Attenuated Coronary Flow Reserve and Vascular Remodeling in Patients With Hypertension and Left Ventricular Hypertrophy

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OBJECTIVES
The purpose of this study was to evaluate the association between hypertension and left ventricular hypertrophy (LVH) with both coronary vascular remodeling and endothelial function.

BACKGROUND
The association between endothelial and nonendothelial coronary flow reserve with vascular remodeling in patients with hypertension and LVH is still unclear.

METHODS
One hundred and eleven patients with normal or mildly diseased coronary arteries at angiography underwent intravascular ultrasound examination of the left anterior descending coronary artery. Patients were divided into three groups: group 1: \( n = 13 \), hypertensive patients with LVH; group 2: \( n = 30 \), hypertensive patients without LVH; group 3: \( n = 68 \), normotensive patients. Vessel and lumen area and atherosclerotic plaque area were evaluated. Vascular reactivity was examined using intracoronary adenosine and acetylcholine.

RESULTS
Vessel area in group 1 (with LVH) was significantly (\( p < 0.01 \)) greater than that in group 2 (without LVH), whereas, vessel area in both groups 1 and 3 was similar (12.8 ± 0.8 mm², 10.7 ± 0.4 mm² and 11.5 ± 0.3 mm²). Coronary blood flow at baseline for patients in group 1 (with LVH) was significantly greater than it was for patients in groups 2 and 3 (81.1 ± 9.9 ml/min, 56.5 ± 6.2 ml/min and 48.1 ± 3.2 ml/min, both \( p < 0.05 \)). In comparison with groups 2 and 3, the response to both acetylcholine and adenosine was significantly impaired in patients with LVH.

CONCLUSIONS
The current study demonstrates that hypertension with LVH is associated with both coronary vascular remodeling and attenuated endothelial and nonendothelial coronary flow reserve.

Arterial hypertension is the most common cause of chronic pressure overload of the left ventricle, and left ventricular hypertrophy (LVH) represents the general structural mechanism of cardiac adaptation in response to chronic pressure overload. Left ventricular hypertrophy is associated with an increased incidence of adverse cardiovascular events (1). Potential mechanisms that might account for this observation include increased vulnerability of the hypertrophied myocardium to ischemic damage and enhanced arrhythmogenesis (2–5). Moreover, patients with hypertension and LVH have signs and symptoms of myocardial ischemia in the absence of significant coronary stenoses (6–8). This may be related to reduced coronary vasodilator capacity (7–9), and, indeed, some investigators demonstrated that, in the absence of obstructive coronary artery disease, the endothelium-dependent vasodilation in both epicardial and resistance coronary arteries was impaired in hypertensive disease (10–13). Coronary vascular remodeling is an active process in hypertension and LVH; in response to increased arterial pressure, the vessel structure may be altered. The increase in luminal dimensions with LVH may represent an adaptive response to maintain coronary flow velocity and shear stress constant (14–16). However, the association between these structural and functional alterations in the coronary circulation in patients with hypertension and LVH is not clear.

The purpose of this study was to assess the association between hypertension and LVH with both coronary vascular remodeling and endothelial and nonendothelial coronary flow reserve (CFR).

METHODS

Study population. One hundred and eleven patients who had been referred for cardiac catheterization to exclude coronary artery disease were prospectively studied. Patients...
were included in this study if they had the following: 1) angiographically smooth arteries, 2) mild irregularities with no coronary artery lesion >30% lumen diameter stenosis by visual assessment in any major epicardial vessel, and 3) the proximal coronary arteries were >2.0 mm in diameter. Patients with an obvious history of variant angina, previous myocardial infarction, previous coronary artery bypass grafting or coronary intervention were excluded from this study. Long-acting nitrates, angiotensin converting enzyme inhibitors or calcium channel blocking agents were withheld for at least 48 h before the study.

The 111 patients of this study were divided into three groups according to their history of hypertension and the presence of hypertensive LVH assessed by echocardiogram. Group 1 consisted of 13 patients who had hypertension with LVH. Group 2 consisted of 30 patients with hypertension without LVH. Group 3 consisted of 68 patients without hypertension. The study was approved by the Mayo Clinic Institution Review Board.

Definition of hypertension and LVH. Patients were considered to have systemic hypertension if they had a history of elevated blood pressure requiring long-term therapy. Left ventricular hypertrophy was defined as posterior wall thickening >13 mm on echocardiogram in hypertensive patients or increased left ventricular mass (LVM) index (LVMi) g/m\(^2\) (17). Left ventricular mass was measured according to the following equation LVMi = 1.04 (\[LVID + IVS + PW\]^3 – LVID^3\] – 13.6 divided by the body surface area, where LVID = left ventricular internal dimension at end-diastole, IVS = septal thickness at end-diastole and PW = posterior wall (17). The control blood pressure in a drug-free period at the time of cardiac catheterization was recorded in all patients. At this time patients with and without hypertension had a mean arterial blood pressure of 111 ± 2 and 102 ± 2 mm Hg, respectively (p < 0.01).

Study protocol. Diagnostic coronary angiography was performed using a 6F Judkins catheter with a standard femoral percutaneous approach. Twenty-five hundred U of heparin were administered at the beginning of the procedure. Nonionia contrast material was used for all patients. No nitroglycerin was given before the diagnostic procedure.

Coronary blood flow reserve in response to acetylcholine and adenosine was studied according to a previously reported protocol (18–20). After control coronary angiograms had been obtained, a 0.014 in. Doppler guidewire (Cardiovascular Imaging Systems, Sunnyvale, California) was introduced through an 8F guiding catheter into the left anterior descending coronary artery. Once baseline flow velocity data were obtained at the position after a stable Doppler signal was obtained, a bolus of intracoronary adenosine (18–54 μg; solution of 6 mg adenosine in one liter of saline) was administered until a plateau was achieved. Then selective intracoronary infusion of increasing concentrations of acetylcholine (10\(^{-6}\), 10\(^{-5}\) and 10\(^{-4}\) mol/liter) was performed for a total duration of 3 min through a 2.2F Tracker coronary infusion catheter (SciMed Life System, Maple Grove, Minnesota) over a 0.014 in. Doppler guidewire (21). Symptoms, hemodynamic data, electrocardiogram and Doppler velocities were recorded at the end of each infusion. If there was severe constriction of the coronary arteries with any dose of acetylcholine, the infusions were stopped. Just before the end of each dose of acetylcholine, angiography was repeated. After infusions of acetylcholine, 300 μg of nitroglycerin was given by an intracoronary route, and angiography was repeated within 2 min after the nitroglycerin was given. The coronary angiograms were performed in the same projection as the baseline coronary angiogram.

Intravascular ultrasound examination. One of three intracoronary ultrasound systems (Endosonics, Rancho Cordova, California; Cardiovascular Imaging Systems and Hewlett-Packard, Boston, Massachusetts) was used in this study. Details of these systems have been described elsewhere (22,23). The intracoronary ultrasound catheters were inserted through the 8F guide catheter and placed into the proximal and middle portion of the left anterior descending artery over a 0.014-in., high torque floppy guidewire (Advanced Cardiovascular Systems, Sunnyvale, California). After optimization of the ultrasound image, continuous real-time images were recorded on 0.5-in. videotape. Four to five segments of the left anterior descending coronary artery were identified.

Quantitative coronary angiography. Analysis of artery diameter from the cine films was done with a modification of the technique previously described by this institution (18,24,25). These measurements were made with no knowledge of the ultrasound findings.

Assessment of coronary blood flow. Doppler flow velocity spectra were analyzed on-line to determine time-averaged peak velocity. Coronary flow reserve (CFR) to adenosine was calculated as the ratio of hyperemic to basal average peak velocity of the distal vessel. Volumetric coronary blood flow (CBF) was determined from the relation: CBF = cross-sectional area × average peak velocity × 0.5 (26). Endothelial-dependent coronary flow reserve was calculated.
as percent change in CBF in response to acetylcholine, as previously described (19,20). Coronary vascular resistance was calculated as the mean arterial pressure divided by the CBF.

**Intracoronary ultrasound image analysis.** An off-line computer-interactive analysis system was used to digitize the intracoronary ultrasound video images onto a 256 × 256-bit matrix. All the data were analyzed without knowledge of the patients' history of hypertension and LVH. Standard calibration markers directly from the ultrasound image were used for calibration of absolute measurements. Measurements of area stenosis and minimal lumen diameter were made of the most severely stenosed region at each specific segment of the artery that had been previously identified. With computer planimetry, the specific segment was assessed quantitatively. The external elastic membrane cross-sectional area, which represents the area within the border between the hypoechoic media and echoreflective adventitia, was a measure of total arterial cross-sectional area (vessel area). Because intravascular ultrasound cannot measure media thickness accurately, plaque plus media cross-sectional area (plaque area), which was calculated as external elastic membrane cross-sectional area (vessel area) minus lumen cross-sectional area (lumen area), was used as a measure of plaque mass. Percent area stenosis was calculated as the ratio of plaque plus media to external elastic membrane cross-sectional area. Morphologic plaque features were classified according to the following definitions by consensus. Segments that had concentric prominent leading edge echo and widened subintimal echolucent zone, with combined thickness <0.3 mm, were classified as normal. Soft plaque was less dense than the reference adventitia. Fibrous plaque is composed of thickened dense echoes involving the intimal leading edge with homogenous echodensity equal to that seen for the adventitia. Hard plaque was more dense than the reference adventitia and had no acoustic shadowing. Calcific tissue produced bright echoes with acoustic shadowing. In segments with a calcium arc >90°, the external elastic lamina was not traced because of potential inaccuracy due to shadowing and were excluded from further analysis.

**Inter- and intraobserver variability.** Two ultrasound sites from 10% of the patients studied were randomly selected and measured by the same observer on two separate occasions and also by a second observer. These measurements were then used to evaluate intra- and interobserver variability on two separate occasions and also by a second observer. These were expressed as linear regression between the two observations and as percent error, derived as the absolute difference between observations.

**Statistical analysis.** Values are expressed as the mean ± 1 SEM. Statistical significance was accepted when the probability value was p < 0.05. The relationship between two parameters was evaluated with a linear regression analysis. Comparisons of the baseline cardiovascular risk variables between the three groups were done with the Pearson’s chi-square test. Comparisons of hemodynamic and echocardiographic data between the study groups were done with one-way analysis of variance.

**RESULTS**

One-hundred and eleven patients with normal and mildly diseased coronary arteries were studied. Thus, a total of 397 segments of 111 patients were evaluated.

**Patient characteristics.** Gender distribution, age and body surface area (BSA) were similar in the three groups. With regard to other coronary risk factors, there was no difference among the study group. Systolic and mean blood pressure at time of catheterization in groups 1 and 2 were similar and significantly greater than those in group 3 (both p < 0.01 and p < 0.05, respectively). Left ventricular posterior wall thickness as well as LVMI in group 1 was significantly higher than that in group 2 (p < 0.01). There was no difference in left ventricular end-diastolic (LVDd) and left ventricular end-systolic (LVDs) dimensions between groups 1 and 2 (Table 1).

**Intravascular ultrasound data.** The dimensions of vessel area: the external elastic membrane cross-sectional area that represents the area within the border between the hypoechoic media and echoreflective; lumen area: lumen cross-sectional area and plaque area: plaque plus media cross-sectional area, which was calculated as vessel area minus lumen area of the three groups, are shown in Figure 1. Plaque area was not significantly different between the three groups: 3.8 ± 0.4 mm² (group 1), 3.4 ± 0.2 mm² (group 2) and 3.2 ± 0.2 mm² (group 3). However, lumen area in the patients with LVH (group 1) and the normotensive patients (group 3) was significantly and significantly (p < 0.01 and p < 0.05, respectively) larger than that in group 2: 9.0 ± 0.6 mm² (group 1), 7.4 ± 0.3 mm² (group 2) and 8.4 ± 0.2 mm² (group 3). In addition, vessel area in group 1 was significantly (p < 0.01) bigger than that in hypertension patients without LVH (group 2): 12.8 ± 0.8 mm² (group 1), 10.7 ± 0.4 mm² (group 2) and 11.5 ± 0.3 mm² (group 3).

Vessel area significantly increased with plaque area in all three groups. Vessel area in the three groups increased 1.39 mm², 1.13 mm² and 1.33 mm² for every 1-mm² increase in plaque area, suggesting that the vessel enlarges in response to plaque accumulation (r = 0.66, p < 0.0001; r = 0.67, p < 0.0001 and r = 0.64, p < 0.0001, respectively).

Percent area stenosis, maximal thickness of plaque and plaque composition are shown in Table 2. Percent area stenosis in group 3 was significantly smaller than that in group 2 (p < 0.05). With regard to plaque composition, the three groups did not differ in any type of plaque.

The interobserver variability was 0.4 ± 2.4% and 1.06 ± 4.3% for the coronary diameter and area measurements,
respectively, and the intraobserver variability was 0.8 ± 1.9% and 1.5 ± 3.3% for the coronary diameter and area measurements, respectively.

**Changes in CBF.** Baseline CBF in group 1 was significantly greater than that in groups 2 and 3 (p < 0.05 and p < 0.01, respectively). The coronary vascular resistance was significantly reduced in group 1 in comparison with the other groups (1.7 ± 0.3, 2.7 ± 0.3 and 2.9 ± 0.2 respectively, both p < 0.05). Furthermore, there was significant correlation between LVH assessed by left ventricular mass and baseline CBF (Fig. 2). The percent increases in CBF induced by acetylcholine in group 1 were significantly smaller than those in group 3 (p < 0.01) and tended to be smaller but not significantly so than those in group 2 (p = 0.18), suggesting that endothelium-dependent vasodilation in hypertensive patients with LVH was impaired.

The calculated CFR examined using adenosine in group 1 was significantly smaller than that in groups 2 and 3 (p < 0.05 and p < 0.01, respectively), suggesting that the dilator

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension With LVH</td>
<td>n = 13</td>
<td>n = 30</td>
<td>n = 68</td>
</tr>
<tr>
<td>Men (%)</td>
<td>3/13 (23%)</td>
<td>10/30 (33%)</td>
<td>30/68 (44%)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55 ± 3</td>
<td>53 ± 2</td>
<td>50 ± 2</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.79 ± 0.06</td>
<td>1.90 ± 0.03</td>
<td>1.91 ± 0.03</td>
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<tr>
<td>Risk factors</td>
<td></td>
<td></td>
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<tr>
<td>Hypercholesterolemia</td>
<td>8/13 (62%)</td>
<td>18/30 (60%)</td>
<td>27/68 (40%)</td>
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<tr>
<td>Diabetes (%)</td>
<td>1/13 (8%)</td>
<td>2/30 (7%)</td>
<td>8/68 (12%)</td>
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<tr>
<td>Smoking (%)</td>
<td>5/13 (38%)</td>
<td>18/30 (60%)</td>
<td>40/68 (59%)</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>8/13 (62%)</td>
<td>19/30 (63%)</td>
<td>42/68 (62%)</td>
</tr>
<tr>
<td>Postmenopause (%)</td>
<td>7/13 (54%)</td>
<td>15/30 (50%)</td>
<td>23/68 (34%)</td>
</tr>
<tr>
<td>Hemodynamics data</td>
<td></td>
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<tr>
<td>Systolic BP (mm Hg)</td>
<td>156 ± 7†</td>
<td>147 ± 4‡</td>
<td>133 ± 3</td>
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<tr>
<td>Diastolic BP (mm Hg)</td>
<td>85 ± 3</td>
<td>83 ± 2</td>
<td>79 ± 1</td>
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<tr>
<td>Mean BP (mm Hg)</td>
<td>114 ± 4†</td>
<td>110 ± 3‡</td>
<td>102 ± 2</td>
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<tr>
<td>Echocardiographic data</td>
<td></td>
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<tr>
<td>LVDd (mm)</td>
<td>45.8 ± 1.3</td>
<td>48.3 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>27.8 ± 1.2</td>
<td>29.8 ± 1.3</td>
<td></td>
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<tr>
<td>LVPW (mm)</td>
<td>13.5 ± 0.2*</td>
<td>9.6 ± 0.2</td>
<td></td>
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<tr>
<td>LVMI (g/m²)</td>
<td>165 ± 7.6*</td>
<td>141.2 ± 7.2</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SE. BP = blood pressure; BSA = body surface area; LVDd and LVDs = left ventricular end-diastolic and end-systolic dimension; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; LVPW = left ventricular post wall thickness. *p < 0.01 versus group 2; †p < 0.01; ‡p < 0.05 versus group 3.

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**Table 2. Plaque Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive With LVH</td>
<td>n = 42</td>
<td>n = 104</td>
<td>n = 251</td>
</tr>
<tr>
<td>Percent area stenosis (%)</td>
<td>29.4 ± 2.3</td>
<td>30.0 ± 1.5</td>
<td>26.4 ± 0.9*</td>
</tr>
<tr>
<td>Maximal plaque thickness (mm)</td>
<td>0.58 ± 0.06</td>
<td>0.59 ± 0.04</td>
<td>0.52 ± 0.03</td>
</tr>
<tr>
<td>Plaque composition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft (%)</td>
<td>19/29 (66%)</td>
<td>39/69 (57%)</td>
<td>103/154 (67%)</td>
</tr>
<tr>
<td>Fibrous (%)</td>
<td>5/29 (17%)</td>
<td>20/69 (29%)</td>
<td>29/154 (19%)</td>
</tr>
<tr>
<td>Hard (%)</td>
<td>1/29 (3%)</td>
<td>3/69 (4%)</td>
<td>8/154 (5%)</td>
</tr>
<tr>
<td>Mixed (%)</td>
<td>4/29 (14%)</td>
<td>7/69 (10%)</td>
<td>14/154 (9%)</td>
</tr>
</tbody>
</table>

Values are mean ± SE. LVH = left ventricular hypertrophy. *p < 0.05 vs. group 2.
capacity of the coronary microcirculation in hypertensive patients with LVH was attenuated (Table 3 and Fig. 3). However, there was no significant correlation between maximal plaque thickness and endothelial function ($r = 0.04$) or endothelial-independent CFR ($r = 0.05$).

**DISCUSSION**

This study demonstrates for the first time in humans with hypertension and LVH that functional abnormalities in CFR are associated with structural changes.

**Effects of LVH on CBF and vascular reactivity.** Several studies have shown that the endothelium is functionally abnormal in hypertensive patients (12,27,28). In response to infusion of acetylcholine, our study showed that endothelium-dependent vasodilation of resistance coronary arteries was nearly identical among normotensive patients and hypertensive patients without LVH. Our results are consistent with the previous studies that arterial hypertension without established LVH had no apparent effect on acetylcholine-induced increases in CBF (29,30). However, hypertensive patients with LVH demonstrated significantly attenuated response to acetylcholine. Additionally, a history of hypertension had no apparent effect on CBF responses to adenosine in our patients, who had no evidence of LVH. However, the presence of LVH was associated with significant impairment of adenosine-induced CBF responses. Furthermore, CBF at rest in patients without LVH or normotensive patients were similar and was significantly smaller when compared with hypertensive patients with LVH. These results are consistent with previous studies that CBF is increased in patients with LVH (31,32). Therefore, in hypertensive patients with LVH, the increased basal CBF to the hypertrophied myocardium leads to the reduction of its functional vasodilator capacity. The attenuated responses to acetylcholine and adenosine in the LVH group do not necessarily mean that endothelial function is altered. It may

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**Table 3.** Coronary Hemodynamic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Hypertensive With LVH</th>
<th>Group 2 Hypertensive Without LVH</th>
<th>Group 3 Normotensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>n = 13</td>
<td>n = 30</td>
<td>n = 68</td>
</tr>
<tr>
<td>CBF at baseline (ml/min)</td>
<td>81.1 ± 9.9*†</td>
<td>56.5 ± 6.2</td>
<td>48.1 ± 3.2</td>
</tr>
<tr>
<td>Coronary flow reserve to adenosine</td>
<td>2.3 ± 0.2*‡</td>
<td>2.7 ± 0.1</td>
<td>2.8 ± 0.1</td>
</tr>
<tr>
<td>Coronary vascular resistance (mm Hg min/ml)</td>
<td>1.7 ± 0.3*‡</td>
<td>2.7 ± 0.3</td>
<td>2.9 ± 0.2</td>
</tr>
<tr>
<td>CBF change induced by acetylcholine (min/ml)</td>
<td>99.3 ± 29.0</td>
<td>78.1 ± 11.5</td>
<td>69.8 ± 6.8</td>
</tr>
<tr>
<td>% change of CBF induced by acetylcholine (%)</td>
<td>1.5 ± 20.5†</td>
<td>46.9 ± 20.2</td>
<td>56.1 ± 13.1</td>
</tr>
<tr>
<td>% change of CAD induced by acetylcholine (%)</td>
<td>-31.6 ± 9.5</td>
<td>-11.3 ± 5.4</td>
<td>-12.3 ± 4.2</td>
</tr>
</tbody>
</table>

*Values are mean ± SE.

CAD = coronary artery diameter; CBF = coronary blood flow; LVH = left ventricular hypertrophy.

* $p < 0.05$ versus group 2; † $p < 0.01$; ‡ $p < 0.05$ versus group 3.
be speculated that there is maximal endothelial and nonendothelial coronary vasodilation to supply increased CBF in order to meet the increased myocardial demand. This hypothesis is supported by the current observation that the coronary vascular resistance was significantly reduced in patients with hypertension with LVH. Thus, with further increase in myocardial demand, myocardial ischemia may occur.

**Structural vascular alterations in LVH.** Hypertensive vessels are characterized by thickened media, reduced lumen and increased extracellular matrix (33,34). The observation in our study of the reduction in lumen area in hypertensive patients without LVH when compared with that in normotensive patients is consistent with these studies. Additionally, vessel and lumen area in hypertensive patients with LVH were significantly enlarged compared with those in hypertensive patients without LVH. These results correspond to previous necropsy studies that had reported an increase in coronary artery diameter in hypertrophied hearts (35,36). These data indicate that lumen and vascular area vary with changing blood flow in hypertensive patients with LVH. This study, however, did not address the structural abnormalities of the intramyocardial arterioles because histologic analysis was not made.

**Mechanisms of coronary remodeling.** In normal subjects, the internal diameter of normal coronary arteries is correlated to blood flow, and changes result mainly from remodeling of the arterial wall (37). The increase in lumen area appears to establish a constant blood flow velocity in the large epicardial coronary artery despite increased total CBF. The maintenance of constant blood flow velocity would maintain normal endothelial function because arterial endothelium appears to be sensitive to shear stress (38). The shear stress mediates the release of the endothelium-derived relaxing factor (39,40). It has been suggested that endothelium-derived relaxing factor is a potent vasodilator (41) that inhibits growth factor stimulated proliferation of vascular smooth muscle cells (42), endothelial movement (43) and extracellular matrix production (44). Thus, endothelium-derived relaxing factor has many of the attributes necessary to suggest its role as a mediator of vascular remodeling. Vascular remodeling with compensatory coronary enlargement tends to normalize coronary flow velocity and, thus, shear stress, resulting in a reduced release of the endothelium-derived relaxing factor. Therefore, chronic epicardial coronary enlargement may be an adaptation to chronically increased release of the endothelium-derived relaxing factor in hypertensive LVH.

**Study limitations.** This study is a cross-sectional study, and its findings may warrant confirmation through a prospective study. Moreover, the administration of intracoronary adenosine rather than intravenous administration prevents us from assessing the coronary vascular resistance ratio.

**Clinical implications.** Reduced CFR is an important feature of hypertrophied ventricle. Although this reduced CFR may not affect left ventricular function at rest, it could cause impaired subendocardial wall function and reduced subendocardial coronary perfusion during periods of stress in the hypertrophied myocardium. Repeated stress and subendocardial ischemia lead to subendocardial fibrosis, which also impairs systolic function. Both the subendocardial ischemia and fibrosis alter left ventricular diastolic function, thereby also impairing systolic function. All of these mechanisms are linked by reduced CFR, which accelerate the progression from compensated left ventricular hypertrophy to failure (45,46).

**Conclusions.** The effect of left ventricular hypertrophy on lumen area may result not from a decrease in plaque area but rather an increase in vessel area reflecting vascular remodeling in hypertensive LVH. Additionally, these structural changes occur in association with impairment of both endothelium dependent and independent vasmotion responses, which could be caused by maximal coronary vasodilation at the level of the resistance vessels. Therefore, in humans with hypertension and LVH, functional abnormalities in CFR are associated with structural changes.

**REFERENCES**

10. Panza JA, Quyyumi AA, Brush JE, Epstein SE. Abnormal