

The Sleeping Heart: Hibernating Myocardium

There has been a noticeable change in our approach to patients with end-stage heart failure. This is reflected in the number of patients previously considered to be candidates for intense anti-failure therapy...who are now undergoing revascularization procedures.

By Gurpreet Parmar and
Akbar V. Lalani, MSc, MBBS, FRCP(C), FACC

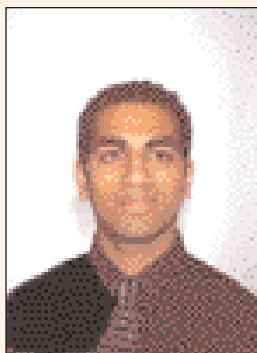


Introduction

Classical teaching about myocardial ischemia is now being challenged by exciting new concepts that have been evolving over the past two decades. It is now recognized that prolonged myocardial

ischemia does *not* inevitably lead to irreversible necrosis of myocardial tissue. Similarly, segment dysfunction in the ventricle does not necessarily imply that the myocardium in that area has undergone infarction and is permanently scarred. Of great significance is the ability to demon-

About the author...

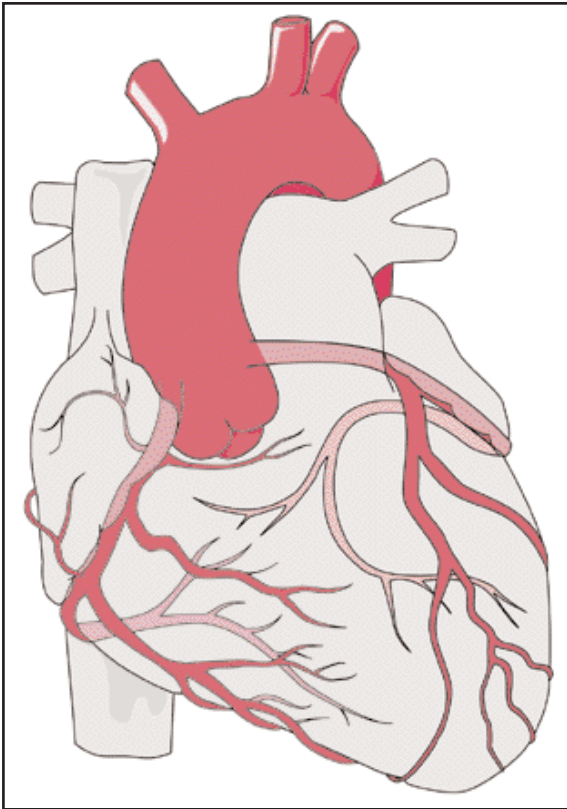


Gurpreet Parmar is currently a third-year medical student at the University of Western Ontario. Prior to medical school, he was involved in undergraduate work in microbiology at the University of British Columbia.

About the author...



Dr. Lalani, MSc, MBBS, FRCP(C), FACC, graduate of Guy's Hospital, London, England, is a consultant cardiologist at the Royal Columbian Hospital. His primary interests are interventional cardiology and coronary flow as well as hypertensive heart disease.



strate that there are segments of myocardial tissue in these so-called scars that are not only viable, but whose contractility is potentially partially, and in some cases fully, recoverable. These dysfunctional segments, originally thought to be infarcted scar tissue, are in a state of chronic ischemia. They are in an altered metabolic state—a state of “hibernation”—a term coined initially by Diamond *et al* and later elaborated upon by Rahimtoola.¹

Reduction of blood flow through the coronary arteries leads to regional disturbance of myocardial contractility. This dysfunction may be in the form of hypokinesis, akinesis or dyskinesis. It might manifest with electrocardiographic signs suggestive of myocardial infarction (MI), namely, Q waves. In some cases, however, the myocardium in those segments continue to remain metabolically active and viable, albeit at a much lower level of function. “Hibernation” can be a protective

mechanism to prevent ischemic myocardial tissue from progressing to irreversible necrosis. The severity and duration of hibernation is variable. In some cases, it may be present with the preservation of near-normal left ventricular ejection fraction. In others, it may cause severe regional, or even global, ventricular dysfunction.

Various reports have shown that in patients with ischemic heart disease, there might be significant amounts of hibernating myocardium present. These may vary from less than 10% to over 70%, depending on the method used to detect them and the extent of dysfunction present. Reperfusing these areas of hibernation could return contractile function to these segments of the ventricle. The clinical implications of this are very exciting, as there is potential to reverse the signs and symptoms of

heart failure in such patients once segments of hibernating myocardium have been identified and reper-

fused. With the rapidly rising incidence of heart failure and significant costs incurred from recurrent hospitalization and treatment of this malady, the clinical and economic implications of recognizing and appropriately managing patients with hibernating myocardium could prove to be enormous.

***“To die—to sleep—no more;
and by a sleep to say we
end the heartache...”***

Shakespeare: “Hamlet”
Act 3: Scene 1

Case Study Illustrating Myocardial Hibernation

While away on a work-related assignment, a 44-year-old diabetic male executive presented to the local hospital with acute shortness of breath and chest pain. He was noted to be normotensive with a regular pulse rate of 88

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beats per minute and had basal crepitations in his lungs on examination. The chest x-ray showed pulmonary venous engorgement and his electrocardiogram (ECG) showed ST elevation of 1.5 to 2 mm in leads 2, 3, VF, V5 and V6 with Q waves in leads 3 and VF.

The decision was made to undertake direct angioplasty, rather than give the patient thrombolytics. He was taken to the cardiac catheterization laboratory for immediate intervention. During the angiogram, doctors noted that his ventricular contraction was abnormal, with significant hypokinesis of the anterior, apical and infero-apical portions of the ventricle, with an ejection fraction of 0.34 (Figure 1a). He was also found to have a totally blocked right coronary artery (RCA) and a total occlusion, likely chronic, of his left anterior descending (LAD) artery. The interventional cardiologist was able to open the acutely occluded RCA, proximally re-establishing free flow (based on TIMI 3) in that artery, rendering the patient angina-free. However, several other lesions presented in the mid and distal portions of the RCA and it was decided not to attempt to dilate these, as the patient's LAD could not be opened during the procedure.

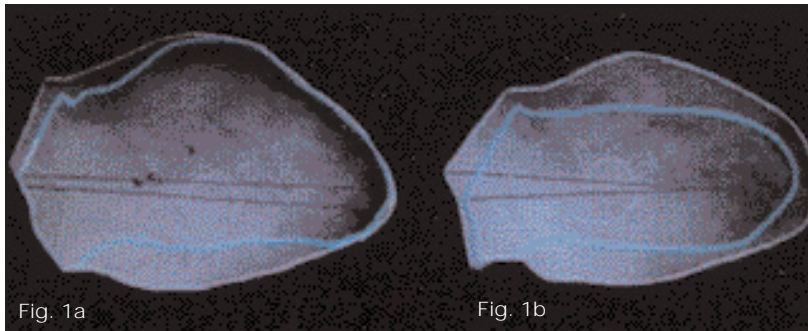
Although the patient had become pain-free, he continued to exhibit signs of left heart failure over the next few days.

An echocardiogram revealed considerable residual hypokinesis of the anterior and apical



walls of the ventricle. Intensified medical therapy produced some symptomatic improvement. A dobutamine echo, therefore, was performed and showed some improvement in the contraction of the anterior wall of the ventricle. Doctors felt there might be potentially viable, hibernating myocardium, which could be salvaged by surgical intervention.

Double-vessel bypass surgery was performed during the same hospital stay, with placement of an internal mammary graft to the mid-LAD and a vein graft to the distal RCA. The patient was discharged a week later, failure-free. Five weeks later, he was



viable, it is insufficient to support contractile function. This region of myocardium becomes hypocontractile or akinetic and behaves like infarcted scar tissue, resulting in LV dysfunction.

brought in for a further dobutamine echocardiogram. It showed a substantial improvement in the contraction pattern of the ventricle, with the ejection fraction (EF) measured at 0.49. Significant return of contractility to the anterior wall was present in the same regions previously indicated by the pre-operative dobutamine study. The patient was no longer in need of diuretics and was being maintained on acetylsalicylic acid (ASA), ramipril, a lipid-lowering agent and a diet for his diabetes.

Ten weeks after the initial event, he returned to work. Six months later, when he complained of chest pains, a repeat angiogram was performed. It showed patent coronary artery grafts and the left ventricular (LV) contraction had been preserved with an EF of 52% (Figure 1b).

Pathophysiology:

The concepts underpinning the pathophysiology of myocardial hibernation are still evolving. There are currently two schools of thought. The traditional view is that hibernation will develop in the myocardium as a result of severe and chronic reduction of blood flow. If this reduction in blood flow persists long enough, a chronic oxygen supply/demand mismatch sets in and hibernation develops as a physiological defense mechanism. The result is that while the blood supply is barely enough to keep the myocytes

The second view is that hibernation develops as a result of repetitive episodes of underperfusion and reperfusion of myocardial tissue. Under these conditions, the dysfunction is short-lived and follows each acute episode of disruption of coronary flow. Initially, as blood flow is restored, the myocardium recovers its contractile function fully. However, with repetitive ischemic insults, recovery becomes delayed and incomplete, finally resulting in total failure to recover at all. This phenomenon of persistent (or even exacerbated) dysfunction, despite restoration of adequate blood flow, has been termed “myocardial stunning.”²

While there is myocardial dysfunction present in both hibernation and stunning, in the former, it is due to a chronic lack of adequate perfusion, while in the latter (despite restoration of blood flow to normal levels) there is a persistence of reduced contractility. Hence “hibernation” is referred to as a chronic, potentially reversible ischemic dysfunction, whereas “stunning” is often defined as transient post-ischemic dysfunction.

In the clinical setting, this is likely to arise under the following conditions. In the presence of a tight coronary lesion, coronary flow may be sufficient to maintain adequate basal perfusion to the myocytes, allowing them to perform their contractile function appropriately. However, during times of increased oxygen demand, such as with physical exertion, the capacity of the partially-occluded vessel to deliver increased blood flow is overwhelmed.



This results in myocardial ischemia and local disturbance of myocardial contractility. With return to resting conditions, flow is once again able to match the reduced demands, the ischemia resolves and normal contractility is once again restored. With repetitive ischemic events, myocardial stunning sets in. After numerous such episodes of stunning and with progressively worsening coronary stenosis, a state of chronic ischemia sets in and the myocardium gradually loses its ability to fully recover its contractile function. It is postulated that this is when myocardial hibernation develops, leading to chronic LV dysfunction.

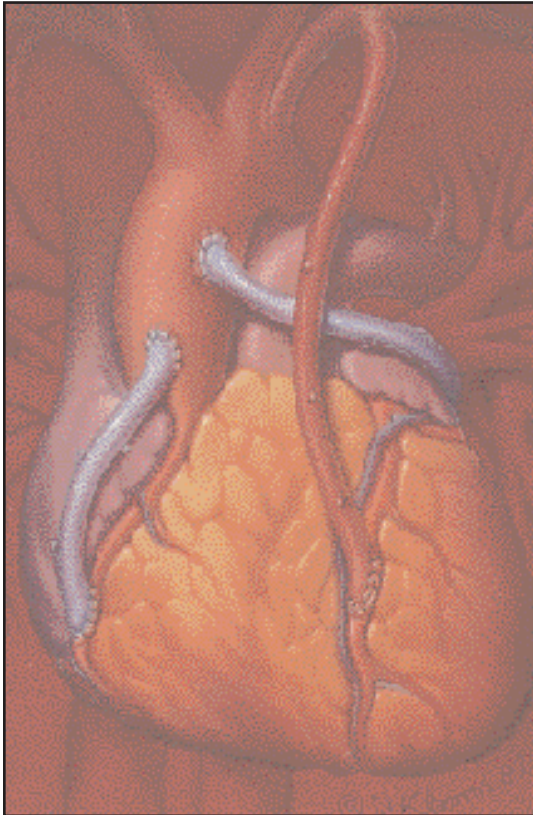
A number of histological changes have also been observed in hibernating tissue, including disorganized contractile proteins and an increase in myocardial apoptosis (programmed cell death).

Clinical Significance of Recognizing Hibernation

Hibernating myocardium may be present in the entire spectrum of myocardial

ischemia, ranging from stable or unstable angina to MI and chronic congestive heart failure. Interestingly, hibernation seems to be more common in patients with unstable angina, as compared to stable angina. This was well demonstrated in a study where patients with unstable angina and ventricular dysfunction were shown to have a better 10-year survival following coronary bypass surgery, compared to a similar patient population with ventricular dysfunction who had stable angina³. Patients with unstable angina have a greater potential for recovery of their dysfunctional myocardium following revascularization—implying that a substantial portion of this muscle tissue is in a state of hibernation. Rankin *et al* have shown that about 40% of patients with unstable angina will show significant improvement in cardiac contractility after revascularization.⁴

In acute MI, the presence of hibernating myocardium can be a harbinger of future adverse events, such as further MIs, death or the need for revascularization.⁵ Studies have shown many of the myocardial segments that



display regional dysfunction (or Q waves) following a MI may be reversible with revascularization. Reperfusion of such segments could contribute to improvement in global LV function, translating into improvement in long-term prognosis.

In the patient population with congestive heart failure (CHF), particularly of ischemic origin, recognition and revascularization of hibernating tissue could significantly affect their ventricular reserve and long-term outlook. In such patients, early identification of the presence of hibernating tissue and timely intervention to restore coronary flow by either coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty, can lead to clear functional improvement. This could lead to a smaller segment of the population requiring future hospitalization for symptoms of CHF and eventually to a decrease in the need for polypharmacy to control and prevent these symptoms.

More importantly, studies have now shown that 10% of patients with end-stage heart failure awaiting cardiac transplantation will also have hibernating myocardial segments. If these patients are identified and treated by revascularization, the need for cardiac transplant could be obviated in them⁶.

From a clinical standpoint, at times the only indicator of potentially viable myocardium in patients with ischemic cardiomyopathy is a history of ongoing angina, since the presence of this symptom implies the presence of viable myocardium. On the other hand, in patients in whom dyspnea, rather than angina, is the primary symptom of myocardial ischemia, some have suggested this is ascribable to chronic LV dysfunction. This could be due to either myocardial scar or hibernating myocardium.

Diagnostic Techniques:

Currently, several methods exist for detection of viable hibernating myocardium. Probably the most sensitive of all is nuclear imaging with thallium, using the re-injection and delayed imaging protocol. On the other hand, positron emission tomography scanning⁷ using fluorodeoxyglucose (FDG) as a tracer, can yield information about underlying metabolic status of potentially viable myocardial tissue. This technique, however, is not generally available and is quite costly.

Perhaps the most widely available non-invasive method of detecting hibernating myocardium is transthoracic echo. The simplest manifestation of hibernation on an echo image is the preservation of diastolic wall thickness of these otherwise dysfunctional segments⁸. During diastole, infarcted and scarred myocardial tissue tends to be thinner. Additionally, its systolic motion is characteristically abnormal. Hibernating myocardial



segments may also exhibit contractile dysfunction during systole. During diastole, however, they tend to retain normal diastolic wall thickness.

Administration of dobutamine, a positive inotrope, tends to transiently restore contractility to those areas of the myocardium that may be hibernating, as was seen in the case study shown above. When dobutamine is administered during a transthoracic echo study, segments with potential viability can be shown to exhibit improvement in their contractile function. This test has been utilized in predicting whether these areas are likely to respond to revascularization procedures such as CABG or percutaneous coronary intervention (PCI).⁹ Dobutamine echo is less sensitive than thallium imaging for areas of hibernating myocardium that have few viable myocytes. However, where there is a substantial amount of potentially viable

myocardial tissue present, dobutamine echo can be equally sensitive to thallium imaging. It is considered the de facto screening test for hibernating myocardium because of its ready availability in most health-care centres and relatively low cost.

The more myocardial tissue that can be returned to normal contractile function, the better the prognostic and clinical outlook of the patient population.

Reversal of Hibernation-Therapeutic Implications

In patients with ischemic LV dysfunction or in acute coronary syndrome including MI, it may be worthwhile to check for the presence of hibernating myocardial tissue. If this is present in a significant number of myocardial segments, an attempt should be made to re-establish normal coronary blood flow to the affected regions. Currently, this revascularization is best achieved with either coronary bypass surgery or PCI (*e.g.* angioplasty). An increase in perfusion to the dysfunctional segment could cause the hibernating tissue to “re-awaken.” This improvement in overall myocardial contractile function has been associated with an improvement in measured ejection fraction and may translate into increased patient survival.¹⁰ Additional benefits may include improvement in the quality of life, improved exercise tolerance, and a decrease in symptoms (particularly in patients with CHF). Revascularization may also improve the electrical stability in the myocardium, resulting in a decrease in the

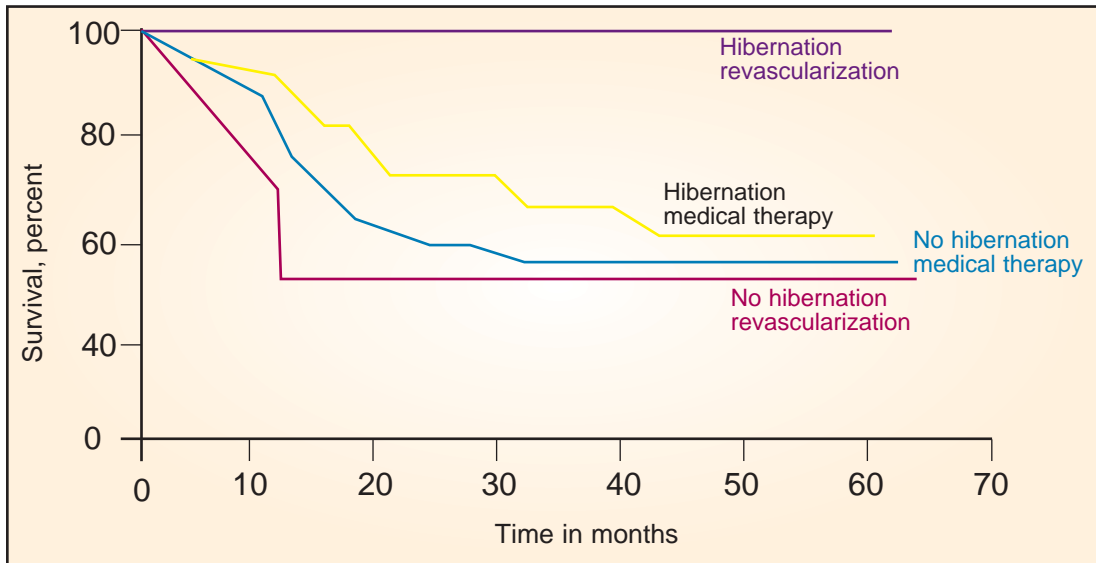


Figure 2.

Hibernation demonstrated by dobutamine echo predicts outcome in patients with ischemic cardiomyopathy. In 87 patients, event-free survival is shown in those patients with and without hibernating myocardium who were treated medically versus revascularization. Mortality was significantly lower in patients with hibernation when treated surgically.

(Adapted from an UptoDate figure based upon original figure which appeared in Senior R, Kaul S, Lahiri A. JACC 1999, 33:1848).

incidence of sudden cardiac deaths and ventricular arrhythmias¹¹.

Clearly, the extent of recovery following revascularization depends on the amount of tissue involved in the process of hibernation. The more myocardial tissue that can be returned to normal contractile function, the better the prognostic and clinical outlook of the patient population. A strong correlation has been shown to be present between the amount of viable myocardium detected with dobutamine echocardiography and the extent of LV function improvement following revascularization (Figure 2). Patients with a large amount of hibernating myocardium have better outcomes following CABG revascularization, compared to patients with little or no hibernating tissue. Survival and long-term outcome, including the number of future cardiac events, can be predicted based on the level of viability detected. This has proved to be a more powerful predictor of prognosis, compared to conventional indicators such as

a patient's age, ventricular contractility (ejection fraction) and extent of disease (number of affected coronary arteries).⁶

To date, ejection fraction of the left ventricle (LVEF) has been considered a reliable predictor of long-term prognosis. However, viability index (VI), which is based on the number of segments of myocardium with potentially viable hibernating myocardium, may be even more reliable and accurate at predicting event-free survival, compared to LVEF as is shown (Figure 3).¹²

Numerous studies have shown patients with hibernating myocardium will do significantly better if treated with revascularization, rather than medical management alone. In one study,¹³ patients with myocardial hibernation and poor left ventricles had a mortality rate of 20% when treated medically. In the subgroup of patients that underwent bypass surgery, however, it was noted to be only 6%. Conversely, Afridi's group¹³ also demonstrated that in the subgroup of patients with little

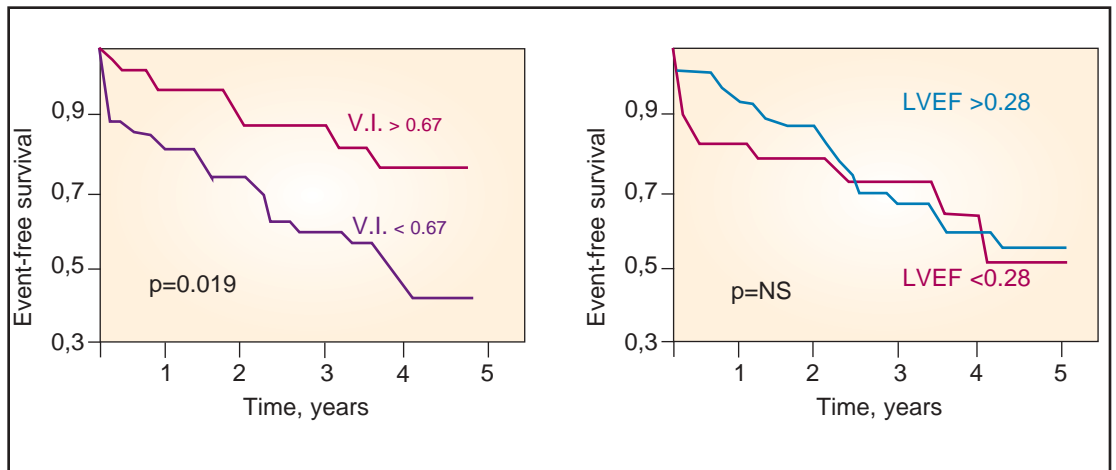


Figure 3:

Predictive ability of Viability Index (VI) vs LV ejection fraction (LVEF) of long term event-free survival.

(Adapted from an UpToDate figure based upon original figure which appeared in Pagley PR, Beller, GA, Watson DD, et al. *Circulation* 1997; 96:793)

or no hibernating myocardium, surgery was accompanied by a significant mortality rate of 20%. In these situations, perhaps unnecessary surgery *could* and *should* be avoided as the benefits are likely to be limited. Revascularization in such patients would largely be offered for symptom control of ischemia where medical treatment has failed.

Patients with moderate or severe chronic LV dysfunction have a poor prognosis and are at increased risk for developing complications during CABG. However, in patients in whom this LV dysfunction is due to the presence of hibernating myocardium, the overall outlook is substantially improved with revascularization *versus* medical management alone. The degree of recovery after restoration of flow to the hibernating segments is determined by many factors, the prime amongst them being the extent of reversibility of dysfunctional segments. Thus, simply detecting viable hibernating myocardium is not an indication *per se*, for referring the patient for CABG or PCI. Only patients with

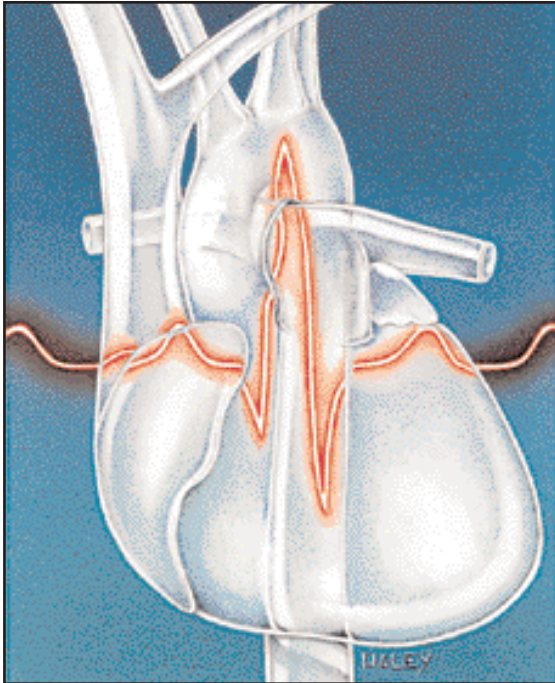
potentially large amounts (over 20% to 25%) of hibernating and viable myocardium may derive real benefits by going on to have revascularization.

Therefore, it may be beneficial to select patients for intervention (either by surgery or PCI) on the basis of the extent of hibernating and potentially recoverable myocardium present. Patients who are selected on this basis are the ones most likely to benefit.

Future Implications:

Coronary revascularization, either by surgery or PCI, currently offers the best potential for revascularization and restoration of viability and contractility to hibernating myocardial tissue. However, better and more readily available diagnostic tools are required to be able to quickly and more easily detect and accurately quantify potentially viable hibernating myocardial tissue in patients with cardiac dysfunction.

An improvement in our understanding of the behaviour of ischemic myocardial tissue



**Thou quiet soul,
sleep thou a quiet sleep;
Dream of success and happy victory.
(Shakespeare: Richard III. Act 5: Scene 3).**

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and the mechanisms underlying hibernation and stunning should lead to innovative pharmacological interventions. These may play an equally important role in the management of patients previously thought to have had irreversible myocardial damage.

Finally, there has been a noticeable change in our approach to patients with end-stage heart failure. This is reflected in the number of patients previously considered to be candidates for intense anti-failure therapy and eventual cardiac transplantation or implantation of ventricular-assist devices, who are now undergoing revascularization procedures. Results from preliminary studies (using this mode of treatment) have been encouraging.

In the case of the "sleeping heart" we have good reason to be optimistic, for as the Ghost of Lady Anne said to Richmond: 