Myocardial perfusion abnormalities in patients with hypertrophic cardiomyopathy: assessment with thallium-201 emission computed tomography

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ABSTRACT  Myocardial ischemia may play a critical role in the symptomatic presentation and natural history of hypertrophic cardiomyopathy (HCM). To assess the relative prevalence and functional significance of myocardial perfusion abnormalities in patients comprising the broad clinical spectrum of HCM, we studied 72 patients (ages 12 to 69 years, mean 40) using thallium-201 emission computed tomography. Imaging was performed immediately after maximal exercise and again after a 3 hr delay. Regional perfusion defects were identified in 41 of the 72 patients (57%). Fixed or only partially reversible defects were evident in 17 patients, 14 of whom (82%) had left ventricular ejection fractions of less than 50% at rest. Twenty-four patients demonstrated perfusion defects during exercise that completely reversed at rest; all had normal or hyperdynamic left ventricular systolic function (ejection fraction >50%). Perfusion abnormalities were present in all regions of the left ventricle. However, the fixed defects were observed predominantly in segments of the left ventricular wall that were of normal or only mildly increased (15 to 20 mm) thickness; in contrast, a substantial proportion (41%) of the completely reversible defects occurred in areas of moderate-to-marked wall thickness (≥20 mm, p < .001). Neither a history of chest pain nor its provocation with treadmill exercise was predictive of an abnormal thallium study, since regional perfusion defects were present in 10 of 18 (56%) completely asymptomatic patients, compared with 31 of 54 (58%) symptomatic patients. These data indicate that myocardial perfusion abnormalities occur commonly among patients with HCM. Fixed or only partially reversible defects suggestive of myocardial scar and/or severe ischemia occur primarily in patients with impaired systolic performance. Completely reversible perfusion abnormalities occur predominantly in patients with normal or supranormal left ventricular systolic function. Such dynamic changes in regional thallium activity may reflect an ischemic process that contributes importantly to the clinical manifestations and natural history of HCM.


THERE ARE several lines of evidence to suggest that myocardial ischemia may play a central role in the pathophysiology and the natural history of hypertrophic cardiomyopathy (HCM). For many patients, chest pain is a prominent feature of the disease, even in the absence of obstructive atherosclerotic coronary artery disease. Such pain can usually be precipitated by atrial pacing, often in association with evidence for inadequate coronary flow reserve, elevated filling pressures, and abnormalities in lactate metabolism.1-3 Morphologic studies4-7 have revealed a variable extent and distribution of fibrous tissue formation in the left ventricular myocardium, ranging from patchy interstitial fibrosis to grossly visible or even transmural scars. Structurally abnormal intramural coronary arteries with markedly thickened walls and apparently narrowed lumens, often within or in close proximity to areas of fibrosis, have been described in a majority of patients with HCM studied at autopsy.8

Given the potential importance of myocardial ischemia in HCM, its identification might provide critical information regarding the specific pathophysiologic mechanisms operative in a given patient with this disease. Myocardial thallium-201 (201TI) perfusion imaging could potentially provide a means of obtaining such data noninvasively. Indeed, regional thallium perfusion defects of both a fixed and reversible nature have been
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The present study was therefore undertaken to assess the prevalence, characteristics, and clinical significance of myocardial perfusion abnormalities in a large group of patients reflecting the broad clinical spectrum of HCM.

Methods

Characterization of patients. The study group was composed of 72 patients with HCM who underwent \(^{201}\text{Tl}\) emission computed tomography in the National Heart, Lung, and Blood Institute between June 1985 and June 1986. In each patient, the diagnosis of HCM was based on echocardiographic demonstration of a hypertrophied, nondilated left ventricle in the absence of another cardiac or systemic disease known to cause left ventricular hypertrophy.13

An effort was made to assemble a large patient group representing many facets of the disease spectrum of HCM, and hence the following patients were selected for study: (1) 46 patients with substantial symptoms of dyspnea, angina, presyncope, or syncope despite medical therapy, (2) 18 asymptomatic patients, and (3) eight patients with previously determined resting left ventricular ejection fractions of less than 50% (a value that represents a reduction in ejection fraction of greater than 2 SDs from the mean for patients with HCM\(^14\)). The 72 study patients ranged in age from 12 to 69 years (mean 40). There were 47 male and 25 female patients.

Coronary arteriographic and cardiac catheterization data from studies performed within 1 year of thallium emission computed tomography were obtained for 38 of the 72 patients. Coronary arteriography was normal in each of these 38 patients. Nine additional patients had undergone catheterization between 1979 and 1983; the coronary arteriograms were normal in all nine of these patients. Coronary artery disease was considered unlikely in the remaining 25 patients; 18 were completely asymptomatic (age 12 to 59 years, mean 33), and of the seven symptomatic patients, four were younger than 33 years of age and the three others had not experienced angina.

The presence of left ventricular outflow tract obstruction under basal conditions was assessed at cardiac catheterization in 38 patients and estimated from the M mode echocardiogram (based on the magnitude and duration of systolic anterior motion of the mitral valve) in the remaining 34 patients.15, 16 Left ventricular outflow tract obstruction under basal conditions (gradient >30 mm Hg) was judged to be present in 23 patients and was absent in the other 49 patients.

Scalar (12-lead) electrocardiography. Supine, resting 12-lead electrocardiograms were obtained in all 72 patients on the day of thallium tomography. Electrocardiographic left hypertrophy was defined with the use of Romhilt-Estes criteria.17 Six of the 72 patients had left bundle branch block or a paced rhythm and were excluded from the electrocardiographic analysis.

Graded treadmill exercise testing. Graded treadmill exercise according to the NIH combined protocol\(^18\) was performed by 68 of the 72 study participants. The other four patients were unable to exercise because of severe symptoms at rest in three and neuromuscular impairment in the fourth. Cardiac medications were successfully withdrawn at least 48 hr before study in 64 of the 68 patients who underwent exercise testing and in three of the four patients studied at rest. The five patients in whom drug therapy could not be withdrawn were all in the subgroup with depressed ejection fractions. Heart rate, rhythm, and systemic blood pressure were monitored during exercise. In each patient, exercise was continued until the development of limiting angina, dyspnea, presyncope, or fatigue. No patient developed high-grade ventricular ectopy or atrioventricular block requiring premature termination of exercise. Thirty-four (50%) of the 68 patients were able to achieve 85% of their predicted maximal heart rate for age. Observational data included treadmill times, rate-pressure products, and the presence or absence of associated electrocardiographic abnormalities that differed significantly from baseline, i.e., a further downward displacement of the ST segment of more than 1 mm. Resting ST-T abnormalities were defined simply by the presence of ST segment depression in excess of 0.5 mm and/or T wave inversions in at least two anatomically grouped leads.

\(^{201}\text{Tl}\) emission computed tomography. At peak exercise, patients received either 2.0 mCi (n = 18) or 3.5 mCi (n = 50) \(^{201}\text{Tl}\) by vein; exercise was continued for an additional 60 sec to allow for adequate circulation of the isotope. Imaging was begun within 10 min of the completion of exercise and again after a 3 hr delay. The studies were performed with a wide-field-of-view rotating gamma camera equipped with a low-energy, medium-resolution, high-sensitivity, parallel-hole collimator (Apex 415, APC-3, Elscint Co., Boston) centered on the 68 keV photo peak with a 20% window. The camera was rotated over 180 degrees in an elliptical orbit about the patient’s anterior thorax from the right anterior oblique (−40 degrees) to the left posterior oblique (+140 degrees) position. Thirty-one images were obtained in a 128 × 128 matrix for 30 sec each at 6 degree intervals. The entire acquisition process required 17 min. Individual count rates varied between 1000 and 5000 counts/sec, depending on the dose of isotope administered and body size. Planar imaging was performed after the tomographic collection in the standard anterior, 40 degree left anterior oblique (LAO), and 70 degree LAO projections for a total of 350,000 counts per projection. Planar images were used to assess visually the orientation, size, and shape of the heart. Since these planar images were obtained after the tomographic collection, beginning usually 20 to 25 min after the injection of thallium, they were not systematically analyzed for regional count differences. The four patients unable to exercise received either 2.0 (n = 2) or 3.5 mCi \(^{201}\text{Tl}\) in the standing position. Imaging was begun in 10 min and again after a 3 hr delay in a manner identical to that used for those patients who did exercise.

The individual rotational images were first reduced to a 64 × 64 format for ease of manipulation with the use of the commercially available reconstruction software. Corrections for nonuniformity, the elliptical orbit, and the center of rotation were performed before the reconstruction. Contiguous transaxial tomograms encompassing the entire heart were reconstructed after filtered backprojection with an all-purpose Hanning filter to reduce statistical noise (cutoff frequency of 0.5 cycles/pixel). Sagittal and short-axis tomograms (figure 1) of 3 pixel thickness (approximately 1.8 cm) were then derived from the transaxial images. All subsequent analyses were performed on anatomically comparable slices from each of these three orthogonal planes for the initial and delayed studies. The slices were chosen according to the method described by Garcia et al.\(^19\) No attenuation or scatter correction was used. For purposes of visual analysis, all tomograms were normalized to the maximal pixel value per slice and the interpretations were performed both with and without a 20% threshold reduction.

Tomographic analysis. The initial and delayed tomographic images were interpreted by three independent observers with a semiquantitative regional scoring system modified from the method developed by Okada et al.\(^20\) for planar studies. Regional perfusion defects were categorized as fixed, partially reversible, or completely reversible as dictated by the scoring system. Complete agreement among all three observers occurred in 61 (85%) of the 72 studies. In the remaining 11 studies, interobserver disagreements were resolved by consensus. The short-
axis tomograms were also analyzed with respect to apparent changes in cavity size between the initial and delayed studies. Studies with apparent cavity dilatation after exercise were identified with unanimous interobserver agreement. Finally, two observers independently graded the pulmonary activity relative to the myocardial activity on the postexercise rotational image nearest to the straight anterior projection (+2 degrees). With the use of the qualitative criteria developed by Boucher et al., abnormal increased pulmonary thallium activity was identified by both observers with complete agreement.

Validation. The techniques used during tomographic acquisition, reconstruction, and analysis were validated in a group of 51 normal volunteers (ages 21 to 58 years, mean 39) who underwent exercise 201TI emission computed tomography between February and May 1986. Heart disease was excluded in these volunteers on the basis of a normal history, physical examination, chest radiography, M mode and two-dimensional echocardiographic studies, and rest and exercise echocardiography. There were 26 men and 25 women, allowing construction of two normal data bases, one for each sex. All normal subjects received 3.5 mCi 201TI at peak exercise. Aside from minor variations in the degree of inferior isotope attenuation, none of the normal subjects manifested regional heterogeneity of 201TI uptake, apparent cavity dilatation, or increased lung uptake during exercise.

Radionuclide ventriculography. Radionuclide ventriculography was performed in all patients at rest in the supine position after the labeling of red blood cells in vivo with 20 to 25 mCi technetium-99m (99mTc). Scintigraphic data were acquired in the LAO position, which allowed optimal visual separation of the right and left ventricles. Left ventricular ejection fraction was computed as previously described. These studies were performed on the same day as the tomographic study for 50 patients, within 6 days for 19, and within 3 months of tomography for the remaining three patients. Because changes in left ventricular size and shape, independent of alterations in myocardial perfusion, can result in apparent regional 201TI defects, radionuclide ventriculography was performed in 11 of the 72 patients both before and 10 min after the completion of upright graded treadmill exercise continued to the same heart rate and blood pressure end points as achieved during the previous 201TI exercise session to evaluate global and regional left ventricular function under conditions simulating those of the 201TI data acquisition. Assessments of left ventricular size and shape and regional wall motion were made by two independent observers. Left ventricular volume changes between the rest and postexercise studies were estimated by the ratios of background-corrected end-diastolic counts, corrected for the decay of 99mTc.

Echocardiographic studies. An Advanced Technology Laboratory (ATL) Mark 500 mechanical sector scanner with a 3 MHz transducer was used to perform the two-dimensional echocardiographic studies. M mode echocardiograms were performed with a dedicated Irex System II ultrasound unit equipped with a 2.25 MHz transducer, or were derived from the two-dimensional image under direct anatomic visualization. The two-dimensional echocardiographic examination, performed to identify the distribution of left ventricular hypertrophy, included the imaging of a number of cross-sectional planes through the heart, as previously described. Assessment of the magnitude and extent of left ventricular hypertrophy was obtained primarily from the parasternal short-axis planes; however, the parasternal long-axis and the apical views were also used to integrate the observations made from the short-axis views. Hypertrophy was considered to be present if the diastolic thickness of the wall was at least 15 mm.

Echocardiographic studies were judged to be technically adequate to determine the presence or absence of hypertrophy in each left ventricular segment in 64 (89%) of the 72 study patients. In these patients, the anatomic location of the 201TI perfusion defect was related to the presence and magnitude of wall thickening in the corresponding left ventricular segment as assessed by echocardiography. Seventy-one patients underwent echocardiographic study within 1 week of their tomographic study and the remaining patient was examined 3 months before tomography.

Statistical methods. Comparisons among groups of patients were performed by one-way analysis of variance and the paired or unpaired t test, where appropriate. Differences in proportions were analyzed with the chi-square test, correcting for small sample sizes when necessary.

Results

201TI emission computed tomography. Regional perfusion defects were identified by visual inspection in 41
(57%) of the 72 study patients (figures 2 to 4). Seventeen patients had fixed or only partially reversible defects, including two of the four patients who could be studied only under resting conditions. Twenty-four patients had perfusion abnormalities on the immediate postexercise images that completely normalized over 3 hr. While perfusion defects were identified most commonly in the ventricular septum (36 of 84 total defects, or 43%), defects were observed in all segments of the left ventricular myocardium (table 1).

Fixed or only partially reversible defects were observed predominantly in patients with depressed resting left ventricular systolic function (table 1; figures 2, 4, and 5). Thus, 14 (82%) of the 17 subjects with such defects exhibited a resting ejection fraction less than 50%. Of the 15 patients identified with an ejection fraction less than 50%, 14 (93%) demonstrated fixed or only partially reversible perfusion abnormalities; the only patient in the subgroup with left ventricular systolic dysfunction who did not manifest a perfusion defect had a borderline resting ejection fraction of 49%. Both patients with systolic dysfunction who were unable to exercise because of severe symptoms at rest nevertheless demonstrated large defects at rest that...
TABLE 1
Regional perfusion abnormalities identified by visual inspection of thallium tomograms

<table>
<thead>
<tr>
<th>Location</th>
<th>n</th>
<th>Fixed or partially reversible</th>
<th>Completely reversible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior septum</td>
<td>22</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Posterior septum</td>
<td>14</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Anterior/lateral free wall</td>
<td>11</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Inferior/posterior free wall</td>
<td>17</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Apex</td>
<td>20</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>3</td>
<td>46</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction; n = number of perfusion abnormalities (29 patients had abnormalities in more than one location).

partially normalized over 3 hr (figure 2). The remaining two patients studied at rest had normal left ventricular systolic function and qualitatively normal $^{201}$TI uptake.

The 24 patients with regional perfusion defects that completely normalized over 3 hr each manifested normal or supranormal left ventricular systolic function (ejection fraction $\geq 50\%$). Of the 57 subjects with ejection fractions of 50% or more, 27 (48%) had perfusion defects; 24 (89%) of these 27 patients demonstrated total reversibility (figures 4 and 5).

Apparent reversible cavity dilatation was observed on the short-axis images of 26 (38%) of the 68 patients who performed treadmill exercise (figure 3). Five of these 26 patients had depressed systolic function; the remaining 21 patients had ejection fractions greater than 50%. No difference was observed with respect to the prevalence of exercise-induced ST-T abnormalities between those patients with and those without apparent reversible cavity dilatation. Abnormally increased pulmonary thallium activity immediately after exercise was observed in 15 (22%) subjects. It should be noted that regional perfusion abnormalities were absent in five of the 26 patients with apparent cavity dilatation and in two of the 15 patients with increased lung activity.

**Correlations among symptoms and electrocardiographic, exercise, and hemodynamic variables.** Dyspnea and fatigue were the only symptoms significantly more common among patients with fixed or only partially reversible defects compared with either patients with

**FIGURE 4.** Flow diagram showing the prevalence and type of abnormal perfusion studies obtained in the 72 study patients with HCM. Numerals in circles refer to number of patients. EF = left ventricular ejection fraction.

**FIGURE 5.** Flow diagram showing the relationship of myocardial perfusion defects to left ventricular systolic function. Abbreviations as in figure 4.
completely reversible abnormalities or those with normal perfusion studies (table 2). Neither a history of chest pain (table 2) nor its provocation with treadmill exercise (table 3) was predictive of an abnormal thallium perfusion study. Ten (56%) of the 18 asymptomatic subjects demonstrated perfusion defects (nine completely reversible and one partially reversible), a prevalence figure that did not differ from that of the symptomatic patients (31 of 54, or 58%) (figures 6 and 7). These frequent abnormalities among the asymptomatic subjects occurred despite their younger age (33 ± 15 vs 43 ± 13 years, p < .05), increased exercise capacity (treadmill time 23 ± 4 vs 10 ± 6 min, p < .001), and ability to achieve a higher double product (28 ± 6 x 10^3 vs 20 ± 7 x 10^3, p < .001) than the symptomatic patients.

### TABLE 2
Relationship between symptoms and regional perfusion abnormalities

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients (n = 72)</td>
<td>Patients with fixed or partially reversible defects (n = 17)</td>
<td>Patients with completely reversible defects (n = 24)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>45</td>
<td>63</td>
<td>15</td>
</tr>
<tr>
<td>Chest pain</td>
<td>36</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Near syncope/syncope</td>
<td>11</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11</td>
<td>15</td>
<td>8.4</td>
</tr>
</tbody>
</table>

Symptoms were reported by 54 of the 72 patients (75%).

* \( p < .02 \) group I vs group II.

* \( p < .05 \) group I vs group III.

* \( p < .01 \) group I vs group II.

* \( p < .01 \) group I vs group III.

### TABLE 3
Relationship between clinical, electrocardiographic, exercise, and hemodynamic findings and regional perfusion abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with fixed or partially reversible defects (n = 17)</td>
<td>Patients with completely reversible defects (n = 24)</td>
<td>Patients without defects (n = 31)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40 ± 12</td>
<td>38 ± 16</td>
<td>43 ± 13</td>
</tr>
<tr>
<td>Percent male patients</td>
<td>53</td>
<td>75</td>
<td>61</td>
</tr>
<tr>
<td>Exercise-induced chest pain</td>
<td>26</td>
<td>42</td>
<td>32</td>
</tr>
<tr>
<td>Estes score ≥4 points</td>
<td>14</td>
<td>50</td>
<td>27</td>
</tr>
<tr>
<td>Resting ST-T abnormalities</td>
<td>71</td>
<td>77</td>
<td>50</td>
</tr>
<tr>
<td>Exercise-induced ST-T abnormalities</td>
<td>16</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td>Treadmill time (min)</td>
<td>10 ± 6</td>
<td>15 ± 8</td>
<td>14 ± 9</td>
</tr>
<tr>
<td>Heart rate-pressure product (x 10^3)</td>
<td>20 ± 9</td>
<td>22 ± 7</td>
<td>24 ± 7</td>
</tr>
<tr>
<td>Percent with subaortic obstruction</td>
<td>6A</td>
<td>50</td>
<td>32</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>15 ± 8 (n = 8)</td>
<td>20 ± 8 (n = 11)</td>
<td>16 ± 6 (n = 20)</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>11 ± 4 (n = 8)</td>
<td>14 ± 7 (n = 12)</td>
<td>12 ± 6 (n = 20)</td>
</tr>
<tr>
<td>Resting LVEF (%)</td>
<td>42 ± 14BC</td>
<td>77 ± 12D</td>
<td>70 ± 11</td>
</tr>
</tbody>
</table>

Values are percentages unless stated otherwise. Mean values are ± SD.

LVEDP = left ventricular end-diastolic pressure; PCW = pulmonary wedge pressure; LVEF = left ventricular ejection fraction.

* \( p < .01 \) group I vs group II.

* \( p < .001 \) group I vs group II.

* \( p < .001 \) group I vs group III.

* \( p < .05 \) group II vs group III.
FIGURE 6. Long-axis (left) and short-axis (right) tomograms of the left ventricle from an asymptomatic 17-year-old girl with HCM. In the long-axis tomograms, the left ventricular apex is oriented to the left and the base to the right, with the anterior myocardium at the top of each image. There is a reversible defect involving the apical portions of the anterior left ventricular wall and ventricular septum after exercise that completely normalized over the 3 hr postexercise period. Apparent cavity dilatation is also present in the immediate postexercise images.

As displayed in table 3, most clinical and hemodynamic variables did not differ among the three patient subgroups. Differences were detected, however, with respect to the prevalence of outflow tract obstruction and, as noted, the mean resting ejection fraction for each subgroup; patients with fixed or only partially reversible defects had a smaller prevalence of resting outflow gradients and a lower ejection fraction.

A separate analysis was performed for that subgroup of patients that had undergone coronary angiography within 1 year of thallium tomography (n = 38). Similar figures were obtained regarding the prevalence (19 of 38 patients, 50%) and type (eight fixed or partially reversible, 11 completely reversible) of perfusion abnormalities. The group comparisons presented in table 3 did not change when applied to this patient subgroup with recent coronary angiography.

Echocardiographic correlations. In the 15 patients with depressed left ventricular ejection fraction, 35 regional perfusion defects (32 fixed or partially reversible, three completely reversible) were identified; 32 of these defects (91%) appeared in regions of myocardium that were either of normal or only mildly increased thickness (i.e., 15 to 20 mm). Of the remaining three defects, two were in areas that were 20 mm thick and one was in an area 25 mm thick.

In contrast, among the 46 patients with preserved ventricular function and technically adequate two-dimensional echocardiographic studies, 19 of 46 regional perfusion defects (41%) occurred in areas of moderate-to-marked wall thickening (i.e., ≥20 mm, upper range 50 mm, p < .001); 43 of these 46 defects were completely reversible in nature.

Radionuclide ventriculographic correlations. To investigate the possibility that the observed perfusion defects could be due in part to dynamic changes in left ventricular size, shape, and segmental wall motion, 11 patients underwent supine radionuclide ventriculography both before and 10 min after upright treadmill exercise performed to the same heart rate and blood pressure end points as those achieved on the earlier thallium treadmill test. Left ventricular ejection fraction did not differ before and after exercise (75 ± 7% vs 76 ± 9%, p = NS), and there were no observed changes in ventricular shape or regional wall motion. The ratio of background-corrected and decay-corrected
end-diastolic counts (an index of left ventricular volume) in the postexercise to preexercise study was 1.06 ± 0.10 for the 11 patients. Reversible, apparent cavity dilatation was observed on the short-axis tomographic images of five of these 11 patients, all five of whom displayed regional perfusion defects. The group mean end-diastolic postexercise-to-preexercise count ratio for these five patients, derived from the radionuclide ventriculographic studies, was 1.09 ± 0.08, as compared with 1.04 ± 0.14 for the six subjects without apparent cavity dilatation (p = NS). These data indicate that the observed thallium perfusion defects were not associated with changes in left ventricular size (volume), shape, or segmental wall motion. These findings also suggest that the apparent cavity dilatation observed in 26 patients after exercise may in fact reflect diffuse subendocardial hypoperfusion rather than actual chamber enlargement.

Discussion

Occurrence of 201Tl perfusion abnormalities. The current study indicates that myocardial perfusion abnormalities, as assessed by 201Tl emission computed tomography, occur commonly in patients with HCM. The results extend previous observations made with thallium perfusion imaging9–12 by the inclusion of a large series of patients encompassing a broad clinical spectrum of HCM, ranging from the asymptomatic to the severely symptomatic, with or without outflow tract obstruction or left ventricular systolic dysfunction. Because of our patient selection criteria, we cannot determine the prevalence of perfusion abnormalities in an unselected population with HCM. However, our data suggest that such abnormalities are not rare.

Analysis of the subgroup of 15 patients with depressed left ventricular function revealed that 14, or 93%, displayed fixed or only partially reversible perfusion defects, findings suggestive of myocardial scarring or severe ischemia.25, 26 These fixed perfusion defects are compatible with previous descriptions of transmural infarction demonstrated at autopsy in similar patients with HCM.7 Hence, abnormalities identified by 201Tl uptake appear to provide an explanation for the associated impairment of regional and global systolic performance seen in this subgroup. Echocardiographic data also oer support for this hypothesis. Virtually all fixed perfusion defects appeared to correspond to areas of the left ventricular wall that were normal or only mildly increased in thickness. Although we did not obtain serial two-dimensional echocardiographic observations in these patients, this finding suggests that those areas of the left ventricular wall with fixed defects may represent regions that have decreased in thickness due to fibrosis and scarring. In contrast, the thallium defects visualized in those patients with normal or hyperdynamic left ventricular function were predominantly reversible in nature, and probably reflect myocardial ischemia.25 These abnormalities occurred in areas of moderate-to-marked left ventricular wall thickness.

Myocardial perfusion abnormalities of any type were visualized independent of either a history of chest pain or the development of chest pain during treadmill exercise. This finding contrasts with that of Pitcher et al.,10 who reported a strong correlation between the prevalence of angina and "ischemic" myocardial scintigrams. Indeed, over 50% of our asymptomatic patients demonstrated regional thallium defects, an observation that suggests that a "silent" form of myocardial ischemia may occur in some patients with HCM. We did find, however, that a history of dyspnea or fatigue was reported more commonly by those patients with fixed or partially reversible defects than by those individuals with completely reversible changes or subjects without perfusion abnormalities. Certainly this must reflect the finding that the majority of patients with fixed or partially reversible defects had left ventricular systolic dysfunction under resting conditions. Impairment of systolic function, owing to myocardial scar or severe ischemia, may also provide an explanation for the rather infrequent occurrence of outflow tract obstruction under basal conditions noted in patients with fixed or partially reversible defects (only one of 17, or 6%). Such patients with depressed contractile performance may not have been able to generate critical hemodynamic forces necessary for obstruction. The remaining clinical, electrocardiographic, exercise, and hemodynamic variables analyzed (table 3) did not distinguish among the three patient subgroups.

Advantages and limitations of thallium tomography. Previous studies using 201Tl emission computed tomography have suggested that this method may be superior to conventional planar imaging with respect to the detection and quantitation of myocardial perfusion defects in patients with coronary artery disease.27–29 The relative advantages in the use of this technique for the study of patients with hypertrophic cardiomyopathy have been demonstrated by Suzuki et al.30 Our experience with planar techniques in patients with HCM also indicates that emission computed tomography is the more useful technique when applied to these subjects, many of whom have massively enlarged hearts in which it is quite difficult to distinguish myocardial
edges and cavity boundaries. Emission computed tomography also provides a mechanism to reduce or eliminate information originating from contiguous, overlapping areas of myocardium outside a region of interest. In an effort to optimize the sensitivity of our technique, we elected to administer a higher dose (3.5 mCi) of $^{201}$Tl in most of our patients and to perform all studies with a high-sensitivity collimator and an elliptical orbit for acquisition.

The technical limitations of our study are chiefly those that have historically plagued myocardial imaging with $^{201}$Tl. These factors include the energy and pharmacokinetic characteristics of the isotope and the lack of appropriate attenuation correction algorithms for the thorax. Also, the images were not gated, due to our desire to complete the acquisition process quickly and thus to minimize both "early redistribution" and patient discomfort. The lack of gating could have detracted from our ability to detect small perfusion differences and may have contributed to an underestimation of their true prevalence. The radionuclide angiographic data obtained in a subset of 11 patients who underwent a second treadmill exercise test suggest that the observed thallium perfusion defects with exercise were not attributable to any demonstrable changes in either left ventricular size (volume), shape, or regional wall motion. In the absence of an associated change in left ventricular volume, we interpret the apparent cavity dilatation on the thallium study after exercise as being caused by subendocardial hypoperfusion. Five patients with apparent cavity dilatation alone and two patients with increased pulmonary thallium activity in the absence of regional perfusion defects were not included in the overall determination of the prevalence of perfusion abnormalities. These exclusions might also have contributed to an underestimation of true prevalence of scintigraphic abnormalities.

Implications. It is reasonable to conclude that the perfusion defects of the fixed or only partially reversible type reflect underlying areas of myocardial fibrosis and scar. Functionally, such defects must contribute importantly to the associated impairment of systolic performance observed in the majority (i.e., over 80%) of the patients with these abnormalities. We recognize, however, that our study does not identify unequivocally the mechanism(s) responsible for the pathogenesis of such defects.

The finding that the majority of the regional perfusion defects were reversible in nature, whether partially or completely, suggests that a dynamic process is operative. Certainly, such areas of inhomogeneity need not necessarily reflect ischemia at the cellular level. Such defects could represent, rather than true ischemia, regional disparities in the distribution of thallium related either to a heterogenous pattern of wall thickening characteristic of HCM, to the marked increase in left ventricular mass per se, or to a defect in the local transmembrane disposition of the isotope. We should emphasize that such attributes of the hypertrophic process render perfusion imaging in these patients even more complex and less precise than comparable studies in subjects with more uniform ventricular geometry. However, convincing evidence exists, independent of thallium perfusion imaging, that myocardial ischemia does not occur in HCM: (1) patients often develop chest pain during rapid atrial pacing, which is accompanied by evidence of limited vasodilator reserve and abnormalities of lactate metabolism (production or diminished consumption),$^{1-3}$ and (2) autopsy studies commonly show fibrous tissue formation ranging from patchy intramyocardial fibrosis to transmural scarring,$^4^-$7 findings suggestive of previous, regional ischemic injury and repair. If viewed in the traditional construct applied to perfusion imaging in patients with epicardial coronary artery disease,$^2^5$ the reversible defects observed in these patients with HCM might also be construed as representative of ischemia.

Myocardial ischemia in HCM may result from one or more of several mechanisms, including an inadequate capillary density relative to the increased myocardial mass,$^{31,32}$ or impaired left ventricular relaxation$^{14,33}$ leading to a decrease in both the rate and amplitude of diastolic coronary blood flow. Abnormalities of the small, intramyocardial coronary arteries, characterized by thickened walls often with apparent luminal compromise,$^8$ may contribute importantly to any limitation of coronary flow reserve. Large vessel coronary artery spasm$^{34}$ and systolic compression of the septal perforator artery$^{35}$ may also contribute to the ischemia present in HCM, but these mechanisms by themselves do not adequately explain the relatively common and anatomically widespread perfusion defects observed in this study. Chronic hypoperfusion from whatever mechanism, even in the absence of symptoms, may eventually lead to necrosis and infarction, and result in left ventricular dysfunction.

In summary, the thallium perfusion abnormalities we identified in a large group of patients representing the broad clinical spectrum of HCM are compatible with the concept that both active (reversible) and end-stage (fixed) ischemic processes are operative in this disease. Reversible defects occurred predominantly in patients with preserved systolic function, whereas
fixed perfusion abnormalities were observed largely in patients with depressed left ventricular function. These findings suggest that myocardial ischemia occurs commonly in HCM and contributes importantly to its natural history.

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