

What is the best stress myocardial perfusion imaging protocol for risk stratification?

A. LAHIRI, V. ANAND, E. LIM

Background

The most commonly used diagnostic and prognostic test for coronary artery disease is exercise electrocardiography. During exercise, coronary blood flow (CBF) must increase to meet myocardial demand. Inadequate coronary flow reserve and failure to increase CBF may result in electrocardiographic changes. Considerable data is available regarding the diagnostic and prognostic significance of exercise electrocardiography, which incorporates magnitude of ST segment shifts, functional capacity, blood pressure response, heart rate response during exercise, heart rate recovery post-exercise and inducible arrhythmias. Aggregate indices such as the Duke treadmill score (which incorporates exercise time, ST segment deviation and angina index) are often used to aid interpretation of the test. However, the overall sensitivity (78%) and specificity (70%) of exercise testing for detection of coronary artery disease remains limited, and it therefore cannot be used as a diagnostic test without consideration of the pre-test probability of disease. Exercise testing performs best as a diagnostic test where there is an intermediate probability of disease. However, patients with a low pre-test probability of coronary artery disease are now more often encountered in contemporary medical practice. Furthermore, many patients are unable to exercise adequately. Both of these reasons limit the utility of exercise electrocardiography.

*Cardiac Imaging and Research Department,
Wellington Hospital, St John's Wood, London, United Kingdom*

Consequently, exercise myocardial perfusion imaging (MPI) is increasingly used to replace exercise electrocardiography. Furthermore, pharmacological stress MPI is available for those unable to attain adequate levels of exercise. Since perfusion abnormalities occur early in the ischaemia cascade (before wall motion abnormalities and electrocardiographic abnormalities), MPI should be a more sensitive and specific test than electrocardiographic changes. It has been estimated that the overall sensitivity and specificity of MPI is approximately 85-90%. The normalcy rate (percentage of normal tests in patients with a 5% probability of coronary artery disease) is 90%. Like exercise electrocardiography, it can also be used as a prognostic test. A recent meta-analysis based on a pooled study population of over 12,000 patients has documented an event rate of only 0.6% per annum in the absence of perfusion defects, irrespective of an abnormal exercise ST-segment response. Even patients with prior revascularisation by coronary artery bypass and a normal MPI result have low cardiac event rates, similar to event rates seen in the general population.

MPI is among the most technically demanding of all the tests in nuclear medicine, and it is important for the physician and technologist to choose the most appropriate stress protocol, and to evaluate all MPI variables in conjunction with the perfusion data. We discuss these considerations in the following article.

Address reprint requests to: A. Lahiri, Cardiac Imaging and Research Department, Wellington Hospital, St John's Wood, London NW9, United Kingdom. E-mail: avijitlahiri@yahoo.com, alahiri@cardiacresearch.co.uk

1. Exercise vs Pharmacological Stress

Coronary blood flow (CBF) must be increased in order to unmask focally diminished flow reserve. This may be achieved via exercise or pharmacological stress. Exercise may be by treadmill or bicycle ergometry, and can potentially increase resting coronary blood flow by a factor of 2-3. Although bicycle ergometry is less expensive, more portable and suitable for those with lower extremity orthopaedic, neurological or vascular disease, the physiological response to bicycle exercise is not the same as treadmill exercise. Moreover, the maximum oxygen uptake is 5% to 20% lower. Treadmill exercise testing is therefore generally preferred to bicycle testing. Although good levels of coronary hyperaemia can be induced through pharmacological stress alone, and the sensitivity and specificity of pharmacological stress MPI is comparable to exercise stress MPI, exercise stress MPI variables are lost; these have important diagnostic and prognostic value (see below). Pharmacological stress should therefore generally only be considered where maximal treadmill testing is not possible.

Incremental value of exercise variables to perfusion variables alone

Adverse exercise stress test variables include: ST segment depression > 2.0 mm, ST segment depression at low workload, ST segment depression lasting > 5 minutes into recovery, low change in HR from rest to exercise, abnormal blood pressure response, inability to achieve > 6 METS workload, exercise-induced VT and abnormal HR recovery post-exercise. Even when added to perfusion and gated SPECT MPI variables, some of these have been shown to retain diagnostic and prognostic value. For example, inability to reach >85% of the maximum predicted heart rate and ischaemia detected by MPI is associated with a significantly worse prognosis than ischaemia alone.

Pharmacological stress and choice of pharmacological stress agent

In 2001, 42% of patients (approximately 3 million patients) undergoing stress MPI in the United States were tested using one of three pharmacological agents:

adenosine or dipyridamole (both vasodilators), or dobutamine (an intravenous inotropic agent).

Vasodilator stress. Adenosine induces coronary hyperaemia through coronary A_{2A} adenosine receptors. Dipyridamole is a nucleoside transport inhibitor and increases plasma and tissue levels of adenosine by reducing clearance due to inhibition of cellular transport. Dipyridamole and adenosine can both increase resting coronary blood flow by a factor of 5; when combined with gentle isometric (bicycle) or dynamic (treadmill) exercise, coronary blood flow increases still further. This also reduces liver and gut uptake artefacts, improving image quality.

The chief problems with adenosine and dipyridamole are the high incidence of side-effects, and the risk of inducing asthma and complete heart block in susceptible individuals. For both adenosine and dipyridamole, patients must also avoid caffeine-containing food and drink for a period of at least 8 hours prior to testing; otherwise, the pharmacological action of both adenosine and dipyridamole are severely attenuated and there is loss of diagnostic sensitivity. Certain medications which are not always stopped prior to MPI have also been shown to affect adenosine A_{2A} receptor mediated coronary vasodilatation in animal models. These include verapamil and KATP channel inhibitors like glibenclamide.

It has been shown that the diagnostic sensitivity and specificity of adenosine and dipyridamole stress MPI are comparable. Vasodilator stress MPI has also been validated as a prognostic test; however, compared to exercise stress MPI, comparable perfusion defects are associated with a higher cardiac event rate and this should be taken into consideration during interpretation. For example, the annual event rate (death or MI) associated with a summed stress score > 5 is approximately 6.8% with vasodilator stress, but only 3.1% with exercise stress. (The summed stress score is a measure of perfusion defect size).

Similar to exercise testing, the haemodynamic response to vasodilator stress may also have incremental prognostic value, but this is less well studied. Recently, it has been shown that patients undergoing adenosine stress MPI with a high resting HR and low peak:rest HR ratio have increased risk of cardiac death, as do male patients with a low peak systolic blood pressure.

Newer vasodilator stress agents. Side effects associated with adenosine and dipyridamole are common. Approximately 10-15% of studies conducted

with dipyridamole may need to be reversed with aminophylline. Because of this, newer selective adenosine A2A receptor agonists with an improved side-effect profile are being developed. At least two are undergoing Phase III clinical trials and should be available for clinical use in the near future.

Intropic stress. Dobutamine is a synthetic catecholamine with α_1 , β_1 and β_2 adrenergic agonist activity. It produces a dose-related increase in myocardial oxygen demand mainly through increases in pulse rate and blood pressure. Early studies suggested dobutamine produces less hyperaemia than adenosine or dipyridamole; more recent studies show that this is not the case using a contemporary dobutamine-atropine protocol. 2 studies with a total of 157 patients comparing dobutamine and vasodilator stress for diagnosis of CAD showed no significant differences in diagnostic sensitivity and specificity. However, dobutamine can induce coronary spasm and ventricular arrhythmias, and often takes longer to administer. It is usually reserved for those unable to tolerate vasodilator stress (usually asthmatics).

Effect of left bundle branch block on diagnostic performance of exercise and pharmacological stress MPI

Left bundle branch block is often but not always associated with underlying coronary artery disease. However, non-invasive assessment of the coronary circulation by MPI is hampered by frequent false positive septal perfusion defects that mimic the appearance of an LAD stenosis. It has been shown that this is much more common during exercise stress MPI compared to vasodilator or dobutamine stress MPI (46% vs 11% and 8% respectively). Pharmacological stress should therefore be preferred in the presence of LBBB.

2. Choice of myocardial perfusion agent

The ideal myocardial perfusion agent should be non-toxic, have a half-life approximately equal to the study duration, with pure low-medium gamma emission, lack interaction with cardiac medications and pharmacological vasodilator stress agents, be taken up well by the myocardium so that there is a high

heart/background ratio, have a high extraction fraction with uptake directly proportional to myocardial blood flow over physiological and supraphysiological ranges and lack redistribution from the heart during the imaging period. No currently used agent meets all these criteria and each have their individual strengths and weaknesses. Three are in current use – ^{99m}Tc -sestamibi, ^{99m}Tc -tetrafosmin and ^{201}Tl .

Thallium-201. ^{201}Tl was the first radionuclide to be used widely in clinical practice. Early studies of MPI used thallium-201 imaging to show that the total ischaemic burden (severity and size of the perfusion defect, reversibility), increased lung uptake of thallium and dilatation of the left ventricular chamber all predicted worse cardiac outcome.

Technetium-99m and Gated SPECT. Technetium-based agents (sestamibi and tetrafosmin) were developed later, and offer a number of advantages. The key advantages include the higher photon flux and higher energy gamma emission compared to thallium-201 (140 keV vs 68-80 keV). This reduces scatter and attenuation artefact, increases spatial resolution and allows gated single photon emission computer tomography (SPECT) to be performed. These agents do not redistribute, and therefore imaging can be carried out at a time remote from exercise, which may be logistically advantageous. However, myocardial uptake is lower than for thallium (1-1.5% versus 3.5-4.5%).

The use of ^{99m}Tc -based agents, permitting gated SPECT, has been a fundamental advance, because it allows simultaneous assessment of perfusion and function. It significantly improves specificity of MPI (without sacrificing sensitivity) by allowing clearer identification of attenuation artefacts (breast and diaphragm). This is particularly important in women, and obese subjects. One study of MPI in women showed that the specificity of thallium-201 SPECT was 67.2% versus 84.4% for ^{99m}Tc -sestamibi SPECT and 92.2% for gated ^{99m}Tc -sestamibi SPECT. Others have also confirmed the value of gated SPECT in decreasing the number of non-diagnostic studies.

Other advantages of gated SPECT include accurate estimation of left ventricular ejection fraction and left ventricular volumes. Both have been shown to be important prognostic variables in their own right, independent from perfusion abnormalities. More recently, the phenomenon of transient ischaemic LV dilatation (TID) has also been described. TID refers to an apparent increase in LV cavity size during stress compared to rest SPECT tomograms. It is probably

due to subendocardial stress-induced ischaemia, and is indicative of significant coronary artery disease even in the absence of any perfusion abnormality. This can occur because unlike PET, MPI detects coronary blood flow heterogeneity and not absolute coronary artery blood flow; with severe disease, 'balanced ischaemia' in all coronary artery territories may occur so that there is no apparent perfusion defect. Without gated SPECT and a careful search for TID, these patients who have severe coronary artery disease would be incorrectly classified as normal. It should be noted that TID is more frequent during pharmacological stress MPI compared to exercise stress MPI.

^{99m}Tc-sestamibi vs ^{99m}Tc-tetrafosmin, vs ²⁰¹Tl

In the ROBUST study, 2,560 patients were randomised one-day stress-rest ^{99m}Tc-sestamibi, one-day stress-rest ^{99m}Tc-tetrafosmin or ²⁰¹Tl MPI. Overall image quality score was superior using technetium, with less low-count artefact and less attenuation. Stress defect depth and extent are slightly greater with ²⁰¹Tl, but there was no difference between ^{99m}Tc-sestamibi and ^{99m}Tc-tetrafosmin. All three tracers performed well in clinical terms, with high sensitivity and specificity for angiographic stenosis, and no differences in accuracy between the tracers. However, when ^{99m}Tc-sestamibi MPI was directly compared to ^{99m}Tc-tetrafosmin in the same patients, it has been shown that tetrafosmin tends to underestimate perfusion defect size in patients with mild-moderate coronary artery disease, when compared to sestamibi, and this should be taken into account during interpretation of MPI.

One day-versus two-day protocols

There are no comparative studies of the diagnostic performance of one-day and two-day protocols. Compared to two-day protocols, one-day protocols are probably associated with improved patient compliance as patients do not need to return for a second study on a separate day, and are less expensive. However, background noise for the second study is greater with the one-day protocol since both studies are performed in close temporal proximity. Particularly when studies are likely to be technically difficult (obese subjects, women with large breasts, patients with heart

failure in whom it is also desirable to assess myocardial viability), the two-day protocol is to be preferred where possible.

3. Use of MPI to detect myocardial viability in patients with heart failure

Heart failure is an emerging epidemic in all the market economies. It is estimated there are at least 400,000 new cases of heart failure diagnosed in the United States per year. 60% or more of these cases are attributable to ischaemic heart disease. Over 50% of these are likely to have significant myocardial viability (that is, potentially recoverable but severely dysfunctional myocardium). A recent meta-analysis has shown that the benefits of surgical revascularisation for ischaemic LV dysfunction is confined to those with significant amounts of viable myocardium.

Several tests can be used to detect viable myocardium, including BMIPP SPECT (fatty acid metabolism), FDG PET/SPECT (glucose metabolism), ²⁰¹Tl SPECT (cell membrane integrity, myocardial perfusion), ^{99m}Tc-sestamibi SPECT (intact mitochondria, myocardial perfusion) and dobutamine stress echocardiography (inotropic reserve). Although these tests assess different characteristics of viable myocardium, each have been shown to be clinically useful. A recent meta-analysis of 105 studies involving 3034 patients has compared the four most common techniques (¹⁸FDG-PET, ²⁰¹Tl-SPECT, ^{99m}Tc-sestamibi / tetrafosmin SPECT, and dobutamine stress echocardiography [DSE]). ¹⁸FDG-PET was the most sensitive test (93%) followed by ²⁰¹Tl reinjection (88%), ²⁰¹Tl rest-redistribution (86%), ^{99m}Tc-sestamibi / tetrafosmin (81%) and DSE (81%). Specificity was highest for DSE (80%), followed by ^{99m}Tc-sestamibi / tetrafosmin SPECT (66%), ²⁰¹Tl rest-redistribution (59%), ¹⁸FDG-PET (58%) and ²⁰¹Tl reinjection (50%). Among the nuclear techniques, there is therefore no clear advantage of ²⁰¹Tl imaging over ^{99m}Tc-sestamibi / tetrafosmin SPECT. While ²⁰¹Tl is more sensitive, it is less specific compared to ^{99m}Tc-sestamibi / tetrafosmin SPECT.

Nitrate-enhanced MPI

The performance of MPI is significantly enhanced by administration of nitrate prior to imaging. Of 20

^{99m}Tc-sestamibi SPECT studies performed without prior nitrate administration, the overall mean positive and negative predictive accuracy was 68% and 72% respectively. In the 7 studies performed after nitrate administration, the corresponding values were 82% and 86% respectively. It is believed that prior administration of nitrates enhances coronary blood flow and tracer delivery to severely hypoperfused myocardium, improving the ability to detect viable myocardium.

4. Summary

Issues Related to Selection of Stressor

1. Exercise is first choice whenever possible
2. Dipyridamole or adenosine in patients unable to exercise adequately or who have resting LBBB; add low level exercise if possible
3. Dobutamine stress with asthma, or those on theophylline or who ingested caffeine
4. Due account should be taken of exercise haemodynamic variables during interpretation
5. Due account should be taken of the stressor used during interpretation; perfusion defects of similar size are associated with a worse prognosis when they are induced by pharmacological stress compared to exercise stress

Issues Related to Stopping Medications Before Testing

1. Beta blockers, nitrates, diltiazem and verapamil should be held for at least 24 hours prior to testing for diagnostic imaging with either exercise or vasodilator stress
2. Verapamil and diltiazem inhibit the vasodilator effect of dipyridamole and adenosine

Other important issues

1. Gated SPECT is preferred whenever possible to decrease the number of non-diagnostic studies, and to measure LV ejection fraction and volumes, and to detect transient ischaemic dilatation,
2. Nitrate should be administered prior to rest scans if the objective is to detect viable myocardium
3. 2 day protocols are preferable for studies that are likely to be technically difficult (obese, women with large breasts)

4. ^{99m}Tc-based perfusion agents are generally preferable over ²⁰¹Tl because they permit gated SPECT, especially for obese female patients; however, ²⁰¹Tl-based MPI is probably more sensitive than ^{99m}Tc MPI for detecting hibernating myocardium
5. ^{99m}Tc-tetrofosmin may underestimate the ischaemic burden compared to ^{99m}Tc-sestamibi

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