Diagnosis of coronary artery disease by radionuclide myocardial perfusion imaging

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Despite advances in the understanding of the pathophysiology of atherosclerosis and an applaudable reduction in cardiovascular mortality over the past 30 years, coronary artery disease (CAD) remains an important cause of mortality and morbidity in the UK. While primary prevention of CAD is a priority for modern medicine, so too is the need for development of non-invasive techniques for imaging of myocardial ischaemia. Radionuclide tests occupy a central position within the cardiac imaging portfolio, and among them myocardial perfusion imaging (MPI) has an obvious place because it is the only widely available and validated method of assessing myocardial perfusion. The aim of this article is to review the literature about the role of tomographic MPI in the diagnosis of CAD in the general population and in specific clinical subsets, comparing it wherever possible with other imaging modalities and to summarise the recommendations from existing guidelines for the use of this technique.

DIAGNOSTIC PERFORMANCE OF TOMOGRAPHIC MYOCARDIAL PERFUSION IMAGING

Coronary angiography and myocardial perfusion

MPI allows direct assessment of myocardial perfusion and therefore has an important role in the diagnosis of CAD in patients presenting with chest pain. An inducible perfusion abnormality indicates impaired perfusion reserve, which in turn usually corresponds to epicardial coronary obstruction. The site, depth, and extent of the abnormality provide diagnostic and management information. Conversely, a normal stress MPI indicates the absence of coronary obstruction and hence of clinically significant disease. A normal perfusion scan does not exclude non-obstructive CAD, but such disease is unlikely to be related to symptoms or to be prognostically important (see article on prognosis by Bateman and Prvulovich on p v10).

Positron emission tomography (PET) is generally considered the gold standard non-invasive technique for the assessment of myocardial perfusion. Although PET may have better accuracy than MPI, its clinical utility is constrained by high cost and poor availability.^{1,2} Therefore, MPI is the standard clinical technique for assessing myocardial perfusion, while coronary angiography is the technique for assessing epicardial coronary anatomy. Complete accuracy of MPI to predict the findings at angiography is neither expected nor necessary for clinical management, and when MPI is used for the diagnosis of CAD, it is not being used purely to predict the presence of epicardial coronary stenoses. Nevertheless, angiography is the accepted standard for imaging coronary arteries, and functional tests such as MPI are frequently compared with it.

Sensitivity and specificity of MPI

Many studies have assessed the diagnostic accuracy of MPI for the detection of CAD, but they are of variable size and quality. Tables 1–4 summarise the findings according to the four main forms of stress; the studies^{3–64} are further graded for quality according to well accepted guidelines for

evaluating diagnostic tests.⁶⁵ The highest quality score is 3 (high), when the study involved a clearly defined population, avoided verification bias, and had independent interpretation of MPI and angiography; a quality score of 2 (medium) fulfilled two of these criteria; a score of 1 (low) fulfilled only one criterion. Because of the variation in study size, quality, and design, no attempt was made to provide weighted means of sensitivity and specificity in the above tables.

In the largest single study of 2560 patients randomised to one of the three commercial perfusion radiopharmaceuticals, and using mainly adenosine stress (the UK based ROBUST study), overall sensitivity in the subset of patients undergoing angiography was 91% and overall specificity was 87%, with no significant difference between the three tracers.⁶⁶ In general, review of the studies included in tables 1–4 showed that the sensitivity of MPI for detecting angiographic CAD was consistently above 70%. Typical sensitivity values were in the region of 85–95% for both thallium-201 (Tl-201)^{6,8} and technetium-99m sestamibi (sestamibi).^{17,20} There was a significant variation in specificity in low quality studies, ranging from 33–100%,^{13,14} but carefully designed studies have reported specificities of around 75% for exercise Tl-201,^{4,10} and sestamibi,^{18,19} and even higher values (up to 94%) with incorporation of ECG gated data.⁶⁷

For pharmacological stress performed with vasodilators, a number of good quality studies showed a sensitivity $\geq 90\%$ for both Tl-201 and sestamibi^{24,27,38} and a specificity $\geq 75\%$,^{10,26,42} with some studies reporting values as high as 100%.^{13,24,38} For dobutamine Tl-201 MPI, the sensitivity was in the region of 90% while the specificity ranged from 70–100%.^{48,52} When it was used in combination with sestamibi, most studies have shown that the sensitivity was above 80%,^{45,60,62} but the specificity ranged from 64–90%.^{59,60}

Fewer diagnostic studies have been performed using technetium-99m tetrofosmin (tetrofosmin) because of its more recent commercial introduction. For exercise tetrofosmin MPI, the sensitivity and specificity values ranged from 81–96%^{14,22,23} and 67–91%,^{14,22} respectively.

COMPARISON OF MPI WITH NON-NUCLEAR TECHNIQUES

Stress echocardiography

Stress echocardiography is a well validated technique for diagnosing CAD and identifies wall motion abnormalities in patients with haemodynamically significant coronary stenoses, induced by exercise or pharmacological stress. Stress induced impairment of regional endocardial excursion and of

Abbreviations: CMRI, cardiac magnetic resonance imaging; CAD, coronary artery disease; DCM, dilated cardiomyopathy; Gd-DTPA, gadolinium diethylenetriaminepenta acid; HCM, hypertrophic cardiomyopathy; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; MCE, myocardial contrast echocardiography; MPI, myocardial perfusion imaging; PET, positron emission tomography; sestamibi, technetium-99m sestamibi; SPECT, single photon emission computed tomography; tetrofosmin, technetium-99m tetrofosmin; Tl-201, thallium-201

Table 1 Diagnostic performance of exercise single photon emission computed tomography (SPECT) MPI

Author	Number of patients	Tracer	Analysis	MI excluded	Quality	Sensitivity	Specificity
Tamaki 1984 ³	104	Tl-201	Q	*both	Medium	98%	91%
DePasquale 1988 ⁴	210	Tl-201	Q	*both	Medium	95%	74%
Fintel 1989 ⁵	135	Tl-201	V	no	Medium	83%	–
Iskandrian 1989 ⁶	193	Tl-201	V	yes	Medium	86%	62%
Maddahi 1989 ⁷	110	Tl-201	Q	*both	High	95%	56%
Mahmorian 1990 ⁸	296	Tl-201	Q	*both	High	87%	87%
Van Train 1990 ⁹	242	Tl-201	Q	*both	Medium	94%	43%
Coyne 1991 ¹⁰	100	Tl-201	V	no	Medium	81%	74%
Quinones 1992 ¹¹	112	Tl-201	V	yes	Low	77%	81%
Chae 1993 ¹²	243	Tl-201	V	no	High	71%	63%
Grover-McKay 1994 ¹³	18	Tl-201	V	no	Low	91%	86%
Tamaki 1994 ¹⁴	25	Tl-201	V	no	Low	95%	33%
Ho 1997 ¹⁵	51	Tl-201	V	*both	High	76%	77%
Kiat 1990 ¹⁶	53	mibi	Q	*both	Medium	94%	80%
Pozzoli 1991 ¹⁷	75	mibi	V	no	Low	84%	88%
Solot 1993 ¹⁸	78	mibi	V	no	Medium	96%	74%
Marwick 1994 ¹⁹	86	mibi	V	yes	Medium	73%	70%
Van Train 1994 ²⁰	124	mibi	Q	*both	Medium	89%	36%
Tamaki 1994 ¹⁴	26	tetro	V	no	Low	96%	67%
Heo 1994 ²¹	23	tetro	V	no	Medium	87%	–
Benoit 1996 ²²	30	tetro	V	yes	Medium	81%	89%
Shanoudy 1998 ²³	26	tetro	V	no	Medium	96%	–

*Values were calculated for patients with and without myocardial infarction, values shown include those with myocardial infarction.

Sensitivity and specificity values for coronary stenosis $\geq 50\%$. Quality is rated according to the number of quality criteria (adequate description of study group, avoidance of verification bias, avoidance of diagnostic and test review bias) met.

MI, myocardial infarction; mibi, technetium-99m sestamibi; Q, quantitative analysis; tetro, technetium-99m tetrofosmin; Tl-201, thallium-201; V, visual analysis.

myocardial thickening is a specific marker of myocardial ischaemia.

A recent meta-analysis by Geleijnse and Elhendy of seven studies directly comparing exercise echocardiography and exercise MPI revealed comparable sensitivities (78% v 83%, respectively) and specificities (91% v 83%, respectively).⁶⁸ In the same review, the authors also compared dobutamine echocardiography with dobutamine MPI; in eight studies, they found that dobutamine echocardiography had a lower sensitivity than MPI (80% v 86%, $p < 0.05$), but a higher specificity (86% v 73%, respectively, $p < 0.005$).⁶⁸ The sensitivity of vasodilator echocardiography, however, was significantly lower than that of vasodilator MPI (66% v 85%, $p < 0.0001$) in six studies.⁶⁸ This is not surprising since adenosine and dipyridamole cause blood flow heterogeneity, which is useful in MPI, but generally do not result in true myocardial ischaemia, which is required for causing contractile abnormalities.

Another meta-analysis by Schinkel and colleagues examined 17 studies in which MPI was directly compared with stress echocardiography.⁶⁹ Pooled data revealed that MPI was more sensitive than echocardiography (sensitivity 85% v 80%, respectively, $p < 0.05$) but less specific (specificity 77% v 86%, respectively, $p < 0.001$).⁶⁹

Myocardial contrast echocardiography and cardiac magnetic resonance imaging

A small number of studies have directly compared MPI with either myocardial contrast echocardiography (MCE) or cardiac magnetic resonance imaging (CMRI), both of which are novel techniques for the assessment of myocardial perfusion. In a small study of 30 patients who underwent dipyridamole stress testing, Kaul and colleagues found a good agreement ($\kappa = 0.86$) between MPI and MCE for the presence or absence of CAD.⁷⁰ Wei and associates performed a

Table 2 Diagnostic performance of dipyridamole SPECT MPI

Author	Number of patients	Tracer	Analysis	MI excluded	Quality	Sensitivity	Specificity
†Francisco 1982 ²⁴	75	Tl-201	Q	no	Medium	90%	96%
†Huikuri 1988 ²⁵	93	Tl-201	V	no	Medium	96%	75%
Go 1990 ²⁶	202	Tl-201	V	*both	High	76%	80%
†Mendelson 1992 ²⁷	79	Tl-201	V	*both	Medium	90%	–
Cramer 1994 ²⁸	38	Tl-201	V	No	High	90%	71%
Grover-McKay 1994 ¹³	18	Tl-201	V	uns	Low	91%	100%
Ho 1995 ²⁹	54	Tl-201	V	no	High	98%	73%
Watanabe 1997 ³⁰	53	Tl-201	V	yes	Medium	80%	72%
Tartagni 1991 ³¹	30	Tl-201; mibi	V	no	Medium	100%	75%
Miller 1997 ³²	244	Mibi	V	*both	Medium	91%	28%
Schillaci 1997 ³³	40	Mibi	V	yes	Low	95%	72%
Soman 1997 ³⁴	27	Mibi	V	no	High	90%	66%
Ogilby 1998 ³⁵	26	Mibi	V	no	Medium	90%	100%
†Santoro 1998 ³⁶	60	Mibi	V	yes	High	97%	89%
He 1997 ³⁷	64	Tetro	V	no	Medium	85%	54%

*Values were calculated for patients with and without myocardial infarction, values shown include those with myocardial infarction; †coronary stenosis $\geq 70\%$.

Sensitivity and specificity values for coronary stenosis $\geq 50\%$ and for coronary stenosis $\geq 70\%$. Quality is rated according to the number of quality criteria (adequate description of study group, avoidance of verification bias, avoidance of diagnostic and test review bias) met.

MI, myocardial infarction; mibi, technetium-99m sestamibi; Q, quantitative analysis; tetro, technetium-99m tetrofosmin; Tl-201, thallium-201; uns, unspecified; V, visual analysis.

Table 3 Diagnostic performance of adenosine SPECT MPI

Author	Number of patients	Tracer	Analysis	MI excluded	Quality	Sensitivity	Specificity
Nguyen 1990 ³⁸	60	Tl-201	V	no	Medium	92%	100%
Verani 1990 ³⁹	45	Tl-201	Q	no	Medium	83%	94%
Coyne 1991 ¹⁰	100	Tl-201	V	*both	Medium	83%	76%
Nishimura 1991 ⁴⁰	101	Tl-201	V	*both	High	84%	84%
Allman 1992 ⁴¹	76	Tl-201	Q	yes	Low	85%	38%
Pennell 1995 ⁴²	226	Tl-201	V	no	High	96%	78%
Mohiuddin 1996 ⁴³	202	Tl-201	Q	no	High	90%	86%
Amanullah 1993 ⁴⁴	40	mibi	V	no	Medium	94%	100%
Marwick 1993 ⁴⁵	97	mibi	V	yes	Medium	86%	71%
Jamil 1999 ⁴⁶	32	mibi	V	no	Medium	75%	–

*Values were calculated for patients with and without myocardial infarction, values shown include those with myocardial infarction.

Sensitivity and specificity values for coronary stenosis $\geq 50\%$. Quality is rated according to the number of quality criteria (adequate description of study group, avoidance of verification bias, avoidance of diagnostic and test review bias) met.

MI, myocardial infarction; mibi, technetium-99m sestamibi; Q, quantitative analysis; tetro, technetium-99m tetrofosmin; Tl-201, thallium-201; V, visual analysis.

similar comparison in a recent multi-centre study and confirmed these results.⁷¹

CMRI has also been used for detection of CAD in a similar way to stress echocardiography; in a recent review, this technique has been shown to have a mean sensitivity and specificity of 86% and 84%, respectively, for detecting CAD.⁷² In the last few years, direct assessment of myocardial perfusion has become feasible using gadolinium diethylenetriaminepenta acid (Gd-DTPA).⁷³ There have been no studies so far directly comparing the diagnostic accuracies of Gd-DTPA perfusion CMRI and MPI, and the exact role of the former in clinical practice remains to be determined.

FACTORS AFFECTING OBSERVED DIAGNOSTIC PERFORMANCE OF MPI

When the reference standard for diagnosis (in this case coronary angiography) is not used in all patients, and referral to angiography is more likely when MPI is abnormal, then the findings are affected by post-test referral bias and specificity appears falsely low.^{76–77} Indeed, if only patients with abnormal MPI undergo angiography, the observed sensitivity will be 100% and the specificity 0%. The normalcy rate is therefore a better index for assessing the performance

of a test in patients without disease. This is defined as the rate of normal perfusion scans in patients with a low (< 5%) likelihood of CAD based on clinical and exercise ECG features. Studies have consistently reported significantly higher normalcy rates than specificity for MPI in the diagnosis of CAD (table 5). The mean normalcy rate for MPI from 12 studies (543 patients) was 88%.

Another form of bias, the pre-test referral bias, occurs when mainly high likelihood patients are referred for MPI, which increases apparent sensitivity because of the higher proportion of patients with more severe disease.^{77–78} Analysis of the studies quoted in tables 1–4 showed that in the subgroup of studies where the sensitivity of exercise Tl-201 MPI was re-calculated after exclusion of patients with previous myocardial infarction, mean sensitivity fell from 92% to 87% ($p = 0.008$). Sensitivity was also higher with more extensive and severe disease, and lower with single vessel disease (87% v 79%, $p < 0.0001$) or in those with stenoses involving branches of the major vessels. Sensitivity can also be affected by the involved coronary territory; patients with single vessel disease are more likely to have an abnormal study if the lesion is in the left anterior descending than in the left circumflex artery.^{3–29–40}

Table 4 Diagnostic performance of dobutamine SPECT MPI

Author	Number of patients	Tracer	Analysis	MI excluded	Quality	Sensitivity	Specificity
Pennell 1991 ⁴⁷	50	Tl-201	V	no	Medium	97%	80%
Warner 1993 ⁴⁸	16	Tl-201	V	no	Medium	93%	100%
Hays 1993 ⁴⁹	67	Tl-201	Q	no	Medium	86%	90%
Huang 1997 ⁵⁰	93	Tl-201	Q	no	High	90%	81%
Huang 1998 ⁵¹	110	Tl-201	V	yes	High	82%	82%
Caner 1997 ⁵²	29	Tl-201; mibi	V	uns	High	89%	70%
Gunalp 1993 ⁵³	27	mibi	V	yes	Medium	94%	89%
Forster 1993 ⁵⁴	21	mibi	V	yes	High	83%	89%
Marwick 1993 ⁴⁵	97	mibi	V	yes	Medium	80%	74%
Marwick 1993 ⁵⁵	217	mibi	Q	yes	High	76%	67%
Mairesse 1994 ⁵⁶	129	mibi	V	yes	High	76%	65%
Marwick 1994 ¹⁹	82	mibi	V	yes	Medium	65%	68%
Senior 1994 ⁵⁷	61	mibi	V	no	High	95%	71%
Di Bello 1996 ⁵⁸	45	mibi	V	yes	High	87%	86%
Ifthar 1996 ⁵⁹	38	mibi	V	no	Medium	79%	90%
Kisacki 1996 ⁶⁰	69	mibi	V	no	High	96%	64%
Slavich 1996 ⁶¹	46	mibi	V	yes	Medium	82%	83%
San Roman 1998 ⁶²	92	mibi	Q	yes	High	87%	70%
†Santoro 1998 ⁶³	60	mibi	Q	yes	High	91%	81%
Elhendy 1998 ⁶⁴	70	mibi	V	no	Low	64%	72%

*Values were calculated for patients with and without myocardial infarction, values shown include those with myocardial infarction; †coronary stenosis $\geq 70\%$. Sensitivity and specificity values for coronary stenosis $\geq 50\%$ and coronary stenosis $\geq 70\%$. Quality is rated according to the number of quality criteria (adequate description of study group, avoidance of verification bias, avoidance of diagnostic and test review bias) met.

MI, myocardial infarction; mibi, technetium-99m sestamibi; Q, quantitative analysis; tetro, technetium-99m tetrofosmin; Tl-201, thallium-201; uns, unspecified; V, visual analysis.

Table 5 Normalcy rates for SPECT MPI

Author	Number of patients	Tracer	Stress	Normalcy rate
Iskandrian 1989 ⁶	131	Tl-201	Exercise	94%
Maddahi 1989 ⁷	52	Tl-201	Exercise	86%
Van Train 1990 ⁹	76	Tl-201	Exercise	82%
Coyne 1991 ¹⁰	45	Tl-201	Exercise, adenosine	80%
Kiat 1992 ²⁴	55	Tl-201	Exercise	89%
Nishimura 1992 ²⁵	39	Tl-201	Exercise	92%
Nishimura 1992 ²⁵	39	Tl-201	Adenosine	95%
Van Train 1994 ²⁰	37	Tl-201	Exercise	81%
Kiat 1990 ¹⁶	8	mibi	Exercise	88%
Heo 1997 ²¹	61	mibi	Exercise	95%
				88% mean rate

Mibi, technetium-99m sestamibi; Tl-201, thallium-201.

The intensity of stress achieved, particularly with exercise, is another factor that may influence the observed diagnostic performance of MPI by increasing the number of false negative results.⁶⁻⁷⁹ Anti-anginal medication can also reduce sensitivity when using exercise, and medication should ideally be discontinued before diagnostic studies.⁸⁰ Furthermore, β blockers should be discontinued for a dobutamine stress test because they attenuate the heart rate and blood pressure response and can reduce or abolish myocardial ischaemia.⁸¹⁻⁸² The role of anti-anginal medication in vasodilator stress is less clear but one study has shown that they may reduce sensitivity.⁸³

Tracer activity below the diaphragm is commonly seen with sestamibi and tetrofosmin, and this can reduce specificity, as seen in some studies.³²⁻³⁷ Other causes of artefact that can reduce specificity are photon attenuation and scatter, patient motion, low count statistics, reconstruction errors, or processing problems. Experienced practitioners can normally identify these problems and they maintain accuracy not only by recognising common artefactual appearances, but also by taking account of the clinical circumstances. Commercially available software packages incorporate methods for recognising and correcting problems related to these factors. Almost all of these packages will also offer some form of quantitative analysis. The latter can reduce inter-observer variability but its value for accuracy is less clear, with some studies demonstrating improvement,³⁻²⁴⁻³⁹ while others not.⁴⁻⁸ Correction for the undesirable effects of attenuation using simultaneous or sequential transmission imaging is also feasible but its value is not yet clearly established. ECG-gating is another option that improves accuracy and it is now used routinely in many centres. It aids the distinction between true perfusion defects and artefacts, and provides additional prognostic information from global and regional left ventricular function.⁸⁴⁻⁸⁵

Despite their different physical and imaging characteristics, all three radiotracers have comparable diagnostic accuracies for detecting CAD. As technetium-99m labelled tracers have myocardial uptake curves that plateau at lower levels of hyperaemia than Tl-201, it has been suggested that they may not perform well when used with vasodilator stress.⁸⁶ However, several studies with sestamibi indicate that the diagnostic accuracy is not compromised when the latter is used with adenosine or dipyridamole.³⁵⁻⁴⁵ Data from studies with tetrofosmin are less consistent, with some studies reporting good accuracy with vasodilators⁶⁶ and others showing it to be less sensitive than Tl-201 or sestamibi for the detection of mild to moderate angiographic disease.⁸⁷⁻⁸⁸ Such underestimation has also been reported in some, but not all, studies performed with dobutamine sestamibi MPI.⁶⁰⁻⁶⁴

DIAGNOSTIC PERFORMANCE OF TOMOGRAPHIC MPI IN PATIENT SUBGROUPS

Extensive CAD

An important function of any non-invasive test for CAD is its ability to identify patients with extensive disease, as their prognosis is particularly poor and thus demands prompt management. It is well documented that patients with three vessel or left main stem disease almost always have an abnormal MPI study and that the sensitivity is higher in patients with multi-vessel disease compared to those with single vessel disease.⁸⁹ However, the perfusion abnormality will not necessarily reflect involvement of more than one vessel; moreover, less than two thirds of such scans show the typical pattern of multi-vessel disease.⁹⁰

A number of studies have observed a low sensitivity for accurately detecting three vessel disease with visual analysis.³⁻²²⁻³⁴ Quantitative analysis of the washout rate in the areas of normal Tl-201 uptake was found to improve the sensitivity, which can also be increased by incorporation of the clinical response to treadmill testing.⁹¹ Other scintigraphic features such as transient ischaemic dilatation and increased lung uptake of Tl-201 were found by some investigators to be useful predictors of extensive CAD.⁹²⁻⁹³

Geleijnse and Elhendy's meta-analysis of four studies (involving 220 patients) specifically investigating the accuracy of MPI and stress echocardiography for detecting extensive CAD found that sensitivity and specificity were comparable for both imaging modalities.⁶⁸

Women

Women represent a particular group of patients in which the non-invasive diagnosis of CAD may be challenging. Exercise ECG is often used as the initial diagnostic test; however, several studies have demonstrated that it has an unacceptably high false positive rate in women.⁹⁴⁻⁹⁵ This is thought to be partly caused by the lower prevalence of CAD in women, especially in premenopausal women, and partly because the classic ECG criteria for a positive test are based on data obtained in men.

Studies examining the diagnostic performance of MPI in women suspected of having CAD have generally reported higher sensitivity and specificity values when compared with retrospective data on exercise ECG.⁶⁷⁻⁹⁶ A recent review of seven studies involving a total of 1140 female patients reported a mean sensitivity of 78% and specificity of 86% for the diagnosis of CAD by MPI; these values are higher than those usually obtained with exercise ECG.⁹⁷ Studies which have directly compared the two modalities have also reported higher accuracy in the detection of CAD with MPI than with exercise ECG.⁹⁸ On the strength of this evidence, guidelines from the British Cardiac Society/Royal College of Physicians

suggest that in women with an intermediate probability of CAD, MPI should be the non-invasive investigation of choice for the diagnosis of CAD.⁹⁹

Few studies have directly compared MPI and stress echocardiography in women. One study has shown no significant difference between them,⁹⁸ while others have demonstrated a superior specificity of dobutamine echocardiography over dobutamine MPI in women.^{64–100} Based on the existing data, it seems therefore reasonable to suggest that in female patients who are unable to exercise or undergo vasodilator stress, dobutamine echocardiography is a more appropriate form of stress than MPI.

Left bundle branch block (LBBB) and other ECG abnormalities

The non-invasive detection of CAD in patients with resting LBBB poses a particular problem. Although patients with LBBB have a high prevalence of CAD, LBBB also frequently occurs in non-ischaemic cardiomyopathies. ST segment changes on exercise ECG are non-diagnostic in these patients, and abnormal septal motion associated with the conduction abnormality may reduce the diagnostic accuracy of stress/rest regional wall motion comparisons using radio-nuclide ventriculography or echocardiography.¹⁰¹

Even in the presence of angiographically normal coronary arteries, patients with LBBB often have reversible or fixed septal defects on MPI, particularly when combined with exercise or dobutamine stress.^{102–103} The exact mechanism is unclear but it is possible that a delayed activation of the septum in the presence of LBBB may lead to a reduction in coronary flow and hence tracer delivery to the septum. A high heart rate increases the proportion of diastolic filling that is lost, leading to a further reduction in septal coronary flow and therefore more obvious perfusion defects. When stress is performed with dipyridamole or adenosine alone it is less likely to observe such perfusion abnormalities probably because the effect of vasodilators on the heart rate and septal contraction is less than that of dynamic exercise. It has been shown that specificity with vasodilator stress improves by up to 75% and this is achieved without a reduction in sensitivity.¹⁰⁴ Accordingly, the recently published American College of Cardiology/American Heart Association guidelines for the management of patients with stable angina recommend the use of adenosine or dipyridamole SPECT MPI as the preferred imaging modality for patients with LBBB.¹⁰⁵ The committee does not recommend the use of echocardiography because there is only limited information regarding its clinical utility.¹⁰⁶

As in LBBB, perfusion abnormalities may be seen in patients with bifascicular block or right ventricular pacemakers even in the absence of epicardial CAD,¹⁰⁷ therefore if a stress test is required, this should be performed with vasodilators. MPI can also be helpful in patients with resting ECG changes (such as those seen in left ventricular hypertrophy (LVH), pre-excitation or drug effects) because they can reduce the usefulness of exercise ECG for the detection of CAD.¹⁰⁵

Cardiomyopathies and LVH

Dilated cardiomyopathy (DCM) is often associated with perfusion abnormalities and hence the non-invasive detection of concomitant epicardial coronary stenoses can be difficult. Although a normal scan or a study showing patchy non-reversible defects in a patient with DCM virtually exclude the presence of underlying CAD as the cause of cardiomyopathy, the presence of reversible abnormalities is not always the result of CAD.¹⁰⁸ However, if such abnormalities are found in the distribution of coronary territories, then they are more likely to represent underlying CAD and

Figure 1 Sequential Bayesian analysis of CAD probability using MPI. The post-test likelihood of CAD (following MPI) can be estimated by sequential Bayesian analysis using the pre-test likelihood of disease. If MPI is positive, the post-test likelihood is calculated from the upper response line (purple), while if the test is negative, the lower response line (blue) is used. These curves are constructed for a diagnostic test (MPI) with a sensitivity of 90% and specificity of 80%. For example, in a patient with a 50% pre-test likelihood of CAD, a positive MPI scan increases the post-test likelihood of disease to 81.8% (red line), while a negative scan decreases the post-test likelihood of disease to 11.1%. The post-test probability difference for this patient is therefore 70.7%. In contrast, for a patient with a low pre-test likelihood of disease of 5%, a positive MPI scan increases the post-test likelihood of disease to only 19.2%, while a negative scan decreases the post-test likelihood to 0.6%. The post-test probability difference is therefore only 18.6%.

hence, they can help to differentiate between ischaemic and non-ischaemic aetiology. This distinction is important because it has implications for the patient management (see article on myocardial viability and hibernation by Bax and colleagues on p v26).

Patients with hypertrophic cardiomyopathy (HCM) often demonstrate an abnormally thickened septum on MPI. However, this technique is of very limited value in the detection of the condition and confirmation of the diagnosis should be performed with echocardiography or CMRI. Perfusion abnormalities are often seen in patients with HCM in the absence of epicardial coronary disease and typically affect the septum.¹⁰⁹ There is evidence that patients with inducible ischaemia on MPI demonstrate lactate production during rapid atrial pacing.¹¹⁰ This supports the view that such abnormalities represent true myocardial ischaemia, although this is presumably the result of other mechanisms, such as systolic compression of intramyocardial septal vessels, abnormal coronary flow pattern in the left anterior descending artery, or impaired coronary flow reserve. A negative perfusion scan in HCM, on the other hand, suggests that significant underlying epicardial CAD is unlikely. Inducible ischaemia on MPI has been correlated with events (cardiac arrest or syncope) in young patients with HCM,¹¹¹ although not in larger unselected populations.¹¹² At present, the role of MPI in the management of patients with HCM remains undefined.

Inducible perfusion defects can also be seen in patients with more generalised LVH because of abnormalities in the microcirculation which may therefore erode the specificity of MPI for detecting epicardial CAD. The specificity of MPI may be further compromised by changes seen occasionally in the septum and lateral wall in the form of a reversal of lateral

wall to septum tracer uptake ratio, which is not caused by CAD.¹¹³ Dobutamine echocardiography does not suffer from these limitations and although some investigators have found it to be equally effective with MPI for detecting underlying CAD,¹¹⁴ more recent data suggest that the former is probably the technique of choice in this clinical setting.¹¹⁵

USE OF MPI IN THE INVESTIGATIVE STRATEGIES FOR THE DIAGNOSIS OF CAD

According to Bayes theorem, non-invasive tests are of most value in patients with an intermediate probability of CAD (fig 1). Ideally, therefore, such patients should undergo MPI without prior performance of an exercise ECG. Several factors militate against this. The most important is the relative availability of the two techniques, but radiation burden and cost are also relevant. Many centres use a staged approach with the exercise ECG being the initial test followed by MPI if the likelihood of disease is indeterminate after the exercise ECG, or if further information on myocardial perfusion is required to assist management decisions. This strategy has been adopted in recently published guidelines by the British Cardiac Society/Royal College of Physicians and European Society of Cardiology.^{99–116} They also recommend that MPI should be the initial investigation in patients who are unlikely to exercise adequately, in women, and in cases where the exercise ECG is uninterpretable because of resting abnormalities (see above). It is also reasonable to suggest that even patients with a high likelihood of CAD can be considered for MPI before coronary angiography. MPI can assess objectively the extent and severity of myocardial ischaemia allowing accurate risk stratification and influencing management decisions.

The role of MPI in asymptomatic patients with increased cardiovascular risk profiles is not clearly defined. The existing data suggest that MPI should not be used in screening unselected asymptomatic populations,¹¹⁷ but it may have a limited role in selected patients considered to be at a high risk for developing CAD (for example, men ≥ 45 years old with a family history of premature CAD or patients with severe calcification on electron beam computed tomography and resting ECG abnormalities).^{118–119}

CONCLUSION

Radionuclide MPI is a well validated, non-invasive method of assessing myocardial perfusion in men and women. It has the ability to localise haemodynamically important coronary stenoses, and assess the extent and severity of coronary obstruction. It possesses a high overall diagnostic accuracy for detecting CAD, which increases further with incorporation of ECG gated data. A normal myocardial perfusion scan makes it extremely unlikely that a patient has haemodynamically significant CAD, whatever the clinical and ECG features are, and therefore invasive investigations can be avoided in such patients.

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