Radionuclide imaging of the heart

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Nuclear cardiology is an established part of diagnosis and assessment of patients with possible heart disease, the two most common tests being myocardial perfusion imaging and radionuclide ventriculography. Myocardial perfusion imaging comprises approximately 75% of nuclear cardiology studies in the UK, and is used in diagnosis and management of coronary artery disease.

Nuclear cardiology is an established part of diagnosis and assessment of patients with possible heart disease. The two most common tests are myocardial perfusion imaging (MPI) and radionuclide ventriculography (RNV). This review focuses on MPI, which comprises approximately 75% of nuclear cardiology studies in the UK, and its role in the diagnosis and management of coronary artery disease (CAD) (American College of Cardiology/American Heart Association Task Force Report, 1995).

MYOCARDIAL PERFUSION IMAGING

Activity

MPI activity has nearly doubled in recent years in the UK. In 1997, the latest year for which data are available, 1.1 scans were performed per 1000 population per year (Prvulovich, 1999). The inclusion of nuclear cardiology within the training syllabus for cardiology (Hall et al, 1995) and the educational activities of specialist societies such as the British Nuclear Cardiology Society have meant that there is increasing awareness of the role of nuclear techniques in clinical cardiology.

Basic principles

MPI is the only widely available non-invasive method of assessing regional myocardial perfusion and is a robust and reproducible technique. Commercially available tracers are thallium-201, and two technetium-99m labelled analogies of thallium, 2-methoxy-isobutyl-isonitrile (MIBI) and tetrofosmin. Thallium is usually given at peak exercise and the exercise is continued for 2 minutes in order to maintain stable conditions over the period of extraction of tracer by the

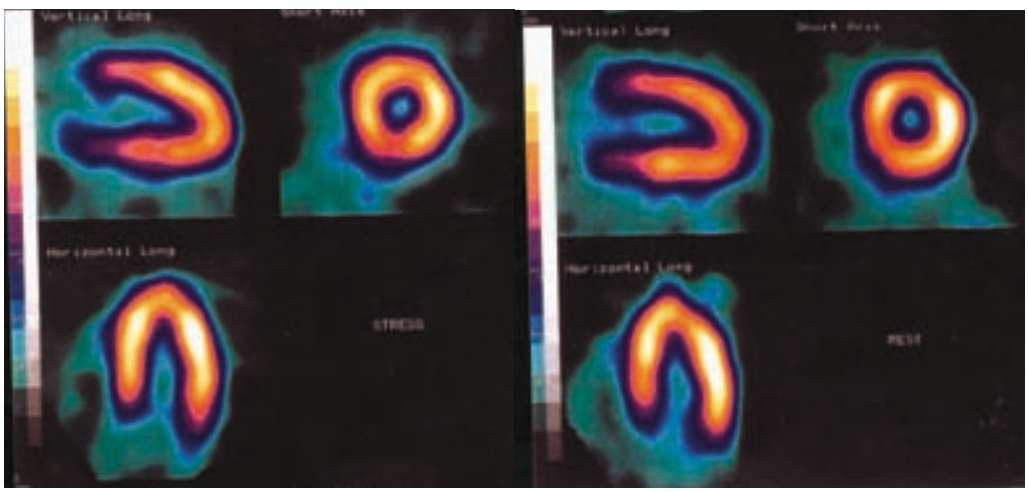

Figure 1. A 51-year-old female had hypertension and atypical chest pain with a normal resting electrocardiogram. The images show homogeneous uptake throughout the myocardium, hence there is no coronary obstruction and the likelihood of future cardiac events is less than 1% per year.

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myocardium. Imaging is begun within 5 minutes of injection and should be completed within 30 minutes. During this period the distribution of thallium within the myocardium is relatively fixed and, despite the cessation of exercise, the images reflect myocardial perfusion at peak stress. In fact, there is a slow equilibration between intracellular thallium and the very low level of intravascular thallium, so that the pattern of distribution slowly alters to reflect the changing conditions. The practical consequence of the slow redistribution of thallium is that the images acquired shortly after injection reflect myocardial perfusion during stress and those several hours later reflect the distribution of viable myocardium (*Figure 1*).

Abnormalities are normally classified by comparing stress and redistribution images as either fixed or reversible and are said to indicate infarcted and reversibly ischaemic myocardium respectively. While this is a good guideline, it is simplistic. Redistribution is often incomplete if imaging is performed at 3–4 hours, but failure to return to normal does not necessarily imply that there is partial infarction since later redistribution imaging or reinjection imaging will often show further improvement (Cloninger et al, 1988; Ziessman et al, 1989). Reinjection of thallium leads to an improvement in up to one third of fixed defects (Dilsizian et al, 1990; Ohtani et al, 1990; Rocco et al, 1990; Tamaki et al, 1990; Yang et al, 1990), suggesting that the presence of viable myocardium can be underestimated by conventional thallium imaging (Brunken et al, 1989). The significance of reinjection and resting injection protocols for the detection of viable and hibernating myocardium is discussed below.

When using $^{99}Tc^{m}$-MIBI or tetrofosmin, separate stress and rest injections have to be given because of the lack of redistribution. The 6-hour half-life of technetium-99m means that the two studies should ideally be performed on separate days if activity from the first injection is not to confuse the images following the second injection. The two studies can be performed on the same day if a larger dose (three to five times) is given on the second occasion in order to swamp the activity remaining from the first injection.

A decision then has to be made on which study to perform first, and this probably depends upon the clinical indication for the study. If the diagnosis of myocardial ischaemia is important then the stress study should be performed first in order to avoid reducing the contrast of a stress-induced defect by a previous normal resting study (Heo et al, 1992). Conversely, if the problem is to detect viable myocardium and reversibility of a defect, perhaps in a patient with previous infarction, then it may be better to perform the rest study first (Taillefer, 1990). Same day protocols are, however, probably inferior to separate day protocols (Whalley et al, 1991).

Another consequence of the lack of redistribution of the technetium-99m tracers is that stress imaging can be delayed for some time after injection. Indeed, it is advisable to do so in order to allow the ratio of myocardial to liver and lung uptake to increase. Best contrast is obtained in images acquired approximately 1 hour after injection. It is therefore not essential to perform exercise close to the gamma camera and injections can be made during normal treadmill exercise testing, in the catheter laboratory, or in the coronary care unit immediately before thrombolysis. Particularly promising studies involve giving the injection before thrombolysis in patients with acute myocardial infarction with imaging several hours later when the clinical condition is stable. These images reflect the territory at risk. Repeat injection and imaging several days later allows the amount of myocardium that has been salvaged by thrombolysis to be established by comparing both images (Wackers et al, 1989). Another feature of the technetium agents, arising from their superior imaging characteristics compared with thallium, is the ability to assess ventricular function either by following the first pass of the tracer through the heart or by electrocardiographically gated acquisition of the myocardial images.

In patients who are unable to exercise, adenosine, dipyridamole or dobutamine are alternative methods of stressing the coronary system (*Table 1*). All of these agents act by dilating coronary arterioles and increasing flow by up to six times for adenosine or two times for dobutamine. Territories subtended by diseased arter-

TABLE 1.
Indications for pharmacological stress during myocardial perfusion imaging

Information on exercise symptoms and capacity is already known
Unlikely to reach 85% of maximal predicted heart rate during dynamic exercise
Relative contraindication to exercise (left ventricle outflow obstruction, unstable coronary symptoms)
More accurate perfusion assessment required despite cardioactive medication
Significant conduction abnormality (left bundle–branch block, bifascicular block, pacemaker)

ies do not increase perfusion and hence there is a disparity in delivery of tracer to normal and diseased territories. It is important to note that perfusion is not necessarily reduced in the abnormal territory although it can be because of the steal phenomenon, and true ischaemia occurs in approximately two thirds of patients. Ischaemia is most likely in a territory with an occluded artery where perfusion is maintained by collateral vessels.

The great value of pharmacological stress in routine practice is the ability to obtain diagnostic information in patients who are unable to exercise maximally, and this can be as many as 50% of patients depending on the population. In our own centres, adenosine combined with dynamic exercise is the routine form of stress because of its simplicity and reliability. In patients with a history of bronchospasm, adenosine is contraindicated and dobutamine is used instead.

DIAGNOSIS OF CORONARY DISEASE

Typical sensitivity and specificity for the detection of CAD using tomographic MPI are 91% and 89% respectively (Maddahi, 1996). These are both higher than for the exercise electrocardiogram (ECG), at 68% and 77% respectively (Gianrossi et al, 1989), because perfusion abnormalities occur at lower levels of ischaemia than either ST segment depression or anginal chest pain (Beller, 1988). MPI offers the additional advantage that it can localize areas of ischaemia and assess their extent and severity (*Figure 2*) (Segall et al, 1995).

Nevertheless, because the exercise ECG does not involve radiation and is widely available it is often the first test for chest pain, with MPI being reserved for patients with reduced exercise tolerance or in whom an exercise ECG is unhelpful or leaves doubt (*Table 2*). This role for perfusion imaging is incorporated into the UK guidelines for the investigation and treatment of stable angina which recommend MPI as the first test for females (in whom the exercise ECG is often falsely positive) and patients unable to exercise maximally or with an abnormal resting ECG (de Bono, 1999). Importantly, the recent EMPIRE study has shown that investigative strategies for patients with chest pain which incorporate MPI are cheaper and at least equally effective compared with strategies that do not use MPI, both for cost of diagnosis and subsequent management (Underwood et al, 1999).

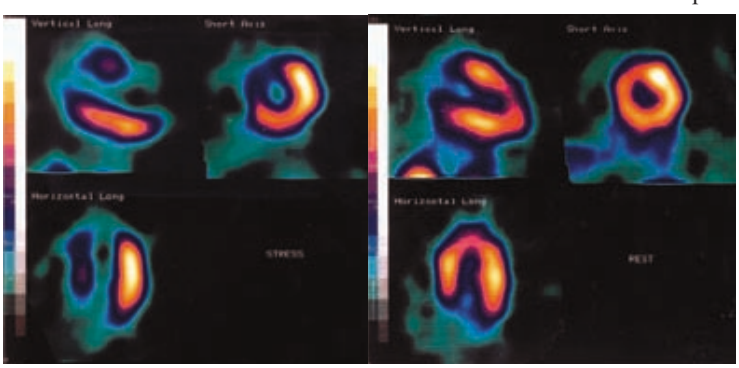

Figure 2. A 68-year-old female had chest tightness unrelated to exercise and no risk factors for coronary artery disease. Exercise electrocardiography was submaximal, limited by fatigue and without ST segment changes. The images show profound ischaemia of the anterior wall, apex and septum, compatible with a tight proximal left anterior descending lesion. Coronary arteriography confirmed the lesion and showed normal circumflex and right coronary arteries. The lesion was angioplastied with resolution of symptoms.

PROGNOSIS

The role of MPI in management arises from the relationship between the depth and extent of perfusion abnormalities and the likelihood of future cardiac events (*Table 3*). A normal MPI study after adequate stress is associated with an annual incidence of hard coronary events (myocardial infarction, unstable angina or death) below 1%, a rate even lower than in an asymptomatic age-matched population (Brown, 1996). Conversely

TABLE 2.
Indications for myocardial perfusion imaging

Instead of exercise electrocardiography	The resting ECG is abnormal
	Restricted exercise tolerance
	Women
After exercise electrocardiography	Equivocal ST segment changes with exercise
	The exercise ECG is abnormal but the pre-test probability of CAD is low
	The exercise ECG is normal but the pre-test probability of CAD is high

CAD = coronary artery disease; ECG = electrocardiogram

TABLE 3.
Clinical settings where myocardial perfusion imaging has prognostic value

The asymptomatic patient with an abnormal exercise electrocardiogram
Investigation of suspected coronary artery disease
Known coronary artery disease with stable angina
After myocardial infarction
After stabilization of unstable angina
After myocardial revascularization
Before non-cardiac surgery

severe and extensive inducible perfusion defects imply a poor prognosis (*Figure 3*) (Ladenheim et al, 1986). Other predictors of high risk are stress-induced ventricular dilation and increased lung uptake, both of which reflect left ventricular dysfunction and are markers of extensive ischaemia (*Table 4*). Patients with a normal scan or low-risk pattern can therefore generally be managed medically in the absence of intractable symptoms, while those with a high-risk pattern should be considered for coronary angiography and revascularization (Hachomovitch et al, 1998).

DETECTION OF VIABLE AND HIBERNATING MYOCARDIUM

Hibernating myocardium is viable (alive) but susceptible to ischaemia and it is akinetic although with the potential to recover function after the ischaemia is abolished by revascularization. The clinical importance of detecting viable myocardium is after infarction when a coronary stenosis is demonstrated but it is not clear whether there is viable but ischaemic myocardium that might benefit from revascularization. The clinical importance of hibernation is slightly different and it is normally in the setting of chronic ischaemic left ventricular dysfunction when symptoms are mainly related to heart failure, and the hope for revascularization is that it will improve ventricular function.

Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose to assess glucose metabolism has been regarded as the reference method for identifying viable myocardium but the simple single photon emission computed tomography (SPECT) tracers of thallium, MIBI and tetrofosmin are normally adequate (Bonow et al, 1991; Dilsizian et al, 1993). Ventricular function is generally assessed by echocardiography, although magnetic resonance imaging (MRI) is superior because it is a three dimensional technique and comparison between viability and function is easier. Gated SPECT has poorer resolution than echocardiography or MRI, but it allows assessment of viability and function in the same image and avoids the need for comparison between different sets of images.

A reasonable approach to the patient with possible hibernating myocardium is to perform gated SPECT first using MIBI or tetrofosmin, ensuring that the resting injection is given under nitrate cover in order to improve the detection of viable myocardium in areas with reduced perfusion at rest. Because of the high sensitivity of this technique, if the area in question has severely reduced tracer uptake (less than 30% of maximum) then there is no significant hibernating myocardium and little benefit would be expected from revascularization. If there is normal or only mildly reduced uptake (greater than 50% of maximum) and the area is ischaemic and akinetic then hibernation is likely and improvement in function can be expected after revascularization.

Most surgeons would require at least three of nine myocardial segments to be hibernating to warrant revascularization. If uptake of tracer is moderately reduced (30–50%) in an akinetic segment with ischaemia, then the amount of hibernating myocardium is borderline to produce an improvement if revascularized. In this setting, further tests such as dobutamine echocardiography or MRI may help by demonstrating the presence of contractile reserve. One caveat is that even in the absence of contractile reserve, viable but ischaemic myocardium may be protected from future damage or remodelling by revascularization, and recovery of function is not the only consideration when considering surgery in patients with ischaemic heart failure.

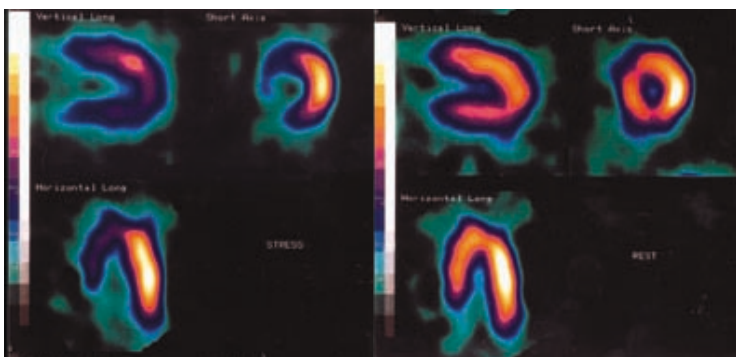

Figure 3. A 73-year-old man had recent onset of exertional chest pain but with some atypical features. He was awaiting hip replacement for osteoarthritis and was unable to exercise. Myocardial perfusion imaging was requested for perioperative risk assessment. The images show profound and extensive ischaemia of the anteroseptal and inferoseptal regions, suggesting a high likelihood of future and perioperative coronary events. Coronary revascularization was recommended before the orthopaedic surgery.

TABLE 4.
Features of myocardial perfusion imaging determining the likelihood of future coronary events

Depth of inducible perfusion abnormality
Extent of inducible perfusion abnormality
Transient left ventricular dilation
Increased lung uptake of thallium
Impaired left ventricular function on gated single photon emission computed tomography

When these principles are applied in patients with ischaemic left ventricular dysfunction, then symptoms and medium-term outcome can be improved (Di Carli et al, 1995; Gunning et al, 1997).

AFTER CORONARY ANGIOGRAPHY

Approximately half of MPI studies are requested by invasive cardiologists (Prvulovich, 1999). Even once coronary angiography has been performed, the most appropriate management may not be clear. For instance, there may be a coronary stenosis of intermediate severity perhaps coupled with atypical symptoms, a vessel may be poorly visualized, or catheter tip spasm may confuse interpretation. MPI can be used to detect myocardial ischaemia in a specific territory and hence act as a guide to the need for intervention.

AFTER INTERVENTION

Coronary angioplasty, bypass surgery and other interventions are performed to improve myocardial perfusion, and hence the counsel of perfection is to perform MPI routinely before and 3 months after intervention in order to assess the effects of intervention and to provide a baseline for the future. In practice, this strategy is uncommon and MPI is reserved for when symptoms recur, but management decisions are simpler if MPI is performed routinely after intervention. Restenosis after angioplasty is common, even after stenting. However, the significance of asymptomatic restenosis is unclear, and patients with recurrent and typical angina can often go straight to repeat angiography. In patients with atypical symptoms, MPI may be the most appropriate first step, allowing angiography to be reserved for those with recurrent ischaemia.

Chest pain is also relatively common after bypass surgery but it is not always the result of ischaemia. Non-ischaemic causes include musculoskeletal pain after thoracotomy or harvesting of the internal mammary artery. The resting ECG may be abnormal after bypass surgery and hence changes during exercise are unhelpful. In contrast, MPI can differentiate ischaemic from non-ischaemic pain, and a normal study will often avoid the need for further investigation.

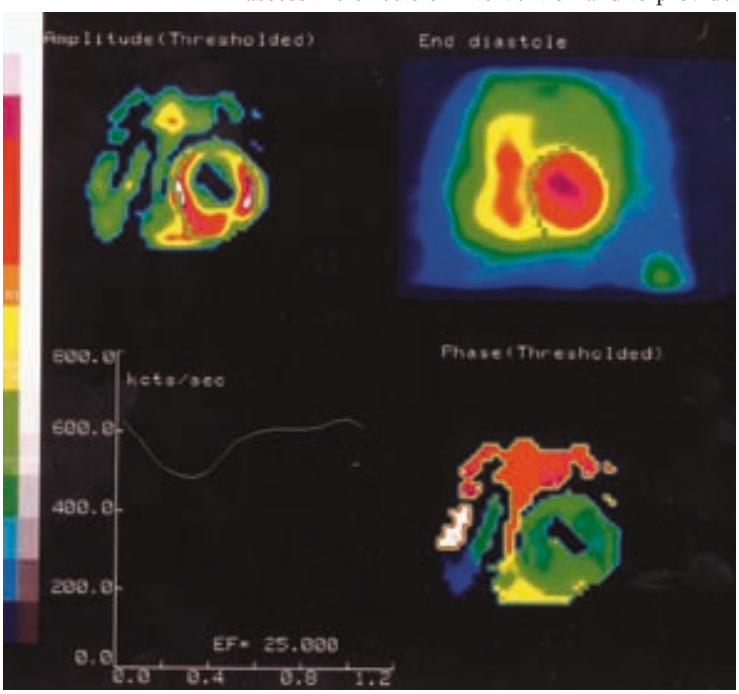

Figure 4. A 60-year-old man had chronic airways disease but no history of coronary artery disease. He presented with a 6-month history of increasing exertional dyspnoea. Echocardiography was suboptimal because of his airways disease. Equilibrium radionuclide ventriculography was performed. The end diastolic image shows a dilated left ventricle (LV) with a normal sized right ventricle. The amplitude image shows a central defect over the LV and the phase image is normal over the LV (the black area is masking of the region with no amplitude). This pattern is typical of extensive inferior akinesis. Resting LV ejection fraction is 25% (normal >45%).

RADIONUCLIDE VENTRICULOGRAPHY

Equilibrium radionuclide angiocardiography (RNA) activity in the UK has remained stable over a number of years (Pennell et al, 1998), in part as a result of the increasing availability of echocardiography. Both techniques provide information about left ventricular function and each has its advantages and disadvantages. Echocardiography is a technique familiar to most cardiologists but RNA is more reproducible (Wackers et al, 1979). The radionuclide technique is therefore largely reserved for patients in whom echocardiography is technically difficult (*Figure 4*) or when serial measurments are important, such as in patients receiving cardiotoxic chemotherapy.

The technique involves in vivo labelling of red cells with technetium-99m pertechnetate and ECG-gated imaging of the blood pool within the heart. Because there is a direct relationship between left ventricular counts and volume, left ventricular ejection fraction can be determined from a graph of counts through the cardiac cycle, corrected for background counts which are normally estimated from a crescentic region of interest lateral to the ventricle.

Regional function can be assessed from parametric images that quantify in each pixel the amplitude and phase (timing) of the changes in counts. The phase image is particularly sensitive to delayed contraction and it is an early marker of myocardial abnormality. Right ventricular

function can also be assessed, although this is most accurate from a first-pass study when the first passage of activity through the central circulation is imaged after rapid injection of a small bolus of activity. Studies can be performed at rest and during dynamic exercise and RNA is the most reliable method of assessing ventricular function during stress. Stress studies have mainly been displaced by MPI in patients with CAD, but they are still useful in patients with valvular regurgitation and with congenital heart disease. HM

Conflict of interest: None

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KEY POINTS

- Myocardial perfusion imaging (MPI) is a robust and accurate method for the assessment of myocardial viability and perfusion. It produces three-dimensional information and with electrocardiographic (ECG) gating it can also assess myocardial motion and thickening.
- MPI can localize and quantify the extent of ischaemia, features that cannot be deduced from the exercise ECG.
- MPI is the single most powerful predictor of outcome in patients with coronary artery disease. A normal study indicates a likelihood of future coronary events below 1% per year, and the extent and severity of inducible abnormalities allow the risk of events to be predicted over at least 2 years.
- Early use of MPI is the most cost-effective strategy for the investigation of patients presenting with chest pain. It should be performed instead of exercise ECG if the resting ECG is abnormal, in women, and in patients who are unlikely to be able to exercise maximally.
- Gated single photon emission computed tomography allows myocardial viability, ischaemia and function to be assessed from a single study and it normally answers relevant clinical questions in patients with ischaemic left ventricular dysfunction.