Non-invasive imaging of coronary artery disease

Non-invasive imaging of the heart is an expanding field in cardiology and appropriate test selection depends on the clinical question and test availability. This article reviews the role of single photon emission computed tomography myocardial perfusion scintigraphy, positron emission tomography and multi-detector computed tomography.

With an ever-increasing patient population looking for diagnosis and risk stratification of potentially cardiac symptoms and an increasing number of cardiac imaging techniques, appropriate test selection is becoming more complex. Patients with a very low pre-test likelihood of coronary artery disease often need no further investigation. Symptomatic patients with a high pre-test likelihood of significant coronary artery disease warrant direct referral for invasive coronary angiography with the option to proceed with percutaneous coronary intervention if necessary. There remains a large cohort of patients at low to intermediate risk of coronary artery disease, with or without symptoms, in whom the immediate use of invasive testing is precluded. Asymptomatic high-risk patients and those with impaired left ventricular function in whom the likelihood of benefit from revascularization must be established are also candidates for further investigation. Single photon emission computed tomography (SPECT), positron emission tomography (PET) and multi-detector computed tomography coronary angiography (CTA) may each be used to image the heart non-invasively. Each test provides different information and correct usage depends entirely on the nature of the clinical question. Key questions are summarized in *Table 1*.

Generally speaking, patients with symptoms require a test that can detect ischaemia; however, there are groups of patients in whom the detection of coronary artery disease, rather than ischaemia, becomes the goal of imaging.

Table 1. Key questions to answer when referring for non-invasive cardiac imaging

What is the pre-test probability of coronary artery disease?
Does the patient have symptoms and how typical are they for cardiac chest pain?
Is the goal of the test to detect coronary artery disease, myocardial ischaemia or myocardial viability?

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Single photon emission computed tomography

Myocardial perfusion scintigraphy

Myocardial perfusion under stress and resting conditions may be assessed using radiotracers labelled with thallium-201 and technetium-99m. Flow-limiting coronary artery disease is suggested by stress defects in myocardial perfusion that reverse, completely or in part, under resting conditions. Such a circumstance implies impaired flow reserve within the coronary artery that subtends the abnormal area. In a stenotic artery at rest, normal luminal diameter (and therefore flow) is maintained by progressive arterial dilatation. Indeed, a coronary artery can maintain normal resting blood flow even with a stenosis in the region of 90% (Gould and Lipscombe, 1974). However, the degree to which a stenosed coronary artery can further dilate to increase coronary blood flow in the setting of increased myocardial work will be reduced. This phenomenon is called impaired coronary vasodilator reserve. Coronary vasodilator reserve begins to fall once a stenosis is >40% of the luminal diameter, and diminishes progressively with worsening stenosis (Uren et al, 1994).

Abnormal myocardial perfusion scintigraphy demonstrates impaired coronary vasodilator reserve and therefore implies functionally significant epicardial coronary artery stenosis. Early coronary disease will cause no decrease in coronary vasodilator reserve. Normal myocardial perfusion scintigraphy, therefore, does not rule out coronary artery disease but rather coronary artery disease of functional significance. An example of a perfusion abnormality in the typical left anterior descending artery distribution is shown in *Figure 1*. Guidelines and appropriateness criteria have been published by the American College of Cardiology and American Society of Nuclear Cardiology (Klocke et al, 2003; Brindis et al, 2005); selected criteria are summarized in *Table 2*.

The location, extent and severity of any abnormality can be used to judge prognosis and guide intervention. Patients with ischaemia involving <10% of the total myocardium have a better prognosis with medical therapy than those who undergo revascularization (Hachamovitch et al, 2003). Asymptomatic high-risk patients also benefit from myocardial perfusion scintigraphy for prognostic purposes. A normal scan in this setting indicates a <1% annual risk of cardiac death or

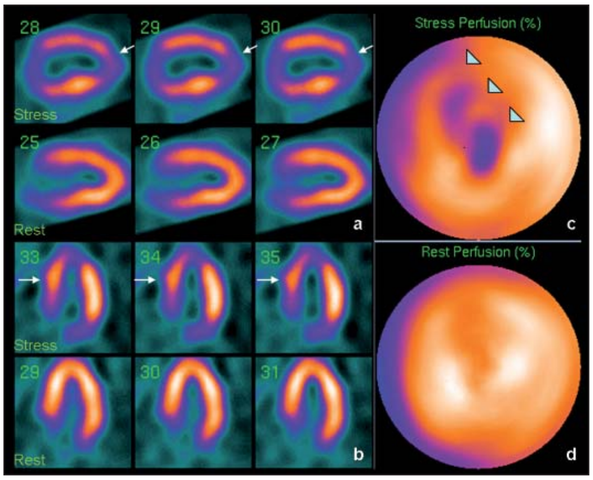


Figure 1. Thallium-201 single photon emission computed tomography myocardial perfusion scintigraphy. a. Reduced tracer uptake can be seen in the left ventricular apex during stress (arrows) which returns to normal after reinjection at rest. b. There is corresponding reduction of uptake in the septum (arrows) during stress which again returns to normal at rest. The myocardial perfusion scintigraphy data may be arranged as a polar plot (c and d) with the apex in the centre of the picture and basal myocardium around the edge. The reduced uptake in the apex, septum and anteroseptal region can be seen clearly (c, arrowheads) with (d) normalization of uptake in the resting images.

myocardial infarction (Klocke et al, 2003). Myocardial perfusion scintigraphy therefore defines prognosis and can guide therapeutic strategy.

Simultaneous electrocardiogram recording during image acquisition allows assessment of left ventricular wall motion and thickening. End-systolic and end-diastolic left ventricular volumes as well as global and regional left ventricular function can therefore be acquired in addition to perfusion of the left ventricular myocardium (*Figure 2*). These parameters provide additional prognostic information to perfusion assessment alone (Travin et al, 2004).

Myocardial viability

The presence of hibernating myocardium can be detected by the presence of ischaemic but viable myocardium which is akinetic under resting conditions. In this circumstance, resting myocardial blood flow is only sufficient to support basic cellular operations, with no reserve for myocardial contraction. Revascularization of substantial hibernating myocardium leads to functional and symptomatic improvement, reduces hospital admissions for heart failure and improves prognosis (Schinkel et al, 2007). The detection of myocardial hibernation is therefore fundamental to guide therapeutic strategy in those with impaired left ventricular function.

Positron emission tomography

Myocardial perfusion scintigraphy

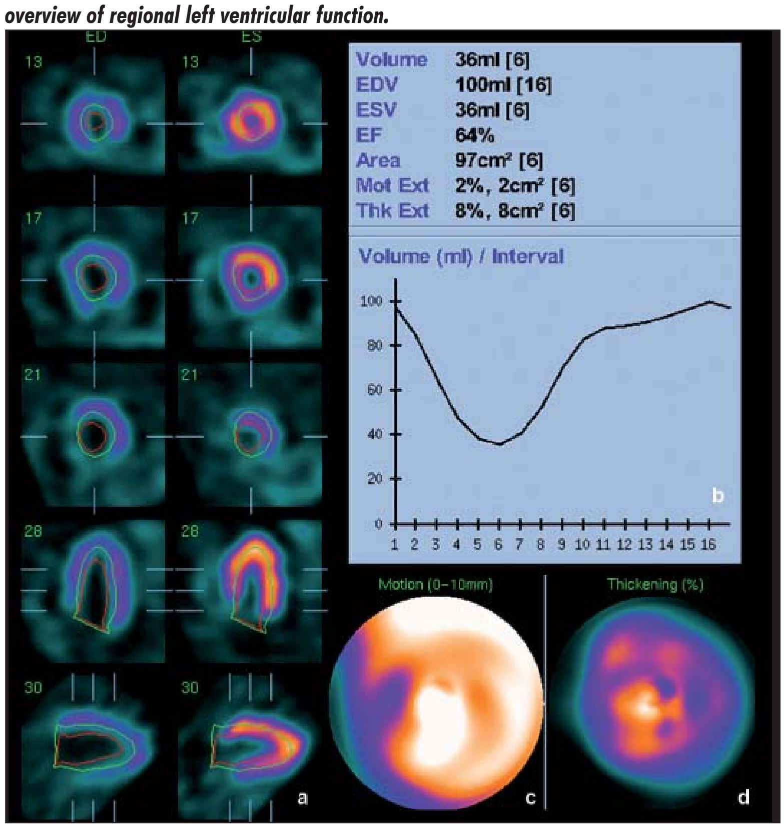
The introduction of rubidium-82 as a tracer of myocardial perfusion has led to increasing use of PET for the

Table 2. Selected American College of Cardiology/American Society of Nuclear Cardiology appropriateness criteria for the use of single photon emission computed tomography myocardial perfusion scintigraphy

	Appropriate	Inappropriate
Evaluation of chest pain syndromes	Intermediate and high-risk patients with or without the capacity to exercise or resting ECG abnormalities	Low pre-test probability and capacity to exercise and normal resting ECG
New onset heart failure	Intermediate risk of coronary artery disease with symptoms, or moderate coronary heart disease risk without symptoms	
Asymptomatic with elevated CAC score	CAC score >400	CAC score <100
Assessment of viability	Known coronary artery disease and patient eligible for revascularization	

CAC = coronary artery calcium; CHD = coronary heart disease; ECG= electrocardiogram. From Brindis et al (2005)

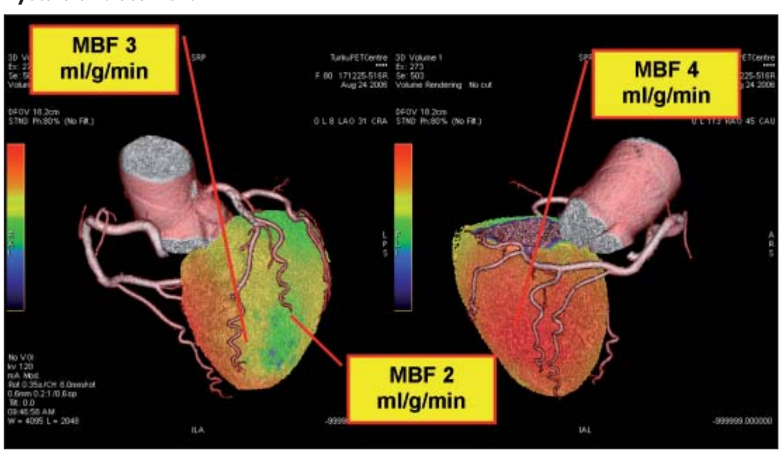
Figure 2. Gated technetium-99m single photon emission computed tomography myocardial perfusion scintigraphy. Data acquired during simultaneous electrocardiogram recording can be divided into 16 frames of the cardiac cycle. This allows assessment of global left ventricular function as well as regional wall motion and thickening. a. The left hand column represents data acquired during end-diastole, while the right represents end-systole. Automatic endocardial border detection at end-systole (red line) and end-diastole (green line) allow calculation of left ventricular volumes and ejection fraction. Colour change between images represents left ventricular wall thickening. b. Extent of wall motion and thickening may be calculated and tabulated with other volumetric data, including variation of left ventricular cavity volume during the cardiac cycle. The corresponding waveform demonstrates left ventricular filling and may indicate diastolic dysfunction. Data for wall motion and thickening may also be represented as polar plots (c and d) which give an overview of regional left ventricular function.



detection of functionally significant coronary artery disease. However, PET remains relatively expensive and is not widely available. The principles underlying the detection of ischaemia are the same as those for SPECT myocardial perfusion scintigraphy, albeit with different tracers. The main feature of PET which increases its value in the clinical setting is in the quantification of myocardial perfusion. SPECT myocardial perfusion scintigraphy lacks this ability, with the suggestion that mild reductions in myocardial perfusion may be missed, particularly in the setting of three-vessel disease. The high energy positron emitters used in PET imaging allow for accurate quantification of myocardial perfusion to all segments and therefore may provide more accurate detection of functionally significant coronary disease (Klocke et al, 2003).

Quantification of myocardial perfusion is possible in part from the use of computed tomography (CT) to provide high quality attenuation maps with which to correct the PET images. With improvements in CT technology, integrated imaging techniques are being developed that combine PET and CT datasets into a single fused image (*Figure 3*). The ability to combine functional and anatomical data into a single image may help in the identification of functionally significant coronary artery stenoses (Di Carli and Dorbala, 2007). It is debatable, however, whether this is any more useful than reviewing the individual images side by side. This point may become moot if and when camera manufacturers provide image fusion software as standard. Should the software become widely available, it is important to realize that the technique has its own set of pitfalls, including misregistration of the two images, which must be overcome before an accurate clinical report can be produced (Bax et al, 2007).

Figure 3. Combined positron emission tomography and computed tomography image showing reduced myocardial perfusion in the left anterior descending artery territory (3 ml/g/min), proportionally worse in the first diagonal territory (2 ml/g/min). Perfusion in the right coronary territory is preserved (4 ml/g/min). Superimposition of the functional perfusion data on the computed tomography coronary angiogram allows precise identification of coronary arteries with functionally significant stenoses. MBF = myocardial blood flow.



Myocardial viability

Myocardial viability may be assessed by comparison of myocardial glucose uptake using fluorine-18 fluorodeoxyglucose (FDG) and myocardial perfusion measured either by nitrogen-13 ammonia PET or SPECT myocardial perfusion scintigraphy. Where a mismatch exists between the two images (intact glucose uptake but diminished or absent perfusion), hibernation is present. The extent of FDG mismatch correlates with outcome after revascularization. In addition, patients with significant mismatch have a substantially higher risk of cardiac events when offered medical therapy compared to revascularization (Schinkel et al, 2007). The American College of Cardiology recommend the use of PET to predict improvement in global and regional left ventricular function (class I indication) and heart failure symptoms (class II indication) after revascularization (Klocke et al, 2003). In comparative terms, PET is slightly less sensitive but more specific than SPECT for the detection of myocardial viability (Bax et al, 1997).

Computed tomography coronary angiography

In asymptomatic intermediate to high likelihood patients, or those with atypical symptoms at low likelihood, the goal of non-invasive cardiac imaging is to demonstrate the presence or absence of coronary artery disease in order to either exclude disease or escalate primary prevention measures. It is in this scenario where computed tomography coronary angiography (CTA) becomes the test of choice.

Figure 4. Unenhanced scan of the heart at the level of the left coronary ostium. There is a significant amount of coronary calcium (arrows) in the left main stem, proximal and mid left anterior descending artery and its diagonal branch.

Assessment of coronary artery calcium

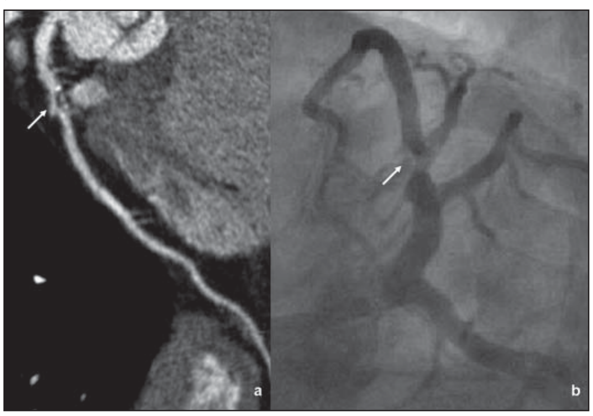
Initially, cardiac CT was limited to the assessment of coronary artery calcium (CAC) burden using electron beam scanners (*Figure 4*). Coronary calcium is a surrogate marker for atherosclerosis (Stary et al, 1995), with high scores correlating with increased risk of significant coronary stenosis (Rumberger et al, 1997). The extent of CAC has been shown to correlate with risk of future cardiac events (Arad et al, 2000; Bellasi and Raggi, 2005). A CAC score of zero confers a ~0.15% per year risk of cardiac events (Bellasi and Raggi, 2005). Conversely, a score of >1000 substantially increases cardiac risk, with one study demonstrating a cardiac event rate of 25% per year (Wayhs et al, 2002). It should be noted that percentile CAC scores, calculated by comparing the index patient with population data from asymptomatic subjects matched for age and sex, provide more meaningful information than the CAC score itself, particularly in young patients and women (Bellasi and Raggi, 2005).

Computed tomography coronary angiography

With improved scanner technology, temporal resolution has increased to the point where cardiac motion is no longer an impediment to accurate coronary assessment. Gating of the dataset is possible, as for SPECT myocardial perfusion scintigraphy, enabling assessment of global and regional left ventricular function. The anatomical nature of the test also lends it well to the study of cardiac, thoracic and vascular anatomy within the chest, especially in the setting of complex congenital heart disease. Although general functional information is available, assessment of myocardial perfusion is still under investigation. Infarct characterization by CT in animals (Lardo et al, 2006) and humans (Henneman et al, 2006) has shown potentially promising results.

CTA compares favourably with invasive coronary angiography (*Figure 5*), with sensitivity of 81% at the per-segment level quoted in a meta-analysis (Hamon et al, 2006).

Figure 5. a. Significant mixed plaque (fibrous and calcified, arrow) in the proximal left anterior descending artery opposite the origin of the first diagonal branch. b. Significant stenosis in the same area (arrow) on invasive coronary angiogram.



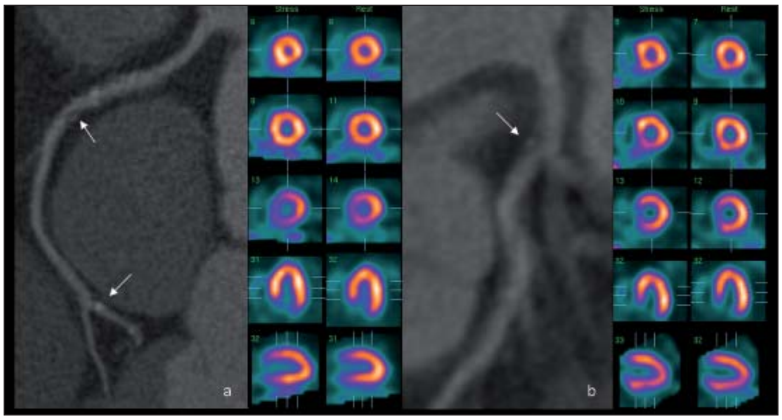


Figure 6. a. Mixed plaque in proximal and distal right coronary artery (arrows) with no evidence of flow-limiting disease on single photon emission computed tomography myocardial perfusion scintigraphy. b. Mixed plaque in proximal left anterior descending artery (arrow), also with normal single photon emission computed tomography myocardial perfusion scintigraphy.

CTA also detects disease that has yet to become functionally significant (*Figure 6*). The major power of CTA, however, comes from its negative predictive value. A normal scan confers a 96.5% negative predictive value of having coronary artery disease (Hamon et al, 2006). It is important to note that heavy calcification, and consequent obscuring of the coronary lumen by blooming artefact, limits the assessment of coronary artery stenosis (*Figure 7*). Most early studies of CTA excluded such segments from analysis and it is likely that the test will perform less well in clinical practice. Given the high prevalence of coronary heart disease in the patient groups studied so far, current data lend weight to the potential role of the technique in low to intermediate risk individuals but indicate poorer utility in those at higher risk.

The American College of Cardiology Foundation, in association with several others, have released appropriateness criteria for the use of CTA (Hendel et al, 2006). Several indications, including the assessment of patients without symptoms but at high risk for coronary artery disease, are still considered uncertain. Selected indications are summarized in *Table 3*.

Figure 7. a. Significant amount of coronary calcium in the proximal left anterior descending artery (arrow), almost completely obscuring the lumen. b. Invasive coronary angiogram in the same patient demonstrating an unobstructed left anterior descending artery.

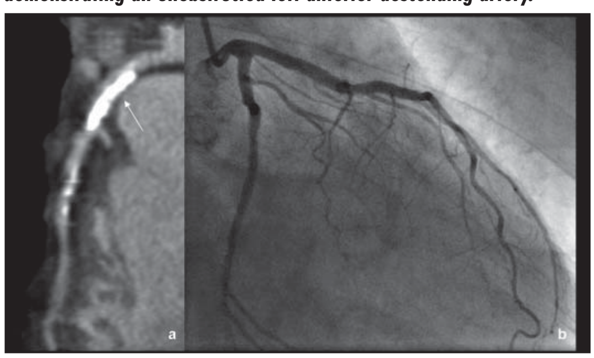


Table 3. Selected American College of Cardiology Foundation appropriateness criteria for the use of cardiac computed tomography

	Appropriate	Inappropriate
Evaluation of chest pain syndromes	Symptomatic: Intermediate pre-test probability and either unable to exercise or resting electrocardiogram abnormalities Evaluation of suspected coronary anomalies	Symptomatic: High pre-test probability of coronary artery disease Asymptomatic: Low to intermediate probability of coronary artery disease
New onset heart failure	Evaluation of coronary arteries to assess aetiology	Evaluation of left ventricular function after myocardial infarction or in heart failure patients
Morphology, intra- and extra-cardiac structures	Evaluation of complex congenital heart disease, cardiac masses, pulmonary and cardiac veins and pericardium	
Evaluation of aortic or pulmonary disease	Evaluation of suspected aneurysm, dissection or embolism	

From Hendel et al (2006)

Conclusions

Although test availability will often determine referral pattern, it is important to appreciate the fundamental differences between the various tests. SPECT myocardial perfusion scintigraphy has been widely validated for diagnosis of functionally important coronary artery disease and experience with its use can be measured over decades. In addition, the evidence for the prognostic value of SPECT myocardial perfusion scintigraphy in a variety of clinical settings is extensive. Although less widely available and relatively more expensive, PET can detect obstructive coronary disease and provide additional information about coronary flow. Assessment of myocardial viability can be achieved by either SPECT or PET; choice is generally determined by availability.

CTA is possibly the real growth area. 64-slice (or greater) scanners are likely to be the technology of choice for any radiology department looking to upgrade. Concomitant purchase of cardiac imaging software packages increases the likelihood that use of CTA will become widespread. The evidence for coronary calcium scoring as a marker of disease burden and cardiac risk is convincing and the correlation between CTA and invasive coronary angiography is good. However, it is fundamentally important that the limitations of the technique are understood and that the right patients are referred. High-risk patients who are likely to have significant coronary calcification, as well as any symptomatic patient with an intermediate or greater risk for coronary artery disease, are not well served by CTA. In the former, calcification will make coronary analysis extremely difficult, leading to an equivocal report and a high likelihood of referral for a functional test such as SPECT myocardial perfusion scintigraphy. In the latter, the presence of coronary artery disease is likely and detection of ischaemia as a cause for their symptoms should be the goal of testing. The pre-test likelihood of coronary artery disease, nature of symptoms and ultimate aim of testing should all be addressed before referral for non-invasive cardiac imaging to ensure appropriate test selection. **BJHM**

KEY POINTS

- In all patients referred for non-invasive coronary artery assessment, the pre-test likelihood of coronary artery disease must be considered, along with the presence and nature of symptoms.
- The choice of test depends on whether the goal of imaging is to detect coronary artery disease or myocardial ischaemia or viability.
- Symptomatic patients generally require a functional test (single photon emission computed tomography, positron emission tomography) as the goal is to detect myocardial ischaemia.
- Single photon emission computed tomography myocardial perfusion scintigraphy is widely validated and identifies flow-limiting coronary artery disease, guides interventional strategy and provides prognostic information in both symptomatic and asymptomatic patients. Positron emission tomography is less widely available but can be used to assess myocardial perfusion.
- In patients without symptoms or at low to intermediate risk with atypical symptoms, detection of coronary artery disease, rather than ischaemic heart disease, is the goal of imaging.
- Coronary artery calcium is a surrogate marker for atherosclerosis; higher scores correlate with an increased chance of significant coronary disease and a worse prognosis.
- Computed tomography coronary angiography correlates well with invasive coronary angiography for the detection of significant coronary stenoses.
- Assessment of myocardial viability is essential to determine the need for revascularization in those with left ventricular dysfunction.

Figure 3 *is reproduced courtesy of Professor Juhani Knuuti, Turku PET Centre, Finland.*

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