Myocardial Viability: Unresolved Issues

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The determination or assessment of myocardial viability has, over the past decade, captured the imagination and interest of many investigators in basic and clinical research using state-of-the-art technologies such as PET, SPECT, MRI and two-dimensional echocardiography (2-DE) (1-12). The emphasis in these studies has been to determine the absolute and comparative accuracy of these techniques (1-3). There are recent studies addressing the evaluation of the effect of viability assessment on patient outcome (13-17). The use of biochemical agents and other imaging methods in viability assessment is complex with many unresolved issues (Table 1) to be considered in the design and implementation of clinical protocols and in routine patient care.

DEFINITION

The issue of myocardial viability is most important in the presence of left ventricular (LV) dysfunction. Viable myocardium may be normal, hibernating or stunned while nonviable myocardium represents scar (1-3). Thus, hibernating myocardium is viable but viable myocardium is not necessarily hibernating. Hibernation refers to systolic LV dysfunction in the presence of hypoperfusion that recovers after coronary revascularization (1,2,18). It may represent a down-regulation of contractile function in response to reduced resting myocardial blood flow. Stunned myocardium refers to systolic LV dysfunction that persists after an ischemic episode despite restoration of flow (19). The distinction between viability and hibernation is important to the understanding of differences between various diagnostic methods that use different markers such as flow, metabolism or function. The flow-metabolism mismatch pattern determined by PET (which reflects reduced resting flow but preserved, albeit altered, metabolism) represents the mainstream description of the pathophysiological changes in hibernation (6,20). A recent study (21), however, raised doubt about the reliability of determining absolute rates of myocardial glucose uptake using the glucose tracer analog 13N-pyruvate, which may not fulfill the same criteria for hibernating myocardium because it may be that mild fixed perfusion defects represent viable myocardium but are not markers of hibernating myocardium (8,9,17). A good example is subendocardial infarction with admixture of scar and normal myocardium in the infarct zone. The subepicardial myocardium is viable but does not have to be hibernating and this zone may very well respond to inotropic stimulation. If LV dysfunction is due to hibernation, it potentially may recover after coronary revascularization while such recovery may not be expected if the dysfunction is due to subendocardial scarring. This may explain the reason why improvement in wall motion on echocardiography with dobutamine has not been a specific marker of recovery of LV function after revascularization (22).

A similar issue may be raised with perfusion imaging. For example, Figure 1 depicts the resting myocardial perfusion on a radionuclide tomogram; area 1 is a region with normal tracer uptake; area 2 is a region with mild fixed defect; area 3 is a region with severe fixed defect and area 4 is a region with

| TABLE 1 |
| List of Unresolved Issues in Myocardial Viability |

1. Definition of viable myocardium
2. Quantification of viable myocardium
3. Correlation between perfusion and function
4. Patient selection
5. Time of follow-up assessment
6. Completeness of revascularization
7. Perioperative myocardial infarction
8. Endpoints

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reversible defect. If reversibility is a marker of hibernation, then only 1 of the 4 regions has hibernating myocardium (reversible defect implies reduced resting myocardial blood flow due to severe coronary stenosis and viable myocardium). On the other hand, if normal uptake, mild fixed defect and reversible defect are considered as markers of viable myocardium, then three of the four regions contain viable myocardium. The question is: which pattern determines the recovery of LV function in this patient? Based on the mismatch pattern by PET, the answer is one region (1,2,6).

**QUANTITATION**

Although it is feasible that a given myocardial region may be entirely hibernating or entirely scarred, more often than not there is a mixture of normal, stunned, hibernating and scarred myocardium (1). The relative proportion of hibernating myocardium to other abnormalities in a given segment will determine the extent of recovery of regional function after coronary revascularization. Thus, in Figure 1, if area 4 is a region with severe defect that is completely reversible, it may be more important than if it is a mild defect that is partially reversible because, in the first example, there is more hibernating myocardium. Similarly, the total extent of hibernation in the LV myocardium will determine the extent of recovery of global LV function measured as ejection fraction (EF). The mere presence of hibernation is not in itself a justification for coronary revascularization. With SPECT, problems related to attenuation, scatter and partial volume effect may make quantitative assessment of hibernating myocardium less reliable than PET.

**CORRELATION BETWEEN PERFUSION AND FUNCTION**

Table 2 lists the relationship between regional LV function and perfusion. A normal perfusion is possible in a region with wall motion abnormality because of stunning, remodeling, malregistration (segments are not comparable), concomitant primary cardiomyopathy and coronary artery disease or because the normal perfusion is relative and not absolute. Abnormal perfusion may exist in a region with normal wall motion because of malregistration or because of misinterpretation of the perfusion pattern (attenuation artifact rather than true abnormality). Also, it is difficult to compare data from three-dimensional perfusion images (by SPECT) to two-dimensional (planar) radionuclide angiography. In the future, SPECT radionuclide angiograms, which provide three-dimensional information, may be preferred to allow more precise segmental registration (1).

**TABLE 2**

<table>
<thead>
<tr>
<th>Item</th>
<th>Perfusion</th>
<th>Wall motion</th>
<th>Issues to be considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Normal</td>
<td>Normal</td>
<td>NA</td>
</tr>
<tr>
<td>2.</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Stunning, remodeling, relative perfusion, malregistration, primary cardiomyopathy*</td>
</tr>
<tr>
<td>3.</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Hibernation ± scar and/or normal myocardium</td>
</tr>
<tr>
<td>4.</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Malregistration, misinterpretation (attenuation artifacts)</td>
</tr>
</tbody>
</table>

*Concomitant primary cardiomyopathy and coronary artery disease. NA = not applicable.

**PATIENT SELECTION**

Many of the published studies involve patients with mild-to-moderate LV dysfunction (4,13–16,22). The selection bias may explain why the various diagnostic techniques provide comparable accuracy in predicting recovery of LV function after revascularization (Fig. 2). It is possible that, as LV dysfunction becomes more severe, the accuracy of these techniques diverge. Myocardial viability assessment is most important in patients with severe LV dysfunction who have no disabling angina but have congestive heart failure because if angina exists that alone may guide therapy. The prognosis of patients with coronary artery disease, severe LV dysfunction and congestive heart failure is poor with medical therapy. Coronary revascularization in selected patients (with viable myocardium) has resulted in improvement in EF, symptoms and survival (5–7, 12–17). In the United States, there are over 3 million patients with congestive heart failure and over 70% of these patients have...
coronary artery disease (23). Aggressive medical therapy including the use of angiotensin-converting enzyme inhibitors increases longevity by 6–12 mo at the most and the limited number of donors and the expense of transplantation would suggest that many patients may be potential candidates for viability assessment to determine if coronary revascularization improves LV function and the functional status (24).

Recent data in patients with acute myocardial infarction suggest gradual improvement of LV function and perfusion pattern after 6 mo; inclusion of these patients in clinical trials may therefore alter the conclusion drawn from viability studies (25).

TIME OF FOLLOW-UP ASSESSMENT
The optimal time to reassess LV function after revascularization has yet to be determined. Most of the studies provide data at 8–12 wk (4, 6, 12). It is possible that recovery, in some patients, may occur at 6–12 mo but, obviously, longer follow-up may be associated with problems of restenosis after angioplasty or graft occlusion after bypass grafting. It may therefore be important to have serial measurements after coronary revascularization.

COMPLETENESS OF REvascularization AND PERIOPErATIVE EVENTS
Assuming that viability assessment is accurate, the recovery of LV function will depend on completeness of revascularization, lack of perioperative myocardial infarction and continued patency of grafts (or angioplasty site). Incomplete revascularization, (for example because of poor distal runoff) especially to the culprit area, may be an important reason for discordance between preoperative assessment and postoperative recovery. In the study by Tamaki et al. (12), 30% of the patients were excluded from intent to treat analysis because of incomplete revascularization. Repeat coronary angiography after revascularization may not be practical in either routine patient care or a clinical research protocol. Another difficult problem is the occurrence of perioperative myocardial infarction. Chairman and Jaffe highlighted the problems of diagnosing acute myocardial infarction in the perioperative period because conventional criteria of symptoms, electrocardiographic changes and enzyme changes are not very reliable (26). Thus, despite correct preoperative assessment of viability, postoperative improvement may not be realized due to perioperative infarction. What criteria should be used to detect perioperative infarction? Worsening of wall motion abnormality, a decrease in LVEF, infarct-avid imaging (using newer imaging agents), new perfusion defects or newer methods of enzymatic analysis (subforms of creatine kinase MB, cardiac troponins and myoglobin) are possible answers (7, 17, 27).

ENDPOINTS
What endpoints should be used to determine the outcome after coronary revascularization? From the patients' viewpoint, improvement in symptoms is far more important than improvement in wall motion abnormality or EF! Yet, from a scientific standpoint, improvement in regional wall motion abnormality and EF are objective and more reliable. Ideally, improvement in EF should be associated with improvement in symptoms and survival. The best primary endpoint appears to be improvement in EF while the secondary endpoints include improvement in symptoms and survival. Although wall motion improvement is useful for segmental analysis it may have limited significance on symptoms, EF and prognosis. Improvement in exercise performance has been used in assessing the efficacy of many medications for angina pectoris or congestive heart failure, but it may not be a reliable endpoint for viability assessment because improvement in exercise tolerance may occur without improvement in EF. Moreover, in some patients, angina pectoris, rather than fatigue or dyspnea, may be the limiting symptom before coronary revascularization (1). It is important that the method for measuring changes in EF be reliable and reproducible (28). The ideal utility of viability studies will be the ability to predict postrevascularization EF based on preoperative EF, extent of hibernation and coronary anatomy (Fig. 3). The ultimate goal is to have postrevascularization EF above 30%–35%—which means that, in a patient with an EF of 10%–20%, more hibernating myocardium should be present than in a patient with an EF of 20%–30% to warrant revascularization. The 30%–35% cutoff is based on studies showing that patients with an EF lower than 30%–35% have a poor prognosis (29–31). The effect of LV dilation on the changes in EF is a subject that needs to be addressed carefully because it is quite conceivable that marked LV dilation may prevent recovery of LV function, despite the presence of viable myocardium (14). The precise degree of dilation beyond which recovery is least likely cannot be answered from existing data.

CONCLUSION
The complexity of issues raised by the different imaging patterns and other factors that determine recovery of function after coronary revascularization, irrespective of perfusion pattern, may explain the relative lack of substantiation in the literature about specific perfusion patterns and specific pathophysiology. These, and other issues not related to perfusion pattern, are relevant to future clinical protocols in viability assessment using any of the diagnostic modalities because they are generic and deal with defining viable myocardium and the endpoint after coronary revascularization. The concept of reversing LV dysfunction and improving survival is a novel one, but implementation of prospective studies to test this hypothesis is at best a difficult one. For ethical and moral reasons, randomization is not possible (e.g., randomization of a patient with clear evidence of extensive hibernation to medical therapy

![FIGURE 3. Schematic presentation of ideal situation in which the radionuclide image predicts the degree of improvement of EF after coronary revascularization, if there is no perioperative myocardial infarction and complete revascularization was feasible (Patient 1). In Patient 2, the scan correctly predicted no improvement.](image-url)
or a clear evidence of extensive scarring to coronary revascularization). Careful consideration of the issues raised above may, however, be helpful in patient care and study design. The relatively high cost involved in the management of patients with congestive heart failure suggests the need of a large trial in this group of patients.

REFERENCES