Non-invasive investigations

C Anagnostopoulos, M Y Henein and S R Underwood
Royal Brompton Hospital and Imperial College School of Medicine, London, UK

The most commonly used techniques for imaging the effects of coronary artery disease (CAD) on the heart are myocardial perfusion scintigraphy (MPS) and echocardiography. Both tests have been validated during exercise and pharmacological stress and they are valuable for the diagnosis and aiding management decisions in patients with suspected or known CAD. In a proportion of these patients, repetitive episodes of myocardial ischaemia can lead to intracellular and extracellular changes so that myocytes, although viable, have insufficient energy to sustain contraction. This phenomenon is known as myocardial hibernation and it can be detected accurately by both MPS and stress echocardiography. The review that follows highlights the role of these techniques as powerful diagnostic and prognostic tools in clinical cardiology. In order to make the best use of them, attention to detail and planning are required to design the test to suit the clinical problem and to obtain the most accurate data possible.

Cardiac imaging is an important component of diagnosis and assessment in cardiology, and it is now essentially a sub-speciality of its own. The imaging techniques include echocardiography, nuclear cardiology, and magnetic resonance imaging, and there are other techniques in which cardiologists have an interest, such as electron beam computed tomography.

Myocardial perfusion scintigraphy: basic principles

Myocardial perfusion scintigraphy (MPS) is the only widely available and validated method of assessing myocardial perfusion and hence is an essential component of modern cardiology. The technique involves the injection of a radioactive tracer followed by imaging of its myocardial distribution using a gamma camera. The images are now almost exclusively tomographic (single photon emission computed tomography, or SPECT) using a rotating gamma camera, often with two heads. Thus, the images are truly three dimensional, albeit of relatively low resolution (10–15 mm).

There are three commercially available tracers of myocardial perfusion, thallium-201 and two thallium analogues, which are also univalent cations labelled with technetium-99m (see below). All three tracers have two requirements for myocardial uptake to be seen. First, there must be viable
myocytes since they are taken up mainly passively across an active myocyte membrane that maintains a negative intracellular potential. Second, there must be adequate myocardial perfusion since the tracers are avidly taken up by the myocardium and their initial distribution is proportional to delivery. Thus, all three tracers are combined tracers of myocardial viability and perfusion.

The normal myocardial perfusion image shows relatively uniform uptake throughout the myocardium (Fig. 1). Areas with either reduced myocyte density (as after infarction) or relatively reduced perfusion (as in inducible ischaemia) show defects. If the tracer is injected during stress, the initial stress images will show a defect in either case. Subsequent rest images (see below) will show a persistent defect with infarction but recovery of uptake if the initial defect is caused by stress-induced ischaemia or perfusion heterogeneity (Fig. 2). This is the basis of defects that are commonly described as fixed or reversible.

**Forms of stress**

Dynamic exercise is the most common type of stress because of the important clinical information that is provided by exercise tolerance and haemodynamic response. However, between one-third and one-half of patients in most centres are not able to exercise adequately and this seriously limits the value of dynamic exercise. In addition, many patients have already had an exercise ECG before referral for perfusion imaging and, in these circumstances, a pharmacological alternative to dynamic exercise is very valuable. The established pharmacological stressors are the coronary vasodilators adenosine and dipyridamole, and the β-agonist dobutamine.

Dipyridamole is administrated intravenously at a dose of 0.14 mg/kg/min for 4 min. The radiotracer is given 4 min after the end of the infusion, at which time vasodilation is maximal. Adenosine is infused at the same dose over 4–6 min with injection of radiotracer 2 min from the end. It is also possible to combine stress techniques; the commonest pairing is dynamic exercise with either adenosine or dipyridamole, which increases sensitivity for the detection of perfusion defects and also their conspicuity. The addition of submaximal exercise has other benefits. It reduces the side-effects caused by peripheral vasodilation, it reduces the incidence of bradyarrhythmia, and it reduces splanchnic uptake of tracer, which can interfere with interpretation of the inferior wall when using the technetium tracers. Patients with left bundle branch block, bifascicular block or paced rhythm should receive adenosine or dipyridamole alone in order to reduce the likelihood of inducing septal perfusion abnormalities related to the conduction abnormality. Adenosine and dipyridamole are
contra-indicated in patients with reversible airways obstruction since they can induce bronchospasm. These patients can, however, safely be stressed by dobutamine. This is normally infused into a peripheral vein starting at 5 µg/kg/min and increasing in increments of 5 µg/kg/min to a maximum of 20 or 40 µg/kg/min, with stages lasting for 2–5 min to allow stabilisation of the haemodynamic effect.

**Radiopharmaceuticals**

Thallous chloride has been used routinely as a tracer of myocardial perfusion for almost 25 years. Imaging starts within 5–10 min of injection and should be completed within 30 min. During this period, the distribution of thallium within the myocardium is relatively fixed and, despite the cessation of stress, the images reflect myocardial distribution at peak stress. Because there is a dynamic exchange of thallium between the intra- and extracellular spaces, redistribution over the next 2–4 h leads to uptake of thallium in all viable myocytes, irrespective of perfusion. The initial images are, therefore, a combination of viability and perfusion, the redistribution images are viability alone, and differences between the images are areas of hypoperfusion at the time of tracer injection. If a stress induced defect is profound, then redistribution is often incomplete at 4 h. In these circumstances, thallium can be injected again at rest and a third set of images acquired. These re-injection images reflect viability more reliably.

Although thallium is an excellent tracer of perfusion and viability, it has some limitations. First, because of its relatively long half-life (72 h), radiation exposure is high: 80 MBq delivers an effective dose equivalent to 18 mSv, which is more than the average exposure during coronary arteriography. Second, only 4% of the injected dose is taken up by the myocardium, which leads to images with relatively low count density. Third, the low energy emission at 80 keV leads to low resolution images with significant attenuation by soft tissues. Technetium-99m (Tc-99m) compounds do not suffer the first and third of these problems, and these include Tc-99m-2-methoxy-isobutyl-isonitrile (MIBI) and Tc-99m-1,2-bis[bis(2-ethoxyethyl) phosphino] ethane (tetrofosmin). The benefits of the technetium tracers include the lower radiation exposure and better quality images in obese patients and women with large breasts.

In contrast to thallium, the technetium tracers do not redistribute and separate injections have to be given in order to assess stress and rest perfusion. The 6 h half-life of Tc-99m means that the two studies should ideally be performed on separate days to allow for the decay and clearance of activity from the first injection. The two studies can be performed on the same day if a larger dose (at least 3-fold) is given on
the second occasion in order to swamp the residual activity from the first injection. The maximum dose allowed for routine use in the UK is 400 MBq each for stress and rest injections on separate days, or a total of 1000 MBq if stress and rest studies are performed on the same day: 1000 MBq corresponds to an effective dose equivalent of 10 mSv.

Myocardial perfusion scintigraphy: clinical applications

Diagnosis of coronary artery disease

Chronic chest pain
MPS has an established role in the detection of perfusion abnormalities caused by coronary artery disease (CAD). Used as a diagnostic tool, it has a sensitivity of 91% and specificity 89%; this is significantly better than exercise electrocardiography, which has a sensitivity of 68% and specificity 77%. Several factors militate against replacing the exercise ECG entirely with MPS. The most important is the relative availability of the two techniques, but radiation burden and cost are also relevant. Although the cost of MPS (£220) is higher than that of the exercise ECG (£70), this is more than outweighed by its greater effectiveness. Studies of cost-effectiveness have shown significant advantages for strategies of investigation using MPS, with savings in total diagnostic and management costs over 2 years in the region of 20% in centres routinely using scintigraphy.

MPS is the most appropriate diagnostic test for patients with an intermediate probability of CAD. This category includes patients with atypical chest pain or asymptomatic individuals with a positive exercise ECG, and those with equivocal ST segment changes or a normal exercise ECG despite a history of typical angina. Perfusion imaging should be the initial investigation in patients who are unlikely to exercise adequately, in women (because of the very high number of false positive ECGs), and if the exercise ECG will be uninterpretable because of resting abnormalities such as left bundle branch block, pre-excitation, left ventricular hypertrophy, or drug effects.

Acute chest pain
Nuclear techniques are less commonly used in patients presenting with acute chest pain, mainly because of the logistical problems of imaging in the emergency department or coronary care unit. Nonetheless, several centres have demonstrated the value of perfusion imaging in the acute setting, especially when the resting ECG is not diagnostic of myocardial ischaemia. The presence of a resting perfusion defect has a high positive predictive value for acute infarction in patients without previous infarction, particularly if it is associated with a wall motion abnormality on gated imaging, and these patients should be admitted to the coronary care unit.
Conversely, a normal perfusion scan excludes acute infarction and suggests that exercise ECG or stress perfusion imaging should be the next diagnostic step. If the perfusion tracer is injected during chest pain, a normal perfusion scan excludes a cardiac cause and allows the patient to be discharged pending further investigation.

**Prognosis of CAD**

**Suspected or known CAD**

Beyond diagnosis, the most valuable contribution that perfusion imaging can make to the management of known or suspected CAD is to assess the likelihood of a future coronary event such as myocardial infarction or coronary death. Prognosis is strongly influenced by the extent and severity of inducible perfusion abnormality and this can guide the need for invasive investigation and revascularisation (Figs 3 & 4). MPI is more powerful as an indicator of prognosis than clinical assessment, the exercise ECG, and coronary angiography, and it provides incremental prognostic value even once the other tests have been performed.

The most important variables that predict the likelihood of future events are the extent and depth of the inducible perfusion abnormality. The relative value of the fixed component of a stress defect is unclear, but it is likely that left ventricular function is the best indicator of prognosis in patients with predominantly fixed defects. Thus the patient with extensive ischaemia is at high risk of a coronary event irrespective of the presence of infarction, and the patient without ischaemia but with a fixed defect is only at risk if the defect leads to significantly impaired function. Additional markers of risk are increased lung uptake on stress thallium images since this indicates raised pulmonary capillary pressure either at rest or in response to stress, and ventricular dilation that is greater in stress thallium images than at rest. Transient ischaemic dilation can also be seen with technetium imaging and it may the result of extensive subendocardial ischaemia giving the impression of cavity dilation (Fig. 5).

In patients with known or suspected CAD, a normal perfusion scan is very valuable because it indicates a likelihood of a coronary events of less than 1% per year, a rate that is lower than that in an asymptomatic population. Thus whether minor coronary disease is present or not, further investigation can be avoided. This negative predictive value is independent of the type of imaging agent and technique, the method of stress, the population studied, and the clinical setting.

**Management after infarction**

An important aspect of clinical management after infarction is to identify patients at high risk of further events such as re-infarction or death, and hopefully to intervene in order to prevent these events. Clinical indicators of
Ischaemic heart disease: therapeutic issues

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6
high risk in the acute phase include hypotension, left ventricular failure, and malignant arrhythmias; these patients are candidates for early coronary angiography. After the acute phase, prognosis is related to the degree of left ventricular dysfunction and the extent and severity of residual ischaemia; both can be assessed objectively by radionuclide imaging. Patients without high risk clinical markers or severely impaired LV function are at lower risk, but some form of stress testing is required in order to assess exercise tolerance and the presence of residual ischaemia. This is often performed by exercise electrocardiography at 6 weeks, but there is increasing evidence that very early stress testing is better since the majority of recurrent clinical events occur early. Perfusion imaging using vasodilator stress is an ideal tool since many physicians are reluctant to exercise patients very early after infarction. In the most aggressive centres, adenosine perfusion imaging will be performed at 5 days and used to guide the need for coronary angiography or discharge and medical therapy.

Risk assessment before non-cardiac surgery
The aim of risk assessment before non-cardiac surgery is to identify myocardial ischaemia and to estimate the risk of peri-operative cardiac events. See page opposite for figures.
Ischaemic heart disease: therapeutic issues

Events. Initial risk assessment is based on clinical risk factors, functional capacity and the risk of the surgery itself. Patients with intermediate clinical predictors (mild angina, prior infarction, treated heart failure, or diabetes) or with minor predictors (age >70 years, abnormal resting ECG, history of stroke or hypertension) and impaired exercise tolerance need further assessment if they are to undergo moderate or high-risk surgery. Patients at high clinical risk (recent infarction or unstable angina, decompensated heart failure, or significant arrhythmias) require investigation even for low risk surgery. When further investigation is required, the first test is most commonly the exercise ECG in patients who are able to exercise. However, if maximal exercise is unlikely or if the resting ECG is uninterpretable, then MPS is the most appropriate investigation.

Myocardial revascularisation

MPS can be valuable both before and after myocardial revascularisation, either by angioplasty or bypass surgery. Neither procedure should be undertaken without objective evidence of ischaemia, and perfusion imaging is often the most reliable way of obtaining this information and of ensuring that angioplasty is targeted at the culprit lesion. It has an excellent negative predictive value for predicting restenosis and clinical events after angioplasty, and this can be particularly helpful in patients with recurrent, but atypical, symptoms. Routine perfusion imaging after angioplasty in the absence of symptoms is not common, although it can sometimes be useful as a new baseline in case symptoms recur. It can, however, be justified routinely in patients with impaired left ventricular function, proximal LAD and multivessel disease, suboptimal results of angioplasty, diabetes, and those with occupations requiring low coronary risk. If perfusion imaging is performed after angioplasty, then it should ideally be performed later than 6 weeks since perfusion abnormalities can persist even with a good anatomical result. Possible exceptions to this are patients with high-risk anatomy who can benefit from earlier imaging.

As with angioplasty, patients who are asymptomatic after bypass surgery do not routinely undergo perfusion imaging, although it can be helpful as a baseline for future management since revascularisation is frequently incomplete. More commonly, it is used for follow-up and it can be used 5 years after surgery to guard against silent progression of prognostically important disease. Patients with symptoms after surgery may benefit from perfusion imaging and the algorithms to be used are very similar to those in the diagnostic setting.

Myocardial viability and hibernation

Perfusion and metabolic tracers play an increasing role in the detection of viable, hibernating and stunned myocardium. The term ‘viable’
strictly refers to myocardium that is alive, without implying any particular state of function, perfusion or metabolism. Sometimes the term is used interchangeably with ‘hibernation’ although it is better to avoid this potentially confusing terminology. Stunning is a state of altered metabolic and contractile function that follows an ischaemic episode and occurs despite restoration of perfusion. In hibernation, the chronic reduction in myocardial perfusion is matched by down-regulation of contractile function. However, the concept of chronic reduced resting flow is disputed, and it has been suggested that hibernation is simply repetitive stunning. In clinical practice, hibernation is assumed if viable myocardium is dysfunctional at rest, but this is only one possible explanation since other pathology such as remodelling and myopathy may present with the same pattern.

Detection of hibernating myocardium is particularly important in patients where left ventricular performance is severely compromised. A pivotal issue in this group is whether revascularisation will lead to a clinically significant improvement in ventricular function which may in turn lead to improved symptoms and survival. Studies have demonstrated that the increase of ejection fraction postoperatively is related to the amount of hibernating myocardium. In addition, revascularisation reduces the risk of infarction and death in patients with impaired left ventricular function and hibernating myocardium demonstrated by positron emission tomography.

Thallium can also be used in several ways to identify viable and hibernating myocardium. Regional uptake of thallium identifies regional viability, and a common threshold for defining clinically significant viability is 50% of maximal uptake. An important additional criterion is the presence of inducible ischaemia before diagnosing hibernation since it is an ischaemic syndrome. Care must be taken in these studies that sufficient time is allowed for redistribution, because the latter may be incomplete even after 4 h. Simple stress and redistribution imaging may, therefore, be insufficient, and alternative strategies are 24 h redistribution imaging, re-injection of thallium-201 at rest after stress and redistribution imaging and resting injection with immediate and delayed imaging. These protocols have been validated in a number of studies and reasonable agreement has been shown between thallium-201 imaging and PET.

MIBI and tetrofosmin have also been used for the detection of viable and hibernating myocardium. In theory, these tracers may underestimate viability in areas with reduced resting perfusion because they are combined tracers of viability and perfusion without the property of redistribution that allows viability to be assessed independently. Some studies have found thallium to be better for the assessment of viability, but others have found them to be similar. It does appear though that...
Ischaemic heart disease: therapeutic issues

if the tracers are given under the cover of intravenous or sublingual nitrates, then resting perfusion is improved and the technetium tracers are good markers of viability.

An important problem in studies of hibernation is that viability and function are often assessed from different techniques, and it can be difficult to be sure that the same myocardial segment is being compared in each. Thus, the ideal technique should combine information on viability, perfusion and function in a single image, and ECG-gated technetium SPECT is very helpful. This is our own initial technique in patients referred for the assessment of hibernation. Although, assessment of regional function is difficult in regions of previous infarction and significantly reduced tracer uptake, this is not a major limitation since these areas contain little myocardium and will not benefit from revascularisation.

Echocardiography

Transthoracic echocardiography provides a simple non-invasive method of assessing ventricular function, and stress echocardiography can be used to assess the severity of ventricular dysfunction associated with exertional symptoms. Intravenous ultrasound allows the arterial wall to be studied in the catheter laboratory, and transoesophageal echocardiography provides a way of assessing proximal coronary flow velocity at the time of bypass surgery or in the early postoperative period, particularly in patients in whom ventricular function is slow to recover.

Resting echocardiography

In patients with previous myocardial infarction, two dimensional transthoracic echocardiography shows obvious wall motion abnormalities. The localised loss of myocardial tissue indicates scar formation when the myocardium decreases in total thickness and the muscle is irreversibly damaged. After antero-apical infarction, an aneurysm may develop that is easily diagnosed by paradoxical motion (Fig. 7). In the absence of myocardial infarction, resting left ventricular echocardiography may be entirely normal as shown by both two-dimensional images and M-mode. Segmental minor axis hypokinesis develops as the disease progresses. Long axis function is particularly sensitive to ischaemia, and this can easily be studied using a M-mode technique with or without tissue Doppler myocardial velocities. Long axis function is remarkably sensitive to coronary artery disease even in the absence of symptoms or ECG changes. Systolic abnormalities in the form
of reduced amplitude of motion and post-ejection shortening are seen after myocardial infarction but, even in the absence of infarction, diastolic disturbances such as delayed onset of lengthening and slow lengthening velocity are associated with inducible ischaemia. These wall motion disturbances can be used as objective markers of disease progression or successful response to revascularisation. Furthermore, these disturbances determine the pattern of mitral flow (Fig. 8), which is predominantly late diastolic. As long as left ventricular function is maintained, colour and continuous wave Doppler can detect mild mitral regurgitation. In more advanced ischaemic heart disease, systolic function is reduced and filling pressures rise resulting in a well-defined restrictive filling pattern, that is always associated with functional mitral regurgitation of varying severity. Similar changes can affect the right ventricle.

**Stress echocardiography**

Stress echocardiography can be used to identify inducible wall motion disturbances in patients with coronary insufficiency, but it is difficult to acquire clear images during dynamic exercise. Pharmacological stress overcomes this problem and agents such as adenosine, dipyridamole, and dobutamine are used. Dobutamine echocardiography has become a common investigation and it is more sensitive than the exercise ECG for the diagnosis of CAD. Standard stress echocardiography involves semi-quantitative analysis of two dimensional echocardiographic images.
Ischaemic heart disease: therapeutic issues

![ECG PCG](image)

![Mitral Doppler](image)

![Long axis](image)

**Fig. 8** Long axis M-mode recording of left ventricular free wall from a normal subject (left) and from a patient with ischaemic heart disease (right). There is abnormal ventricular filling in the patient caused by the incoordinate long axis relaxation.

of the left ventricular short and long axes (Fig. 9). A summed segmental wall motion score is used to assess the extent and severity of stress induced wall motion disturbances. An akinetic segment at rest that does not change with stress represents infarcted myocardium.42

Patients who develop severe ventricular dysfunction are at high risk of future cardiovascular events. The prognostic accuracy of the wall motion score increases when more than one ventricular segment is involved. Also, the diagnostic accuracy of the score index is significantly
Non-invasive investigations

higher in patients with multivessel coronary disease compared with single vessel\textsuperscript{43}. As a marker of global ventricular function, stress ejection fraction can also be used to stratify cardiac risk after myocardial infarction and before non-cardiac surgery\textsuperscript{44}. Although stress-related wall motion abnormalities are obviously different in essence from those of myocardial perfusion, the diagnostic accuracy of the two techniques is similar\textsuperscript{45}. The sensitivity of stress echocardiography has improved with the advent of harmonic imaging\textsuperscript{46} and the use of contrast agents\textsuperscript{47}.

**Myocardial viability and hibernation**

Both resting and stress echocardiography have been used for the assessment of myocardial viability. Resting diastolic wall thickness of 6 mm is commonly used as a sign of viable myocardium\textsuperscript{48}. Hibernation has a biphasic response to dobutamine infusion with contractile reserve at low dose, but deterioration at higher dose\textsuperscript{49}. Hibernation in at least 5 of the 16 conventional segments predicts good recovery of left ventricular function after revascularisation\textsuperscript{50,51}.

**Long axis function during stress**

Ventricular long axis function studied during dobutamine stress is also useful in the diagnosis of CAD (Fig. 10)\textsuperscript{52}. Systolic disturbances such as a decrease in excursion amplitude, correlate with stress induced QRS
Ischaemic heart disease: therapeutic issues

Broadening. Diastolic disturbances such as slow lengthening velocity correlate with delayed repolarisation (prolonged QTc interval). This close association between electrical and mechanical function is not surprising. Uncoordinated long axis function during stress compromises ejection and filling times, and this relationship is independent of inotropic state. Abnormalities are also seen in patients with rate-related left bundle branch block but normal coronary arteries. In this condition, the diastolic incoordination itself can compromise subendocardial perfusion and lead to angina. Right ventricular ischaemia also leads to abnormalities.

References

4 Pennell DJ, Mavrogeni SI, Forbat SM, Karwatowski SP, Underwood SR. Adenosine combined with dynamic exercise for myocardial perfusion imaging. J Am Coll Cardiol 1995; 25: 1300–9
14 Kontos MC, Jesse RL, Schmidt KL, Ornato JP, Tatum JL. Value of acute rest sestamibi perfusion imaging for evaluation of patients admitted to the emergency department with chest pain. J Am Coll Cardiol 1997; 30: 976–82
17 Marie PY, Danchin N, Durand JF et al. Long-term prediction of major ischemic events by exercise thallium-201 single-photon emission computed tomography. Incremental prognostic value.
compared with clinical, exercise testing, catheterization and radionuclide angiographic data. J Am Coll Cardiol 1995; 26: 879–86
Ischaemic heart disease: therapeutic issues


52 Xiao HB, Gibson DG. The effect of intermittent left bundle branch block on left ventricular diastolic function – a case report. *Heart* 2001; 85: 411–6