Verapamil Prevents Silent Myocardial Perfusion Abnormalities During Exercise in Asymptomatic Patients With Hypertrophic Cardiomyopathy

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Recent studies indicate that reversible $^{201}$TI perfusion defects, compatible with silent myocardial ischemia, commonly develop during exercise in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy (HCM). To determine whether this represents a dynamic process that may be modified favorably by medical therapy, we studied 29 asymptomatic or minimally symptomatic patients with HCM, aged 12–55 years (mean, 28), with exercise $^{201}$TI emission computed tomography under control conditions and again after 1 week of oral verapamil (mean dosage, 453 mg/day). Treadmill time increased slightly during verapamil (21.0±3.6 to 21.9±2.7 minutes, p<0.005), but peak heart rate–blood pressure product was unchanged (26.3±6.0×10³ compared with 25.0±6.4×10³). Two midventricular short-axis images per study were divided into five regions each, and each of these 10 regions was then analyzed on a 0–2 scale by three observers blinded with regard to the patients’ therapy. Average regional scores of 1.5 or less were considered to represent perfusion defects, and a change in regional score of 0.5 or more was considered to constitute a significant change. During control studies, 15 patients (52%) developed perfusion defects with exercise (average, 3.7 regions per patient). In 14 of these patients, all perfusion defects completely reversed after 3 hours of rest; one patient had fixed defects. After administration of verapamil, exercise perfusion scores improved in 10 of the 14 patients (71%) with reversible defects; there was overall improvement in 34 of 50 (68%) regions with initially reversible perfusion defects. Verapamil completely normalized all regional perfusion defects that were apparent during exercise under control conditions in eight patients (average, 3.9 regions per patient). No region developed a new or worse perfusion defect during verapamil in any patient. Thus, exercise-induced regional myocardial perfusion defects improved during verapamil in the majority of asymptomatic patients with HCM and in many cases improved completely. These data suggest that verapamil may prevent or diminish inducible silent ischemia in many asymptomatic patients with HCM. (Circulation 1989;79:1052–1060)

Myocardial ischemia plays an important role in the pathophysiology and natural history of hypertrophic cardiomyopathy (HCM). This concept is supported by the occurrence of angina pectoris (either at rest, during exercise, or precipitated during atrial pacing), abnormal lactate metabolism during atrial pacing, and reduced coronary vasodilator reserve.1–3 Postmortem studies demonstrate patchy or transmural areas of fibrous tissue deposition, which may represent the long-term sequelae of the ischemic process.4–7

Exercise $^{201}$TI scanning has provided a noninvasive means of identifying myocardial perfusion abnormalities in HCM.8–12 Recent studies from our laboratory involving a large heterogeneous group of patients with HCM12 demonstrated that thallium perfusion defects occur in the majority of patients, including over 50% of those without symptoms. Of particular relevance to asymptomatic patients is the histopathologic evidence at necropsy, found in young
HCM patients who died suddenly without previous cardiac symptoms, of structurally abnormal intramural coronary arteries with thickened media and apparent luminal compromise.7

These morphologic findings, as well as the noninvasive evidence of exercise-induced reversible perfusion abnormalities in patients with HCM, raise the possibility that some asymptomatic patients may experience recurrent episodes of silent myocardial ischemia. To test the hypothesis that this is a dynamic abnormality that could be favorably modified by therapy, we studied the effects of verapamil on myocardial perfusion and function in a group of asymptomatic or mildly symptomatic patients with HCM.

Methods

Patient Selection

We studied 29 asymptomatic or minimally symptomatic patients with HCM. Twenty-four patients were completely asymptomatic in the absence of medical therapy, and the other five patients had only occasional mild angina, atypical chest pain, or dyspnea (New York Heart Association functional Class II). In each patient, HCM was defined as the echocardiographic demonstration of a hypertrophied, nondilated left ventricle in the absence of another cardiac or systemic disease that itself could produce left ventricular hypertrophy.13 There were 21 men and eight women, aged 12–55 years (mean, 28). Because of the lack of important symptoms, the patients did not routinely undergo cardiac catheterization as part of this protocol. The presence of left ventricular outflow obstruction was assessed at cardiac catheterization in three patients and from the M-mode echocardiogram, based on the magnitude and duration of systolic anterior motion of the mitral valve,14,15 in the other 26 patients. Eleven patients (38%) had evidence of resting left ventricular outflow obstruction. Eighteen of the 29 patients had an identifiable family history of HCM in a first-degree relative.

Study Protocol

Patients were studied by 201Tl scintigraphy and radionuclide angiography under control conditions and then again during treatment with oral verapamil. For the control studies, all patients were withdrawn from cardiac medications for at least 48 hours, or 96 hours if they were taking long-acting β-blocking agents. Verapamil was then administered orally at dosages of 240–320 mg/day and then increased as tolerated to a dosage of 480 mg/day. This was successful in 24 patients. Smaller doses were used in five patients because of conduction disturbances (three patients) or age and body size (two patients). Thus, the verapamil dosage at the time of repeat study ranged from 240 to 480 mg/day (mean, 453), and this dosage was maintained for a mean of 6.7 days (range, 2–56) before the repeat study. The verapamil studies were performed 1–16 weeks (mean, 6±5) after the initial control studies.

The order of the studies was not random, and verapamil administration was not blinded; however, the main end-point of the study, the 201Tl scintigrams, were read in a blinded fashion.

Graded Treadmill Exercise Testing

Graded treadmill exercise was performed by all participants with the National Institutes of Health combined protocol.16 Heart rate, rhythm, and systemic blood pressure were monitored during exercise. Each patient continued exercising until exhaustion or dyspnea developed. One patient experienced mild, nonlimiting angina during exercise; none developed high grade ventricular ectopy or atrioventricular block requiring premature termination of exercise. For the verapamil study, patients exercised to a similar subjective physical end-point or the same double-product, whichever occurred first, to match myocardial oxygen demand as much as possible.

To evaluate exercise tolerance in this group of patients, we used a normal data base developed in our laboratory,12 consisting of 51 subjects without any history of cardiac symptoms and with normal noninvasive tests, including physical examination, electrocardiogram, chest radiograph, M-mode and two-dimensional echocardiogram, and exercise electrocardiogram.

201Tl Emission Computed Tomography

At peak exercise, patients received either 2.0 (n=28) or 1.5 mCi (n=1) 201Tl intravenously; exercise was continued for an additional 60 seconds to allow for adequate circulation of the isotope. Imaging was begun within 12 minutes of the completion of exercise and again after a 3-hour 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, Boston, Massachusetts) centered on the 68 kev photo peak with a 20% window. The camera was rotated over 180° in an elliptical orbit about 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. The entire acquisition process required 17 minutes. Individual count rates varied between 1,000 and 3,000 counts/sec, depending on the dose of isotope administered and body size. 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 back projection with a 10% Hanning filter to reduce statistical noise (cut-off frequency, 0.5 cycles/pixel). Sagittal and short-axis tomograms of three-pixel thickness (approximately 2.0 cm) were then derived from the transaxial images. The slices were chosen according to the method described by Garcia et al.17 No attenuation or scatter correction was employed.
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 using a semi-quantitative regional scoring system modified from the method developed by Okada et al.\(^1\) for planar studies. Two contiguous midventricular short-axis tomograms (each approximately 2 cm in thickness) for both the control and verapamil study were each divided into five regions, corresponding anatomically to the anterior and posterior septum and the anterior, lateral, and inferoposterior walls; hence, 10 segments for each patient study were analyzed. Segments were assigned a score from 0 to 2, in 0.5 increments, with a score of 2 signifying normal activity and 0 signifying no activity. The inherent physical properties of the tomographic technique may make the region to region comparison within one tomographic slice unreliable when imaging an asymmetrically hypertrophied ventricle.\(^19\) Therefore, each segment from the control study was also compared directly with its anatomically comparable segment from the verapamil study. Although both the control and verapamil tomograms were interpreted by direct comparison with each other, these studies were displayed in random order, such that the three observers were unaware as to which tomographic slices represented the control study and which the verapamil study. The observers were also blinded to the identity of the patient. Scores for each segment were averaged; a score of 1.5 or less was considered to represent a perfusion defect, and a change of 0.5 or more was considered a significant change in perfusion. For all regions scored as normal or abnormal under control conditions, there was complete agreement in scoring among all three observers in 81% and 82% of regions, respectively. Similarly, for all regions scored as having a change in perfusion during verapamil, all three observers’ scores agreed in 81% of regions.

**Radionuclide Ventriculography**

Radionuclide ventriculography was performed in all patients at rest in the supine position after the in vivo labeling of red blood cells with 20–25 mCi \(^{99m}\)Tc. These studies were performed on the same day as the tomographic study for 27 patients, within 1 week in one patient, and within 5 weeks in the remaining patient. Scintigraphic data were acquired in the modified left anterior oblique position, which allowed optimal visual separation of the right and left ventricles. Left ventricular ejection fractions were computed as previously described.\(^20\) Peak left ventricular filling rates were determined by fitting third-order polynomial functions to the rapid diastolic filling portion of the high temporal resolution time-activity curve by a least-squares technique. The time of occurrence of the peak filling rate was obtained by setting the second derivative of the polynomial function to 0. Time to peak filling rate was measured relative to end systole (minimum volume on the time-activity curve). Peak filling rate was computed in counts per second, normalized for the number of counts at end diastole, and expressed as end-diastolic volumes per second.\(^20\) Radionuclide ventriculography was repeated in each patient during verapamil treatment.

**Changes in left ventricular volume after upright exercise.** Because left ventricular volume changes at the time of imaging, independent of alterations in myocardial perfusion, can result in apparent regional \(^{201}\)TI defects,\(^21\) radionuclide ventriculography was performed in six of the 29 patients both before and 10 minutes after upright graded treadmill exercise continued to the same heart rate and blood pressure endpoints as those achieved during the previous \(^{201}\)TI exercise session. All studies were performed on the same day as the thallium scan, and all of these patients were studied in this manner off medication and again during verapamil therapy. 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 \(^{99m}\)Tc. The results from the control and verapamil study were compared to determine whether changes in left ventricular cavity size after exercise may have contributed to any apparent changes in regional perfusion from the control to verapamil study.

**Echocardiographic Studies**

Two-dimensional echocardiographic studies were performed with an Advanced Technology Laboratory (ATL) Mark 500 mechanical sector scanner with a 3 MHz transducer. 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.

**Extent of left ventricular hypertrophy.** 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.\(^22\) Twenty-eight patients underwent echocardiographic study within 1 month of their tomographic study, and the remaining patient was examined 12 months before tomography. In 28 of the 29 study patients, echocardiographic studies were judged to be technically adequate to permit assessment of the presence or absence of hypertrophy in each left ventricular segment. Overall extent of left ventricular hypertrophy was defined as follows: mild, involving only one left ventricular segment; moderate, involving two segments; and severe, involving three or four segments.\(^23\) The assessment of magnitude of left ventricular hypertrophy as mild, moderate, and severe has previously been shown to have satisfactory reproducibility.\(^23\)
Effects of exercise on regional wall motion. Changes in regional left ventricular wall motion, independent of the heterogeneity of perfusion, have also been reported to result in apparent regional $^{201}$Tl perfusion defects. Therefore, we performed M-mode echocardiograms immediately after exercise in the supine position in 10 patients, during both the control and verapamil study, to examine the potential effect of verapamil on ventricular septal and posterior wall dynamics. One observer, blinded to the $^{201}$Tl perfusion results, measured absolute systolic excursion and percent systolic thickening of both the ventricular septum and posterior wall, averaged over three cardiac cycles.

Statistical Methods

Comparisons among groups of patients were performed with one-way analysis of variance and the paired or unpaired Student’s $t$ test, where appropriate. Differences in proportions were analyzed with the $\chi^2$ test, correcting for small sample sizes when necessary by Fisher’s exact test.

Results

Exercise Testing

During the control study, exercise duration ranged from 14.2 to 27.7 minutes (mean, 21.0±3.6 [±SD] minutes). For all but two patients, this exercise time was within 2 SDs of the mean of the 51 normal volunteers who underwent treadmill testing (mean, 23.4±4.0 minutes). Peak heart rate was 170±16 beats/min, peak systolic blood pressure was 154±30 mm Hg, and the rate pressure product was 26,320±6,000. During verapamil therapy, exercise time increased slightly but significantly to 21.9±2.7 minutes ($p<0.005$ compared with control). Peak heart rate decreased to 156±17 beats/min ($p<0.001$ compared with control), peak systolic blood pressure was unchanged (159±34 mm Hg), and rate-pressure product tended to decrease (24,980±6,400), but the change was not significant.

$^{201}$Tl Tomography

During control conditions, 15 of the 29 patients (52%) developed regional $^{201}$Tl perfusion defects during exercise (Figure 1). A total of 56 myocardial regions were abnormal, an average of 3.7 abnormal regions per patient. Anatomically, 39 (70%) of the perfusion defects were located in the ventricular septum, 13 (23%) in the posterior free wall, three (5%) in the anterior free wall, and one (2%) in the lateral free wall. All perfusion defects were reversible from the exercise to the redistribution rest study, with the exception of six regions in one patient, which were all fixed defects. This patient had the lowest ejection fraction (41%) in this study, associated with an anteroseptal wall motion abnormality at rest on radionuclide angiography.

During verapamil therapy, regional perfusion improved during exercise in 10 of the 14 patients (71%) with reversible perfusion abnormalities during exercise under control conditions (Figure 1), while in four patients there were no significant changes. The one patient with fixed perfusion defects did not exhibit any changes during verapamil. The improved perfusion defects during exercise included 68% (25 of 37) of the septal, 73% (eight of 11) of the posterior, 0% (0 of one) of the lateral, and 100% (one of one) of the anterior wall perfusion defects. Overall, perfusion during exercise improved during verapamil in 34 of the 50 initially reversible abnormal regions (68%). All of the initially abnormal regions (an average of 3.9 regions per patient) returned completely to normal during exercise in eight of the 10 patients whose regional perfusion improved with verapamil (Figures 2 and 3). Importantly, no region in any patient developed a new or worse perfusion defect with exercise during verapamil therapy.

There was no relation between a family history of hypertrophic cardiomyopathy and either the development of $^{201}$Tl perfusion defects under control conditions or an improvement in perfusion during verapamil. Perfusion patterns under control conditions or changes in perfusion with verapamil also did not differ among patients with obstructive or nonobstructive hypertrophic cardiomyopathy.

To evaluate the possibility that the beneficial effect of verapamil resulted merely from a primary decrease in myocardial oxygen demand, we com-
pared the exercise variables in six patients in whom exercise-induced $^{201}$Tl defects improved during verapamil and in whom echocardiography indicated no outflow obstruction. In the absence of resting or provokable obstruction, the systemic blood pressure-heart rate double product would reflect relative myocardial oxygen demand and provide a reasonable basis to compare control and verapamil studies. In these six patients, there was no difference in peak heart rate (167±15 compared with 156±16 beats/min, \( p = \text{NS} \)), peak systolic blood pressure (152±24 compared with 163±36 mm Hg, \( p = \text{NS} \)), or double product (25.6±5.1 compared with 25.4±6.1×10³, \( p = \text{NS} \)) between the control and the verapamil studies.

Of the five patients receiving verapamil doses less than 480 mg/day, four had perfusion defects with exercise during control studies. In two of the four patients perfusion improved (one completely) during verapamil. Thus, the effect was similar to that in patients receiving higher doses. Similarly, duration of therapy was also unrelated to the verapamil effects. Twenty-six of the 29 patients received the highest dose of verapamil for three to seven days before repeat testing. Both the patient treated for two days and the patient treated for 56 days had

**FIGURE 2.** Short-axis tomograms obtained immediately after maximal treadmill exercise (top) and after 3 hours of rest (bottom) in an 18-year-old asymptomatic man with hypertrophic cardiomyopathy. Under control conditions (left), reversible septal and inferoposterior perfusion defects develop during exercise and are improved at rest. There is also apparent cavity dilatation induced by exercise. During oral verapamil (right), myocardial perfusion and apparent cavity dilatation are improved during exercise.

**FIGURE 3.** Short-axis tomograms obtained immediately after treadmill exercise (top) and after 3 hours of rest (bottom) in a 19-year-old asymptomatic man with hypertrophic cardiomyopathy. There are anterior and posterior septal and inferoposterior perfusion defects during exercise, with apparent cavity dilatation, during exercise under control conditions, which improve at rest. These abnormalities are prevented with verapamil.
multiple regional perfusion abnormalities during the control exercise study, and both completely normalized with verapamil.

**Radionuclide Angiographic Results**

Left ventricular ejection fractions under control conditions ranged from 41% to 93% (mean, 75±12%); the normal range for our laboratory is 45–72%.[20] During oral verapamil therapy, there was no significant change in resting ejection fraction (73±11%) or heart rate. Peak left ventricular filling rate increased significantly during verapamil (from 3.7±1.1 to 4.1±1.2 EDV/sec, p<0.001), consistent with previous reports from our laboratory in symptomatic patients with hypertrophic cardiomyopathy.[20] Time to peak filling rate was reduced by verapamil, but not significantly (211±72 to 188±32 msec, p=NS).

In patients who developed perfusion defects during exercise under control conditions, the left ventricular peak filling rate at rest was significantly lower than in patients with normal perfusion patterns (3.3±1.0 compared with 4.2±1.1 EDV/sec, p<0.05), and time to peak filling rate was longer, although not significantly (235±91 compared with 185±27 msec, p=NS). There were no significant differences in ejection fractions (77±13% compared with 74±12%, p=NS) or heart rates (65±9 compared with 62±10 beats/min, p=NS) between the group with and the group without perfusion defects. Among the patients with perfusion defects, those with improved perfusion during verapamil had a greater increase in peak filling rate than those without a change in perfusion, which was of borderline significance (0.6±0.3 compared with −0.1±0.6 EDV/sec, p<0.10). In addition, there was a significant correlation in patients with improved perfusion during verapamil between the number of regions scored as improved and the change in peak filling rate (r=0.64, p<0.05). These data suggest that functional abnormalities of left ventricular filling were associated with the presence and extent of 201TI perfusion defects.

In the six patients studied by radionuclide angiography before and after treadmill exercise, there was no significant difference in left ventricular end-diastolic counts between the resting and 10-minute post-treadmill study, either under control conditions or during verapamil. The ratio of post-treadmill to pretreadmill end-diastolic counts, corrected for background and decay, was 1.05±0.08 for control studies and 1.07±0.08 during verapamil (p=NS). Thus, it is unlikely that stress-induced left ventricular dilatation could account for perfusion defects under control conditions or that a relative decrease in the magnitude of such dilatation during verapamil could account for the apparent improvement in defects.[21]

**Echocardiographic Results and Correlation With 201TI Tomography**

Three patients had mild left ventricular hypertrophy, ten had moderate hypertrophy and 16 had severe hypertrophy. Maximum left ventricular wall thickness ranged from 15 to 50 mm (mean, 26±9 mm).

Patients with more extensive left ventricular hypertrophy were more likely to have abnormal regional 201TI perfusion patterns during exercise than those with less severe hypertrophy (Figure 4). One of three patients with mild, two of 10 patients with moderate, and 12 of 16 patients with severe hypertrophy had perfusion defects during exercise under control conditions. All of the 10 patients in whom perfusion improved after verapamil therapy had severe hypertrophy. Thus, the effects of verapamil on myocardial perfusion during exercise was most pronounced in patients with the greatest degree of hypertrophy (Figure 4).

Data were technically adequate for analysis in nine of the 10 patients who underwent echocardiography immediately after exercise for analysis of septal and posterior wall dynamics during both control and verapamil studies. There were no significant differences between the control and verapamil studies in septal excursion (5.2±1.4 compared with 4.8±1.5 mm, p=NS) or percent systolic thickening of the septum (15.8±14.8% compared with 15.5±18.2%, p=NS); neither were there differences in posterior wall excursion (16.1±4.9 compared with 16.1±3.8 mm, p=NS) or percent systolic thickening (81.9±31.6% compared with 80.0±29.0%, p=NS). Thus, improved septal perfusion during verapamil did not result from a change in septal or posterior wall dynamics.

**Discussion**

The results of the present investigation indicate that silent myocardial perfusion defects commonly develop during exercise in asymptomatic and minimally symptomatic patients with HCM and that verapamil prevents these defects in the majority of patients. Previous studies have demonstrated the efficacy of verapamil in symptomatic patients with...
HCM in treating angina or dyspnea and in improving exercise tolerance. Evidence for hemodynamic improvement with verapamil include enhanced diastolic performance, and reduction in outflow tract gradient. Our results extend the spectrum of effects of verapamil in HCM to include the prevention of exercise-induced regional myocardial perfusion abnormalities (probably representing silent myocardial ischemia) in the subgroup of patients who are asymptomatic or minimally symptomatic.

The exact mechanisms responsible for causing myocardial ischemia in HCM are not known. Our results indicate, however, that the presence of extensive hypertrophy in and of itself is not responsible for the \(^{201}\)TI perfusion defects, as some patients with mild to moderate hypertrophy developed exercise-induced ischemia, and many patients with severe hypertrophy and perfusion defects under control conditions exhibited a normal perfusion pattern during verapamil therapy. Thus, our results suggest that the reversible ischemia developing with exercise is caused by some process that is associated with (rather than caused by) hypertrophy and that may be modified by verapamil therapy. The mechanism could relate to an increase in myocardial oxygen demand beyond the capacity of the vascular bed to supply oxygen (primarily in those patients with obstruction to left ventricular outflow) to a vascular bed that has not grown in proportion to the degree of hypertrophy, to a limitation of coronary reserve due either to elevated left ventricular-filling pressures, or to functional or fixed vascular abnormalities of the small intramural coronary arteries.

In this regard, in a histopathologic study of patients with HCM at necropsy, wall thickening and luminal compromise of intramural coronary arteries were observed in over 80% of patients; although these abnormalities were most commonly present in the ventricular septum, they were not confined to this region of the left ventricle. Of particular relevance to the results of the present study is the fact that abnormal intramural coronary arteries are also frequently seen in young, previously asymptomatic patients who died suddenly from HCM.

Moreover, a subset of patients with HCM progress to a stage of left ventricular wall thinning and cavity enlargement, usually associated with severe symptoms. This process is related to the development of myocardial fibrosis, which may be extensive or transmural. Of note, abnormalities of the intramural coronary arteries are more commonly present near or within areas of myocardial fibrosis. It is thus possible that ischemia caused by these vascular abnormalities may eventually result in myocardial scarring and diminished left ventricular function. If this hypothesis is correct, then the results of the present study suggest that verapamil, by preventing repetitive ischemic episodes, may also have a role in preventing the progression to irreversible abnormalities in ventricular function related to myocardial fibrosis. Of possible relevance to this hypothesis are the findings in the hereditary dilated cardiomyopathy of the Syrian hamster, which suggest that vasospasm of the intramural coronary vessels is a major pathophysiologic factor and in which therapy with verapamil has been shown to diminish the extent of myocardial necrosis.

There are several mechanisms, alone or in combination, by which verapamil may have improved regional myocardial perfusion during exercise in our patients. First and most likely, verapamil may have improved regional coronary reserve, either via a direct coronary vasodilating action or via improved left ventricular relaxation, such that coronary flow during exercise was enhanced. Second, apparent regional perfusion abnormalities (especially septal) under control conditions may have resulted from the disparity in demand (and thus perfusion) between a thickened, hypokinetic septum and a relatively thin, hyperkinetic posterior wall, as differences in extent of regional wall motion may account for heterogeneous \(^{201}\)TI uptake. Verapamil may then have merely made demand more homogeneous by exerting a negative inotropic action on the posterior wall, resulting in more uniform \(^{201}\)TI uptake. This scenario seems unlikely in light of the fact that verapamil produced no identifiable alteration in global ejection fraction or left ventricular wall dynamics. In addition, previous studies in a model of regional myocardial ischemia in dogs have shown that verapamil exerts no significant negative inotropic effect in nonischemic regions. Therefore, it seems unlikely that primary changes in regional wall motion influenced our results.

A third potential mechanism relates to possible left ventricular cavity dilatation during stress, resulting in apparent \(^{201}\)TI perfusion abnormalities. These abnormalities might be attenuated by verapamil, since in experimental models apparent radionuclide perfusion defects may be produced by increases in cavity size and attenuated by decreases in cavity size. The radionuclide angiographic findings indicating no significant differences in left ventricular end-diastolic counts before or after treadmill exercise, either with control or verapamil studies, are evidence that the changes in myocardial perfusion during verapamil did not arise from primary changes in left ventricular cavity size. Although these particular results are based on a small sample of six patients, they are identical to previous studies in a group of 11 other asymptomatic patients with HCM studied in our laboratory.

Fourth, verapamil may have primarily reduced myocardial oxygen demand. The similarity of exercise rate-pressure product during both control and verapamil studies in the six patients with nonobstructive HCM in whom perfusion defects improved during verapamil mitigates against this possibility. In the absence of provokable outflow obstruction, the exercise rate-pressure product, derived from
measurements of systemic blood pressure, would be a reasonable reflection of relative myocardial oxygen demand. Therefore, it is doubtful that changes in myocardial oxygen demand were the sole cause of the improvement in regional perfusion during exercise produced by verapamil.

Whether the perfusion defects described in this study represent true myocardial ischemia cannot be definitively answered by the current data. As noted in a previous study from our laboratory,12 it is possible that the regional heterogeneity of uptake of the 201TI isotope may represent abnormal local transmembrane cation transport. That such an energy requiring process should be abnormal in HCM and be reversed by verapamil would itself be of interest. However, we believe that the association of perfusion defects in this study with functional abnormalities of left ventricular filling, as well as previous studies demonstrating the common occurrence of myocardial ischemia in HCM,1,3,6-8,12 and the necropsy evidence of small vessel pathology in asymptomatic HCM patients who died suddenly, are strong, albeit circumstantial evidence that silent myocardial ischemia was indeed present in this group of HCM patients.

We did not attempt to examine exercise-induced changes in systolic wall motion as indicative of the presence of ischemia. Wall motion of the thickened septum is hypokinetic or akinetic at rest in the majority of patients with HCM,24,25 and many patients in the absence of associated coronary artery disease manifest marked regional left ventricular asynchrony.38 Thus, changes in septal wall dynamics during exercise would not be expected to have adequate positive or negative predictive value for the presence or absence of ischemia.

We cannot exclude the possibility that occult obstructive disease of the epicardial coronary arteries was present in some study patients and contributed to exercise-induced regional perfusion abnormalities. However, we believe this possibility is very remote because only one of the 14 patients with exercise-induced perfusion defects was over the age of 35.

Partial volume effects, related to physical imaging characteristics in the acquisition of tomographic images when the ventricular walls vary in thickness in the same patient may create apparent deficiencies in perfusion; the thinner myocardial segments would appear to have diminished perfusion.19 This aspect of tomographic imaging tends only to strengthen the findings in the present study because the defects were observed predominantly in the thickest portion of the ventricle (i.e., the septum).

In summary, treadmill exercise may induce regional myocardial perfusion defects, as demonstrated by 201TI tomography, in asymptomatic or minimally symptomatic patients with HCM. The stress-induced perfusion abnormalities are prevented in the majority of these patients by verapamil therapy. The mechanism of this effect of verapamil is likely to involve either direct effects on the small coronary vessels or improved regional myocardial relaxation. If ischemia indeed plays a role in sudden cardiac death and progressive left ventricular dysfunction in HCM, our data raise the possibility that verapamil may be of use in preventing these devastating outcomes, although long-term clinical studies are needed to evaluate these important therapeutic implications.

References

15. Pollick C, Rakowski H, Wigle ED: Muscular subaortic stenosis: The quantitative relationship between systolic ante-


34. ten Cate FJ, Roelandt J: Progression to left ventricular dilatation in patients with hypertrophic obstructive cardiomyopathy. Am Heart J 1979;97:762–765


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