

Nuclear medicine and positron emission tomography imaging in cardiology

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Nuclear medicine imaging in cardiology

During the past two decades the clinical role of nuclear medicine procedures in cardiology has evolved significantly. At the beginning, the diagnostic role of nuclear medicine in detecting myocardial ischemia in patients with suspected coronary artery disease has been emphasized. Subsequently, cardiac radionuclide imaging has made significant advances in the determination of prognosis in patients with ischemic heart disease, preoperative risk assessment for patients undergoing non cardiac surgery and assessment of the efficacy of revascularization in patients undergoing coronary artery bypass surgery or interventional procedures. More recently, particularly attention has been focused on the ability of nuclear cardiology to characterize myocardial tissue and to assess myocardial viability in patients with ischemic left ventricular (LV) dysfunction.

Diagnosis of coronary artery disease

Myocardial perfusion imaging with exercise or pharmacological stress testing is an accepted technique for the detection and localization of coronary artery disease [1, 2]. During exercise or pharmacological stress, the vasodilating capacity of microcirculation is limited and obstruction in the epicardial coronary arteries become physiologically important, providing a mechanism for the noninvasive diagnosis of obstructive coronary artery disease.

Myocardial perfusion abnormalities detected during either exercise or pharmacological stress are due to differential blood flow between normal and stenotic arteries. The determination of these disparities is dependent on the ability of different tracers to reflect the changes in increased blood flow produced by the stressors. All myocardial perfusion imaging agents available for clinical use have shown a linear relationship with up to approximately twofold higher than baseline. Beyond this level, there appears to be a decrease in the uptake of most agents in relation to blood flow. The plateau effect of various tracers has been demonstrated to be different. It should be considered that exercise is typically accompanied by two to threefold increase in myocardial blood flow that typically increases three to eightfold (compared with resting blood flow) in response to all pharmacological agents. Myocardial perfusion tracers available for clinical use include thallium-201 and technetium-99m (Tc-99m) labelled agents: sestamibi and tetrofosmin. The relationship between blood flow and these tracers has been widely studied. Blood flow and thallium activity shows a linear relationship to at least 3 ml/min/gm. However, at approximately 3 ml/min/gm, there appears to be a plateau effect such that, despite increases in blood flow, thallium activity does not change. The extraction fraction of sestamibi is less than thallium. Data from animal studies demonstrate a linear relationship of sestamibi uptake to approximately 2 ml/min/gm. Above this level, uptake is not linear with increasing flow. Similar data are emerging for tetrofosmin but this tracer demonstrates a plateau during stress at a blood flow level lower than that of sestamibi. Thus, thallium as well as sestamibi and tetrofosmin exhibits a plateau effect that is generally above the blood flow range of exercise or most pharmacological stress. The Tc-99m labeled tracer with the best extraction fraction (higher than thallium) is teboroxime, that has shown a linear correlation within the range of pharmacological stress. However, the rapid clearance of this tracer from the myocardium has made this agent difficult to use clinically. All these tracers have different kinetic characteristics that must be considered to maximize their clinical applications for stress imaging. Moreover, it should be also considered that in clinical imaging ideal conditions do not always exist.

Despite the differences in tracer kinetic among these tracers, comparative studies involving thallium and Tc-99m labeled agents have failed to show significant differences. Several clinical studies have documented the clinical impact of thallium imaging in the detection of patients with coronary artery disease. In particu-

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lar, the sensitivity of single-photon emission computed tomography (SPECT) thallium imaging has been reported to be approximately 90% with a relative low specificity, ranging from 60% to 70%. Since their introduction, sestamibi and tetrofosmin have been compared to thallium as the gold standard in the identification of patients with coronary artery disease. The reported average sensitivity and specificity of sestamibi and tetrofosmin in the identification of coronary artery disease were very similar to those obtained with thallium imaging. However, some data reported that sestamibi and tetrofosmin might underestimate the total extent of myocardial ischemia as compared to thallium imaging in patients with coronary artery disease [3]. On the other hand, significant differences regarding the image quality has been reported in all comparative studies performed. In particular, images obtained using sestamibi or tetrofosmin were of superior quality than those obtained with thallium and tended to show fewer artifacts due to soft tissue attenuation. Better definition of the myocardium, endocardial and epicardial borders, and perfusion defects has been observed. In general, there was much less statistical noise using these Tc-99m labeled tracers and the myocardial to background ratios were similar to those obtained with thallium imaging. Moreover, the permissible administered dose is much larger than for thallium. It resulted in an increase in pixel count densities for Tc-99m labeled tomographic projection images and it permits the use of higher resolution filters during studies reconstruction. Nuclear cardiology imaging techniques as well as the development of Tc-99m labeled perfusion tracers now permits combined myocardial-perfusion and LV function studies at a single testing interval. Thus, the potential advantages of simultaneous assessment of myocardial perfusion and LV function have been recently outlined [4]. Gated imaging of the perfused myocardium is a well-established technique for this purpose, with a single injection of a Tc-99m labeled perfusion tracer. Recent data have demonstrated the impact and clinical role of these studies in the diagnosis of patients with suspected or known coronary artery disease. The addition of functional information to perfusion data has shown to improve the detection of multivessel disease.

Prognosis in patients with coronary artery disease

Another key role of myocardial perfusion imaging has been its ability to provide prognostic information in patients after acute myocardial infarction, in patients with chronic coronary artery disease and in patients scheduled for major surgery [5]. The utility of thallium scintigraphy associated with exercise pharmacological stress testing for this purpose has been widely documented. In particular, it has been demonstrated that in patients without prior myocardial infarction the number of reversible thallium defects is the most important statistically significant predictor of future cardiac events. Moreover, the extent and severity of thallium defects correlate with the occurrence of cardiac event. Several studies have reported similar results on the prognostic value of thallium stress imaging after myocardial infarction and in patients with suspected or known coronary artery disease. These data demonstrated that the extent of perfusion abnormality on SPECT imaging is the single most important prognostic predictor. More recently, the prognostic value of Tc-99m labeled myocardial perfusion agents

has been demonstrated with concordant data as compared to thallium imaging. In particular, the extent of hypoperfusion on post-stress sestamibi images can be factored into a decision-making process relative to selecting medical therapy or revascularization. Patients with mild reversible perfusion defects judged to be not at high risk could most often be treated medically whereas patients with high-risk SPECT reversibility findings are candidates for further invasive strategies. Moreover, a strategy incorporating stress myocardial perfusion imaging is also cost-effective. A large study comprising stable angina patients referred for stress myocardial perfusion SPECT imaging or direct catheterization revealed that costs were higher for the initial invasive strategy in clinical subsets with low, intermediate or high pretest likelihood of disease. Diagnostic follow-up costs of care were 30% to 41% higher for patients undergoing direct catheterization without any reduction in mortality or infarction compared with patients having stress perfusion imaging as the initial test for coronary artery disease detection.

Myocardial viability

It has been demonstrated that one-third of patients with chronic coronary artery disease and LV dysfunction have the potential for significant improvement in ventricular function after myocardial revascularization procedures. These findings have several implications. First, given the important relationship between LV function and patients survival. During the past years, numerous studies have demonstrated that nuclear cardiology techniques involving SPECT provide important viability information in patients with coronary artery disease and impaired ventricular function [6–12]. Although positron emission tomography (PET) remains the most accurate technique for the detection of viable myocardium different thallium protocols have been used in previous studies to assess myocardial viability in patients with previous myocardial infarction and chronic LV dysfunction. In particular, if the clinical issue to be addresses is the viability of one or more ventricular regions with systolic dysfunction and not whether there is also inducible ischemia, rest-redistribution thallium imaging can yield useful viability data. In particular, it has been demonstrated that quantitative analysis of rest-redistribution images predicts recovery of regional LV function and compares favorably to the results of both thallium reinjection imaging and metabolic PET imaging [7]. Optimal interpretation of thallium imaging for the detection of myocardial viability can be accomplished by measuring regional tracer uptake and by selecting the most appropriate cutoff to differentiate reversible from irreversible LV dysfunction [8–10]. Furthermore, sestamibi and tetrofosmin showed similar results to those of thallium scintigraphy in the identification of viable myocardium [8]. A quantitative analysis of tracers' content as well as the administration of nitroglycerin prior to tracer injection increases the overall accuracy of Tc-99m labeled agents for identifying viable myocardium. Recent data indicated that in patients with chronic myocardial infarction and impaired LV function on nitrate treatment, quantitative analysis of resting thallium and sestamibi regional activities comparably predicts recovery of regional and global ventricular function following revascularization procedures [11]. Nitroglycerin most likely enhances myocardial viability detection by increasing coronary collateral flow, decreasing pre-load and after-load, and direct vasodilatation of stenotic segments in coronary

arteries [12–14]. These physiological effects in combination should enhance the delivery of myocardial perfusion agents to regions of myocardium supplied by severely stenotic vessels. In the assessment of myocardial viability myocardial perfusion in combination with wall motion analysis by gated images has been used [15]. Despite the recovery of regional function after revascularization was the more considered gold standard to detect myocardial viability, the clinical outcome after revascularization is a better and more valuable end-point. The criteria for viability determination with respect to its true clinical impact should be the prediction of short- and long-term outcomes such as cardiovascular mortality and recurrent myocardial infarction [16]. It should be considered that preserved myocardial perfusion tracer uptake in zones of asynergy might have a sub-optimal positive predictive value for predicting improved segmental function after revascularization. However, it appears to predict a high cardiac death and infarction rate with medical therapy and identifies a group of patients with hibernating myocardium who would be predicted to have an excellent outcome after revascularization. Has been demonstrated that the amount of dysfunctional myocardium with preserved thallium uptake provided independent prognostic information that were incremental to those obtained by clinical, functional, and angiographic data in patients with chronic ischemic LV dysfunction. In particular, patients with a substantial amount (> 30% of the total left ventricle) of dysfunctional myocardium with preserved tracer activity exhibited the greatest LV functional benefit after successful revascularization [17]. Moreover, patients with more than 50% of viable myocardium represented a subgroup at high-risk of cardiac death in whom successful revascularization improved survival [17]. All together these observations seem to lend further support to the choice of coronary revascularization in patients with evidence of a substantial amount of dysfunctional myocardium with preserved myocardial perfusion tracer activity. Thus, it appears that the assessment of myocardial viability should become a mandatory step in the clinical decision-making of patients with reduced global and regional LV systolic function to better predict the potential value of revascularization in improving survival and functional status.

Evaluation after coronary revascularization

The use of exercise or pharmacological myocardial perfusion imaging in the assessment of interventions in chronic ischemic heart disease is indicated for the evaluation of restenosis after percutaneous transluminal coronary angioplasty (PTCA) in symptomatic patients, in the assessment of ischemia in symptomatic patients after coronary artery bypass grafting (CABG). Radionuclide techniques are also indicated in the assessment of selected asymptomatic patients after PTCA or CABG, such as patients with an abnormal electrocardiographic response to exercise or those with rest electrocardiographic changes precluding identification of ischemia during exercise. SPECT exercise imaging is an excellent tool for the detection of restenosis and disease progression after PTCA in the settings of one and multivessel angioplasty and complete and partial revascularization. Hecht et al. [18], studying exercise tomographic thallium imaging in the detection of restenosis after PTCA, showed sensitivity of 93% for scintigraphic studies and 52% for exercise electrocardiographic studies, specificity

of 77% versus 64% and accuracy of 86% versus 57%, respectively. Moreover, it has been demonstrated that after PTCA sensitivity and accuracy of exercise electrocardiography in the detection of restenosis were significantly less than those of SPECT imaging for both patients with silent and symptomatic ischemia [19]. Patients with less typical symptoms and intermediate probability of restenosis can be accurately assessed for this PTCA complication by myocardial perfusion imaging studies. In the patients with recurrent atypical symptoms, stress perfusion imaging should be performed soon after the onset of symptoms in order to determine whether persistent myocardial ischemia is the cause of chest pain. Myocardial imaging studies offer several advantages over stress electrocardiography, particularly in patients with abnormalities of the resting electrocardiogram, multivessel coronary disease, or a limitation to exercise stress testing. After PTCA nuclear cardiac imaging procedures are not generally recommended in the absence of recurrent symptoms, particularly since imaging abnormalities would not likely result in change in therapeutic regimen or repeat revascularization. However, recent data demonstrated that extent and severity of myocardial ischemia at exercise SPECT performed between 12 and 18 months after percutaneous coronary intervention (PCI) predicts cardiac events during long-term follow-up in symptomatic and symptom-free patients [20].

Exercise scintigraphy after CABG demonstrates improved regional myocardial perfusion in most patients. After CABG, the New York Heart Association's functional class improved significantly. Early (less than 3 month) post-CABG myocardial imaging may be useful for the detection of perioperative infarction or if early graft closure with recurrence of angina symptoms is suspected. Beyond 3 months, and following the recovery of hibernation effects, noninvasive cardiac imaging is useful to detect asymptomatic graft attrition and the recurrence of myocardial ischemia. However, this approach cannot be routinely recommended in all patients who underwent CABG because it would not be cost-effective to screen this large population in the 1 to 2 years following CABG surgery.

PET imaging in cardiology

PET imaging has been shown to be a method for the detection and characterization of coronary artery disease showing superior results as compared to SPECT imaging. The experimental and clinical experience with metabolic imaging led to the development of 18F-fluorodeoxyglucose (FDG) as a marker of tissue viability in patients with advanced coronary artery disease. Based on these studies, PET became an accepted clinical tool for the detection of coronary artery disease as well as assessment of tissue viability. PET imaging has been validated also for the non-invasive characterization of coronary artery disease and other cardiovascular disorders. In particular, to describe the interaction of various substrates for cardiac energy metabolism.

One of the applications of PET for the detection of coronary artery disease is the assessment of regional myocardial tracer distribution under rest and stress conditions. Most commonly, pharmacological stress testing has been employed in order to assess coronary reserve. The quantification of coronary flow reserve has been advocated for the functional assessment of the severity of coronary artery stenosis in patients with coronary artery disease. The parameter flow reserve integrates the functional

significance of a given coronary lesion, vascular reactivity and collateral blood flow in the post-stenotic vascular territories. It has been hypothesized that such functional measurements may complement the anatomic description of coronary artery disease and may be helpful in the selection of patients for revascularization. Adding functional information to an angiographic description of coronary artery disease increases objectivity in the evaluation of disease severity and provides a noninvasive means to follow progression and regression of coronary artery disease [21, 22]. PET imaging with N-13 ammonia and O-15 water has been used for the evaluation of coronary flow reserve in normal heart, in patients with coronary artery disease and non coronary artery disease. Assessment of relative coronary reserve by PET imaging relies on the hypothesis that at least one segment of the myocardium displays a normal coronary reserve. This segment serves as an internal standard to which all other segments are normalized. However, this may not be possible in patients with severe triple-vessel disease or other diseases affecting coronary reserve measurements. It has been demonstrated a relationship between coronary reserve measurements and age in subjects without coronary artery disease. Moreover, considering hemodynamic parameters such as blood pressure and heart rate, the decreased coronary reserve values in elderly persons may be primarily due to increased resting blood flow as a consequence of higher heart rate and blood pressure in elderly population. Clinical data have indicated that arterial hypertension leads to reduced coronary flow reserve. It has been shown using PET that therapy of patients with arterial hypertension may improve regional coronary reserve measurements. In patients with coronary artery disease coronary flow reserve measurements are reduced. Several studies indicated a correlation between the severity of coronary artery disease and severity of flow reserve impairment. However, in the range of intermediate coronary artery stenosis more discrepancies between angiographic and PET results are present. It may be best explained considering different aspects such as the complex geometric shape of atherosclerotic plaques that may be difficult to judge from angiographic views. Moreover, collateral blood flow may alter the relationship of coronary stenosis and blood flow measurements to the stenosis site. All these factors emphasize the importance of blood flow measurements to document the functional severity of a given angiographic lesion. Quantitative flow measurements with PET have been employed in patients with cardiac transplantation to study coronary physiology and in patients with cardiomyopathy. Due to the improved image technology, PET perfusion imaging has been shown to be a superior method for the detection and the characterization of coronary artery disease as compared to SPECT. Thus, noninvasive detection of coronary artery disease by PET allows better definition of the functional importance of known coronary artery stenosis. Clinic data combining the results of different studies in about 300 patients suggest that PET imaging improve the diagnostic accuracy of SPECT by about 10%. However, the relative higher cost of PET as compared to SPECT and lesser availability of the former should be considered when selecting the imaging technique. Therefore, although PET is an effective modality for noninvasive diagnosis of coronary artery disease it should be considered for routine diagnostic purposes only if its costs are equivalent or less than those of SPECT imaging in the same environment.

The scintigraphic methods for evaluation of myocardial viability could be broadly categorized into SPECT with agents assessing both perfusion and metabolic activity, and PET with tracers assessing coronary blood flow and metabolic activity, including evaluation of both fatty acid and glucose metabolism. Although quantitative approaches to viability assessment using SPECT and standard tracers may provide valuable information with regard to myocardial viability, PET offers different advantages. An accurate quantification of tracer distribution after correction for attenuation, enhanced spatial resolution and the possibility to use tracers that are specifically targeted at defining a certain metabolic parameter (e.g. glucose utilization or oxidative metabolism). Given the technical superiority of PET over SPECT, PET would appear to be the preferred technique to assess both perfusion and metabolism in patients with chronic coronary artery disease and left ventricular dysfunction. However, by serving as a reference standard, PET has played an important role in recent modifications and improvements of SPECT technology and protocols. In particular, more recently it has been suggested that F-18 FDG SPECT can be used as alternative to PET and SPECT with perfusion tracers for the assessment of viability. In fact, the availability and high cost of PET and cyclotron technology have limited the clinical application of this technique. Moreover, because of the relatively long physical half-life of F-18 (110 min), off-site production of labeled FDG and subsequent transport to satellite laboratories have been proposed. This, combined with the advent of high-energy gamma camera collimators, has made possible the use of FDG SPECT for detection of myocardial viability. However, although FDG SPECT significantly increases the sensitivity for detection of viable myocardium in tissue declared nonviable by thallium (to 88% of the sensitivity achievable by PET), it will occasionally (27% of the time) result in falsely identifying as viable tissue that has been identified as nonviable by both PET and thallium [23]. Clinical studies have been performed comparing fatty acid and glucose metabolism in relation to functional recovery of ischemic myocardium after coronary revascularization. Bax et al. [24] suggested that tomographic metabolic imaging with FDG may be useful in the prediction of improvement of LV function after revascularization in patients with coronary artery disease. In a recent study by Sato et al. [25] it has been demonstrated that combined metabolic SPECT imaging with FDG and iodine-123 (I-123) labeled methyl-iodophenyl-pentadecanoic acid (BMIPP) have the potential to identify severely impaired ischemic myocardium leading to more efficient therapeutic management of patients with coronary artery disease. In fact, areas with discordant BMIPP uptake less than thallium are often seen in patients with coronary artery disease, which may represent ischemic but viable myocardium where increased glucose metabolism was also observed. Further information regarding functional recovery in patients studied with FDG SPECT imaging is needed to confirm this point and to define the relationship between FDG uptake on SPECT imaging and functional outcome.

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