The term hibernating myocardium was first proposed by S. Rahimtoola in 1985 to describe a state of left ventricular dysfunction at rest caused by reduced coronary blood flow, which can be reversed by restoring myocardial oxygen supply or reducing myocardial oxygen demand. The clinical context in which it was first recognized, viz, impaired left ventricular function at rest that recovers after revascularization, was refined further when it was recognized that "fixed" defects on [201 Tl] perfusion images could improve after revascularization or with redistribution or reinfarction. To date, the molecular mechanisms underlying myocardial hibernation have remained elusive.

Hibernation defines one form of pathophysiological response to myocardial ischemia, the two being stunning and ischemic preconditioning. Myocardial stunning is defined as ventricular dysfunction that recovers gradually after a brief period of severe ischemia, and ischemic preconditioning is defined as the ability of the myocardium to tolerate an acute ischemic episode with limited ventricular dysfunction as a result of prior brief episodes of ischemia. As one might imagine, these three myocardial responses to ischemia are not mutually exclusive of one another: For example, repetitive stunning superimposed on reduced basal blood flow may contribute to the development of hibernation, and repetitive stunning likely promotes ischemic preconditioning.

Hibernation is currently viewed not as a simple consequence of an oxygen deficit, but as an adaptive response to maintain cardiomyocyte viability in the setting of reduced blood flow. Characterization of the physiology of hibernation shows that perfusion and contractile function seem to be matched, and that myocardial substrate utilization and energy metabolism tend to recover over hours despite active ischemia. Reduced calcium responsiveness and alterations in adrenergic receptor density have been proposed as mechanisms for the decreased contractility. Characteristic ultrastructural changes occur in hibernating human myocardium, including loss of myofibrils, either through degeneration or dedifferentiation of cardiomyocytes, with a loss of mitochondria and increased storage of glycogen. Although myocardial necrosis essentially is absent, cell loss may occur through programmed cell death, or apoptosis.

In the present issue of Circulation, Kalra and colleagues provide evidence that tumor necrosis factor-α (TNF-α) and inducible nitric oxide synthase (iNOS) play a role in mediating myocardial hibernation. In patients undergoing coronary artery bypass surgery, they obtained transmural left ventricular biopsies from dysfunctional or normal myocardial segments as assessed by preoperative dobutamine echocardiography. They extracted the mRNA from these segments and performed reverse transcriptase–polymerase chain reaction using primers for TNF-α and iNOS, and they found dramatic increases in the expression of both of these inducible gene products in dysfunctional segments compared with normal segments. The highest levels of expression of both TNF-α and iNOS were observed in myocardial segments without evidence of contractile reserve as assessed by preoperative dobutamine stress imaging, as well as absence of functional improvement by 3 months after revascularization. Hibernating segments showed levels of expression intermediate to those with normal resting function and those without contractile reserve. There was also a significant correlation between changes in ventricular function 3 months postoperatively and changes in serum TNF-α or nitrite levels, suggesting that the changes in gene expression in myocardial tissue contribute mechanistically to physiological phenotype.

These observations support the notion that TNF-α and iNOS cause dose-dependent changes in myocardial dysfunction, with moderate increases leading to reversible myocardial dysfunction, and greater increases contributing to irreversible injury. The negative inotropic effects of TNF-α and the role of iNOS-derived nitric oxide in the control of cardiac function have been well characterized both in vitro and in vivo. TNF-α depresses myocardial contractility by two mechanisms: Within minutes, it causes acute contractile dysfunction by decreasing calcium transients through a sphingosine signaling intermediate; within hours, it induces iNOS gene expression, which increases nitric oxide production, leading to sustained contractile dysfunction. iNOS generates nitric oxide at high flux rates, leading to concentrations in the steady state that are 100- to 1000-fold greater than those produced by endothelial or neuronal NOS. These concentrations of nitric oxide act through a cyclic GMP–dependent mechanism to attenuate the cyclic AMP–dependent increase in contractility with β-adrenergic receptor stimulation.
Perhaps more intriguing is the notion that the moderate increases in TNF-α and iNOS in the hibernating myocardium are a requisite part of the adaptive response necessary to maintain myocardial viability in the face of chronically reduced blood flow. Cardiomyocytes increase expression of TNF-α and iNOS after exposure to ischemia-reperfusion and oxidant stress.18–20 TNF-α stimulation has dual effects on mitochondrial function and metabolism via both nitric oxide and the lipid second messenger ceramide. Nitric oxide reversibly decreases mitochondrial respiration by uncoupling oxidative phosphorylation,20 shifts energy substrate utilization from fatty acids to lactate,21 and in the ischemic heart preserves calcium sensitivity and contractile function without an added energy cost.22 Similarly, ceramide also can alter mitochondrial function directly and decrease oxidative phosphorylation.23 Although ceramide can additionally cause release of cytochrome c and activation of apoptotic proteases, this action may be counterbalanced by the inhibitory effect of nitric oxide on these cascades, thereby leading to a form of reversible cell injury, or apoptosis interuptus,24 as observed in hibernating myocardium.

TNF-α is a potent stimulus for the expression and activity of the antioxidant mitochondrial enzyme manganese superoxide dismutase (MnSOD), which may play a role in protecting the hibernating myocardium from injury. Through increased mitochondrial formation of reactive oxygen species, MnSOD is upregulated,25 an effect that has been implicated in the delayed preconditioning that occurs after brief ischemia.26 An increase in MnSOD activity presumably would be critical for maintaining low levels of superoxide anion, thereby maintaining the bioavailability of nitric oxide by preventing formation of cytotoxic peroxynitrite.27 In this context, it would be interesting to examine the levels of expression and activity of MnSOD and other antioxidant enzymes in the hibernating myocardium.

There is, however, a “dark side” to these local adaptive changes that can promote the development of irreversible myocardial dysfunction. For example, when TNF-α is administered systemically to a rat, there is a sustained decrease in ventricular function and ventricular dilation. Discontinuing the TNF-α treatment after 14 days leads to contractile function recovery; however, ventricular dilation persists.28 More prolonged myocardial exposure to higher levels of TNF-α through transgenic overexpression leads to more severe myocardial injury and dysfunction with changes in myocardial collagen deposition.29 TNF-α may promote scar formation through alterations in interstitial matrix turnover in ischemic myocardium via a transforming growth factor (TGF)-β–dependent mechanism. Recent data suggest that collagen deposition is increased in hibernating myocardium through this mechanism, but to a lesser extent than in irreversibly dysfunctional myocardium.30

Although TNF-α and nitric oxide have cytoprotective effects in some contexts, as discussed above, they also can induce myocyte death. Both TNF-α and nitric oxide can promote cardiomyocyte apoptosis: the former by activating the TNF type 1 receptor and the Fas receptor18; the latter by several mechanisms, including the direct production of DNA damage, increases in expression of the tumor suppressor p53, generation of ceramide, selective (ie, cell type–specific) kinase activation, and induction of mitochondrial dysfunction.31 Although TNF-α overexpression alone is sufficient to lead to myocardial injury and increase myocyte apoptosis,29 robust overexpression of iNOS is not.32 This difference in the action of these effectors suggests that the cytotoxicity of iNOS occurs in the context of other stresses—for example, ongoing myocardial ischemia. The ability of iNOS to generate superoxide anion33 (ie, enzyme “uncoupling”) and thereby increase cellular oxidative stress under conditions of limited L-arginine or cofactor availability (as might occur in severe ischemia) may also play a role in the cytotoxic effects of iNOS.

Taken together, these data suggest that the molecular underpinnings of hibernating myocardium are part of a spectrum of responses to chronic ischemia involving similar effectors. Hibernation stands at one end of the spectrum and irreversible injury at the other. The expression of a specific phenotype at any given time is governed by the magnitude of induction of effectors and their resulting local concentration; the duration of enhanced expression; the presence of pre-existing protective adaptations (eg, ischemic preconditioning, collateral vessel formation); and the presence of pre-existing adverse factors (eg, increased wall stress). It is likely that this spectrum is manifest within a given individual as a continuum, with microenvironments of the chronically ischemic heart containing hibernating cardiomyocytes adjacent to microenvironments containing irreversibly injured cardiomyocytes with extensive apoptosis, necrosis, and scar formation. The question of whether or not exceeding a threshold level of TNF-α or iNOS, or expression of one or more as yet unidentified additional factor(s), is sufficient or necessary for the conversion from reversible to irreversible dysfunction remains unanswered. In addition, the therapeutic implications of these observations are unclear, particularly given that TNF-α and iNOS expression accompanies both hibernation and irreversible injury.

Like an anesthetic, these endogenous agents that induce hibernation have a narrow toxic-therapeutic window. Exceeding the therapeutic threshold converts the reversible sleep of hibernation into irreversible injury and cell death. What precisely governs this conversion and what effectors may be used to modulate it are important questions that need to be addressed in future studies.

References


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