

Nuclear cardiology in the new millennium

Cardiología Nuclear en el nuevo milenio

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During the past twenty years the clinical role of nuclear cardiology has evolved significantly. At the beginning, the diagnostic role of nuclear medicine procedures in detecting myocardial ischemia in patients with suspected coronary artery disease has been emphasized. 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 dysfunction. 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 noncardiac surgery and assessment of the efficacy of revascularization in patients undergoing coronary artery bypass surgery or interventional procedures.

DIAGNOSIS AND PROGNOSIS 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. 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 radiotracers 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 ^{201}Tl -thallium and $^{99\text{m}}\text{Tc}$ labeled 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 $^{99\text{m}}\text{Tc}$ 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. Des-

pite the differences in tracer kinetic among these tracers, comparative studies involving thallium and ^{99m}Tc 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 CAD. In particular, the sensitivity of 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 CAD. The reported average sensitivity and specificity of sestamibi and tetrofosmin in the identification of CAD were very similar to those obtained with thallium imaging.

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 CAD and in patients scheduled for major surgery. 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 was the most important statistically significant predictor of future cardiac events. Moreover, the extent and severity of thallium defects correlated 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 CAD. 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 ^{99m}Tc labeled myocardial perfusion agents has been demonstrated with concordant data as compared to thallium imaging. In particular, the extent of hypoperfusion on poststress 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 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 CAD detection.

MYOCARDIAL HIBERNATION, STUNNING, AND VIABILITY

The presence of myocardial necrosis, postischemic stunning and hibernation, in patients with coronary artery disease and previous myocardial infarction, can determine extensive regional left ventricular (LV) dysfunction with a depression of LV ejection fraction, leading to ischemic heart failure. Several studies have shown that in patients with ischemic heart failure, greater is the extent of myocardial viability, better is the outcome after revascularization procedures. Therefore, an accurate noninvasive assessment of myocardial viability with the preoperative differentiation between myocardial hibernation or stunning and irreversibly necrotic tissue, may be useful for clinical decision making to select patients with ischemic heart failure candidates for revascularization. It is well known that patients with extensive areas of hibernation treated medically have a significantly worse prognosis as compared to those who undergo revascularization with a similar extent of viable but dysfunctional myocardium.

Radionuclide imaging techniques evaluating myocardial perfusion, cell membrane integrity and cardiac metabolism have demonstrated clinical utility in the assessment of myocardial viability. Stress ^{201}Tl -thallium imaging has played an important role in identifying patients at high risk. However, this technique may often underestimate the presence of severe myocardial ischemia, as compared with thallium rest-redistribution, thallium reinjection and metabolic imaging with fluorodeoxyglucose (FDG). In patients with previous myocardial infarction and LV dysfunction, thallium reinjection provides incremental prognostic information over those obtained from conventional stress-redistribution imaging. In such patients LV ejection fraction, but not the number of diseased coronary vessels, provides additional prognostic information to thallium imaging. Thallium scintigraphy at rest is useful in preoperative risk stratification for identification of patients more likely to benefit from revasculari-

zation. In patients with chronic coronary artery disease and evidence of dysfunctional but viable myocardium at thallium imaging, the beneficial effects of successful revascularization on regional myocardial perfusion and LV function are still detectable after 1-year follow-up and these effects are greater in patients with more severe LV dysfunction at baseline. Successful revascularization of dysfunctional but viable myocardium improved survival and LV ejection fraction in such patients. Myocardial perfusion imaging with ^{99m}Tc labeled agents, such as sestamibi and tetrofosmin, is useful in the evaluation of myocardial viability in patients with chronic ischemic heart disease. Experimental studies have shown that myocardial retention of sestamibi and tetrofosmin is dependent not only on blood flow but also on cellular viability. Clinical reports suggest that quantitative analysis of sestamibi and tetrofosmin uptake enhances the differentiation between viable myocardium and necrotic tissue. Nitrates administration may improve the detection of dysfunctional but viable myocardium using ^{99m}Tc labeled perfusion agents.

Positron emission tomography (PET) allows metabolic assessment *in vivo*. Preserved FDG uptake indicates ischemic but viable myocardium, which is likely to improve regional dysfunction after revascularization. In addition, FDG PET is useful for selecting a high risk subgroup. Recently, FDG scintigraphy with conventional tomographic gamma camera has been introduced as an alternative method for FDG PET imaging. Preliminary results suggest that tomographic metabolic imaging with FDG may be useful in the prediction of improvement of LV function after revascularization in patients with chronic coronary artery disease. A number of iodinated synthesized fatty acid compounds have been developed for probing myocardial energy metabolism *in vivo* with conventional tomographic gamma camera. Among them, a straight-chain fatty acid analog, 15-(para-iodine-123-phenyl)-pentadecanoic acid (IPPA), and branched fatty acid analog, 15-(p-iodophenyl)-3R,S-methyl pentadecanoic acid (BMIPP), have been used. IPPA has unique capability for assessing both fatty acid uptake and beta-oxidation. On the other hand, BMIPP provided excellent images of the myocardium because of long residence time in the cardiac cells. 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 me-

tabolism was also observed. Therefore, the combined imaging with BMIPP and perfusion agent permits detection of ischemic but viable myocardium on the basis of alteration of myocardial energy metabolism. Finally, preliminary data suggest that decreased BMIPP uptake relative to thallium activity is a valuable predictor of future cardiac events in patients with previous myocardial infarction.

FUTURE OF NUCLEAR CARDIAC IMAGING

At the moment, myocardial perfusion imaging is an integral part of the assessment of patients with cardiovascular diseases. Nuclear cardiology imaging plays a major role in four distinct but interconnected areas: a) diagnosis and prognosis of coronary artery disease, including new pharmacological stressors b) infarct diagnosis and risk stratification c) evaluation of ventricular function in patients with congestive heart failure d) myocardial hibernation, stunning and viability. An ideal imaging agent is one with a high myocardial extraction that is maintained through the increased range of blood flow attainable during exercise or pharmacological stress test. The available radionuclide tracers are clinically useful for all different clinical purposes, however the ideal agent has not yet been found. The future of nuclear cardiology involves instrumentation, conventional radioactive tracer development and may also depend on more basic areas. In particular, the union of nuclear cardiology with molecular biology may develop a «molecular imaging» approach to the study of coronary artery disease. In fact, nuclear cardiac imaging may explore a variety of different physiological processes at cellular and subcellular level. With respect to imaging the vascular wall, a number of different targets have already been studied. These involve proliferating smooth muscle cells, macrophages and lipid pool. The use of monoclonal antibody specific for proliferating smooth-muscle cells might allow the imaging of atherosclerosis *in vivo*. Thrombus imaging using newly developed peptides may in the future target different platelet receptors. The role of apoptosis has been demonstrated in several heart diseases, such as atherosclerosis, coronary artery disease, transplant rejection, cardiomyopathy and arrhythmic disorders. Initial studies have demonstrated the possibility to image *in vivo* the apoptotic process. Moreover, one of the most exciting new directions in nuclear ima-

ging involves the imaging of gene expression. Two general approaches have been developed to date. One involves imaging gene expression with reporter gene/reporter probe systems to image the expression of endogenous or exogenous genes. The second involves the use of antisense oligodeoxynucleotides that

are radionuclide labeled and targeted at a specific mRNA of a particular gene. Both techniques are in their earliest phases of study. Therefore, the field of nuclear cardiology holds great promise for future progress. Much research is required to advance the field of nuclear cardiology.