

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 ^{99m}Tc Technetium based agents such as ^{99m}Tc sestamibi and ^{99m}Tc 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

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and thickening can be quantitated accurately with GSPECT when compared to echocardiography.⁹ The clinical impact of these developments include enhanced specificity for the diagnosis of CAD, particularly in women,¹⁰ (because gated SPECT allows attenuation artifact to be differentiated from infarct), improved confidence of interpretation of studies,¹¹ 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 studies¹² and in many patient populations, including women, elderly patients, patients unable to exercise requiring pharmacologic stress,¹³ 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 ^{99m}Tc-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.¹⁴ Berman et al¹⁵ 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 patients¹⁶ who had a low-risk ^{99m}Tc-sestamibi scan, the catheterisation rate was only 1%. The cost-effectiveness of this approach has also been evaluated in a large observational study¹⁷ (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 defects¹⁸ 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 ^{99m}Tc-sestamibi imaging can be used for risk stratification after myocardial infarction. In a recent multicentre trial¹⁹ in which dipyridamole ^{99m}Tc-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 ^{99m}Tc-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 study²⁰ (Adenosine Tc99m 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 ^{99m}Tc-sestamibi or ^{99m}Tc-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 centre²¹⁻²⁴ and multicentre studies.²⁵ More recently, Udelson et al,²⁶ 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 ^{99m}Tc-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 enhance 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, remain elusive.

Hypoxia markers are being studied for their potential use for detection hypoxia in the myocardium. Two classes of ^{99m}Tc -labelled hypoxic agents^{36,37} 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,³⁸ ^{18}F FDG 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 ^{123}I -iodophenyl pentadecanoic acid (IPPA) which undergoes active metabolism and ^{123}I -beta methyl-iodophenyl pentadecanoic acid (BMIPP)³⁹ which is trapped within myocytes.

A functional approach involves ^{123}I 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.

^{99m}Tc -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

Table 1. New Radiopharmaceutical Approaches for Nuclear Cardiology

Myocardial perfusion	N-NOET
Myocardial fatty acid metabolism	IPPA, BMIPP
Neuronal integrity	MIBG
Necrosis	Glucarate
Vascular proliferating smooth muscle cells	Z2D3 endothelin derivatives, diadenosine polyphosphate
Vascular lipid pools	Antibody to oxidised LDL-C
Apoptosis	Annexin V
Gene expression	PET reporter genes/reporter probes, antisense oligodeoxynucleotides

BMIPP: ^{123}I -beta methyl-iodophenyl pentadecanoic acid;

IPPA: ^{123}I -iodophenyl pentadecanoic acid;

LDL-C: low density lipoprotein-cholesterol;

MIBG: metaiodo-benzyl-guanidine;

N-NOET: N-ethoxy N ethyl dithiocarbamate nitrido

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 ^{99m}Tc -diadenosine polyphosphate for non-invasive imaging of active atherosclerotic process, ^{99m}Tc endothelin analogue for endothelin receptors present on sacrolemmal surface of proliferating smooth muscle cells, antibodies to adhesion molecules and ^{99m}Tc -labelled annexin V for imaging apoptosis (Table 1).

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.

REFERENCES

1. Sundram FX, Lam LK, Ang ES, Goh AS, Johan A, Tan AT, et al. Tomographic thallium-201 stress scintigraphy in the evaluation of coronary artery disease. *Ann Acad Med Singapore* 1986;15:471-5.
2. Lam LK, Tang KF, Sundram FX, Ang ES, Johan A, Chia BL, et al. Thallium-201 myocardial stress imaging: a study of its value in the diagnosis of coronary artery disease and the location of the diseased vessel. *Singapore Med J* 1987;28:6-12.
3. Woo BY, Sundram FX, Goh AS, Tan AT. Nuclear cardiology in the detection of coronary artery disease – an overview of its role in the Singapore General Hospital. *Ann Acad Med Singapore* 1990;19:104-7.
4. Chua T, Kiat H, Germano G, Maurer M, Van Train K, Friedman J, et al.

- Gated technetium-99m sestamibi for simultaneous assessment of stress myocardial perfusion, postexercise regional ventricular function and myocardial viability. Correlation with echocardiography and rest thallium-201 scintigraphy. *J Am Coll Cardiol* 1994;23:1107-14.
5. Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, et al. Automatic quantification of ejection fraction from gated sestamibi SPECT. *J Nuclear Med* 1995;36:2138-47.
 6. Nichols K, DePuey EG, Rowanski A. Automation of gated tomographic left ventricular ejection fraction. *J Nucl Cardiol* 1996;3:475-82.
 7. DePuey EG, Nichols K, Dobrinsky C. Left ventricular ejection fraction assessed from gated Tc-99m sestamibi SPECT. *J Nucl Med* 1993;34:1871-6.
 8. Chua T, Lee CY, Tan HT, Tai BC, Ding ZP, Lim YL. Accuracy of automated assessment of left ventricular function using gated perfusion SPECT in the presence of perfusion defects and left ventricular dysfunction: correlation with equilibrium radionuclide ventriculography and echocardiography. *J Nucl Cardiol* 2000;7:301-11.
 9. Chua T, Lee CY, Keng F, Ding ZP, Lim YL. Automated quantification of regional function by gated perfusion tomography: determination of a normal range and correlation with echocardiography for detection of abnormal wall motion [abstract]. *J Am Coll Cardiol* 2001;37:393A (ACC 2001).
 10. Taillefer R, DePuey EG, Udelson JE, Beller GA, Latour Y, Reeves F. Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. *J Am Coll Cardiol* 1997;29:69-77.
 11. Smanio PE, Watson DD, Segalla DL, Vinson EL, Smith WH, Beller GA. Value of gating of technetium-99m sestamibi single-photon emission computed tomographic imaging. *J Am Coll Cardiol* 1997;30:1687-92.
 12. Brown KA. Prognosis in stable coronary artery disease. In: Zaret BL, Beller GA, editors. *Nuclear Cardiology: State of the Art and Future Directions*. 2nd ed. St Louis, Mo: Mosby, 1999:331-45.
 13. Hachamovitch R, Berman DS, Kiat H, Cohen I, Lewin H, Amanullah A, et al. Incremental prognostic value of adenosine stress myocardial perfusion single-photon emission computed tomography and impact on subsequent management in patients with or suspected of having myocardial ischemia. *Am J Cardiol* 1997;80:426-33.
 14. Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. *J Am Coll Cardiol* 1998;32:57-62.
 15. Berman DS, Hachamovitch R, Kiat H, Cohen I, Cabico JA, Wang FP, et al. Incremental value of prognostic testing in patients with known or suspected ischemic heart disease: a basis for optimal utilization of exercise technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography [published erratum appears in *J Am Coll Cardiol* 1996; 27:756]. *J Am Coll Cardiol* 1995;26:639-47.
 16. Hachamovitch R, Berman DS, Kiat H, Cohen I, Cabico JA, Friedman J, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. *Circulation* 1996;93:905-14.
 17. Shaw LJ, Hachamovitch R, Berman DS, Marwick TH, Lauer MS, Heller GV, et al. The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia: the Economics of Noninvasive Diagnosis (END) Multicenter Study Group. *J Am Coll Cardiol* 1999;33:661-9.
 18. Brown KA, Boucher CA, Okada RD, Guiney TE, Newell JB, Strauss HW, et al. Prognostic value of exercise thallium-201 imaging patients presenting for evaluation of chest pain. *J Am Coll Cardiol* 1983;1:994-1001.
 19. Brown KA, Heller GV, Landin RS, Shaw LJ, Beller GA, Pasquale MJ, et al. Early dipyridamole 99mTc-sestamibi single photon emission computed tomographic imaging 2-4 days after acute myocardial infarction predicts in-hospital and postdischarge cardiac events: comparison with submaximal exercise imaging. *Circulation* 1999;100:2060-6.
 20. INSPIRE results. Late-breaking clinical trials sessions at ACC 2004. *J Am Coll Cardiol* 2004. In press.
 21. Hilton TC, Thompson RC, Williams HJ, Saylor R, Fulmer H, Stowers SA. Technetium-99m sestamibi myocardial perfusion imaging in the emergency room evaluation of chest pain. *J Am Coll Cardiol* 1994; 23:1016-22.
 22. Hilton TC, Fulmer H, Abuan T, Thompson RC, Stowers SA. Ninety-day follow-up of patients in the emergency department with chest pain who undergo initial single-photon emission computed tomographic perfusion scintigraphy with technetium 99m-labeled sestamibi. *J Nucl Cardiol* 1996;3:308-11.
 23. Varetto T, Cantalupi D, Altieri A, Orlandi C. Emergency room technetium-99m sestamibi imaging to rule out acute myocardial ischemic events in patients with nondiagnostic electrocardiograms. *J Am Coll Cardiol* 1993;22:1804-8.
 24. Tatum JL, Jesse RL, Kontos MC, Nicholson CS, Schmidt KL, Roberts CS, et al. Comprehensive strategy for the evaluation and triage of the chest pain patient. *Ann Emerg Med* 1997;29:116-25.
 25. Heller GV, Stowers SA, Hendel RC, Herman SD, Daher E, Ahlberg AW, et al. Clinical value of acute rest technetium-99m tetrofosmin tomographic myocardial perfusion imaging in patients with acute chest pain and nondiagnostic electrocardiograms. *J Am Coll Cardiol* 1998;31:1011-7.
 26. Udelson JE, Beshan, JR. RN, Ballin, Feldman JA, Griffith JL, Handler J, et al. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial [Published erratum in *JAMA* 2003;289:178]. *JAMA* 2002;288: 2693-700.
 27. Keng FY, Chua TS, Goh AS, Ang ES, Sundram FX, Tan AT. Technetium-99m sestamibi for the assessment of myocardial salvage following reperfusion therapy in acute myocardial infarction. *Ann Acad Med Singapore* 2000;29:224-30.
 28. Siebelink HM, Blanksma PK, Crijns HJ, Bax JJ, van Boven AJ, Kingma T, et al. No difference in cardiac event-free survival between positron emission tomography-guided and single-photon emission tomography-guided patient management: a prospective, randomized comparison of patients with suspicion of jeopardized myocardial. *J Am Coll Cardiol* 2001;37:81-8.
 29. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol* 2002;39:1151-8.
 30. Pagley PR, Beller GA, Watson DD, Gimple LW, Ragosta M. Improved outcome after coronary bypass surgery in patients with ischaemic cardiomyopathy and residual myocardial viability. *Circulation* 1997; 96:793-800.
 31. Pasquet A, Robert A, D'hondt AM, Dion R, Melin JA, Vanoverschelde JL. Prognostic value of myocardial ischaemia and viability in patients with chronic left ventricular ischaemic dysfunction. *Circulation* 1999;100:141-8.
 32. Gioia G, Powers J, Heo J, Iskandrian AS. Prognostic value of rest-redistribution tomographic thallium-201 imaging in ischemic cardiomyopathy. *Am J Cardiol* 1995;75:759-62.
 33. DiCarli MF, Davidson M, Little R, Khanna S, Mody FV, Brunken RC, et al. Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with coronary artery disease and left ventricular dysfunction. *Am J Cardiol* 1994;73:527-33.
 34. DiCarli MF, Asgarzadi EF, Schelbert HR, Brunken RC, Laks H, Phelps ME, et al. Quantitative relation between myocardial viability and improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy. *Circulation* 1995;92:3436-44.
 35. Marwick TH, Zuchowski C, Lauer MS, Secknus MA, Williams J, Lytle

- BW. Functional status and quality of life in patients with heart failure undergoing coronary bypass surgery after assessment of myocardial viability. *J Am Coll Cardiol* 1999;33:750-8.
36. Sinusas AJ. New approaches to myocardial imaging with hypoxia markers. In: Iskandrian AS, editor. *New Developments in Cardiac Nuclear Imaging*. Armonk, NY: Futura Publishing Co, 1998:203-18.
37. Okasa RD, Johnson G III, Nguyen KN, Carlson LR, Beju D. HL-91-technetium-99m: a new marker of viability in ischemic myocardium. *J Nucl Cardiol* 1999;6:306-15.
38. He ZX, Shi RF, Wu YJ, Tian YQ, Liu XJ, Wang SW, et al. Direct imaging of exercise-induced myocardial ischemia with fluorine-18-labeled deoxyglucose and Tc-99m-sestamibi in coronary artery disease. *Circulation* 2003;108:1208-13.
39. Tamaki N, Kudoh T, Tadamura E. Fatty acid imaging. In: Zaret BL, Beller GA, editors. *Nuclear Cardiology: State of the Art and Future Directions*. 2nd ed. St Louis, Mo: Mosby, 1999:573-86.
40. Narula J, Petrov A, Pak KY, Lister BC, Khaw BA. Very early noninvasive detection of acute experimental nonreperfused myocardial infarction with 99mTc-labeled glucarate. *Circulation* 1997;95:1577-84.
41. Narula J, Petrov A, Bianci C, Ditlow CC, Lister BC, Dilley J, et al. Noninvasive localisation of experimental atherosclerosis lesions with mouse/human chimeric Z2D3 F(ab')₂ specific for the proliferating smooth muscles of human atheroma; imaging with conventional and negative charge-modified antibody fragments. *Circulation* 1995;92:474-84.
42. Carrio I, Pieri PL, Narula J, Prat L, Riva P, Pedrini L, et al. Noninvasive localisation of human atherosclerotic lesions with indium 111-labeled monoclonal Z2D3 antibody specific for proliferating smooth muscle cells. *J Nucl Cardiol* 1998;5:551-7.
43. Tsimikas S, Palinski W, Halpern SE, Yeung DW, Curtiss LK, Witztum JL. Radiolabeled MDA2, an oxidation-specific monoclonal antibody, identifies native atherosclerotic lesion in vivo. *J Nucl Cardiol* 1999;6:41-53.