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# Myocardial perfusion imaging

## A validated and mature cardiac imaging modality

**BACKGROUND**

Nuclear myocardial perfusion imaging (MPI) involves the use of radiotracers to generate scintigraphic images of the myocardium. It is the best validated and most standardised of all cardiac imaging modalities, demonstrating regional perfusion ventricular wall motion and accurately calculating reproducible left ventricular ejection fraction. Physiological or pharmacological stress can be used to uncover myocardial ischaemia.

**OBJECTIVE**

This article provides an update on the use of MPI for the triaging of chest pain, monitoring of known ischaemic heart disease, and cardiac event prediction in the general practice setting.

**DISCUSSION**

A normal stress MPI study is an unambiguous outcome. A perfusion defect on a stress MPI study may be produced by stress ischaemia, stable infarction, hibernating myocardium, or by a variable mixture of all three. Patient access to nuclear MPI is good with most nuclear medicine departments offering nuclear cardiology services. Nuclear cardiology is safe and reliable, and deserves to be a part of the routine diagnostic armamentarium in general practice.

### **MPI shows relative regional perfusion of ventricular myocardium.**

Myocardial perfusion imaging (MPI) uses a tracer amount of radioactive compound taken up and retained in heart muscle. The cardinal imaging product of MPI is an objective, quantifiable three dimensional map of radiotracer concentration within ventricular myocardium. The tracer intensity in any one part of the map directly reflects the adequacy of blood flow to the corresponding part of myocardium; or the proportion of live myocardium to scar; or a combination of the two. In diagnostic clinical practice the radiotracer concentration map is normalised to an area of myocardium with the most intense uptake (or to a part of known normal myocardium), and the map is therefore one of relative regional myocardial perfusion.

### **MPI accurately shows regional ventricular wall motion and accurately calculates reproducible left ventricular ejection fraction.**

All myocardial perfusion tracers used in modern MPI are imaged with electrocardiogram (ECG) gating. Regional wall motion abnormalities are shown on a cine loop, and left ventricular function is objectively evaluated through calculation of left ventricular end diastolic volume, end systolic volume, time-volume curve, and left ventricular ejection fraction (LVEF). All these parameters, and in particular LVEF, are reproducible and allow accurate serial monitoring (*Figure 1*).

### **MPI at physiological stress uncovers regional myocardial ischaemia. Direct comparison with a resting perfusion map separates myocardial ischaemia (reversible) from infarct (irreversible).**

Coronary blood flow can rise to as much as four times its resting value in response to rising cardiac output, and failure of coronary blood flow to keep pace with cardiac work produces myocardial ischaemia.

The most informative way to achieve myocardial

physiological stress is with graded exercise ECG. This demonstrates the patient's exercise response and may also elicit index symptoms. The radiotracer is injected either at peak exercise, or with symptoms. Where the patient is unable to exercise, MPI can still produce meaningful results by using pharmacologic stress. The most common way to achieve this is with intravenous infusion of coronary vasodilators, either dipyridamole ('Persantin') or adenosine ('Adenoscan'). Both cause nondemand coronary hyperaemia; both are contraindicated in asthma and second degree heart block. The physiological action of both is blocked by xanthines, and therefore we ask patients referred to MPI to abstain from all caffeine and theophylline containing food, drink and medication for 24 hours before testing.

The second line pharmacological agent – dobutamine – is administered as a graded intravenous infusion and acts via beta adrenergic receptors to increase both heart rate and power of myocardial contraction.

A normal stress MPI study is an unambiguous outcome. A perfusion defect on a stress MPI study may be produced by stress ischaemia, stable infarction, hibernating myocardium, or by a variable mixture of all three. Differentiation is achieved by comparison with a resting MPI study (Figure 2). A reversible perfusion defect is the cardinal MPI sign of reversible ischaemia, and its severity in turn reflects the severity of ischaemia. A fixed perfusion defect indicates either a fixed infarct (severity of perfusion defect reflecting the thickness of the infarct) or (infrequently) hibernating myocardium.

### Myocardial viability imaging shows hibernating myocardium.

Hibernating myocardium is defined as noncontractile but viable myocardium which regains some degree of useful function following revascularisation (definition is retrospective). An extension of usual MPI techniques to detect hibernating myocardium using thallium as the radiotracer and a long time delay between injection and imaging is both possible and accurate.<sup>1</sup> The application is termed 'myocardial viability imaging'.

### Safety of cardiac stress testing

Exercise ECG stress testing has an excellent safety profile (mortality generally quoted at 0.01%), and the addition of radiotracer injection does not affect it. Dipyridamole and adenosine stress testing have a low risk of cardiac death or myocardial infarction (<0.05%), but carry a 0.1% risk of bronchospasm.<sup>2,3</sup> A review of 1012 patients undergoing dobutamine stress MPI reported no deaths or myocardial infarctions.<sup>4</sup>

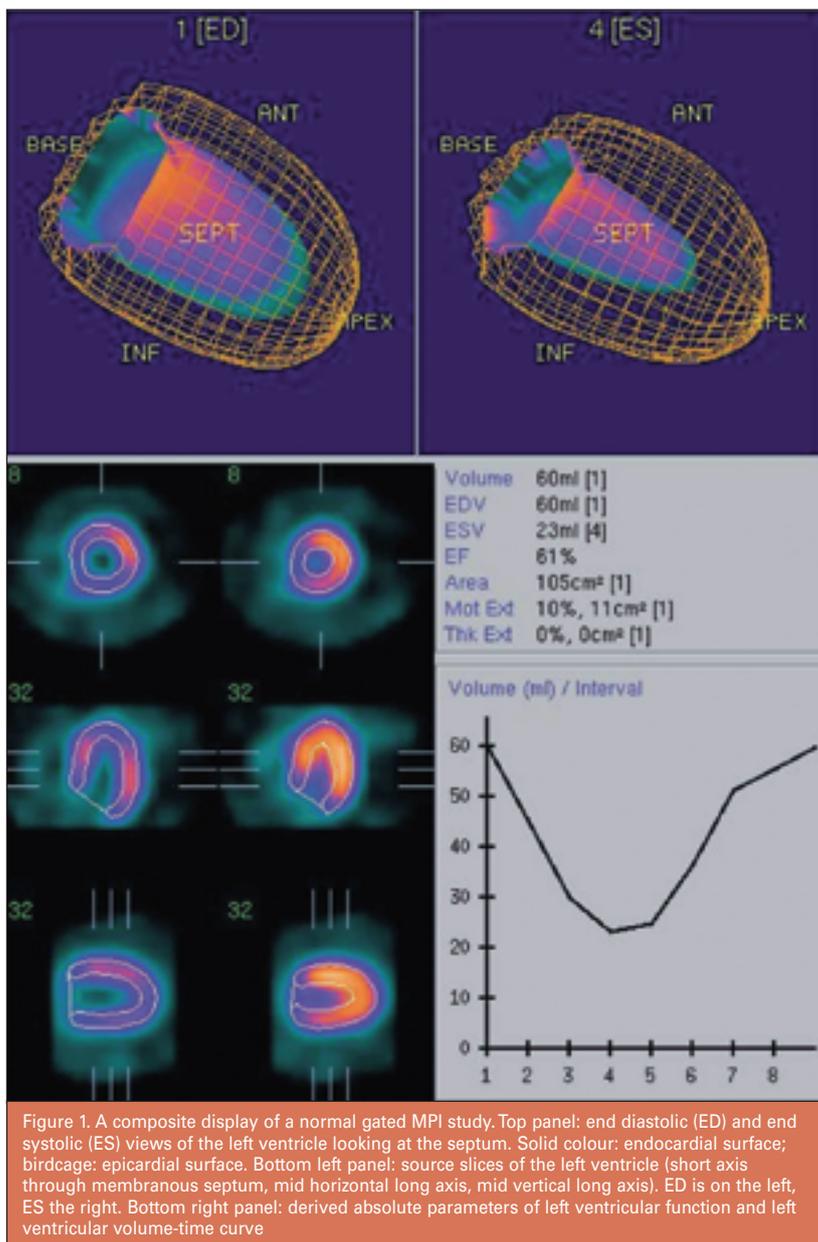


Figure 1. A composite display of a normal gated MPI study. Top panel: end diastolic (ED) and end systolic (ES) views of the left ventricle looking at the septum. Solid colour: endocardial surface; birdcage: epicardial surface. Bottom left panel: source slices of the left ventricle (short axis through membranous septum, mid horizontal long axis, mid vertical long axis). ED is on the left, ES the right. Bottom right panel: derived absolute parameters of left ventricular function and left ventricular volume-time curve

### Evidence base and clinical utility

Nuclear myocardial perfusion imaging is the best validated and most standardised of all cardiac imaging modalities. Standardisation of the reporting lexicon, myocardial segmentation models and defect severity quantitation has resulted in portability, reproducibility and comparability of nuclear MPI studies acquired in different centres and at different times.<sup>5</sup> This has made it possible to produce an outstanding nuclear MPI evidence base of over 20 000 patients.<sup>6</sup>

Large, statistically significant normal MPI study databases are available in clinical practice for all radiotracers for both men and women. Standardisation of wall motion analysis algorithms has resulted in portability,

reproducibility and accuracy of myocardial wall motion parameters, especially LVEF.

**Nuclear MPI predicts clinical cardiac outcome, and does so equally well in men and women, diabetics and nondiabetics, patients who can exercise and those who cannot. In addition, left ventricular function parameters predict the risk of cardiac death.**

In the general patient population, a normal nuclear MPI study carries the risk of cardiac death, myocardial infarction or myocardial revascularisation (hard cardiac events) of less than 1% per annum. A meta-analysis of 14 prognostic studies and 12 000 patients reported a cardiac death and myocardial infarction rate of 0.6% per annum for a normal study, compared to 7.4% for an abnormal study.<sup>7</sup>

Patients with no known coronary artery disease, and a normal exercise MPI study (n=3926) had a hard cardiac event rate of 0.2% per annum with a 'warranty period' of 2 years. The 'warranty period' depends on underlying

comorbidities and is shorter if the risk profile is adverse.<sup>8</sup>

A number of studies have explored the risk stratification role of MPI in women,<sup>9</sup> with data from over 8000 women in total suggesting that cardiac event rate is less than 1% per annum for a normal study.

In 1080 diabetics, a normal or near normal MPI study conferred a hard cardiac event rate of less than 2% per annum, while a moderate or severely abnormal scan resulted in a rate of 5.8% (exercise) and 9.9% (adenosine).<sup>10</sup>

Where the patient cannot exercise and dipyridamole or adenosine are used, the risk of hard events depends on coexistent comorbidities, particularly age, pre-existent ischaemic heart disease and diabetes mellitus. For a general pharmacological stress population without known ischaemic heart disease, a normal scan carried the cardiac death rate of 1.1% per year in 2163 patients.<sup>11</sup>

Left ventricular ejection fraction is routinely reported with modern nuclear MPI and provides survival information. In a study of 1680 patients, LVEF of more than 45% carried the cardiac mortality rate of less than 1% per annum regardless of perfusion abnormalities, while patients with LVEF less than 45% and left ventricular end systolic volume of more than 70 mL had a cardiac death rate of 7.9% per year.<sup>12</sup>

### False positives and false negatives

False positives and false negatives imply that a gold standard must exist, and its selection is not trivial. The most significant gold standard (and the one chosen for the performance benchmarks of MPI quoted above) is the clinical cardiac outcome of the patient. Cardiac catheterisation is often regarded as the absolute gold standard for ischaemic heart disease, but is itself not infallible.<sup>13</sup>

In general, false positive MPI studies predict significant myocardial ischaemia where none exists. These patients will almost always have a normal or near normal coronary angiogram. Because provocative coronary angiography is not a common test in Australia, these patients will not be easy to differentiate from patients with impaired coronary vasodilation or vasospasm induced ischaemia (MPI true positive, coronary angiography false negative).<sup>14</sup>

False negative MPI studies are uncommon, but include the dreaded 'balanced triple vessel disease' where perfusion to all myocardial territories is equally compromised and therefore no normal myocardium exists for comparison. Sometimes no identifiable explanation exists for a false negative result. As elsewhere in clinical medicine, Bayesian statistics apply in nuclear MPI. Where pretest probability (read 'clinical suspicion') of significant

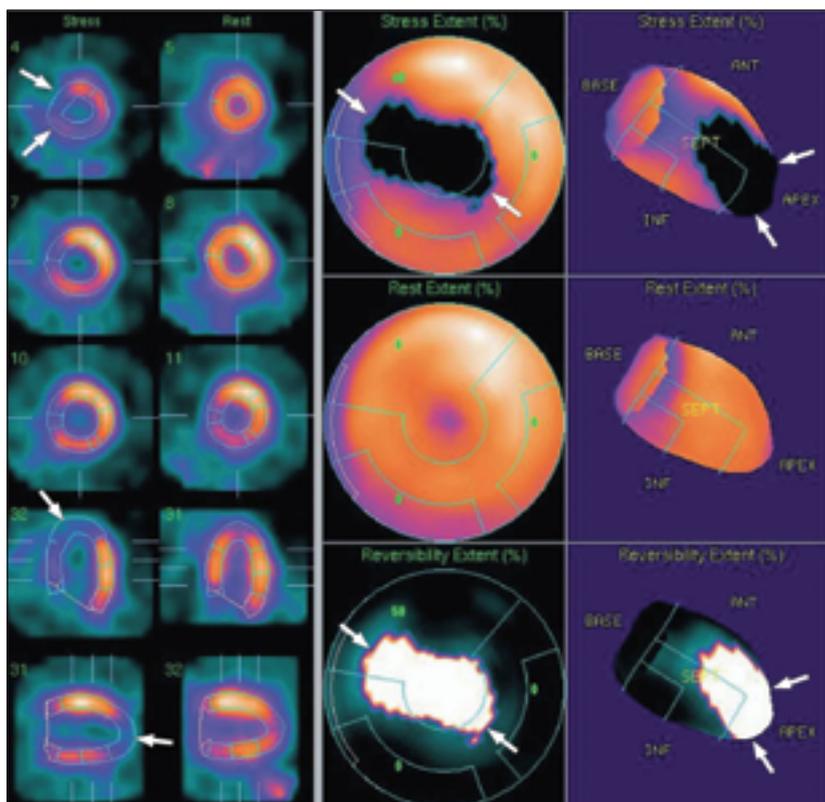


Figure 2. A composite display of a large, reversible stress perfusion defect in the left anterior descending (LAD) artery territory (arrows). Left panel: source slices (representative short axis, mid horizontal long axis, mid vertical long axis). The defect involves the apex and distal anteroseptal wall. Right panel top: left ventricular perfusion at stress on polar map and 3D map (polar map has apex in centre). Right panel mid: left ventricular perfusion at rest. Bottom panel: extent of reversibility of the defect (in this case, totally reversible)

ANT = anterior, INF = inferior, EDV = end diastolic volume, ESV = end systolic volume, EF = ejection fraction

myocardial ischaemia is very high and the MPI study is negative, the post-test probability will still be insufficiently low to dismiss. The same is true where ongoing symptoms or other clinical developments contradict negative MPI results. In both these circumstances it makes good sense to refer the patient for further cardiac investigation that uses a different physiological paradigm.

## Applications in general practice

### Triaging of chest pain

#### **Nuclear MPI effectively segregates important myocardial ischaemia from all other causes of chest pain. In unstable angina, nuclear MPI predicts cardiac outcome.**

Very little consensus exists on what chest pain is significant, and the differentiation between 'typical' and 'atypical' chest pain is in itself an exercise in cardiac risk stratification. In patients with atypical chest pain, validity of nuclear MPI is the same as in the general population. A normal MPI study confers the same cardiac prognosis whether chest pain is present or not,<sup>15</sup> and provides reassurance to both patient and doctor.

In unstable angina, patients with a normal scan have a significantly better outcome than those with an abnormal scan, while patients with reversible perfusion abnormalities (ie. myocardium at risk) have the worst prognosis.<sup>16</sup>

Exercise stress testing is a traditional noninvasive method for assessing chest pain. Multiple studies in different patient cohorts have shown greater accuracy of MPI over exercise stress testing. A study of 1137 patients<sup>16</sup> showing that MPI identifies higher and lower risk patients regardless of exercise stress test results, is noteworthy for its 6 year follow up. After positive (n=136), strongly positive (n=127) and nondiagnostic (n=273) exercise stress testing a normal MPI study had 0%, 3.5% and 6.0% rate of hard cardiac events respectively, and an abnormal MPI study had 11.7%, 15.2% and 15.8% rate respectively. In the 601 patients with a negative exercise stress test, a normal MPI (n=252) had a hard event rate of 2.8% and an abnormal MPI (n=349) conferred a hard event rate of 7.2%. In addition, MPI was able to predict occurrence of myocardial infarction, but exercise stress testing was not.

### Monitoring of known ischaemic heart disease

#### **Nuclear myocardial perfusion monitors known ischaemic heart disease. It objectively documents exercise performance, severity and progression of ischaemic perfusion and nonrecurrence of treated ischaemic disease.**

Nuclear MPI predicts further cardiac events following myocardial infarction by showing the extent of residual at risk myocardium. Studies show better predictive power than angiography.<sup>18</sup>

Coronary artery bypass grafting, coronary angioplasty and coronary stenting have real and progressive rates of ischaemia recurrence. If a baseline MPI study is acquired shortly after a revascularisation procedure, serial MPI studies become a very powerful tool in the early detection of deterioration, and allow fine tuning of when to intervene. Similar benefits of MPI exist for patients managed medically. Myocardial perfusion imaging is an impartial, objective standard: intensive medical therapy of coronary atherosclerosis and invasive angioplasty both of which produce equal decrease in MPI abnormalities confer the same risk profile and outcome.<sup>19</sup>

### Cardiac event prediction

#### **In patients without chest pain, nuclear MPI provides an accurate cardiac event prognosis specific to the patient's clinical situation. Prediction of cardiac events in asymptomatic patients is particularly relevant for preoperative patients, before major physical stresses, and where silent myocardial ischaemia is likely (diabetics, other adverse risk factors).**

Assessment for coronary ischaemia before major surgery is a traditional pre-admission clinic task.<sup>20</sup> Myocardial perfusion imaging successfully predicts risk of intra-operative cardiac events for major vascular and nonvascular surgery and can be performed in the outpatient setting. Pharmacologic stress testing is particularly relevant before joint replacement surgery when exercise is not an option.

On the other hand, the general practitioner is often confronted by the patient who wants to undertake new strenuous physical activity, and wants to know whether he or she will 'suffer a heart attack'. A few patients (drivers recovering from myocardial infarction and professional pilots) may be required to document this as part of their employment. The benefit of nuclear MPI here is objectively showing the maximal exercise effort possible by the patient and the state of underlying myocardial perfusion at such an effort.

Silent myocardial ischaemia is particularly common in diabetes and is well documented even in its absence. Even in the absence of symptoms, where multiple comorbidities result in an adverse risk profile, MPI is an appropriate method of stratifying patients toward aggressive medical therapy versus referral for surgical (or endovascular) intervention.

## Conclusion

Nuclear MPI is a physiologically sound, extremely well validated, safe and practically useful cardiac imaging modality. In Australia most nuclear cardiology procedures are eligible for a Medicare rebate. Patient access to nuclear MPI is good, with most nuclear medicine departments offering nuclear cardiology services. Nuclear cardiology deserves to be a part of the routine diagnostic armamentarium in general practice.

Conflict of interest: none declared.

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