Hibernating Myocardium
New Answers, Still More Questions!

Gerd Heusch, Rainer Schulz

In the early 1980s, Rahimtoola reviewed the results of coronary bypass surgery trials and identified patients with coronary artery disease and chronic left ventricular dysfunction that improved upon revascularization. He proposed the concept of hibernating myocardium as “prolonged ischemia... in which myocardial metabolism and ventricular function are reduced to match the reduced blood supply... a new equilibrium... whereby necrosis is prevented, and the myocardium is capable of returning to normal or near-normal function on restoration of an adequate blood supply.” This clinically based concept quickly found its experimental counterpart in a number of studies that characterized acute and subacute ischemia by proportionate reductions in blood supply and contractile function, i.e., perfusion-contraction matching. Also, the recovery of initially disturbed substrate and energy metabolism during ongoing ischemia supported the notion that downregulation of contractile function permitted the myocardium to recover its metabolism and sustain its viability.

Emerging Controversies: Reduced Versus Normal Baseline Flow; Short-Term Versus Chronic Hibernation

Vanoverschelde et al. using PET in patients with collateral-dependent myocardium found a significant 19% reduction in blood flow in dysfunctional versus remote reference regions; because this degree of flow reduction was modest in relation to the severity of dysfunction, they reasoned that this was a situation of cumulative stunning with normal flow rather than hibernation with reduced resting flow. The majority of PET studies in patients with chronic hibernation report reduced resting flow; the amount of blood flow reduction is only modest (20% to 30%) as compared to the severity of dysfunction. However, in these PET studies, transmural resolution was lacking and more severe subendocardial ischemia could not be ruled out, and it is subendocardial blood flow that determines transmural wall function. Nevertheless, others found no reduction in resting blood flow at all in patients with chronic hibernation, and in pigs with an ameroïd coronary constrictor there was no significant reduction in blood flow at the time of maximum reduction of systolic wall thickening. Collectively, these authors dismissed the concept of chronic hibernation as adaptation to a persistent reduction in baseline blood flow, emphasized the idea of cumulative stunning as the underlying mechanism and criticized the available studies on short-term hibernation for their insufficient observation period. In fact, a subsequent study confirmed that in a pig model of subacute ischemia, perfusion/contraction matching and viability were maintained for 90 minutes but progressively lost when ischemia was extended to 12 or 24 hours.

Canty and Fallovolita reconciled these, at the time, heated controversies on reduced versus normal baseline blood flow. Using a model in which a fixed stenosis is implanted in juvenile pigs and becomes progressively flow-limiting when they grow, they reported normal resting blood flow but reduced function 1 to 2 months after stenosis placement, consistent with cumulative stunning, and both decreased blood flow and function 3 to 4 months after stenosis placement, consistent with hibernation. Thus, there appeared to be a temporal progression from stunning with perfusion/contraction mismatch to hibernation with perfusion/contraction match. A limitation of these elegant studies was, however, that although episodes of stunning were observed they were neither systematically monitored nor systematically induced. Also, it was unclear whether the observations in juvenile hearts with their presumably greater plasticity were also true for adult hearts.

Rapid Progression From Perfusion-Contraction Mismatch to Match in the Adult Heart

The present study by Thomas et al. in this issue of Circulation Research corroborates the earlier findings and extends them to adult hearts. The fact that 15-minute partial coronary occlusion and reperfusion through a critical stenosis resulted in matched decreases in flow and function already after 1 week minimizes the vocal concerns that lack of chronicity was a major shortcoming of the studies on short-term hibernation and points to mechanistic differences.

There were also signs of myolysis and increased glycogen content, similar to those observed in human hibernating myocardium, however, not restricted to the dysfunctional area. Finally, the dysfunctional myocardium had reduced sarcoplasmic reticulum (SR) ATPase and phospholamban protein levels. Along with earlier findings of reduced calcium responsiveness in short-term hibernation these alterations in calcium-handling proteins point to altered excitation-
contraction coupling as a potential underlying mechanism of the observed dysfunction.

**Remaining Questions**

**Morphology**

The modest morphological alterations in the present study contrast to reports of much more severe degenerative changes and alterations in connective tissue in human hibernating myocardium. The fact that myolysis equally affects the dysfunctional and remote myocardium is disconcerting and makes intraindividual control samples for future studies on human hibernating myocardium mandatory. However, more disturbingly, because it does not at all affect contractile function in the normoperfused myocardium, what is the meaning of myolysis in this setting?

**SR Proteins**

The reduced SERCA and phospholamban protein levels are advocated as almost pathognomonic for hibernating myocardium. Although this is possibly true, a progression from reduced SERCA and phospholamban mRNA levels at 24 hours to reduced protein levels at 2 weeks in the absence of a critical stenosis and with full recovery of function is also possible and not excluded by respective controls. Finally, are reduced SR proteins the cause or consequence of reduced function?

**Mandatory Reperfusion**

It is a strength of the present study that stunning was induced systematically and then after reperfusion through a critical stenosis followed until hibernation developed. The single animal in the online data supplement that was followed for 1 week with a critical stenosis but without induced stunning would suggest that chronic dysfunction also develops without the initial period of stunning; however, resting flow remained normal in this animal. Because there was no continuous monitoring of flow and function, we do not know how many spontaneous episodes of ischemia/reperfusion and subsequent stunning this animal may have experienced. Although technically demanding, continuous monitoring will be needed to decide whether stunning is mandatory for hibernation to develop.

**Stimulus and Signal Transduction**

All experimental and clinical studies agree that a critical stenosis that limits coronary reserve is a mandatory prerequisite. As long as baseline flow is not reduced, the only stimulus that the myocardium might sense is reduced perfusion pressure. Otherwise the limitation of coronary reserve is a hypothetical condition that becomes real only when an increase in blood flow would be needed. This emphasizes once more the need for continuous monitoring of spontaneous episodes of ischemia/reperfusion. Even then, is ischemia per se the stimulus or ischemia with subsequent stunning? This could be tested by controlled multiple episodes of ischemia of too short duration each as to induce stunning. Finally, why do both flow and function in hibernation fall below levels that the remaining dilator reserve would permit. Are there also alterations in function and/or phenotype of the coronary circulation?

We know little about the signal transduction of hibernating myocardium to develop. All previous studies were confined to models of short-term hibernation and, driven by potential analogy to ischemic preconditioning, turned out negative for adenosine, 

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\text{K}_{\text{ATP}}$ -channels, opioids, and NO. Recent studies in human hibernating myocardium suggest that inflammatory processes, including TNF-$\alpha$ and iNOS, may be involved. These findings are remarkably reminiscent of what is seen in an experimental model of coronary microembolization where progressive contractile dysfunction is induced through an inflammatory signal cascade. Are showers of microemboli originating from epicardial atherosclerotic plaques in humans or chronic stenoses in animals responsible for the hibernation phenotype?

The attraction of hibernating myocardium roots in its potential exploitation as an adaptation to ischemia/reperfusion. In the context of adaptation, collateral growth must not be forgotten. A 150% increase in collateral blood flow in the present study may not be statistically significant for a variety of reasons, but nevertheless be of great functional importance. Many more questions must be answered before exploitation of the hibernation paradigm is possible.

**References**


**KEY WORDS:** hibernating myocardium myocardial ischemia stunning coronary stenosis coronary reserve
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