Gated Technetium-99m-Tetrofosmin SPECT and Cine MRI to Assess Left Ventricular Contraction

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This study investigates the value of ECG-gated ^{99m}Tc-tetrofosmin SPECT in the assessment of resting left ventricular (LV) function by comparison with cine MRI. **Methods:** Twenty-eight patients were recruited prospectively from those referred for routine myocardial perfusion scintigraphy. Eight had three-vessel coronary artery disease, two had two-vessel disease, five had single-vessel disease and thirteen had not previously undergone coronary angiography. Twelve patients had previous myocardial infarction. After i.v. injection at rest of 750 MBq ^{99m}Tc-tetrofosmin, ECG-gated tomograms (16 frames per cardiac cycle) were acquired after 30 min. A nine-segment model of the LV was used and images were interpreted by two observers independently. Wall motion was assessed using a six-point scale (including unclassified where no judgment was possible), and systolic wall thickening was assessed from count changes through the cycle using a five-point scale. Tracer uptake was scored using a four-point scale. Diastolic wall thickness was assessed using a four-point scale. Cine magnetic resonance images were acquired in the same planes and analyzed in an identical fashion. **Results:** There was good overall agreement between the techniques for wall motion, thickness and thickening (κ = 0.55–0.66), although 15 of the 252 (6%) segments were unclassified on radionuclide imaging. While there was absolute agreement in the assessment of all parameters in 10 patients with normal wall motion by MRI, agreement was less good in the 8 patients with three-vessel disease and poor left ventricular function (mean LVEF = 26%, mean LVEDV = 241 ml) (κ = 0.37–0.48). Where tracer uptake was normal, there was good agreement between imaging techniques (κ = 0.64–0.75), but where uptake was absent or nearly absent, agreement was poor (κ = 0–0.61), and 15 of 22 segments were unclassified on SPECT. **Conclusion:** Gated ^{99m}Tc-tetrofosmin imaging provides an accurate assessment of myocardial wall motion, thickening and thickness in normal left ventricles but is less valuable in poorly functioning ventricles. Six percent of segments could not be assessed because of inadequate tracer uptake.

Key Words: gated SPECT; technetium-99m-tetrofosmin; magnetic resonance imaging; left ventricular function

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Several techniques can assess either left ventricular function or myocardial perfusion, but few can do both simultaneously. Cross-sectional echocardiography (*1,2*), cine MRI (*3,4*) and electron beam computed x-ray tomography (*5*) are all powerful techniques for assessing myocardial motion, thickness and thickening, and they have all been used to assess perfusion. None, however, is more accurate than radionuclide scintigraphy (*6–8*) for detecting perfusion abnormalities.

Gated ^{99m}Tc-MIBI imaging has been used to measure perfusion and function simultaneously with both planar (*9–11*) and tomographic techniques (*12–15*). ECG-gating has also been used with planar ^{201}Tl imaging to improve interpretation of the perfusion pattern (*16*), but the physical properties of ^{201}Tl (*17*) make it unsuitable for gated tomographic imaging and, hence, for tomographic assessment of ventricular function. Gated ^{99m}Tc-MIBI studies have been validated by comparison with both echocardiography (*15,18*) and with cine MRI (*19*), but there has been no previous validation of gated ^{99m}Tc-tetrofosmin imaging.

Technetium-99m-tetrofosmin is a cationic diphosphine and it compares well with ^{201}Tl in the assessment of myocardial perfusion (*20,21*), and it has been used in evaluating left ventricular function by first-pass blood-pool imaging (*22*). The aim of this study was to validate the assessment of left ventricular myocardial motion, thickening and thickness using ECG-gated SPECT by comparison with cine MRI.

MATERIALS AND METHODS

Patients

Twenty-eight patients (20 men, 8 women; median age 58 yr; range 36–76 yr) referred for routine myocardial perfusion scintigraphy were selected for study prospectively. Eight patients had three-vessel coronary disease, two patients had two-vessel disease, five patients had single-vessel disease and 13 had not previously undergone coronary angiography. Twelve patients had a history of previous myocardial infarction, including all eight of those with three-vessel coronary disease. Coronary disease was defined by coronary angiography as stenosis of 50% diameter or more.

Technetium-99m-Tetrofosmin Imaging

All patients underwent both stress and rest ^{99m}Tc-tetrofosmin myocardial perfusion imaging on the same day, although for the purposes of this study only the resting images were analyzed. Stress was performed using an infusion of adenosine (140 μg/kg/min) for 6 min combined with submaximal exercise in 2-min stages from 25 W to 75 W. After 4 min, 250 MBq ^{99m}Tc-tetrofosmin were administered, and images were acquired 20 min later using a dual-headed gamma camera.

Four hours after stress imaging, 750 MBq ^{99m}Tc-tetrofosmin were injected at rest, and images were acquired 30 min later. Sixty-four projections of 50 sec each were acquired over an arc of 180° from the right anterior oblique to the left posterior oblique using ECG-gating, 16 frames per cycle and rejection of cycles outside 5% of the mean RR interval. Total acquisition time was 27 min. High-resolution collimators were used with a 20% window centrally placed around the 140-keV photopeak.

Tomographic reconstruction used a Hann prefilter with a cutoff frequency of 0.8 cycles/cm and a ramp filter during backprojection. The transaxial tomograms were reoriented into vertical and horizontal long-axis and short-axis tomograms, each with 16 frames per cycle. Mean processing time was 14.3 (s.d. 1.1) min.

MRI

Cine magnetic resonance images were acquired at rest, on the same day as the ^{99m}Tc-tetrofosmin studies using a 1.5 Tesla (Picker International Inc, HPQ) system. Images were acquired in the anatomical short-axis (basal and apical) and long-axis (vertical and horizontal) of the left ventricle, using an ECG-triggered gradient

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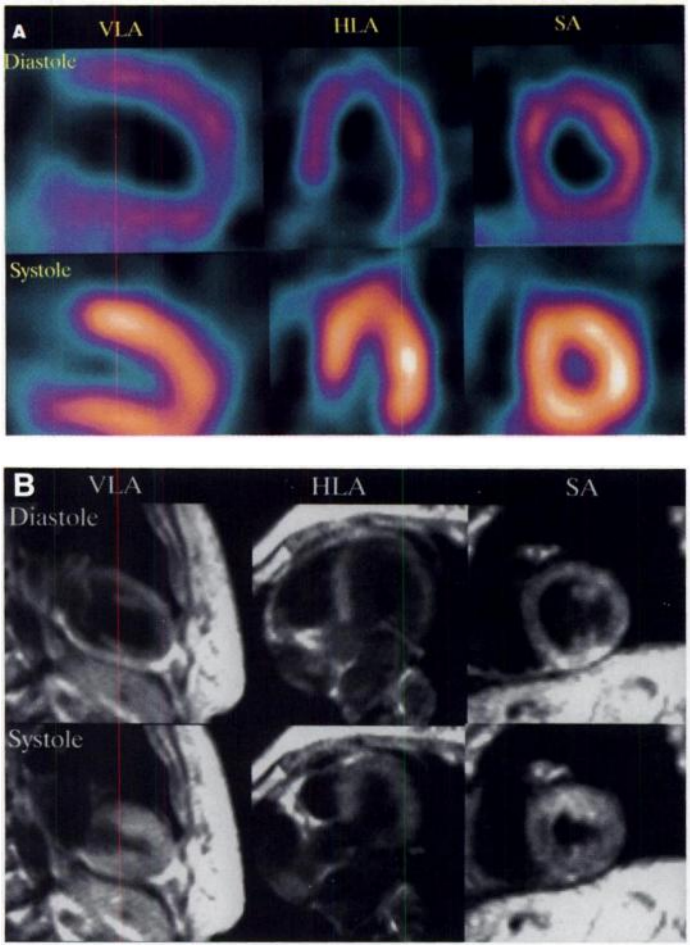

FIGURE 1. Gated ^{99m}Tc-tetrofosmin SPECT (A) and cine MRI (B) of left ventricle of a 69-yr-old woman presenting with a history of exertional chest pain. Perfusion and contractility were normal. VLA = vertical long-axis; HLA = horizontal long-axis; SA = short-axis.

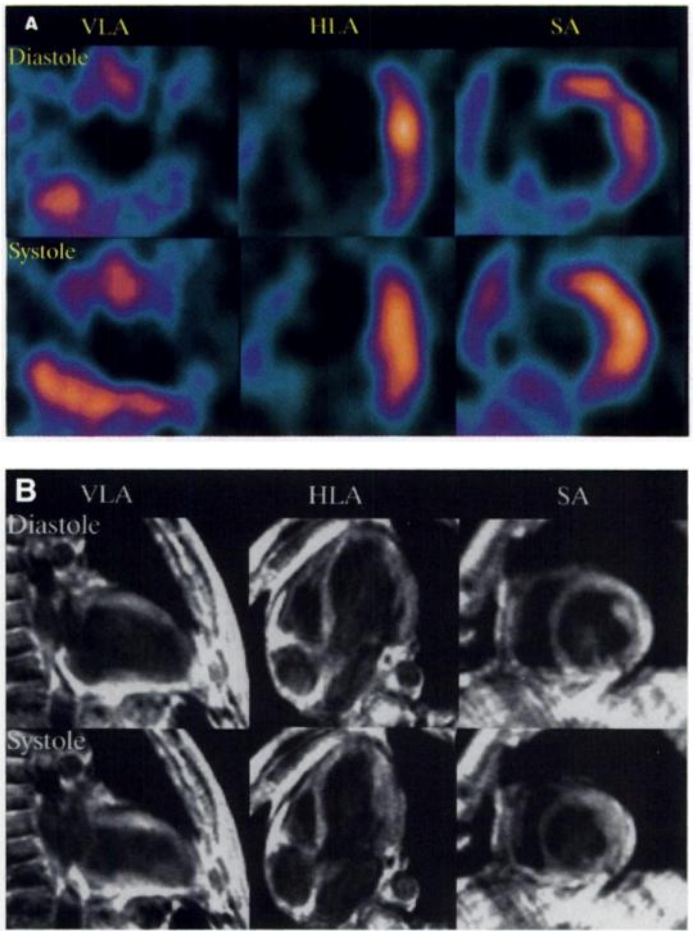

FIGURE 2. Gated ^{99m}Tc-tetrofosmin SPECT (A) and cine MRI (B) of the left ventricle of a 58-yr-old man with a history of myocardial infarction and heart failure and three-vessel coronary disease demonstrated on angiography.

echo sequence (TE 4.6 msec; flip angle 25°; 2 averages of 128 phase-encoding steps; slice thickness 10 mm; field of view 400 mm; 12 frames per cardiac cycle). A 5-mm presaturation band was placed on either side of the slice to depress signal from blood and to provide a "black-blood" cine.

Image Analysis

The images were analyzed independently and semiquantitatively by two observers without knowledge of the findings of the other imaging technique. The ventricle was divided into nine segments: the basal and apical parts of the septum, anterior, lateral and inferior walls, with the apex as the ninth segment. These segments were viewed using the central vertical and horizontal long-axis slices, together with a basal and an apical short-axis slice. For the magnetic resonance images, endocardial motion in each segment was scored using a six-point scale (normal, mildly hypokinetic, severely hypokinetic, akinetic, paradoxical and unclassified where no judgment was possible). Systolic myocardial thickening was scored using a five-point scale (normal, mildly reduced, markedly reduced, absent, unclassified), and diastolic myocardial thickness was scored using a four-point scale (normal, mildly reduced, markedly reduced, unclassified).

The gated SPECT images were analyzed in an identical fashion using a cine monochrome display to assess motion and a color display to assess thickening as an increase in counts in systole. Tracer uptake was assessed visually using a four-point scale (normal, mildly reduced, markedly reduced, absent/near absent tracer uptake).

In addition to these regional measurements, global function was assessed from the magnetic resonance images using a biplane area-length technique from the vertical and horizontal long-axis images. Left ventricular end-diastolic volume, end-systolic volume, stroke volume and ejection fraction were calculated.

Analysis was conducted on the study group as a whole and on subgroups defined by MRI characteristics as follows: Group 1, patients with normal regional function in all myocardial segments, and Group 2, patients with abnormal regional function in one or more segments (n = 18). The patients in Group 2 were further subdivided according to values for ejection fraction: Group 2a, patients with ejection fraction >35% and Group 2b, patients with ejection fraction <35%.

Statistical Analysis

The agreement between gated ^{99m}Tc-tetrofosmin tomography and cine MRI for assessment of wall motion, thickening and thickness was compared using a weighted kappa statistic (where numbers on the line of identity were assigned a value of 1, and numbers directly adjacent to the line of identity were assigned a value of 0.5). Similarly, the kappa statistic was applied to the agreement between observers and repeated measurements by the same observer. Segments scored as "unclassified" were excluded from the comparative analysis.

RESULTS

The mean left ventricular end-diastolic volume and ejection fraction for the whole group were 146 ± 59 ml and 50% ± 15%, respectively. Table 1 illustrates findings for Subgroups 1, 2a and 2b.

TABLE 1
Characteristics and Left Ventricular Parameters of Patients in Subgroups Defined by MRI

	Group		
	1	2a	2b
No. of Patients	10	10	8
Mean LVEDV	118 ± 47 ml	98 ± 42 ml	241 ± 51 ml
Mean LVEF	61% ± 5%	58% ± 7%	26% ± 12%
Prior MI	0	4	8
Coronary angiography	1 single-vessel disease	2 two-vessel disease 4 single-vessel disease	8 three-vessel disease

Subgroups: 1 = patients with normal contractility on MRI, 2a = patients with abnormal contractility on MRI [LVEF > 35%], 2b = patients with abnormal contractility on MRI [LVEF < 35%]; MI = myocardial infarction; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction.

Fifteen of the 252 segments analyzed (6%) could not be classified by gated SPECT because of inadequate tracer uptake. In the remaining segments, intra- and interobserver variation for the assessment of wall motion, thickening and thickness images was good, with all but one value of kappa exceeding 0.8 (Table 2). Absolute agreement of categories between two observers exceeded 80%, and absolute agreement for two readings by a single observer exceeded 90%.

Table 3 shows the comparison between gated SPECT and MRI for the assessment of wall motion, thickening and thickness, respectively. Table 4 shows the analysis of agreement for subgroups defined according to the uptake of tetrofosmin. For the whole group, agreement between gated SPECT and MRI was good, with only the kappa value for wall thickness being below 0.6. With decreasing tracer uptake, agreement became less good, and agreement for wall thickness was generally worse than for the other categories. While the values for total agreement between techniques for wall motion and thickening appear to be acceptable in segments with Grade 0 tracer uptake, 15 of the 22 segments thus graded were unclassified on gated SPECT and therefore could not be included in comparative statistical analysis.

DISCUSSION

We have shown good inter- and intraobserver correspondence for assessment of left ventricular wall motion, thickening and thickness using ^{99m}Tc-tetrofosmin gated SPECT (Figs. 1 and 2). We have also shown good agreement with cine MRI for the assessment of these parameters, although a few segments could not be assessed because of inadequate tracer uptake and agreement between the techniques in segments with reduced uptake is less good.

As in previous studies (*15*), we chose to assess wall motion in the gated SPECT images from visual inspection of systolic excursion of the myocardium, and myocardial thickening was assessed from the systolic increase in myocardial counts. This effect depends on partial volume errors (*23*). Thus, it is an indirect assessment of thickening that relies on the relatively low spatial resolution of the images. We compared tracer uptake with myocardial thickness from magnetic resonance images. Indirect comparison would be good only if the amount of viable myocardium correlated closely with myocardial thickness. There is some evidence to support this assumption (*24,25*), but the reduced agreement for assessment of myocardial thickness that we found is not surprising.

Cine MRI has been well-validated for the assessment of left ventricular function in both normal and dilated ventricles (*26,27*). It has relatively high spatial and temporal resolution, and it is a tomographic technique that can be compared directly with gated SPECT images.

Previous Studies

Gated imaging with myocardial perfusion tracers has been studied previously: to assess perfusion and function simultaneously and to improve the quality of the perfusion images. Image quality can be improved by ECG-gating for both planar (*9,10,16*) and tomographic imaging (*28*), and this may result in clinical benefit (*29*). Thallium-201 tomograms however, are not suitable for functional imaging with ECG-gating and most of this work has used ^{99m}Tc-MIBI.

Gated ^{99m}Tc-MIBI imaging has been validated by comparison with echocardiography (*10,15,18*) and with cine MRI (*19*).

TABLE 2
Interobserver and Intraobserver Agreement for Gated Technetium-99m-Tetrofosmin SPECT Assessment of Myocardial Motion Thickening and Thickness in 252 Segments

	Interobserver		Intraobserver	
	Percent agreement	Kappa	Percent agreement	Kappa
Motion	84	0.74	94	0.85
Thickening	88	0.80	91	0.84
Thickness	89	0.79	93	0.85

TABLE 3
Segmental Agreement between SPECT and MRI for Wall Motion, Thickness and Thickening for Study Population and Subgroups

	Percent agreement	Kappa
Total (n = 252 segments, 15 unclassified on SPECT)		
Motion	78	0.66
Thickening	78	0.62
Thickness	80	0.55
Group 1 (n = 90)		
Motion	100	1.0
Thickening	100	1.0
Thickness	100	1.0
Group 2a (n = 90, 2 unclassified)		
Motion	85	0.54
Thickening	77	0.39
Thickness	78	0.34
Group 2b (n = 72, 13 unclassified)		
Motion	56	0.48
Thickening	51	0.41
Thickness	52	0.37

TABLE 4
Percent Agreement between Categories and Kappa Values for Agreement between Gated SPECT and MRI Separated According to Tetrofosmin Uptake Grade

	Percent agreement	Kappa
Uptake grade 3 (n = 146)		
Wall motion	90	0.75
Wall thickening	91	0.74
Wall thickness	87	0.64
Uptake grade 2 (n = 58)		
Wall motion	72	0.61
Wall thickening	80	0.60
Wall thickness	79	0.45
Uptake grade 1 (n = 26)		
Wall motion	46	0.44
Wall thickening	40	0.34
Wall thickness	45	0.31
Uptake grade 0 (n = 22, 15 unclassified)		
Wall motion	71	0.61
Wall thickening	57	0.12
Wall thickness	40	0

Grade 3 = normal; grade 2 = mild reduction; grade 1 = moderate reduction; grade 0 = severe reduction.

Tischler and colleagues found good agreement between gated planar MIBI imaging and echocardiography (*18*), while Chua and colleagues (*15*) and Anagnostopoulos and colleagues (*19*) found good agreement between gated SPECT and echocardiography and MRI, respectively, in well-perfused segments. Agreement was less good, however, in segments with severe perfusion defects, with function in up to 33% of these segments being uninterpretable.

Takahashi and colleagues used first-pass radionuclide ventriculography combined with stress-rest SPECT to assess function and perfusion simultaneously (*22*). This technique increased sensitivity for the detection of coronary disease from 69% to 77%, but it has the disadvantage that assessment of function is not three-dimensional, and it is therefore difficult to compare perfusion and function on a regional basis. While gated SPECT allows for such a simultaneous assessment, the difficulty in evaluating function in segments with poor tracer uptake remains a significant limitation of this imaging technique.

As we have confirmed, similar results would be expected with ^{99m}Tc-tetrofosmin because it has similar properties to ^{99m}Tc-MIBI (*20,21,30*), although it does have some practical advantages in preparation (*31*) and in clearance from the lung and liver (*32*). We chose to gate images acquired after the resting injection from a same day stress-rest protocol to maximize available counts, but previous studies with ^{99m}Tc-MIBI have acquired images approximately 1 hr after a stress injection (*15,18*). Both of these techniques assess wall motion at rest, although there is the theoretical disadvantage that images acquired too soon after a stress study may underestimate myocardial function if recovery of stress-induced dysfunction is delayed.

It has been suggested that the ability of gated SPECT to assess perfusion, viability and function simultaneously may give it a role in the detection of portions of the myocardium that may improve in function after revascularization. Several techniques have been investigated in this application, including ionotropic reserve in response to dobutamine infusion (*33,34*), thallium scintigraphy (*35,36*) and PET (*37,38*). The role of technetium-labeled perfusion tracers without ECG-gating is debated, with some studies suggesting that MIBI may underestimate viable myocardium compared with thallium (*39,40*), and others finding the two to be comparable (*41*). Although our study does not address the question directly, it is possible that the combination of viability assessment from the degree of tracer uptake combined with functional assessment from myocardial thickening may be helpful. The reduced accuracy of gated SPECT for assessing function when tracer uptake is low may not be a hindrance, since it is likely that only segments with tracer uptake exceeding 50% of maximum contain a clinically significant amount of myocardium and therefore have potential for postrevascularization recovery.

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Effect of β_1 Adrenergic Receptor Blockade on Myocardial Blood Flow and Vasodilatory Capacity

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The β_1 receptor blockade reduces cardiac work and may thereby lower myocardial blood flow (MBF) at rest. The effect of β_1 receptor blockade on hyperemic MBF is unknown. **Methods:** To evaluate the effect of selective β_1 receptor blockade on MBF at rest and during dipyridamole induced hyperemia, 10 healthy volunteers (8 men, 2 women, mean age 24 ± 5 yr) were studied using ^{13}N-ammonia PET (two-compartment model) under control conditions and again during metoprolol (50 mg orally 12 hr and 1 hr before the study). **Results:** The resting rate pressure product (6628 ± 504 versus 5225 ± 807) and heart rate (63 ± 6–54 ± 5 bpm) declined during metoprolol ($p < 0.05$). Similarly, heart rate and rate pressure product declined from the baseline dipyridamole study to dipyridamole plus metoprolol ($p < 0.05$). Resting MBF declined in proportion to cardiac work by approximately 20% from 0.61 ± 0.09–0.51 ± 0.10 ml/g/min ($p < 0.05$). In contrast, hyperemic MBF increased when metoprolol was added to dipyridamole (1.86 ± 0.27–2.34 ± 0.45 ml/g/min; $p < 0.05$). The decrease in resting MBF together with the increase in hyperemic MBF resulted in a significant increase in the myocardial flow reserve during metoprolol (3.14 ± 0.80–4.61 ± 0.68; $p < 0.01$). **Conclusion:** The β_1 receptor blockade increases coronary vasodilatory capacity and myocardial flow reserve. However, the mechanisms accounting for this finding remain uncertain.

Key Words: myocardial blood flow; myocardial flow reserve; β_1 receptor blockade; PET

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Myocardial β_1 receptors modulate heart rate, systolic blood pressure and myocardial contractility in response to adrenergic stimulation. Blockade of myocardial β_1 receptor activity reduces myocardial oxygen requirements and myocardial blood flow (*1*). The beta blocker-induced reduction in myocardial oxygen demand has been used successfully in the treatment of chronic and acute coronary artery syndromes (*2,3*). The beta-receptor blockade might also alter myocardial blood flow during near maximal coronary vasodilation. This is, because beta-receptor blockade reduces myocardial contractility that may reduce extravascular resistive forces. Such forces have been demonstrated to impede coronary blood flow during pharmacological vasodilation (*4*). On the other hand, the reduction in heart rate associated with β_1-receptor blockade results in an increased duration of the diastolic coronary flow phase that may result in increases in hyperemic blood flow (*5*).

However, the net effect of such intervention on hyperemic blood flow and myocardial flow reserve have not been quantified in humans. This can now be accomplished with dynamic PET and ^{13}N-ammonia as a tracer of myocardial blood flow (*6–9*). The aim of this study was, therefore, to quantify noninvasively with ^{13}N-ammonia PET the effect of β_1-receptor blockade on myocardial blood flow and vasodilatory capacity in humans.

STUDY POPULATION

The study population consisted of 10 healthy volunteers (8 men, 2 women, mean age 24 ± 5 yr) with a low likelihood for coronary artery disease, as evidenced by a normal physical examination, normal resting ECG and absence of any significant risk factors (*10*). None of the participants had a history of cigarette smoking, elevated serum cholesterol levels, hypertension or diabetes and none was on any medication. To avoid

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