

Radionuclide Imaging in Patients with Ischemic Heart Failure

Wanda Acampa, Mario Petretta, Laura Evangelista, Andrea Petretta and Alberto Cuocolo*

Department of Biomorphological and Functional Sciences, University Federico II, Napoli; Institute of Biostructure and Bioimages, National Council of Research, Napoli; Department of Clinical Medicine, Cardiovascular and Immunological Sciences, University Federico II, Napoli; and [#]IRCCS Neuromed, Pozzilli, Italy

Abstract: Nuclear imaging procedures are well-established diagnostic tools in clinical cardiology, providing noninvasive information about myocardial perfusion, cardiac function and metabolism. Scintigraphic parameters provide relevant information that aids in everyday clinical decision making for referring physicians. In patients with coronary artery disease, the presence of myocardial necrosis, postischemic stunning and hibernation can determine left ventricular dysfunction leading to ischemic heart failure. The prognosis of these patients is still poor and the long-term results of medical management remain discouraging. It is now well established that ventricular dysfunction is often a reversible process and ventricular function may improve following myocardial revascularization. Patients with extensive areas of hibernation treated medically have a worse prognosis as compared to those who undergo revascularization with a similar extent of viable myocardium. Therefore, an accurate non-invasive assessment of myocardial viability with the preoperative differentiation between hibernation and stunning and irreversibly necrotic tissue is important for clinical decision-making to select patients candidates for revascularization. Radionuclide imaging techniques evaluating myocardial perfusion, cell membrane integrity, ventricular function and cardiac metabolism have demonstrated clinical utility in the assessment of myocardial viability and in predicting improvement of ventricular function and prognosis after coronary revascularization.

Keywords: Radionuclide cardiac imaging, ischemic heart failure, myocardial viability.

ISCHEMIC HEART FAILURE: PATHOPHYSIOLOGICAL ASPECTS

Under certain conditions, when viable myocytes are subject to ischemia, prolonged alterations in regional or global left ventricular function may occur and this dysfunction may be completely reversible. This condition may be related to two pathophysiological states: stunned and hibernating myocardium. Stunned myocardium refers to the state of persistent regional dysfunction after a transient period of ischemia that has been followed by reperfusion, and is mainly present in acute coronary syndromes. Myocardial hibernation refers to persistent regional left ventricular dysfunction secondary to prolonged, subacute or chronic myocardial hypoperfusion under resting conditions in which myocytes remain viable but regional contractility is reduced to match the reduced blood supply [1, 2]. It has been suggested that during hibernation a new state of equilibrium is reached between blood flow (oxygen supply) and contraction (oxygen demand) whereby myocardial necrosis is prevented. Therefore, hibernation is considered a protective response of decrease oxygen demand in the setting of decrease oxygen availability [3]. Early studies suggested that resting blood flow is severely reduced in hibernating myocardium. However, more recent data obtained with quantitative measurements of myocardial blood flow indicate that during hibernation resting blood flow may be normal or only moderately reduced, with a disproportional decline in contractile function [4, 5]. These findings suggest that

myocardial hibernation may involve, at least in part, repetitive myocardial stunning, which determines protracted contractile dysfunction. Moreover, it is conceivable that some cases of presumed hibernation may represent stunning and other cases may represent intermittent stunning with hibernation, in which chronically underperfused myocardium becomes transiently ischemic (regional oxygen supply-demand imbalance).

ASSESSMENT OF MYOCARDIAL VIABILITY: RADIONUCLIDE IMAGING WITH SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY

Different radionuclide approaches have been used in the assessment of myocardial viability in patients with stunned and hibernating myocardium. The common accepted gold standard of myocardial viability is represented by the recovery of regional systolic function and global left ventricular ejection fraction in patients with moderate or severe impairment of ventricular function. Thus, the accuracy of any technique evaluating myocardial viability is tested against the predictability of the effects of myocardial revascularization on regional systolic function. However, the recovery of regional function after revascularization may be not the gold standard for assess myocardial viability and perhaps the clinical outcome after revascularization is a better and more valuable end-point. All studies performed have been utilized different gold standard. Research in this area is undergoing on the nuances and differences in tracers and methodologies for the determination of accuracy in the detection of preserved viability. Various perfusion tracers have been used in combination with single-photon emission computed tomography (SPECT) to assess myocardial viability. The largest experience has been obtained with

*Address correspondence to this author at the Department of Biomorphological and Functional Sciences, University Federico II, Via Pansini, 5, 80131 Napoli, Italy; Tel: +39 081 7462044; Fax: +39 081 5457081; E-mail: cuocolo@unina.it

[#]IRCCS: Scientific Institute of Research and Cure

thallium-201 and technetium-99m (Tc-99m) sestamibi. Thallium-201 imaging relies on the principle that integrity of cell membrane is the hallmark of viable myocardium [6]. Many protocols using thallium-201 imaging have been used to detect myocardial viability. The most accurate protocols appear to be stress-redistribution-reinjection [7] and rest-redistribution [8] thallium-201 imaging. It has also been demonstrated that in patients with previous myocardial infarction and left ventricular dysfunction, the extent of viable myocardium by thallium-201 reinjection at rest provides incremental prognostic information over those obtained from conventional stress-redistribution imaging [9]. In such patients, left ventricular ejection fraction but not the number of diseased coronary vessels provides additional prognostic information to thallium-201 imaging [10]. Imaging protocols with thallium-201 showed high sensitivity (average 88%) to predict functional recovery after revascularization while the specificity was rather low (49%), indicating that thallium may overestimate functional recovery in some dysfunctional regions.

Myocardial perfusion imaging with Tc-99m labeled agents, such as sestamibi and tetrofosmin, is useful in the evaluation of patients with chronic ischemic heart disease. The uptake and retention of these tracers are dependent both on cell membrane integrity and mitochondrial function [11] and may reflect cellular viability. Experimental studies have shown that myocardial retention of sestamibi and tetrofosmin is dependent not only on blood flow but also on cellular viability [12]. Recent clinical reports suggest that quantitative analysis of tracers content increase the overall accuracy of Tc-99m labeled agents for identifying viable myocardium [13-15]. The pooled results of the available studies using sestamibi to predict functional outcome after revascularization demonstrated an average sensitivity of 83% and a specificity of 69 % [16].

RADIONUCLIDE IMAGING AFTER NITRATE ADMINISTRATION

It has been demonstrated that nitrate administration may improve the detection of viable myocardium using Tc-99m labeled perfusion agents [17-19] (Fig. 1). Nitroglycerin most likely enhances myocardial viability detection by increasing coronary collateral flow, decreasing preload and afterload, and direct vasodilatation of stenotic coronary arteries [20-22]. These physiological effects in combination should enhance the delivery of myocardial perfusion agents to regions of myocardium supplied by severely stenotic vessel [23]. However, it has not been established whether nitrate imaging would be more efficient and cost-effective as compared to conventional protocols. It appears that nitroglycerin imaging should be used with different tracers to maximize tracer uptake in asynergic myocardial region [24-26]. Despite the increasing number of studies performed using nitrates before tracer administration, only after a large multicenter clinical trial we can better define the usefulness of nitroglycerin myocardial perfusion imaging in identifying viable myocardium.

GATED SPECT

Nuclear cardiology imaging techniques as well as the development of Tc-99m labeled perfusion tracers now permits combined myocardial-perfusion (Fig. 2 and 3) and left ventricular function studies at a single testing interval (Fig. 4 and 5). Thus, the potential advantages of simultaneous assessment of myocardial perfusion and left ventricular function have been recently outlined [27]. 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, prognosis

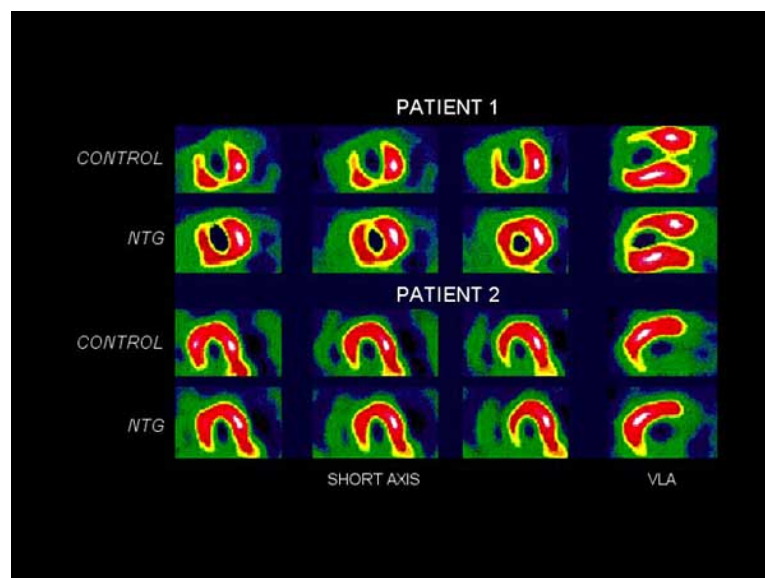


Fig. (1). Patient 1 (top panels): reduced tracer uptake in the antero-septal wall at baseline (CONTROL) and increased tracer uptake after nitrate administration (NTG). Patient 2 (bottom panels) with reduced tracer uptake in the inferior wall at baseline (CONTROL) and no change after nitrate administration (NTG).

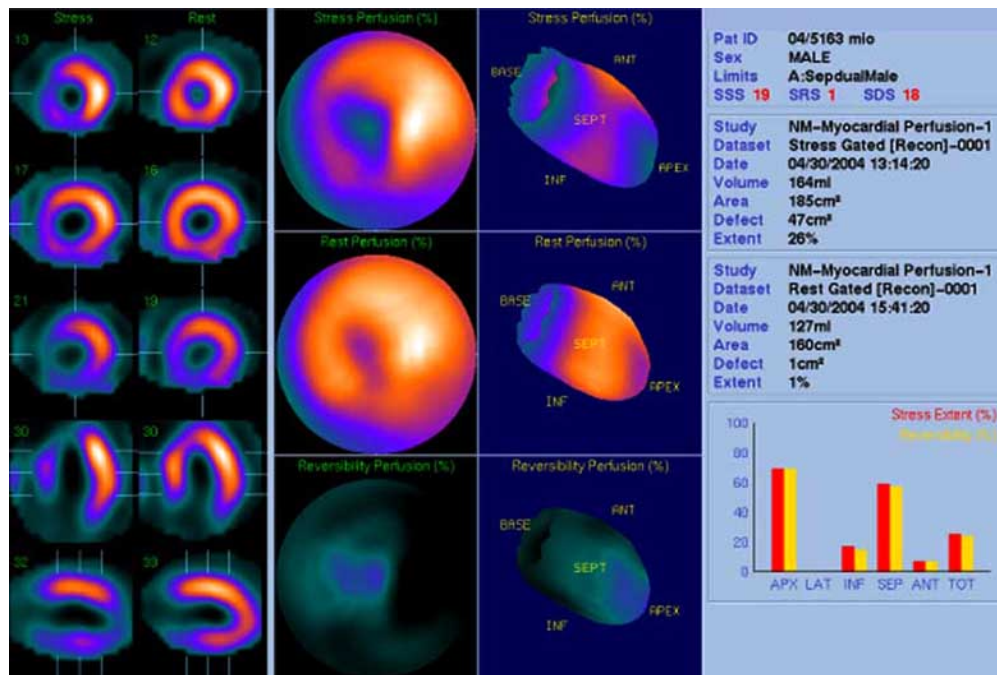


Fig. (2). Quantitative display output for the Cedars-Sinai Quantitative Perfusion SPECT (QPS) program. Stress and rest myocardial tomographic images, percent abnormal for defect extent and reversibility, and automatically generated perfusion score output are presented demonstrating a reversible perfusion defect in the distribution of the left anterior descending coronary artery in a patient with coronary artery disease.

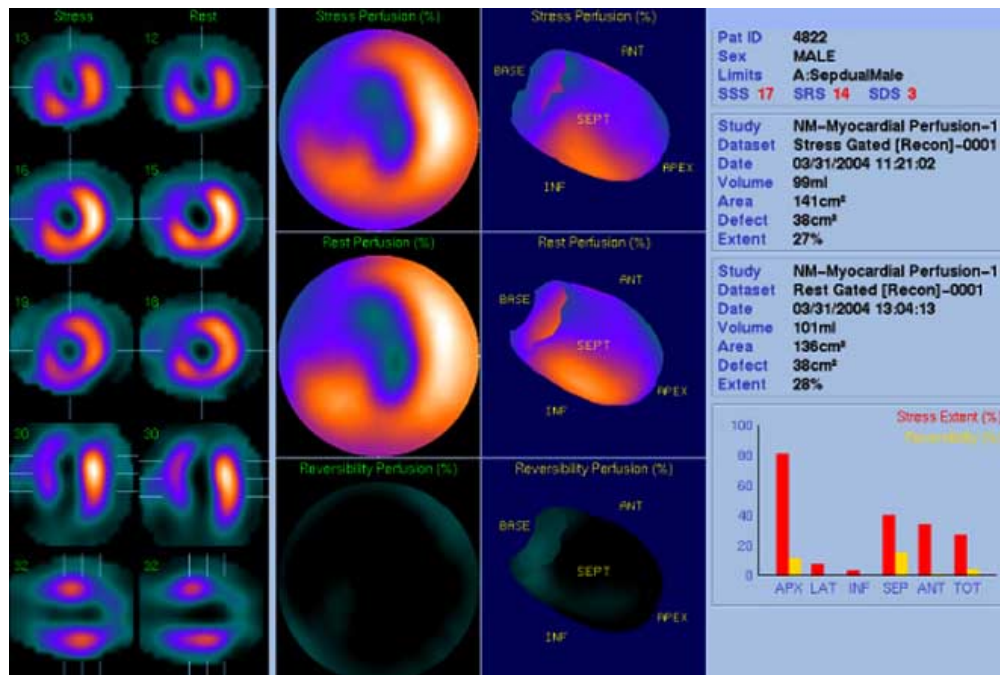


Fig. (3). Quantitative display output for the Cedars-Sinai Quantitative Perfusion SPECT (QPS) program. Stress and rest myocardial tomographic images, percent abnormal for defect extent and reversibility, and automatically generated perfusion score output are presented demonstrating an irreversible perfusion defect in the distribution of the left anterior descending coronary artery in a patient with prior myocardial infarction.

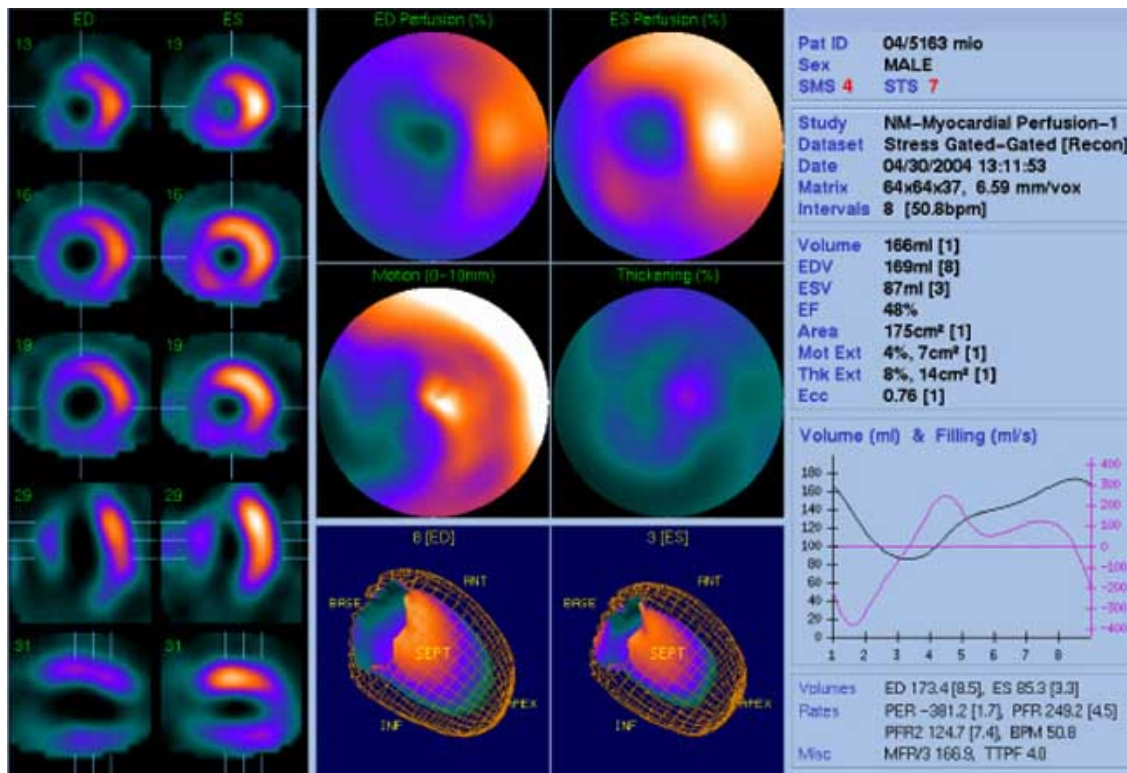


Fig. (4). Quantitative gated SPECT (QGS) analysis of the patient in Figure 2. The left ventricular ejection fraction is normal at 48%.

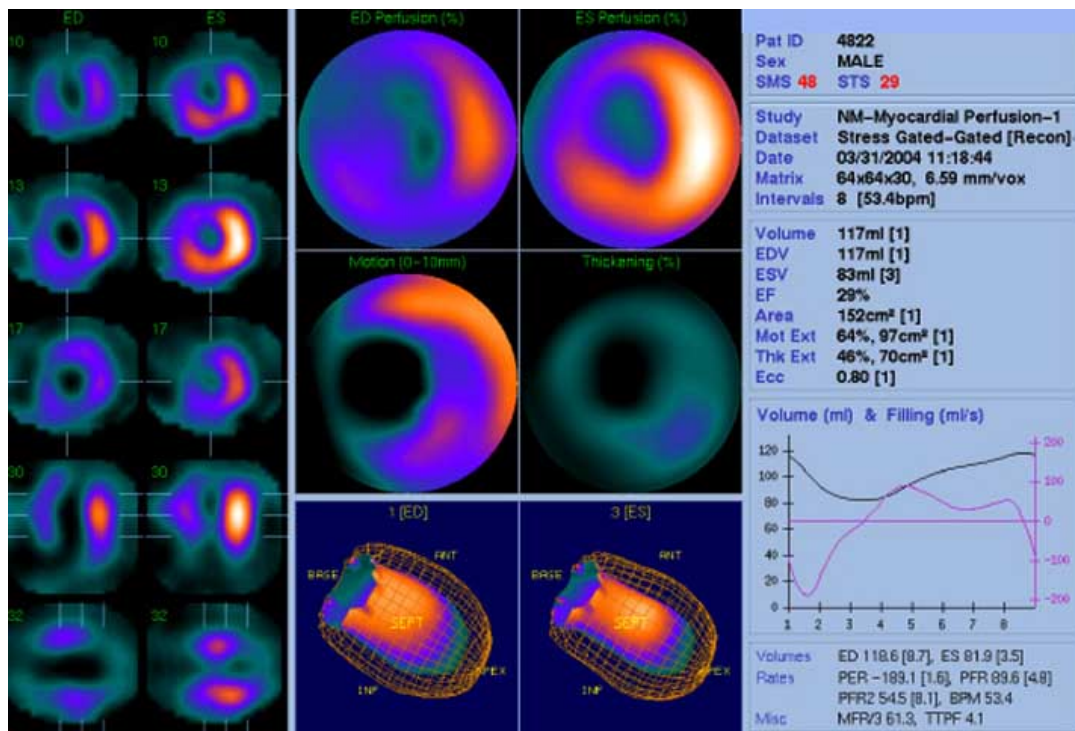


Fig. (5). Quantitative gated SPECT (QGS) analysis of the patient in Figure 3. The left ventricular ejection fraction is abnormal at 29%.

and risk stratification 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. Most recent data have also shown the ability of these combined measurements to improve the prediction of hard cardiac events [28]. It appears that the role of each of these may differ, depending on the patient population, particularly in relation to gender and type of stress test performed. Finally, a third area of potential application of this combined technique would be in the assessment of myocardial viability using pharmacological stress test in combination with wall motion analysis by gated images of the perfused myocardium.

METABOLIC IMAGING AND POSITRON EMISSION TOMOGRAPHY

The scintigraphic methods for evaluation of myocardial viability could be broadly categorized into SPECT with agents assessing both perfusion and metabolic activity, and positron emission tomography (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 for assessing 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 fluorine-18-fluorodeoxyglucose (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. FDG SPECT significantly increases the sensitivity for detection of viable myocardium in tissue nonviable by thallium-201 (to 88% of the sensitivity achievable by PET). However, it will occasionally (27% of the time) result in falsely identifying as viable tissue that which has been identified as non-viable by both PET and thallium-201 [29]. Clinical studies have been performed comparing fatty acid and glucose metabolism in relation to functional recovery of ischemic myocardium after coronary revascularization. Metabolic imaging with SPECT FDG may be useful in the prediction of improvement of left ventricular function after revascularization [30]. It has been demonstrated that combined metabolic SPECT imaging with FDG and iodine-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 [31]. 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.

CLINICAL IMPLICATIONS

As pointed out, 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. In particular, the specificity and positive predictive value of all different techniques used for detection of myocardial viability should be the prediction of short- and long-term outcomes, such as cardiovascular mortality and recurrent myocardial infarction [32]. Underlying the importance of combined measurements of perfusion and function, in a previous study we observed a marked separation of high- and low-risk subsets when using a combined variable derived for resting echocardiography and resting thallium-201 scintigraphy (the extent of viable dysfunctional myocardium) [33]. Moreover, the combination of echocardiographic and scintigraphic data provided significant additional prognostic information to clinical, thallium, and left ventricular functional data, whereas the number of diseased vessels did not [33]. The findings of this study extend previous observations of our group who showed that in post-infarction patients thallium-201 reinjection imaging provided incremental prognostic information to clinical, exercise, and thallium stress-redistribution data [9]. The sum of abnormal myocardial regions that were reversible and moderately irreversible after reinjection (viable tissue) was more predictive of hard events than simply the extent of defect reversibility. That is, the extent of viable and potentially jeopardized myocardium is an excellent predictor of subsequent mortality in patients undergoing medical therapy. Conversely, patients with poor viability and predominantly myocardial scar as the cause of their left ventricular dysfunction seem to have a poor outcome when undergoing coronary revascularization. Pagley et al [34] studied 70 patients with multivessel coronary artery disease and a left ventricular ejection fraction of less than 40% who had undergone coronary artery by-pass grafting, at a median follow-up of 1177 days. There were 6 cardiac deaths and no transplants in the 33 patients with greater viability, as assessed by a "viability score", compared with 15 cardiac deaths and 2 transplants in patients with lesser viability. Moreover, the extent of myocardial viability was the best predictor of transplant-free survival rate among many clinical and angiographic variables, including the extent of coronary artery disease and the resting preoperative left ventricular ejection fraction.

Therefore, 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 [35]. It should be considered that preserved myocardial perfusion tracer uptake in zones of asynergy might have a suboptimal 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. In a recent study by our laboratory, we observed that the amount of dysfunctional myocardium with preserved thallium-201 uptake provided independent prognostic information that was incremental to those obtained by clinical, functional and angiographic data in patients with chronic ischemic left ventricular dysfunction. In particular, patients with a substantial amount (>30% of the total left ventricle) of dysfunctional myocardium with preserved tracer activity exhibited the greatest left ventricular functional benefit after successful revascularization [35]. Moreover, patients with more than 50% of viable myocardium represented a subgroup at high risk of cardiac death in whom successful revascularization improved survival [35]. 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 an essential step in the clinical decision-making of patients with reduced global and regional left ventricular systolic function to better predict the potential value of revascularization in improving survival and functional status.

REFERENCES

- [1] Rahimtoola SH. The hibernating myocardium. *Am Heart J* 1989; 117: 211-21.
- [2] Rahimtoola SH. A perspective on the three large multicenter randomized clinical trials of coronary by-pass surgery for chronic stable angina. *Circulation* 1985; 72: V123-V135.
- [3] Ross Jr J. Myocardial perfusion-contraction matching. Implication for coronary heart disease and hibernation. *Circulation* 1991; 83: 1076-83.
- [4] Sun KT, Czernin J, Krivokapich J, *et al.* Effects of dobutamine stimulation on myocardial blood flow, glucose metabolism, and wall motion in normal and dysfunctional myocardium. *Circulation* 1996; 94: 3146-54.
- [5] Vanoverschelde JJ, Wijns W, Borges M, *et al.* Chronic myocardial hibernation in humans. From bedside to bench. *Circulation* 1997; 95: 1961-71.
- [6] Bonow RO, Dilsizian V. Assessing viable myocardium with thallium-201. *Am J Cardiol* 1992; 70: 10E-17E.
- [7] Dilsizian V, Rocco TP, Freedman NMT, Leon MB, Bonow RO. Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging. *N Engl J Med* 1990; 323: 141-6.
- [8] Ragosta M, Beller GA, Watson DD, Kaul S, Gimple LW. Quantitative planar rest-redistribution Tl-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.
- [9] Petretta M, Cuocolo A, Bonaduce D, *et al.* Incremental prognostic value of thallium reinjection after stress-redistribution imaging in patients with previous myocardial infarction and left ventricular dysfunction. *J Nucl Med* 1997; 38: 195-9.
- [10] Petretta M, Cuocolo A, Bonaduce D, *et al.* Prognostic value of coronary angiography in patients with chronic ischemic left ventricular dysfunction and evidence of viable myocardium on thallium reinjection imaging. *J Nucl Cardiol* 1997; 4: 387-95.
- [11] Beanlands RSB, Dawood F, Wen WH, *et al.* Are the kinetics of technetium 99m-methoxy isobutyl isonitrile affected by cell metabolism and viability? *Circulation* 1990; 82: 1802-14.
- [12] Sinusas AJ, Bergin JD, Edwards NC, *et al.* Redistribution of Tc-99m sestamibi and Tl-201 in the presence of a severe coronary artery stenosis. *Circulation* 1994; 89: 2332-41.
- [13] Maes AF, Borges M, Flameng W, *et al.* Assessment of myocardial viability in chronic coronary artery disease using technetium-99m sestamibi SPECT. Correlation with histologic and positron emission tomographic studies and functional follow-up. *J Am Coll Cardiol* 1997; 29: 62-9.
- [14] Matsunari I, Fujino S, Taki J, *et al.* Quantitative rest technetium-99m tetrofosmin imaging in predicting functional recovery after revascularization: comparison with rest-redistribution thallium-201. *J Am Coll Cardiol* 1997; 29: 1226-32.
- [15] Cuocolo A, Acampa W, Nicolai E, *et al.* Quantitative thallium-201 and technetium-99m sestamibi tomography at rest in detection of myocardial viability and prediction of improvement in left ventricular function after coronary revascularization in patients with chronic ischemic left ventricular dysfunction. *J Nucl Cardiol* 2000; 7: 8-15.
- [16] Bax JJ, Wijns W, Cornel JH, Visser FC, Fioretti PM. Accuracy of currently available techniques for prediction of functional recovery after revascularization in patients with left ventricular dysfunction due to chronic coronary artery disease. Comparison of pooled data. *J Am Coll Cardiol* 1997; 30: 1451-60.
- [17] Maurea S, Cuocolo A, Soricelli A, *et al.* Enhanced detection of viable myocardium by technetium-99m MIBI imaging after nitrate administration in chronic coronary artery disease. *J Nucl Med* 1995; 36: 1945-52.
- [18] Bisi G, Sciagrà R, Santoro GM, *et al.* Sublingual isosorbide dinitrate to improve technetium-99m-teboroxime perfusion defect reversibility. *J Nucl Med* 1994; 35: 1274-8.
- [19] Bisi G, Sciagrà R, Santoro GM, *et al.* Technetium-99m-sestamibi imaging with nitrate infusion to detect viable hibernating myocardium and predict postrevascularization recovery. *J Nucl Med* 1995; 36: 1994-2000.
- [20] Brown BG, Bolson E, Peterson RB, Pierce CD, Dodge HT. The mechanisms of nitroglycerin action: stenosis vasodilation as a major component of the drug response. *Circulation* 1981; 64: 1089-97.
- [21] Fujita M, Yamanishi K, Hirai T, *et al.* Significance of collateral circulation in reversible left ventricular asynergy by nitroglycerin in patients with relatively recent myocardial infarction. *Am Heart J* 1990; 120: 521-8.
- [22] Rafflenbeul W, Urthaler F, O'Russel R, *et al.* Dilatation of coronary artery stenoses after isosorbide dinitrate in man. *Br Heart J* 1980; 43: 546-9.
- [23] Greco C, Ciavolella M, Tanzilli G, *et al.* Preoperative identification of viable myocardium: effectiveness of nitroglycerin-induced changes in myocardial sestamibi uptake. *Cardiovasc Surg* 1998; 6: 149-55.
- [24] Oudiz R, Smith D, Pollack A, *et al.* Nitrate-enhanced thallium-201 single-photon emission computed tomographic imaging in hibernating myocardium. *Am Heart J* 1999; 138: 369-75.
- [25] Sias TM, Watson DD, Beller GA. Is nitroglycerin useful for the enhancement of viability detection with myocardial perfusion imaging? *Am Heart J* 1999; 138: 206-9.
- [26] He ZX, Verani MS. Evaluation of myocardial viability by myocardial perfusion imaging: should nitrates be used? *J Nucl Cardiol* 1998; 5: 527-32.
- [27] Fagret D, Marie PY, Brunotte F, *et al.* Myocardial perfusion imaging with technetium-99m-NOET. Comparison with thallium-201 and coronary angiography. *J Nucl Med* 1995; 36: 936-43.
- [28] Srinivasan G, Kitsiou AN, Bacharach SL, Barlett ML, Miller-Davis C, Dilsizian V. (F-18)-Fluorodeoxyglucose single photon emission computed tomography: can it replace PET and thallium SPECT for the assessment of myocardial viability? *Circulation* 1998; 97: 843-50.
- [29] Bax JJ, Cornel JH, Visser FC, *et al.* Prediction of recovery of myocardial dysfunction after revascularization: Comparison of fluorine-18 fluorodeoxyglucose/thallium-201 stress-reinjection SPECT and dobutamine echocardiography. *J Am Coll Cardiol* 1996; 28: 558-64.

- [30] Sato H, Iwasaki T, Toyama T, *et al.* Prediction of functional recovery after revascularization in coronary artery disease using (18)F-FDG and (123)I-BMIPP SPECT. *Chest* 2000; 117: 65-72.
- [31] Borges-Neto S, Shaw LK. The added value of simultaneous myocardial perfusion and left ventricular function. *Curr Opin Cardiol* 1999; 14: 460-3.
- [32] Beller GA, Ragosta M. Extent of myocardial viability in regions of left ventricular dysfunction by rest-redistribution thallium-201 imaging. A powerful predictor of outcome. *J Nucl Cardiol* 1998; 5: 445-8.
- [33] Petretta M, Cuocolo A, Nicolai E, Acampa W, Salvatore M, Bonaduce D. Combined assessment of left ventricular function and rest-redistribution regional myocardial thallium-201 activity for prognostic evaluation of patients with chronic coronary artery disease and left ventricular dysfunction. *J Nucl Cardiol* 1998; 5: 378-86.
- [34] Pagley PR, Beller GA, Watson DD, Gimple LW, Ragosta M. Improved outcome after coronary bypass surgery in patients with ischemic cardiomyopathy and residual myocardial viability. *Circulation* 1997; 96: 793-800.
- [35] Cuocolo A, Petretta M, Nicolai E, *et al.* Successful coronary revascularization improves prognosis in patients with previous myocardial infarction and evidence of viable myocardium at thallium-201 imaging. *Eur J Nucl Med* 1998; 25: 60-8.

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