Myocardial hibernation

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Patients with chronic coronary artery disease frequently have contractile dysfunction that recovers upon reperfusion. The concept of myocardial hibernation views the observed reduction in contractile function not as the result of an ongoing energetic deficit, but as an adaptive down-regulation that serves to maintain myocardial integrity and viability. In the experiment, perfusion-contraction matching during the initial hours of ischemia, recovery of energy and substrate metabolism during ongoing ischemia, the potential for recruitment of inotropic reserve, lack of necrosis, and therefore recovery of function upon reperfusion are established features of hibernation. Apart from reduced calcium responsiveness, the underlying mechanisms are still unclear. In patients, the importance of reduced baseline blood flow vs that of superimposed repetitive stunning is somewhat controversial; however, in most studies blood flow is reduced, and the myocardium must be ischemic often enough to have persistent dysfunction. Morphologically, hibernating myocardium displays features of dedifferentiation, with loss of cardiomyocytes and myofibrils, and of degeneration, with increased interstitial fibrosis. Patients with hibernating myocardium must be identified and undergo revascularization. With a better understanding of the underlying mechanisms of hibernation, these adaptive responses to ischemia can potentially be recruited and reinforced pharmacologically to delay impending myocardial infarction.

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The concept of myocardial hibernation

By reviewing the results of coronary bypass surgery trials, patients with coronary artery disease and chronic left ventricular dysfunction were identified who benefited from revascularization. Rahimtoola[1,2] proposed that the observed dysfunction was not the result of an ongoing energetic deficit, but an adaptive down-regulation of contractile function to preserve myocardial integrity and viability. Shortly thereafter, the concept of myocardial hibernation was further popularized by Braunwald and Rutherford[3] who emphasized the need for its recognition and therapy through revascularization. The primarily clinical concept of myocardial hibernation subsequently merged with experimental observations. In chronically instrumented conscious dogs, regional myocardial function and blood flow were reduced proportionately during ischemia[4,5], i.e. there was no imbalance between demand/function and supply/flow as previously assumed, but a state of perfusion-contraction matching[6] that could be sustained for 5 hours of coronary stenosis without development of necrosis and with eventual full recovery of function upon reperfusion[7]. In anesthetized pigs with regional ischemia, metabolic parameters such as myocardial lactate consumption[8] and creatine phosphate content[9] recovered towards their pre-ischemic baseline values during ongoing ischemia, consistent with the idea that the reduced function was an adaptation to reduced blood flow which, in fact, permitted the recovery of the initially perturbed metabolic balance[10]. Further experimental studies documented the persistence of an inotropic reserve in hibernating myocardium[11], and this primarily experimental finding prompted again clinical studies using stress echocardiography to demonstrate viability of dysfunctional myocardium in patients with coronary artery disease[12].

Blood flow in myocardial hibernation: persistent ischemia or cumulative stunning, or both?

Experimental studies with controlled coronary hypoperfusion identified features consistent with myocardial hibernation, i.e. perfusion-contraction matching, recovery of myocardial substrate and energy metabolism during ongoing ischemia, persistent inotropic reserve, and lack of necrosis[12]. Bolli[13] was the first to propose that the phenotype of hibernating myocardium, i.e.

chronic, yet reversible contractile dysfunction in the setting of coronary artery disease, could also arise from repetitive/cumulative stunning with or without an underlying reduction of baseline blood flow. This idea was quickly picked up by other investigators. When challenging the idea of reduced baseline blood flow in hibernating myocardium Vanoverschelde et al.[14] nevertheless found significantly reduced flow in patients with collateral-dependent dysfunctional myocardium using positron emission tomography (PET) of $^{13}NH_3$, but the severity of dysfunction appeared indeed out of proportion compared to that of flow reduction. In fact, the vast majority of PET studies in patients using different flow tracers almost invariably shows a 20-30% reduction of baseline blood flow in hibernating myocardium[12]. Apart from one study that reported almost normal subendocardial baseline flow and anecdotal episodes of stunning in pigs with chronic coronary stenosis[15], most animal studies with chronic coronary stenosis also found reduced resting blood flow in the dysfunctional myocardium[12,16].

In our view, the mechanistic distinction of reduced baseline blood flow from repetitive stunning as alternative and contrasting mechanisms of hibernation is artificial when based on single point measurements and distracts from the concept of myocardial hibernation. As originally proposed by Bolli[13], many patients with coronary artery disease will have both, reduced baseline flow and superimposed repetitive episodes of stress-induced ischemia with subsequent stunning in their daily life. Indeed, within an individual heart[17] the entities (hibernation, stunning) might coexist in patients with chronic coronary artery disease, i.e. some (32-50%) but not all areas with contractile dysfunction display reduced myocardial blood flow, and the same has recently been seen in chronically instrumented dogs[18].

Also, even with controlled coronary hypoperfusion for 12-24 hours in anesthetized pigs, contractile function deviates with time from the initial perfusion-contraction matching such that function continues to decline, and apparently factors other than the initial adaptation to reduced blood flow act to further reduce function; however, the close matching of myocardial function and oxygen consumption is maintained[19], still supporting the idea of an adaptive response to ischemia.

Morphology of hibernating myocardium

In biopsies from human hibernating myocardium, the loss of contractile function is associated with loss of cardiomyocytes and myofilaments, loss of sarcoplasmic reticulum and disorganization of the cytoskeleton. The interstitium contains cellular debris, increased numbers of macrophages and fibroblasts and increased collagen[20,21]. Recently, apoptosis was also detected in human hibernating myocardium[22], and confirmed in pigs with chronic coronary stenosis[23].

Whereas Borgers and Ausma[20] emphasized the dedifferentiated phenotype of human hibernating myocardium and proposed contractile unloading as the underlying mechanism, Elsässer and Schaper[21] emphasized more its degenerative nature with more severe cardiomyocyte alterations and increased fibrosis. The extent of fibrosis appears to be the major determinant of postoperative functional recovery after revascularization[22,24].

Mechanism(s) of myocardial hibernation

The mechanism(s) responsible for the development of myocardial hibernation, in particular the biochemical signal that rapidly reduces contractile function in proportion to reduced blood flow, are largely unclear. Alterations in β-adrenoceptor density and affinity[25], adenosine[26], activation of ATP-dependent K-channels[26] and opioids[27] have been excluded. Calcium responsiveness in experimental myocardial hibernation is reduced, and this reduction is not related to decreased calcium sensitivity, but to decreased maximal calcium-activated force[28]. The expression of calcium regulatory proteins is not altered during 90 min experimental short-term hibernation[29], but such alterations may contribute to contractile dysfunction over longer periods of time. Endogenous nitric oxide is not involved in the immediate down-regulation of contractile function, but acts to preserve calcium sensitivity during ongoing ischemia and to improve contractile function for any given blood flow, without any additional impact on myocardial energetic state[30]. Mechanistic studies are clearly the domain of more reductionist experimental approaches, and – given the lack of information here – it is not surprising that there are no clinical mechanistic studies so far.

Conclusions and perspectives

The existence and importance of hibernating myocardium is beyond doubt. Clearly, chronically dysfunctional myocardium in patients with coronary artery disease is frequently viable, amenable to reperfusion/revascularization, and its reperfusion is associated with improved prognosis. Most experimental and clinical studies are consistent with the original idea that myocardial hibernation is an adaptive response to ischemia. The issue of reduced baseline blood flow is still controversial, although the vast majority of clinical and experimental studies found reduced baseline flow, and the myocardium is clearly ischemic at some point in time (otherwise it could not be cumulatively stunned). Therefore, this controversy is, in our view, fruitless. Also, the issue of dedifferentiation vs degeneration is unresolved, but this distinction may be more semantic with respect to functional recovery and pa-

tients' prognosis and is not based on truly different pathogenesis. Regardless of whether or not hibernating myocardium has reduced baseline blood flow, and regardless of whether its morphology appears more dedifferentiated or degenerative, it will benefit from reperfusion, as will the patients' prognosis.

Conceptually, the process of hibernation appears to involve an initial biochemical signal that rapidly induces contractile quiescence and energetic recovery[12,31], possibly followed by altered gene and protein expression and finally altered morphology, including apoptosis, to cope with reduced myocardial blood flow and maintain myocardial viability in the affected region. Unless there is a better understanding of the underlying mechanism(s), this endogenous adaptive response to ischemia cannot be recruited and exploited pharmacologically; however, this is ultimately an attractive goal.

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