Hibernating Myocardium
Is the Program to Survive a Pathway to Failure?
Rosemary F. Kelly, Wim Sluiter, Edward O. McFalls

Winter hibernation carries the promise of rejuvenation in the spring. In a similar fashion, myocardial “hibernation” describes a clinical phenomenon in which patients with ischemic left ventricular dysfunction demonstrate improved cardiac function following bypass surgery.1 The signature of myocardial hibernation is decreased blood flow with preserved glucose uptake, as demonstrated by positron emission tomography imaging, and identifies individuals with ischemic cardiomyopathy who may benefit from revascularization.2 In experimental models of hibernating myocardium, oxygen consumption is reduced in the absence of active ischemia.3,4 This implies that hibernation is a coordinated response to balance myocardial energy utilization with energy production capacity.5 However, within hibernating myocardium, several morphological and functional changes have been observed that can identify regions in which complete revascularization may not result in normalization of contraction.6–10 In fact, those myocardial regions with the greatest metabolic abnormalities in the hibernating tissue demonstrate the longest delay in recovery.11

In the current issue, Page et al12 demonstrate that the process of hibernation is associated with altered expression of mitochondrial proteins. Using 2D differential-in-gel electrophoresis and matrix-assisted laser desorption ionization time-of-flight mass spectrometry in a swine model of hibernation, they have found that key mitochondrial proteins associated with the electron transport chain are reduced. The functional importance of the decreased protein expression is documented by reduced activity measurements of the pyruvate dehydrogenase complex, cytochrome c oxidase, and citrate synthase. The parallel reductions in mitochondrial proteins and contractile function 5 months after placement of the coronary artery constrictor suggest that the “downregulation” of electron transport proteins is related to the reduced oxygen consumption. In fact, the reductions in ATPase correlate with the reduction in subendocardial blood flows in the hibernating myocardium. In addition, “upregulation” of several cytosolic proteins has been observed, including the antioxidant enzyme superoxide dismutase 1, highlighting a potential role for repetitive ischemia–reoxygenation in the stress response. Interestingly, the temporal increase in the antioxidant proteins coincides with the time that apoptosis is diminished in this model.13 A logical hypothesis is that superoxide production stimulates a stress response, including superoxide dismutase 1 expression, which, in turn, reduces subsequent reactive oxygen species (ROS) production and thus promotes a survival pathway within the mitochondria.14 Although the findings are novel, a causal relationship between the observed decreased expression of mitochondrial proteins and persistent reductions in oxygen consumption and contractile function remains speculative. Clearly, more studies are needed to identify whether interventions that restore blood flow to the hibernating tissue will reprogram mitochondria to a normal expression of key proteins.

Mitochondrial Adaptations to Brief Myocardial Ischemia (Preconditioning)
It is well recognized that the heart can favorably adapt to sustained reductions in oxygen availability. Since the seminal observation of ischemic myocardial preconditioning in the anesthetized canine model,15 evidence has emerged that the mitochondria can be primed into a “stress-resistant state,” so that cell death is reduced following a subsequent period of ischemia and reperfusion.16 Although the signal transduction pathway is complex, mitochondria within preconditioned myocardium are altered so that the release of cytochrome c and proapoptotic factors and generation of ROS following ischemia are reduced.17 It has been proposed that the preconditioned mitochondrial phenotype is characterized by slight depolarization of the inner membrane of the mitochondria.18,19 As a consequence of this decrease in the membrane potential (ΔΨm), decreased ROS production is expected.20 One potential mechanism of depolarization of the inner membrane is a proton leak, from activation of adenine nucleotide translocation, the permeability transition pore, or uncoupling proteins.22 Uncoupling proteins are expressed and activated by superoxide23 (a potential feedback loop) and, along with their relationship with fatty acids,24 lead to a proton leak through the inner membrane into the matrix. Activation of these uncoupling proteins reduce ROS generation25 and exert a protective effect against oxidant damage during the second window of preconditioning.26

Although the mechanisms that lead to myocardial hibernation are unclear, it is likely that ischemic preconditioning and hibernation share common signaling pathways that modify the severity of an energy supply/demand imbalance associated with limited blood flow. In a swine model of chronic hibernation, we have observed increased activation of p38...
Mitochondrial Adaptations to Chronic Myocardial Ischemia

In response to chronic reductions in blood flow that result in myocardial hibernation, Page et al.\(^{12}\) have found a reduction in proteins that contribute NADH equivalents to complex I, which would be expected to slow electron flow and reduce the generation of ROS during or following ischemia (Figure).\(^{20}\) They also show decreased expression of cytochrome \(bc_1\), which would have a similar effect on complex III–generated ROS, which are released toward the outer membrane. In this protected state of hibernation, isolated mitochondria demonstrate reduced superoxide generation, likely in part, because of increased expression of uncoupling proteins. The observations of Page et al.\(^{12}\) provide additional evidence that mitochondria in hibernating tissue adapt in a way that reduces ROS production. A fundamental question is whether the mitochondria have acquired a program to reduce electron transport at the expense of limiting maximal oxygen consumption and possibly contraction.

Mitochondrial proteins limits the maximal rate of oxygen expenditure available for contraction in hibernating myocardium. Altered proteins in hibernating myocardium are listed in gray, with red borders for decreased and blue borders for increased expression. The arrows with dotted lines indicate adaptations that would result in reduced oxidant damage. SOD1 indicates superoxide dismutase 1.

Hypothetical scheme that illustrates how altered mitochondrial proteins in the electron transport chain may alter electron transport and reduce ROS generation in hibernating myocardium. Within the hibernating tissue, key enzymes that contribute NADH equivalents into complex I, as well as proteins directly related to subunits of the electron transport chain, are decreased, including cytochrome \(bc_1\) (complex III) and cytochrome c oxidase (complex IV). The overall effect may be to decrease the generation of superoxide (\(O_2^-\)) by decreasing the reduced state of the respiratory chain complexes. Decreasing complex V activity would also have an effect of preventing its ATPase activity elicited by the diminished membrane potential (\(\Delta\psi_m\)). Together with increased expression and activation of uncoupling proteins (UCP), these effects could lead to slight depolarization in \(\Delta\psi_m\) and reduced superoxide generation. It is unclear whether these mitochondrial adaptations occur in response to oxidant damage induced by repetitive supply/demand ischemia and, more importantly, whether the “downregulation” in mitochondrial pro-

mitogen-activated protein kinase, enhanced GLUT4 translocation, and increased calcium-independent NO synthase activity,\(^{27}\) all of which have been observed in preconditioning. As demonstrated in preconditioned mitochondria, isolated mitochondria from hibernating tissue have acquired a stress-resistant phenotype that is characterized by preserved state 3 respiration following in vitro anoxia and reoxygenation.\(^{28}\) In this protected state of hibernation, isolated mitochondria demonstrate reduced superoxide generation, likely in part, because of increased expression of uncoupling proteins. The observations of Page et al.\(^{12}\) provide additional evidence that mitochondria in hibernating tissue adapt in a way that reduces ROS production. A fundamental question is whether the mitochondria have acquired a program to reduce electron transport at the expense of limiting maximal oxygen consumption and possibly contraction.

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A reduction in the capacity to produce energy to the contractile apparatus may exacerbate the depressed contractile function in hibernating myocardial tissue. A major unresolved question in cardiovascular physiology is which factors in the cascade of ATP production, transport, and utilization control the maximal performance of a normal heart or contribute to the dysfunction of a failing heart. The relationships between steady-state myocardial concentrations of ATP, ADP, free inorganic phosphate, creatine (Cr), and phosphocreatine (PCr) and the mitochondrial ATP production capacity also remain unclear, in part, because, in the normal heart, the in vivo maximal ATP synthetic capacity likely exceeds maximal ATP expenditure, as estimated by measurements of myocardial oxygen consumption. In patients with congestive heart failure, the PCr/ATP ratio, as determined by 31P-NMR spectroscopy, predicts the severity of left ventricular dysfunction and the risk of sudden death.\(^{31,32}\) Our swine model of hibernation with reduced blood flow and function indicates that the PCr/ATP ratio derived by 31P-NMR spectroscopy is normal at rest and remains normal during a 2-fold increase in the double product induced by an infusion of dobutamine, even in the presence of ATP-dependent potassium channel (\(K_{ATP}\)) blockade with glibenclamide.\(^{33}\) The finding of a normal PCr/ATP ratio during basal conditions and especially during a high cardiac work state supports the concept that the reduction in the blood flow in hibernating myocardial tissue is proportional to a reduction in energetic demands\(^5\) and that this occurs by a mechanism that is independent of \(K_{ATP}\) channel opening.\(^{34}\)
Clinical Perspective
In many individuals with ischemic cardiomyopathy, progressive heart failure may persist, despite successful revascularization. Several morphological and structural changes have been identified that may limit contraction within hibernating myocardium.

It is also possible that alterations in the mitochondria that are initially programmed to reduce oxidant damage and prevent cell death in response to repetitive supply/demand ischemia, could act to limit maximal ATP production. Defining the factors that lead to this coordinated process to balance oxygen supply and expenditure, whether through mitochondrial adaptations or other signaling pathways, is critical for understanding the pathophysiology and advancing new therapies for hibernating myocardium and heart failure.

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None.

References

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