Hibernating Myocardium in Patients with Coronary Artery Disease: Identification and Clinical Importance

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Summary. The term hibernating myocardium describes a particular outcome of myocardial ischemia in which myocytes show a chronically depressed contractile ability but remain viable. Revascularization of hibernating tissue causes a recovery of mechanical function that correlates with long-term survival. Therefore it is important clinically to distinguish hibernating from infarcted myocardium, since asynergies due to hibernation will improve on reperfusion, whilst those due to infarct will not. One suggested technique to identify hibernating myocardium is to stimulate the myocytes acutely, but briefly, by administration of inotropic agents while monitoring contractile function by echocardiography. We report our experience on the use of low dosages of dobutamine. Myocardial viability was validated by measuring the recovery in contraction of the akinetic areas after coronary artery bypass surgery by means of intraoperative epicardial echocardiography. The test has a sensitivity of 93% and a specificity of 78%. It is useful for identification of viable myocardium and also for quantification of intraoperative risk in individual patients. Limitations of this test are related to the presence of downregulation of beta receptors and to the impossibility of differentiating hibernating from stunned myocardium. Another useful technique of identifying hibernating myocardium is the use of radionuclear markers for viability. In our experience the two most important tests are (1) rest-redistribution imaging of thallium 201 (which has a high sensitivity of 93% but a low specificity of 44%) and (2) 99mTc-Sestamibi imaging, which provides information on both perfusion and function with a single injection. This latter technique allows differentiation between stunning and hibernating on the basis of coronary flow, which is preserved in stunning and reduced in hibernation.

Key Words. hibernating myocardium, echocardiography, dobutamine, nuclear cardiology

For many years physicians have considered persistent severe left ventricular dysfunction in patients with coronary artery disease to be synonymous with myocardial infarction and irreversible myocardial damage. This concept was based on the assumption that normal, viable myocytes would indeed contract, whilst those injured would not. The clinical implications are important, as often the presence of a chronic myocardial asynergy is considered evidence against revascularization.

It is now clear that chronic myocardial asynergy is not necessarily due to infarction nor is it always irreversible. In some patients with coronary artery disease (CAD), the asynergy will reverse upon revascularization, proving that the earlier concept was wrong.

In recent years we have learned that viable myocytes subjected to ischemia may show prolonged alterations in function, even after reperfusion. Such "new conditions" of viable myocytes with relatively prolonged abnormalities in contractile function have been named stunned and hibernating myocardium.

This article will review some general concepts related to the hibernating myocardium, with particular emphasis on clinical techniques used to identify this condition. We will not describe the relevance of positron emission tomography in distinguishing infarcted from stunned or hibernating myocardium, as this topic is covered elsewhere in this focused issue.

Outcomes of Myocardial Ischemia

We have recently learned that there are several potential manifestations and outcomes associated with myocardial ischemia and reperfusion. These are schematically shown in Figure 1. Without a doubt ventricular dysfunction (either systolic or diastolic) of the ischemic zone is the most reliable clinical sign of ischemia, since ECG changes and symptoms are often absent. The ischemia-induced ventricular dysfunction, at least initially, is reversible, as early reperfusion of the myocardium results in restoration of normal
metabolism and contraction. In the ischemic zone, recovery of contraction might occur instantaneously or, more frequently, with a considerable delay, thus yielding the condition recently recognized as the stunned myocardium [1-3].

On the other hand, when ischemia is severe and prolonged, cell death might occur. Reperfusion at this stage is associated with the release of intracellular enzymes, disruption of cell membranes, influx of calcium, persistent reduction of contractility, and eventual necrosis of at least a portion of the tissue [4-6]. This entity has been called reperfusion damage by those who believe that much of the injury is the consequence of events occurring at the moment of reperfusion rather than a result of changes occurring during the period of ischemia [5,6]. The existence of reperfusion damage, however, has been questioned, and it has been argued that reperfusion causes further injury [8]. The existence of such an entity has clinical relevance, as it would imply the possibility of improving recovery with specific interventions applied at the time of reperfusion.

In 1985 Rahimtoola described another possible outcome of myocardial ischemia [9,10]. He demonstrated that late reperfusion (after months or even years) of an ischemic area showing ventricular wall-motion abnormalities might restore normal metabolism and function. He was the first to introduce the term hibernating myocardium [9], referring to ischemic myocardium in which the myocytes remain viable but in which contraction is chronically depressed.

It is interesting to recall that while the concept of stunning was first derived from experimental models, the concept of hibernation derives from clinical studies documenting that persistent left ventricular wall-motion abnormalities in patients with chronic angina were reversed to normal by successful coronary artery bypass surgery [11-21] or angioplasty [22,23].

**Determinants of Hibernating Myocardium**

Currently very little is known regarding the molecular mechanisms of the hibernating myocardium, basically because of the difficulty in reliably reproducing in animal models persistent low-flow ischemia. Two independent laboratories have partially succeeded in such an attempt using either dogs [24] or pigs [25] subjected to a partial but prolonged reduction in coronary artery diameter. They showed that myocardial contractile function declines with the onset of ischemia to eventually reach a steady state in which myocard-