Abstract:

Nuclear cardiology is an extremely important modality in the management of coronary artery disease. Information about myocardial perfusion, myocardial function, myocardial metabolism, myocardial innervation, myocardial infarction and apoptosis, atherosclerosis and gene therapy can be obtained with nuclear cardiology scans. Nuclear cardiology involves use of radiopharmaceuticals to study the function of the heart. Radiopharmaceuticals which have affinity for the myocardium are injected intravenously and with the help of a gamma camera, functional images of the heart are obtained. Two technologies are used: single photon emission computed tomography (SPECT) which uses single, dual or triple headed gamma cameras and isotopes of 99mTechnetium, and positron emission tomography (PET) which uses short-lived isotopes of 18F, 14O, 13N, and 11C which are produced in cyclotrons and imaged with special PET cameras. Information about absolute myocardial blood flow and myocardial flow reserve can be obtained non invasively in every patient with PET-CT. These 2 parameters are of crucial importance in detecting microvascular disease which is undetectable on coronary angiography.

Key words: myocardial perfusion, Myocardial flow reserve, PET, viability

MYOCARDIAL PERFUSION

Myocardial perfusion imaging (MPI) is now a well-established regularly used method in evaluation of a patient with ischaemic heart disease. The procedure involves injection of radiopharmaceutical intravenously during exercise followed by acquisition of post exercise images with a gamma camera (Tables 1 and 2). The patient is re-injected at rest followed by resting image acquisition. The stress and rest images are then compared. The radiopharmaceutical, usually Thallium or 99mTc methoxy isobutyl isonitrile (MIBI) is selectively picked up by the myocardium in proportion to blood flow. Areas supplied by stenosed coronary arteries do not get adequate supply of the radiopharmaceutical as compared to areas supplied by normal arteries. This is seen as a ‘perfusion defect’. If this defect disappears on the resting study, ischaemia is diagnosed. If the defect persists, then infarction is likely to be present.

Coronary blood flow increases several fold during exercise or following adenosine infusion, in the normal coronary vascular bed due to coronary vasodilatation in response to metabolic demand. It fails to increase appreciably in the territory of an obstructed coronary artery or arteries or in arteries with diffuse endothelial dysfunction. The ratio of resting flow to flow after maximal coronary dilatation is called the coronary flow reserve (CFR). Measurement of CFR is being increasingly recognised as vital information for making management decisions about intervention in CAD.

Table 1: Radiopharmaceuticals Used in Myocardial Perfusion Imaging

SPECT

201 Thallium, 99mTc-MIBI, 99mTc-Tetrofosmin, 99mTc-Teboroxime

PET
Table 2: Indications for Performing Myocardial Perfusion Imaging

1. Patients with abnormal baseline ECG (LBBB, LVH, digitalis therapy, WPW syndrome) where treadmill stress test interpretation is difficult.

2. Women: high rate of false positive stress test results.

   Patients unable to perform treadmill stress test (severe arthritis, neurological disorders, lack of motivation. Pharmacological stress test with adenosine/dobutamine can be done).

3. Asymptomatic or mildly symptomatic individuals with risk factors for ischaemic heart disease.

4. Patients with diagnosed coronary artery disease by angiography; for risk stratification and for evaluation of physiological significance of coronary stenosis.

5. Post-angioplasty for evaluation of re-stenosis.


7. Post-myocardial infarction for risk stratification and viability assessment.

Based on the scan findings, the results are classified into high, intermediate and low-risk scans. Patients demonstrating ‘low-risk scan’ pattern can be managed medically even in presence of abnormal coronary angiograms (Table 3).

Patients showing ‘high-risk scan’ pattern should be sent for coronary angiogram (if not already performed) and for revascularisation. Myocardial perfusion imaging (MPI) thus performs ‘gatekeeper’ function in CAD management.

It has been demonstrated by large volume of data over last several years that the size and severity and reversibility of perfusion defects demonstrated on a myocardial perfusion have significant prognostic value. Small defects (low-risk scan) indicate <1% probability of cardiac events (myocardial infarct, death) in the following 2 years. Large defects (high-risk scans) indicate >8% probability of cardiac events.

Table 3: The Scan Patterns

Scan patterns

Low-risk scan

Normal perfusion, or Small perfusion defects <10% of myocardium

Intermediate risk scan

Medium defect 10% to 20% of the myocardium, or Small perfusion defect + LV dilatation or lung uptake of tracer

High-risk scan
Large defects >20% of myocardium, or Medium perfusion defect + transient dilatation of LV or lung uptake of tracer

Higher the quantity of ischaemic myocardium (>12.5% of total myocardium), the better the results from interventional treatment strategies (CABG, angioplasty) rather than medical management.

Thus, MPI identifies patients who should be managed by medical versus revascularisation strategies.

PET technology allows absolute quantification of myocardial blood flow in ml/g/min and also estimates the CFR.

Coronary angiography is blind to vessels <400 microns in diameter. A significant portion of disease involves these vessels. The only way to assess these vessels is through the estimation of CFR (Table 4).

**Table 4: The Utility of Estimating CFR**

**Potential clinical applications of PET MPI and CFR estimation**

**Impaired CFR in early coronary atherosclerosis**

- Hypertension
- Hyperlipidaemia
- Diabetes
- Smoking

**Impaired CFR in coronary stenosis and advanced coronary atherosclerosis**

- Evaluation of functional significance of coronary lesions (intermediate lesions)
- Detection/delineation of multi-vessel CAD
- Track disease progression/regression

**Impaired CFR in non-atherosclerotic microvascular disease**

- Syndrome X, cardiomyopathies (HCM, DCM), hypertensive heart disease

CFR is found to be impaired in patients with hypertension, hyperlipidaemia, diabetes, and in smokers long before they develop manifest atherosclerosis and coronary disease. Corrective measures have shown normalisation or improvement in CFR.

In some patients with so called ‘balanced triple vessel disease’ where there is similar degree of stenosis in all three coronary arteries, a SPECT myocardial perfusion scan will look spuriously normal since the tracer will go equally badly in all stenosed territories and there will be no relative hypoperfusion in a particular territory. In this situation, an absolute quantification of blood flow will show low values in all territories and the CFR will show low reserve.
In the recently concluded FAME trial, it was observed that routine measurement of CFR in patients with multivessel coronary artery disease who are undergoing PCI with drug eluting stents, significantly reduces the rate of composite end point of death, non-fatal MI and repeat revascularization at 1 yr. The 1 year event rate in the angiography alone group was 18.3% while in the group with CFR was 13.2%.

This underscores the importance of PET scans in evaluation of MPI and CFR. Limited at the moment due to its high cost and limited availability, PET MPI and CFR will in future become the main tests in evaluation of ischaemic heart disease.

**MYOCARDIAL METABOLISM**

The normal myocardium predominantly uses fatty acids for its metabolic needs, to produce energy for contraction. In ischaemic conditions, the metabolism switches to the use of glucose in order to produce ATP. This is an inefficient way of producing energy, but the only way available for the myocardium in times of ischaemia.

It is possible with SPECT and PET techniques to evaluate myocardial metabolism of fatty acids as well as glucose (Table 5).

Evaluation of glucose metabolism has become the mainstay in detection of viable myocardium.

The switch in metabolism from fatty acids to glucose metabolism can be used to diagnose myocardial ischaemia. If a fatty acid tracer is injected during stress, ischaemic areas would show reduced uptake of fatty acid tracer. If 18F-FDG is injected during stress, ischaemic areas would show increased uptake of the glucose tracer. The normal areas would show no uptake of 18F-FDG. Stress FDG imaging is undergoing clinical studies. Hence, in patients coming to hospital with acute chest pain, a fatty acid tracer would immediately identify if there is ongoing ischaemia, showing reduced uptake of the tracer in ischaemic areas.

**Table 5: Available Techniques for Imaging Myocardial Metabolism**

**Evaluation of myocardial metabolism with SPECT and PET**

**SPECT tracers**

Fatty acid metabolism

123I-BMIPP, IPPA, DMIPP

**PET tracers**

Fatty acid metabolism

11C-Palmitate

Glucose metabolism

18F-FDG (Fluoro-deoxy-glucose)
Many times after a large myocardial infarction with a resultant low left ventricular ejection fraction, it is necessary to know if there is viable myocardium in the infarct zone. It has been conclusively shown that revascularisation provides better clinical outcomes in terms of survival and symptomatic improvement in patients with viable myocardium as compared to medical therapy. Therefore, identification of viable myocardium is of great importance post myocardial infarction. Several techniques are available for this identification, namely low-dose dobutamine stress echocardiography, delayed enhanced MRI, and 18F-FDG myocardial PET. Currently, 18F-FDG PET remains the ‘gold standard’ for detecting myocardial viability. Viable myocytes retain capability of metabolising glucose. Dead myocytes or scar tissue cannot metabolise glucose. Hence, if a resting myocardial perfusion shows a severe perfusion defect and an FDG scan shows uptake of tracer in the same area (perfusion-metabolism mismatch), then viability is present.

MYOCARDIAL INFARCTION

On standard MPI, an area of infarction is seen as a persistent perfusion defect on both the stress and rest images (fixed defect). Tracers have been developed which would be concentrated in infarcted tissue.

Glucaric acid localises in necrotic (not normal or ischaemic) tissue. Acute MI can be visualised within 1 to 2 hours of the onset of pain, in patients with or without thrombolytic therapy. Infarcts older than 2 to 3 days are not likely to show up on imaging. Tc-glucaric acid imaging will provide an important triage function in the emergency room in the evaluation of acute coronary syndromes. It will also detect peri-operative infarcts following CABG.

MYOCARDIAL RECEPTORS

Non-invasive assessment of cardiac pre-synaptic sympathetic nerve activity is possible with 123I-MIBG SPECT and 11C metahydroxyephedrine (HED) PET. Myocardial receptor imaging has a potential diagnostic and prognostic role in patients with heart failure and cardiomyopathies. Regional uptake and washout of the radiotracer are expressed as heart to upper mediastinum (H/M) ratio in the early and late images of 123I-MIBG SPECT. A low H/M ratio strongly predicts poor outcome. Other applications include detection of diabetic autonomic neuropathy, cardiac transplant, re-innervation and re-entrant arrhythmias post-myocardial infarction.

Regional heterogeneities in β-adrenergic receptor number and reuptake occur in subjects with sudden cardiac death, and may be predictive for future events. Genetic variations in β-adrenergic receptors have major implications in terms of future development of CHF and early associated mortality. As newer third generation beta blockers like carvedilol become available, it will become increasingly important to identify markers predictive of drug efficacy for individual heart failure patients, based on sympathetic nerve imaging.

APOPTOSIS IMAGING

Pathological insults can induce apoptosis in various cardio-vascular disorders, e.g. infarction and reperfusion injury, myocarditis, heart failure, heart transplant rejection. Identification of apoptosis is possible by imaging with 99mTc- annexin. The usefulness of serial imaging has been demonstrated clinically in early detection of cardiac transplant rejection by positive scans. Upon immunosuppressive therapy with cyclosporine the scans become negative within two days.
ATHEROSCLEROSIS AND GENE THERAPY IMAGING

For ensuring success of gene and cell based therapies, it is of prime importance to develop technology for non-invasive monitoring of the location and duration of gene expression, distribution and targeting of therapeutically engineered cells and vector particles in vivo. A number of advances have been achieved in high resolution, in vivo imaging methods, such as bioluminescence imaging, MRI, PET and various fluorescence imaging techniques, including fluorescence-mediated tomography (FMT) and near infrared fluorescence (NIRF) reflectance imaging.

Identifying patients at high-risk for an acute cardiovascular event such as myocardial infarction or stroke and assessing the total atherosclerotic burden are clinically important. Currently available imaging modalities can delineate vascular wall anatomy and, with novel probes, target biologic processes important in plaque evolution and plaque stability.

CONCLUSION

Nuclear cardiology has established itself as a very important diagnostic tool in the management of heart disease. By its unique ability to study physiological processes and their alteration in health and disease, it provides important diagnostic and prognostic information vital for making appropriate management decisions. Information from anatomical modalities should be combined with physiological information from nuclear cardiology techniques for full understanding of disease pathophysiology and appropriate management.

RECOMMENDED READINGS