

Editorial Comment

Importance of Diagnosing Hibernating Myocardium: How and in Whom?*

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Hibernating myocardium (1-3) can be described by the clinical situation, that is, it is impaired left ventricular (LV) function at rest that is reversible by revascularization. Hearse (4) has defined hibernating myocardium as "exquisitely regulated tissue successfully adapting its activity to prevailing circumstances." Initially, the two clinical syndromes diagnosed in patients with coronary artery disease (CAD) were angina and myocardial infarction (MI). Subsequently, it was recognized that these two conditions could be painless, and the syndromes of unstable angina and non-Q wave MI were also diagnosed. Hibernating myocardium is one of three myocardial states of new ischemic syndromes (5) (Fig. 1) and is one of the myocardial states that may be present in patients in areas of LV dysfunction at rest (Table 1).

There is a considerable body of evidence (which is progressively increasing) showing that hibernating myocardium is a result of, and is associated with, reduced myocardial blood flow (MBF) or reduced myocardial perfusion at rest and that hibernating myocardium is normalized or improved with increasing MBF, reperfusion or myocardial revascularization (6,7). Hibernating myocardium, if revascularized, is associated with a lower cardiovascular event rate (8). Coronary bypass surgery, if it increases or normalizes MBF, reduces or eliminates the frequency and severity of angina and the need for pharmacologic treatment (9). Randomized trials in selected patients have documented better survival in those "assigned to" coronary bypass surgery than in those "assigned to" medical treatment in patients with left main CAD; three-vessel CAD with normal LV function; and two-vessel CAD if one of the vessels was the proximal left anterior descending coronary artery (2,10,11). In patients with LV dysfunction at rest, randomized trials of coronary bypass surgery have shown an improved survival (2,10), particularly in patients with three-vessel CAD (12). Complete revascularization is important for

improving the long-term outcome of severely symptomatic patients with three-vessel CAD and LV dysfunction (13). Percutaneous transluminal coronary angioplasty has been documented in randomized trials of selected patients to have results (both short term and intermediate up to 5 years) similar to those of coronary bypass surgery (14-17). The conclusions from these studies were that revascularization was of benefit in patients with hibernating myocardium and that it was also needed in selected patients with CAD to improve survival and the symptomatic state. As a result, the "conventional wisdom" developed that if patients had LV dysfunction at rest and had unstable angina or stable chronic angina and left main or three-vessel CAD, they should undergo revascularization by interventional techniques, without the need for documenting the presence and extent of hibernating myocardium.

In the current issue of the Journal, Haas et al. (18) describe their findings in patients with "advanced" three-vessel CAD and severe LV dysfunction (LV ejection fraction [LVEF] ≤ 0.35) who underwent coronary bypass surgery. Thirty-five patients had coronary bypass surgery on the basis of clinical presentation and angiographic data (group A), and 34 patients had coronary bypass surgery on the basis of positron emission tomographic (PET) findings in addition to the clinical presentation and angiographic data (group B). The PET findings included presence of viable myocardium (see later) and subjectively determined the extent of necrosis and viable tissue. Group B patients had a lower hospital mortality rate (0% vs. 11.4%, $p = 0.04$), a lower rate of complicated postoperative recovery (33% vs. 67%, $p = 0.05$), a lower incidence of low output syndrome (3% vs. 17%, $p = 0.05$) and a lower proportion of patients who needed catecholamine support (0% vs. 29%, $p = 0.002$). Furthermore, the 1-year survival rate was better ($97 \pm 8\%$ vs. $79 \pm 8\%$, $p < 0.01$); and, in selected patients studied postoperatively, the LVEF increased from 26% to 35% ($p = 0.003$) in group B, but the change in LVEF in group A (30% to 34%) was not statistically significant. These data support the notion that testing for hibernating myocardium is important in determining improved patient outcomes in patients with three-vessel CAD and severe LV dysfunction (LVEF ≤ 0.35).

However, there are limitations to the study of Haas et al. (18), some of which the authors themselves have described: 1) The study was a retrospective review of the patients, which means that it is uncertain whether the two groups were identical, even though there were no statistically significant differences in the preoperative characteristics that were examined, and that the patients in this study were a highly select subgroup; 2) whether the symptomatic state was due to angina or heart failure, or both, was not well documented; 3) LVEF was assessed preoperatively by contrast LV angiography and postoperatively by radionuclide angiography, and only three-fourths of the surviving patients had postoperative studies (postoperative LVEF in patients who subsequently died was not documented); 4) the functional outcome of regional myocardial segments after coronary bypass surgery was not inves-

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Abbreviations and Acronyms	
ALCAPA	= anomalous left coronary artery from pulmonary artery
CAD	= coronary artery disease
F-18 FDG	= fluorine-18 fluorodeoxyglucose
LV	= Left ventricle, left ventricular
LVEF	= left ventricular ejection fraction
MBF	= myocardial blood flow
MI	= myocardial infarction
PET	= positron emission tomography (tomographic)
SPECT	= single-photon emission computed tomography (tomographic)

tigated; and 5) the extent of “scar” tissue was visually estimated. Other limitations are that 1) wall motion was evaluated subjectively; and 2) the time lag between assessment of LV function at angiography and PET studies to assess viability is not stated.

Other problems relate to recognizing differences between MBF and assessment of perfusion and criteria for viability. The authors describe “normal or near-normal blood flow” in some group B patients; however, they did not actually measure MBF but subjectively determined tracer uptake of nitrogen-13 ammonia, which evaluates “perfusion.” Perfusion, determined in patients, is related to MBF but is not a direct measurement of MBF. In discussing hypoperfusion or reduced MBF in hibernating myocardium, it needs to be emphasized that LV contraction is most importantly related to subendocardial MBF (6,19,20). It is known from experimental studies that 1) when subendocardial MBF falls by only 10% to 20%, regional myocardial function is severely impaired (19,20); and 2) there is a sensitive coupling between subendocardial MBF and function in conscious dogs with acute myocardial ischemia (19). No technique currently available can measure subendocardial MBF in humans. Even PET, which measures transmural MBF, at the present time cannot determine subendocardial MBF in humans because it lacks sufficient spatial resolution. However, if transmural MBF is reduced, a greater reduction in subendocardial MBF is present (6). Experimental studies indicate that when transmural MBF falls by ~22%, subendo-

Figure 1. Evolution of the various clinical syndromes in patients with CAD. AMI = acute myocardial infarction.

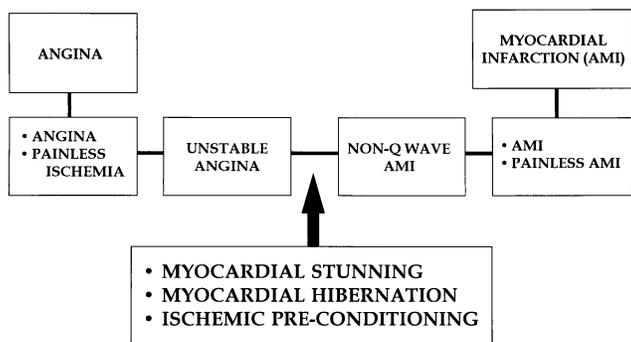


Table 1. Myocardial States Frequently Present in Patients in Areas of Left Ventricular Dysfunction at Rest

State of Myocardium	LV Dysfunction at Rest					
Irreversibly damaged	+	+	+	+	-	-
Viability and at risk						
Hibernating	-	+	-	+	+	+
Ischemic on “stress”	-	-	+	+	-	+

LV = left ventricular; + = yes; - = no.

cardial MBF falls by ~38 to 48% (20,21). Haas et al. (18) also assessed myocardial viability, but there are several different myocardial states that are viable (Table 2). Thus, the question is, What myocardial states are present in their group B patients who had viable myocardium in areas of LV dysfunction? One subset in group B is labeled “mismatch” by PET (22), defined in the study as “reduced blood flow with preserved or increased FDG [fluorine-18 fluorodeoxyglucose] uptake”; this indicates that hibernating myocardium was present in areas of wall motion abnormalities in these patients. The other subset in group B is labeled “normal” by PET, which was defined in the study as “normal or near-normal blood flow” (not defined by the authors) with normal or increased F-18 FDG uptake. It is uncertain what is normal or near-normal blood flow because the authors have actually evaluated tracer uptake of nitrogen-13 ammonia by subjective means (see earlier). For example, 1) can one reliably detect a 10% to 20% reduction in subendocardial MBF by subjective evaluation of transmural tracer uptake?; and 2) comparison of tracer uptake evaluated subjectively in areas of LV dysfunction with other areas in patients with severe multivessel CAD may be problematic, at least in some patients (6). The number of patients in group B who had mismatch or a normal pattern is not stated, and details for each individual patient in group B are not given (6), as was done recently by Sun et al. (23). Therefore, there is uncertainty about the myocardial state in the subset of group B patients labeled “normal” (6). Nevertheless, the study of Haas et al. (18) is important because it provides some data that question the conventional wisdom. At first, a challenge to the conventional wisdom may seem inappropriate and unreasonable. However, LV dysfunction at rest can result from a variety of myocardial states (Tables 1 and 2), and studies that documented an improvement in survival with coronary bypass surgery in patients with LV dysfunction (see earlier) did not study or document the mechanism or mechanisms by which

Table 2. Areas of Left Ventricular Myocardium That Have Viable Myocardium

Normal LV function at rest
LV dysfunction on stress
LV dysfunction at rest
Stunned myocardium
Hibernating myocardium

LV = left ventricular.

coronary bypass surgery produced this benefit. The improvement in survival could have been a result of salvage of hibernating myocardium, prevention of subsequent myocardial infarction, particularly in areas that were ischemic on "stress," or both. The randomized trials of coronary bypass surgery have not documented a significant reduction of the incidence of subsequent acute MI, and thus it is possible that an important mechanism for the improvement in survival with coronary bypass surgery was the salvage of hibernating myocardium (3,13). Moreover, studies that have shown a benefit with coronary bypass surgery in patients with rest LV dysfunction were associated with operative and late mortality (2,10,12, 13,24-26), which presumably could have been lower if those undergoing operation had included only patients with a "significant" amount of hibernating myocardium as the major cause of the LV dysfunction, as is suggested by the study of Haas et al. (18). Therefore, it is reasonable that an assessment of hibernating myocardium could allow better assessment of the risks and benefits in patients with LV dysfunction who are to undergo revascularization (18), as well as allowing better selection of patients who should undergo revascularization. This premise is further supported by studies in patients with severe chronic heart failure and patients being considered for heart transplantation (27-33). Documentation of hibernating myocardium in such patients has allowed the choice of appropriate therapy—revascularization rather than transplantation (27,28,31-33).

Diagnostic testing for hibernating myocardium. An important question is, Who should undergo diagnostic testing for hibernating myocardium? It is not possible to provide a definite answer because we do not know 1) which test or combination of tests is best, that is, with a very high positive and negative predictive accuracy, for the diagnosis of hibernating myocardium. The most commonly used tests for diagnosing hibernating myocardium are dobutamine echocardiography, thallium and sestamibi single-photon emission computed tomographic (SPECT) myocardial perfusion imaging and PET. Bonow (34), after a review of published reports, documented that the predictive accuracies for the three techniques was 83%, 69% and 82%, respectively, for positive test results, and 81%, 90% and 83%, respectively, for negative test results. However, in an individual center, any two tests may have similar accuracy (35), and the sensitivity and specificity of tests can be altered, depending on the criteria used (36). Moreover, there are few data on the accuracy of these tests in any one of the several clinical syndromes in which hibernating myocardium has been documented so far (Table 3). Moreover, frequently the protocol for performing the test or tests is not standardized, the data obtained are subjectively evaluated and not quantified, and the standards for assessing the accuracy may be inadequate. 2) Additional newer tests, for example, PET imaging with carbon-11 acetate alone or in combination with other tracers (37-39) and advances with SPECT imaging (40,41), also need to be evaluated, 3) We cannot reliably diagnose the amount of hibernating myocardium and the amount of irreversibly damaged myocardium, although some

Table 3. Clinical Syndromes in Which Hibernating Myocardium Has Thus Far Been Documented

Angina
Chronic stable
Unstable
Acute myocardial infarction
Heart failure and/or severe LV dysfunction
ALCAPA

ALCAPA = anomalous left coronary artery from pulmonary artery; LV = left ventricular.

initial data are promising (42). Uniform and generally accepted standards for these tests are needed.

Nevertheless, it is possible to provide some guidelines based on the assessment and consideration of 1) the severity of LV dysfunction; 2) the extent and severity of CAD and the state of the distal coronary arteries; and 3) the clinical syndromes in which hibernating myocardium has been documented so far (Table 3).

Patients with normal LV function and those with coronary arteries that are not suitable for revascularization do not need to be tested (Table 4). At the present time, transmural laser revascularization is still on experimental procedure.

Diagnostic testing for hibernating myocardium is needed 1) in patients known to have significant CAD and in those with suspected CAD or suspected idiopathic dilated cardiomyopathy who are being considered for heart transplantation; 2) in all patients with significant CAD and severe LV dysfunction (i.e., LVEF \leq 0.35); and 3) in all patients with CAD and LV dysfunction who are asymptomatic or have symptoms due to heart failure or LV dysfunction or who have only mild or minimal angina.

If patients do not fit into these subgroups, that is, mainly patients with mild to moderate LV dysfunction (LVEF 0.36 to 0.49), one may need to consider the clinical syndrome with which they present. Diagnostic testing is probably not indicated in patients with unstable angina, that is, angina at rest,

Table 4. Diagnostic Testing for Hibernating Myocardium*

Usually not needed†
Normal LV function
Coronary arteries not suitable for revascularization
Usually needed‡
Suspected CAD/IDCM, being considered for heart transplantation
CAD plus severe LV dysfunction (LVEF \leq 0.35)
CAD plus dysfunction in patients who are asymptomatic or have heart failure symptoms: mild/minimal angina
Individualize‡
Unstable angina/severe stable angina
Acute MI
ALCAPA

*Only needed in patients with left ventricular dysfunction at rest. †Clinical judgment may be needed. ‡Clinical judgment frequently needed. CAD = coronary artery disease; IDCM = idiopathic dilated cardiomyopathy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; other abbreviations as in Table 3.

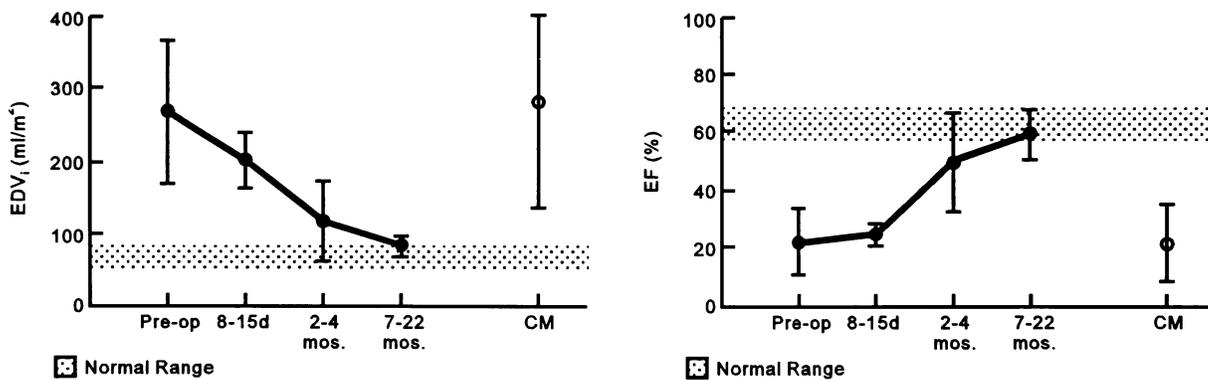


Figure 2. Preoperative (Pre-op) and postoperative LV end-diastolic volume (EDV) index (left) and LV ejection fraction (EF) (right) in five patients 2 to 8.5 years old who underwent surgical correction for ALCAPA. d = days after operation; mos = months after operation; CM = data from patients with IDCM at the author's institution. Reproduced, with permission, from Rein et al. (49).

progressively increasing angina despite medical therapy and angina ≤ 2 weeks after MI, (43) that is, those in Braunwald classes B and C; II and III (44), and in most patients with severe, chronic stable angina, because revascularization is often undertaken in these patients for relief of symptoms. However, one must recognize that 1) the severity of angina may not relate to the extent of myocardium at risk, extent and severity of CAD and LV function (45); 2) in patients with angina (if one excludes unstable angina), the extent of CAD and LV function and the extent and severity of ischemia are predictors of outcome but angina is not (2,46,47); and 3) documentation of the amount of hibernating myocardium may allow better assessment of the risks and benefits of revascularization (see above). Post-MI patients pose a more difficult problem because of the complexity and variety of clinical situations that may be present. These include the clinical state of the patient, location of the MI, extent and severity of CAD, extent and severity of LV dysfunction and the feasibility of revascularizing all dysfunctional myocardial segments; thus, the need to revascularize some or all dysfunctional LV segments may require evaluation by testing for hibernating myocardium. Anomalous left coronary artery from pulmonary artery (ALCAPA) is a congenital disorder that often presents with LV dysfunction or heart failure with or without mitral regurgitation, and the clinical findings may be similar to those for idiopathic dilated cardiomyopathy. The severe LV dysfunction and dilation improves or normalizes after surgical correction (48-54) (Fig. 2). Pathologic studies of transmural myocardial biopsy specimens have shown changes that are those of "structural adaptation to chronic ischemia" (53) and are similar to those described in hibernating myocardium. Patients with ALCAPA should be diagnosed early and should have early reimplantation of the left coronary artery into the aorta. Those with severe LV dysfunction may need testing for

hibernating myocardium. In all the above clinical syndromes, there is a need for clinical judgment. It must also be borne in mind that in all the above subgroups of patients, assessment of hibernating myocardium may allow better assessment of the risks and benefits of revascularization; however, additional studies are needed that document this premise.

Revascularization for hibernating myocardium. Function in hibernating myocardium improves or normalizes with revascularization, but the effects of optimal medical therapy have not been evaluated. Factors to be considered in recommending revascularization are shown in Table 5. Important factors that are likely to determine the expected improvement in LV function and hence patient outcome are an estimate of the extent of irreversibly damaged myocardium and the extent of hibernating myocardium (55,56). Haas et al. (18) used three criteria to recommend revascularization for patients in Group B, one of which was viable myocardium (see earlier). The other two were extent of necrosis and viable tissue. Although these were determined subjectively, it is, nevertheless, an important direction to pursue in determining whether patients should undergo revascularization. Additional studies are needed.

Some additional studies that are needed. The need for large, randomized studies to confirm the finding of Haas et al. (18), as suggested by the authors, may be premature at this time (57) because of the limitations of their study. The predictive accuracy of tests for diagnosis of hibernating myocardium may be inaccurate in 15% to 30% of patients; we do not know which test or combinations of tests is best for diagnosis of hibernating myocardium in each clinical syndrome

Table 5. Some Factors to Be Considered in Clinical Decision Making When Considering Revascularization for Hibernating Myocardium

Suitability of coronary arteries for revascularization
Severity of LV dysfunction
Symptoms, especially angina
Extent of irreversibly damaged myocardium
Extent of HM
Risks of revascularization
Estimate of LV functional recovery after revascularization

HM = hibernating myocardium; LV = left ventricular.

in which hibernating myocardium has so far been described; and we may not have enough data to estimate the number of patients that may be needed for each clinical syndrome to have a good chance of obtaining definite answers.

There is a need for 1) well designed studies that evaluate the predictive accuracy of various tests, singly or in combination, for diagnosing hibernating myocardium in the different clinical syndromes; 2) well designed studies that evaluate the risks and benefits of revascularization after testing for hibernating myocardium in each clinical syndrome; 3) well designed studies that reproducibly and accurately quantitate the amount of irreversibly damaged myocardium and hibernating myocardium; and most importantly 4) studies that evaluate whether optimal medical therapy by current standards is of benefit in hibernating myocardium. At such time, one can determine whether prospective, randomized trials are needed. If it is determined that randomized trials are necessary, then a well designed trial or trials can be initiated, keeping in mind that outcomes may be different for the different clinical syndromes (Table 3).

Addendum. After this editorial was submitted, Pagley et al. (58) documented, by a retrospective review of 70 patients undergoing coronary bypass surgery for "ischemic cardiomyopathy," that 33 patients with a myocardial viability index >0.67 (determined by thallium-201 scintigrams) had a significantly better short- and long-term cardiac event-free survival ($p = 0.019$) than 37 patients with a viability index ≤ 0.67 .

The two subgroups were similar with regard to age, gender, presenting clinical syndrome, electrocardiogram, hemodynamic variables, number of diseased coronary arteries and LVEF. The viability index was the only independent predictor of a 3-year survival free of a cardiac event. Thus, this study also documents the importance of diagnosing the presence and extent of hibernating myocardium.

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