Hypertrophic Cardiomyopathy Complicated with Ventricular Aneurysm and Myocardial Necrosis

Case Presentation and Discussion: Hiroyuki Matsuura

Guest Editor: Tsunehiro Yasuda

From the case records of the Massachusetts General Hospital, Boston, Massachusetts and Harvard Medical School, Boston, Massachusetts

J Nucl Med 1993; 34:2227–2235

Hypertrophic cardiomyopathy (HCM) is characterized by disproportionate hypertrophy of the left ventricle and occasionally also of the right ventricle, which typically involves the septum more than the free wall but occasionally is concentric. Typically, left ventricular volume is normal or reduced (*1*). Chest pain is one of the major symptoms in patients with HCM and may be so severe that acute myocardial infarction would be suspected as a primary possible diagnosis even when we know that the patient does not have significant coronary artery disease. Repetitive myocardial necrosis in hypertrophic cardiomyopathy is believed to result in the dilated stage of cardiomyopathy with poor prognosis (*2,3*). Thus, myocardial necrosis would significantly alter the clinical picture of hypertrophic cardiomyopathy. Since, abnormal Q-waves and ST-T changes mimicking myocardial infarction are not unusual in patients with HCM, the electrocardiographic abnormalities may make a precise diagnosis of acute myocardial infarction difficult. Myocardial imaging with ^{111}In-antimyosin antibody or ^{99m}Tc-pyrophosphate could be of great value in such cases because necrotic myocardial segments are visible as hot regions with these agents. We present two cases of HCM complicated by ventricular aneurysm and myocardial necrosis.

CLINICAL HISTORY

Patient 1

A 66-yr-old woman presented to the emergency ward with substernal chest pain lasting more than 1 hr. She had a 3-yr history of chronic stable angina which usually responded to sublingual nitroglycerin. She noted decreased exercise tolerance and increasing fatigue in the 3–4 wk prior to admission. While at the theater, she developed substernal chest pain associated with palpitation and dyspnea; she was brought to the emergency room that same evening.

She had a past medical history of hypertension, hypercholesterolemia and rheumatoid arthritis. Her medications on admission were propranolol and verapamil. Family history revealed that her father had a myocardial infarction.

On examination she was afebrile. Her blood pressure was 109/76 mmHg, heart rate was 90 bpm and her respiratory rate was 20 per minute. She appeared to have difficulty breathing and was diaphoretic. Jugular venous distension was observed. Auscultation revealed crackles half way up her lungs bilaterally. Cardiac examination revealed an S_3 gallop and a systolic ejection murmur of II/VI over the aortic valve area. Her abdomen was unremarkable and her extremities showed no edema and good distal circulation.

While in the emergency room, the patient developed acute pulmonary edema after intravenous infusion of 500 cc of normal saline administered for the management of hypotension that was induced by sublingual nitroglycerin. She was brought to the coronary care unit where intubation and mechanical ventilation requiring 40%–60% of FIO_2 combined with intravenous administration of furosemide and morphine were done. Her electrocardiogram showed normal sinus rhythm (92 bpm) without any evidence of ischemia (Fig. 1A).

Echocardiography demonstrated asymmetric septal hypertrophy, a left ventricular apical aneurysm, systolic anterior movement of the mitral valve with dynamic left ventricular outflow obstruction, moderate mitral regurgitation, and left atrial enlargement. The pulmonary arterial line revealed a right atrial pressure of 10 mmHg, a right ventricular pressure of 45/10 mmHg, a pulmonary arterial pressure of 45/30 mmHg and pulmonary capillary wedge pressure of 30 mmHg. Emergency cardiac catheterization was

Received Jun. 22, 1993; revision accepted Aug. 15, 1993.
For reprints contact: Tsunehiro Yasuda, MD, Div. of Nuclear Medicine, MGH, 32 Fruit St., Tilton 2, Boston, MA 02114.

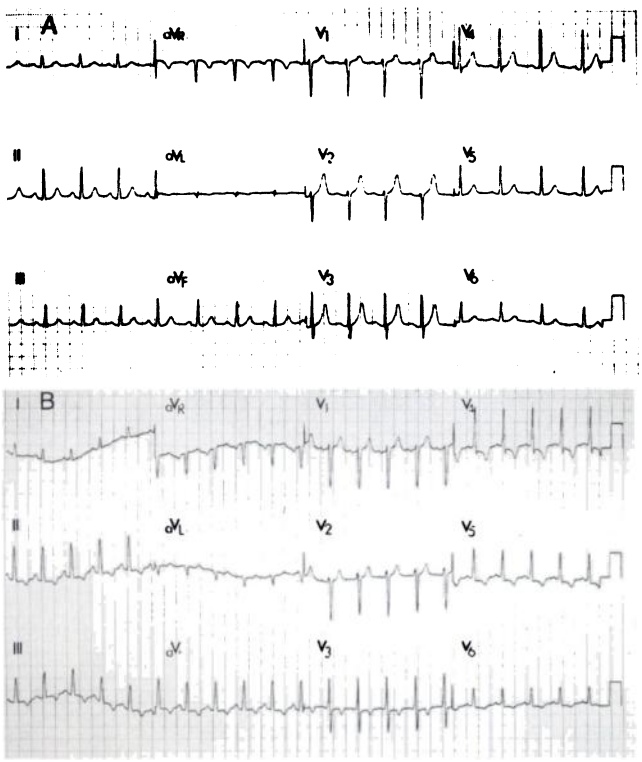

FIGURE 1. (A) Patient 1. Electrocardiogram on admission demonstrates normal sinus rhythm. There was no evidence of ischemia or myocardial infarction. (B) Electrocardiogram on the third day of hospitalization. New T-wave inversions were observed in V_3-V_6 and inferior leads.

performed the following morning, which revealed a subaortic systolic pressure gradient of 45 mmHg, with left ventricular pressure of 165/25 mmHg and aortic pressure of 120/70 mmHg. Coronary angiography and left ventriculography showed normal coronary arteries, a large left ventricular aneurysm in the diaphragmatic wall with akinesis in the adjacent wall and mild mitral regurgitation. Her electrocardiogram revealed new T-wave inversions in the inferior and anterolateral leads (V_3-V_6) on the third day of hospitalization (Fig. 1B). She demonstrated elevated levels of serum creatine kinase for 5 days, with a peak level of 387 U/liter (MB fraction: 22.5%) on her first hospital day (the normal value of serum creatine kinase was 40–150 U/liter, with a MB fraction of less than 3.0%). Serum levels of creatine kinase slowly trailed off over the next two days to the normal range. She gradually responded to treatment with a multiple dose of furosemide for congestive heart failure. The patient was extubated on the fifth day.

On the sixth day, the patient underwent resting ^{201}Tl perfusion scintigraphy for assessment of viability of the aneurysmal area. The general uptake of thallium was heterogeneous. The images demonstrated distal anterolateral, apical and inferoapical ischemia accompanied by a small apical perfusion defect (Fig. 2). The perfusion defect appeared to be much smaller than the aneurysm observed on left ventriculograms (Fig. 3). The inferior wall looked well perfused and viable. On the ninth day of hospitalization, she had another episode of precordial chest pain, but creatine kinase was not elevated at this time. Right ventricular endomyocardial biopsy performed on the twelfth day revealed prominent T lymphocyte infiltration, healed focal ischemic necrosis and interstitial fibrosis. The histology was interpreted as borderline myocarditis based on the Dallas criteria (*4*). Indium-111-antimyosin antibody scanning performed on the following day showed intense global uptake in the left ventricle, indicating acute and severe myocardial necrosis (Fig. 4). She was eventually placed on coumadin and captopril. Her general condition and congestive heart failure improved and were uneventful thereafter.

Patient 2

A 39-yr-old male was admitted to the hospital with a chief complaint of abrupt loss of consciousness 2 days prior to admission.

His past medical record was remarkable for "idiopathic hypertrophic subaortic stenosis" (hypertrophic obstructive cardiomyopathy) since age 16. He had smoked cigarettes, 1 pack a day, for 25 years. He also had been smoking marijuana. He usually drank 9–10 cans of beer over the weekend. His family history is remarkable in that his younger sister and elder brother had HCM. Furthermore, his father had diabetes mellitus, and his mother died of subarachnoid hemorrhage.

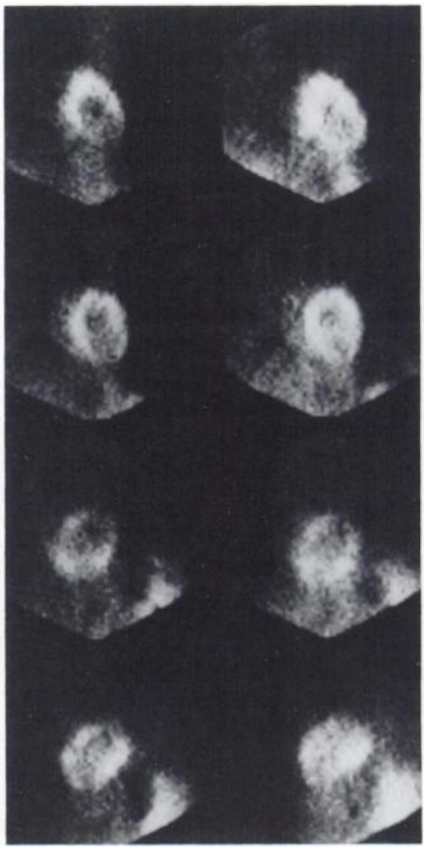

FIGURE 2. Resting ^{201}Tl perfusion scintigraphy of Patient 1 performed on the sixth day of hospitalization. The images demonstrate distal anterolateral, apical, and inferoapical ischemia. The images are anterior, LAO 40, LAO 70 and left lateral projections from top to bottom (left column: initial images, right column: delayed images).

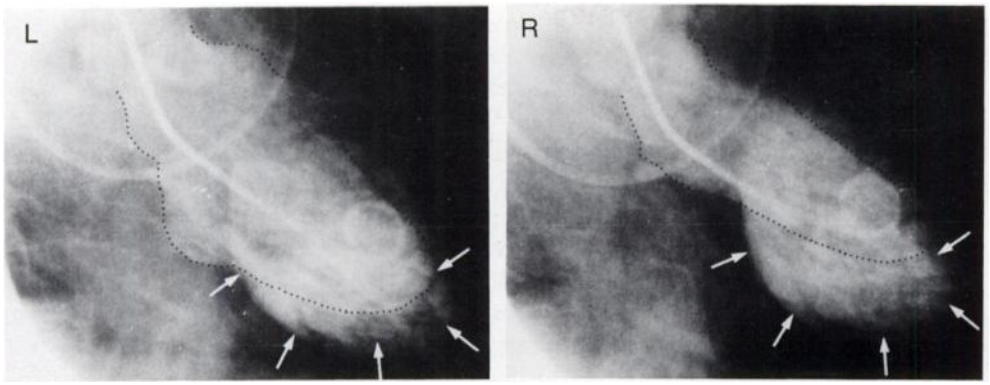

FIGURE 3. Left ventriculograms (left: endodiastolic, right: endosystolic) of Patient 1 performed on the 12th day of hospitalization. Arrows indicate apical aneurysm and the dotted line indicates the left ventricle. The "normal apex" was inserted to contrast the abnormal apical dilatation by the dotted line.

The diagnosis of "idiopathic hypertrophic subaortic stenosis" (hypertrophic obstructive cardiomyopathy) was made during cardiac catheterization 13 yr ago. He was placed on propranolol and did well except for occasional episodes of dizziness, palpitation and dyspnea on exertion. He experienced severe shortness of breath and dizziness 12 yr ago, when he developed atrial fibrillation with rapid ventricular response. A second cardiac catheterization and angiography revealed severe concentric hypertrophy with the gradient of 100 mmHg between the left ventricular apex and the base. Mild stenosis in his right ventricular outflow tract was also demonstrated along with marked concentric hypertrophy involving the ventricular septum. Therapy with digoxin was begun and his symptoms remained stable on propranolol and digoxin for the last 12 yr.

His clinical course had been uneventful until 2 days prior to admission, when he developed syncope without any warning. Upon regaining consciousness within 15 sec, he noticed fast heart beats and felt nauseous. Since he remained nauseated all through the following day, he came to the emergency room on the second day after loss of consciousness and was admitted. Blood pressure on admission was 123/81 mmHg, the pulse was irregular at 93 bpm, and his respiratory rate was 18 per minute.

Physical examination revealed bilateral basilar crackles, normal S_1 and S_2 with S_3 and diastolic rumble of II/VI. There was no edema in his lower extremities. Computerized tomography (CT) of his head did not demonstrate any intracranial lesions. The electrocardiogram on admission revealed atrial fibrillation/flutter, with a ventricular rate of 91 bpm (Fig. 5). Several hours later, he developed multiple episodes of unifocal ventricular tachycardia which subsided spontaneously within 10 sec. Serial electrocardiograms demonstrated elevation of ST segments with a maximum elevation of 1 mm in V_5. He also complained of severe pleuritic chest pain, and significant elevation of creatine kinase and its MB fraction were documented. The peak value of creatine kinase was observed on the day of admission with creatine kinase of 1401 U/liter (normal for man: 60–400 U/liter) and MB fraction of 9.7% (normal: ≤3%). He underwent cardiac catheterization the day after admission, and an intraventricular pressure gradient of 100 mmHg was found. Angiography revealed normal coronary arteries with an akinetic segment in the apex.

Technetium-99m-pyrophosphate scintigraphy performed after cardiac catheterization revealed intense uptake in the anterior wall, interventricular septum and apex that were heterogeneous and inconsistent with myocardial infarction secondary to coronary artery occlusion commonly seen in the coronary care unit (Fig. 6). The patient underwent a rest and redistribution thallium study on the fourth day of

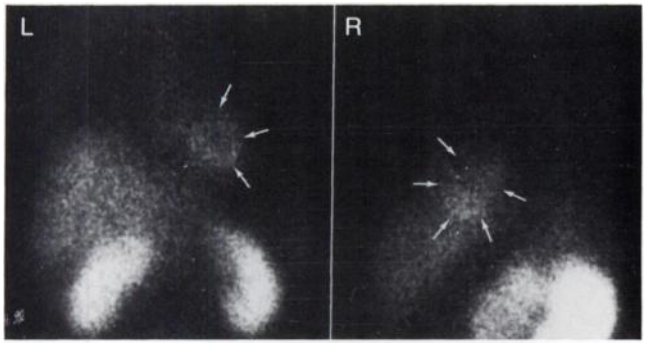

FIGURE 4. Indium-111-antimyosin antibody imaging (left: anterior view, right: LAO view) of Patient 1 performed on the 13th day of hospitalization. Global uptake in the left ventricle was observed (→). The visual uptake score in the heart is 4+.

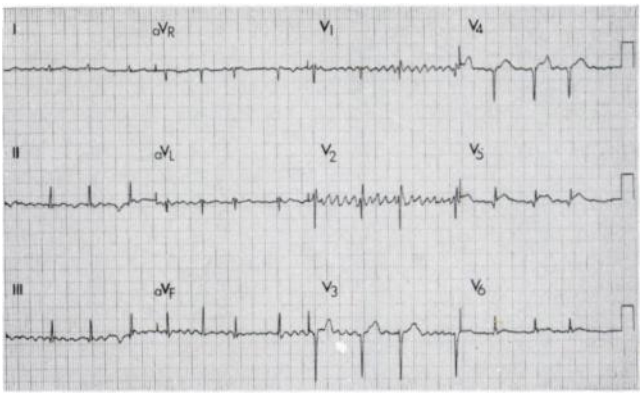

FIGURE 5. Patient 2. Electrocardiogram on admission shows atrial fibrillation/flutter with moderate ventricular response (91 bpm), incomplete right bundle branch block and possible anterior myocardial infarction.

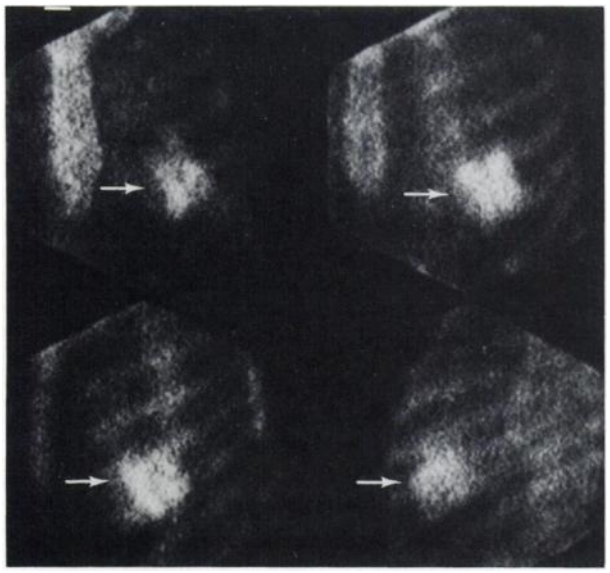

FIGURE 6. Technetium-99m-pyrophosphate scintigraphy of Patient 2 performed on the day after admission revealed multiple areas of intense uptake (→). The uptake is irregular and does not conform to the coronary artery territory. This is an unusual appearance for myocardial infarction due to coronary artery occlusion. Upper panel: anterior and LAO 30. Lower panel: LAO 60 and left lateral.

hospitalization (Fig. 7). The initial images revealed significantly increased pulmonary activity and strikingly inhomogeneous distribution of the tracer within the left ventricle. Global redistribution of tracer was noted in the septum, anterior and inferior walls in the delayed images.

DISCUSSION

The clinical presentation of the first case was apparently most consistent with acute myocardial infarction, however, the histological diagnosis from a right ventricular endomyocardial biopsy was borderline myocarditis. Myocardial necrosis was likely to involve the anterior wall of the left ventricle extending to the apex. Thallium-201 scintigraphy was consistent with ischemia in the distal anterior, apical and inferoapical regions. The widespread hypokinesis may be responsible for the deterioration of cardiac function and the symptoms of congestive heart failure during the 3–4 wk prior to admission.

Transiently elevated creatine kinase and its MB fraction were also suggestive of acute myocardial necrosis. However, the diagnosis of acute myocardial necrosis was not immediately apparent, because neither Q-waves on electrocardiograms nor atheromatous coronary artery disease on coronary angiography were observed. Moreover, creatine kinase seemed to be too low for transmural myocardial infarction of this size. Therefore, myocardial necrosis took place sometime in the past, or infarction was aborted by an unknown mechanism or natural course that frequently causes dilated aneurysmal apex. Nonetheless, the pattern of antimyosin antibody uptake is homogeneous, global and consistent with moderately severe, recent acute myocardial cell necrosis such as myocarditis or other diffuse processes of myocardial necrosis. It is unusual to see this degree of global uptake in patients with acute myocardial infarction secondary to coronary artery disease (*5*).

The second patient exhibited significant changes in his clinical course during the 23-yr follow-up period. In his early clinical course, the patient's signs and symptoms were typical of hypertrophic obstructive cardiomyopathy. He had a positive family history strongly suggestive of genetically transmitted HCM. Subsequently, his symptoms were complicated with both supraventricular and ventricular arrhythmias, which are not unusual in patients with HCM. However, HCM itself could not explain the dilated and akinetic segment in the left ventricular apex without a complication of myocardial necrosis. Significant elevation of creatine kinase and its MB fraction at the time of chest pain is strongly indicative of myocardial necrosis. However, his serial electrocardiograms were not conclusive for acute myocardial infarction. Moreover, selective coronary angiography failed to demonstrate any lesions in the major coronary arteries. Only ^{99m}Tc-pyrophosphate scintigraphy was positive for acute myocardial necrosis, with possible ischemic myocardium demonstrated by multiple well-demarcated hot regions. The pattern of uptake of ^{99m}Tc-pyrophosphate was not typical of acute myocardial infarction secondary to coronary artery occlusion.

These two cases present several clinically important issues regarding myocardial necrosis in HCM. There are,

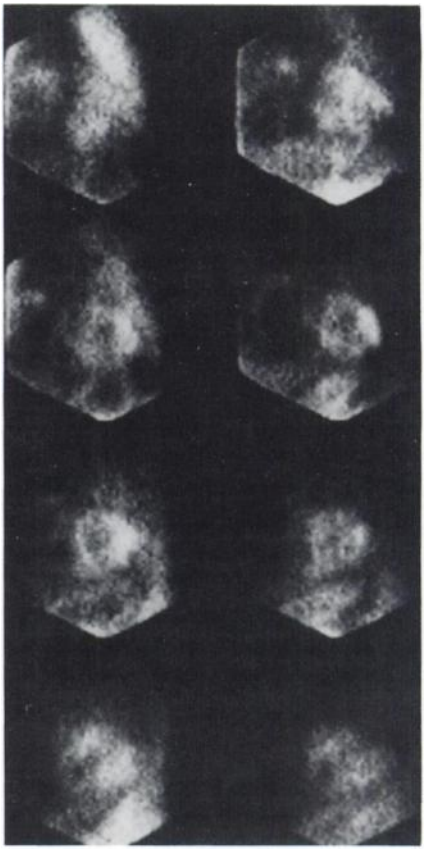

FIGURE 7. Rest (left column) and redistribution (right column) thallium study of Patient 2 performed on the fourth day of hospitalization. The images are anterior, LAO 40, LAO 70 and left lateral projections from top to bottom. Note the substantial pulmonary activity and global inhomogeneity in the initial images. It was almost difficult to identify each myocardial region. The delayed images demonstrated global redistribution in most of the perfusion defects seen in the initial images, although the redistributions were incomplete. The posterolateral wall appeared best perfused in the delayed images.

TABLE 1
Etiology of Myocardial Necrosis and Evolution of Congestive Heart Failure in Patients with HCM

- Atherosclerotic coronary artery disease (*8,17,18*)
- Intramural coronary arteries ("small vessel disease") (*2,3*)
- Impaired vasodilator reserve of coronary artery (*21,22*)
- Elevated left ventricular filling pressure (*6,22,56*)
- Compression of septal perforator (*24*)
- Myocardial bridging (*25*)
- Spasm of coronary artery (*26*)
- Mismatching of supply/demand in oxygen consumption (*8,23*)
- Anomalous coronary arteries (*8,18*)
- Septal myectomy (*15*)
- Embolism to a major coronary artery branch (*15,27,31*)
- Intraventricular pressure gradient (*15,24*)
- Myocarditis (Case 1 of this presentation)

however, instances of "myocardial infarction" without significant coronary artery disease in patients with HCM; the pathophysiology of this condition and a diagnostic approach for acute myocardial necrosis in patients with HCM are discussed below.

Pathophysiology of Myocardial Necrosis in Patients with HCM

It is understood that chest pain in patients with HCM results from insufficient coronary perfusion to meet the increased oxygen demands of hypertrophied myocardium. Chest pain and ischemia can occur, however, regardless of the patient's age (*2,6*) and the presence or absence of atheromatous coronary artery disease (*7*). Analysis of the clinical and electrocardiographic data of the patients with HCM cannot predict a subpopulation of the patients with anomalous origins of coronary artery or ischemic coronary artery diseases (*8*).

Some patients with HCM could have a dilated heart with poor left ventricular function that would be indicative of poor prognosis (*2*). Repetitive and transmural myocardial necrosis might involve both left and right ventricles (*2,9*) and may be responsible for a gradual deterioration to congestive heart failure over several years (*2,10–13*). The incidence of this complication is estimated to represent less than one-tenth of adult patients with HCM and is even rarer in childhood (*9,11,14,15*). The risk for this complication of the dilated form of HCM increases, especially when patients have coronary artery disease (*16*). Significant coronary artery disease was found in 14%–19% of patients with HCM (*8,17,18*). Patients aged 45 or older have a higher incidence of coronary artery disease than younger patients with HCM (*8*). If clinically indicated, coronary angiography is necessary to investigate the diagnosis and cause of chest pain and to prevent the deterioration of left ventricular function. Myocardial perfusion imaging is frequently positive in the absence of coronary artery disease (*19*).

The regions of myocardial necrosis in patients with HCM do not always correspond to any particular coronary artery distribution (*2*). Myocardial necrosis has been reported in infants and children with HCM (*3,9,20*). These facts indicate that myocardial necrosis in patients with HCM can occur without significant stenotic lesions in the proximal coronary arteries. Several hypotheses have been proposed as underlying mechanisms responsible for the evolution of the dilated form of HCM (Table 1).

Small-Vessel Disease. Intramural coronary arteries in patients with HCM are characterized by significantly thick vessel walls and a decrease in luminal size. Maron et al. extensively investigated these coronary arteries and called them "small vessels" (*2*). These abnormal coronary arteries were more frequently observed in the interventricular septum where scarring secondary to myocardial necrosis was abundant. Microscopic examination revealed that proliferation of smooth muscle cells and collagen lead to the endothelial hyperplasia and medial hypertrophy (*2,3*). These small vessels could produce patchy and diffuse myocardial fibrosis which does not correspond to the usual major coronary distribution.

Impaired Coronary Reserve. In patients with HCM, regional coronary perfusion to the hypertrophic myocardium has been investigated. At rapid heart rates, impairment of coronary vasodilator reserve ("coronary blood flow reserve") becomes apparent. Some patients develop ischemia manifested by angina, ST-segment depression in electrocardiograms or production of lactate (*21,22*). Patients with HCM usually achieve maximum coronary vasodilatation and flow at modest increases in heart rate. Further increase in the heart rate fails to increase flow and causes myocardial ischemia with an elevation of left ventricular filling pressure followed by a fall in coronary flow (*22*). Regional myocardial blood flow measured by ^{13}N-ammonia does not show a significant difference in coronary reserve between the nonhypertrophied left ventricular free wall and hypertrophied interventricular septum. Therefore, the abnormality in coronary vasodilator reserve in patients with HCM appears to be a primary dysfunction of the coronary artery itself rather than secondary to myocardial hypertrophy (*21,22*).

Left Ventricular Filling Pressure. Coronary perfusion is affected by left ventricular diastolic pressure. The elevation of left ventricular filling pressure is remarkable with pacing-induced rapid heart rate in patients with HCM. As the heart rate increases, a combination of shortened diastolic filling time and a relatively fixed systolic time interval further decrease coronary blood flow (*23*). Evidence of ischemia is apparent when patients experience typical chest pain associated with ST changes and elevation of left ventricular diastolic filling pressure associated with decreased coronary flow and production of lactate during pacing (*22*). During pacing, patients with HCM have decreased coronary arteriovenous oxygen differences despite metabolic evidence of myocardial ischemia assessed by lactate consumption. The reduced arteriovenous oxygen difference combined with an apparent decline of coronary

flow could result in myocardial ischemia in these patients with HCM (*22*).

Mechanical Compression of Coronary Arteries. Compression of coronary arteries may induce significant ischemia in patients with hypertrophic myocardium. Patients with HCM showed a high incidence (detected by coronary angiography) of myocardial bridging of the left anterior descending coronary arteries with various degrees of obstruction. In addition, selective coronary angiography also revealed compression of the septal perforator branches and diagonal branches in patients with HCM (*24,25*). These mechanical obstructions usually occur in systole and seem to correlate with the degree of left ventricular outflow tract obstruction (*24,25*). Even complete occlusion of the affected coronary artery may be observed in the most severe cases; the compression is released instantly with the initiation of diastole (*25*). Hence, it is not necessarily explained by this hypothesis that dynamic stenosis of coronary arteries in patients with HCM would lead to a high risk of myocardial infarction. Furthermore, the presence of myocardial bridging itself does not adversely affect the long-term survival of the patients with HCM (*25*).

Coronary Artery Spasm. Coronary spasm in some patients with HCM could cause chest pain, arrhythmias, syncope and even sudden death regardless of the presence or absence of left ventricular outflow obstruction (*26*). It has been postulated that the coronary arteries of some patients with HCM might be prone to vasospasm due to increased sensitivity to catecholamine. Consequently, myocardial infarction could occur unless the spasms subsided spontaneously or coronary vasodilators such as nitroglycerin were given.

Supply/Demand Mismatching. Acute myocardial infarction in the presence of normal coronary arteries might occur when too much myocardium is perfused by too little hemoglobin or a reduced perfusion pressure (*27*). Mild and nonsignificant coronary atherosclerosis usually does not cause infarction in normal subjects. However, even nonsignificant lesions in coronary arteries could result in insufficient coronary perfusion in patients with HCM, particularly during stress, because myocardial oxygen consumption could significantly increase in these patients (*8,23*). The recent observation that the mean septal thickness of patients with abnormal ^{201}Tl scans was significantly greater than those with normal thallium perfusion scans (*28*) supports this hypothesis. Coronary blood flow per unit mass of ventricular myocardium at rest was reported to be lower in patients with HCM than normal controls in spite of the significantly increased oxygen consumption. Moreover, despite a greater myocardium mass, the amount of increase in coronary blood flow in patients with HCM was blunted compared to normal controls during pacing (*23*).

Anomalous Coronary Artery. Walston and co-workers reported three cases of anomalous coronary arteries among 42 patients with HCM (*8*). There has been no evidence that congenital anomaly of coronary arteries per se would increase the risk of acute myocardial necrosis in patients with HCM (*8,18*). However, anomalous origin of coronary arteries necessitates an abnormally long course for coronary arteries. It is not surprising that these abnormal vessels could be compressed just at their origin or along the course in the hypertrophic myocardium. The incidence of anomalous coronary arteries in 3 of 42 patients appears to be much higher than the usual population encountered in the cardiac catheterization laboratory.

Complications of Surgery. Coronary artery bypass graft surgery may not be sufficient to reduce ischemic episodes in patients with "idiopathic hypertrophic subaortic stenosis" (hypertrophic obstructive cardiomyopathy) and coronary artery disease. A septal myectomy in combination with coronary bypass operation can provide consistent relief of symptoms in these patients (*29*). However, the risk of sudden death in patients with idiopathic hypertrophic cardiomyopathy in the postoperative period [approximately 2% per year (*29*)] does not differ from that previously reported in patients with HCM (*6*) who do not undergo surgery. Moreover, there is some risk of myocardial infarction after coronary artery bypass grafting in patients with ischemic heart disease without HCM (*30*). Some investigators also noted a possible correlation between septal myectomy and myocardial necrosis in the interventricular septum in patients with HCM (*15*). The decision whether or not to operate and which procedure to choose, either septal myectomy or septal myectomy with coronary bypass, must be made carefully.

Embolism. An occlusive embolus or thrombus may cause myocardial infarction in patients with angiographically normal coronary arteries. These thrombi may have been spontaneously lysed when angiography was performed. This gives an impression of acute myocardial infarction associated with normal coronary arteries. It is possible that the abnormal myocardial surface attracts thrombi which subsequently travel to the coronary artery system and cause myocardial infarction (*15,27,31*). An autopsy case of HCM and myocardial infarction in which the patient had a completely occluded right coronary artery by organizing clot has been reported (*2*).

Intraventricular Pressure Gradient. Chest pain in patients with HCM occurs in the absence of left ventricular outflow obstruction (*6,32*). Nonetheless, the intraventricular pressure gradient is more common and severe in patients who subsequently develop left ventricular hypokinesis than those who do not (*15*). Pichard et al. (*24*) reported that patients with "idiopathic hypertrophic subaortic stenosis" (hypertrophic obstructive cardiomyopathy) with no pressure gradient at rest had a milder degree of septal perforator narrowing than patients with a pressure gradient at rest. The degree of coronary artery narrowing was also associated with the severity of outflow tract obstruction during provocation such as Valsalva maneuver or isoproterenol infusion.

Diagnosis of Myocardial Necrosis in HCM

Electrocardiographic abnormalities such as ST-T depression, T-wave inversion and new Q-waves are frequently encountered in patients with HCM. These electrocardiographic abnormalities would appear suddenly, even without chest pain (*33*). Therefore, the diagnosis of ischemic heart disease is often difficult in these patients with HCM, even though the analysis of vectors of Q-waves and T-waves can be useful to some degree (*34*). Demonstration of necrotic myocardium by a specific agent would be especially beneficial for the diagnosis of myocardial necrosis in the presence of electrocardiographic pseudo-infarction pattern in patients with HCM. Radionuclide imaging with ^{111}In-antimyosin antibody or ^{99m}Tc-pyrophosphate is a practical approach to this problem because of their reasonable specificity and high sensitivity for detecting myocardial necrosis (*5,35,36*).

Antimyosin Antibody Imaging

The permeability of the plasma membrane of cardiomyocytes significantly increases when ischemic insults cause myocardial necrosis. This change in permeability allows influx of relatively large molecules as antimyosin antibody into necrotic cardiomyocytes. Antimyosin antibody, which is specific to the myosin heavy chain of cardiomyocytes, binds with residual intracellular myosin (*37*). Indium-111-antimyosin antibody thereby visualizes the areas of acute myocardial necrosis as regions of increased radioactivity (*36,38*). Both animal experiments and clinical experience in humans suggest that antimyosin scans reflect the extent of necrotic myocardium more accurately than ^{99m}Tc-pyrophosphate imaging (*36*). Allergic reactions have not been observed even after multiple injections (*37,39,40*). The antibody cross-reacts with skeletal muscle myosin, but accumulation in thoracic muscles does not appear to interfere with the diagnosis of acute myocardial infarction, even in patients with blunt chest trauma (*41*). Antimyosin antibody is able to reach the necrotic myocardium through residual blood flow and via diffusion in areas of inflammation (*42*).

The usefulness of the antimyosin scan has been well recognized in the diagnosis of myocarditis (*5,43*), cardiac transplant rejection (*44*) and idiopathic dilated cardiomyopathy (*45*) as well as acute myocardial infarction. The antimyosin scan also provides images of necrotic myocardium in patients with HCM as demonstrated in Figure 1. The pattern of uptake in Patient 1 is very similar to myocarditis, and there is no focal or regional uptake to suggest coronary occlusion. Right ventricular endomyocardial biopsy revealed borderline myocarditis. The degree of necrosis in the biopsy appears to be much milder than the degree of necrosis shown by the antimyosin scan. Therefore, Patient 1 (Fig. 1) is likely to have global "HCM related myocardial necrosis" and possibly complicated with myocarditis. Acute occlusion of the major coronary artery is virtually excluded by this scan. This approach to delineate necrotic cardiomyocytes seems to be especially useful when HCM evolves into dilated form after complication of myocardial infarction or HCM-related myocardial necrosis. Conventional methods often fail to disclose myocardial necrosis in patients with HCM complicated by dilated cardiomyopathy (*45–47*).

The half-life of antimyosin antibody in the blood circulation has two components: 0.8 hr for the fast component and 12 hr for the slow component (*42*). Normal subjects will show mild blood-pool activity at 24 hr (*39*), and by 48 hr, only negligible activity remains in the blood (*42*). The optimal interval for imaging is about 16–24 hr in patients with myocardial infarction, since intense uptake of antimyosin antibody is visible through the residual blood pool (*42*). When imaging patients with HCM in the dilated phase complicated by ischemic myocardial necrosis, 48-hr imaging is most appropriate (*47*). In these cases, SPECT can be helpful (*36*).

The pathophysiology of myocardial necrosis in patients with HCM is complex. Nakata et al. reported two cases of HCM with diffuse and intense antimyosin uptake despite normal left ventricular wall motion and thallium perfusion (*46*). These discrepant results suggest necrotic cardiomyocytes are interspersed and coexist with viable cells. Furthermore, the mismatch results between ^{201}Tl and antimyosin scans might suggest that these two patients were at risk for further ischemia (*48*).

The two patients presented here demonstrated heterogeneous uptake of thallium with multiple perfusion defects. The delayed images showed partial normalization in these areas. Areas of perfusion defect and antimyosin uptake did not match. In acute myocardial infarction due to occlusion of the coronary artery, the thallium perfusion defect should match an area of antimyosin uptake. A ^{99m}Tc-pyrophosphate scan also demonstrated rather widespread uptake and there was no clear matching in the abnormal regions in the second patient. As long as viable and functioning cardiomyocytes compensate for necrotic cardiomyocyte function, symptoms may not be overt until myocardial necrosis progresses gradually and insidiously to congestive heart failure (*45,47*). Subendocardial ischemia in the presence of marked cardiac dilatation might also contribute to myocardial necrosis in these patients in the dilated stage of HCM (*49*). Further investigation is necessary to define the prognostic value of the antimyosin scan (*47*), since intense and diffuse uptake of the antimyosin scan may or may not predict an unfavorable outcome in patients with HCM.

Technetium-99m-Pyrophosphate Imaging

Few investigators have reported on ^{99m}Tc-pyrophosphate myocardial imaging in patients with HCM complicated by myocardial necrosis. Sasidharan Nair et al. (*50*) reported on a 19-yr-old man who complained of crushing retrosternal chest pain soon after the initiation of strenuous exercise in a low temperature environment. Although the elevated levels of enzymes, including creatine kinase, were significant, the electrocardiogram recorded on admission was not conclusive for acute myocardial infarction. Myocardial scanning with ^{99m}Tc-pyrophosphate revealed local-

ized and intense uptake in the left ventricular lateral wall which was consistent with the region of T-wave inversion in the initial electrocardiogram. The coronary arteries were widely patent without angiographic evidence of stenosis.

Technetium-99m-pyrophosphate imaging of acute myocardial necrosis may be more convenient than antimyosin imaging, because imaging is possible within several hours after injection of the agent (*51*). In contrast to the antimyosin scan, however, the accumulation of ^{99m}Tc-pyrophosphate does not involve specific interaction with cardiac myosin. Rather, pyrophosphate reacts with intramitochondrial calcium deposited secondary to ischemia (*52*). There is evidence of technetium pyrophosphate accumulation in ischemic (non-necrotic) myocardium (*38*). Maximal uptake of this agent occurs at the periphery of the infarcted myocardial region where regional flow is 30%–40% of normal (*52,53*). Therefore, the central zone of infarction remains relatively "cold" compared to the "edge" of infarction. The high probability of ischemia and necrosis without atherosclerotic coronary artery disease in HCM make it likely that images in these patients will be abnormal.

Thallium-201 Perfusion Study

Perfusion abnormalities are commonly observed in patients with HCM (*23*). Neither a history of chest pain nor its provocation with treadmill exercise predicts an abnormal thallium scan in patients with HCM (*19*). However, the negative predictive value of a normal thallium scan may be high (*28*). The histopathology of perfusion abnormalities is not fully understood in patients with HCM. Nonetheless, extensive fibrosis seen on right ventricular endomyocardial biopsy specimens are frequently encountered in patients with HCM who show persistent perfusion defects on dipyridamole-thallium scans (*54*). In addition, perfusion abnormalities are associated with complications of ventricular tachycardia and/or conduction defects that require pacemakers in patients with HCM (*28*). These facts suggest that an abnormal thallium scan is a reflection of severe myocardial ischemia, fibrosis or scar in patients with HCM.

Patients with HCM demonstrating fixed perfusion defects have lower left ventricular ejection fractions compared to patients with completely reversible perfusion abnormalities (*19,28,54*). Furthermore, pretreatment with oral dipyridamole for 2 wk improved the incidence and degree of the thallium perfusion abnormality as well as cardiac function in patients with nonobstructive hypertrophic cardiomyopathy (*55*). However, intravenous administration of dipyridamole should be carefully done in patients with HCM because it may cause severe preload reduction and induce chest pain in association with significant ST-segment depression (*21*).

In summary, thallium perfusion imaging cannot predict the presence of atherosclerotic coronary artery disease in patients with HCM. Negative results can, however, rule out the presence of disease. Thallium imaging results may explain the ischemic process which affects clinical manifestations and natural history (*19*).

REFERENCES

1. WHO/ISFC Task Force. Report of the WHO/ISFC task force on the definition and classification of cardiomyopathies. *Br Heart J* 1980;44:672–673.
2. Maron BJ, Epstein SE, Roberts WC. Hypertrophic cardiomyopathy and transmural myocardial infarction without significant atherosclerosis of the extramural coronary arteries. *Am J Cardiol* 1979;43:1086–1102.
3. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural ("small vessel") coronary artery in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1986;8:545–557.
4. Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis, a histologic definition and classification. *Am J Cardiovasc Pathol* 1986;1:3–14.
5. Narula J, Khaw BA, Dec Jr GW, et al. Brief report: recognition of acute myocarditis masquerading as acute myocardial infarction. *N Engl J Med* 1993;328:100–104.
6. Hecht GM, Panza JA, Maron BJ. Clinical course of middle-aged asymptomatic patients with hypertrophic cardiomyopathy. *Am J Cardiol* 1992;69: 935–940.
7. Braunwald E, Lambrew CT, Rockoff SD, Ross JJ, Morrow AG. Idiopathic hypertrophic subaortic stenosis: I. A description of the disease based upon an analysis of 64 patients. *Circulation* 1964;29–30(suppl IV):IV-3–IV-119.
8. Walston II A, Behar VS. Spectrum of coronary artery disease in idiopathic subaortic stenosis. *Am J Cardiol* 1976;38:12–16.
9. Beder SD, Gutgesell HP, Mullins CE, McNamara DG. Progression from hypertrophic obstructive cardiomyopathy to congestive cardiomyopathy in child. *Am Heart J* 1982;104:155–157.
10. Newman H, Sugrue D, Oakley CM, Goodwin JF, McKenna WJ. Relation of left ventricular function and prognosis in hypertrophic cardiomyopathy: an angiographic study. *J Am Coll Cardiol* 1985;5:1064–1074.
11. ten Cate F, Roelandt J. Progression to left ventricular dilatation in patients with hypertrophic obstructive cardiomyopathy. *Am Heart J* 1979;97:762–765.
12. Nagata S, Park Y-D, Minamikawa T, et al. Thallium perfusion and cardiac enzyme abnormalities in patients with familial hypertrophic cardiomyopathy. *Am Heart J* 1985;109:1317–1322.
13. Hamada M, Shigematsu Y, Fujiwara Y, Sumimoto T, Hiwada K, Kokubu T. Persistent elevation of cardiac enzymes in a patient with hypertrophic cardiomyopathy: with special reference to electrocardiographic, echocardiographic, and ^{201}Tl myocardial scintigraphic findings. *Jpn Circ J* 1990;54: 354–360.
14. Adelman A, Wigle E, Ranganathan N, et al. The clinical course in muscular subaortic stenosis: a retrospective and prospective study of 60 hemodynamically proved cases. *Ann Intern Med* 1972;77:515–525.
15. Fighali S, Krajcer Z, Edelman S, Leachman RD. Progression of hypertrophic cardiomyopathy into a hypokinetic left ventricle: higher incidence in patients with midventricular obstruction. *J Am Coll Cardiol* 1987;9:288–294.
16. Lazzeroni E, Rolli A, Aurier E, Botti G. Clinical significance of coronary artery disease in hypertrophic cardiomyopathy. *Am J Cardiol* 1992;70:499–501.
17. Cokkinos DV, Krajcer Z, Leachman RD. Coronary artery disease in hypertrophic cardiomyopathy. *Am J Cardiol* 1985;55:1437–1438.
18. Lardani H, Serrano JA, Villamil RJ. Hemodynamics and coronary angiography in idiopathic hypertrophic subaortic stenosis. *Am J Cardiol* 1978;41: 476–481.
19. O'Gara PT, Bonow RO, Maron BJ, et al. Myocardial perfusion abnormalities in patients with hypertrophic cardiomyopathy: assessment with thallium-201 emission computed tomography. *Circulation* 1987;76:1214–1223.
20. Waller BF, Maron BJ, Epstein SE, Roberts WC. Transmural myocardial infarction in hypertrophic cardiomyopathy. *Chest* 1981;79:461–465.
21. Camici P, Chiriatti G, Lorenzoni R, et al. Coronary vasodilatation is impaired both in hypertrophied and nonhypertrophied myocardium of patients with hypertrophic cardiomyopathy: a study with nitrogen-13 ammonia and positron emission tomography. *J Am Coll Cardiol* 1991;17:879–886.
22. Cannon ROI, Rosing DR, Maron BJ, et al. Myocardial ischemia in patients with hypertrophic cardiomyopathy: contribution of inadequate vasodilator reserve and elevated left ventricular filling pressure. *Circulation* 1985;71: 234–243.
23. Pasternac A, Noble J, Streulens Y, Elie R, Henschke C, Bourassa M. Pathophysiology of chest pain in patients with cardiomyopathies and normal coronary arteries. *Circulation* 1982;65:778–789.
24. Pichard AD, Meller J, Teichholz LE, Lipnik S, Gorlin R, Herman MV. Septal perforator compression in idiopathic hypertrophic subaortic stenosis. *Am J Cardiol* 1977;40:310–314.
25. Kitazume H, Kramer JR, Krauthamer D, Tobgi SE, Proudfit WL, Sones

FM. Myocardial bridges in obstructive hypertrophic cardiomyopathy. *Am Heart J* 1983;106:131–135.
26. Mautner RK, Thomas I, Dhurandhar R, Phillips JH. Hypertrophic obstructive cardiomyopathy and coronary artery spasm. *Chest* 1979;76:636–639.
27. Arnett E, Roberts WC. Acute myocardial infarction and angiographically normal coronary arteries: an unproven combination. *Circulation* 1976;53: 395–400.
28. von Dohlen TW, Prisant LM, Frank MJ. Significance of positive or negative thallium-201 scintigraphy in hypertrophic cardiomyopathy. *Am J Cardiol* 1989;64:498–503.
29. Gill CC, Duda AM, Kitazume H, Kramer JR, Loop FD. Idiopathic hypertrophic subaortic stenosis and coronary atherosclerosis: results of coronary artery bypass and myectomy combined with coronary artery bypass. *J Thorac Cardiovasc Surg* 1982;84:856–860.
30. Cheng DC, Chung F, Burns RJ, Houston PL, Feindel C. Postoperative myocardial infarction documented by technetium-pyrophosphate scans using single-photon emission computed tomography: significance of intraoperative myocardial ischemia and hemodynamic control. *Anesthesiology* 1989;71:818–826.
31. Fine DG, Clements IP, Callahan MJ. Myocardial stunning in hypertrophic cardiomyopathy: recovery predicted by single photon emission computed tomographic thallium-201 scintigraphy. *J Am Coll Cardiol* 1989;13:1415–1418.
32. Henry WL, Clark CE, Epstein SE. Asymmetric septal hypertrophy (ASH): the unifying link in the IHSS disease spectrum. *Circulation* 1973;47:827–832.
33. Alfonso F, Balaguer J, Grande A, Palomo J, Macaya C, Zarco P. Sudden appearance of giant negative T-waves in patients with hypertrophic cardiomyopathy. *Am Heart J* 1992;123:1392–1394.
34. Goldberger AL. Q-wave, T-wave vector discordance in hypertrophic cardiomyopathy: septal hypertrophy and strain pattern. *Br Heart J* 1979;42: 201–204.
35. Kumar S. Persistent ST-segment elevation in hypertrophic subaortic stenosis. *Arch Intern Med* 1982;142:1957–1958.
36. Khaw BA, Gold HK, Yasuda T, et al. Scintigraphic quantification of myocardial necrosis in patients after intravenous injection of myosin-specific antibody. *Circulation* 1986;74:501–508.
37. Khaw BA, Beller GA, Haber E, Smith T. Localization of cardiac myosin-specific antibody in myocardial infarction. *J Clin Invest* 1976;58:439–446.
38. Johnson LL, Lerrick KS, Coromilas J, et al. Measurement of infarct size and percentage of myocardium infarcted in a dog preparation with single photon-emission computed tomography, thallium-201 and indium 111-monoclonal antimyosin Fab. *Circulation* 1987;76:181–190.
39. Carrió I, Bernà L, Ballester M, et al. Indium-111-antimyosin scintigraphy to assess myocardial damage in patients with suspected myocarditis and cardiac rejection. *J Nucl Med* 1988;29:1893–1900.
40. Dec GW, Palacios I, Yasuda T, et al. Antimyosin antibody cardiac imaging: its role in the diagnosis of myocarditis. *J Am Coll Cardiol* 1990;16:97–104.
41. Hendel RC, Cohn S, Aurigemma G, et al. Focal myocardial injury following blunt chest trauma: a comparison of indium-111 antimyosin scintigraphy with other noninvasive methods. *Am Heart J* 1992;123:1208–1215.
42. Khaw BA, Yasuda T, Gold HK, et al. Acute myocardial infarct imaging with indium-111-labeled monoclonal antimyosin Fab. *J Nucl Med* 1987;28: 1671–1678.
43. Yasuda T, Palacios IF, Dec GW, et al. Indium 111-monoclonal antimyosin antibody imaging in the diagnosis of acute myocarditis. *Circulation* 1987; 76:306–311.
44. Frist W, Yasuda T, Segall G, et al. Noninvasive detection of human cardiac transplant rejection with indium-111 antimyosin (Fab) imaging. *Circulation* 1987;76(suppl V):V81–V85.
45. Obrador D, Ballester M, Carrió I, Bernà L, Pons-Lladó G. High prevalence of myocardial monoclonal antimyosin antibody uptake in patients with chronic idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1989;13: 1289–1293.
46. Nakata T, Gotoh M, Yanekura S, et al. Myocardial accumulation of monoclonal antimyosin Fab in hypertrophic cardiomyopathy and postpartum cardiomyopathy. *J Nucl Med* 1991;32:2291–2284.
47. Nishimura T, Nagata S, Uehara T, Hayashida K, Mitani I, Kumita S-I. Assessment of myocardial damage in dilated-phase hypertrophic cardiomyopathy by using indium-111-antimyosin Fab myocardial scintigraphy. *J Nucl Med* 1991;32:1333–1337.
48. Johnson LL, Seldin DW, Keller AM, et al. Dual isotope thallium and indium antimyosin SPECT imaging to identify acute infarct patients at further ischemic risk. *Circulation* 1990;81:37–45.
49. Unverferth DV, Magorien RD, Lewis R, Leier CV. The role of subendocardial ischemia in perpetuating myocardial failure in patients with nonischemic congestive cardiomyopathy. *Am Heart J* 1983;105:176–179.
50. Sasidharan Nair M, Duvernoy WF, Zobl EG. Acute myocardial infarction in idiopathic hypertrophic subaortic stenosis. *JAMA* 1980;243:1552–1555.
51. Krause T, Kasper W, Zeiher A, Schuemichen C, Moser E. Relation of technetium-99m pyrophosphate accumulation to time interval after onset of acute myocardial infarction as assessed by a tomographic acquisition technique. *Am J Cardiol* 1991;68:1575–1579.
52. Buja LM, Parkey RW, Dees JH, et al. Morphologic correlates of technetium-99m stannous pyrophosphate imaging of acute myocardial infarcts in dogs. *Circulation* 1975;52:596–607.
53. Zaret BL, DiCola VC, Donabedian RK, et al. Dual radionuclide study of myocardial infarction: relationship between myocardial uptake of potassium-43, technetium-99m stannous pyrophosphate, regional myocardial blood flow and creatine phospholinase depletion. *Circulation* 1976;53:422–428.
54. Mori T, Yamabe H, Yokota Y, Fukuzaki H. Clinical significance of dipyridamole Tl-201 emission computed tomography perfusion abnormality for evaluating pathophysiological and pathological aspects in hypertrophic cardiomyopathy. *Jpn Circ J* 1988;52:111–118.
55. Koga Y, Kihara K, Yamaguchi R, Wada T, Toshima H. Therapeutic effect of oral dipyridamole on myocardial perfusion and cardiac performance in patients with hypertrophic cardiomyopathy. *Am Heart J* 1992;123:433–438.
56. Marshall RC, Tillisch JH, Phelps ME, et al. Identification and differentiation of resting myocardial ischemia and infarction in man with positron computed tomography, ^{18}F-labeled fluorodeoxyglucose and N-13 ammonia. *Circulation* 1983;67:766–778.