Myocardial Perfusion Scintigraphy in Patients with Mitral Valve Prolapse

Its Advantage over Stress Electrocardiography in Diagnosing Associated Coronary Artery Disease and Its Implications for the Etiology of Chest Pain

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SUMMARY Patients with mitral valve prolapse (MVP) frequently experience chest pain which may, especially in older subjects and males, be difficult to differentiate from angina pectoris. Electrocardiographic (ECG) changes, ventricular arrhythmias, metabolic abnormalities and rare reports of myocardial infarction and sudden death further suggest the presence of an ischemic process in these patients. The recognition of accompanying coronary artery disease (CAD) and exclusion of other causes of ischemia, therefore, may be important in determining the prognosis and appropriate therapy for such patients.

CHEST PAIN is a prominent symptom and may be a difficult management problem in patients with the mitral valve prolapse or click-murmur syndrome.1-3 However, the etiology of this pain remains obscure. Although the nature of the pain is commonly not typical of angina pectoris, patients frequently manifest resting1-7 and exercise-induced8-14 electrocardiographic changes, as well as metabolic abnormalities characteristic of cardiac ischemia.15-17 A number of possible mechanisms for the production of ischemia have been advanced, but none has been widely accepted, and whether or not ischemia is actually present remains controversial. The occasional, possibly etiologic, association between coronary artery disease and mitral valve prolapse further complicates the assessment of chest pain in this group.5, 6, 18-20 Life-threatening arrhythmias,14, 15 myocardial infarction18, 24 and sudden death14 have all been reported in patients with mitral valve prolapse as well as those with coronary artery disease. Since the prognosis and therapy of the click-murmur syndrome are quite different from those of coronary artery disease, the recognition and differentiation of these two entities is critical.

Myocardial perfusion scintigraphy during exercise stress, employing a variety of radionuclides, has recently been demonstrated to be a reliable technique for detecting regions of segmental ischemia secondary to coronary artery disease.25-29 However, there is little published experience with perfusion imaging in patients with chest pain syndromes associated with angiographically normal coronary arteries.30 The present study was undertaken first, to determine the reliability of perfusion imaging in the diagnosis and especially the exclusion of concomitant coronary artery disease in a group of patients with mitral valve prolapse; and second, to investigate the possibility that some of these patients, despite having normal large coronary arteries, might demonstrate segmental perfusion deficits, thereby suggesting ischemia as an etiologic factor for their symptoms.

Patients and Methods

Study Population

The study population consisted of 25 patients with confirmed mitral valve prolapse who were evaluated for chest pain. The possibility of underlying or accompanying coronary artery disease was the reason for referral and subsequent studies in each case. As a result, this group was older (mean age 52, range 25-69) and contained a higher proportion of males (13 of 25) than other reported series of patients with the click-murmur syndrome. In seven patients, chest pain was typical of angina pectoris. In 14 others, the characteristic pain pattern, its distribution, relation to stress, or relief by rest or nitrates were suggestive of angina pectoris. In the remaining four patients, pain was atypical of cardiac ischemia. Nine patients had been previously hospitalized for possible myocardial infarction, but in only two had an infarction been confirmed. Nineteen were receiving medical therapy for angina pectoris.

Each patient had signs of mitral valve prolapse on physical examination: 21 had nonejection mid-systolic clicks, 20 had apical systolic murmurs which were mid or late-systolic in 17 and holosystolic in three, and 16 manifested both findings. In each patient the diagnosis of mitral valve...
prolapse was confirmed by echocardiography (19 patients),
left ventricular cineangiography (23 patients) or both (17
patients).

Relevant clinical information and the results of the confir-
matory diagnostic tests are listed in Table 1.

Echocardiogram

Echocardiograms were performed using commercially
available equipment and standard techniques. The echocar-
diograms were interpreted as positive for prolapse if the
mitral valve demonstrated more than 2 mm holosystolic or
late-systolic motion posterior to a line connecting the C and
D points of its cycle.

Ventriculograms and Coronary Arteriograms

Left ventricular angiograms were performed using biaxial
cinefluorographic technique in the 30° right anterior oblique
and 60° left anterior oblique projections. Mitral valve
prolapse was diagnosed according to previously published
criteria.4

Selective coronary arteriograms were obtained by the
Judkins technique and were interpreted by two independent
observers. Significant large vessel coronary artery disease
was diagnosed if a stenosis greater than 70% of the luminal
cross-sectional area was present in one or more of the major
vessels or their visualized major branches. Anatomical
variations, in particular absence of a vessel in the atrioven-
tricular groove, were noted. Functional abnormalities, such
as myocardial bridges or coronary artery spasm, were
sought. Ten patients without stenotic lesions had arteriograms repeated after the administration of
ergonovine, 0.4 mg intravenously, in an attempt to produce
spasm.

Treadmill Exercise Tests

Patients were tested in the fasting state after they had
given informed consent. The standard 12-lead electro-
cardiogram and 1-minute rhythm strip were taken prior to
exercise. A CM, bipolar precordial lead was monitored at
rest, while standing, during and following hyperventilation
and during graded treadmill exercise, which was performed
according to the Bruce protocol.31 Exercise was terminated
only by the appearance of disabling cardiopulmonary symp-
toms or by limiting fatigue. Patients were considered to have
electrocardiographic evidence of ischemia if there was
horizontal or downsloping ST-segment depression of 1 mm
or more over baseline, .03 sec from the J point, occurring at
peak stress or during recovery.

Relative Myocardial Perfusion Scintigraphy

Relative myocardial perfusion scintigraphy was per-
formed in association with stress testing. As the exercise end
point approached, 2 mCi of isotopic tracer (rubidium-81 in
the initial three patients, thallium-201 in all subsequent pa-
tients) were injected through an indwelling intravenous infu-
sion line, and exercise was continued for 30–45 seconds.
Scintigraphy was completed within 30 minutes of injection.
Rubidium-81 scintigraphy was performed according to the
methodology published previously.32 Thallium-201 scinti-
tigraphy was performed with a Searle Pho-Gamma IV scin-
tillation camera, using a converging collimator and a 20% window centered at 75 keV. Images were obtained in the

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**Group II: Coronary Artery Disease**

| 20/68/F          | Suggestive, R/O MI    | None    | MSC, SM               | Prolapse       | Prolapse       |
| 21/54/M          | Typical               | Propranolol, TNG | SM        | Inadequate   | Prolapse       |
| 22/56/F          | Typical, previous MI  | Propranolol | MSC, SM             | Prolapse       | Prolapse       |
| 23/56/M          | Typical               | Propranolol, TNG | MSC, SM       | Prolapse       | Prolapse       |
| 24/46/M          | Suggestive, previous MI | TNG        | MSC, SM               | Negative       | Prolapse       |
| 25/60/M          | Suggestive            | Propranolol | MSC, SM             | Prolapse       | Prolapse       |

Abbreviations: MSC = mid-systolic click; SM = systolic murmur; R/O MI = hospitalization for possible myocardial infarction; TNG = Nitroglycerin.
anterior, 45° left anterior oblique and left lateral projections, and were taken to 200,000 counts in the anterior view and equal time in the remaining views. Patients with abnormal scintigrams returned one week later for perfusion scintigraphy at rest to differentiate stress-induced ischemia from prior myocardial infarction. Scintigrams were interpreted by two independent observers, who were unaware of the patients' clinical presentation or arteriographic findings, and agreement was reached by consensus between them. Scintigrams were considered abnormal if absent or relatively decreased perfusion of a region was present in two projections. Apical “slit-like” defects were classified as abnormal only if they appeared at rest. Relatively decreased perfusion of the inferior wall in the left lateral view was not considered abnormal unless it was confirmed in another projection. For the present study scintigrams showing perfusion abnormalities during exercise were considered positive for coronary artery disease. Only those patients with normalization or improvement of these abnormalities in subsequent rest scintigrams were considered to have scintigraphic evidence of stress-induced ischemia.

Results

Coronary Arteriograms

Coronary arteriographic findings, together with the results of the electrocardiograms, exercise tests and perfusion scintigrams for each patient are listed in table 2. Nineteen patients (numbers 1–19) were free of significant coronary artery stenotic lesions. No suggestion of spasm was present either on the initial injections or after ergonovine in the 10 patients to whom it was administered. The right coronary artery was anatomically dominant in 21, and the left coronary artery in four. A vessel was present in the A-V groove in all but one patient, as a branch of the left circumflex coronary artery in 20 and as a continuation of a dominant right coronary artery in four. These 19 patients with mitral valve prolapse, but without large vessel coronary

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*chest pain during exercise or recovery.
†Coronary arteriograms also normal after ergonovine.
Abbreviations: AF = atrial fibrillation; Ant = anterior wall; Circ = left circumflex coronary artery; RCA = right coronary artery; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; Sept = septum; RCA = left anterior descending coronary artery; LAHB = left anterior hemiblock; LBBB = left bundle branch block; Inf = inferior.
artery disease, are classified as group I.

The remaining six patients (numbers 20–25) had significant stenotic lesions of one or more coronary arteries and have been designated as group II.

**Electrocardiograms**

Resting electrocardiograms manifested ST and T wave abnormalities consistent with left ventricular ischemia in nine of 19 group I patients and two of six group II patients. Other electrocardiographic abnormalities included left ventricular hypertrophy, left anterior hemiblock, first degree atrioventricular block, atrial fibrillation and frequent ventricular ectopic beats. One subject in group II had an electrocardiogram diagnostic of previous transmural myocardial infarction. Normal electrocardiograms were present in only six group I patients and two group II patients.

**Exercise Tests**

Ten of the group I patients had positive exercise electrocardiograms and four of these developed more than a 2 mm depression of the ST segment over baseline. Four of the 10 with positive tests, as well as two of the nine with negative tests, had 1 mm or greater baseline ST-segment depression. Stress testing was negative in only nine of the patients with normal coronary arteries, one of whom had a positive test one month earlier. Pain occurred during exercise in nine group I patients, five of those with positive tests and four with negative tests. Frequent, coupled or multifocal ventricular premature beats appeared during exercise in nine group I subjects.

Among the patients with significant coronary obstructions, stress electrocardiograms were positive in three and negative in three. Three patients, two of whom had positive tests, experienced chest pain during exercise. Ventricular premature beats occurred during testing in two patients.

**Relative Myocardial Perfusion Scintigrams**

All 19 patients with normal coronary arteriograms had normal stress perfusion scintigrams. Figures 1 to 3 display the resting electrocardiogram, echocardiogram, stress test and scintigrams from patient 1, a 55-year-old man with a recent history of increasing stress-related chest pain, who had recently been hospitalized for a prolonged episode of chest pain thought to represent a myocardial infarction. Physical examination suggested, and echocardiography confirmed, the diagnosis of mitral valve prolapse. The resting electrocardiogram manifested inferolateral ST-segment depres-

**FIGURE 1.** *Resting electrocardiogram from patient 1 demonstrating inferolateral ST-segment depression and T wave inversion suggestive of ischemia. This patient presented with a three-month history of progressive precordial pain, occurring both with exercise and at rest. During a recent admission for possible acute myocardial infarction, serial electrocardiograms had manifested new, subsequently persistent T wave inversions, but there was no enzymatic confirmation of necrosis.*

**FIGURE 2.** *Echocardiogram from the same patient, demonstrating mid and late-systolic mitral valve prolapse (indicated by arrow) and thereby confirming the diagnosis of click-murmur syndrome which had been previously made by auscultation. ALMV = anterior leaflet of the mitral valve; ECG = electrocardiogram; Sept = interventricular septum.*
sion and T wave inversion, suggestive of ischemia, and the treadmill stress test was strongly positive. However, stress scintigraphy and coronary arteriography were both normal.

The six group II patients each had one or more segmental perfusion defects during exercise in the distribution of involved coronary arteries. Patients 20 to 23 had complete resolution of their stress-induced scintigraphic abnormalities on follow-up rest scintigrams, indicating the presence of stress-induced ischemia. Figure 4 illustrates the studies from patient 24, a 46-year-old man with a mid-systolic click and late-systolic murmur, ventriculographic evidence of mitral valve prolapse and severe two-vessel disease involving the right and left anterior descending coronary arteries. This patient had noted the recent onset of chest pain at rest, but not with stress. He had previously suffered an anterior myocardial infarction, documented by the appearance of significant new Q waves. Despite a high level of exercise, this patient had a negative stress electrocardiogram. The stress perfusion scintigrams demonstrated markedly decreased perfusion of the interventricular septum in the left anterior oblique projection, and decreased perfusion of the anterior wall, apex and adjacent inferior wall in the anterior and left lateral views. The comparison rest scintigram showed persistent abnormalities, but demonstrated a definite improvement in the perfusion of the interventricular septum and the anterior and inferior walls, indicating the presence of stress-induced ischemia as well as prior myocardial infarction, and suggesting an ischemic etiology for his chest pain. In contrast, patient 25 had an inferior wall perfusion deficit at exercise, which was unchanged at rest, suggesting prior myocardial infarction without evidence of ischemia. This patient had no historical or electrocardiographic evidence of an old infarction, but the left ventricular angiogram demonstrated a corresponding area of akinesia and the right coronary artery was totally occluded. In this patient perfusion scintigraphy indicated the presence of coronary disease, but did not clarify the etiology of the patient’s chest pain, since ischemia was not demonstrated.

Discussion

Mitral Valve Prolapse and Coronary Artery Disease

Chest pain has been noted to be a common complaint in patients with a click murmur syndrome since the recognition and characterization of this entity.1-3 This pain is frequently troublesome to the patient and may be worrisome to the physician. The character of the pain is usually not typical of angina pectoris. It is frequently sharp, without typical radiation and may be fleeting in duration or last many hours. It is commonly not exercise-related and is not usually responsive to nitrates. However, some patients may have pain which is indistinguishable from angina pectoris.

![Figure 3](image_url)  
**Figure 3.** Stress electrocardiogram and thallium-201 myocardial perfusion scintigrams from the same patient. The exercise test was positive for ischemia, with the baseline 0.5 mm ST segment progressively deepening to 2.5 to 3.0 mm horizontal depression during peak stress. The perfusion scintigrams demonstrated the normal pattern of homogeneous isotope uptake throughout the left ventricular myocardium. Subsequently performed coronary arteriograms were normal. Ant = anterior; LAO = left anterior oblique; LLAT = left lateral.

![Figure 4](image_url)  
**Figure 4.** Electrocardiograms and scintigrams from patient 24, who had previously suffered an anteroseptal myocardial infarction and had recently noted the recurrence of chest pain. The auscultatory findings of mid-systolic click and a late systolic murmur together with the somewhat atypical nature of his pain cast doubt on the ischemic origin of his symptoms. Despite the appearance of chest pain during exercise, the stress electrocardiogram was negative. However, the perfusion scintigrams clearly demonstrated the presence of both prior anteroseptal infarction and stress-induced ischemia of the anterior and inferior walls and the interventricular septum, implicating ischemia as the origin of his symptoms.
The possibility that concomitant coronary artery disease may be responsible for the chest pain in some of these patients is reinforced by the occurrence in approximately one-third of ST-T wave abnormalities, most frequently in the inferolateral leads, which are indistinguishable from those produced by ischemia. Also consistent with ischemia is the high incidence of ventricular arrhythmias, both at rest and with exercise. Indeed, a causative relationship between coronary artery disease and mitral valve prolapse has been suggested by several authors, but remains controversial. Crawford recently clearly documented one case in which the physical and angiographic findings of mitral valve prolapse first occurred after a myocardial infarction. Obviously, when patients are older and when they are males, the risk of coronary disease and thus the likelihood of such association increases.

Our patients each presented a difficult diagnostic problem and were therefore referred for cardiac catheterization and coronary arteriography. Only one of our subjects was a young woman in whom chest pain, even if suggestive of ischemia, could be ascribed to the click-murmur syndrome alone with some confidence. Most also manifested the previously described electrocardiographic abnormalities.

Exercise Testing in Patients With Mitral Valve Prolapse

There is little published information about the reliability of exercise testing in patients with click-murmur syndrome. Several reports have documented the high incidence of exercise-induced arrhythmias in these patients, while abnormal ST-segment depression has only occasionally been noted. In the present study, we found exercise testing was not helpful and frequently misleading; 53% (10 of 19) of patients with normal coronary arteriograms had positive stress tests, and four of these manifested greater than 2 mm ST-segment depression. Indeed, in eight of these patients the positive stress test influenced the decision to perform cardiac catheterization. Only one patient with a false positive exercise test was receiving digitalis, and none had left ventricular hypertrophy. Four of these patients, however, did have resting ST-segment deviation, which has also been associated with an increased incidence of false positive tests. This is a selected group of patients — those in whom catheterization was felt to be necessary to exclude coronary disease — and therefore we cannot comment on the prevalence of false positive exercise tests in the general population of patients with mitral valve prolapse. However, our experience and that of others suggests that this is not a rare problem, at least in those with chest pain. The presence or absence of pain during exercise testing was also not helpful, since nine of 19 group I, but only three of six group II, patients experienced pain. Stress testing also proved to be insensitive in detecting coronary disease in this small group, with only three of six patients manifesting ST-segment changes. Because of this lack of sensitivity and the low degree of specificity resulting from the large number of false positive tests, stress testing had only a 48% overall accuracy in this group.

Relative Myocardial Perfusion Scintigraphy

Relative myocardial perfusion scintigraphy is a new non-invasive technique for diagnosing and excluding coronary artery disease. Currently, thallium-201 is the isotope best suited for this application. Defects present during exercise, which are not present at rest, correspond to areas of exercise-induced ischemia. Defects present at rest in asymptomatic patients generally correspond to areas of infarcted myocardium. Recent reports have documented the sensitivity and specificity of this technique, and have noted its particular utility in identifying false positive stress tests and clarifying the interpretation of tests performed in the presence of baseline abnormalities.

Our results confirm the utility of performing myocardial perfusion scintigraphy in this setting. All patients with normal coronary arteriograms had normal exercise scintigrams, indicating that the radionuclide technique is highly specific for the diagnosis of coronary artery disease in these subjects. In addition, each of the six patients with coronary artery disease had segmental perfusion deficits in the distribution of one or more involved arteries, giving the stress scintigram a 100% accuracy in the diagnosis of coronary artery disease in this small patient group, a significant improvement over the stress electrocardiogram (P < 0.001). The smaller number of group II patients, however, does not allow us to assess the sensitivity of scintigraphy itself or in comparison to stress electrocardiography, but our prior studies correlating stress perfusion scintigrams and coronary arteriograms in larger groups of patients being investigated for coronary artery disease have revealed an 80-90% sensitivity and, therefore, an occasional false negative test in these patients is to be expected.

Although in our group of patients positive scintigrams were present in those with accompanying coronary artery disease, these scintigraphic abnormalities do not necessarily confirm that ischemia is responsible for the patients’ chest pain. In those patients in whom exercise-induced defects resolve or improve at rest (such as patients 20 to 24), coronary disease is probably responsible for at least part of their symptoms. In subjects with persistent, unchanged abnormalities at rest (such as patient 25), suggesting prior myocardial infarction without associated ischemia, the etiology of the present pain remains unsettled. More significant, however, is our finding that a negative exercise perfusion scintigram makes the presence of significant coronary artery disease unlikely and may, therefore, obviate the need for invasive studies in some of these patients.

Our findings are similar to those recently reported in preliminary form by Gaffney et al. who also performed stress scintigrams in patients with mitral valve prolapse. Although their series was smaller, consisted primarily of young women, and included only four patients with coronary arteriograms and only one with associated coronary artery disease, they also found scintigraphy to be more accurate than stress electrocardiography in diagnosing large vessel ischemia.

Significance of Negative Scintigrams in the Absence of Coronary Artery Disease

The etiology of chest pain in patients with the click-murmur syndrome without accompanying coronary artery disease is uncertain. Several findings suggest myocardial ischemia. The high incidence of resting and exercise-induced electrocardiographic abnormalities has been dis-
discussed previously. In addition, several preliminary studies have documented abnormal lactate extraction during pacing in patients with the click-murmur syndrome.24-26 If confirmed, this would constitute strong evidence for myocardial hypoxia. Especially troublesome, and also suggestive of ischemia, are the documented occurrence of both sudden death2-4 and acute myocardial infarction26, 24 in the presence of arteriographically normal coronary arteries in patients with mitral valve prolapse.

Several possible explanations for these findings have been put forth and it is worthwhile to consider these in light of the normal relative myocardial perfusion demonstrated in these patients. Barlow and Pocock have hypothesized that the abnormal movement of the mitral valve anulus or the valve leaflets may result in compression of the left circumflex coronary artery, thereby producing posterior-inferior myocardial ischemia.1, 6 Gentzler et al. found that the atrioventricular branch of the left circumflex coronary artery was congenitally absent in a high proportion of patients with mitral valve prolapse,26 but Glassman7 failed to confirm these arteriographic findings, as did we in the present study. Coronary artery spasm has also been postulated in patients with click-murmur syndrome,24 but was not seen here, although it was actively sought in 10 patients. The normal radionuclide studies are against these explanations, since compression, absence or spasm of a portion of the circumflex system producing such ischemia during exercise should have resulted in an area of decreased perfusion. Small regions of ischemia, however, could conceivably go undetected due to limited image resolution.

A number of angiographic studies in patients with the click-murmur syndrome have noted segmental asynergy of the left ventricle of the type most typically seen in coronary artery disease.10, 11, 38-40 Different authors have thought this to be both the cause and the result of the malfunction of the mitral valve apparatus. The segmental nature of these abnormalities raises the possibility of a vascular etiology, but, again, the normal perfusion scintigrams are against underlying ischemia or a secondary scar.

The radionuclide perfusion studies do not by any means exclude myocardial ischemia or hypoxia in patients with mitral valve prolapse. Tissue hypoxia could occur on a nonvascular basis and, therefore, be unrelated to perfusion. It is also possible that at the time of exercise stress the usual mechanisms for the production of ischemia were not operating, but it is noteworthy that nine of the subjects experienced pain during the test and 10 manifested ischemic electrocardiographic changes. More likely explanations are that the ischemia is generalized and not detectable by a method measuring relative myocardial perfusion, or that the ischemic area is smaller than the limits of resolution of present scintigraphic techniques. Indeed, a recent experimental study indicated that such small regions of decreased perfusion may not be appreciated as regions of decreased uptake on scintigrams.41

Barlow and Pocock and a number of other investigators have suggested that the increased tension transmitted to the papillary muscle from taut chordae tendineae attached to the mitral leaflets might produce focal papillary muscle ischemia, either by impairing blood supply or causing an imbalance between supply and demand.1, 2, 4, 6 LeWinter et al. were able to reproduce chest pain in eight of nine patients with mitral valve prolapse who had previously experienced it by phenylephrine infusion.42 They postulated that this agent, by increasing myocardial wall tension, produced localized ischemia at the base of the papillary muscles.

Such a focal area of ischemia would almost certainly be undetectable by perfusion scintigraphy. It is not clear, however, why ischemia of such a small volume of the myocardium should produce widespread electrocardiographic changes or metabolic abnormalities detectable in the coronary sinus. A more generalized process, either a small vessel angiopathy or a cardiomyopathy, might better explain these findings. A recent study demonstrating increased interstitial and endocardial fibrosis provides some evidence for the latter.17 Again, such a process would not be recognizable by relative myocardial perfusion scintigraphy.

In summary, relative myocardial perfusion scintigraphy during stress, in contrast to exercise electrocardiography, was helpful in defining the subgroup of patients with the click-murmur syndrome who also have significant large vessel coronary artery disease. The uniformly normal perfusion scintigrams in the remaining patients suggest that if myocardial ischemia is occurring during exercise stress, it is not present as a large segmental abnormality due to either anatomical or functional stenosis of the major coronary arteries. However, our findings do not exclude ischemia as the cause for symptoms and electrocardiographic abnormalities accompanying isolated mitral valve prolapse. An ischemic zone could either be very focal, such as a papillary muscle, and therefore be beyond the resolution of the technique, or it could be generalized, resulting from a scintigraphically undetectable homogeneous decrease in myocardial perfusion.

Acknowledgment

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