Regional Myocardial Blood Flow and Glucose Utilization in Symptomatic Patients With Hypertrophic Cardiomyopathy

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Background. Previous studies suggested the presence of myocardial ischemia in symptomatic patients with hypertrophic cardiomyopathy. Positron emission tomography, a technique that can identify metabolic consequences of ischemia in coronary artery disease, permits the noninvasive measurements of regional myocardial blood flow and glucose metabolism. This new quantitative imaging approach should therefore be suitable for detecting a possible enhancement of glucose utilization in myocardium of patients with hypertrophic cardiomyopathy and thus may help to elucidate the pathomechanism of ischemia in this disease.

Methods and Results. In 13 symptomatic patients with hypertrophic cardiomyopathy, myocardial blood flow and glucose utilization were measured with intravenous N-13-ammonia and F-18 deoxyglucose at rest and, in four patients, again during supine bicycle exercise. At rest, blood flow was significantly lower in hypertrophied than in normal myocardium (0.78±0.19 versus 0.99±0.13 mL·min⁻¹·g⁻¹, p<0.025), whereas rates of glucose utilization were similar (0.88±0.31 versus 0.87±0.35 µmol·min⁻¹·g⁻¹). With exercise, blood flow and glucose utilization failed to increase in hypertrophic and normal segments but became more heterogeneously distributed throughout the left ventricular myocardium. Blood flow–metabolism mismatches indicative of myocardial ischemia were noted in three patients at rest and in three of the four patients during exercise and were due to reduced flow in the presence of maintained glucose uptake. The discordance between flow and glucose metabolism in hypertrophied myocardium was significantly more prominent in younger than in older patients.

Conclusions. Normal or even elevated rates of glucose utilization and the presence of diminished blood flow in hypertrophied relative to normal myocardium suggest the presence of myocardial ischemia in symptomatic hypertrophic cardiomyopathy. The age dependence of blood flow metabolism disparity suggests differences in the underlying pathophysiology or severity of disease. (Circulation 1993;87:1580–1590)

Key Words • glucose metabolism • myocardial blood flow • positron emission tomography • hypertrophic cardiomyopathy

Typical as well as atypical chest pain are common symptoms in patients with hypertrophic cardiomyopathy. Several pieces of evidence suggest the possibility of microvascular ischemia associated with these clinical symptoms. ²⁰¹Tl imaging has revealed both reversible and irreversible perfusion defects,¹–³ whereas invasive techniques have demonstrated increased myocardial lactate production as metabolic evidence of ischemia.⁴ In addition, tissue histology has revealed focal myocardial scarring⁵ and narrowing of intramural septal arteries.⁶ However, little is known about the metabolic state and regional blood flow in myocardium of symptomatic patients with hypertrophic cardiomyopathy.

Studies from several institutions have indicated that regionally enhanced glucose uptake relative to blood flow is a sensitive index of myocardial ischemia.²–⁶ With high temporal resolution positron emission tomography (PET), both regional myocardial blood flow and glucose utilization can now be quantified noninvasively in humans. In contrast to a previous investigation from this laboratory on asymptomatic patients with hypertrophic cardiomyopathy,¹¹ the purpose of this study was to assess quantitatively regional myocardial blood flow and potential alterations in regional glucose metabolism in patients with symptomatic hypertrophic cardiomyopathy, who are possibly a different clinical entity than asymptomatic patients. The underlying hypothesis was

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that such measurements might reveal metabolic evidence of regional myocardial ischemia in highly symptomatic patients.\textsuperscript{12-14}

\textbf{Methods}

\textbf{Patient Population}

Thirteen symptomatic patients were studied at rest with PET and intravenous N-13 ammonia and F-18 deoxyglucose. In addition, four of the patients were studied again during and immediately after symptom-limited supine bicycle exercise. Nine of the patients were men and four were women. Their age averaged 43±18 years, ranging from 20 to 69 years. All patients met clinical, echocardiographic, and angiographic criteria of hypertrophic cardiomyopathy such as a noddilated asymmetrically hypertrophied left ventricle and absence of other cardiac or systemic diseases causing left ventricular hypertrophy.\textsuperscript{12,15} All patients had normal coronary angiograms within the preceding 3 months and none was known to suffer from a metabolic disorder or had a history of diabetes. The left ventricular ejection fraction averaged 73±9\% (range, 55–80\%) as determined by contrast ventriculography in 10 patients and by two-dimensional echocardiography in three patients. Three patients had a significant outflow tract gradient at rest and two with provocation by postextrasystolic potentiation. Ten patients received a daily dose of 240–720 mg verapamil, one patient was on 80 mg propranolol per day, and two did not take medication. Clinical symptoms ranged from moderate to severe exertional angina, typical chest pain, and palpitations to dyspnea of New York Heart Association grades II and III. Anginal episodes tended to be more frequent and severe in younger patients; three patients had a familial history of hypertrophic cardiomyopathy (Table 1).

\textbf{Tomographic Imaging Protocol}

Each patient gave informed consent in writing after the investigative nature and possible risk of the study had been explained in detail. The study protocol and informed consent form had been approved by the Human Subject Protection Committee of the University of California, Los Angeles. Patients were requested to fast for at least 4 hours and to discontinue cardiac medications for at least 24 hours. An off-drug period of more than 5 half-times was achieved in all cases for both verapamil (T/2=4.0±1.5 hours) and propranolol (T/2=3.9±0.4 hours);\textsuperscript{16} most patients were off medication for 48 hours. Before PET, a 12-lead ECG, venous blood samples, sphygmomanometric blood pressure, and two-dimensional and M-mode echocardiograms were obtained in standard fashion.\textsuperscript{13}

The patients were then positioned supine in a whole-body tomograph (ECAT III, Computer Technology Inc., Knoxville, Tenn.), which acquires simultaneously three transaxial planes (two direct and one interpolated central cross plane).\textsuperscript{17} The planes were spaced 9 mm apart. The effective (reconstructed) in-plane resolution was 11.6 mm, and the axial resolution was \approx 10 mm (full-width at half-maximum).\textsuperscript{18} Consistency in patient positioning was achieved by marking the chest with a felt pen and aligning the marks with the tomograph’s low-energy neon laser beam. After recording of transmission images for subsequent correction of photon attenuation (using an external gallium-68 ring source), positron emitting tracers were given as a single bolus under resting conditions. N-13 ammonia was administered first; serial images were recorded for 10 minutes starting with a standardized intravenous 30-second bolus of \approx 10 mCi (370 MBq) of N-13 ammonia.\textsuperscript{18,19} The image acquisition sequence consisted of 12×10-second images, 4×30-second images, and one final 360-second image that served as a static image as well (17 serial images over 10 minutes).

While maintaining the patients in exactly the same position by aligning ink marks on the patient’s chest with the laser beam of the scanner, 10 mCi (370 MBq) of F-18 deoxyglucose was administered intravenously.\textsuperscript{20,21} F-18 deoxyglucose was injected 35–40 minutes after N-13 ammonia over a 20-second period; serial images were acquired as follows: 12×10-second images, 12×30-second images, 10×120-second images, 6×300-second images, and, finally, acquisition of one 600-second image amounting to a total acquisition time of 67 minutes. The last set of three contiguous images served as static images that were compared with the corresponding static N-13 ammonia images.

To examine the effect of exercise stress on regional myocardial blood flow and glucose utilization, the imaging protocol was repeated in four patients 22±7 days after the resting study during symptom-limited supine bicycle exercise. A bicycle ergometer was mounted to the tomograph’s bed to allow comfortable cycling while the patients were positioned supine in the tomograph and fixed by a shoulder support. The exercise started at a level of 25 W and 60 rpm. The work load was increased by 25-W increments every 2 minutes until limiting symptoms such as angina or dyspnea occurred. N-13 ammonia was injected while the acquisition of serial imaging commenced, and the patients continued cycling for an additional 60 seconds. About 30 minutes later, the exercise test was repeated in an identical fashion and continued for 60 seconds after injection of F-18 deoxyglucose while serial image acquisition was started. The ECG was continuously monitored, and blood pressure measurements were taken at intervals of 2 minutes during and after the exercise test.

The specific tracer activities were 150–200 Ci/mmol (5.5×10\textsuperscript{4} to 7.4×10\textsuperscript{4} MBq/mmol) for N-13 ammonia and 2 Ci/mmol for F-18 deoxyglucose (7.4×10\textsuperscript{4} MBq/mmol) with radiochemical purities exceeding 99\%.\textsuperscript{22} Typically only about 5 \textmu mol of F-18 deoxyglucose was given; to enhance myocardial glucose utilization and standardize dietary state, 30–50 g of glucose (Trutol) were given orally 60 minutes before the F-18 deoxyglucose injection. The total body radiation dose from the double tracer study amounted to <0.5 rad (1.2 rad effective dose equivalent).

\textbf{Blood Sampling}

Venous blood samples were drawn before and during the tomographic imaging studies of F-18 deoxyglucose for measuring plasma levels of insulin, lactate, glucose, free fatty acids, and triglycerides. In patients 7–12, the insulin levels were not repeatedly measured at the time of the PET study because earlier insulin samples were within normal limits. These patients were instructed to
fast while waiting for up to 2 hours before the PET study and to limit fluid intake to water only.

Analysis of Tomographic Images

A VAX 780 computer (DEC) was used for analysis of the serially acquired PET images, for the circumferential profile analysis, and for quantification of regional myocardial blood flow and glucose metabolism.

Circumferential profile analysis. An operator-interactive computer program delineated the inner and outer boundaries of the left ventricular myocardium on the last of the serially acquired F-18 deoxyglucose images, using a Gaussian-fit edge detection algorithm. The outline of the myocardial contour on the F-18 deoxyglucose images was copied to the last of the serially acquired N-13 ammonia images, ensuring identical angular position for both. The same long-axis orientation was then applied to the other image planes in a given patient. The circumferential profiles as set by the operator after determination of the long axis of the left ventricle started at the posterior position on a midventricular image. The circumference was divided into 60 sectors of $6^\circ$, each proceeding in a clockwise fashion. Maximal activity in each sector was normalized to maximal activity in the circumferential profile and graphically displayed as a function of the angle about the ventricular long axis. Count profiles for N-13 and F-18 activities on the static images of each patient were compared with a data base of normals derived previously in 11 healthy volunteers. A regional blood flow–metabolism mismatch pattern was considered present if the ratio of regional F-18 to N-13 counts exceeded 2 SD above the mean of the normal data base in more than nine contiguous sectors of $6^\circ$ each. The extent of blood flow–metabolism mismatches was defined as the number of $6^\circ$ sectors of the circumferential profile with an abnormal F-18 to N-13 count ratio. The dual isotope approach as applied for F-18 to N-13 count ratios eliminates effects of regional partial volume on count recovery because it is identical for both tracers and thus cancels out. Therefore, the circumferential profile activities were not corrected for regional variations in partial volume effect as a result of regional differences in left ventricular myocardial thickness.

Quantification of Regional Myocardial Blood Flow and Glucose Utilization

Regional time–activity curves. These were generated by placing elliptical regions of interest to hypertrophied septal and to nonhypertrophied myocardium (which served as a reference) as well as in the left ventricular cavity. The regions of interest were then copied to all serial images recorded after N-13 ammonia and after F-18 deoxyglucose administration. The average (rather than maximum) N-13 or F-18 activity counts derived from each region of interest on the serial images then were corrected for dead time and partial volume, and time–activity curves for myocardium and the left ventricular blood pool were obtained. Corrections for partial volume effects and, thus, for the underestimation of counts in normal walls, were based on echocardiographic measurements of regional wall thickness in both hypertrophied and nonhypertrophied myocardium. The accuracy of measurements of the arterial tracer input function and of the regional myocardial tracer tissue concentrations was based on in vivo echocardiographic measurements of wall thickness validated previously in animal experiments and in studies with humans.

Regional myocardial blood flow. This was quantified with a two-compartment tracer kinetic model for N-13 ammonia including correction for spillover of activity from blood into myocardium. The model fit was applied to the initial 90 seconds of the myocardial time–activity curves and yielded estimates of regional myocardial blood flow (mL min$^{-1}$ g$^{-1}$) as described previously.

### Table 1. Demographics, Symptoms, Wall Thickness, and Positron Emission Tomography Findings at Rest

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)/sex</th>
<th>LVEF (%)</th>
<th>Symptoms</th>
<th>HR (bpm)</th>
<th>BP (mm Hg)</th>
<th>RPP (x&lt;0.01)</th>
<th>MRGlc (µmol min$^{-1}$ g$^{-1}$)</th>
<th>MBF (mL min$^{-1}$ g$^{-1}$)</th>
<th>WT (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>20/F</td>
<td>78</td>
<td>Angina pectoris</td>
<td>60</td>
<td>110/80</td>
<td>66.0</td>
<td>1.06</td>
<td>0.64</td>
<td>2.5</td>
</tr>
<tr>
<td>2*</td>
<td>32/F</td>
<td>68</td>
<td>Angina pectoris</td>
<td>60</td>
<td>110/80</td>
<td>66.0</td>
<td>0.64</td>
<td>0.51</td>
<td>1.8</td>
</tr>
<tr>
<td>3*</td>
<td>49/F</td>
<td>72</td>
<td>Palp, dyspnea</td>
<td>56</td>
<td>110/70</td>
<td>61.6</td>
<td>1.05</td>
<td>1.06</td>
<td>2.5</td>
</tr>
<tr>
<td>4*</td>
<td>34/M</td>
<td>85</td>
<td>Exertional angina</td>
<td>56</td>
<td>105/80</td>
<td>58.8</td>
<td>NA</td>
<td>0.80</td>
<td>2.2</td>
</tr>
<tr>
<td>5</td>
<td>42/M</td>
<td>60</td>
<td>Exertional angina</td>
<td>72</td>
<td>120/80</td>
<td>86.4</td>
<td>1.07</td>
<td>0.53</td>
<td>2.0</td>
</tr>
<tr>
<td>6</td>
<td>69/M</td>
<td>80</td>
<td>Angina</td>
<td>70</td>
<td>130/80</td>
<td>91.0</td>
<td>1.20</td>
<td>0.73</td>
<td>1.4</td>
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<tr>
<td>7</td>
<td>68/M</td>
<td>68</td>
<td>Angina, dyspnea</td>
<td>78</td>
<td>135/95</td>
<td>105.3</td>
<td>0.89</td>
<td>0.90</td>
<td>2.0</td>
</tr>
<tr>
<td>8</td>
<td>58/M</td>
<td>55</td>
<td>Angina</td>
<td>112</td>
<td>125/85</td>
<td>140.0</td>
<td>NA</td>
<td>0.81</td>
<td>1.6</td>
</tr>
<tr>
<td>9</td>
<td>62/M</td>
<td>77</td>
<td>Angina</td>
<td>72</td>
<td>144/78</td>
<td>103.7</td>
<td>1.16</td>
<td>0.97</td>
<td>1.6</td>
</tr>
<tr>
<td>10</td>
<td>65/M</td>
<td>80</td>
<td>Angina, dyspnea</td>
<td>58</td>
<td>120/75</td>
<td>69.6</td>
<td>0.60</td>
<td>0.60</td>
<td>2.0</td>
</tr>
<tr>
<td>11</td>
<td>66/M</td>
<td>80</td>
<td>Angina, dyspnea</td>
<td>64</td>
<td>115/70</td>
<td>73.6</td>
<td>0.54</td>
<td>1.12</td>
<td>2.2</td>
</tr>
<tr>
<td>12</td>
<td>63/M</td>
<td>65</td>
<td>Angina</td>
<td>74</td>
<td>140/90</td>
<td>103.6</td>
<td>1.22</td>
<td>0.92</td>
<td>2.5</td>
</tr>
<tr>
<td>13</td>
<td>28/F</td>
<td>80</td>
<td>Angina, dyspnea</td>
<td>76</td>
<td>110/70</td>
<td>83.6</td>
<td>0.31</td>
<td>0.56</td>
<td>2.7</td>
</tr>
<tr>
<td>Mean</td>
<td>50.5</td>
<td>73</td>
<td></td>
<td>70</td>
<td>121/79</td>
<td>85.3</td>
<td>0.88</td>
<td>0.78</td>
<td>2.1</td>
</tr>
<tr>
<td>SD</td>
<td>±17</td>
<td>±9</td>
<td></td>
<td>±14 ±12 ±7 ±23.2</td>
<td>±0.31</td>
<td>±0.19</td>
<td>±0.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; HR, heart rate; bpm, beats per minute; BP, blood pressure; RPP, rate–pressure product; MRGlc, regional myocardial glucose utilization; MBF, myocardial blood flow; WT, wall thickness; MM, metabolic mismatch; palp, palpitations; sept, septal mismatch; + denotes mismatch present; − denotes mismatch absent. *Patients with additional exercise positron emission tomography studies (see Table 2). Numbers in parentheses denote extent of MM in degrees on the circumference.
TABLE 1. Continued

<table>
<thead>
<tr>
<th>Nonhypertrophied segment</th>
<th>MRGlc (μmol·min⁻¹·g⁻¹)</th>
<th>MFB (mL·min⁻¹·g⁻¹)</th>
<th>WT (cm)</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.22</td>
<td>0.94</td>
<td>1.2 + Sept (35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.69</td>
<td>1.03</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.10</td>
<td>1.19</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>0.90</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.73</td>
<td>0.79</td>
<td>1.6 + Sept (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.70</td>
<td>1.15</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.08</td>
<td>0.95</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.21</td>
<td>0.76</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.19</td>
<td>1.04</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.57</td>
<td>0.92</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.70</td>
<td>1.10</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.40</td>
<td>1.05</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.24</td>
<td>1.21</td>
<td>1.0 + Sept (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.82</td>
<td>0.99</td>
<td>1.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>±0.38</td>
<td>±0.13</td>
<td>±0.23</td>
<td></td>
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</tr>
</tbody>
</table>

The flow estimates had been shown previously to correlate linearly to independent measurements of blood flow with microspheres in canine myocardium.²⁷

**Regional rates of myocardial glucose utilization.** Rates (μmol·min⁻¹·g⁻¹) were derived from the serial F-18 deoxyglucose images using the PATLAK graphical analysis.²⁸ Estimates of rates of exogenous glucose utilization with this modified graphical analysis approach were found to correlate well with those derived by the conventional microparameter fit, which in turn correlated well with those by the Fick method; the graphical analysis included correction for regional partial volume effect based on individual echocardiographic measurements of wall thickness.²⁹

**Echocardiography**

Two-dimensional transthoracic echocardiography was performed in all patients for identification of the regional myocardial hypertrophy to exclude valvular heart disease or abnormalities in regional wall motion. Echocardiograms were obtained with 2.25- and 3.0-MHz transducers attached to phased-array scanners (model 77020, Hewlett Packard) and evaluated without knowledge of clinical or other imaging data. The thickness of the septal and posterior wall segments was determined with calibrated electronic calipers; endocardial and epicardial borders were identified by viewing the pertinent portions in slow motion and real time. Hypertrophy of the anterior septum or the posterior free wall was present when diastolic wall thickness was ≥15 mm; hypertrophy of the posterior septum and the lateral free wall was defined as a diastolic thickness ≥17 mm.³⁰ At a complete diagnostic echocardiographic evaluation, measurements of wall thickness were quantitated from M-mode recordings at the level of the mitral valve or distal to the mitral leaflets, depending on maximal thickness, primarily using parasternal short-axis and long-axis views.³¹,³²

**Electrocardiography**

Twelve-lead standard ECGs were obtained in each patient at the time of the PET study. ECG criteria for left ventricular hypertrophy were S in V₁+R in V₅ or V₆≥35 mm.³³

**Statistical Analysis**

Mean values are given with standard deviations unless otherwise specified. Group data were analyzed with Students' t test for paired or unpaired data. Subgroups of patients were compared using the Wilcoxon signed rank test. A value of p<0.05 was considered statistically significant.

**Results**

Demographic information, clinical findings, and morphological as well as imaging data obtained at rest are summarized in Table 1. All patients had a history of clinical symptoms ranging from moderate to severe dyspnea to angina pectoris and palpitations or a combination of all; three patients had a familial history of hypertrophic cardiomyopathy, and younger patients tended to be more severely symptomatic. Five patients had severe systolic anterior motion of the mitral valve (patients 1, 6, 9, 10, and 13). All patients had an increased septal thickness ranging from 1.6 cm to 2.7 cm, with a mean value of 2.1±0.4 cm compared with a myocardial thickness of 1.25±0.23 cm in the nonhypertrophied wall (p<0.001) (Table 1). Resting heart rate averaged 70±14 beats per minute. The arterial blood pressure was within normal limits; systolic and diastolic blood pressure averaged 121±12.3 and 79±7.2 mm Hg, respectively. The rate–pressure product averaged 8,530±2,320 beats per minute×mm Hg. ECG criteria of left ventricular hypertrophy were present in 10 patients. One patient had a first-degree atrioventricular block, and three patients revealed no definite ECG criteria of left ventricular hypertrophy. No other conduction abnormalities or tachyarrhythmias were observed during the tomographic imaging studies.

**Myocardial Blood Flow and Glucose Utilization at Rest**

Transaxial images of blood flow and glucose utilization in two patients are shown in Figure 1. As indicated in Table 1, myocardial blood flow was rather heterogeneous in most patients and, further, varied considerably between patients. For the group of 13 patients, blood flow averaged 0.99±0.13 mL·min⁻¹·g⁻¹ in nonhypertrophied myocardium; flow to the hypertrophied myocardium was significantly lower and averaged 0.78±0.19 mL·min⁻¹·g⁻¹ (p<0.025). Ratios of blood flow in hypertrophied to nonhypertrophied myocardium ranged from 0.46 to 1.07 and thus reflected the considerable intra- and interindividual heterogeneity of myocardial blood flow. As this ratio averaged 0.79±0.20, blood flow was on average 21% lower in hypertrophied than in nonhypertrophied myocardium.

Compared with blood flow, the regional rates of glucose utilization were more homogeneous. Ratios between hypertrophied and nonhypertrophied myocardium ranged from 0.77 to 1.29 and averaged 1.06±0.30. Absolute rates of exogenous glucose utilization were similar for hypertrophied (0.88±0.31 μmol·min⁻¹·g⁻¹) and nonhypertrophied myocardium (0.87±0.35 μmol·min⁻¹·g⁻¹, p=NS). Regional rates of exogenous glucose utilization divided by regional blood flow yielded values of the regional extraction of glucose in
micromoles of glucose per milliliter of blood. Because of lower blood flows, hypertrophied myocardium extracted significantly more glucose (1.19±0.47 µmol/mL) than nonhypertrophied myocardium (0.80±0.35 µmol/mL, p<0.05). Circumferential profile analysis revealed in three of the 13 patients a blood flow–metabolism mismatch at rest.

**Effect of Exercise**

Four patients could be subjected to supine bicycle exercise during a second PET study (Table 2); the remaining patients did not tolerate an additional study because of their aggravating symptoms. These four patients were younger (20–49 years; mean, 33 years) than the remaining nine patients (28–69 years; mean, 58 years; p<0.002). The septal wall thickness averaged 2.25±0.28 cm in these four patients compared with 2.00±0.42 cm in the nine patients who were studied only at rest (NS). With exercise, the heart rate rose to 133±8 beats per minute, and systolic and diastolic blood pressures increased to 149±9 and 94±8 mm Hg, respectively (p<0.001 versus rest). Accordingly, the rate–pressure product increased from 6,310±360 to 19,960±2,800 beats per minute×mm Hg with exercise (p<0.002).

Transaxial images at rest and during exercise in one patient are shown in Figure 2. Circumferential profile analysis demonstrated in two of the four patients new blood flow–metabolism mismatches after exercise that had not been present at rest. In a third patient, a mismatch observed already at rest increased in size after exercise. Blood flow during exercise averaged 0.91±0.10 mL·min⁻¹·g⁻¹ in nonhypertrophied myocardium and thus did not significantly change from rest (1.01±0.11 mL·min⁻¹·g⁻¹). In hypertrophied segments, however, blood flow during exercise averaged only 0.57±0.33 mL·min⁻¹·g⁻¹ compared with 0.75±0.23 mL·min⁻¹·g⁻¹ at rest; this difference failed to attain statistical significance. Nevertheless, myocardial blood flow became more heterogeneous with exercise; the ratio of blood flow to hypotrophied to nonhypertrophied myocardium averaged 0.74±0.18 at rest and 0.61±0.37 during exercise. Similarly, exercise led to increased regional differences in myocardial glucose utilization rates. The rate of exogenous glucose utilization in hypertrophied myocardium was 0.92±0.19 µmol·min⁻¹·g⁻¹ at rest and 0.79±0.25 µmol·min⁻¹·g⁻¹ with exercise (NS). In nonhypertrophied myocardium, the utilization rate averaged 1.0±0.2 µmol·min⁻¹·g⁻¹ at rest and 0.48±0.30 µmol·min⁻¹·g⁻¹ immediately after exercise. Thus, the ratio of glucose metabolic rates in hypertrophied to nonhypertrophied myocardium increased from 0.92±0.04 to 2.38±1.42 after exercise (p<0.01). Because quantitation of glucose uptake at rest was unavailable, patient 4 was not taken into account.

**Patients With Blood Flow–Metabolism Mismatches**

As described above, circumferential profile analysis identified blood flow–metabolism mismatches at rest or
with exercise in five patients. Blood flow and glucose utilization were more heterogeneous in these patients than in patients without an apparent blood flow–metabolism mismatch. Compared with nonhypertrophied myocardium, blood flow to hypertrophied segments was 45% lower (0.52±0.24 versus 0.92±0.16 mL·min⁻¹·g⁻¹, p<0.025). Relative blood flow, assessed as flow ratios of hypertrophied versus nonhypertrophied myocardium, was more severely reduced in patients with (0.58±0.25) than in patients without blood flow–metabolism mismatches (0.86±0.14, p<0.025). Conversely, glucose extraction was higher in hypertrophied myocardium of those five patients with blood flow–metabolism mismatches (1.55±0.62 versus 0.52±0.33 μmol·min⁻¹·g⁻¹, p<0.05). Accordingly, the ratio of glucose utilization in hypertrophied to nonhypertrophied myocardium was higher in patients with than without blood flow–metabolism mismatches (1.79±1.12 versus 1.11±0.4, p<0.05). The absolute rates of glucose utilization tended to be higher in hypertrophied regions with mismatches than those without mismatches; however, the difference failed to attain statistical significance, presumably as a result of the small sample size (0.73±0.32 versus 0.46±0.27 μmol·min⁻¹·g⁻¹, NS).

The follow-up of those patients with metabolic mismatches appeared to be less favorable, since patient 1 underwent myectomy, patients 2 and 3 continued to have severe, limiting angina and dyspnea, and patient 13 continued to exhibit episodes of self-terminating ventricular tachycardia and of palpitations under oral sotalol. Follow-up information on patient 5 was not available.

**Age-Related Differences**

Other interesting findings pertain to differences in the age of the patients. When the patients were grouped into those <50 years of age (younger group, n=6) and those ≥50 years (older group, n=7), several differences became apparent. Septal myocardium was hypertrophied more severely in the younger than in the older group (2.28±0.34 cm versus 1.90±0.39 cm, p<0.05), whereas no difference existed with regard to the thickness of “reference myocardium” (1.17±0.23 cm versus 1.31±0.25 cm, NS). Relative to nonhypertrophied myocardium, blood flow in the hypertrophied myocardium of the younger patient group was depressed more severely than in the older group (flow ratios of 0.68±0.18 and 0.87±0.17, respectively, p<0.05). Glucose utilization rates and their distributions throughout the left ventricular myocardium were not significantly different. However, in the younger group, glucose extraction was significantly higher in hypertrophied than in nonhypertrophied myocardium (1.29±0.57 versus 0.80±0.41 μmol/mL, p<0.05); in the older patient group the regional inhomogeneity of glucose uptake was less pronounced (1.11±0.39 μmol/min in hypertrophied versus 0.91±0.33 μmol/min in nonhypertrophied segments, p=NS), possibly reflecting a more generalized form of hypertrophic cardiomyopathy than seen in younger patients. Patients with a blood flow–metabolism mismatch were in fact younger than patients without a mismatch (34±10 versus 61±11 years, p<0.01).
PLASMA SUBSTRATE LEVELS

Immediately before the PET studies, plasma substrate levels were in the normal range. Insulin was 14.1±8.3 IU/L; lactate, 7.1±2.9 mg/dL; glucose, 106±38 mg/dL; free fatty acid, 0.37±0.08 mg/dL; and triglycerides, 139±103 mg/dL. At the time of the F-18 deoxyglucose injection, 1 hour after oral glucose, the plasma glucose level averaged 132±49 mg/dL, lactate levels were 7.1±2.8 mEq/L, and free fatty acid levels were 0.20±0.58 mEq/L. As a physiological response, insulin levels rose to 27.1±25.3 IU/L (p<0.05). Plasma glucose levels were elevated at 207 mEq/L in one case (patient 8), whereas free fatty acid levels were 0.24 mEq/L, triglyceride levels were 401 mg/dL, and previously determined insulin was normal at 18 IU/mL; this patient revealed relatively poor myocardial uptake of F-18 deoxyglucose that precluded quantification of glucose utilization in the hypertrophied segment and later showed an abnormal oral glucose tolerance test suggestive of a prediabetic state. In another instance (patient 12), the resting glucose level was 197 mg%; it rose to 223 mg% after oral glucose loading and fell to 193 mg% after completion of metabolic imaging. Other metabolic parameters including plasma insulin had been found to be within normal limits at the time of the initial diagnostic workup. In addition, the quality of the F-18 deoxyglucose images was adequate for quantitative analysis. There were no significant differences in plasma substrate levels between the older and younger patient group.

Measurements of plasma substrate levels in three of the four patients subjected to exercise revealed no significant changes in glucose and fatty acid levels from rest to exercise but did reveal a physiological increase in plasma lactate levels (8.8±1.6 mg/dL at rest versus 27.5±19.4 mg/dL during exercise, p<0.05).

DISCUSSION

Evaluation of relative distributions as well as quantification of regional myocardial blood flow and exogenous glucose utilization with PET revealed an inhomogeneous pattern in symptomatic patients with hypertrophic cardiomyopathy. Despite this variability, blood flow for the whole group of 13 patients was significantly lower in hypertrophied than in nonhypertrophied myocardial regions, whereas rates of glucose utilization were similar. This disparity between blood flow and glucose metabolism resulted in a blood flow–metabolism mismatch at rest in three patients. With exercise, blood flow failed to increase in nonhypertrophied regions and fell slightly in hypertrophied myocardial regions. Therefore, two patients developed new blood flow–metabolism mismatches, and one patient with a mismatch at rest developed an enlarging mismatch with exercise. There were five different patients with mismatches (Tables 1 and 2).

The results of this study suggest the presence of "metabolic ischemia" in the hypertrophied myocardium of patients with hypertrophic cardiomyopathy and expand on findings with 201Tl and 13N ammonia suggesting myocardial ischemia based on mere perfusion abnormalities32,33 or lactate production.34 In addition to metabolic evidence of ischemia in the hypertrophied segment, quantitative measurements revealed an abnormal flow response to physical stress not only confined to regions of hypertrophy but also in adjacent nonhypertrophied segments. Similar to results by Camici et al,32 who reported resting blood flows of 0.90±0.35 and 1.14±0.43 mL·min⁻¹·g⁻¹ in nonhypertrophied and hypertrophied myocardium, respectively, the current study revealed a resting flow of 0.99±0.13 and 0.78±0.19 mL·min⁻¹·g⁻¹ in the free wall and the septum, respectively. In contrast to an attenuated increase in flow to 1.47±0.58 mL·min⁻¹·g⁻¹ after dipyridamole challenge as described by these authors, the current study did not demonstrate a significant augmentation of blood flow to nonhypertrophied and hypertrophied myocardium in response to symptom-limited exercise; a physiological exercise-induced augmentation of blood flow has been previously shown in normal subjects.26 In contrast to the vasodilating action of dipyridamole used by Camici et al32 to assess flow reserve, the current study used ergometric stress. Unlike pharmacological vasodilation, physical stress in these patients leads to an increase in left ventricular end-diastolic pressure, causing a further impairment of diastolic function35,36 and subendocardial perfusion and possibly a limited increase in cardiac output.37,38 In addition, intramyocardial "squeezing" forces may be more vigorous with physical stress and further obstruct blood flow.14 The concerted action of the tachycardia-related diminution in diastolic filling time, impaired muscle relaxation, and increased wall tension resulting from an elevated diastolic filling pressure with exercise may therefore have been responsible for the lack of increased flow during exercise.

Interestingly, wall thickness in hypertrophied segments with a blood flow–metabolism mismatch was
TABLE 2. Continued

<table>
<thead>
<tr>
<th>MRGl (μmol·min⁻¹·g⁻¹)</th>
<th>MBF (mL·min⁻¹·g⁻¹)</th>
<th>WT (cm)</th>
<th>Work load</th>
<th>MM</th>
<th>W</th>
<th>Min</th>
<th>RPP (±0.01)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.40</td>
<td>0.89</td>
<td>1.20</td>
<td>+ Sept (102)</td>
<td>50</td>
<td>3</td>
<td>179.2</td>
<td></td>
</tr>
<tr>
<td>0.11</td>
<td>0.78</td>
<td>1.00</td>
<td>+ Sept (30)</td>
<td>100</td>
<td>4</td>
<td>236.2</td>
<td></td>
</tr>
<tr>
<td>0.83</td>
<td>0.95</td>
<td>1.10</td>
<td>+ Sept (45)</td>
<td>75</td>
<td>3</td>
<td>176.1</td>
<td></td>
</tr>
<tr>
<td>0.58</td>
<td>1.02</td>
<td>1.10</td>
<td>-</td>
<td>100</td>
<td>4</td>
<td>207.0</td>
<td></td>
</tr>
<tr>
<td>0.48</td>
<td>0.91</td>
<td>1.10</td>
<td></td>
<td></td>
<td></td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>±0.30</td>
<td>±0.10</td>
<td>±0.08</td>
<td></td>
<td></td>
<td></td>
<td>±28</td>
<td></td>
</tr>
</tbody>
</table>

2.5±0.3 cm and, thus, tended to be higher than in hypertrophied segments without mismatch (1.9±0.4 cm, NS). A correlation, however, between wall thickness and regional glucose utilization could not be demonstrated. Moreover, patients with a blood flow–metabolism mismatch were significantly younger than patients without a mismatch. Thus, our observations might imply an earlier and more severe manifestation of impaired myocardial perfusion in a subset of young patients with hypertrophic cardiomyopathy. This notion may be supported by the observation recently reported by Kagaya et al.\(^9\) that the regional heterogeneity of F-18 deoxyglucose uptake is higher in young patients with hypertrophic cardiomyopathy than in an older group; these authors speculate that the more heterogeneous uptake of glucose in young patients may be related to a more nonhomogeneous sympathetic discharge or catecholamine receptor activities. In our set of patients, however, regional glucose utilization failed to correlate both with regional wall thickness and the evidence of familial hypertrophic cardiomyopathy. At present, it is unclear whether this observation may identify a more rapid progression of hypertrophy or a special subset of patients. The observation of a slight decrease in F-18 uptake with exercise was probably caused by an exercise-related increase in plasma lactate and, possibly, catecholamine levels, which are known to lower myocardial glucose utilization.

A reduction of blood flow to hypertrophied myocardium as noted in this study has been previously suggested using \(^20^\)TI scintigraphy; \(^20^\)TI imaging uncovered decreased tracer uptake in the interventricular septum of patients with hypertrophic cardiomyopathy, either with atrial pacing or isoproterenol stress, dipyriramole challenge, or even at rest.\(^1\),\(^3\),\(^33\),\(^37\) These observations are supported by our findings of a relatively low septal blood flow of 0.78 mL·min⁻¹·g⁻¹ at rest and further reduction induced by exercise in four patients. Abnormalities of the intramural septal coronary arteries,\(^5\) microvascular disease,\(^4\) and focal scarring as observed on histological examination\(^32\),\(^45\) could provide an anatomic explanation, whereas the low ratio of vessel density to myocardial mass and the abnormal diastolic function could offer a physiological explanation for the lack of a normal augmentation of flow with exercise.\(^1\),\(^14\),\(^35\),\(^50\) Less certain are the reasons as to why blood flow to nonhypertrophied myocardium failed to increase with exercise in four patients, unless the disease process of hypertrophic cardiomyopathy also involves nonhypertrophied segments, as suggested by Spirito and Maron.\(^26\) or diastolic abnormalities that interfere with an adequate flow response.\(^4\),\(^44\) Another possibility, although

TABLE 3. Subgroup Analysis of All Patients With Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>All patients (n=13)</th>
<th>Complete rest/stress protocol (n=4)</th>
<th>Studies at rest (n=9)</th>
<th>MM at rest (n=3)</th>
<th>No MM (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At rest</td>
<td>SL exercise</td>
<td>MM</td>
<td>W</td>
<td>Min</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50±17</td>
<td>73±9</td>
<td>76±6</td>
<td>76±7</td>
<td>72±9</td>
<td>73±9</td>
</tr>
<tr>
<td>70±14</td>
<td>58±3.31</td>
<td>133±8</td>
<td>75±15</td>
<td>69±7</td>
<td>70±16</td>
</tr>
<tr>
<td>DP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85.3±23.2</td>
<td>63.1±3.6</td>
<td></td>
<td>199.6±28.0</td>
<td>95.2±20.0</td>
<td>78.7±11.1</td>
</tr>
<tr>
<td>0.88±0.29</td>
<td>0.92±0.19</td>
<td>0.79±0.25</td>
<td>0.87±0.32</td>
<td>0.81±0.35</td>
<td>0.91±0.26</td>
</tr>
<tr>
<td>MRGlhyp (μmol·min⁻¹·g⁻¹)</td>
<td>0.82±0.36</td>
<td>1.00±0.22</td>
<td>0.48±0.26t</td>
<td>0.75±0.38</td>
<td>0.73±0.40</td>
</tr>
<tr>
<td>MRGlref (μmol·min⁻¹·g⁻¹)</td>
<td>78±19</td>
<td>75±20</td>
<td>57±28</td>
<td>79±20</td>
<td>58±5†</td>
</tr>
<tr>
<td>MBF hyp (mL·min⁻¹·g⁻¹)</td>
<td>99±13*</td>
<td>99±9</td>
<td>91±10</td>
<td>100±15</td>
<td>98±17†</td>
</tr>
<tr>
<td>MBFref (mL·min⁻¹·g⁻¹)</td>
<td>2.10±0.39</td>
<td>2.25±0.28</td>
<td>2.00±0.42</td>
<td>2.40±0.30</td>
<td>1.98±0.36</td>
</tr>
<tr>
<td>WThyp (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.25±0.23</td>
<td>0.10±0.10</td>
<td>1.31±0.27</td>
<td>1.27±0.25</td>
<td>1.22±0.23</td>
<td></td>
</tr>
<tr>
<td>MRGl/MBFhyp (μmol·mL⁻¹)</td>
<td>0.012±0.004</td>
<td>0.013±0.004</td>
<td>0.015±0.005</td>
<td>0.010±0.006</td>
<td>0.014±0.006</td>
</tr>
<tr>
<td>MRGl/MBFref (μmol·mL⁻¹)</td>
<td>0.008±0.003*</td>
<td>0.010±0.004</td>
<td>0.005±0.003†</td>
<td>0.007±0.004</td>
<td>0.008±0.005</td>
</tr>
</tbody>
</table>

SL, supine leg; MM, metabolic mismatch; LVEF, left ventricular ejection fraction; HR, heart rate; bpm, beats per minute; DP, double product; MRGlhyp and MRGlref, regional metabolic rate of glucose utilization in hypertrophied and control (reference) myocardium; MBFhyp and MBFref, myocardial blood flow in hypertrophied and control (reference) regions; WThyp and WThref, wall thickness of hypertrophied and control (reference) myocardial regions.

\(\ast p<0.05\) vs. hypotrophy; \(\dagger p<0.05\) vs. hypotrophy; \(\ddagger p<0.05\) vs. no mismatch; \(\$ p<0.002\) vs. hypotrophy; \(\| p<0.002\) vs. exercise; \(\% p<0.001\) vs. hypertrophy.
less likely, is that exercise was continued for only 60 seconds after tracer injection, whereas 90 seconds of the N-13 ammonia time–activity curves were analyzed. Although this limitation might have slightly attenuated an increase in blood flow, it is unlikely to account entirely for the absence of a flow increase, because most of the trapping of tracer occurs within the initial 60 seconds. Moreover, a similar study and data analysis could show a physiological increase in blood flow with exercise in normal volunteers. Resting and exercise PET measurements were separated by 22±7 days. Heart rate and systolic and diastolic blood pressures immediately before the exercise study were similar to those at the time of the initial PET study at rest.

The current findings in symptomatic patients differ from those in asymptomatic or mildly symptomatic patients. Grover-McKay et al11 found a 32% reduction in blood flow to the hypertrophied interventricular septum associated with an even greater reduction in glucose utilization in patients with minimal symptoms and good exercise tolerance. Conversely, patients in the current study were highly symptomatic, and only four could be studied under exercise conditions; 12 of the 13 patients had angina either at rest or on exertion; five patients had shortness of breath. Thus, patients in the current study had more severe disease.

Study Limitations and Technical Considerations

Only four of the 13 patients could be submitted to exercise studies; severe symptoms precluded repeated sustained bicycle exercise in the remaining patients. Nevertheless, the changes induced by exercise were rather consistent and suggestive of similar observations in patients who could not be subjected to an exercise study.

Measurements of true tracer tissue activity concentrations, critical for quantification of physiological processes by PET, are complicated by the partial volume effect. The true activity concentration is underestimated when the size of the imaged object or the thickness of the myocardial wall is less than twice the spatial resolution of the imaging system. Although this effect is usually negligible in hypertrophied regions, given a wall thickness in excess of 20 mm (as compared with an in-plane image resolution of 11.6 mm), it is significant for nonhypertrophied myocardium. Correction for partial volume effect in this study was based on regional wall thickness measurement by M-mode echocardiography, which has been shown previously to correlate closely to wall thickness by magnetic resonance imaging.11 Therefore, by matching the tomograms with a corresponding echogram, care was taken to avoid misalignment between the sites of wall thickness measurements and the placement of regions of interest. Nevertheless, whereas such misalignments were avoided by two-dimensional echo orientation and M-mode measurements, slightly variable measurements may not be totally excluded but would be expected to be random rather than distributed unidirectionally.

Both resting and exercise blood flow measurements were quantified from the initial 90 seconds of the time–activity curves; however, the aggravation of angina or dyspnea precluded continuation of exercise beyond 60 seconds. Therefore, the obtained values of blood flow may have theoretically underestimated true flows during peak exercise. However, first, heart rate did not decline by >15% within the initial 30 seconds after stopping exercise, and second, >90% of ammonia becomes trapped within the first 60 seconds; therefore, a potential underestimation is likely to be negligible. This notion does not apply to the quantitative glucose studies because most of the metabolic trapping occurred after the initial 60 seconds; thus, the derived values for glucose metabolism mostly reflect conditions immediately after exercise.45

Finally, the image quality after injection of F-18 deoxyglucose was usually good or excellent, and uptake was documented in all regions of the myocardium, indicating that all patients were imaged under fasted condition regardless of mildly elevated plasma glucose levels in two cases. Only one patient (No. 8) had inadequate uptake in the septum that precluded quantitation.

Clinical Implications

An augmentation in regional glucose utilization relative to regional perfusion is considered a sensitive index of regional myocardial ischemia. With the advent of
quantitative assessment of both regional blood flow and glucose uptake, PET not only provides a sensitive and powerful tool to identify myocardial hyperperfusion under physiological conditions but also may elucidate the role of metabolic ischemia in hypertrophic cardiomyopathy. Different from the viability issue in coronary artery disease with mismatches as markers of viable tissue, in hypertrophic cardiomyopathy the emphasis is placed on the quantitative relation of a relatively increased glucose utilization rate and regional blood flow at rest or with physical stress in order to identify ischemia in this group of patients and to shed light on the pathomechanism of asymptomatic focal infarction as frequently seen on histological sections. Moreover, because therapeutic concepts for hypertrophic cardiomyopathy are mainly based on empirical and clinical judgment, the quantitative assessment of flow and metabolism could possibly elucidate effects of medical therapy and may also provide an effective way of therapy control. Finally, regardless of the conflicting data on risk stratification in hypertrophic cardiomyopathy, evidence of myocardial ischemia may also have prognostic impact. Considering that 22% of persons dying from sudden unexpected death under the age of 40 years suffer from hypertrophic cardiomyopathy, it may be conceivable that within a heterogeneous spectrum of this disease, an extensive disarray of myocardial architecture implies focal ischemia and may serve as a nidus of ventricular arrhythmias predisposing to sudden death. Especially young patients with extensive hypertrophy and severe symptoms suggestive of ischemia are threatened by syncope and sudden death. Further prospective studies are needed relating the pattern of regional perfusion and metabolism to the individual clinical outcome in order to characterize a potential prognostic impact of metabolic abnormalities in hypertrophic cardiomyopathy.

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