Impact of Surgical Relief of Outflow Obstruction on Thallium Perfusion Abnormalities in Hypertrophic Cardiomyopathy

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Background. To assess the impact of surgical relief of left ventricular outflow obstruction on myocardial perfusion abnormalities in patients with obstructive hypertrophic cardiomyopathy, 20 symptomatic patients who underwent a septal myectomy or mitral valve replacement were studied with assessment of myocardial perfusion during exercise by $^{201}$TI emission computed tomography before and 6 months after surgery.

Methods and Results. Before surgery, 15 patients had myocardial perfusion defects during exercise that completely normalized at rest, one patient had both reversible and fixed perfusion defects, two patients had fixed defects only, and two patients had normal exercise and rest thallium scans. After surgical relief of left ventricular outflow obstruction (basal gradient reduced from 62±40 to 7±12 mm Hg, $p<0.001$; peak provokable gradient reduced from 131±27 to 49±36 mm Hg, $p<0.001$), repeat exercise thallium studies showed complete normalization of perfusion defects in 11 patients, including the two patients with fixed defects alone before surgery, and improvement in the magnitude and distribution of perfusion defects in five additional patients. This was associated with a significant reduction in the number of patients with reversible regional defects (five patients compared with 13 patients before surgery, $p=0.026$) and of patients with endocardial hypoperfusion (four patients compared with 12 patients before surgery, $p=0.024$). Furthermore, increased lung uptake of thallium was noted in five patients after surgery, compared with 12 patients before surgery ($p=0.055$). Only two patients with reversible perfusion defects before surgery had unchanged postoperative studies. However, four patients acquired new fixed defects as a consequence of surgery, and two of these four had the greatest severity and distribution of left ventricular hypertrophy by echocardiography. These four patients experienced a substantially greater decrease in ejection fraction ($-26±15\%$) after surgery than the remaining patients ($-3±14\%, p<0.01$).

Conclusions. Surgical relief of left ventricular outflow obstruction results in normalization or improvement of myocardial perfusion in the majority of patients with reversible and fixed perfusion defects by $^{201}$TI scintigraphy. However, surgery may result in myocardial injury and scarring, with consequent decreased left ventricular ejection fraction in some patients. (Circulation 1992;85:1039–1045)

Key Words • hypertrophic cardiomyopathy • $^{201}$TI • scintigraphy • myocardial ischemia • left ventricle

For patients with obstructive hypertrophic cardiomyopathy who remain symptomatic despite medical therapy, surgical reduction of left ventricular outflow obstruction can substantially improve symptom status.1-14 We have previously shown that surgical reduction of left ventricular outflow obstruction is associated with left ventricular hemodynamic and metabolic benefit, with great cardiac vein flow measurements suggesting more advantageous matching of myocardial oxygen delivery to oxygen demands during stress.15 However, these measurements were made during pacing stress, which differs from the cardiac and peripheral hemodynamic responses to exercise stress. Reversible myocardial perfusion defects by $^{201}$TI scintigraphy have been shown to accurately reflect myocardial ischemia during stress in patients with hypertrophic cardiomyopathy.16 Thus, thallium scintigraphy was used in the present study to assess the impact of surgery on exercise-induced myocardial ischemia in this disease.

Methods

The study population was drawn from two periods of time during which tomographic $^{201}$TI studies were commonly performed in patients with hypertrophic cardiomyopathy at the National Institutes of Health. Between June 18, 1985, and September 1, 1986, and between August 10, 1989, and July 26, 1990, 63 patients with hypertrophic cardiomyopathy, defined as the echocardiographic demonstration of a hypertrophied, nondilated left ventricle in the absence of another cardiac or systemic disease that...
produces left ventricular hypertrophy,17 underwent initial surgery for relief of left ventricular outflow obstruction. Of these 63 patients, 33 underwent preoperative 201TI studies while receiving no medication; one of these patients died during the perioperative period. Of the remaining 32 postoperative patients who had preoperative 201TI studies, 23 underwent postoperative 201TI studies, with three having scans unsatisfactory for interpretation and comparison with the preoperative 201TI scan. Thus, the study population comprised 20 patients with hypertrophic cardiomyopathy who underwent both preoperative and postoperative hemodynamic and exercise 201TI studies. There were 13 men and seven women (age range, 28–65 years; average, 48 years). All patients were in New York Heart Association functional class III or IV before surgery and were considered surgical candidates on the basis of failure of medical management to control symptoms. A decision to perform septal myectomy versus mitral valve replacement was based on septal morphology and thickness. Studies were performed at least 2 days or five drug half-lives after discontinuation of cardiac medications and were repeated approximately 6 months after surgery. Informed written consent was obtained from all patients.

Echocardiography

Echocardiographic examinations were performed using commercially available instruments. Images were obtained in a number of cross-sectional planes using standard transducer positions.18 With previously described methods,19 the distribution of left ventricular hypertrophy was assessed primarily in the parasternal short-axis plane, although parasternal long-axis and apical views were also used to integrate the information obtained from the short-axis images.

In the short-axis plane, the left ventricle was divided into four segments that comprised the anterior and posterior ventricular septa and anterolateral and posterior left ventricular free walls.20 Presence and extent of left ventricular hypertrophy in these four left ventricular regions were evaluated in diastole directly from the television monitor with the aid of calipers. Wall thickness was measured at the levels of both the mitral valve and papillary muscles.19,20 For each region of the left ventricle, that portion that showed the greatest thickness (whether situated basal or apical) was reported as the maximal thickness of that segment.

A wall thickness index was also used to assess the magnitude of left ventricular hypertrophy. This index was calculated by adding the measurements of maximum wall thickness obtained in each of the four left ventricular segments.20 This calculated score has previously been used as a quantitative expression of the overall magnitude of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy.20–23 All wall measurements were made without knowledge of the patient’s thallium studies.

Cardiac Catheterization Studies

After an overnight fast and sedation with 10 mg oral diazepam, patients had left ventricular pressures obtained with a 7F end-hole pigtail catheter, with attention paid to avoid entrapment artifact,24 referenced to the side-arm of an 8F vascular sheath apparatus in the femoral artery. A balloon-tipped thermodilution catheter was advanced into a pulmonary artery for measurement of pulmonary artery pressure, pulmonary artery wedge pressure, and cardiac index (average of triplicate cardiac outputs divided by body surface area). After measurement of the basal left ventricular outflow gradient, provokable gradients were measured in 17 patients by the Valsalva maneuver, amyl nitrite inhalation, and isoproterenol infusion titrated to achieve a heart rate of 120 beats per minute. Contrast left ventriculography and coronary angiography were performed during the catheterization before surgery. All patients had angiographically normal coronary arteries, as interpreted by an experienced angiographer, with review of cines at a weekly staff conference.

Exercise Testing and 201TI Tomography

Symptom-limited graded treadmill exercise was performed in seven patients using the National Institutes of Health combined protocol25 and in 13 patients using the standard Bruce protocol. The postoperative studies used the same exercise protocol for each patient as was used before surgery. A 12-lead ECG was monitored throughout exercise, and blood pressure was obtained at 1-minute intervals. At peak exercise, patients received 2.0–3.5 mCi 201TI iv. Exercise was continued for an additional 60 seconds to allow adequate circulation of the isotope. Imaging was begun within 10 minutes of completion of exercise and repeated after a 3–4-hour delay. Thallium emission computed tomographic 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, Boston) centered on the 68-keV photopeak with a 20% window. The camera was rotated over 180° in an elliptical orbit around the patient’s anterior thorax from the right anterior oblique (−40°) to the left posterior oblique (+140°) position. Thirty images were obtained in a 64×64 matrix for 30 seconds, each at 6° intervals. Details of count acquisition and analysis have been described previously.26,27 Tomographic images were graded by consensus of at least two independent observers using a semiquantitative regional scoring system. Interobserver variability of this method applied to patients with hypertrophic cardiomyopathy has been previously reported.29 Regional thallium uptake was graded on a scale of from 0 to 2.0 in increments of 0.5, with a score of 2 signifying normal activity and a score of 0 signifying absent activity. Scores for each segment were averaged; a score of ≤1.5 was considered to represent a perfusion defect, and a score of ≥0.5 from exercise to redistribution study was considered a significant change in perfusion. A counts-based quantitative analysis based on absolute thallium activity was not performed because the marked regional heterogeneity of wall thickness in hypertrophic cardiomyopathy would accentuate partial volume effects in a region-to-region comparison within one tomographic plane.28 Exercise-induced cavity dilatation and increased lung uptake were also assessed qualitatively as absent, mild, or marked, as determined by consensus among the observers.

Radionuclide Ventriculography

Radionuclide ventriculography was performed in 19 patients in the supine position after in vivo labeling of red
Table 1. Hemodynamics Before and 6 Months After Surgery for Left Ventricular Outflow Obstruction

<table>
<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>After surgery</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PA (mm Hg)</td>
<td>25±12</td>
<td>20±6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean PAW (mm Hg)</td>
<td>16±7</td>
<td>12±5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean LVEDP (mm Hg)</td>
<td>22±7</td>
<td>14±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.7±0.4</td>
<td>2.5±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>LVOT gradient (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>62±40</td>
<td>7±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak provokable</td>
<td>131±27</td>
<td>49±36</td>
<td>&lt;0.001</td>
</tr>
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PA, pulmonary artery; PAW, pulmonary artery wedge; LVEDP, left ventricular end-diastolic pressure; CI, cardiac index; LVOT, left ventricular outflow tract.

blood cells with 20–25 mCi 99mTc and was performed on the same day as the 201Tl tomographic study. Scintigraphic data were acquired in the modified left anterior oblique position, which allowed optimal visual separation of the left and right ventricles. Left ventricular ejection fractions were computed as previously described.29

Statistical Analysis

All data are reported as mean±1 SD. Continuous variables were compared by the two-tailed paired or unpaired t test where appropriate. Differences in proportions were compared by the χ² or Fisher’s exact test. Subgroup comparisons for surgical reduction of left ventricular outflow obstruction and end-diastolic pressure were performed by analysis of variance. A value of p<0.05 was considered statistically significant.

Results

Echocardiography

In each of the 20 study patients, left ventricular hypertrophy (i.e., wall thickness >13 mm) involved at least three of the four regions into which the left ventricle had been divided. Maximal wall thickness ranged from 20 to 40 mm (mean, 26±6 mm). The left ventricular segment showing the maximum degree of hypertrophy was the anterior ventricular septum in 18 patients, the anterolateral free wall in one patient, and both the anterior and posterior ventricular septa in the remaining patients. Left ventricular wall thickness index ranged from 63 to 109 mm (mean, 79±13 mm).

Hemodynamic Results

Septal myectomy (15 patients), mitral valve replacement (four patients), and a combined operation (one patient) resulted in significant reduction in the basal left ventricular outflow tract gradient (62±40 to 7±12 mm Hg, p<0.001), peak provokable left ventricular outflow tract gradient (131±27 to 49±36 mm Hg, p<0.001), and left ventricular end-diastolic pressure (22±7 to 14±5 mm Hg, p<0.001) (Table 1). Mean pulmonary artery and pulmonary artery wedge pressures were also reduced, although these differences did not achieve statistical significance. The cardiac index was unchanged by surgery. The left ventricular ejection fraction measured by radionuclide angiography in 19 patients decreased from 72±12% before surgery to 64±16% after surgery (p<0.05).

Exercise Stress Testing

Before surgery, the seven patients exercised by the National Institutes of Health combined protocol achieved 9.0±5.2 minutes at peak heart rate of 134±12 beats per minute and peak systolic blood pressure of 144±44 mm Hg. After surgery, these seven patients were able to exercise 12.5±6.8 minutes, an increase of 3.5±3.7 minutes (p<0.05) at a heart rate (134±22 beats per minute) and peak systolic blood pressure (142±37 mm Hg) similar to those achieved during the preoperative exercise test. The 13 patients exercised by the standard Bruce protocol achieved 5.7±2.7 minutes at a heart rate of 137±14 beats per minute and peak systolic blood pressure of 135±28 mm Hg before surgery. After surgery, these 13 patients were able to exercise 6.8±2.9 minutes, representing a 1.3±1.3-minute increase in duration compared with before surgery (p<0.01). This was achieved at a peak heart rate of 146±17 beats per minute and a peak systolic blood pressure of 155±31 mm Hg.

ECGs after surgery showed that 14 patients had acquired new left bundle branch block patterns as a consequence of septal myectomy. One patient had persistence of the same left bundle branch block pattern as noted on the preoperative ECG, and five patients had no change in their ECGs (including the four patients who underwent mitral valve replacement as their only procedure).

201Tl Emission Computed Tomography

Before surgery, 15 patients had myocardial perfusion defects that normalized by 3 hours after exercise, two patients had myocardial perfusion defects that remained unchanged in appearance by 3 hours after exercise (fixed defects), one patient had both reversible and fixed perfusion defects, and two patients had entirely normal rest and exercise scans (Figure 1). Of the patients with reversible defects, nine patients had coexistence of regional myocardial perfusion defects and apparent cavity dilatation (evidence for subendocardial hypoperfusion during stress46,29), four patients had regional myocardial perfusion defects alone, and three patients had apparent cavity dilatation alone. Twelve patients had increased lung uptake of thallium after exercise.

Six months after surgery, repeat thallium studies showed complete elimination of perfusion defects in 11 patients, including nine patients who had reversible defects alone before surgery and the two patients with fixed defects alone before surgery (Figure 1). Examples of elimination of reversible and fixed thallium defects by surgery are shown in Figures 2 and 3. Five additional patients showed improvement in myocardial perfusion compared with before surgery, as manifest by fewer and/or smaller defects compared with the preoperative study. Of the 18 patients with thallium perfusion defects during preoperative exercise studies, only two patients had no change in the appearance of their thallium scans after surgery. Only three patients demonstrated lung uptake of thallium in their postoperative study that was unchanged from the appearance of their preoperative study, and two patients had lung uptake of thallium that was less severe compared with their preoperative study. One patient who received a mitral valve prosthesis was found to have increased lung uptake of thallium on the
postoperative scan; it was not noted on the preoperative scan. This was associated with a 13-mm-Hg mean gradient across the prosthetic mitral valve. With regard to the distribution of thallium perfusion abnormalities after surgery, four patients had apparent cavity dilatation compatible with endocardial hypertrophy compared with 12 patients before surgery (p = 0.024), and five patients had regional perfusion defects after surgery compared with 13 patients before surgery (p = 0.026).

The 11 patients with elimination of their perfusion defects after surgery had a reduction in basal left ventricular outflow gradient of 64±45 mm Hg; the five patients showing an improvement in their perfusion defects after surgery had a somewhat lesser reduction in gradient (46±22 mm Hg). The two patients with unchanged abnormal studies had the least change in their left ventricular outflow tract gradient (16±4 mm Hg). The reduction in peak provokable gradient was similar for the patients whose preoperative thallium defects were eliminated (82±36 mm Hg), improved (85±55 mm Hg), or unchanged (93±11 mm Hg). Patients with elimination or improvement in the appearance of their perfusion defects after surgery had average reductions in their left ventricular end-diastolic pressure of 8±10 and 8±6 mm Hg, respectively. In contrast, the two patients with no change in their abnormal scans had a reduction of only 2±1 mm Hg. Patients with elimination or improvement in lung uptake of thallium after surgery had average reductions in their left ventricular end-diastolic pressure of 9±10 and 13±3 mm Hg, respectively. In contrast, the two patients with unchanged lung uptake of thallium had only a 1±1-mm-Hg reduction in left ventricular end-diastolic pressure after surgery. Because of small numbers in each subgroup, ANOVA did not show these differences in left ventricular outflow tract pressure or end-diastolic pressure reduction to be of statistical significance.

**New Perfusion Defects After Surgery**

After surgery, five patients, all of whom underwent septal myectomy, acquired perfusion defects not noted on their preoperative study. In one patient, a fixed apical defect was noted at the site of a reversible apical defect on the preoperative study. In a second patient,
multiple fixed defects were noted, one of which corresponded to a reversible septal defect before surgery. This patient (see Figure 4) experienced a particularly complicated surgical course, requiring a left ventricular assist device for several days because of poor postoperative left ventricular function. Of note, these two patients had the highest left ventricular wall thickness indexes (105 mm each), reflecting both the magnitude and distribution of hypertrophy, of all of the study patients (average, 79±12 mm). A third patient who had no reversible regional defects before surgery was found to have a new fixed defect in the inferior septum on the postoperative study. A fourth patient was noted to have a new fixed inferior wall defect at the site of a reversible defect before surgery and also developed a mild reversible septal defect not noted on his preoperative scan, possibly a consequence of a new left bundle branch block. These four patients with new fixed regional defects not noted on the preoperative study experienced a substantially greater decrease in left ventricular ejection fraction (−26±15%) than the remaining patients (−3±14%, p<0.01) (Figure 5). Although all patients undergoing septal myectomy had elevations in total creatine kinase and the MB fraction of this enzyme, three of these four patients had the highest peak creatine kinase values (9,212, 3,743, and 1,708 units/l) of the 16 patients who underwent this procedure. The fifth patient developed a reversible defect in the septal region that was not present on his preoperative study. This patient also developed a new left bundle branch block as a consequence of his left ventricular myectomy. Overall, of the 14 patients who developed new left bundle branch blocks as a consequence of left ventricular myectomy, only two demonstrated new reversible septal thallium defects. Three patients, however, had persistent reversible septal perfusion abnormalities after surgery in conjunction with development of a new left bundle branch block.

Discussion

Our previous investigations have demonstrated that myocardial ischemia as evidenced by myocardial lactate production during rapid atrial pacing or isoproterenol stress or by reversible thallium defects during exercise stress is common in hypertrophic cardiomyopathy. For patients with obstructive hypertrophic cardiomyopathy who remain symptomatic despite conventional medical approaches to this disease, surgical relief of obstruction can improve symptoms and effort tolerance, primarily by reducing myocardial oxygen demands and thus allowing more favorable matching of myocardial blood flow to myocardial oxygen demands during stress. However, these observations regarding the coronary and myocardial hemodynamic consequences of surgical relief of obstruction were made during pacing stress. The present study extends these observations by demonstrating that myocardial perfusion abnormalities induced by exercise stress are improved or eliminated after surgical relief of left ventricular outflow obstruction. These observations provide further evidence for the pathophysiological relevance of left ventricular outflow gradients in hypertrophic cardiomyopathy. Patients with
the greatest reduction in rest outflow gradient were found to have improvement or elimination of myocardial perfusion abnormalities in the postoperative study. In contrast, the two patients with persistent postoperative thallium perfusion defect had very small preoperative rest left ventricular outflow gradients (12 and 20 mm Hg). A third patient with no preoperative rest gradient converted a reversible inferolateral defect to a fixed inferior defect after surgery, along with development of a new reversible septal defect. However, the pathophysiological relevance of provokable outflow gradients is less certain from our study; there was no relation between changes in peak provokable gradients and the changes in the appearance of thallium studies after surgery.

This study also extends our observations regarding the relation of elevated left ventricular filling pressures and apparent cavity dilatation. We had previously shown that this scintigraphic finding was not associated with actual left ventricular cavity enlargement after exercise,16 and thus was most likely indicative of subendocardial hypoperfusion. The association of this finding with elevated left ventricular filling pressures at rest and after pacing suggested compressive effects of elevated left ventricular filling pressures on the endocardial microcirculation. Furthermore, this scintigraphic finding was commonly associated with increased lung uptake of thallium, compatible with pulmonary congestion. In the present study, surgical relief of obstruction resulted in significant reduction of the basal left ventricular end-diastolic pressure. Along with improvement or elimination of regional myocardial perfusion defects, it is likely that postoperative exercise was associated with no ischemia or, compared with preoperative exercise, with less deleterious impact on left ventricular filling pressures during exercise stress. This probably accounts for the reduction in the prevalence of endocardial hypoperfusion and lung thallium uptake during stress after surgery.

Before surgery, three patients were observed to have myocardial perfusion defects during exercise that remained unchanged after 3 hours of rest. In patients with coronary artery disease, such "fixed defects" have usually been interpreted as indicative of nonviable myocardium or scar tissue, although recent studies with reinjection of thallium at 3 hours have shown uptake of the isotope consistent with myocardial viability in some fixed defects of patients with coronary artery disease.32 Of the three patients in this study who had fixed defects, two had normalization of these defects after surgical relief of obstruction, suggesting that myocardial tissue in these regions was viable and more completely perfused after reduction in left ventricular systolic pressures. Whether reinjection of thallium in the preoperative studies would have correctly identified these myocardial regions is unknown.

In most patients, left ventricular function as assessed by radionuclide ventriculography changed little after surgery. Thus, the beneficial impact of surgical relief of obstruction on myocardial perfusion defects was unlikely to have been a consequence of a negative inotropic effect of substantial reduction in left ventricular function as a result of surgery. Indeed, several patients had significant increases in left ventricular ejection fraction after surgery, along with normalization of thallium perfusion defects noted during their preoperative study. However, four patients developed new fixed defects after surgery that were associated with a substantial decline in resting left ventricular ejection fraction compared with minimal overall change in patients who did not develop new fixed defects as a consequence of surgery. In three patients, the fixed defects were noted in areas of reversible defects on preoperative studies. In the fourth patient, there was no reversible defect on preoperative study that corresponded with the new fixed defect in the inferoseptal region. One patient in whom a fixed defect occurred in the region of a reversible preoperative defect in addition to new fixed defects was particularly notable for her complicated perioperative course, during which a left ventricular assist device was necessary to maintain survival for several days after surgery. The mechanism responsible for left ventricular dysfunction and new irreversible thallium defects cannot be determined from our study but may relate to incomplete myocardial protection during surgery, possibly as a consequence of small vessel disease, abnormal myocardial architecture, or massive hypertrophy with consequent myocardial ischemia, injury, and scarring. In partial support of this concept is the observation that two patients who developed new fixed defects (including the patient who required the left ventricular device) had the most severe and widespread hypertrophy of all of the study patients. Two patients developed new reversible septal defects; both acquired left bundle branch blocks as a consequence of their ventricular myocardectomy. However, nine other patients who developed left bundle branch blocks had no new reversible septal defects, and an additional three patients maintained preexisting septal defects after surgery.

**Study Limitations**

Not all patients with obstructive hypertrophic cardiomyopathy who underwent surgery during the time periods covered in this study had preoperative and postoperative thallium studies. Although there was no effort to select patients for thallium studies by symptoms, a selection bias may exist. Thus, our data may not be representative of all patients undergoing surgery. However, the symptom status of our patient population and the hemodynamic response after surgery are consistent with those of previous
reports from our institution, leading us to believe that our study population is representative of patients undergoing surgical relief of obstruction.

Conclusions

Exercise-induced thallium defects are common in symptomatic patients with hypertrophic cardiomyopathy who are candidates for surgical relief of obstruction. In our study population, the majority demonstrated improvement or elimination of preoperative perfusion defects on their postoperative studies, most likely representing reduction or relief of stress-induced myocardial ischemia. This was related to the magnitude of reduction of basal left ventricular outflow gradient and left ventricular end-diastolic pressure; thus, these hemodynamic responses may be important in improving or eliminating perfusion defects. Fixed defects using conventional thallium tomographic imaging techniques in patients with left ventricular outflow gradients may be eliminated by surgery and thus represent viable myocardium. Finally, new thallium defects may develop as a consequence of surgery and are associated with substantial reduction in left ventricular ejection fraction, suggesting that they may represent scarring as a consequence of perioperative infarction.

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