# Advances in SPECT in evaluating coronary disease

***Myocardial perfusion scintigraphy is the longest established of the functional imaging investigations for patients with known or suspected coronary artery disease. This article describes recent technical and clinical advances that are ensuring that the technique remains relevant some 40 years after its first introduction.***

Over the past 40 years, myocardial perfusion scintigraphy (MPS) has come to dominate the non-invasive imaging of patients with suspected or known coronary artery disease. Camera technology, radiopharmaceuticals and pharmacological stress agents have significantly improved since the original exercise-redistribution planar thallium scans were performed in the mid-1970s. MPS as routinely performed today – with pharmacological stress, technetium-99m-labelled radiopharmaceuticals, and single photon emission computed tomographic (SPECT) imaging with gating – has been well-established since the early 1990s. However, it would be wrong to regard it as a static, non-evolving technique that is ready to be superseded by newer imaging modalities. This review focuses on some recent technical and clinical advances in MPS that will ensure that it continues to play an important role in the investigation of coronary disease.

## Advances in pharmacological stress

The essence of MPS is comparison of myocardial perfusion during coronary arteriolar vasodilation (stress) with that at rest. Dynamic exercise remains the stress method of choice for patients able to achieve target heart rate on a treadmill or ergometer, but many patients referred for MPS are unable to exercise satisfactorily and require pharmacological stress, usually with a primary vasodilator drug. Dipyridamole was introduced in the late 1970s, and adenosine in the early 1990s. Both act via adenosine $A_{2a}$-receptors on coronary arterioles, adenosine directly and dipyridamole indirectly by inhibiting the cellular reuptake of endogenous adenosine (a breakdown product of ATP). Dipyridamole and adenosine are widely used, effective and generally safe. However, the administration protocols are relatively time-consuming, and the lack of $A_{2a}$-selectivity gives the potential for bronchoconstriction via $A_3$-receptors, or complete heart block via $A_1$-receptors. Therefore both drugs are contraindicated in patients with reactive airways disease. Moreover, while they can be combined with exercise (by injecting dipyridamole beforehand, or adenosine as a continuous infusion), this must be planned in advance.

Regadenoson is a newly introduced vasodilator drug which addresses many of the limitations of dipyridamole and adenosine. It received Food and Drug Administration approval for use in the USA in 2008, and now accounts for approximately 75% of pharmacological stress tests in that large market. In the UK, it is now the first-line pharmacological stress agent in many large centres. It is a selective adenosine $A_{2a}$-receptor agonist, so can safely be administered to asthmatics (Prenner et al, 2012). The drug causes maximal coronary vasodilation within 30–60 s, and has a half-life of 2–4 minutes. Thus the stress protocol is very short: regadenoson is given as an intravenous injection of 400 µg over 10 s, followed by a 10 s saline flush, and then the radiopharmaceutical perfusion tracer. While any minor side effects can take a few minutes longer to resolve than with adenosine, patients can be processed through a stress room far more rapidly than with any other stress method. From a diagnostic perspective, the large ADVANCE MPI Study showed that regadenoson is equivalent to adenosine in inducing myocardial perfusion abnormalities (Mahmarian et al, 2009).

The rapid onset of action of regadenoson makes it easy to combine with exercise. Patients of questionable fitness can attempt treadmill or ergometer exercise, in the knowledge that regadenoson can be given quickly before the radiopharmaceutical should they be unable to achieve target heart rate. Useful information is obtained about exercise capacity and symptoms, side effects are reduced compared with pharmacological stress alone, and image quality is optimal as a result of exercise-induced splanchnic vasoconstriction (Parker et al, 2013; Thompson et al, 2013).

## Advances in SPECT hardware and processing

The first Anger gamma camera came onto the market in 1961, but the underlying principles of the imaging detector have hardly changed over 50 years. Sequential technical refinements have led to great improvements in image quality, but gamma camera technology has reached the point where performance is essentially limited by the underlying physics. A typical gamma camera scintillation detector consists of a large flat sodium iodide crystal, with a hexagonal array of photomultiplier tubes on the side away from the patient. Incident gamma photons are absorbed by the crystal, where their energy is converted into visible light photons. These light photons are detected by the photocathode of a photomultiplier tube, where they are converted to photoelectrons which are amplified.

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A lead parallel-hole collimator, placed on the side of the crystal facing the patient, ensures that gamma photons can only enter the detector if they are travelling perpendicular to its surface. Thus the spatial distribution of scintillation events within the crystal represents the spatial distribution of gamma photons emitted from the patient.

The growth in MPS in the USA has driven development of inexpensive dedicated cardiac gamma cameras, with small fixed heads. These are very useful for providing a high-volume service when space is limited, but imaging can be performed equally well on a large general-purpose dual-headed gamma camera. SPECT is performed by rotating the head(s) of the gamma camera (usually two, positioned at 90° to each other) around the front of the patient over a 180° orbit. The gantry stops every few degrees acquiring a sequence of planar images (usually 32 or 64), and a typical SPECT acquisition will take 10–20 minutes. Each planar projection can be electrocardiogram-gated to 8–16 frames to give information about left ventricular function. Increases in computing power have led to improvements in SPECT image processing, with filtered back projection giving way to iterative reconstruction methods. Iterative reconstruction is relatively resistant to low count statistics, and tends to generate fewer artefacts.

## Attenuation correction

Photons travelling to the camera from the walls of the left ventricle are attenuated to a varying degree by overlying soft tissues. In women breast tissue causes anterior attenuation artefact, while in men the diaphragm causes inferior attenuation artefact. A combination of reporter experience, clinical context, and the examination of raw data and gated tomograms usually allows attenuation artefacts to be differentiated from real perfusion defects. However, situations arise where it is impossible to make the distinction.

The effects of soft tissue attenuation can be removed by using a transmission map to correct the emission (SPECT) scan when it is reconstructed (*Figure 1*). The transmission scan is produced by using a radioactive gadolinium line source or X-ray computed tomography (if a SPECT-computed tomography scanner is used). Attenuation correction of SPECT can be of great value for less experienced reporters, by increasing the level of confidence in normal or abnormal appearances. It also increases the proportion of patients in whom a resting study can be avoided, by increasing the level of confidence in the normality of the stress study alone – if perfusion is normal during stress it must be normal at rest (Heller et al, 2004). This increases camera capacity and reduces patient radiation dose (up to 75% if a 1-day stress-rest protocol is used).

## Depth-dependent resolution recovery software

An important property of a parallel-hole collimator is that image resolution deteriorates with distance from it. This occurs in a highly predictable way for a given gamma camera and collimator, which has allowed manufacturers to develop 'depth-dependent resolution recovery' software to refine iterative reconstruction (*Figure 1*). This can be used to reduce acquisition times or tracer doses, while maintaining image quality. Applying depth-dependent resolution recovery to half-count studies (half the time or half the dose) yields images equivalent to full-count studies processed conventionally (Venero et al, 2009).

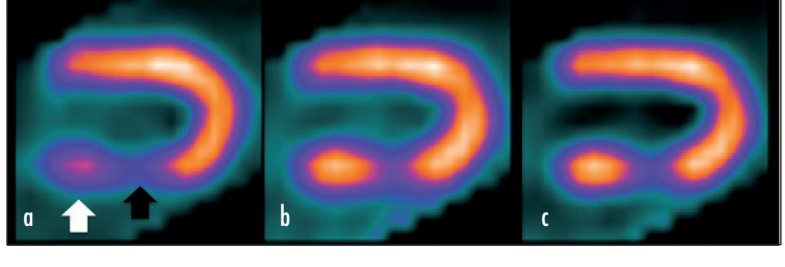
## Solid-state gamma cameras

The design of the Anger gamma camera leads to relatively inefficient detection (sensitivity) and localization (spatial resolution) of photons emitted from the patient. The requirement for collimation allows only about 1% of available photons into the crystal. The use of a scintillator and photomultiplier tubes to convert gamma photons into electrical pulses results in relative uncertainty in localization of scintillation events, with image blurring and suboptimal spatial resolution. Moreover, only about two-thirds of the optical photons even reach a photomultiplier tube, while only 25% of these are converted into electrons.

Cameras have been developed which use solid-state detectors, usually composed of cadmium zinc telluride. A 5 mm thick cadmium zinc telluride crystal has metal contacts deposited onto its surface to extract electrical signals, and is bonded to electronics to become a self-contained miniature detector. Absorption of a gamma photon results in direct production of a pair of charges – electron and 'hole' – which are swept towards a positive and negative electrode respectively. This results in a discrete 'all or none' electrical output signal, in contrast to the blurred Gaussian output of a conventional sodium iodide detector. Two companies produce cardiac cameras that use cadmium zinc telluride detectors: Spectrum Dynamics (D-SPECT), and GE Healthcare (Discovery NM 530c). The D-SPECT camera uses nine rotating vertical cadmium zinc telluride detector columns to image patients semi-supine in a reclining chair. The Discovery camera uses nineteen immobile cadmium zinc telluride detectors, each fitted with a pin-hole collimator, to image patients supine.

Compared to a standard gamma camera, cadmium zinc telluride cameras offer far better sensitivity and spatial resolution. This allows very high quality images to be obtained

***Figure 1. Vertical long axis slice of a cardiac phantom with a small filling defect placed in the apical inferior wall. a. Standard iterative reconstruction, showing relatively blurred true defect (black arrow) with attenuation artefact affecting the basal inferior wall (white arrow). b. Attenuation correction, showing normalization of the basal inferior wall. c. Attenuation correction and depth-dependent resolution recovery, showing thinner-looking myocardium, improved contrast between the myocardium and left ventricular cavity, and a more sharply defined defect.***



with a fraction of the acquisition time (and/or tracer dose) required for conventional SPECT, typically 2–5 minutes compared with 10–20 minutes (Esteves et al, 2009; Sharir et al, 2010). The superior energy resolution of cadmium zinc telluride detectors gives the potential to perform simultaneous dual isotope imaging (e.g. 99mTc with 123I or 201Tl), which would further shorten imaging protocols, benefitting both patients and departments. The high count-rate capability and acquisition of three-dimensional datasets allows first-pass absolute myocardial flow quantification to be performed, as well as obtaining the usual steady-state perfusion images later (Ben-Haim et al, 2013). Such information could be of great benefit in assessing patients with mutivessel coronary disease, where relative inducible hypoperfusion may not be apparent in all affected territories.

### SPECT-computed tomography scanners

The number of combined SPECT-computed tomography scanners in service has increased dramatically, driven mainly by the needs of non-cardiac imaging. Scanners are available with 64 or more X-ray computed tomography detectors, making them suitable for coronary imaging (calcium scoring and angiography) as well as SPECT MPS. Combined (hybrid) anatomical-physiological imaging for selected patients is therefore feasible. Coronary computed tomography has excellent negative predictive value for exclusion of coronary disease, but its positive predictive value is poorer because of a tendency to overestimate stenosis severity, especially when lesions are calcified.

Adding MPS to an abnormal computed tomography scan improves overall positive predictive value (in one study from 31% to 77%) compared to invasive coronary angiography (Rispler et al, 2007). Moreover, the combination of non-invasively obtained functional and anatomical information gives a more complete prognostic assessment than either type of information alone (van Werkhoven et al, 2009). In everyday practice, it is hard for a busy department to proceed directly from computed tomography coronary angiography to MPS on an ad-hoc basis. However, for selected patients, the advantages of combined anatomical and functional imaging, with image fusion if required, can be realized even if scans are obtained at different visits.

## Radiation exposure

An important consideration when performing SPECT MPS rather than an alternative functional imaging investigation such as stress echo or perfusion cardiac magnetic resonance imaging is the exposure to ionizing radiation. For a standard 2-day stress-rest technetium-99m protocol using 400 MBq on each day, the effective dose equivalent is 6–7 mSv, which is the equivalent of 2–3 years of background radiation. The technical refinements outlined above allowed this to be reduced substantially. Routine use of attenuation correction allows a higher proportion of stress acquisitions to be classed as definitely normal, obviating the resting study and halving the overall radiation exposure. Depth dependent resolution recovery software and solid-state gamma cameras have tended to be used to reduce image acquisition times – to as little as one third to one fifth of those needed for standard SPECT. However, these technologies could equally be used to reduce tracer doses instead. It is feasible to perform a 2-day technetium-99m protocol using as little as 150 MBq on each day, reducing the effective dose equivalent to 2–3 mSv (1–2 mSv in patients where stress-only imaging is possible).

## Clinical uses of SPECT

### Diagnosis of coronary disease

Early clinical studies of MPS focussed on its ability to exclude or predict the presence of obstructive coronary artery disease at angiography. Coronary disease was considered synonymous with luminal stenoses, hence angiography was the 'gold standard' investigation. Using this approach, MPS never achieved diagnostic sensitivities (proportion of patients with the disease who have an abnormal test) of more than 90%, with even lower specificities (proportion of patients without the disease who have a normal test) (Underwood et al, 2004). Normalcy rates (proportion of patients at low risk of the disease who have a normal test), which avoid the post-test referral bias that pushes down specificities, were significantly better at about 90%.

CE-MARC and MR-IMPACT II have challenged the diagnostic value of MPS compared with perfusion imaging performed using cardiac magnetic resonance (Greenwood et al, 2012; Schwitter et al, 2013). The sensitivity of MPS was poorer than expected from historical studies (59% and 67%) and inferior to that of cardiac magnetic resonance (67% and 87%), although in MR-IMPACT II its specificity was superior (72% *vs* 61%). Unfortunately MPS in these studies was less than 'state-of-the art', while there are indications that image quality, interpretation and analysis were suboptimal. While these studies have undoubtedly confirmed the value of cardiac magnetic resonance as a useful investigation, the findings with regard to MPS should be viewed with caution.

### Prognosis in coronary disease

Irrespective of its ability to mirror the results of invasive angiography, it is increasingly apparent that MPS can predict the prognosis of patients with known or suspected coronary artery disease. This is independent of clinical factors, results of exercise testing, and even angiographic findings. A particular strength is the prognostic reassurance provided by a normal result: the annual risk of cardiac death or non-fatal myocardial infarction is consistently below 1% (0.6% in a large meta-analysis) (Iskander and Iskandrian, 1998). Clinical factors influence the duration for which the low risk applies, the so-called 'warranty period' of a normal scan (Hachamovitch et al, 2003b). Thus a patient without diabetes or a background of proven coronary disease might have a warranty period of 5 years or more, while the presence of one or other high-risk characteristics could shorten it to 2 years or even less. The simple prognostic message provided by a normal scan has led to the adoption of MPS

by bodies such as the Civil Aviation Authority and Driver and Vehicle Licensing Agency in the UK.

While a normal MPS study predicts a benign prognosis, the less favourable outlook after an abnormal study is not 'all-or-none' (*Figure 2*). The landmark study of Ladenheim et al (1986) demonstrated that the cardiac event rate after MPS increased progressively with the extent and severity of perfusion abnormalities. More recent studies based on large patient populations have had the statistical power to identify which features of the imaging study predict which components of cardiac risk. In simplistic terms, the results of multivariate analysis suggest that the likelihood of non-fatal myocardial infarction increases exponentially with the extent of inducible hypoperfusion, while the likelihood of cardiac death is inversely related to left ventricular ejection fraction from gated SPECT (*Figure 3*) (Sharir et al, 2001).

As SPECT MPS shows relative rather than absolute myocardial perfusion, an acquisition can appear normal if all myocardial regions are hypoperfused to an equivalent degree: so-called 'balanced ischaemia'. This depends on the presence of multivessel coronary disease, creating the worry for both inexperienced referrers and reporters that high-risk coronary anatomy is hiding behind every apparently normal scan. In practice completely balanced ischaemia is very rare, although it is not uncommon for the full extent of ischaemia to be underestimated in multivessel disease as the least hypoperfused coronary territory must always be scaled as normal. In the unusual situation of fully balanced ischaemia, high-risk findings are almost always present which point to the true situation (*Figure 4*).

## Guiding therapy in coronary disease

Identification of a patient at high risk of cardiac events is of limited value unless this guides subsequent management and thereby improves the outcome. An important study examined the effect of the extent of inducible hypoperfusion on MPS on the risk of cardiac death in

***Figure 3. Quantification of left ventricular systolic function from gated single photon emission computed tomography in a patient with an extensive anteroapical and septal infarct. Left panel shows end-diastolic slices (left column) compared with end-systolic slices (right column). From top to bottom: apical, mid and basal short-axis slices, horizontal long-axis slice, vertical long-axis slice. Right panel shows calculated volumes and ejection fraction (middle box), with time-volume curve (bottom box).***

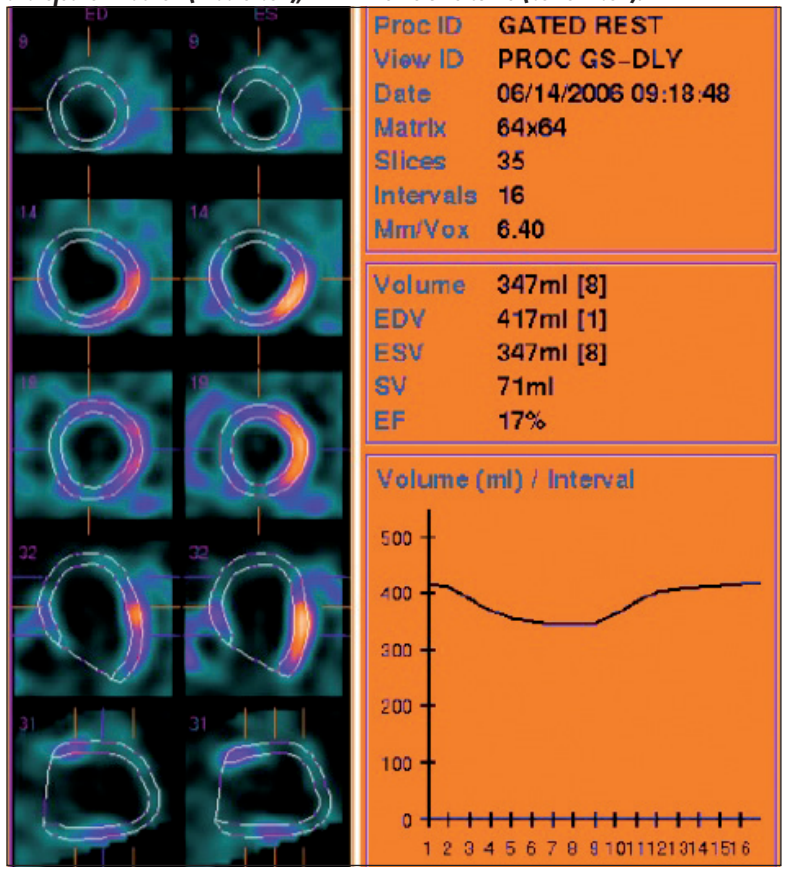
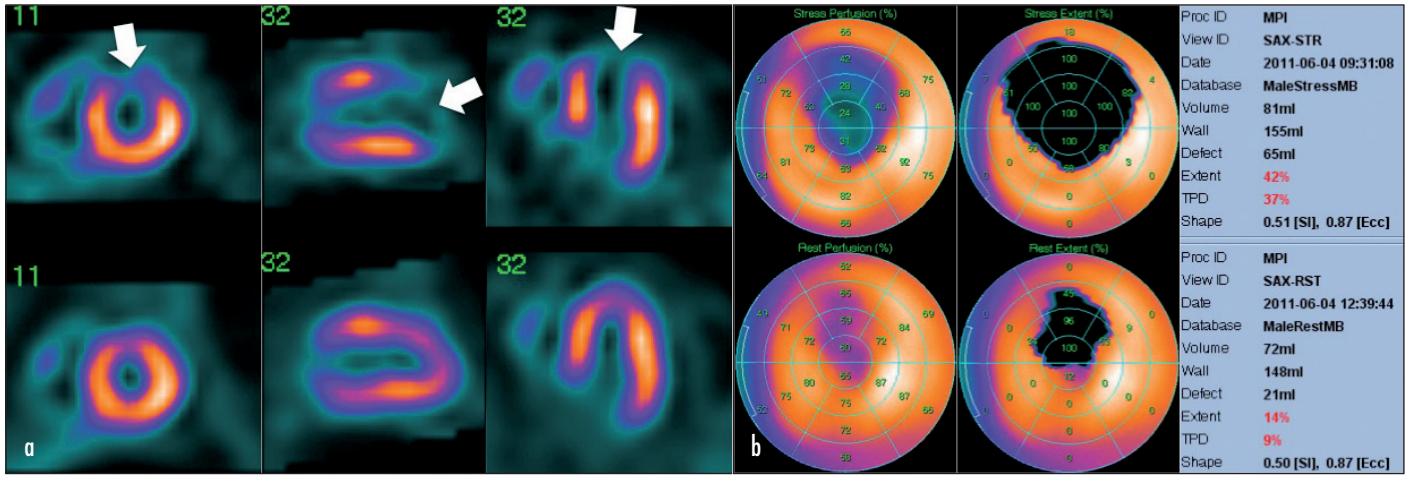


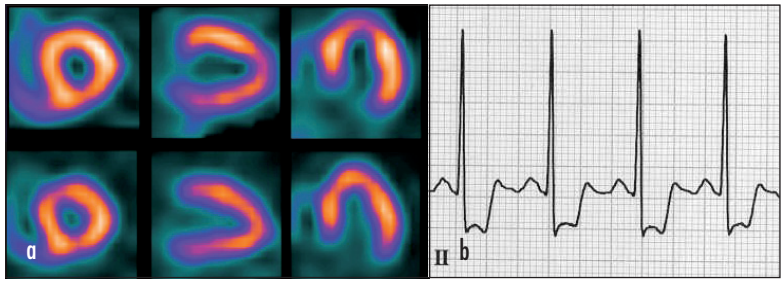

***Figure 2. A 'high risk' single photon emission computed tomography myocardial perfusion scintigraphy study. a. Representative short-axis (left column), vertical long-axis (middle column) and horizontal long-axis (right column) slices, comparing stress (top row) with rest (bottom row). Note the extensive and severe (largely) reversible anteroapical perfusion defect (white arrows). b. Analysis using quantitative software. Left panel: polar plots of the same study (stress above rest). Middle panel: defect defined automatically in black, by comparison with a normal database, using Cedars-Sinai QPS software. Right panel: quantitative measurements indicate a stress defect that represents 42% of the left ventricular myocardium.***



patients managed conservatively *vs* those managed with revascularization (Hachamovitch et al, 2003a). For patients with extents below 12.5% of the total left ventricular myocardium, the rate of cardiac death was lower with medical management than with revascularization. Above this threshold revascularization appeared to provide benefit over medical management, the magnitude of which increased progressively with the extent of inducible hypoperfusion. Despite being based on a large patient population, this study was retrospective so the results of MPS will inevitably have biased subsequent patient management. Nevertheless, the findings supported the hypothesis that revascularization of coronary stenoses that are not physiologically significant does not improve prognosis.

The use of inducible hypoperfusion on MPS to guide prognostic revascularization was given further weight by nuclear substudies of the larger COURAGE and BARI 2D Trials (Shaw et al, 2008, 2012). These were large randomized trials of, respectively, percutaneous coronary intervention *vs* optimal medical therapy, and revascularization (percutaneous coronary intervention or coronary artery bypass grafting) *vs* optimal medical therapy in patients with type 2 diabetes. Both studies failed to demonstrate any additional prognostic benefit of revascularization (Boden et al, 2007; The BARI 2D Study Group, 2009). MPS was performed in subgroups of patients before randomized treatment and 6–18 months afterwards (COURAGE), or 1 year after randomization (BARI 2D). Together, the findings of these substudies suggest that greater reductions in inducible hypoperfusion and/or smaller residual amounts after treatment are associated with better outcomes, and revascularization tends to reduce inducible hypoperfusion more than medical treatment alone. A first-line strategy of revascularization is likely to be appropriate for patients with a large burden of inducible hypoperfusion, although the threshold level remains ill-defined. At the very least, such patients should undergo serial MPS if treated medically to ensure that the inducible hypoperfusion has substantially resolved.

***Figure 4. Balanced multivessel ischaemia in a 76-year-old woman with longstanding chest pain. a. Single photon emission computed tomography slices showed homogeneous tracer uptake throughout the myocardium on both stress and rest acquisitions (layout as in Figure 2a). However, the left ventricular cavity was markedly larger and more spherical on stress acquisition than at rest, a high-risk finding termed 'transient ischaemic dilatation'. b. During treadmill exercise stress, she was limited by chest pain at very low workload, with marked downsloping ST depression inferolaterally. She went on to have coronary angiography, which showed severe three vessel (including left mainstem) coronary disease, as anticipated.***




## Assessment of myocardial viability in ischaemic left ventricular dysfunction

MPS is commonly used to identify hibernating myocardium (as opposed to infarction) in patients with severe left ventricular dysfunction as a result of coronary disease. Regional and global left ventricular dysfunction is demonstrated by gated SPECT, viability by preserved tracer uptake on the resting SPECT acquisition, and inducible hypoperfusion by reduced tracer uptake on the stress SPECT acquisition. Myocardial segments with more than 50–60% of maximal counts on resting SPECT have a greater than 50% chance of contractile recovery following revascularization (Perrone-Fiardi et al, 1996). Few studies have examined improvement in global (as opposed to segmental) left ventricular function, but it is suggested that at least 25% of the myocardium needs to be dysfunctional and viable for ejection fraction to increase (Bax et al, 2001). Evidence that MPS (or any other imaging modality) predicts prognostic improvement after revascularization is remarkably weak, and is limited to a few retrospective and non-randomized studies, where there is likely to have been heavy selection bias in clinical management.

In clinical practice, patients with ischaemic left ventricular dysfunction are a complex, heterogeneous and high-risk group. The risk of revascularization itself, which usually needs to be surgical, is very high, and may overwhelm any prognostic benefit in the survivors. Only a prospective randomized trial could hope to address the difficulties, but to date only one has been performed and published. The STICH Trial randomized 1212 patients with multivessel coronary disease and left ventricular ejection fraction <35% to medical management or bypass surgery, but failed to show any difference in all-cause mortality (Velazquez et al, 2011). This was regardless of the presence or absence of viability or inducible hypoperfusion or ischaemia in the subgroup investigated using SPECT or dobutamine echocardiography (Bonow et al, 2011; Panza et al, 2013). The results were disappointing, but the trial methodology has been heavily criticized. In particular, trial enrolment was difficult and slow, the decision to test for viability was not randomized, echo and SPECT definitions of 'viability' were questionable, and only 19% of tested patients were considered 'non-viable'.

In the absence of more compelling data from randomized trials, the management of patients with obstructive coronary disease and impaired left ventricular function must be tailored to each patient. Those with exertional angina should generally be revascularized. Patients without ischaemic symptoms should be considered for revascularization on prognostic grounds, but only after a careful multidisciplinary discussion of the risks and benefits, informed by imaging results (using SPECT or another modality).

## Conclusions

Sequential technical refinements in SPECT MPS now allow very high quality images to be obtained in shorter times and with lower radiation doses than have been pos-

sible historically. A large scientific literature underpins its use, not merely to detect or exclude angiographic stenoses, but more importantly to predict prognosis and the likely prognostic benefit of coronary revascularization. Other functional imaging techniques such as stress echocardiography and cardiac magnetic resonance are undoubtedly of value, but SPECT MPS will remain important in the investigation of patients with known or suspected coronary disease for some time to come. **BJHM**

*Conflict of interest: none.*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## KEY POINTS

- Pharmacological stress testing has been simplified by the introduction of regadenoson, a selective adenosine $A_{2a}$-receptor agonist. This drug is easy to administer, can be combined with dynamic exercise, and has almost no contraindications.
- Many technical refinements have been made to single photon emission computed tomography image acquisition and processing over the last few years. These allow higher quality images to be obtained in shorter times with lower tracer doses.
- The clinical focus of single photon emission computed tomography myocardial perfusion imaging has shifted away from simple diagnosis or exclusion of angiographic coronary disease, towards prognostic assessment and guidance of revascularization.