The Evolving Roles of Nuclear Cardiology

Andrea De Lorenzo*

Instituto Nacional de Cardiologia, Rio de Janeiro, Brazil

Abstract: The use of cardiac imaging modalities has grown steadily, and cardiac nuclear studies constitute a large part of this number. Nuclear Cardiology is often mistakenly considered a synonym of myocardial perfusion imaging (MPI), but has broader applications, including metabolic imaging, innervation imaging, among other technologies. MPI has been a powerful diagnostic and prognostic tool in the assessment of patients for known or suspected CAD for decades, and is now increasingly used for the evaluation of the anti-ischemic effects of various therapies, according to changes in left ventricular perfusion defect size defined by sequential MPI. Neuronal dysfunction identified with iodine-123-metaiodobenzylguanidine may give information on prognosis in different disease conditions, such as after myocardial infarction, in diabetes and dilated cardiomyopathy. Molecular imaging may identify the predominant cellular population in the atherosclerotic plaque and help predict the likelihood of clinical events. Therefore, although its usefulness is well established, Nuclear Cardiology remains a moving science, whose roles keep in pace with evolving clinical needs and expectations.

Keywords: Myocardial perfusion imaging, single-photon emission computed tomography, positron emission tomography.

In association with the elevated prevalence, morbidity and mortality of coronary artery disease (CAD) worldwide, there has been a steady increase in the use of cardiac imaging techniques, including those based on Nuclear Medicine. In fact, cardiac studies have outgrown Nuclear Medicine and have constituted an individual subspeciality, Nuclear Cardiology. This imaging modality is often, although incorrectly, considered as a synonym for myocardial perfusion imaging (MPI), which by its turn means the evaluation of myocardial perfusion after stress versus at rest, using a variety of tracers and stressor agents in different protocols. It extends far beyond, though, including metabolic imaging, innervation imaging, among other technologies. This review will discuss current and evolving applications of Nuclear Cardiology, starting with MPI, which remains its cornerstone.

MYOCARDIAL PERFUSION IMAGING

For the last 2 decades, MPI has been an essential part of the diagnostic and prognostic assessment of patients for known or suspected CAD. However, as time went by and new demands and technologies have been developed, other applications of MPI have emerged, and its roles have advanced continuously. In the 1980’s, planar and then tomographic (single photon emission computed tomography, SPECT) perfusion imaging was found to reliably diagnose CAD [1,2]. In the 1990’s the prognostic value of MPI was defined [3-5]. Later, with the advent of gating, left ventricular ejection fraction could be obtained, thus providing additional diagnostic and prognostic information [6,7].

Diagnostic Assessment

MPI is a useful tool for the diagnosis of CAD [1,2]. It is most effective when used in patients with an intermediate pretest likelihood of CAD, since if the likelihood is low, a perfusion abnormality may be a false-positive finding, while in those with a high pretest likelihood of CAD a normal MPI study may be a false-negative for the presence of angiographically significant coronary obstruction (i.e., coronary stenoses > 50% of luminal diameter) and the test may not able to exclude the presence of CAD. Nonetheless, even in patients with high likelihood of CAD, MPI can still be used for risk stratification [8]. In fact, the principles regarding diagnostic applications of MPI have not changed over the years, in contrast to the prognostic use of MPI, which has grown significantly.

Prognostic Assessment

MPI may be applied for prognostic evaluation both for patients with known or suspected CAD. It relies on 2 principles: first, a normal MPI study confers a low (<1%) short-term risk of cardiac events [9]; second, there is a relationship between myocardial ischemia and cardiac events such that the risk of events increases exponentially as ischemia increases. Even in patients with a high likelihood of CAD or definite CAD, a normal MPI defines those who have a < 1% risk of cardiac events in the next 1-2 years. This usually defines a group in which conservative management (i.e., avoiding myocardial revascularization) is appropriate [10]. When some conditions are present, like diabetes, inability to exercise leading to the use of pharmacologic stress, abnormal rest ECG or exercise-induced ST segment depression, a normal MPI study still delineates low risk, but somewhat increased compared with patients with normal MPI and none of those [11,12]. For patients with abnormal studies, the risk of events is associated with the magnitude of ischemia. The latter is the strongest determinant of the referral to coronary angiography and also the strongest predictor of benefit with revascularization [13]. Besides that,
a number of other findings obtained from MPI studies, such
as abnormal lung uptake or transient left ventricular
dilatation, have consistently been associated with increased
risk [14, 15].

**Therapeutic Assessment/MPI as a “Gatekeeper”**

An increasingly used application of Nuclear Cardiology is
to evaluate the anti-ischemic effects of various therapies
by means of identifying changes in left ventricular perfusion
defect size by sequential MPI and thereby track patient risk
for subsequent cardiac events on the basis of the magnitude
of ischemia suppression. An example is the COURAGE
(Clinical Outcomes Utilizing Revascularization and Aggres-
sive Drug Evaluation) trial [16], which evaluated percu-
taneous coronary intervention (PCI) plus optimal medical
therapy (OMT) vs. OMT alone in stable CAD patients. A
subgroup of the total population had MPI performed before and
after treatment (mean 1 year after enrollment), and in this
nuclear substudy, the results showed that ischemia reduction
was greater with PCI+OMT than with OMT alone
(33.3% versus 19.8% had ≥5% reduction of ischemia). For
all patients combined, the death or myocardial infarction rate
was 13.4% for patients who had ≥5% reduction of ischemia
and 24.7% for those who did not have reduction at the
follow-up study. This study indicated that, for stable CAD
patients, having knowledge of the ischemic burden is helpful
in decision-making with respect to selecting initial therapy,
and regardless of the therapeutic modality used, assessment
of the response to therapy, which is related to long-term
outcome, is also important. Another aspect of this same
application of MPI is the identification of revascularization
candidates according to the amount of jeopardized myo-
cardium and the survival benefit that a patient may obtain
from a specific therapy as a function of MPI results. MPI has
been able to discriminate (as a “gatekeeper”) which patients
will likely benefit from invasive coronary angiography
followed by coronary revascularization and who may be well
suited with medical therapy [13]. Quantitative analysis of
MPI studies has been important in this regard, since this kind
of analysis relies on the demonstration of a threshold value
of ischemia which will lead to each type of management.

**Screening Asymptomatic Populations for CAD**

The noninvasive detection of silent CAD is an important
clinical goal in certain high-risk asymptomatic populations.
Occult CAD precedes the onset of clinically manifest CAD,
which too often presents as sudden death or acute myocardial
infarction. Detection of occult CAD in a preclinical stage
might lead to risk factor modification and institution of
treatment, which would prevent or delay the onset of clinical
disease, since there is now good evidence that aggressive
risk factor modification can slow the progression of athero-
sclerosis. Bayesian analysis indicates that the detection of
occult CAD by noninvasive testing should be more accurate
in asymptomatic groups with high CAD prevalence, since
test performance is worse in low prevalence populations
[17]. As a result, screening is not considered appropriate for
the general population, given the sensitivity and specificity
of even the best noninvasive test. Screening seems more
suitable for selected, high risk groups, such as patients with
chronic renal failure, metabolic syndrome, and diabetics; in
the latter, several studies have demonstrated a high
prevalence of silent CAD detected with MPI [18, 19].

**Myocardial Viability**

Noninvasive imaging to determine the presence and
extent of dysfunctional but viable myocardium has become
an important component of the diagnostic assessment of
patients with CAD and depressed left ventricular function.
It is now well established that left ventricular dysfunction in
patients with CAD is not always an irreversible process
related to previous myocardial infarction because left ventri-
cular function may improve substantially after revas-
cularization procedures in patients with chronic CAD, and
this may translate into an improvement in survival [20]. The
differentiation of viable from nonviable myocardium is
highly relevant in patients with left ventricular dysfunction
considered for revascularization, because these procedures
often have high morbidity and mortality rates in this subset
of patients, even though this is the population that ultimately
benefits most from revascularization. Therefore, accurate
methods to detect viable myocardium are essential to select
the patients for whom the risks are justified. Nuclear
Cardiology techniques to assess viability have evolved
tremendously in recent years. In SPECT, there are various
imaging protocols, the most frequently used being the
thallium-201 protocols (rest/redistribution and reinjection
studies) [21, 22]. According to the hypothesis of resting hyp-
operfusion (hibernation), rest images demonstrate thallium
uptake early after injection, which represent regional
myocardial blood flow, whereas delayed uptake reflects cell
membrane integrity. Since 3-4 hour redistribution images
may underestimate the presence of viable myocardium,
reinjection of thallium at rest after redistribution imaging
may improve the assessment of myocardial ischemia and
viability in up to 49% of apparently irreversible defects [22].
As technetium-99m tracers are widely used due to favorable
imaging properties compared to thallium, the use of these
tracers for the assessment of viability has been studied,
and quantitative measures of regional technetium-99m sestamibi
activity have been shown to correlate with estimates of
viability with other techniques [23]. Glucose metabolism
assessment with F-18 fluorodeoxyglucose (FDG) positron
emission tomography (PET) also allows the identification of
viable myocardium, with higher sensitivity; a perfusion-
metabolism mismatch (reduced blood flow associated with
preserved or enhanced FDG uptake) identifies potentially
reversible myocardial dysfunction [24].

**MYOCARDIAL INNERVATION IMAGING**

Iodine-123-metaiodobenzylguanidine (MIBG) was first
reported as a potential neuronal imaging agent for detection
of pheochromocytoma, since it has structural similarity with
norepinephrine and therefore is taken up by peripheral
sympathetic nerves. Further studies have shown reduced
localization in denervated regions of the myocardium, after
myocardial infarction, in diabetes and dilated cardiomyo-
athy, among other conditions [25, 26]. MIBG imaging
evaluates the sympathetic nervous system and has been
shown to be an important prognosticator in patients with
heart failure [27].
POSITRON EMISSION TOMOGRAPHY (PET)

The lack of widespread availability of PET cameras and radiotracers, their high costs and reimbursement issues have limited the clinical use of this technology. Recent developments are likely to change this scenario, though, since there has been a growth in the number of PET cameras and rubidium-82 generators used for perfusion imaging. This leads to real benefit, as positron emission tomography (PET) has several technical advantages over SPECT, including higher spatial resolution, accurate attenuation correction, higher temporal resolution and quantitative imaging capability that afford measurement of rapidly changing radiotracer activity concentrations in blood and myocardium. All of those determine a clinical advantage over SPECT, which often uncovers only the territory supplied by the most severe stenosis and therefore may underestimate the significance of coronary lesions; in this regard, PET has superior capability to detect multi-vessel CAD [28,29].

THE ASSOCIATION WITH COMPUTED TOMOGRAPHY: SPECT-CT/ PET-CT

Computed tomography of the coronary arteries (CTA) has gained enormous popularity in a short time period, and has been taken by some as a “threat” for Nuclear Cardiology. CTA and MPI differ in what each evaluates— anatomy for one and physiology for the other. Hybrid systems are now available allowing the combined assessment of anatomy and function, linking the anatomic richness of CTA and the functional importance of perfusion either from PET or SPECT. MPI and CTA are most likely complementary imaging modalities, with the choice and sequence of testing depending on the particular clinical question and specific patient population being evaluated [30, 31].

FATTY ACID IMAGING

BMIPP is a fatty acid analog which allows metabolic imaging since most of the energy requirement of the normal myocardium under aerobic status is derived from the metabolism of fatty acids. Since under ischemia or in heart failure, beta-oxidation of fatty acids in mitochondria is reduced, early washout of BMIPP from the myocardium occurs and the uptake detected by SPECT is reduced. BMIPP imaging may be used in unstable angina, vasospastic angina and cardiomyopathies, among other indications [32,33]. In particular, BMIPP metabolic imaging may be used to reveal “ischemic memory”, since even after resolution of chest pain, metabolic abnormalities may persist, and BMIPP images may be abnormal, with sensitivity of ~70-80% and specificity of ~90% [34].

MOLECULAR IMAGING/PLAQUE IMAGING

The management of CAD has almost always been based on demonstration of the severity of luminal stenosis; such an approach, however, does not characterize the plaque morphology that happens to be the major determinant of clinical outcome [35,36]. Appropriate targeting strategies with radionuclide imaging techniques may identify the predominant cellular population in the atherosclerotic plaque and help predict the likelihood of clinical events. It is now well recognized that progressive luminal stenosis of the coronary artery is generally not associated with an acute event and that thrombotic occlusion usually occurs as a result of plaque rupture [37, 38]. The plaques that are vulnerable to rupture have large lipid cores, attenuated fibrous cap and intense infiltration of macrophages, which release metalloproteinases that digest matrix and induce fibrous cap rupture. Plaque rupture exposes thrombogenic lipid core leading to thrombotic luminal obstruction. Plaque imaging in Nuclear Cardiology has targeted most often macrophages or lipid cores. However, the uptake of radiolabeled antibodies or cells in the atherosclerotic lesion is a small fraction of the injected dose, what makes the background radioactivity a major contributor to the image and decreases the contrast between lesion and nonlesion tissue. The difficulty in identifying lesions in vivo is a problem and highlights the difficulty in the use of this innovative technique. In the carotids, F-18 FDG has been studied for plaque inflammation and technetium-99m-annexin SPECT has been evaluated for apoptosis within the plaque, both known markers of plaque instability [39,40].

CONCLUSION

Although initially applied for diagnostic purposes, Nuclear Cardiology has grown and keeps moving. Many advances have increased its applications, and many more, regarding novel instrumentation techniques and new tracers are on their way to clinical practice. Perhaps the greatest potential for the future of Nuclear Cardiology lies in molecular imaging, and Nuclear Cardiology may hopefully achieve one of the most difficult goals in Cardiology: to identify the vulnerable, rupture-prone coronary plaque.

REFERENCES

[1] Botvinick EH, Tarashad MR, Shames DM, et al. Thallium-201 myocardial perfusion scintigraphy for the clinical clarification of normal, abnormal and equivocal electrocardiographic stress tests. Am J Cardiol 1978; 41: 43-51.
[2] Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging. A diagnostic tool comes of age. Circulation 1991; 83: 363-81.
[3] Berman DS, Hachamovitch R, Kiat H, 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. J Am Coll Cardiol 1995; 26: 639-47.
[4] Brown KA. Prognostic value of myocardial perfusion imaging: State of the art and new developments. J Nucl Cardiol 1996; 3: 516-37.
[5] Boyle TS, Koplan BA, Parsons WJ, et al. Predicting adverse outcome with exercise SPECT technetium-99m sestamibi in patients with suspected or known coronary artery disease. Am J Cardiol 1997; 79: 270-4.
[6] Sharir T, Germano G, Kavanagh PB, et al. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single-photon emission computed tomography. Circulation 1999; 100: 1035-42.
[7] Sharir T, Germano G, Kang X, et al. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: risk stratification by the amount of stress-induced ischemia and the poststress ejection fraction. J Nucl Med 2001; 831-7.
[8] Hachamovitch R, Hayes S, Friedman JD, et al. Stress myocardial perfusion SPECT is clinically effective and cost-effective in risk stratification of patients with a high likelihood of CAD but no known CAD. J Am Coll Cardiol 2004; 43: 200-8.
[9] Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol 2004; 11: 171-85.
[10] Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging.
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Executive Summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). Circulation 2003; 108: 1404-18.

Kang X, Berman DS, Lewin H, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. Am Heart J 1999; 138: 1025-32.

Hachamovich R, Hayes S, Friedman JD, et al. Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: what is the warranty period of a normal scan? J Am Coll Cardiol 2003; 41: 1329-40.

Hachamovich R, Hayes S, Friedman JD, et al. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation 2003; 107: 2900-7.

Boucher CA, Zir LM, Beller GA, et al. Increased lung uptake of thallium 201 during exercise myocardial imaging: clinical, hematologic and angiographic implications in patients with coronary artery disease. Am J Cardiol 1980; 46: 189-96.

Chouraqui P, Rodrigues E, Berman D, et al. Significance of dipyridamole-induced transient dilation of the left ventricle during thallium 201 scintigraphy in suspected coronary artery disease. Am J Cardiol 1990; 66: 689-94.

Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden. Results from the COURAGE trial nuclear substudy. Circulation 2008; 117: 1283-91.

Rittkin RD, Hood WB, Jr. Bayesian analyses of electrocardiographic exercise stress testing. N Engl J Med 1977; 297: 681-6.

De Lorenzo A, Lima RSL, Siqueira-Filho AG, et al. Prognostic value of stress technetium-99m sestamibi myocardial perfusion imaging in asymptomatic diabetics. Am J Cardiol 2002; 90: 827-32.

Wackers FJ, Young LH, Inzucchi SE, et al. Detection of silent myocardial ischemia in asymptomatic diabetics: the DIAD study. Diabetes Care 2004; 27: 1954-61.

Elefteriades JA, Jolis G, Levi E, et al. Coronary artery bypass grafting in severe left ventricular dysfunction: excellent survival with improved ejection fraction and functional state. J Am Coll Cardiol 1993; 22: 1411-7.

Ragosta M, Beller GA, Watson DD, et al. Quantitative planar rest-redistribution TI-201 imaging in detection of myocardial viability and prediction of improvement in left ventricular function after coronary artery bypass surgery in patients with severely depressed left ventricular function. Circulation 1993; 87: 1630-41.

Dilsizian V, Rocco TP, Freedman NM, et al. Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging. N Engl J Med 1990; 323: 141-6.

Kitsiou AN, Srinivasan G, Quyyumi AA, et al. Stress-induced reversible and mild-to-moderate irreversible thallium defects are they equally accurate for predicting recovery of regional left ventricular function after revascularization? Circulation 1998; 98: 501-8.

Bonow RO. Identification of viable myocardium. Circulation 1996; 94: 2674-80.

Doe M, DeMarco T, Botvinick E, et al. Scintigraphic assessment of MBG uptake in globally denervated human and canine hearts-implications for clinical studies. J Nucl Med 1992; 33: 1444-50.

Langer A, Freeman MR, Josse RG, et al. I-123 Metaiodobenzylguanidine in diabetes mellitus: assessment of cardiac sympathetic denervation and its relation to autonomic dysfunction and silent myocardial ischemia. J Am Coll Cardiol 1995; 25: 610-8.

Merlet P, Vallette H, Dubois R, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. J Nucl Med 1992; 33: 471-7.

DiCarli MF. Advances in positron emission tomography. J Nucl Cardiol 2004; 11: 719-32.

Parkash R, deKemp RA, Ruddy TD, et al. Potential utility of rubidium-82 PET quantification in patients with 3-vessel coronary artery disease. J Nucl Cardiol 2004; 11: 440-9.

Berman DS, Hachamovich R, Shaw LJ, et al. Roles of Nuclear Cardiology, cardiac computed tomography and cardiac magnetic resonance: assessment of patients with suspected coronary artery disease. J Nucl Med 2006; 47: 74-82.

Berman DS, Hachamovich R, Shaw LJ, et al. Roles of Nuclear Cardiology, cardiac computed tomography and cardiac magnetic resonance: noninvasive risk stratification and a conceptual framework for the selection of noninvasive imaging tests in patients with known or suspected coronary artery disease. J Nucl Med 2006; 47: 1107-18.

Chikamori T, Yamashina A, Hida S, et al. Diagnostic and prognostic value of BMIPP imaging. J Nucl Cardiol 2007; 14: 111-25.

Kobayashi H, Kusakabe K, Momose M, et al. Evaluation of myocardial perfusion and fatty acid uptake using a single injection of iodine-123-BMIPP in patients with acute coronary syndromes. J Nucl Med 1998; 39: 1117-22.

Kawai Y, Tsukamoto E, Nozaki Y, et al. Significance of a reduced uptake of iodinated fatty acid analogue for the evaluation of patients with acute chest pain. J Am Coll Cardiol 2001; 38: 1888-94.

Mizuno K, Satomura K, Miyamoto A, et al. Angiographic evaluation of coronary artery thrombi in acute coronary syndromes. N Engl J Med 1992; 326: 958-965.

Hodgson JM, Reddy KG, Suneja R, et al. Intravascular ultrasound imaging: correlation of plaque morphology with angiography, clinical syndrome and procedural results in patients undergoing coronary angioplasty. J Am Coll Cardiol 1993; 21: 35-44.

Ross R. The pathogenesis of atherosclerosis- an update. N Engl J Med 1986; 314: 488-500.

Lees RS, Lees AM, Strauss HW. External imaging of human atherosclerosis. J Nucl Med 1983; 24: 154-6.

Lees RS, Lees AM, Schoen FJ, et al. Imaging human atherosclerosis with Tc-99m Labeled LDL. Atherosclerosis 1988; 8: 461-70.

Rudd JH, Warburton EA, Fryer TD, et al. Circulation 2002; 105: 2708-11.