26 *Recent Advances in Nuclear Cardiology*

Pankaj Dougall

Abstract: Nuclear cardiology uses radioisotopes to study various aspects of cardiac pathophysiology. Using the techniques of SPECT (Single Photon Emission Computed Tomography) and PET (Positron Emission Tomography) one can study myocardial function, perfusion, metabolism, receptors, infarction, atherosclerosis, apoptosis and success of gene therapy. Gated Blood Pool (GBP / MUGA) studies provide an accurate, reproducible and operator independent method for accurate estimation of left and right ventricular ejection fractions. Exercise MUGA/GBP studies provide a sensitive and specific tool for detecting myocardial ischemia and have excellent prognostic value. Myocardial perfusion scans performed with thallium, Tc-MIBI, tetrofosmin or with PET tracers like rubidium and ammonia, provide vital information on inducible myocardial ischemia. This information is important for making decisions about surgical versus medical management for coronary artery disease. Acute infarcts can be diagnosed in situations with equivocal ECG and cardiac enzyme findings at an early stage. The adrenergic innervation of the heart can be studied with 123I-MIBG and has prognostic value in heart failure and in predicting arrythmias. The heart uses fatty acids and glucose as its metabolic substrate. This utilization is altered in several disease states. PET scans are used to study cardiac metabolism in health and disease. Recent research is directed at imaging the unstable plaque with radiotracers. Apoptosis or programmed cell death can be studied with ^{99m}Tc-annexin V and is valuable in cardiac transplants in predicting rejection and in infarction. Finally, delivery and localization of stem cells can be followed with radionuclide techniques as also delivery and expression of therapeutic genes.

INTRODUCTION

Nuclear medicine uses radiopharmaceuticals tagged with isotope markers, and injected intravenously to study function of different organs of the body, e.g. ^{99m}Tc-tetrofosmin for myocardial perfusion. Radioisotopes emit gamma rays, which are picked up by a gamma camera and converted into an image. When the camera which may have single or multiple detectors rotates around the body the technique is called SPECT or Single Photon Emission Computed Tomography. Tomographic images of the distribution of the radiopharmaceutical in the body are thus obtained in 3 dimensions. Sometimes the radioisotopes are very short lived and emit positrons. These are produced in a cyclotron and imaged with a special camera combined with a

CT scanner. The technique is then called PET or positron emission tomography. This technique allows quantification of the various metabolic processes in the body.

Table 26.1 lists the areas of applications in Nuclear Cardiology.

Table 26.1: Scope of nuclear cardiology

- Myocardial function
- Myocardial perfusion
- Myocardial metabolism
- Myocardial infarcts
- Myocardial receptors
- Atherosclerosis imaging
- Apoptosis imaging
- Gene therapy, stem cell therapy imaging

Myocardial Function

Development of equilibrium radionuclide angiocardiography (RNV), or gated blood pool (GBP/ Muga) imaging, in the 1970s was another landmark development in cardiology. This was the first noninvasive modality for the assessment of left ventricular wall motion and ejection fraction. This technique has, to a large extent, been replaced by other imaging modalities. However, gated blood pool imaging continues to be the most reliable, reproducible, and objective technique for the assessment of left ventricular wall motion and ejection fraction.

GBP studies were the first studies to be used for measuring left ventricular ejection fraction (LVEF). The patients red blood cells are labelled with the isotope technetium (^{99m}Tc). The ECG trigger is then used to begin and end acquisition of the blood pool in the heart (gating). A cine image of the beating heart is obtained and various parameters of left and right ventricular systolic and diastolic function, such as ejection fraction, regional wall motion, peak filling and emptying rates can be obtained. These studies are cheap, reproducible and operator independent. Exercise LVEF has great diagnostic and prognostic value in ischemic heart disease. A fall in LVEF on exercise indicates high risk for future coronary events and indicates need for coronary angiography with subsequent revascularization. Regional wall motion abnormalities developing during exercise or dobutamine infusion are sensitive and specific for myocardial ischemia. GBP scans are routinely used in following up patients on chemotherapy to monitor cardiotoxicity of the drugs. Apart from accurate estimation of LVEF and RVEF, various mathematical images called parametric images like stroke volume image, amplitude image helps in identifying regional wall motion abnormalities. Phase images allow study of cardiac asynchrony and aid in localizing and following up conduction abnormalities.

Myocardial Perfusion

A major breakthrough in cardiovascular nuclear imaging came with the development of myocardial perfusion imaging (MPI) using radiopharmaceuticals. This was the first noninvasive imaging technique for the detection of coronary artery disease. Despite the development of a number of other competing modalities, MPI using radiopharmaceuticals (Thallium-201, ^{99m}Tc sestamibi, ^{99m}Tc tetrofosmin, ^{99m}Tc Tebroxime) continues to be the most widely used noninvasive test for the detection of coronary artery disease and remains the gold standard for comparison with emerging new imaging modalities.

Gated Myocardial Perfusion SPECT

Over the last few decades, the assessment of myocardial perfusion from stress and rest myocardial perfusion SPECT has become central to the management of patients with known or suspected coronary artery disease (CAD).[1] More recently, ECG-gated SPECT, with the ability to measure left ventricular LVEF and ventricular volumes, as well as to evaluate presence of

regional wall motion abnormalities (RWMA), has become a routine part of clinical protocols, expanding the clinical utility of MPI. Recent American College of Cardiology/American Heart Association/American Society of Nuclear Cardiology guidelines for the clinical use of cardiac radionuclide imaging consider ECG-gated SPECT as the "current state of the art". In addition to accurate, objective information on segmental myocardial perfusion, the ability of gated SPECT to provide measurement of LVEF, RWMA, and absolute LV volumes also adds to the prognostic information.[2] Gated SPECT has been used extensively for management decisions in suspected CAD (Fig. 26.1), risk stratification in known CAD, functional significance of angiographically documented lesions, post MI evaluation, follow up after therapy, pre-operative evaluation in non-cardiac disease and assessment of myocardial viability.

Advances in Software for Gated SPECT

Besides the progress in development of the radiopharmaceuticals and the camera computer systems that could acquire high-quality gated images, a highly important achievement along this path was development of commercially available software packages, allowing quick and automated quantification of parameters of both myocardial perfusion and function. Software developed at Cedars-Sinai Medical Center was the first totally automated "suite" of computer programs, called QGS (quantitative gated SPECT),[3] capable of providing simultaneous assessment of LV perfusion; global function (either systolic and diastolic); regional wall thickening and motion; and separate analysis of diastolic, systolic, and ungated data sets; as well as quantification of multiple ancillary parameters (LV mass, geometry, lung-heart ratio, transient ischemic dilation ratio). In addition to ventricular function measurements, these software packages are able to quantify regional myocardial perfusion parameters, as well as the ventricular function measurements. For both function and perfusion computer assessments, there has also been extensive research demonstrating excellent repeatability of the results.

Gated Myocardial Perfusion SPECT in the Era of Multi-detector CT

Multislice computed tomographic angiography (CTA) has taken the cardiology community by storm. Fundamentally, CTA and MPI differ in what each evaluates-anatomy for one and physiology for the other. Although we use MPI to infer whether a patient has CAD, more specifically, we use MPI to determine whether any CAD that is present results in ischemia. In the first decade of significant clinical use of MPI, the 1980s, planar and SPECT MPI was found to reliably diagnose CAD. In its second decade it was demonstrated that MPI could determine the importance of CAD by its ability to predict short- and intermediate-term prognosis. Not only could MPI determine ischemic burden, but by gating the images, the ejection fraction could be obtained, providing additional prognostic information. It should be noted that one imaging modality did not "replace" the other; hence, neither should CTA replace MPI. Just because this new noninvasive "rough" coronary angiogram can be easily done does not mean that it should be easily ordered. In some patients with suspected CAD, the diagnostic use of MPI will be replaced by CTA, given its direct, rather than inferred, coronary assessment. Clinicians, however, have accepted that physiology trumps anatomy in the prognostic assessment of patients with suspected and known CAD. Iskandrian, et al demonstrated in 1993, among 316 men and women who underwent both exercise thallium 201 testing and diagnostic angiography, that angiographic results added no incremental prognostic value over the combination of gender, metabolic equivalents achieved, and SPECT perfusion results.

As CTA proliferates, it behoves the cardiology community to bear in mind that this "ischemia-driven" paradigm has served us well over the last several decades, a time in which the age-adjusted cardiac mortality rate decreased by a mean of 3% per year (in the United States). However, CAD has certainly not been eliminated, and the first clinical manifestation among more than half of those patients in whom CAD develops is myocardial infarction or death. As Schuijf, et al suggest, the sweet spot for CTA will likely fall in the evaluation of patients with

potential CAD - an attempt to diagnose CAD before its unwanted clinical manifestation. As CTA is increasingly used, the well established prognostic value of MPI provides great opportunities for its continued use and further research development. Combining these two techniques either sequentially or with hybrid PET-CT or SPECT-CT equipment, provides yet another opportunity for further blossoming of MPI during its third decade of widespread clinical use.

PET and Imaging of Myocardial Metabolism

Noninvasive regional flow measurements have become possible by using PET scanning. This technique has the advantage of allowing noninvasive quantitative assessment of regional coronary blood flow measurements (ml/min per100 g myocardium) at the same time as myocardial imaging; furthermore, it can analyze metabolic changes, especially myocardial glucose or fatty acid metabolism, and thus adds to our understanding of myocardial metabolism in man in general.

PET scanning uses special short-lived isotopes such as ^{15}O, ^{11}C, ^{13}N, ^{82}Rb or ^{18}F. ^{11}C-palmitate, a marker of fatty acid metabolism, ^{18}F-2-fluorodeoxyglucose, as marker of glucose metabolism, ^{13}N or ^{11}C amino acids, as well as ^{13}N-ammonia and rubidium-82 as a markers for flow, has allowed the in vivo study of metabolic pathways in the human myocardium as well as the noninvasive measurement of myocardial blood flow, especially during ischemia or other metabolic abnormalities (Ter-Pogossian 1979; Sobel, et al, 1977, 1984; Selwyn, et al, 1982; Henze, et al, 1984; Henze 1987; Schelbert 1984, 1985).

In studies of wall motion, the identification of viable myocardium in akinetic areas, representing stunned myocardium (Braunwald and Kloner 1982), has become of utmost importance (Schelbert 1984). Now, it is possible to distinguish between post-ischemic, stunned myocardium, which could be revitalized through CABG or PTCA, and irreversibly damaged scar tissue. Estimation of viability by PET, has remained the 'gold standard' for several years and continues to be used as a reference standard for optimizing newer technologies like echo, MRI, etc.

Imaging Apoptosis and Necrosis

Necrosis and apoptosis are distinct forms of cell death, although their boundaries in heart muscle cell death are relatively hazy. Injured cardiomyocytes, depending upon their cellular energy reserves, may shuffle between necrotic and apoptotic cascades and may result in classic apoptosis, orthodox necrosis, or a hybrid thereof. Much work recently involved the targeting of the process of apoptosis (programmed cell death). This process involves translocation of phosphatidyl serine groups from the inner to outer portion of the cell membrane. Annexin V has been known to adhere to these phosphatidyl serine residues. This principle has been used for many years with annexin V as a histologic stain. Annexin V labeled with ^{99m}Tc has been used to demonstrate the correlation of this uptake with the apoptotic process both in small animals and in single-cell preparations. Hofstra, et al[5] also have demonstrated uptake of annexin in acute myocardial infarction in human beings (Fig. 26.2). This was the first definition of the potential imaging of the apoptotic process in human beings. Narula, et al subsequently demonstrated uptake of annexin in human beings undergoing cardiac transplant rejection. Currently, there remains some question concerning the specificity of this abnormal uptake with respect to apoptosis. Further work in this area is clearly required.

Imaging Myocardial Innervation

The heart is innervated by sympathetic and parasympathetic nerve fibers, which modify cardiac performance to respond quickly and effectively to changing demands on cardiovascular performance. Modifications of cardiac neuronal function have been reported in the

pathophysiology of various cardiovascular diseases such as heart failure, arrhythmias, ischemic heart disease, and diabetes.

Several radiolabeled compounds have been synthesized to probe the sympathetic and parasympathetic nervous system at the pre- and postsynaptic levels. SPECT and PET tracers can be divided into radiolabeled catecholamines and catecholamine analogues. The most commonly employed SPECT tracer is metaiodobenzylguanidine (mIBG), which represents an analogue of the antihypertensive drug guanethidine. Radiolabeled catecholamine analogues for PET include metaraminol, metahydroxyephedrine, and phenylephrine. These "false adrenergic neurotransmitters" share the same reuptake mechanism and endogenous storage with the true neurotransmitters, but are neither metabolized nor do they interact with postsynaptic receptors.

The scintigraphic visualization of cardiac innervation using radiopharmaceutical agents developed for PET or SPECT allows a unique pathophysiologic evaluation of disease processes that affect the autonomic nervous system (Fig. 26.3). However, most of these imaging approaches have been used predominantly for clinical research. The clinical application of these innovative methods will depend on future documentation of their diagnostic and prognostic value in patients with cardiovascular disease. Particularly, the initial results in patients with congestive heart failure are promising but require confirmation in prospective multicenter trials[6] (Fig. 26. 4).

Radionuclide Imaging of Atherosclerotic Lesions

The management of coronary artery disease has traditionally been based on assessment of the severity of stenosis of the vascular lumen. Although the degree of luminal encroachment by the plaque may determine the severity of anginal symptoms, it does not predict the outcomes such as likelihood of development of acute coronary syndromes including sudden cardiac death. Limited success has been achieved by the use of angioscopy and intravascular ultrasonography or more recently with optical coherence tomography and MRI in the assessment of plaque morphology. Appropriate targeting strategies with radionuclide imaging techniques could identify the predominant cellular population and biochemistry of the atherosclerotic plaque and help predict the likelihood of clinical events.[7] Approaches for detection of atherosclerosis and vascular vulnerability include targeting proliferating smooth muscle cells, angiogenesis, vascular injury, inflammation through a variety of mechanisms, defining cell death and protease activation, and imaging gene expression.

Stem Cell Imaging

The newest target for nuclear molecular imaging is stem cells. Work in this area has also been proceeding in parallel with competing technology such as magnetic resonance imaging. Recently, Aicher, et al demonstrated stem cell cardiac uptake after the administration of In-111-labeled endothelial progenitor cells in a rat model. Uptake was greatest in the heart after intracavitary as opposed to intravenous injection. Similar kinetic studies have also been demonstrated by use of ^{99m}Tc-labeled cells. More recently, Wu, et al, used the PET reporter gene approach to labeling stem cells administered to the rat after myocardial infarction. This technique proved efficacious for micro PET imaging of direct stem cell transfer into infarcted myocardium. It is likely that other approaches to stem cell imaging will be developed in the near future.

Gene Therapy

Improved understanding of the molecular and genetic basis of coronary heart disease has made gene therapy a potential new alternative for the treatment of cardiovascular diseases. Experimental studies have established the proof-of-principle that gene transfer to the cardio-vascular system can achieve therapeutic effects. First human clinical trials provided initial evidence of feasibility and safety of cardiovascular gene therapy. However, phase II/III clinical

trials have so far been rather disappointing and one of the major problems in cardiovascular gene therapy has been the inability to verify gene expression in the target tissue. New imaging techniques could significantly contribute to the development of better gene therapeutic approaches. Although the exact choice of imaging modality will depend on the biological question asked, further improvement in image resolution and detection sensitivity will be needed for all modalities as we move from imaging of organs and tissues to imaging of cells and genes.

CONCLUSION

The nuclear cardiology of the future will be based on new clinical and biologic targets. It will be driven by modern concepts of molecular and cell biology and molecular genetics.

The legacy of nuclear cardiology, however, goes beyond that of imaging with radiotracers and gamma cameras. Clinical nuclear cardiology can rightfully claim that, by its achievements during the past 2 decades, it has truly changed the practice of clinical cardiology. Nuclear cardiology can be credited with demonstrating that the value of anatomic information is limited and that assessing the pathophysiologic significance of disease is of greater importance and that it predicts future outcome. Nuclear techniques introduced the routine calculation of left ventricular ejection fraction, initially alone and later in combination with assessment of regional myocardial blood flow. Nuclear cardiology has also shown the importance of quantifying the degree of abnormalities. These important nuclear cardiology parameters will continue to be pursued and measured in patients with suspected or known heart disease by whatever future diagnostic imaging modality.

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