Editorial

Cellular models of hibernating myocardium: implications for future research

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See article by Dispersyn et al. [1] (pages 230–240) in this issue.

1. Introduction

In the current issue of Cardiovascular Research, Dispersyn and colleagues [1] describe a novel in vitro model of cardiomyocyte de-differentiation similar to that seen in hibernating myocardium. By co-culturing adult rabbit cardiomyocytes with cardiac fibroblasts, ultrastructural changes including sarcomere depletion and disalignment, appearance of aberrantly shaped mini-mitochondria, and progressive dispersion of nuclear heterochromatin were seen within the cardiomyocytes beginning several days after their establishment of cell–cell apposition with fibroblasts. These ultrastructural findings are nearly identical to those seen in both large animals [2] and humans [3] with hibernating myocardium with the one exception being that the cultured cells did not demonstrate a significant increase in glycogen content within the regions of sarcomere loss, a change typically considered among the hallmarks of hibernating myocardium [4]. In addition to the ultrastructural alterations, Dispersyn and colleagues also demonstrated changes in the pattern of expression of the structural proteins titin, desmin, cardiotin, α-actinin, and α-smooth muscle actin characteristic of de-differentiation and similar to that described previously in myocardial tissue from patients with chronic hibernating myocardium [4]. As outlined below, this and other in vitro cellular models may prove helpful in identifying those mechanisms involved in the development and progression of the hibernating phenotype as well as therapeutic strategies aimed at halting the progression and speeding reversal following revascularization.

2. Development of the hibernating phenotype

Consensus exists that myocardial hibernation describes chronic, reversible left ventricular dysfunction at rest due to coronary artery disease [4,5]. However, intense controversy surrounds the underlying pathophysiology of the condition, as has been well-publicized in several recent reviews [6–8]. As originally described [9], hibernating myocardium was felt to result from a chronic reduction in myocardial blood flow at rest to the dysfunctional yet viable regions with the affected segments down-regulating their function to match perfusion deficits (perfusion–contraction matching [10]). This “smart heart” hypothesis [5] was subsequently challenged when chronic experimental studies were unable to reproduce the apparent human condition in an animal model [11,12]. As a result, the mechanism of hibernation was attributed to repetitive episodes of stunning where myocardial blood flow to the hibernating segments was felt to be normal or near-normal at rest but coronary flow reserve impaired. As such, the regions became ischemic during periods of stress and the persistent left ventricular dysfunction observed at rest was attributed to prolonged post-ischemic dysfunction [4,7,8]. However, recent studies from several independent laboratories [2,13–15] have conclusively demonstrated that chronic low-flow myocardial hibernation is a real phenomenon. For example, Fallavollita et al. [13] instrumented swine with high-grade proximal left anterior descending (LAD) coronary artery stenoses and found significant reductions in resting myocardial blood flow in the hibernating regions 3 to 4 months after instrumentation. The reduced resting myocardial perfusion was of a magnitude similar to that seen in humans with hibernating myocardium [6]. Chronic low-flow hibernation has been documented to persist for up to 6 months in swine with an experimental high-grade coronary stenosis [16].

To date it remains unsettled as to whether these regions of low-flow perfusion–contraction match can result from
an intrinsic ability of the heart to spontaneously downgrade its contractile function and energy requirements in the face of a sustained reduction in myocardial blood flow or whether antecedent repetitive stunning is necessary with the chronic reductions in flow being a consequence rather than a cause of the observed contractile dysfunction [7,8]. Fallavollita and Canty [17] examined animals at earlier time points (1 to 2 months after instrumentation) using their LAD stenosis model and found resting perfusion to be normal despite regional left ventricular dysfunction, a picture consistent with chronic stunning. Based on their earlier work demonstrating hypoperfusion in the dysfunctional regions 3 to 4 months after stenosis creation, they suggested a temporal progression of physiological adaptation in viable, chronically dysfunctional myocardium with a transition from chronic stunning to low-flow hibernation over time. This hypothesis is supported by work by Firoozan and colleagues [14], who prospectively demonstrated that decrements in regional wall thickening preceded reductions in resting myocardial blood flow in dogs with multi-vessel ameroid constrictor placement who eventually developed significant and proportionate decreases in regional myocardial flow and function.

Nevertheless, the possibility that low-flow hibernation can develop without antecedent stunning has not yet been disproven. For example, in the studies of both Fallavollita [13,17] and Firoozan [14], the degree of coronary stenosis was gradually progressive such that initially the stenosis was not severe enough to produce a significant reduction in flow at rest but over time the narrowing progressed to where it became continuously flow-limiting. This may not represent the clinical situation where the process of atherogenesis leading to coronary stenosis is neither linear nor predictable. For example, new high-grade lesions often appear in segments of an artery which were previously normal only months earlier and up to two-thirds of patients with acute coronary syndromes may have rapid progression from mild coronary lesions to severe stenosis [18]. Indeed, St. Louis et al. [2] have demonstrated chronic low-flow hibernation using PET and dobutamine echocardiography as early as 3 days after the production of a high-grade coronary stenosis in swine, suggesting that a transition from chronic stunning may not always be necessary.

Cellular models of hibernating myocardium will likely prove helpful in better elucidating the underlying pathophysiology of the condition. The present study by Dispersyn and colleagues [1] suggests that reduced oxygen availability is not a prerequisite to the development of many of the structural changes seen in chronic hibernating myocardium, as the phenotypic alterations were seen despite normal oxygen tension. However, the findings also indirectly support clinical and experimental observations that some degree of ischemia is necessary to produce the condition, as the cultured cells did not demonstrate a significant increase in glycogen content within the regions of sarcomere loss. The glycogen deposition seen in hibernating cardiomyocytes is potentially related to the increased glucose extraction and diminished β-oxidation of nonesterified fatty acids present during periods of sublethal myocardial ischemia [19]. Casey and Arthur [20] using a different cellular preparation have recently shown that isolated noncontracting neonatal mammalian cardiomyocytes are capable of metabolic downregulation with reduced rates of oxygen consumption in response to reduced oxygen availability. These findings suggest that the metabolic downregulation associated with myocardial hibernation may not be exclusively due to reduced rates of contractile activity and also lend support to the “smart heart” concept [5] as a potential mechanism responsible for producing the hibernating phenotype.

3. Reversal of the hibernating phenotype

The morphologic characteristics of hibernating myocardium have been well-described and include structural alterations that affect both the cardiomyocytes and the extracellular matrix [2–8,21]. There is a loss of contractile material within cardiomyocytes with the space previously occupied by the myofilaments filled with glycogen. Other findings include small mitochondria scattered throughout the myolitic cytoplasm, tortuous nuclei with uniformly dispersed heterochromatin, and a virtual absence of sarcoplasmic reticulum and T tubules. Levels of the contractile protein myosin, thin filament complex, titin, and α-actinin are also reduced and the distribution of titin within the cardiomyocyte is altered. Expression of the major gap junction protein connexin-43 as well as the nuclear A-type lamins is reduced as well. Finally, changes affecting the interstitial space include increases to various degrees in the extracellular matrix, collagen, and fibronectin [8,21]. Whether these structural changes represent de-differentiation and/or degeneration is unclear at the present time [8]. What is clear, however, is that the structural changes are progressive [21,22] and patients with more advanced cardiomyocyte deterioration have less return of function after revascularization than those with less advanced changes [21–24]. Elsässer and colleagues [21] have described a self-perpetuating “vicious cycle” in hibernating myocardium where a regional inflammatory reaction in the ischemic regions leads to an upregulation of TGF-β1 and angiotensin converting enzyme (ACE), ultimately yielding progressive fibrosis and cellular degeneration. Similarly, Lai et al. [25] prospectively studied swine with an experimentally produced LAD coronary stenosis and found evidence for progressive left ventricular remodeling with increases in ventricular volume, mass, and interstitial fibrosis over a 4-week period of myocardial hibernation. These changes were partially reversible after 3 weeks of reperfusion. These authors also postulated a
mechanism whereby regional wall thinning and left ventricular cavity dilatation lead to increased wall stress and, through neural or endocrine activation, produce progressive myocyte degeneration and fibrosis if revascularization is not performed in a timely fashion [25]. Finally, Beanlands and colleagues [26] studied the effects of the timing of surgical revascularization on the recovery of left ventricular function and survival in patients with low ejection fraction and evidence of hibernation by PET and found that delayed revascularization was associated with increased preoperative mortality and a lack of improvement in left ventricular function compared to those operated on early. Consequently, the greatest potential utility for cellular models of hibernating myocardium such as that of Dispersyn et al. [1] appears to lie in further defining the process by which these structural alterations come about. In this manner, in vitro testing of novel therapies targeted to halt or reverse the phenotypic changes might be possible on a larger scale than is possible using the relatively labor-intensive animal models currently available.

4. Summary

Hibernating myocardium describes chronic reversible left ventricular dysfunction at rest secondary to intermittent, stress-induced hyperperfusion, chronic hyperperfusion at rest, or a combination of the two. The chronic dysfunction appears secondary to reduced metabolic and contractile function in association with ultrastructural changes, which appear to represent degeneration and/or de-differentiation. The treatment of the condition, regardless of the underlying etiology, is early revascularization, which is associated with improvements in ventricular function and patient survival. Newly developed cellular models of myocardial hibernation will likely provide further insights into the pathophysiology of the condition and potentially lead to the development of new therapies aimed at improving functional recovery and outcomes following revascularization.

References


