects on contiguous conduit and resistance coronary artery endothelial function. We found that conduit coronary vessels are affected earlier and more prominently when compared with resistance arteries. In hypertensive patients in our study, endothelial dysfunction was generally manifested as frank constriction in conduit vessels and as depressed dilation in resistance vessels. However, we observed increasing frequency of coronary resistance artery constriction with increased severity of hypertension during submaximal (\(\leq 10^{-6}\) mol/liter) infusion of ACh. This constriction was subsequently reversed during maximal (\(\geq 10^{-6}\) mol/liter) infusion of ACh in nearly all patients, suggesting that an endothelium-derived relaxing factor ultimately overcame constriction. Other studies have reported the presence of resistance or conduit vessel constriction during submaximal infusions of ACh (9,10,27,40). The observations that hypertensive conduit coronary vessels constrict in a progressive fashion and resistance arteries demonstrate dilation or a biphasic response after ACh suggest once again that the endothelium-derived relaxing factor is qualitatively or quantitatively different among conduit and resistance coronary arteries (17).

Hypertension may lead to coronary atherosclerosis, LVH and cardiomyopathy. Development of atherosclerosis in conduit arteries is generally believed to be a consequence of endothelial dysfunction in response to multiple known risk factors (41). However, the etiology of cardiomyopathy secondary to hypertension is not fully understood. One contributory factor may be diffuse resistance vessel endothelial dysfunction resulting in depressed dilation or even transient constriction. This could lead to intermittent vascular insufficiency, patchy myocardial necrosis and ultimately cardiomyopathy.

**Study limitations.** A number of different technologies are available for quantifying coronary diameter changes during infusion of vasoactive drugs. Two techniques, automated edge-detection quantitative coronary angiography and cinevideo-densitometry, allow accurate estimates of coronary diameter and area in the absence of eccentric lesions (42–45). Electronic digital calipers are useful for performing serial angiographic measurements because of simplicity and low cost. Although this technique has been shown to consistently overestimate the true diameter of phantoms, when serial measurements are expressed as percent diameter change from baseline (as was done in our study), comparable results were found using either digital calipers or automated quantitative coronary angiography (42).

Because specific blockers of endothelium-derived relaxing factors were not administered, we cannot definitively establish that there were qualitative or quantitative differences in the relaxing factor released by the endothelium of conduit and resistance coronary arteries among our study patients. Administration of such blockers in nitric oxide–deficient blood vessels would be expected to show little change in the ACh responses, but significantly less dilator responses and greater vasoconstriction in those vessels with normal or near normal nitric oxide production (46). Additional studies are required using specific blockers of nitric oxide production such as N\(^{3}\)-monomethyl-L-arginine or N\(^{6}\)-nitro-L-arginine. An alternative but less sensitive approach would involve studying the response of conduit and resistance vessels to infusion of L-arginine, the precursor of nitric oxide in patients with demonstrable endothelial dysfunction.

Although our investigation focuses on vasomotor changes in hypertension, there are multiple other conditions or factors that may be involved in individual patients, including idopathic depression in microvascular relaxation (syndrome X), resistance to adenosine or ACh effect, variability in Doppler velocity or epicardial diameter measurements and the other classic risk factors for coronary atherosclerosis.

Our study design did not include the additional complexity of simultaneous left ventricular diastolic pressure measurements, which would be necessary for accurate calculation of microvascular diastolic resistance. Therefore, this study cannot differentiate between the effects of tissue compression secondary to LVH and direct vasomotor changes, both of which could contribute to impaired microvascular relaxation.

Although the patients in our study had normal coronary arteriograms, their referral for cardiac catheterization because of chest pain differentiates them from a purely volunteer group with normal coronary arteries. Thus, our findings may not be generalizable to normal subjects or those with causes of endothelial dysfunction other than hypertension.

**Conclusions.** Despite angiographically normal coronary arteries, heterogeneous vasomotor responses (dilation and constriction) were demonstrated in contiguous conduit and resistance arteries in normotensive subjects and hypertensive patients referred for cardiac catheterization because of chest pain. In addition to more severe endothelial dysfunction among conduit and resistance arteries, greater frequency of discordant conduit and resistance artery responses and resistance vessel constriction were found with increasing severity of hypertension. Our results suggest that the endothelium-derived relaxing factor elicited by ACh may differ in a qualitative or quantitative fashion among conduit and resistance coronary arteries in hypertensive subjects referred for cardiac catheterization because of chest pain.

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References


