Diagnosis of coronary artery disease by radionuclide myocardial perfusion imaging

C Y Loong, C Anagnostopoulos

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 summarising 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 Prulovitch on p 10).

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. 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 studies5–64 are further graded for quality according to well accepted guidelines for evaluating diagnostic tests. 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. 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) and technetium-99m sestamibi (sestamibi). There was a significant variation in specificity in low quality studies, ranging from 33–100%, but carefully designed studies have reported specificities of around 75% for exercise Tl-201 and sestamibi, and even higher values (up to 94%) with incorporation of ECG gated data.

For pharmacological stress performed with vasodilators, a number of good quality studies showed a sensitivity ≥ 90% for both TI-201 and sestamibi and a specificity ≥ 75% with some studies reporting values as high as 100% for dobutamine TI-201 and sestamibi. For dobutamine TI-201 MPI, the sensitivity was in the region of 90% while the specificity ranged from 70–100%. When it was used in combination with sestamibi, most studies have shown that the sensitivity was above 80%, but the specificity ranged from 64–90%.

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% and 67–91% 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...
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% vs studies directly comparing exercise echocardiography and ischaemia.

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Tracer</th>
<th>Analysis</th>
<th>MI excluded</th>
<th>Quality</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<td>Tamaki 1984</td>
<td>104</td>
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<td>Q</td>
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<td>Medium</td>
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<td>91%</td>
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<td>95%</td>
<td>74%</td>
</tr>
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<td>135</td>
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<td>V</td>
<td>no</td>
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<td>–</td>
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<tr>
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<td>67%</td>
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<tr>
<td>Hoo 1994</td>
<td>23</td>
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<td>89%</td>
</tr>
<tr>
<td>Shanoudy 1998</td>
<td>26</td>
<td>tetro</td>
<td>V</td>
<td>no</td>
<td>Medium</td>
<td>96%</td>
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*Values were calculated for patients with and without myocardial infarction, values shown include those with myocardial infarction. Sensitivity and specificity values for coronary stenosis >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.

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% vs 80%, respectively, p < 0.05) but less specific (specificity 77% vs 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 (κ = 0.86) between MPI and MCE for the presence or absence of CAD.70 We and associates performed a
similar comparison in a recent multi-centre study and confirmed these results.17

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.18 In the last few years, direct assessment of myocardial perfusion has become feasible using gadolinium diethylene-triaminepenta-acid (Gd-DTPA).19 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 (542 patients) was 89%. 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 TI-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.2 25 40

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Diagnostic performance of adenosine SPECT MPI</th>
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<td>Author</td>
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<td>Nguyen 1990</td>
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<td>Mohaddadi 1996</td>
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<td>Ananthanarayanan 1993</td>
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<td>97</td>
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<td>Jamil 1999</td>
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*Values were calculated for patients with and without myocardial infarction, values shown include those with myocardial infarction. Sensitivity and specificity values for coronary stenosis ≥50% and coronary stenosis ≥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; TI-201, thallium-201; V, visual analysis.

<table>
<thead>
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<td>Hays 1993</td>
<td>67</td>
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<td>Huang 1997</td>
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<td>Huang 1998</td>
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<td>Caner 1997</td>
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<td>Gundel 1993</td>
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<td>Forster 1993</td>
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<td>Marwick 1993</td>
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<td>217</td>
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<td>Mairesse 1994</td>
<td>129</td>
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<td>Marwick 1994</td>
<td>82</td>
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<td>Senior 1994</td>
<td>61</td>
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<td>Di Bello 1994</td>
<td>45</td>
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<td>Ilfiher 1996</td>
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<td>Slovick 1996</td>
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<td>Elhendy 1998</td>
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*Values were calculated for patients with and without myocardial infarction, values shown include those with myocardial infarction; coronary stenosis ≥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; TI-201, thallium-201; V, visual analysis.
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. Anti-anginal medication can also reduce sensitivity when using exercise, and medication should ideally be discontinued before diagnostic studies. 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. The role of anti-anginal medication in vasodilator stress is less clear but one study has shown that they may reduce sensitivity.

Tracer activity below the diaphragm is commonly seen with sestamibi and tetrofosmin, and this can reduce specificity, as seen in some studies. 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 while others not. 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.

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 TI-201, it has been suggested that they may not perform well when used with vasodilator stress. However, several studies with sestamibi indicate that the diagnostic accuracy is not compromised when the latter is used with adenosine or dipyridamole. Data from studies with tetrofosmin are less consistent, with some studies reporting good accuracy with vasodilators and others showing it to be less sensitive than TI-201 or sestamibi for the detection of mild to moderate angiographic disease. Such underestimation has also been reported in some, but not all, studies performed with dobutamine sestamibi MPI. 

### 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. 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.

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

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.

#### 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. 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. 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. Studies which have directly compared the two modalities have also reported higher accuracy in the detection of CAD with MPI than with exercise ECG. 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.109

Few studies have directly compared MPI and stress echocardiography in women. One study has shown no significant difference between them,110 while others have demonstrated a superior specificity of dobutamine echocardiography over dobutamine MPI in women.111 112 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 radionuclide ventriculography or echocardiography.113

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.114 115 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.116

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.117

As in LBBB, perfusion abnormalities may be seen in patients with bifascicular block or right ventricular pacemakers even in the absence of epicardial CAD,118 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.119

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.120 However, if such abnormalities are found in the distribution of coronary territories, then they are more likely to represent underlying CAD and 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.121 There is evidence that patients with inducible ischaemia on MPI demonstrate lactate production during rapid atrial pacing.122 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,123 although not in larger unselected populations.124 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.\textsuperscript{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\textsuperscript{114} more recent data suggest that the former is probably the technique of choice in this clinical setting.\textsuperscript{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.\textsuperscript{109,116} 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;\textsuperscript{117} it may have a limited role in selected patients considered to be at a high risk for developing CAD (for example, men \(\geq 45\) years old with a family history of premature CAD or patients with severe calcification on electron beam computed tomography and family history of premature CAD or patients with severe coronary artery disease – effect of exercise level on accuracy. Cardio 1997;\textsuperscript{88}:379–85.

**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, whereas the clinical and ECG features are, and therefore invasive investigations can be avoided in such patients.

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**Authors’ affiliations**

C Y Loong, National Heart & Lung Institute, Imperial College London, London, UK

C Anagnostopoulos, Department of Nuclear Medicine, Royal Brompton Hospital, London, UK

Correspondence to: Dr C Anagnostopoulos, Department of Nuclear Medicine, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; c.anagnostopoulos@imperial.ac.uk

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Diagnosis of CAD by myocardial perfusion imaging


Diagnosis of coronary artery disease by radionuclide myocardial perfusion imaging

C Y Loong and C Anagnostopoulos

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