Nuclear Cardiology in Singapore: A Review

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Abstract

Since its introduction in Singapore more than 10 years ago, nuclear cardiology has now become an integral part of comprehensive cardiac workup of patients with a variety of cardiac diseases. We trace its local development from the 1980s to its present-day role in cardiac evaluation, and into the potential future of genetic and molecular cardiology.

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Introduction

The past decade has witnessed significant advances and rapid growth in the field of nuclear cardiology. In Singapore, our experience has been similar to the United States, with a 10% to 15% yearly growth in volume of cardiac nuclear studies now performed at many institutions since its introduction in 1983. The aims of this review were to analyse the factors contributing to the growth in this field, and to provide an assessment of emerging trends and their impact on cardiac nuclear imaging.

Myocardial Perfusion Imaging versus the Exercise Electrocardiogram

Conventional exercise electrocardiogram (ECG) testing is widely used because of its low cost, simplicity and widespread availability, but it has some limitations, such as the inability to test patients who are unable to exercise and the confounding effect of resting ECG abnormalities. In contrast, stress myocardial perfusion imaging can be utilised in patients who are unable to exercise or who have resting ECG abnormalities that confound detection of myocardial ischemia.

Myocardial perfusion imaging was first introduced in Singapore in 1983 by the Department of Nuclear Medicine, in collaboration with the Department of Cardiology in the Singapore General Hospital (SGH), using planar and subsequently a tomographic thallium approach. The sensitivity and specificity for detection of coronary artery disease (CAD) averaged 91.3% and 88.9%, respectively.1,2

Technetium-99m Perfusion Agents

Despite its pioneering role in perfusion imaging, 201Thallium has significant limitations. Its relatively long half-life limits the maximum dose possible, resulting in suboptimal image quality. In contrast, newer 99mTc-based agents such as 99mTc sestamibi and 99mTc tetrofosmin have a shorter half-life that allows close to 10-fold higher dose (for the same radiation exposure) as 201Thallium. These differences result in higher counts, better image quality, higher specificity, and greater confidence in interpretation. Technetium-99m Sestamibi was introduced in Singapore in 1988, with reported sensitivity and specificity of 92% and 100%, respectively.3

Gated Single Photon Emission Computed Tomography Imaging

Tc-99m agents, due to their higher counts, are also optimal for the performance of ECG-gated single photon emission computed tomography (GSPECT). GSPECT is a modification of conventional SPECT, whereby multiple images, each corresponding to a specific part of the cardiac cycle, are acquired. When displayed in a continuous cine-loop, a visual assessment of cardiac function throughout the cardiac cycle can be made.4 End-diastolic and end-systolic images can be identified, which are then used to determine left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV), and thus left ventricular ejection fraction (LVEF).5 Computer software program that provide sophisticated 3-D analysis and display of global and regional myocardial perfusion and function in a quantitative, objective way are widely available. These data are provided at no additional cost or radiation exposure to the patient and have been extensively validated.6-8 Preliminary work also suggests that regional wall motion
and thickening can be quantitated accurately with GSPECT when compared to echocardiography. The clinical impact of these developments include enhanced specificity for the diagnosis of CAD, particularly in women, (because gated SPECT allows attenuation artifact to be differentiated from infarct), improved confidence of interpretation of studies, detection of cardiomyopathy and additional information on regional and global myocardial function. Gated SPECT is now routinely performed in all perfusion studies in Singapore.

These developments increased confidence in the clinical value of perfusion imaging, resulting in increased demand. Thus, in 1995, collaboration between the Departments of Nuclear Medicine and Cardiology led to the establishment of an additional gamma camera and radiopharmacy at the newly opened National Heart Centre. In addition, by 2000, 3 other hospitals in Singapore had also established nuclear cardiology services.

**Prognostic Value of Perfusion Imaging**

The overall result of a stress perfusion study depends on multiple physiologic factors such as the haemodynamic effect of coronary stenosis (dependent on lesion morphology, length and location), collateral flow, the area supplied by an artery, and the level of stress achieved. This physiologic data are complementary to the anatomic information provided by coronary angiography, and appear to have clinical and prognostic significance as shown in multiple studies and in many patient populations, including women, elderly patients, patients unable to exercise requiring pharmacologic stress, and patients with established CAD and post-myocardial infarction. Although many of the initial studies were performed using Thallium-201, the prognostic value of stress 99mTc-sestamibi perfusion imaging has been shown to be comparable in an analysis of 14 prognostic studies comprising more than 12,000 patients by Iskander and Iskandrian. Berman et al demonstrated that the cardiac event rate for patients with normal scans was low for all levels of pretest likelihood of CAD based on exercise treadmill testing. Since the overall risk for myocardial revascularisation ranges from 1% for percutaneous transluminal coronary angioplasty (PTCA) to 2%-3% for coronary artery bypass grafting, it has been argued that revascularisation is unlikely to benefit these patients and coronary angiography can be deferred safely. In a series of 834 patients who had a low-risk stress 99mTc-sestamibi scan, the catheterisation rate was only 1%. The cost-effectiveness of this approach has also been evaluated in a large observational study (the Economics of Non-Invasive Diagnosis Study or ENDS) of 11,372 consecutive patients assessed using a strategy of initial stress myocardial perfusion imaging with selective cardiac catheterisation versus direct catheterisation without imaging. Both the diagnostic and follow-up costs were higher for the direct catheterisation strategy rather than the perfusion imaging strategy regardless of the pre-test likelihood of CAD, yet the subsequent cardiac event rate was no different between the 2 strategies.

Established adverse prognostic perfusion imaging variables include a large defect size (>20% of the left ventricle), multiple defects signifying multi-vessel involvement, multiple reversible defects reflective of inducible ischemia, transient or permanent dilatation of the left ventricle, increased 201Tl lung uptake and a depressed left ventricular ejection fraction of <40%. The main goal of risk stratification with myocardial perfusion imaging is to identify subsets of patients with high risk of cardiac death or non-fatal myocardial infarction so that appropriate measures can be instituted promptly. Conversely, patients with low risk of cardiac event can be spared unnecessary invasive procedures. This approach is supported by established guidelines.

Following myocardial infarction, there also appears to be a role for perfusion imaging. Pharmacological 99mTc-sestamibi imaging can be used for risk stratification after myocardial infarction. In a recent multicentre trial in which dipyridamole 99mTc-sestamibi was performed 2 to 4 days after admission for an acute myocardial infarction, the study demonstrated that the extent and severity of defect reversibility provided significant incremental prognostic value. Patients with a low-risk dipyridamole 99mTc-sestamibi scan had a cardiac event rate at 2 years of <2% per year. Vasodilator stress imaging also can be used as an alternative to exercise stress imaging with a high degree of safety. The preliminary results of the multicentre INSPIRE study (Adenosine Te99m Sestamibi Post-Infarction Evaluation) in which our centre participated suggest that perfusion imaging soon after infarction is a powerful prognostic tool for risk stratification and evaluation of the effectiveness of post-infarction treatment, with negligible risk to the patient.

**Assessment of Acute Chest Pain**

The evaluation of patients presenting with angina-like chest pain and non-diagnostic ECG is a major common clinical problem for which nuclear imaging may have a role. Using a rest injection of a 99mTc-sestamibi or 99mTc-tetrofosmin at the time of chest pain followed by SPECT imaging, a number of studies have shown high sensitivity for detecting patients at risk of subsequent infarct or unstable angina in a number of single centre and multicentre studies. More recently, Udelson et al in a randomised trial comparing a strategy of standard emergency room assessment versus standard combined with imaging, demonstrated a significantly lower admission rate (48% vs 56%) using the imaging added strategy, with no difference.
in the 30-day mortality or event rate.

These studies show that a normal result is associated with a very low likelihood of myocardial infarction but it does not rule out underlying CAD. In our own hospital, a randomised trial of exercise perfusion imaging in patients being seen with chest pain and non-diagnostic ECGs has been conducted by the Emergency Department in collaboration with the Departments of Nuclear Medicine and Cardiology, and the results are being analysed. In summary, there is evidence that perfusion imaging can be used to help risk stratify patients presenting to emergency departments with chest pain so as to reduce unwarranted admissions. However, the clinical benefits must be carefully weighed against the logistics and cost implications.

Assessment of Myocardial Salvage

Myocardial perfusion imaging using Tc-99m tracers, such as sestamibi, has also been used to measure the amount of myocardial salvage provided by reperfusion therapy in acute infarction. Since sestamibi does not redistribute, it can be injected immediately at the time of presentation of acute myocardial infarction, and imaging performed many hours later after reperfusion treatment with PTCA or thrombolysis has taken place. This allows for an assessment of the size of myocardium at risk from the infarct. A repeat study approximately a week later allows delineation of the amount of myocardium salvaged, by comparison with the initial image. Such an approach to the assessment of myocardial salvage has been validated in animal studies and used in several landmark studies to compare the efficacy of different reperfusion strategies.

A collaborative study27 between SGH’s Nuclear Medicine and Cardiology Departments demonstrated that assessment of myocardial salvage using 99mTc-sestamibi SPECT imaging after instituting reperfusion therapy was feasible. It allowed for quantitation of myocardium at risk and the amount of myocardial salvage, which was not possible by angiography alone. However, the technique requires considerable logistic support and is usually used as a research tool.

Myocardial Viability

In patients with chronic CAD and impaired resting left ventricular function, one of the most critical diagnostic challenges is the detection of hibernating myocardium and the prediction of improvement following revascularisation. Considerable effort has been devoted to identifying hibernating myocardium by a wide variety of nuclear and non-nuclear methods, such as dobutamine echocardiography, conventional SPECT perfusion imaging as well as positron emission tomography (PET) and more recently, magnetic resonance imaging. In general, there is agreement that thallium in combination with a stress-redistribution-reinjection protocol or rest-redistribution protocol provides high sensitivity but limited specificity. In combination with quantitative analysis, thallium SPECT imaging has been shown to have high concordance (>80%) with PET imaging, which is often regarded as the gold standard for viability detection. Metabolic imaging using fluorine-18-deoxyglucose (18FDG) and PET is now available in Singapore and should enhancement detection of viability in such patients. Its present limitations include increased cost compared to standard SPECT techniques and availability. Although more controversial, there is now accumulating evidence that Tc-99m Sestamibi can also be used for viability assessment. A randomised trial comparing a strategy of PET FDG imaging with Tc-99m Sestamibi imaging was unable to detect a difference in clinical outcomes.28

A recent meta-analysis by Allman et al29 demonstrated that the use of non-invasive imaging techniques to search for viable myocardium in patients with CAD and significant LV dysfunction identifies a subset of patients with substantial risk of death, which can be reduced by successful revascularisation. On the other hand, patients without evidence of myocardial viability did not show significant difference in outcomes, regardless of treatment strategies. This is consistent with earlier observational studies of patients with little preoperative myocardial viability who underwent coronary bypass surgery. As compared with patients with significant viability,30,31 the first group had a higher incidence of cardiac mortality and a greater need for cardiac transplantation. Other retrospective studies also demonstrated that patients with large areas of viable myocardium had better event-free survival with revascularisation compared to medical therapy.32,33 In addition, the improvement in heart failure symptoms and exercise tolerance was proportional to the amount of viable myocardium.34,35

Ongoing Studies

What does the future hold? In the clinical arena, a number of major trials are in progress that will better define the role of perfusion imaging in the screening of asymptomatic patients with diabetes for associated CAD (Detection of Myocardial Ischemia in Asymptomatic patients with Diabetes or DIAD), heart failure (Investigation of Myocardial Gated SPECT Imaging as Initial Strategy in Heart Failure or IMAGING in Heart Failure trial) and assessment of the impact of percutaneous coronary intervention plus intensive medical therapy versus intensive medical therapy alone (COURAGE – Clinical Outcomes Utilizing Revascularisation and Aggressive Drug Evaluations Trial).
Another development in the field of nuclear cardiology that should improve the accuracy of SPECT is by correcting for attenuation artifact using transmission imaging with one or more line sources. A number of reports have described various systems, some of which are commercially available. However, more time is needed to determine if these systems provide consistently more accurate results than a combination of gated SPECT and clinical judgement. There are added costs and greater technical requirements for quality control.

**Newer Imaging Agents**

New radioactive tracer pharmaceutical agents are also being studied. The ideal perfusion tracer, whose myocardial uptake with respect to flow is linear across the wide range of myocardial blood flow that occurs throughout dynamic conditions of rest and stress, yet is retained in myocardium for optimal imaging, remains elusive.

Hypoxia markers are being studied for their potential use for detection hypoxia in the myocardium. Two classes of 99mTc-labelled hypoxic agents36,37 whose myocardial uptake increases in the presence of hypoxia have shown promising preliminary results. These new agents may allow identification and quantification of zones of myocardial hypoxia. In a recent study published by He et al,18 18FDG has also been used as a hypoxic marker.

Fatty acid uptake and metabolism reflects the metabolic state of the myocardium. Two new radiolabelled fatty acids have been used extensively in Japan, namely 123I-iodophenyl pentadecanoic acid (IPPA) which undergoes active metabolism and 123I-beta methyl-iodophenyl pentadecanoic acid (BMIPP)39 which is trapped within myocytes.

A functional approach involves 123I metaiodobenzyl-guanidine imaging, which provides presympathetic neuronal occupancy, used mainly in studies of congestive heart failure. The presence of decreased tracer uptake, increased washout and heterogeneous uptake in congestive heart failure offers important prognostic information regarding sudden cardiac death.

99mTc-glucarate has being proposed as a marker of myocardial necrosis for early detection of myocardial infarction.40 This agent is still under study.

**Molecular and Vascular Imaging**

The next frontier in nuclear cardiology will be its application in molecular and cellular biology. Much interest has been generated in detection of early atherosclerosis and the unstable plaque. A radiolabelled antibody against an antigenic component of the proliferating smooth muscles has been studied. Narula et al41 demonstrated that a murine monoclonal antibody (Z2D3) was highly specific for proliferating smooth muscles found in atherosclerotic plaques. Carrio et al42 was successful in using the same tracer to image atherosclerotic plaque in human carotid arteries.

Another approach is to image the rich lipid pool in atherosclerotic lesions. Recently, Tsimikas et al43 demonstrated increased uptake of a radiolabelled monoclonal antibody for oxidised LDL-C in lipid laden regions of aorta of rabbits with hereditary hyperlipidaemia.

Other areas of interest include 99mTc-diadienosine polyphosphate for non-invasive imaging of active atherosclerotic process, 99mTc endothelin analogue for endothelin receptors present on sacrolemmal surface of proliferating smooth muscle cells, antibodies to adhesion molecules and receptors present on sacrolemmal surface of proliferating smooth muscle cells, antibodies to adhesion molecules and receptors present on sacrolemmal surface of proliferating smooth muscle cells, antibodies to adhesion molecules and receptors present on sacrolemmal surface of proliferating smooth muscle cells.

**Conclusions**

From its humble beginning, nuclear cardiology has now entered into the era of molecular cardiology. It has proved its usefulness in assessment of ischemic heart disease and myocardial viability. With the advancement of technology, it is envisioned that nuclear cardiology will remain in the forefront of cardiac evaluation.

**Table 1. New Radiopharmaceutical Approaches for Nuclear Cardiology**

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<th>Myocardial perfusion</th>
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<tr>
<td>Myocardial fatty acid metabolism</td>
<td>IPPA, BMIPP</td>
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<td>Neuronal integrity</td>
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<td>Necrosis</td>
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<td>Vascular proliferating smooth muscle cells</td>
<td>Z2D3 endothelin derivatives, diadenosine polyphosphate</td>
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<td>Gene expression</td>
<td>PET reporter genes/reporter probes, antisense oligodeoxynucleotides</td>
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**REFERENCES**


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