IMAGING TECHNIQUES

Myocardial perfusion imaging

Raymond J Gibbons

Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA

Non-invasive images of the myocardium that reflect myocardial perfusion can be obtained either by using conventional nuclear medicine radiopharmaceuticals and cameras or by positron emission tomography (PET). This review will focus on myocardial perfusion imaging using conventional approaches; a subsequent article in this series will focus on PET.

Imaging fundamentals

Comprehensive reviews of imaging fundamentals and procedures are available.^{1,2} The two most commonly used isotopes for myocardial perfusion imaging are thallium-201 and technetium-99m. Thallium-201 is generated by a cyclotron. It is then transported as a finished product to the location where it is used, which is feasible because it has a half life of 73 hours. The isotope decays by a reasonably complex scheme, but most of the photons have an energy of about 80 keV, which is a low energy. Technetium-99m is bound to other compounds for the purposes of myocardial perfusion imaging. It is formed on site by elution from a molybdenum-99 generator. Technetium-99m is a meta-stable compound which is constantly formed from molybdenum-99 within the generator. Technetium-99m has a half life of about six hours, and emits photons with a 140 keV energy. This energy is much higher than the emissions of thallium, but much lower than the 511 keV emissions of PET radiopharmaceuticals. The differences in physical properties between thallium-201 and technetium-99m are relevant to the choice of radiopharmaceutical, which will be discussed later.

Both thallium-201 and technetium-99m radiopharmaceuticals are most commonly imaged using single photon emission computed tomography (SPECT). This technique employs many of the same back projection techniques that have been applied to conventional radiographs for CT scanning. Although multiple view planar images were first employed for myocardial perfusion imaging, they have been largely replaced by SPECT, which is superior from the standpoint of localisation, quantification, and image quality. Regardless of the radiopharmaceutical used, SPECT imaging is performed at rest and during stress to produce images of myocardial regional uptake that reflect relative regional myocardial blood flow. During maximal exercise or vasodilator stress, myocardial blood flow is typically

increased three- to fivefold compared to rest. In the presence of a significant coronary stenosis, myocardial perfusion will not increase appropriately in the territory supplied by the artery with the stenosis, creating heterogeneous uptake. In patients who are unable to exercise, either one of the two coronary vasodilators, adenosine or dipyridamole, may be used to increase blood flow. Asthma, or chronic lung disease with a significant bronchospastic component, is a contraindication to the use of either one of these two agents. In such circumstances, dobutamine is used as an alternative, although it does not increase blood flow to the same degree.

Thallium-201 is a potassium analogue that is taken up by viable myocardial cells in direct proportion to coronary blood flow. The initial thallium injection is performed at peak stress, when hypoperfused myocardium will have less uptake than myocardium with normal perfusion. Over the next few hours "redistribution" of thallium occurs as a result of a fairly complex process. Thallium will wash out of the myocardium at a rate dependent on local myocardial perfusion. At the same time, thallium will be redelivered to the myocardium from a large reservoir in the blood pool. The final result of this process is that a region of ischaemic but viable myocardium which initially has less than normal uptake will become equal to normal regions over time. This "redistribution" is then detected on subsequent imaging. In contrast, areas of infarction or fibrosis will have reduced uptake initially that does not change over time. Reinjection of a small additional amount of thallium before acquisition of delayed images or repeat images after a longer delay of 24 hours may be used to enhance the detection of ischaemic but viable myocardium.

Several technetium-99m labelled agents have been developed, including teboroxime, tetrofosmin, and sestamibi. Teboroxime has a very short myocardial retention time which requires very rapid imaging. This practical limitation has limited its use. Sestamibi is the most studied of these agents, and is currently

Acronyms

- CHEER: Chest pain evaluation in the emergency room
- ERASE: Emergency room assessment of Sestamibi for evaluation of chest pain
- OASIS: Organisation to assess strategies for ischaemic syndromes
- PET: Positron emission tomography
- SPECT: Single photon emission computed tomography
- VANQWISH: Veterans' Affairs non-Q wave infarction strategies in hospital

Correspondence to:
Professor R J Gibbons,
Mayo Clinic, 200 First
Street SW, Rochester,
MN 55905, USA
email: gibbons.
raymond@mayo.edu

the most widely used. Tetrofosmin was developed after sestamibi and has been the subject of far fewer studies. Either tetrofosmin or sestamibi distribute to the myocardium in relation to blood flow. Their uptake requires a viable myocardial cell and an intact cell membrane. Both of these agents have far less redistribution than thallium, as they are bound within the myocardial cell in a nearly irreversible fashion. As a result, they must be injected twice, once at rest, and once during stress. Uptake on the resting injection will reflect relative resting blood flow to areas of viable myocardium.

A variety of different imaging protocols have been employed with thallium-201 and technetium-99m agents in order to optimise the detection of ischaemia and infarction. These are discussed below.

Clinical applications

Although myocardial perfusion imaging can be used in a wide variety of clinical settings, this review will focus on its primary application in adults with coronary artery disease. SPECT perfusion imaging may be used in patients with known or suspected stable angina for the purposes of both diagnosis and risk stratification. It may be employed in patients with acute ischaemic syndromes (unstable angina/myocardial infarction) for acute triage as well as risk stratification.

Diagnosis of stable angina

Patients with known or suspected stable angina have been the subject of clinical practice guidelines issued by the British Cardiac Society³ and jointly by the American College of Cardiology and the American Heart Association.⁴ The interested reader is referred to these documents for a more comprehensive description of the evaluation and treatment of this clinical problem. SPECT myocardial perfusion imaging is often useful for the diagnosis of coronary artery disease in such patients. It should be used selectively as part of a careful strategy that begins with a clinical estimation of the likelihood of significant coronary artery disease on the basis of the patient's history of chest pain, risk factor assessment, and physical examination.

The proper choice of non-invasive tests should carefully consider the patient's ability to exercise and the resting ECG. In patients who are able to exercise, the exercise ECG is the preferred initial diagnostic test in most patients. However, there are important patient subsets in whom SPECT myocardial perfusion imaging is preferred. Exercise SPECT myocardial perfusion imaging is preferred in patients with > 1 mm ST depression or pre-excitation syndrome on their resting ECG, because of the reduced specificity of additional ST depression in these circumstances. Exercise SPECT myocardial perfusion imaging is also preferred in patients who have undergone percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG), be-

Stress SPECT perfusion imaging as the initial test for the diagnosis of coronary artery disease

- ≥ 1 mm ST depression at rest
- Pre-excitation (Wolff-Parkinson-White) syndrome
- Prior revascularisation (PTCA/CABG)
- Left bundle branch block
- Ventricular pacing
- Unable to exercise
- (Possibly) left ventricular hypertrophy or digoxin use with < 1 mm ST depression at rest

cause of its superior ability to localise ischaemia, and its increased sensitivity in patients with one vessel coronary artery disease. Patients with < 1 mm ST depression on their resting ECG, but with digoxin use or resting left ventricular hypertrophy, should also be considered for SPECT myocardial perfusion imaging, although the advantage of SPECT perfusion imaging in such patients is less well established. Patients with ventricular pacing or left bundle branch block should be assessed with SPECT perfusion imaging, as their exercise ECGs are uninterpretable. However, since these electrocardiographic abnormalities may cause perfusion defects during exercise stress in the absence of coronary artery disease, adenosine or dipyridamole SPECT perfusion imaging is preferred.⁵ Adenosine or dipyridamole SPECT perfusion imaging is preferred in patients who are unable to exercise.

Multiple studies have examined the sensitivity and specificity for SPECT perfusion imaging for the detection of coronary artery disease. The reported sensitivity has generally ranged from 70–90%, and the reported specificity from 60–90%. These reports should be interpreted cautiously, as they do not reflect the effects of a type of bias called work up verification, or post-test referral, bias.⁶ Such bias occurs whenever the results of a non-invasive test are used to decide which patients should have the diagnosis of coronary artery disease verified or ruled out by coronary angiography. Thus, patients with positive results on non-invasive tests are referred for coronary angiography, and patients with negative results are not. This selection process reduces the number of true negative results. The effect of this bias is to raise the measured sensitivity and lower the measured specificity in relation to their true values.

Risk stratification

SPECT perfusion imaging is also useful for the purpose of non-invasive risk stratification to identify patients who have the greatest risk for subsequent death and myocardial infarction.

High risk (> 3% annual mortality) features on stress SPECT perfusion imaging

- Post-stress ejection fraction < 35% (technetium-99m)
- Stress induced large perfusion defect
- Stress induced multiple perfusion defects of moderate size
- Large, fixed perfusion defect with left ventricular dilatation or increased lung uptake (thallium-201)
- Stress induced moderate perfusion defect with left ventricular dilatation or increased lung uptake (thallium-201)

Modified from ACC/AHA/ACP-ASIM guidelines for the management of patients with stable angina³

Figure 1: Cumulative survival in 5183 consecutive patients who underwent dual isotope (rest thallium-stress sestamibi) SPECT perfusion imaging as a function of the scan results. The rate of death increased significantly with worsening scan abnormalities. (Reproduced from Hachamovitch *et al.* Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death. *Circulation* 1998;97:535, with permission of the American Heart Association.)

As for diagnosis, perfusion imaging should be employed as part of a strategy which includes careful clinical assessment as well as a resting ECG. Normal stress SPECT myocardial perfusion images are highly predictive of a benign prognosis. Multiple studies involving thousands of patients followed for several years have found that a normal stress perfusion study is associated with a subsequent rate of cardiac death and myocardial infarction of less than 1% per year, which is nearly as low as that of the general population.⁷ Although the published data are limited, the only exceptions would appear to be patients with normal perfusion images in the presence of either a high risk treadmill ECG score or severe resting left ventricular dysfunction.

In contrast, several different abnormal findings on stress SPECT perfusion imaging have been associated with severe coronary artery disease, and subsequent cardiac events. Large stress induced perfusion defects,⁸ as well as defects in multiple coronary artery territories, are adverse prognostic signs (fig 1). Transient post-stress ischaemic left ventricular dilatation is also associated with an adverse prognosis.⁹ In patients studied with thallium-201, increased lung uptake on postexercise or pharmacologic stress images is an indicator of stress induced global dysfunction, and it provides independent and incremental prognostic information compared to clinical, electrocardiographic, and

Figure 2: Cardiac survival in patients with intermediate risk exercise ECGs, subgrouped on the basis of their findings on perfusion imaging. The three subgroups shown—patients with normal perfusion scans and normal heart size; patients with near normal scans and normal heart size; and patients with cardiac enlargement—were significantly different from one another ($p < 0.001$). Both of the subgroups with normal heart size had a low risk of subsequent cardiac death, with an annual cardiac mortality of less than 0.5%. (Reproduced from Gibbons *et al.*¹² with permission of the American Heart Association.)

catheterisation data.¹⁰ The results of SPECT perfusion imaging can be used to identify a “high risk” patient subset. These patients, who have a greater than 3% annual mortality rate, should be considered for early coronary angiography, as their prognosis may be improved by revascularisation.¹¹

SPECT perfusion imaging is also of proven utility in selected situations following treadmill exercise testing. Patients with an intermediate risk treadmill score comprise between a third and two thirds of all patients undergoing exercise ECG testing. Approximately 50% of such patients will have normal or near normal images on exercise SPECT perfusion imaging. The subsequent cardiac event rate in these patients is extremely low, and coronary angiography is not warranted¹² (fig 2).

Acute ischaemic syndromes

Triage of acute chest pain

The emergency department evaluation of patients with chest pain but without electrocardiographic ST elevation is challenging. Although serum markers and transient ST depression may help to identify a subset of patients who clearly merit hospital admission, many patients with an intermediate risk of short term cardiac events will lack these findings. Hospital admission rates for such patients, who consume a large amount of health care resources, vary widely. A variety of different chest pain unit triage systems have been developed. Myocardial perfusion imaging is an integral part of many of these. One of the largest reported series performed resting SPECT sestamibi imaging as part of a comprehensive strategy that relied on initial clinical assessment and ECG findings to categorise the patients into one of five levels of risk.¹³ Gated rest sestamibi imaging was performed on all patients assigned to two of these five levels. More than 75% of these patients had normal SPECT perfusion images and were discharged home without adverse

events. The quarter of patients with abnormal images were admitted to the hospital, and had a significant rate of death and myocardial infarction in the ensuing year. A large, multicentre trial (ERASE chest pain), which utilises a similar strategy, is currently underway with results expected shortly.

Although the early results from these studies are certainly promising, it must be recognised that emergency department imaging is not universally available and is often associated with potential patient delays. A strategy using SPECT perfusion imaging is less useful in patients with prior myocardial infarction, and more costly than strategies based on treadmill exercise testing, which have also yielded positive results.¹⁴ Most importantly, these strategies should use SPECT perfusion imaging selectively on the basis of clinical and electrocardiographic findings, rather than in an indiscriminate fashion for all patients.

Risk stratification as part of a clinical management strategy

Several randomised trials have examined the utility of SPECT perfusion imaging as part of a non-invasive or conservative strategy to risk stratify patients in order to decide which are candidates for coronary angiography and invasive treatment. The TIMI IIIb trial randomised 1473 patients with non-Q wave myocardial infarction or unstable angina to an early invasive strategy, using coronary angiography or an early conservative strategy which reserved coronary angiography for patients with recurrent ischaemia or an abnormal stress thallium test.¹⁵ The combined end point of death, myocardial infarction, or ischaemia on a treadmill performed six weeks later showed no difference between the two strategies.

Subsequently, the VANQWISH trial randomised 920 patients with non-Q wave myocardial infarction to an early invasive strategy using coronary angiography and an early conservative strategy that utilised stress thallium imaging to select patients for coronary angiography.¹⁶ There was again no significant difference in outcome between the two strategies, and all cause mortality was actually slightly lower in patients in the conservative strategy group (fig 3). On the basis of both of these randomised trials, stress SPECT perfusion imaging would appear to have great utility for the non-invasive assessment of patients with unstable angina and non-Q wave myocardial infarction. The advantages of such a conservative strategy are further reinforced by data from the OASIS registry,¹⁷ which found that early coronary angiography was more prevalent in institutions and countries where catheterisation laboratories were available. This increased rate of catheterisation did not reduce the rate of subsequent death or myocardial infarction, but did lead to an increased incidence of stroke.

Myocardial viability

SPECT perfusion imaging is often used to evaluate the possible contribution of ischaemia

Figure 3: Survival of patients in the VANQWISH trial, as a function of randomisation to the invasive strategy (early coronary angiography) or the conservative strategy (selective coronary angiography using perfusion imaging). There was no significant difference in outcome comparing the two strategies. (Reproduced from Boden *et al*¹⁶ with the permission of the Massachusetts Medical Society.)

to ventricular dysfunction. The detection of viable myocardium—either stunned or hibernating—in such cases implies that revascularisation will lead to improved regional and global function.

The presence of stress induced ischaemia has long been recognised as a highly specific indicator of viable myocardium. However, because its sensitivity was clearly less than 100%, the criteria to detect viable myocardium were eventually expanded to include “fixed” defects—that is, those without evidence of stress induced ischaemia, on resting (technetium-99m) or redistribution (thallium-201) images that were only mild to moderate in severity.¹⁸ Despite these expanded definitions, and a wide variety of imaging protocols (see below), SPECT imaging has a slightly lower sensitivity than PET for the detection of stunned or hibernating myocardium. Although some recent studies have suggested that the specificity (and positive predictive value) of SPECT perfusion imaging is as low as 50%, these estimates are probably erroneously low because of the effect of post-test referral bias. Although the redistribution of thallium-201 can potentially detect ischaemia at rest, which technetium-99m cannot, the prevalence of this finding, and its overall clinical significance, are not well established. In most patients, resting thallium-201 and technetium-99m images provide similar information (fig 4).

Controversies

Stress echocardiography or stress SPECT

Both stress echocardiography and stress myocardial perfusion imaging are feasible and effective alternatives to treadmill exercise testing in suitable patients. As indicated previously, imaging studies should be used selectively in patients who will benefit most from the technology, which is associated with considerable additional expense. Both stress echocardiography and stress SPECT imaging studies have advantages and disadvantages. The choice between the two tests depends on many factors, including these relative advantages and disadvantages, the individual patient, local expertise, and the anticipated impact of an

Figure 4: Comparison of segmental activity on a resting technetium-99m sestamibi scan with segmental activity on the redistribution image from a resting thallium-201 scan in segments with abnormal contractile function. There was a significant correlation ($r = 0.78$) between segmental activity on the two scans, although there was some variability. More importantly, activity in those segments with dysfunction which improved after revascularisation generally exceeded 60% of peak counts on both scans. In contrast, dysfunctional segments that did not improve following revascularisation, presumably because they were fibrotic, generally had activity at less than 60% of peak counts on both scans. (Reproduced from Udelson *et al.* Predicting recovery of severe regional ventricular dysfunction. Comparison of resting scintigraphy with thallium-201 and technetium-99m sestamibi. *Circulation* 1994;89:2552, with permission of the American Heart Association.)

Relative advantages of stress echocardiography and SPECT perfusion imaging

- Echocardiography
 - higher specificity
 - availability/convenience
 - structural/valvar evaluation
 - lower cost
- SPECT
 - higher sensitivity
 - higher success rate
 - better evaluation of ischaemia in presence of regional dysfunction
 - greater evidence base

Modified from ACC/AHA/ACP-ASIM guidelines for the management of patients with stable angina³

imaging study on clinical decision making. Ongoing technical developments related to both techniques should lead to improved diagnostic accuracy.

Choice of radiopharmaceutical

Both thallium-201 and technetium-99m based perfusion agents are widely available. Although some laboratories have chosen to use one or the other exclusively, the clinician is often faced with a choice between the two. Most of the advantages of technetium-99m perfusion agents have been better established for sestamibi, although they should also theoretically apply equally well to tetrofosmin. In general, the better image quality and ventricular function assessment that is achieved with technetium-99m perfusion agents are the most important considerations, and account for the increasing use of these agents in most nuclear cardiology laboratories.

Choice of imaging protocol

Laboratories which employ thallium-201 generally use one of three protocols. The traditional protocol involves stress imaging, redistribution imaging three or four hours later, and, when necessary, delayed imaging approximately 24 hours later to evaluate fixed defects. The most common modification of this protocol involves performance of the optional delayed images on the same day following a reinjection of a small amount of thallium in patients with fixed defects. The third thallium protocol is commonly used by large volume laboratories. The three to four hour redistribution images are only performed after reinjec-

Relative advantages of thallium-201 and technetium-99m

- Thallium
 - lower cost
 - greater evidence base
 - assessment of lung uptake
 - less bowel/liver uptake
 - detection of ischaemia at rest
- Sestamibi
 - better images
 - assessment of left ventricular ejection fraction/regional function
 - better quantification
 - faster imaging protocols

tion of a small amount of thallium. Delayed imaging at 24 hours is still performed when necessary. Thus, all of these three protocols involve stress and delayed images with a third set of images in a subset of patients.

Laboratories which employ sestamibi generally use one of four different protocols. The original protocol developed for technetium-99m perfusion agents involve two injections of radiopharmaceutical—one at rest and one during stress—on different days. For patient convenience, this was subsequently modified to perform both studies on the same day by using a low dose for the first study and a high dose for the second study. The sequence of images may be either rest-stress, which is the most common, or stress-rest. The fourth protocol is the so called “dual isotope” protocol, in which thallium imaging is first performed following resting injection. The technetium-99m based perfusion agent is then injected during stress testing, which follows immediately thereafter, and subsequently imaged. Each of these protocols has its proponents, who usually emphasise the practical logistical consequences, as the available scientific evidence has not established the clear superiority of any one of these protocols.

Any one of these protocols may be used to detect stress induced ischaemia (and therefore myocardial viability), which is usually sufficient for clinical decision making. In an occasional patient with known severe coronary artery disease and significant left ventricular dysfunction, only resting imaging may be required in order to demonstrate normal or near normal uptake of either radiopharmaceutical (and therefore viability) in dysfunctional regions that are presumed to be ischaemic.

Technical developments

There are a number of newer technical developments that are already available or proposed for SPECT imaging. Gating of SPECT images is now widely available, and software for processing the images is available on most camera systems.¹⁹ The increased cost and logistical difficulty of gating are generally felt to be justified by the ability to measure ejection fraction and to assess regional wall motion. The assessment of regional wall motion is primarily helpful in the case of mild fixed defects

to make certain that they represent diaphragmatic or breast attenuation. A careful review of the literature suggests that the actual percentage of cases whose interpretation is modified is small.²⁰

Attenuation of the diaphragm, breast, or other soft tissue is a major limitation of SPECT imaging with either thallium-201 or technetium-99m, although it is more pronounced with the former, because of its lower energy emission. Although systems for attenuation correction are now available on several commercial camera systems, they have not yet proven to be of clear benefit. Further developments in this regard are anticipated.

Differences in image reconstruction involving iterative processes have been proposed to replace back projection. They may help to address the problem of extracardiac activity which sometimes reduces the quality of technetium-99m images. Partial volume effects and "balanced ischaemia" (a near uniform reduction in flow that is not detected by a relative flow technique) are occasionally significant limitations of SPECT perfusion images with no definitive solution on the horizon.

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