Ischemic Heart Failure: Radionuclide Imaging and Clinical Implications

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

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]. 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 and LV function studies at a single testing interval. Thus, the potential advantages of simultaneous assessment of myocardial perfusion ad LV 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 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 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 PET

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 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 18F-fluorodeoxyglucose (18F-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 18F (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 (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 [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 LV function after revascularization [30]. It has been demonstrated that combined metabolic SPECT imaging with FDG and 123I 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 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 LV 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 postinfarction patients thallium reinjection imaging provided incremental prognostic information to clinical, exercise, and thallium stress-redistribution data [9]. The sum of abnormal segments that were reversible and moderately irreversible after reinjection 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 with medical therapy. Conversely, patients with poor viability and predominantly myocardial scar as the cause of their LV 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 LV ejection fraction of less than 40% who had undergone coronary artery bypass 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 LV 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 [36]. 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 TI uptake provided independent prognostic information that was 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 [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 LV systolic function to better predict the potential value of revascularization in improving survival and functional status.

References


Top

Updating: 09/08/2003