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EDITORIAL REVIEW

"Hibernating" Myocardium: Asleep or Part Dead?

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Chronic ischemic dysfunction of the left ventricle is commonly presumed to represent "hibernating" myocardium. The implication of this assumption is that with successful reperfusion, systolic function will improve. Several diagnostic techniques including dobutamine stress echocardiography have been used to detect "viable" myocardium in the setting of chronic left ventricular dysfunction. Predictive accuracies of 70% to 85% have been reported for identifying myocardium that recovers function. Recovery of function has been variable and often dependent on the severity of dysfunction. All current models have presumed that chronically dysfunctioning myocardium is "hibernating." Obviously, in the chronic setting, dysfunction may have many causes and include components of transmural and nontransmural infarction as well as hibernating myocardium. This review focuses on the independent role that nontransmural infarction may play in chronic dysfunction and suggests its impact on diagnostic techniques used to identify hibernating myocardium.

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The accurate identification of "hibernating" and "stunned" myocardium and separation of these entities from infarcted myocardium has become a major goal in cardiovascular imaging. Accurate identification of viable myocardium may allow a more rational recommendation for coronary revascularization. The underlying premise is that viable but dysfunctional myocardium will recover function if revascularized. The two entities under consideration, myocardial stunning and hibernation, are distinct with respect to their origin and natural history. Myocardial stunning is a well defined phenomenon that is the result of an acute ischemic insult (1–5). Excellent animal models for myocardial stunning exist and the human corollaries of the stunning that occurs after coronary angioplasty and after lytic therapy have been fairly well described (5,6). Myocardial hibernation refers to chronic ischemic dysfunction of myocardium subtended by a critical coronary stenosis (7,8). The mechanism for chronic dysfunction is probably multifactorial—including ultrastructural alterations of the myocardium (9), calcium overload (10) and depletion of adenosine triphosphate (11)—which result in excitation-contraction uncoupling. Unlike acute ischemic stunning, clinically relevant myocardial hibernation has no effective animal models.

Methods for Detecting Viable Myocardium

Several techniques have been proposed for the detection of myocardial viability. These have included the early techniques of postextrasystolic potentiation (12), redistribution thallium techniques (13–16) and positron emission tomography for evaluation of myocardial metabolism and perfusion (17,18).

More recently, the response to low dose dobutamine augmentation of acutely stunned (19–21) or chronically dysfunctioning (22–29) myocardium has been described. The standard for viability in most studies has been recovery of systolic function. As discussed subsequently, this may be an inappropriate standard for myocardial viability. Comparative studies have suggested rough equivalence among these techniques with respect to predicting recovery of function, and overall predictive accuracies range from 70% to 85% (23,25–27,29). In general, the techniques tend to agree more for myocardial segments that have relatively mild degrees of dysfunction and less well for segments that are frankly akinetic (23,27,29). Radionuclide and metabolic studies tend to predict more viable segments than are apparent by echocardiographic imaging (25,27,28). The rest echocardiogram alone provides valuable clues to myocardial viability. Myocardial segments that have preserved wall thickness and are only hypokinetic (as opposed to akinetic) more often are viable when evaluated with more complex techniques such as dobutamine augmentation or perfusion imaging (26,28). Recently, myocardial contrast echocardiography has also been shown to be a marker of myocardial viability (30,31) but likewise to predict more viable segments than are apparent by dobutamine augmentation (32).

The ability of dobutamine stress echocardiography to detect stunned myocardium and to separate it from irreversibly infarcted myocardium was first demonstrated by Pierárd and colleagues (19). After myocardial infarction, they noted that patients with dobutamine augmentation had intact metabolism but that only those with preserved flow had subsequent recovery of function. There was an excellent concordance between nonviability by positron emission tomography and failure to augment with low dose dobutamine. In a similar fashion, Barilla and colleagues (20) suggested that dobutamine aug-

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mentation was a marker for viable myocardium but that recovery of function occurred only if the infarct vessel was revascularized. Myocardial stunning, by definition, is a transient phenomenon. Once vessel patency has been documented, the incremental value of a diagnostic test such as dobutamine stress echocardiography or thallium perfusion imaging may be quite limited. Conversely, hibernation is a more clinically relevant target for investigation, as the patency of coronary arteries is often unknown but obstructive coronary disease presumably exists. In patients with chronic ischemic dysfunction, identification of potentially viable myocardium may provide the impetus for revascularization in an effort to improve left ventricular systolic function, reduce symptoms of heart failure and, presumably, improve survival.

Prevalence of Hibernation and Its Response to Revascularization

The actual prevalence of hibernating myocardium remains unknown. Several studies (22–29,33) have indirectly addressed the issue, and from these it appears that a substantial proportion of patients with chronic coronary artery disease may have myocardial segments best described as hibernating. An early study by Lewis and colleagues (33) evaluated 252 consecutive patients who presented with chest pain but had not had documented myocardial infarction. Wall motion abnormalities at rest were noted on echocardiography in 77 (31%) of these patients, 32 of whom subsequently underwent revascularization. Follow-up echocardiograms were available in 19 patients and demonstrated improved segmental wall motion in the majority. More recently, Afridi and colleagues (23) evaluated 20 patients with severe coronary disease who subsequently underwent successful balloon dilation. Rest wall motion abnormalities were present in all. After successful angioplasty, recovery of baseline function occurred in 33% of dysfunctional segments. As with the earlier study of Lewis et al. (33), the presumption was that the rest wall motion abnormalities represented chronic ischemic dysfunction due to hibernation, which then reversed after restitution of normal coronary blood flow.

Standards for Viability

The appropriate standard for determining viability is not the presence of metabolic activity with positron emission tomography, perfusion on thallium redistribution or systolic augmentation during dobutamine infusion. The appropriate standard is recovery of function and reduction in symptoms after revascularization. The currently employed diagnostic techniques are designed simply as markers of myocardial viability rather than as the standard. Several definitions of recovery of function can be utilized. Mechanical function can be analyzed on either a regional or a global basis. Investigational data support improvement in either or both. Many patients presumed to have hibernation probably have a combination of hibernation and nontransmural infarction, and the latter may result in a failure to recover baseline function. In these instances, recovery of cardiovascular reserve, ideally quantified by increasing exercise tolerance and decreasing symptoms, is likewise a marker of myocardial viability. Finally, patient survival is probably the ultimate goal of preservation of viable myocardium. Two recent studies (34,35) have suggested that patients with areas of viable myocardium who undergo revascularization have a lower event rate than do those without revascularization.

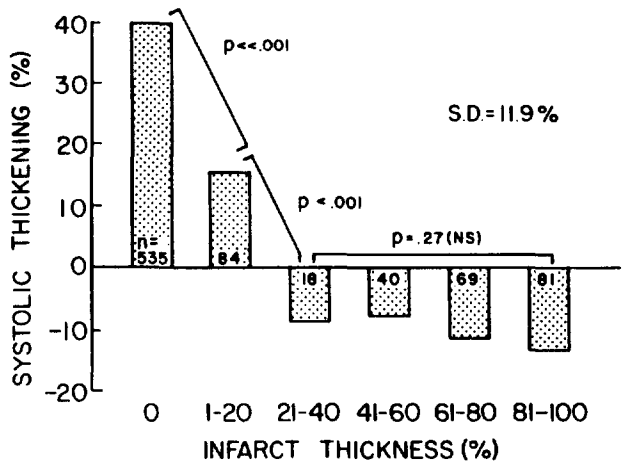


Figure 1. Relation of percent myocardial infarct thickness to systolic thickening. Complete cessation of systolic thickening occurs at a threshold of 21% infarct thickness, and a significant decrease in wall thickening is seen with a lesser degree of nontransmural infarction. Reprinted from Lieberman et al. (37) with permission of the American Heart Association.

Just as the optimal standard for viability has not been fully established, the "threshold" level of viable myocardium required to be present to provide clinical benefit after revascularization has not been determined. It has been suggested (26) that revascularization of only 18% of the left ventricle may reduce the frequency of subsequent clinical events. A greater mass of myocardial viability may be necessary for revascularization to result in augmented left ventricular function at rest.

Role of Nontransmural Infarction

It has been known for more than a decade that a threshold of myocardial injury occurs, after which regional wall motion becomes abnormal (37,38). Recently, the disproportionate role that the subendocardial layer of myocardium plays in overall wall thickening was further elucidated (39,40). The early animal work by Lieberman et al. (37) suggested that gross systolic dysfunction did not occur in a myocardial region until the transmural extent of necrosis exceeded 20% (Fig. 1). Above the threshold of 20% wall thickness necrosis, there was an abrupt cessation of systolic function (37). The clinical corollary of this experimental study is that a patient with a nontransmural myocardial infarction involving only 5% to 10% of the wall thickness will have essentially normal function at

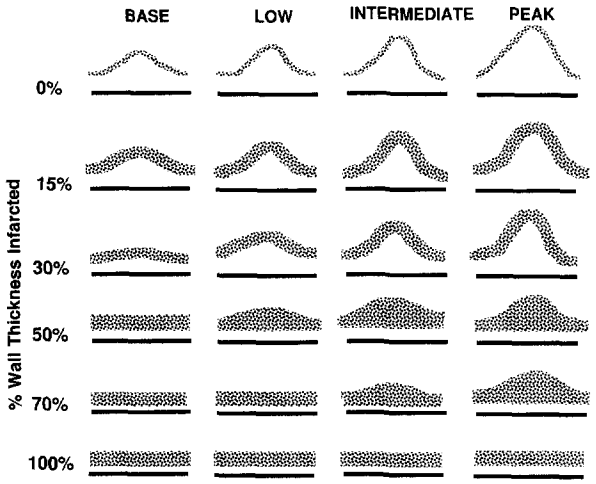


Figure 2. Hypothetic relation between dobutamine responses and degree of nontransmural infarction. Anticipated responses at baseline (BASE) and low, intermediate and peak doses of dobutamine stimulation are presented as they relate to degrees of nontransmural infarction ranging from 0 to 100%. This hypothetic model hypothesizes decreased baseline function with increasing degrees of transmurality of infarction with blunted augmentation dependent on percent myocardial infarction.

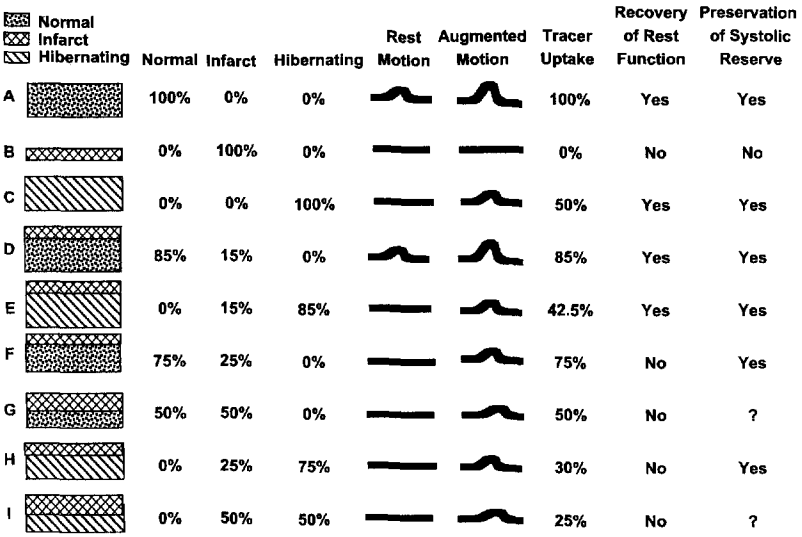
rest in that region. A segment with fully transmural infarction obviously has no motion at baseline. At a threshold of infarction of ~20% transmurality, rest function would be anticipated to be markedly abnormal. However, as 80% of the wall thickness is viable, augmentation with low dose dobutamine, or presumably with physiologic exercise, would result in improved function in that region. Obviously one can extrapolate gradations of responses of the myocardium to incremental dobutamine infusion (and presumably to physiologic exercise) dependent on the degree of transmural infarction. Figure 2 is a schematic of the hypothesized responses of myocardium to graded dobutamine infusions depending on the degree of myocardial necrosis present. This scheme assumes normal coronary flow to the remaining viable myocardium. Two recently published animal studies (41,42) have indirectly supported this concept.

The "Ischemic Cardiomyopathy"

Virtually all patients with chronic ischemic dysfunction and congestive heart failure have a combination of previous nontransmural myocardial infarction (often unrecognized) as well as multiple areas of myocardial hibernation and of normal perfusion and function. Thus, the combinations of responses seen are far more complex than the typical biphasic response of augmentation followed by deterioration or continued augmentation (23,43). Figure 3 outlines a variety of contractile responses that appear theoretically sound on the basis of current data. Many of these responses have been clinically demonstrated.

The simplest scenarios represent the major extremes (Fig. 3, panels A to C). Panels A and B represent fully normal or fully infarcted myocardium. Panel C represents the situation of full thickness stunned or hibernating myocardium. During low dose dobutamine infusion, inotropic stimulation is sufficient to overcome the depression of contractility and wall motion increases. With increasing doses of dobutamine, oxygen demand increases, and in the presence of critical coronary stenosis, ischemia ensues and wall motion deteriorates. It has been suggested (23) that this biphasic response, indicating viable myocardium subtended by a critical coronary stenosis, may be the most accurate echocardiographic marker of myocardial viability. The level at which the response becomes biphasic—that is, turns from augmentation to deterioration—presumably is related to the severity of the coronary stenosis and the magnitude of flow reduction. If appropriately revascularized, such a segment would be expected to recover function and to have near normal systolic reserve.

Intermediate levels of nontransmural infarction would be expected to augment only at higher doses of dobutamine



	Normal	Infarct	Hibernating	Rest Motion	Augmented Motion	Tracer Uptake	Recovery of Rest Function	Preservation of Systolic Reserve
A	100%	0%	0%			100%	Yes	Yes
B	0%	100%	0%			0%	No	No
C	0%	0%	100%			50%	Yes	Yes
D	85%	15%	0%			85%	Yes	Yes
E	0%	15%	85%			42.5%	Yes	Yes
F	75%	25%	0%			75%	No	Yes
G	50%	50%	0%			50%	No	?
H	0%	25%	75%			30%	No	Yes
I	0%	50%	50%			25%	No	?

Figure 3. Synopsis of anticipated dobutamine augmentation responses and likelihood of recovery of baseline function and preservation of systolic reserve based on different proportion of normal, infarcted and hibernating myocardium. See text for details.

infusion (Fig. 2). One could hence hypothesize that systolic augmentation at any level of dobutamine infusion serves as a marker of viable tissue; however, only segments that augment with low dose stimulation have the requisite mass of viable myocardium to recover basal function after revascularization.

Although it appears that the underlying pathophysiology (43) and clinical implication (23) of the biphasic response have been reasonably well elucidated, the pathogenesis and implications of other responses such as continued worsening, continued improvement and no change are less well understood. The biphasic response clearly represents augmentation of myocardium with sufficient mass to override the hibernating phenomenon or nontransmural infarct area, which then deteriorates at higher metabolic loads. Sustained improvement would be expected to occur in the presence of hibernating myocardium or of nontransmural infarction when no critical coronary stenosis is present. Thus, revascularization of such an area, because there is no underlying critical stenosis, would not result in improved baseline function. Myocardial segments that show no response may either represent hibernation to a degree that increasing metabolic activity is not feasible or segments in which a threshold of nontransmural infarction has been reached such that the doses of dobutamine infused are not sufficient to result in augmentation (Fig. 2). Although no definite evidence exists to prove any of the preceding hypotheses, many of these scenarios can be supported by drawing on known observations.

Hypothetically, and using the data of Lieberman and colleagues (37), as a starting reference, a segment of myocardium with 20% transmural myocardial infarction would be expected to be hypokinetic or akinetic at rest. However, as 80% of the wall is viable, augmentation at low levels of dobutamine may allow the viable myocardium to override the infarct area. In this situation augmentation of systolic function would occur at low doses of inotropic stimulation. The next stage of myocardial necrosis would be typified by a segment with 30% to 40% transmural necrosis. In this instance, as for the 20% transmural infarct, rest function would be abnormal. Because the ratio of normal to infarcted myocardium is lower than in the previous example, augmentation will not occur until intermediate doses of dobutamine are employed. At higher doses, ischemia may again ensue and wall motion deteriorate. The preceding examples presume a fairly simple distinction between infarcted and normal myocardium. In the latter case, however, revascularization would not result in recovery of baseline systolic function because the 20% threshold of myocardial necrosis has been exceeded (Fig. 3, panels F to I). However, as perfusion to the remaining normal myocardium has been restored, systolic reserve may be restored.

Hibernating myocardium will behave in a virtually identical manner to that just noted. Hypothetically, in the preceding scenario, one could substitute hibernating myocardium for normally contracting myocardium in varying ratios. When this occurs, the same patterns of increasing contractility at variable low and intermediate doses of dobutamine would be anticipated, with further deterioration at higher doses depending on the severity of flow-limiting coronary stenoses. Both of these scenarios probably occur clinically, obviously could coexist in any given patient and may be indistinguishable from an imaging standpoint.

Role of Radionuclide Imaging

Radionuclide imaging techniques likewise have proved valuable methods for detecting myocardial viability (13–16,25,27,29). Positron emission tomography, with imaging to detect metabolic activity, has been considered a reference standard for viable myocardium (17–19,28). As noted earlier, metabolic activity is not the appropriate standard; rather, recovery of function and improved symptomatic status are more appropriate end points. Both thallium scintigraphy and dobutamine echocardiography compare favorably with positron emission tomography, although in general positron emission tomography tends to detect more viable segments than the other two techniques. On the basis of these considerations, one should expect discrepancies among viability determinations obtained with metabolic tracers, flow tracers and functional assessment as each technique has a different threshold level of activity or function for separating viable from nonviable myocardium. Because the spatial resolution of radionuclide imaging techniques is not sufficient to accurately determine myocardial thickness, nontransmural myocardial infarction cannot be reliably detected on the basis of scintigraphic anatomy. On the basis of assumed kinetics of thallium activity, nontransmural infarction should be manifest as reduced overall wall activity. In a similar fashion, chronic reduction in myocardial flow also will be manifest as reduced thallium activity.

By using very simple assumptions, anticipated thallium patterns can then be fit to the echocardiographic responses and patterns of anatomy depicted in Figure 3. Assuming that normal myocardium, subtended by a nonflow restrictive coronary artery, has a thallium uptake of 100% and that fully infarcted myocardium has a thallium uptake of 0%, fairly simple and obvious patterns can be derived. If one then assumes that hibernating myocardium subtended by a critically stenosed coronary artery has an initial activity level of 50% of normal myocardium, anticipated levels of thallium activity for the different combinations of the normal, hibernating and infarcted myocardium presented in Figure 3 can then be predicted. On the basis of these fairly simple assumptions, it should be appreciated that a range of thallium activity can be present in the different combinations of infarct/normal/hibernating myocardium. Depending on the balance of normal versus hibernating myocardium, an individual myocardial segment may have recovery of function with a relatively low thallium uptake whereas a neighboring segment with higher thallium uptake may not recover rest function. This would be typified by comparing examples E, F and G in Figure 3. In example E, 15% transmural myocardial infarction is present, but the remaining 85% is hibernating. One would anticipate a thallium activity of ~40%. Because 85% of the myocardium is

viable, it would be expected to recover function after reperfusion; hence, an ~40% thallium uptake would be associated with recovery of function. Panel G represents a situation in which there is a 50% transmural infarct with normal perfusion of the remaining 50% of the myocardium. Thallium activity would be expected to be 50% (probably indistinguishable from the 42.5% in panel E), yet recovery of function would not occur because of the underlying extent of the nontransmural infarction. Panel F represents a situation in which 25% of the wall thickness is infarcted. One would anticipate thallium activity of 75%, possibly indistinguishable from normal; however, recovery of function would not occur because of the underlying myocardial infarction. On the basis of these fairly simple assumptions and the obvious corollaries to dobutamine responses, one should not expect 100% concordance among the diagnostic tests, or between any given diagnostic test and regional recovery of function. Obviously the initial and delayed thallium activity will be dependent on timing of imaging after injection and the actual severity of flow-limiting lesions.

Mechanism of Patient Improvement and Improved Survival

Clinicians have long linked reduced systolic function to worsened survival and symptomatic status. It appears that, as revascularization is extended to higher risk patients with worse left ventricular systolic function, surgical outcome may be more favorable than previously presumed. The mechanism by which this occurs is probably twofold. First and simplest, revascularization reduces the likelihood of new ischemic episodes, protects myocardium that is potentially viable and at least arrests any further deterioration in systolic function. Second, although revascularization cannot reduce the total amount of nontransmural myocardial infarction, by improving myocardial flow to the hibernating myocardium it allows recovery of those segments and, in some cases, recovery of baseline function. By improving function to both hibernating and nonhibernating myocardium, even in regions with >20% nontransmural infarction, there may be restitution of systolic reserve, such that during physiologic stress the normally perfused residual myocardium may be able to override the adverse effects of nontransmural segments with overall improvement of function. These events would have an obviously beneficial effect on exercise tolerance and symptoms of congestive heart failure.

Summary and Conclusion

Myocardial hibernation, nontransmural infarction and normally functioning nonischemic myocardium probably all coexist in any given patient with chronic ischemic left ventricular function. The current methodologies of dobutamine augmentation and thallium redistribution appear to be accurate markers for myocardial segments that contain viable myocardium but may be less accurate in predicting segment by segment recovery because of the mixed nature of the previous ischemic insult. Nevertheless, patients with substantial areas of viable myocardium will have regions likely to recover baseline function as well as regions with recovery of systolic reserve. Whereas restitution of baseline function will result in an increase in baseline systolic performance, restoration of flow to regions with greater degrees of nontransmural infarction will not. However, in the latter instance, cardiac reserve will be protected and symptomatic status will presumably improve. Therefore, failure of rest function to improve after revascularization should be construed not as a failure of the diagnostic test but as a limitation of the factors noted.

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