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Seminars in
NUCLEAR
MEDICINE

Assessment of Myocardial Viability

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The prevalence of left ventricular (LV) dysfunction and resultant congestive heart failure is increasing. Patients with this condition are at high risk for cardiac death and usually have significant limitations in their lifestyles. Although there have been advances in medical therapy resulting in improved survival and well being, the best and most definitive therapy, when appropriate, is revascularization. In the setting of coronary artery disease, accounting for approximately two thirds of cases of congestive heart failure, LV dysfunction often is not the result of irreversible scar but rather caused by impairment in function and energy use of still viable-myocytes, with the opportunity for improved function if coronary blood flow is restored. Patients with LV dysfunction who have viable myocardium are the patients at highest risk because of the potential for ischemia but at the same time benefit most from revascularization. It is important to identify viable myocardium in these patients, and radionuclide myocardial scintigraphy is an excellent tool for this. Single-photon emission computed tomography perfusion scintigraphy, whether using thallium-201, Tc-99m sestamibi, or Tc-99m tetrofosmin, in stress and/or rest protocols, has consistently been shown to be an effective modality for identifying myocardial viability and guiding appropriate management. Metabolic imaging with positron emission tomography radiotracers frequently adds additional information and is a powerful tool for predicting which patients will have an improved outcome from revascularization, including some patients referred instead for cardiac transplantation. Other noninvasive modalities, such as stress echocardiography, also facilitate the assessment of myocardial viability, but there are advantages and disadvantages compared with the nuclear techniques. Nuclear imaging appears to require fewer viable cells for detection, resulting in a higher sensitivity but a lower specificity than stress echocardiography for predicting post-revascularization improvement of ventricular function. Nevertheless, it appears that LV functional improvement may not always be necessary for clinical improvement. Future directions include use of magnetic resonance imaging, as well as larger, multicenter trials of radionuclide techniques. The increasing population of patients with LV dysfunction, and the increased benefit afforded by newer therapies, will make assessment of myocardial viability even more essential for proper patient management.

Semin Nucl Med 35:2-16

There is an increasing number of patients with disabling heart conditions related to left ventricular dysfunction. In the developed world, two thirds of cases of left ventricular dysfunction are the result of coronary artery disease,[1] and the improved ability to treat and decrease the initial mortality from acute coronary syndromes has contributed to the increased prevalence of this condition. Not only are these patients at high risk for subsequent cardiac death, severe morbidities, and recurrent hospitalizations for congestive heart failure, they also frequently have severe limitations in their lifestyles and well being. The estimated annual treatment cost in the United States is more than 10 billion dollars per year.[2]

Although there have been significant advances in medical therapy for left ventricular dysfunction and resulting symptoms of heart failure, including angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, nitrates, hydralazine, β-blockers, aldosterone blockade, natriuretic peptides and, most recently, biventricular pacing,[3-9] the prognosis from heart failure remains extremely poor, with an annual mortality ranging from 10% to 50% per year. The total number of deaths has risen 148% between 1979 and 2000.[10]

It has been known for some time that left ventricular dysfunction is not always the result of irreversible myocardial

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0001-2998/05/$-see front matter
doi:10.1053/j.semnuclmed.2004.09.001

necrosis and scarring. After an initial ischemic injury, various processes can occur that lead to left ventricular dysfunction, including left ventricular remodeling, impairment of energetics, myocyte dysfunction, and cell death via necrosis and/or apoptosis.[11] Other than cell death, these processes are, to an extent, reversible, and left ventricular function often can be improved, resulting in better patient outcome. Although medical therapy can be extremely beneficial, revascularization in the appropriate patient often is the best therapy.

Left ventricular dysfunction, in some cases, is the result of "stunned myocardium," which is defined as myocardium that has become dysfunctional because of a transient coronary occlusion, has been salvaged by coronary reperfusion, yet exhibits prolonged but transient postischemic dysfunction, lasting hours to weeks.[12] Thus, in myocardial stunning, blood flow has been restored but contraction has not returned to baseline, ie, there is a flow-contraction mismatch.

Stunned myocardium, global or regional, often occurs in the setting of acute myocardial infarction that has been followed by spontaneous or induced reperfusion. Stunning also can occur after cardioplegic arrest during open heart surgery, as well as after exercise-induced ischemia. Episodes that lead to stunning can be single or multiple, brief or prolonged, but by definition are not severe enough to result in myocardial necrosis.

Topol and coworkers evaluated myocardial functional recovery in 20 consecutive patients with acute myocardial infarction who received thrombolytic therapy and, in some cases, coronary angioplasty.[13] Although there was no immediate or 24-hour improvement in wall motion after revascularization of infarcted areas, after 10 days, 85% of reperfused infarct zone segments demonstrated improved wall motion compared with 30% of nonreperfused segments ($P = 0.01$).

The exact pathogenesis of myocardial stunning is unclear and may be caused by a variety of factors, including the presence of oxygen free radicals and/or calcium overload.[14] Structural changes in collagen, including the collagen present in myocyte to myocyte struts, also have been seen in stunned myocardium.[11]

Left ventricular dysfunction, in other cases, is the result of "hibernating myocardium," which is defined as a state of persistently impaired left ventricular function at rest as the result of reduced coronary blood flow. It is hypothesized that the deprived myocytes are preferentially using the energy that they are able to generate to preserve cellular integrity at the expense of contractile function. Myocyte function can be partially or completely restored to normal if the myocardial oxygen supply/demand relationship is favorably altered, either by improving blood flow and/or by reducing demand.[15] By this definition, hibernating myocardium is a flow-contraction match. One of the first reported cases was in 1982, when Rahimtoola[16] described a patient with an occluded left anterior descending coronary artery, an akinetic anteroapical wall, and a global ejection fraction of 37%. After bypass surgery, function of the anteroapical region returned to normal, and the ejection fraction increased to 76%.

However, recent data suggest that resting blood flow in hibernating myocardial segments is not decreased to the extent that would account for the degree of cardiac dysfunction, but rather it is flow reserve that is impaired.[17,18] Some investigators contend that hibernating myocardium is actually a manifestation of repetitive myocardial stunning.

Observations suggest that hibernation may be a temporal progression of chronic, repetitive stunning with an initial state of normal or near-normal flow but reduced flow reserve, leading eventually to decreased resting flow.[19] Over time, there also appears to be structural changes in the myocardium, including alteration of structural proteins, metabolism to a more fetal form, disorganization of the cytoskeleton, loss of myofilaments, occurrence of large areas filled with glycogen, and sarcomeric instability. There also may be progressive apoptosis.[20]

Regardless of the mechanism, it is important to identify hibernating myocardium because ventricular function will generally improve after revascularization or other therapies. In the recently published Christmas trial (Carvedilol Hibernation Reversible Ischemia Trial), 59% of patients with class I-III heart failure (most class II) were found to have hibernating myocardium, on average, affecting 30% of the myocardium. Patients without hibernating myocardium had no improvement in ejection fraction after carvedilol treatment, whereas patients with 5 or more segments affected had an absolute 7% increase in ejection fraction.[21,22]

If indicated, it appears that revascularization should be undertaken as soon as possible to prevent progressive morphologic changes that can become irreversible.[23] Beanlands and coworkers[24] showed improved left ventricular function and lower mortality in patients who underwent revascularization within 35 days of diagnosis compared with patients who were revascularized later.

Clinical Importance of Identifying Viable Myocardium

Patients with depressed left ventricular systolic function have a worsened prognosis. In the CASS (Coronary Artery Surgery Study) registry, for the cohort of patients treated with medical therapy, those with a left ventricular ejection fraction of 50% or greater had a 10-year survival of approximately 90%, compared with a survival of 60% for those with an ejection fraction of 35% to 49%, and a survival of 30% for those with an ejection fraction less than 35% ($P < 0.001$).[25]

The principal goal of myocardial viability assessment is to identify patients whose symptoms and natural history may improve after revascularization. Recent publications have consistently shown that among patients with abnormal left ventricular systolic function, those with hibernating, ie, viable myocardium, have the poorest prognosis if they are not referred for a revascularization procedure. Comparable patients whose left ventricular function is predominantly the result of myocardial scarring appear not to be helped with revascularization and with medical therapy alone have a better prognosis than patients with viable myocardium.

For example, Gioia and coworkers[26] performed rest-redistribution thallium imaging in 81 medically treated patients