Effect of Left Ventricular Hypertrophy on Myocardial Blood Flow and Ventricular Performance in Systemic Hypertension

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SUMMARY  The effect of myocardial hypertrophy resulting from chronic pressure overload upon myocardial blood flow (MBF) and left ventricular (LV) performance was studied in 17 hypertensive patients, nine of whom had left ventricular hypertrophy (LVH), and nine normotensive controls. Mean LV MBF was measured at cardiac catheterization using the regional xenon-133 washout technique.

In hypertensive patients with LVH, LV MBF was reduced at rest (35.0 ± 5.4 ml/100 g/min) compared with controls (64.8 ± 7.6 ml/100 g/min, p < 0.01) and hypertensive patients without LVH (62.6 ± 14.5 ml/100 g/min, p < 0.01). Coronary vascular resistance was also elevated in the hypertensive patients with LVH (37.6 ± 6.6 dyn * cm⁻² * g⁻¹, p < 0.01). In contrast, ejection fraction, mean velocity of circumferential fiber shortening (MVcf) and end-systolic and end-diastolic volumes were not significantly different among the three groups. Peak systolic stress was significantly lower (p < 0.01) in the hypertensive patients with LVH (225 ± 45 dyn * cm⁻² * 10⁻⁶) than in the controls (385 ± 114 dyn * cm⁻² * 10⁻⁶) and the hypertensive patients without LVH (395 ± 39 dyn * cm⁻² * 10⁻⁶).

A multivariate regression equation was developed relating MBF to heart rate (HR), MVcf, and peak LV wall stress: MBF = 22.2 MVcf + 10.6 stress + 0.38 HR − 48.2 (r = 0.89, p < 0.01). When MBF was adjusted for differences in stress among patients using the regression equation, there was no significant difference in MBF between hypertensive patients with and without LVH. These results indicate that (1) resting LV myocardial blood flow is normal in hypertensive patients without LVH; (2) resting MBF is reduced in controlled hypertensive patients with LVH as a consequence of reduced wall stress; and (3) resting LV performance measured by ejection phase indexes is well preserved in hypertensive patients with and without LVH. These results also provide additional evidence that resting MBF in patients with normal coronary arteriograms is related to hemodynamic indexes of the major determinants of myocardial oxygen consumption.

CONCENTRIC LEFT VENTRICULAR hypertrophy develops in response to sustained pressure overload of the left ventricle in systemic hypertension. Although myocardial hypertrophy is believed to be a fundamental compensatory mechanism that benefits performance of the pressure-loaded ventricle by reducing myocardial wall stress, the question of whether stable concentric left ventricular hypertrophy is associated with normal or decreased myocardial performance remains controversial. The contractile function of isolated papillary muscles from hypertrophied animal ventricles has been reported to be depressed in some studies and normal in others. In intact hearts of animals exposed to chronic pressure overload, ventricular performance has been reported to be depressed or enhanced. In hypertensive patients with left ventricular hypertrophy, exercise tolerance has been reported to be reduced, and echocardiographic studies have shown cardiac performance to be normal or reduced.

Similar uncertainty exists regarding the effect of pressure-induced myocardial hypertrophy on myocardial blood flow per unit mass of tissue. Studies of myocardial blood flow per unit mass of tissue measured in animals with pressure-induced myocardial hypertrophy have shown normal, increased or decreased resting left ventricular myocardial blood flow. However, coronary vascular resistance per unit mass was increased at rest and during maximal coronary vasodilation, and in some studies there was a relative diminution of subendocardial flow during interventions that induced hyperemia.

In studies from this laboratory, resting left ventricular myocardial blood flow per unit mass was reduced in patients with left ventricular hypertrophy associated with congestive and hypertrophic cardiomyopathy and severe aortic stenosis. In patients without valvular obstruction, the resting mean left ventricular blood flow was significantly related to indexes of the major determinants of myocardial oxygen consumption: heart rate, contractility and peak systolic ventricular wall stress. These observations raised the possibility that the characteristics of left ventricular performance in hypertensive patients with and without concentric hypertrophy may alter resting myocardial blood flow by influencing the major determinants of myocardial oxygen consumption.

The present study was undertaken to investigate the relationship between resting left ventricular myocardial blood flow and ventricular performance in systemic hypertension. The study had three objectives:
(1) to measure resting mean left ventricular myocardial blood flow per unit mass in hypertensive patients with and without concentric hypertrophy; (2) to determine if ejection phase indexes of left ventricular performance are impaired by myocardial hypertrophy; and (3) to relate resting left ventricular myocardial blood flow in hypertensive patients to indexes of three determinants of myocardial oxygen consumption.

Methods

Patient Selection

All patients who underwent cardiac catheterization and coronary arteriography at Columbia-Presbyterian Medical Center between 1972–1978 were considered potential candidates for the study. The clinical indication for coronary arteriography in each patient was recurrent chest pain suggestive of coronary artery disease. Twenty-six patients agreed to participate in the protocol: nine normotensive control subjects and 17 patients with previously documented hypertension, defined as an elevation of arterial blood pressure greater than 140/90 mm Hg on repeated occasions. Patients with valvular heart disease, previous myocardial infarction or coronary artery disease were excluded from the study, as were three patients with technically inadequate ventriculograms that precluded quantitative analysis. Informed consent was obtained from each patient for the measurement of regional myocardial blood flow according to protocols approved by the Institutional Review Board and the Joint Radioisotope Committees of the Columbia-Presbyterian Medical Center.

The 26 patients were subdivided into three groups: Group 1 consisted of nine normotensive control patients, three males and six females (mean age 50 years), who were normal by physical examination, chest radiograph and ECG.

Group 2 consisted of eight patients (mean age 52 years) with hypertension and normal left ventricular
wall thickness determined angiographically. Normal left ventricular end-diastolic wall thickness was arbitrarily defined as less than 10 mm; in published reports, normal wall thickness has not exceeded this value.

Group 3 consisted of nine patients (mean age 38 years) with hypertension, concentric left ventricular hypertrophy and left ventricular wall thickness greater than or equal to 10 mm.

Diagnostic and pertinent clinical data for the hypertensive patients in groups 2 and 3 are detailed in Table 1. ECGs demonstrated left ventricular hypertrophy by the criteria of Romhilt and Estes in three patients in group 2 and seven of nine patients in group 3. Four of the patients in group 3 described typical exertion-induced angina pectoris; six patients in group 2 and all patients in group 1 described atypical chest pain unrelated to exertion.

Hypertensive patients were not subjected to cardiac catheterization until their arterial pressures were reduced by bed rest or antihypertensive treatment or both. All of the patients in groups 2 and 3 were being treated with antihypertensive medications, which were discontinued in all but five patients (table 1) during hospitalization before catheterization. On the day of catheterization, none of the patients received antihypertensive medications. All patients were premedicated with 50–100 mg of secobarbital and 25 mg of promethazine hydrochloride.

**Cardiac Catheterization Technique**

Left ventricular catheterization and coronary arteriography were performed percutaneously by the Judkins technique. Intracardiac pressures were recorded on a switched-beam oscillographic recorder using Statham P23Db pressure transducers positioned to a zero level 5 cm below the sternal angle. Coronary arteriograms were recorded on 35-mm cine film at 50 frames/sec with a 6-inch, cesium-iodine image intensifier. Films were interpreted independently by a cardiovascular radiologist and a cardiologist, and a consensus was reached. Ten minutes after coronary arteriography and before left ventriculography, left ventricular myocardial perfusion was measured by intracoronary injection of xenon-133 and monitoring with a scintillation camera.
Left ventriculography was performed at least 20 minutes after coronary arteriography with the patient in the shallow (25°) right anterior oblique position. During held inspiration, 40 ml of Renografin-76 was power injected through a pigtail catheter over 2–3 seconds into the left ventricular cavity. The first fully visualized normal beat was chosen for analysis to minimize myocardial depressant effects of contrast material. Postextrasystolic beats were not used. All patients were in normal sinus rhythm, and none had a significant change in heart rate during the ventriculogram. A radiopaque grid, cross-hatched in 1-cm squares, was filmed at the transducer level as a spatial reference.

Diastolic pressure-time index (DPTI), systolic pressure-time index (SPTI), and DPTI:SPTI ratio were calculated by the method of Buckberg et al.\textsuperscript{31} from left ventricular and aortic pressure tracings obtained during pull-back recordings across the aortic valve. DPTI was calculated from the planimetered area between the aortic and left ventricular pressure curves from the dicrotic notch to aortic valve opening. SPTI was calculated from the area beneath the left ventricular pressure curve from the onset of ventricular systole to the dicrotic notch.

### Determination of Mean Left Ventricular Myocardial Blood Flow

Myocardial perfusion was measured from the clearance of xenon-133 from the left ventricular myocardium using a multicrystal scintillation camera.\textsuperscript{32, 33} Approximately 20 mCi of xenon-133 dissolved in 1–2 ml of sterile pyrogen-free saline was injected rapidly into the left main coronary artery. Clearance of xenon-133 from the myocardium was recorded with a multicrystal scintillation camera (model 5600, Autofluoroscope or System 70, Baird Atomic, Inc.) Counts per second recorded by each crystal were processed by computer. The slope (k) of the initial portion of the myocardial xenon-133 clearance curve recorded by each crystal was calculated by monoexponential analysis of the first 40 data points after the peak count. Regional myocardial blood flow rates were calculated for each crystal by the Kety formula\textsuperscript{34, 35}: \( F = 100 \times k \times \lambda / \rho \), where \( F \) is the myocardial capillary blood flow (ml/100 g/min), \( \lambda \) is the blood-myocardium partition coefficient for xenon\textsuperscript{36} in the normal dog heart (0.72) and \( \rho \) is the specific gravity of tissue (1.05).

The pattern of regional myocardial perfusion rates so obtained was then superimposed upon the "a" tracing of the patient's left anterior oblique coronary arteriogram. Alignment and appropriate magnification of the patterns were facilitated by the presence of the same radioactive radiopaque markers on both the arteriograms and on the computer printout of local myocardial blood flow rates. The mean left ventricular myocardial perfusion rate per unit mass was calculated by averaging the local blood flows recorded by all of the crystals overlaying the left ventricle. Mean left ventricular myocardial blood flow rates per unit mass measured by the xenon-133 clearance technique have correlated well with blood flow measured with microspheres in experimental animals.\textsuperscript{37}

Coronary vascular resistance (CVR) per gram of myocardial tissue was calculated as follows:

\[
CVR = \frac{AoP - LVEDP}{MBF/100}
\]

where MBF = mean left ventricular myocardial blood flow (ml/100 g/min), AoP = mean aortic pressure measured during xenon-133 clearance and LVEDP = the left ventricular diastolic pressure measured at the peak of the ECG T wave from five consecutive heart beats.

### Ventriculographic Analysis

Left ventricular dimensions were measured from tracings of the ventricular silhouettes at end-diastole and end-systole. In drawing the chamber silhouettes, the tracings were always made to the outside margins of the papillary muscles. The long axis of the left ventricle was taken as the longest measured line from the apex to the margin of the aortic valve.

Ventricular volumes were calculated using the single-plane, area-length method of Sandler and Dodge.\textsuperscript{38} Regression equation corrections were not used for reasons previously reported.\textsuperscript{39}

Mean velocity of circumferential fiber shortening (MVcf) was calculated from the formula\textsuperscript{40}:

\[
MVcf = \frac{EDD - ESD}{EDD \times LVET}
\]

Where EDD = left ventricular minor diameter at end-diastole, ESD = left ventricular minor diameter at end-systole and LVET = left ventricular ejection time (seconds) measured angiographically. For this calculation, the end-diastolic and end-systolic minor diameters were calculated by the area-length method.

Left ventricular wall thickness was measured directly from the anterior wall segment below the equatorial plane of the ventriculogram in the right anterior oblique projection and corrected for image magnification.\textsuperscript{41} Only ventriculograms that clearly displayed the epicardial and endocardial borders were analyzed. Left ventricular mass was calculated by the method of Rackley et al.\textsuperscript{42} Mean interobserver variability for ventricular wall thickness measured by this method was 12.7%; mean intraobserver variability was 9.3%. Peak left ventricular wall stress was calculated using the thin-wall formula of Sandler and Dodge:\textsuperscript{43}

\[
\text{Stress} = \frac{Pb}{h} \left[ 1 - \frac{4b^2}{a^2(2b + h)} \right]
\]

Where \( P \) = pressure (dyn.cm\textsuperscript{-2}); \( b \) = minor semiaxis; \( a \) = major semiaxis and \( h \) = wall thickness (cm). The dimensions of the left ventricle used in these formulas were taken from the end-diastolic tracing of the left
ventricular silhouette, which assumes that there are no significant changes in these dimensions from end-diastole to peak stress. Peak systolic pressure was measured from the left ventricular pressure curve immediately before the ventriculogram, which assumes there is no change during the subsequent few beats.

Left ventricular tension was calculated as the product of left ventricular stress and wall thickness. Stroke work was calculated by multiplying the developed ventricular pressure by the stroke volume determined angiographically.

### Myocardial Blood Flow During Rapid Atrial Pacing

After myocardial blood flow was measured at rest, flow measurements were repeated during rapid atrial pacing in four patients in group 1, four patients in group 2 and five patients in group 3. A bipolar pacing electrode was positioned under fluoroscopic control in the lateral right atrial wall, and the heart rate was increased in 10-beat increments of 1 minute each until a maximal heart rate of 150 beats/min was attained. The tachycardia was then sustained for several minutes under electrocardiographic monitoring while myocardial blood flow was measured again by repeat intracoronary injection of xenon-133. The double product of heart rate times systolic blood pressure was used as an index of myocardial oxygen consumption.33

### Statistical Analysis

Group differences were evaluated by analysis of variance.46 Relationships between variables were tested by linear regression or multiple regression.46

### Results

Tables 1 and 2 summarize the hemodynamic and

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**Table 2. Myocardial Perfusion, Coronary Resistance and Determinants of Myocardial Oxygen Consumption in Control and Hypertensive Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>LV MBF (ml/100 g/min)</th>
<th>LV MBF/beat (ml/100 g/beat)</th>
<th>Total MBF (ml/min)</th>
<th>CVR (dyn-cm⁻²·g⁻¹)</th>
<th>Peak stress (dyn·cm⁻² X 10⁻¹)</th>
<th>Peak tension (dyn·cm⁻¹ X 10⁻¹)</th>
<th>MVCF (circ/sec)</th>
<th>DPTI</th>
<th>SPTI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1 (control patients)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>64.8</td>
<td>0.77</td>
<td>83</td>
<td>17.9</td>
<td>385</td>
<td>298</td>
<td>1.35</td>
<td>0.91</td>
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<tr>
<td>sd</td>
<td>7.6</td>
<td>0.16</td>
<td>17</td>
<td>2.9</td>
<td>114</td>
<td>64</td>
<td>0.18</td>
<td>0.24</td>
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<tr>
<td><strong>Group 2 (hypertensive patients without LVH)</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>53 ± 10</td>
<td>0.74</td>
<td>46</td>
<td>30.2</td>
<td>242</td>
<td>442</td>
<td>1.28</td>
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<tr>
<td>2</td>
<td>64 ± 14</td>
<td>0.71</td>
<td>109</td>
<td>21.2</td>
<td>394</td>
<td>333</td>
<td>1.42</td>
<td>0.94</td>
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<tr>
<td>3</td>
<td>55 ± 15</td>
<td>0.61</td>
<td>64</td>
<td>24.7</td>
<td>388</td>
<td>287</td>
<td>1.65</td>
<td>0.57</td>
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<tr>
<td>4</td>
<td>43 ± 12</td>
<td>0.41</td>
<td>65</td>
<td>30.7</td>
<td>340</td>
<td>289</td>
<td>1.43</td>
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<tr>
<td>5</td>
<td>65 ± 10</td>
<td>0.81</td>
<td>36</td>
<td>21.2</td>
<td>349</td>
<td>261</td>
<td>1.81</td>
<td>0.49</td>
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<tr>
<td>6</td>
<td>63 ± 11</td>
<td>0.68</td>
<td>145</td>
<td>26.9</td>
<td>416</td>
<td>399</td>
<td>1.42</td>
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<tr>
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<td>93 ± 10</td>
<td>0.85</td>
<td>96</td>
<td>12.8</td>
<td>384</td>
<td>276</td>
<td>2.04</td>
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<tr>
<td>8</td>
<td>65 ± 14</td>
<td>0.92</td>
<td>79</td>
<td>21.5</td>
<td>445</td>
<td>345</td>
<td>1.29</td>
<td>0.68</td>
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<tr>
<td><strong>Mean</strong></td>
<td>62.6</td>
<td>0.72</td>
<td>80</td>
<td>23.8</td>
<td>395</td>
<td>308</td>
<td>1.54</td>
<td>0.68</td>
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</tr>
<tr>
<td><strong>sd</strong></td>
<td>14.5</td>
<td>0.16</td>
<td>36</td>
<td>5.8</td>
<td>39</td>
<td>47</td>
<td>0.27</td>
<td>0.20</td>
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<td><strong>Group 3 (hypertensive patients with LVH)</strong></td>
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<td>9</td>
<td>39 ± 5</td>
<td>0.53</td>
<td>65</td>
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<td>274</td>
<td>279</td>
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<tr>
<td>10</td>
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<td>0.41</td>
<td>151</td>
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<td>143</td>
<td>282</td>
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<tr>
<td>11</td>
<td>40 ± 11</td>
<td>0.63</td>
<td>51</td>
<td>35.3</td>
<td>234</td>
<td>218</td>
<td>1.88</td>
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<tr>
<td>12</td>
<td>35 ± 8</td>
<td>0.47</td>
<td>78</td>
<td>36.9</td>
<td>237</td>
<td>291</td>
<td>1.63</td>
<td>1.18</td>
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<tr>
<td>13</td>
<td>41 ± 7</td>
<td>0.52</td>
<td>226</td>
<td>52.3</td>
<td>166</td>
<td>419</td>
<td>1.46</td>
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<tr>
<td>14</td>
<td>34 ± 7</td>
<td>0.47</td>
<td>64</td>
<td>35.3</td>
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<td>1.58</td>
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<tr>
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<td>29 ± 9</td>
<td>0.43</td>
<td>121</td>
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<td>258</td>
<td>402</td>
<td>1.24</td>
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<tr>
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<td>0.41</td>
<td>96</td>
<td>31.5</td>
<td>240</td>
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<tr>
<td>17</td>
<td>25 ± 6</td>
<td>0.43</td>
<td>78</td>
<td>43.2</td>
<td>206</td>
<td>301</td>
<td>1.09</td>
<td>0.92</td>
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<tr>
<td><strong>Mean</strong></td>
<td>35.0</td>
<td>0.48</td>
<td>103</td>
<td>37.6</td>
<td>225</td>
<td>307</td>
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<tr>
<td><strong>sd</strong></td>
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<td>6.6</td>
<td>45</td>
<td>63</td>
<td>0.28</td>
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</table>

**Abbreviations:** LV MBF = left ventricular myocardial blood flow; CVR = coronary vascular resistance; MVCF = mean velocity of circumferential fiber shortening; SWI = stroke work index; DPTI = diastolic pressure-time index; SPTI = systolic pressure-time index.
ventriculographic data for the three groups of patients at cardiac catheterization.

**Ventricular Function**

At cardiac catheterization, mean aortic blood pressure was higher in the hypertensive patients without left ventricular hypertrophy (group 2) (117 ± 11 mm Hg) than in control patients (94 ± 10 mm Hg, p < 0.05). Mean aortic blood pressure was not significantly elevated in the hypertensive patients with left ventricular hypertrophy (group 3, 110 ± 25 mm Hg), compared with group 1. The average heart rate did not differ significantly among the three groups (group 1, 89 ± 16 beats/min, group 2, 89 ± 14 beats/min, group 3, 74 ± 11 beats/min). In addition to increased wall thickness, left ventricular mass index was also significantly greater (p < 0.01) in group 3 (164 ± 81 g/m²) than in group 2 (79 ± 21 g/m²) or group 1 (76 ± 14 g/m²).

Left ventricular end-diastolic volume index did not differ significantly among the three groups of patients (group 1, 67 ± 13 ml/m³; group 2, 68 ± 16 ml/m³; group 3, 59 ± 14 ml/m³). Although the average end-systolic volume index was lower in the hypertensive patients, differences among the three groups were not statistically significant (group 1, 21 ± 7 ml/m³; group 2, 18 ± 6 ml/m³; group 3, 17 ± 7 ml/m³).

Figure 1 depicts two angiographic indexes of left ventricular performance in the three groups of patients. The mean left ventricular ejection fraction (fig. 1A) was not significantly different from control in the hypertensive patients (group 1, 69 ± 5%; group 2, 73 ± 6%; group 3, 72 ± 7%). Similarly, MVcf was not significantly different from control in the hypertensive groups (group 1, 1.35 ± 0.18 circ/sec, group 2, 1.54 ± 0.27 circ/sec, group 3, 1.42 ± 0.28 circ/sec) (fig. 1B).

Figure 2 shows the peak systolic equatorial left ventricular wall stress in the individual patients. Peak left ventricular stress was significantly lower (p < 0.01) in hypertensive patients with hypertrophy (group 3, 225 ± 45 dyn · cm⁻² · 10⁻⁸) than in the patients in group 2 (395 ± 39 dyn · cm⁻² · 10⁻⁸) or group 1 (385 ± 114 dyn · cm⁻² · 10⁻⁸). Left ventricular wall tension, however, was not significantly different among the three groups (group 1, 298 ± 64 dyn · cm⁻¹ · 10⁻⁴; group 2, 308 ± 47 dyn · cm⁻¹ · 10⁻⁴; group 3, 307 ± 63 dyn · cm⁻¹ · 10⁻⁴). DPTI:SPTI was not significantly different among the three groups (group 1, 0.91 ± 0.24; group 2, 0.68 ± 0.20; group 3, 0.93 ± 0.27).

**Myocardial Blood Flow**

The data on myocardial blood flow are summarized in table 2 and figure 3. The mean left ventricular myocardial blood flow per unit weight in the hypertensive patients without hypertrophy (group 2, 62.6 ± 14.5 ml/100 g/min) was not significantly different from that of the normotensive controls (group 1, 64.8 ± 7.6 ml/100 g/min). Left ventricular myocardial blood flow was significantly reduced (p < 0.01) in the hypertensive patients with left ventricular hypertrophy (group 3, 35.0 ± 5.4 ml/100 g/min) compared with the other two groups. Similarly, left ventricular myocardial blood flow normalized for heart rate was significantly reduced in group 3 (0.48 ± 0.07 ml/100 g/beat) compared with group 2 (0.72 ± 0.16 ml/100 g/beat) and group 1 (0.77 ± 0.16 ml/100 g/beat) (both p < 0.01).

Resting left ventricular myocardial blood flow per unit mass in the hypertensive patients (groups 2 and 3) did not correlate significantly with mean aortic pressure (r = 0.24), diastolic aortic pressure (r = 0.11) or stroke work (r = 0.23). Resting blood flow correlated significantly with the DPTI:SPTI (r = -0.59, p < 0.05).

Coronary vascular resistance per gram of myocardium was not significantly increased in the hypertensive patients without left ventricular hypertrophy compared with normotensive controls (group 2, 23.8 ± 5.8 dyn · cm⁻¹ · g⁻¹ vs group 1, 17.9 ± 2.9 dyn · cm⁻¹ · g⁻¹). Coronary vascular resistance was increased significantly in the hypertensive patients with left ventricular hypertrophy (group 3, 37.6 ± 6.6 dyn · cm⁻¹ · g⁻¹, p < 0.01). Mean values for myocardial blood flow, coronary vascular resistance and double product of heart rate and systolic blood pressure measured during rapid atrial pacing in 13 patients from the three groups are presented in figure 4. During pacing, none of the patients developed chest pain or electrocardiographic changes indicative of ischemia. The increment in
myocardial blood flow was not significantly different among the three groups; the absolute level of myocardial flow during maximal pacing in the group with left ventricular hypertrophy (54 ± 25 ml/100 g/min) was less than the maximal flow measured in group 1 (82 ± 12 ml/100 g/min) and group 2 (77 ± 27 ml/100 g/min), but the differences were not statistically significant. There was a significant decrease in coronary vascular resistance during atrial pacing in patients with left ventricular hypertrophy (group 3) (p < 0.05), indicating that the elevated coronary vascular resistance in these patients was not fixed.

Relationship Between Myocardial Blood Flow and Determinants of Myocardial Oxygen Consumption

In previous studies from this laboratory of patients with congestive or hypertensive cardiomyopathy and patients with severe aortic stenosis, resting mean left ventricular myocardial blood flow per unit mass was related to hemodynamic indexes that reflect three of the major determinants of myocardial oxygen consumption: heart rate, contractility and peak systolic ventricular wall stress. In the study of patients with cardiomyopathy, multivariate regression analysis of

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**Figure 2.** Peak left ventricular (LV) wall tension and wall stress for the three groups of patients. Mean wall tension was not significantly different among the three groups. Mean wall stress was significantly reduced (p < 0.01) for hypertensive patients in group 3 with left ventricular hypertrophy.

**Figure 3.** Mean left ventricular (LV) myocardial blood flow per unit mass (MBF) and coronary vascular resistance for normotensive controls (group 1), hypertensive patients without left ventricular hypertrophy (group 2) and hypertensive patients with left ventricular hypertrophy (group 3). Mean LV MBF was significantly (p < 0.01) reduced in patients with left ventricular hypertrophy. Coronary resistance was significantly increased in hypertensive patients with left ventricular hypertrophy (p < 0.01).
the data yielded the relationship: MBF = 16.9 MVcf + 9.30 stress + 0.26 HR = 26.4 (r = 0.79), where MBF = myocardial blood flow (ml/100 g/min), stress = calculated peak systolic stress (dyn cm⁻²), and HR = heart rate.

Multiple regression analysis of the data from the hypertensive patients in groups 2 and 3 yielded the following expression: MBF = 22.2 MVcf + 10.6 stress + 0.38 HR = 48.2 (r = 0.89, p < 0.01). Myocardial blood flow was significantly and independently related to each of these indexes, which reflect hemodynamic determinants of myocardial oxygen consumption. Eighty percent of the total variation in left ventricular myocardial blood flow per unit mass in the hypertensive patients was explained by variation in these three determinants of myocardial oxygen consumption (fig. 5). The relationship in the hypertensive patients did not differ significantly from that of normal subjects, patients with hypertrophic cardiomyopathy and patients with congestive cardiomyopathy in the previous study.

Figure 6 shows myocardial blood flow rates for the two groups of hypertensive patients adjusted for differing degrees of wall stress using the multivariate regression equation developed for these patients. Myocardial blood flow adjusted for stress was not significantly different between the two groups, indicating that lower blood flow in group 2 is explained by the lower level of left ventricular wall stress. For all three groups, myocardial blood flow per beat correlated with peak left ventricular wall stress (r = 0.80, p < 0.01).

**Discussion**

The present study was designed to measure left ventricular blood flow per unit mass in hypertensive patients with and without left ventricular hypertrophy, and to test the hypothesis that resting myocardial blood flow in these patients is related to indexes of left ventricular performance that reflect the major determinants of myocardial oxygen consumption. Myocardial blood flow was related to angiographic indexes of left ventricular performance to explain variations of flow associated with myocardial hypertrophy and to characterize left ventricular performance in hypertensive patients determined angiographically.

**Myocardial Blood Flow**

Mean left ventricular myocardial blood flow per unit mass of tissue was normal at rest in patients with systemic hypertension without left ventricular hyper-
trophy, confirming observations of Bing et al. and Rowe et al., who used nitrous oxide to measure coronary flow. In contrast, Strauer et al. reported that resting left ventricular myocardial blood flow measured by the argon method was 18% higher in hypertensive patients than in normotensive control patients. This difference probably relates to the higher levels of arterial pressure and systolic wall stress present in the latter patients at cardiac catheterization. In each of these studies, coronary vascular resistance per unit mass of tissue was significantly elevated in hypertensive patients. Our observations in the present study that resting left ventricular myocardial perfusion per unit mass of tissue was reduced in the hypertensive patients with left ventricular hypertrophy and that coronary vascular resistance per unit mass was elevated to a greater degree in these patients (table 2) have not been reported previously.

In animal models of pressure-induced left ventricular hypertrophy, normal increased and reduced left ventricular perfusions per unit mass have been reported. These differences may be related to variations in ventricular performance or to differences in the duration of ventricular hypertrophy. In a study of puppies with left ventricular hypertrophy induced by banding the ascending aorta for 6 weeks, Rembert et al. found increased mean left ventricular perfusion per unit mass, which they attributed to resting tachycardia in the banded dogs. In contrast, Malik et al. used coronary flow probes and microspheres to study mean left ventricular perfusion in dogs 6 months and 1 year after aortic banding, and found significantly reduced mean left ventricular perfusion per unit mass in both groups of dogs with stable concentric left ventricular hypertrophy.

Vascular resistance in regional circulatory beds may be increased in hypertensive patients because of functional vasoconstriction or because of structural alterations in the blood vessels induced by the elevated blood pressure. The increased coronary vascular resistance in the hypertensive patients with left ventricular hypertrophy in the present study was not fixed but functional. This was indicated by the fact that mean left ventricular perfusion increased and coronary vascular resistance per gram decreased significantly during atrial pacing. In addition, none of the patients developed chest pain or electrocardiographic signs of ischemia during atrial pacing (fig. 4).

In this study we did not attempt to dilate the coronary circulation maximally to assess whether the capacity of the coronary vascular bed in the hypertensive patients had been compromised. However, Strauer reported that minimal coronary vascular resistance is increased in hypertensive patients during coronary vasodilation induced by adenosine or diprydamole infusion. Similarly, minimal coronary vascular resistance has been found to be consistently higher than control in animals with several forms of left ventricular hypertrophy when coronary flow is increased by reactive hyperemia, exercise, or when maximal coronary vasodilation is induced by diprydamole, adenosine or chronomar (cardiocromen).

O'Keefe et al., Bache and Vrobel and Rembert et al. observed that the ratio of endocardial to epicardial flow decreased slightly but significantly in hypertrophied canine ventricles during pharmacologic coronary vasodilation, reactive hyperemia and exercise. The ratio of endocardial to epicardial flow cannot be estimated in patients by the xenon-133 clearance method used to measure mean left ventricular myocardial blood flow in these studies. If a similar transmural flow redistribution occurs in hypertensive patients with left ventricular hypertrophy in response to increased demand, relative subendocardial hypoperfusion may explain the electrocardiographic signs of ischemia often observed in such patients during exercise.

### Left Ventricular Performance in Hypertensive Patients

Ejection phase indexes were used in the present investigation to assess ventricular contractile performance because they are more sensitive than isovolumic indexes for separating patients with different levels of cardiac function. Ejection fraction, MVcf and end-diastolic and end-systolic volumes were not significantly different from control values in...
the two groups of hypertensive patients. There was no significant difference in ejection fraction or MVcf between the hypertensive patients with or without left ventricular hypertrophy.

The ejection phase indexes were normal in the hypertensive patients despite increased afterload, suggesting that left ventricular function at rest is well preserved in compensated systemic hypertension. The finding that ventricular end-systolic volumes were well within the normal range in the hypertensive patients despite elevated peak systolic pressures is additional evidence that left ventricular contractile function was normal. These observations are consistent with recent angiographic and echocardiographic studies that have shown that ejection phase indexes of left ventricular performance remain normal in patients with moderate hypertension. These indexes were depressed, however, in patients with very severe hypertension. In the present study, patients with uncontrolled, severe hypertension were not subjected to cardiac catheterization.

The finding of normal ejection phase indexes of cardiac performance in compensated hypertensives with left ventricular hypertrophy is consistent with recent experimental results in animal models of pressure-induced hypertrophy. In intact animal hearts with chronic left ventricular hypertrophy induced by aortic constriction or renal hypertension, isovolumic indexes of cardiac function have been normal or slightly increased and ejection phase indexes have also been normal. However, the performance of hypertrophied ventricles was depressed in animals with incipient cardiac failure during acute volume and pressure stresses.

In a study of changes in ejection phase indexes during adaptation to chronic pressure overload in conscious dogs, Sasayama et al. found that these indexes were initially depressed by chronically elevated afterload but normalized after development of adequate ventricular hypertrophy. In animals with chronic left ventricular hypertrophy and in control animals, these investigators found that MVcf decreased slightly if arterial pressure was raised acutely. At any level of arterial pressure, however, MVcf was significantly higher in the animals with left ventricular hypertrophy. Because the inverse relationship between wall tension and MVcf fell along a single line in the animals with and without hypertrophy, the authors argued that the hypertrophied ventricle exhibited hyperfunction but had a normal inotropic state.

**Left Ventricular Stress in Hypertensive Patients**

The finding that peak left ventricular wall stress was reduced in the hypertensive patients with hypertrophy below the values found in the normotensive controls and the hypertensive patients without hypertrophy may be explained by the modest levels of systemic hypertension present during left ventriculography. Hypertension in patients of groups 2 and 3 was controlled to varying degrees by drug treatment, and blood pressures tended to decline more during hospitalization before cardiac catheterization. The combination of a thickened left ventricular wall and reduced systolic pressure resulted in values for peak systolic stress that were lower than in the control patients. Because it is generally assumed that the pressure-loaded ventricle hypertrophies sufficiently to normalize an elevated wall stress, it is conceivable that under ambulatory outpatient conditions, wall stress in the patients in group 3 would have been higher. The present data are analogous to observations in dogs by Sasayama et al., who found that wall stress decreased below normal in dogs with chronic left ventricular hypertrophy due to aortic constriction when arterial pressure was reduced by unbanding the aorta.

**Mechanisms of Reduced Myocardial Perfusion in Hypertensive Patients with Left Ventricular Hypertrophy**

Several mechanisms may explain the reduction in resting mean left ventricular perfusion per unit mass in the patients with left ventricular hypertrophy. The possibility that the flow levels were reduced in the patients with left ventricular hypertrophy because of replacement fibrosis within the myocardium seems unlikely for several reasons. First, pathologic studies of hearts with left ventricular hypertrophy due to essential hypertension or pressure-induced experimental left ventricular hypertrophy have revealed a low percentage of scar. Second, the capillary blood flow rates in scar and fibrous tissue are low. If a low-flow compartment (fibrosis) in parallel with the normal myocardial muscle were present, little xenon-133 would have entered this compartment during the initial bolus injection (which is distributed according to local flow rates) and little tracer would have exited (because of the low flow rates) during the first 40 seconds of tracer washout to which a monoexponential analysis was applied. Therefore, it is unlikely that a low-flow compartment due to fibrosis would be detected in the type of measurement performed in this study. Finally, coronary flow increased and coronary vascular resistance decreased significantly during atrial pacing in the hypertensive patients with hypertrophy, a finding that would not be anticipated if the resting level of perfusion were reduced because of myocardial fibrosis.

Another possible explanation for reduced blood flow per unit mass relates to alterations in phasic coronary flow during systole and diastole induced by left ventricular hypertrophy. Increased peak systolic pressure may accentuate systolic compression of the coronary arteries, resulting in reduced coronary blood flow during systole. Malik et al. found that peak systolic flow was reduced in dogs with pressure-induced hypertrophy, whereas peak diastolic flow was unchanged. However, because only a small fraction of coronary blood flow normally occurs during systole, it is unlikely that reduced systolic flow accounts for the reduction in resting mean left ventricular flow.

A third explanation for the reduction in flow in hypertensive patients may be microvascular
alterations in the structure of coronary resistance vessels induced by sustained hypertension. Post-mortem studies of hypertrophied ventricles of hypertensive patients have revealed medial hypertrophy of myocardial arterioles, reduced myocardial capillary density, possibly inadequate epicardial coronary vessels and increased resistance to coronary perfusion. However, the decrease in coronary vascular resistance and the lack of electrocardiographic or clinical evidence of ischemia during pacing suggests that fixed medial hypertrophy of coronary resistance vessels was not the explanation for the reduced resting myocardial flow in the group with left ventricular hypertrophy.

We cannot exclude the possibility that mean left ventricular perfusion was reduced in the patients with left ventricular hypertrophy because of subendocardial hypoperfusion. Several groups have reported slight reductions of subendocardial perfusion in experimental animals with pressure-induced left ventricular hypertrophy. However, in studies performed in the resting state, the ratio of endocardial to epicardial flow was only slightly reduced. In the present study, DPTI:SP1 was calculated because depression of this ratio has been associated with subendocardial hypoperfusion in experimental animals and patients with subendocardial hypoperfusion. The DPTI:SP1 ratio did not differ significantly among the three groups of patients. In addition, there was not a positive correlation between the DPTI:SP1 ratio and mean left ventricular perfusion in the hypertensive patients. Microsphere experiments suggest that the myocardial blood flow rate measured by the xenon-133 clearance technique represents a weighted average of all flow compartments within the solid range of tissue viewed by each detector. Thus, resting subendocardial perfusion may have contributed to the reduced mean left ventricular myocardial blood flow in the hypertensive patients with hypertrophy. However, the present data provide no experimental evidence for or against this possibility.

A fifth hypothesis is that the reduced left ventricular perfusion per unit mass in the hypertensive patients with hypertrophy is related to altered ventricular function. Myocardial blood flow has been shown experimentally to be directly related to myocardial oxygen consumption. Braunwald and co-workers have developed an extensive body of experimental data that indicates that the three most important determinants of myocardial oxygen consumption are heart rate, contractility and peak systolic wall stress. In a previous study from this laboratory, resting left ventricular myocardial blood flow in normotensive subjects with normal ventricular function and in patients with abnormal ventricular function due to congestive and hypertrophic cardiomyopathy was significantly related to indexes of three major determinants of myocardial oxygen consumption — heart rate, MVc and peak left ventricular wall stress. Multivariate regression analysis of the data from the 17 hypertensive patients in the present study indicated that heart rate, MVc and peak systolic wall stress were independently and significantly related to the mean left ventricular perfusion per unit mass. Eighty percent of the variation in the left ventricular myocardial blood flow rates measured in the hypertensive patients with and without left ventricular hypertrophy could be explained by these three variables. In addition, the regression equation developed for the hypertensive patients was not significantly different from the equation developed in three groups of patients with normal blood pressure, one of which had left ventricular hypertrophy. Collectively, these studies indicate that resting left ventricular myocardial blood flow in patients with normal coronary arteriograms is significantly related to hemodynamic indexes of the major determinants of myocardial oxygen consumption.

The data in figure 6 indicate that there was no significant difference between the myocardial blood flow rates for the hypertensive patients with and without left ventricular hypertrophy when the measured flow rates were adjusted for wall stress using the multivariate regression equation developed for these patients. This suggests that the lower resting blood flow in the patients with left ventricular hypertrophy in group 3 was due to the lower level of wall stress.

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