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Review

The pathological basis of myocardial hibernation

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Summary. Myocardial hibernation refers to a state of persistent regional ventricular dysfunction, in patients with coronary artery disease that is reversible with revascularization. It is part of the spectrum of pathophysiological responses to myocardial ischemia and is a particularly important concept in understanding the development and progression of ischemic cardiomyopathy. Hibernating myocardium may be associated with chronic hypoperfusion, or result from repetitive episodes of ischemia with a cumulative effect on contractile function. Mechanistic studies on myocardial hibernation have been hampered by the difficulty in developing a reproducible and reliable animal model. This review describes the pathologic changes found in hibernating myocardial segments discussing the potential mechanisms involved in their development. Depletion of cardiomyocyte contractile elements, loss of myofilaments and disorganization of cytoskeletal proteins are among the most consistently reported morphological alterations found in hibernating myocardial segments. In addition, the cardiac intersitium exhibits inflammatory changes, leading to fibrotic remodeling. Induction of cytokines and chemokines suggests an active continuous inflammatory process leading to fibrosis and dysfunction. Although, the initial response may be adaptive to ischemia, if timely revascularization is not performed, irreversible tissue injury, fibrosis and myocyte degeneration may develop. Understanding the role of inflammatory mediators in the development and progression of the cardiomyopathic process may lead to the development of specific therapeutic strategies aiming at preventing irreversible fibrosis and dysfunction.

Key words: Hibernation, Myocardium, Ischemia, Chemokine, Fibrosis

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Introduction: The concept of myocardial hibernation

The pathophysiological concept of "myocardial hibernation" was proposed by Rahimtoola to describe a state of persistent regional contractile ventricular dysfunction, in patients with coronary artery disease that is reversible with revascularization (Rahimtoola, 1985; Rahimtoola, 1999; Heusch, 1998; Wijns et al., 1998). Systematic review of the results of the coronary bypass surgery trials identified patients with coronary artery disease and chronic regional left ventricular dysfunction that improved after revascularization (Rahimtoola, 1985). Chronic ischemic heart disease may be associated with reduced myocardial perfusion, which may be still sufficient to maintain viability. Rahimtoola proposed that in many cases impaired perfusion may create a situation in which myocardial contractility and ventricular function are reduced to match the reduced blood supply. The hypocontractility that characterizes myocardial hibernation may serve as a protective mechanism, reducing the oxygen demands of the hypoperfused myocardium and limiting ischemia and necrosis (Braunwald and Rutherford, 1986). Hibernation needs to be distinguished from myocardial stunning, which refers to the mechanical dysfunction that persists after reperfusion following a discrete episode of ischemia (Kloner et al., 1998; Bolli and Marban, 1999), despite the absence of irreversible damage and the restoration of normal or near-normal coronary flow. In contrast, hibernating myocardium results from months or years of ischemia and ventricular dysfunction persists until blood flow is restored in the hypoperfused segment.

Detection of hibernating myocardium in patients with ischemic heart disease and left ventricular dysfunction is important in guiding therapy; revascularization of the hypocontractile viable myocardium may lead to post-operative recovery of function and improved survival. Various imaging modalities, such as 201Tl Single Photon Emission Computed Tomography (SPECT), Positron emission tomography (PET) imaging, dobutamine echocardiography and Magnetic Resonance Imaging (MRI) (Beller et al., 1992; Cigarroa et al., 1993; Afridi

et al., 1995; Gunning et al., 1998; Narula et al., 2000; Bax et al., 2001; Mari and Strauss, 2002) have been used to assess myocardial viability, identify hibernating segments and predict recovery of function following revascularization. However, despite the availability of numerous diagnostic tools to identify and diagnose myocardial hibernation, our understanding of the pathogenetic mechanisms responsible for this pathological condition remains rudimentary. This review will focus on the pathological characteristics and the morphological alterations associated with human myocardial hibernation. In addition, we will attempt to explore the potential mechanisms responsible for the pathogenesis of hibernation.

Coronary flow and contractile function in the hibernating myocardium

The relation between coronary flow and contractile function in patients with ischemic cardiomyopathy remains a matter of intense debate (Rahimtoola, 1996). The original concept of hibernation suggested that depressed contractile function that recovered after revascularization was associated with reduced resting blood flow (Rahimtoola, 1985). Numerous studies using nuclear imaging techniques demonstrated reduced myocardial perfusion in patients with chronic regional contractile dysfunction (Tilsch et al., 1986; Qureshi et al., 1997). Recently, an alternative idea was proposed: myocardial hibernation may result from repetitive brief episodes of ischemia that may have a cumulative effect on contractile function (Bolli et al., 1995) in the absence of chronic hypoperfusion (Vanoverschelde et al., 1993; Bolli and Marban, 1999). According to this concept a patient with normal coronary perfusion at rest may develop segmental contractile dysfunction as a result of repeated brief ischemic episodes involving a territory with impaired coronary reserve. Both mechanisms may be important in the pathogenesis of myocardial hibernation.

Morphological alterations in human hibernating myocardial segments

Our understanding of the pathologic features of myocardial hibernation is based on studies using transmural myocardial biopsies obtained under guidance with transesophageal echocardiography (TEE) in patients with ischemic ventricular dysfunction undergoing bypass surgery (Ausma et al., 1995a; Elsasser et al., 1997; Nagueh et al., 1999). Although these investigations have significant limitations due to the small size of the biopsied samples, they give us insight into the pathologic basis of hibernation, generating interesting hypotheses regarding the mechanisms involved in the pathogenesis of non-infarctive ischemic cardiomyopathy. The structural alterations found in hibernating myocardial segments involve both the cardiomyocytes and the cardiac interstitium, and reflect the progressive course of ischemic cardiomyopathy in the absence of a completed infarction.

Depletion of contractile elements, loss of myofilaments and disorganization of cytoskeletal proteins are among the most consistently reported myocyte changes found in hibernating myocardial segments (Fig. 1) (Borgers et al., 1993; Vanoverschelde et al., 1993, 1997; Maes et al., 1994; Borgers and Ausma, 1995; Frangogiannis et al., 2002a). Similar alterations have been reported in the myocardium from patients with dilated cardiomyopathy (Schaper et al., 1991; Heling et al., 2000) and may be directly involved in the dysfunction associated with heart failure. In addition, cardiomyocytes from hibernating segments exhibit cytoplasmic accumulation of glycogen (Vanoverschelde et al., 1993; Pagano et al., 2000), changes in mitochondrial size and shape, and nuclear changes such as heterochromatin dispersion. Certain investigators suggested that cardiomyocytes in hibernating myocardial segments may undergo adaptive dedifferentiation assuming phenotypic characteristics of embryonic cells (Ausma et al., 1995b, 1996, 1998), however definitive proof of this concept is lacking. On the other hand, degenerative changes are prominent in hibernating myocytes and may be directly involved in the pathogenesis of contractile dysfunction (Elsasser et al., 1997, 2002; Elsasser and Schaper, 1995). In addition, apoptotic cardiomyocytes have been identified in the hibernating myocardium using the terminal deoxynucleotidyl transferase end-labeling method and electron microscopy (Elsasser et al., 1997) indicating a potential role for programmed myocyte death in the progression of the myopathic process.

The cardiac interstitium also demonstrates significant morphological changes in hibernating myocardial segments. Enlarged interstitial space with increased collagen deposition has been a consistent finding in most studies (Fig. 1) (Elsasser et al., 1998; Nagueh et al., 1999; Frangogiannis et al., 2002a,b). Fibrotic remodeling of the interstitial space is associated with deposition of the matricellular protein tenascin suggesting an active continuous process (Frangogiannis et al., 2002a). Hibernating segments exhibit inflammatory activity showing high expression of mononuclear cell chemoattractants, such as the C-C chemokine Monocyte Chemoattractant Protein (MCP)-1 (Frangogiannis et al., 2002b) and Transforming Growth Factor (TGF)- ß1 (Elsasser et al., 2000). Recent experiments from our laboratory (Frangogiannis et al., 2002b) demonstrated active recruitment of inflammatory leukocytes in myocardial segments with reversible contractile dysfunction (hibernating segments). Leukocyte recruitment was diminished in segments with irreversible dysfunction. These findings suggest that ischemic cardiomyopathy in the absence of a completed infarction is a continuous process initially associated with leukocyte infiltration and an active inflammatory response that induces fibrotic interstitial remodeling. At

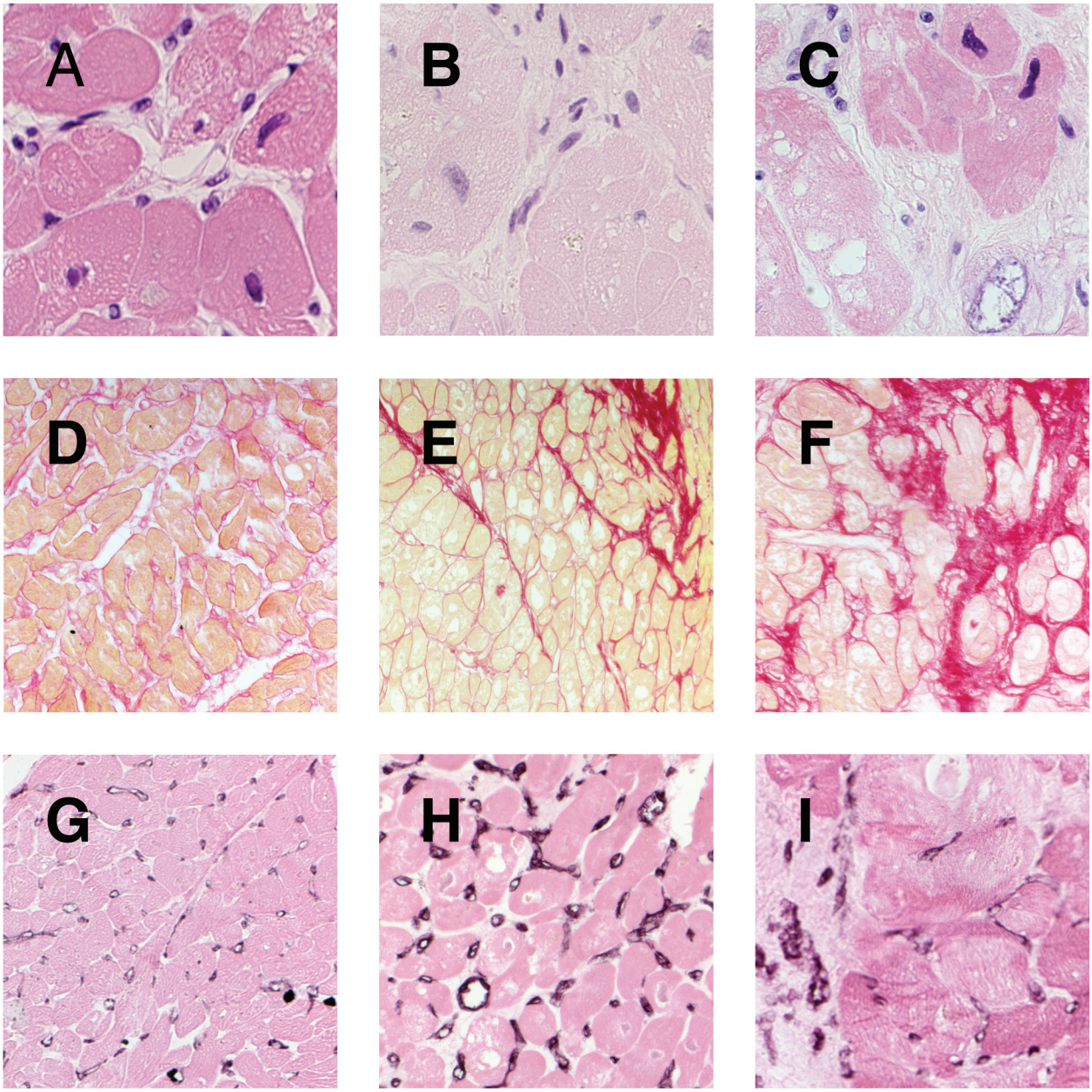

Fig. 1. Morphologic alterations in the hibernating human myocardium. Selected myocardial segments from patients undergoing aortocoronary bypass surgery were biopsied under TEE guidance. Segments with contractile dysfunction were followed echocardiographically for recovery of function three months after revascularization. **A,B,C:** Hematoxylin eosin staining x 400. **D,E,F:** Picrosirius red staining to identify collagen fibers. x 200. **G, H, I:** Staining for CD31 labeling the vascular endothelium. x 200. **A.** Hematoxylin-eosin staining of a myocardial segment with normal systolic function obtained from a patient with ischemic cardiomyopathy undergoing bypass surgery demonstrates preserved myocyte architecture. **B.** In contrast, a dysfunctional segment with recovery of function following revascularization shows significant morphological alterations affecting both the cardiomyocytes and the interstitium, such as contractile protein depletion and widening of the interstitial space. **C.** A segment with persistent contractile dysfunction demonstrates marked degenerative changes and extensive matrix deposition. **D.** Picrosirius red staining identifies collagen fibers in a segment with normal systolic function. **E.** A segment with reversible dysfunction exhibits interstitial fibrosis. **F.** A segment with persistent dysfunction shows marked collagen deposition. **G**. Staining for CD31 identifies the cardiac microvasculature in a cardiac segment with normal contractile function. Dysfunctional segments (**H**: recovery of function and **I:** no recovery) often showed morphological alterations of the microvasculature. Although significant overlap was observed, segments with decreased microvascular density (<800 microvessels/mm^2) generally did not recover after revascularization **(I)**.

a later stage locally induced mediators downregulate the inflammatory process, however extensive tissue injury may have already occurred, decreasing the likelihood of recovery after revascularization. Expression of other inflammatory mediators, such as Tumor Necrosis Factor (TNF)-α and nitric-oxide synthase (NOS)-2 (Baker et al., 2002; Kalra et al., 2002), may contribute to the depression of contractile function noted in hibernating myocardial segments.

The morphological changes outlined above are relatively non-specific findings associated with ischemic cardiomyopathy. In order to understand the mechanisms involved in myocardial hibernation, we need to identify specific pathological features, or molecular signals associated with functional recovery. Many studies have documented that the extent of fibrosis is an important negative predictor of recovery of function after revascularization (Schaper et al., 1991; Depre et al., 1995; Hennessy et al., 1998; Nagueh et al., 1999). In addition, segments with a higher degree of preservation of the myocyte fraction have a higher potential of recovery (Gunning et al., 2002). Besides these rather obvious determinants, the reasons why certain myocardial segments recover following revascularization, whereas others with similar fibrotic content do not, remain very poorly understood. Our recent work suggested that newly recruited leukocytes, suggestive of active inflammation, are more numerous in segments demonstrating recovery of function (Frangogiannis et al., 2002b). Furthermore these segments exhibit higher expression of the matricellular protein tenascin, an indicator of active remodeling (Frangogiannis et al., 2002a). Our findings suggest that myocardial hibernation is a dynamic process with several stages and that we are sampling in a continuum. The early stage of high inflammatory activity may be associated with chemokine induction and leukocyte recruitment. In contrast, segments with persistent dysfunction may have reached a "point of no return", where long-standing hypoxia-mediated inflammatory reaction has led to extensive tissue injury.

Limited information is available on the characteristics of the microvasculature in hibernating myocardial segments. Elsasser and co-workers found that dysfunctional segments without recovery of function after revascularization had a lower capillary density and higher intercapillary distance (Elsasser et al., 2000). Our recent experiments identified microvessels in the human myocardium using CD31 immunohistochemistry (Frangogiannis et al., 2000; Ren et al., 2002) (Fig. 1) and demonstrated that microvascular density, capillary density, and capillary area were highest in segments with normal function, lowest in dysfunctional segments without recovery, and intermediate in segments with recovery of function. Overall, however, a significant overlap was observed in microvascular density (Shimoni et al., 2002). Segments with low microvascular density (<800 microvessels/mm^2) generally did not recover function after revascularization. In contrast, a preserved microvascular density did not necessarily imply recovery of function at follow-up (Shimoni et al., 2002).

Recent investigations have examined the distribution of α and ß adrenergic receptors in hibernating myocardial segments (Shan et al., 2000). An increase in α adrenergic receptor density and a decrease in ß receptor density were observed in dysfunctional viable myocardium, irrespective of whether viability was assessed as recovery of myocardial function, presence of contractile reserve, or preserved radionuclide uptake. Changes in adrenergic receptor content may be mechanistically important in mediating the contractile impairment associated with ischemic cardiomyopathy.

Animal models of myocardial hibernation

Investigations examining the mechanisms responsible for reversible ischemic myocardial dysfunction have been hampered by the difficulty in developing reproducible animal models of hibernating myocardium (Ross, Jr., 1991; Camici et al., 1997; Canty Jr. and Fallavollita, 1999, 2001), Obviously, myocardial hibernation is a clinical entity with a rather complex pathological substrate. Reduced coronary myocardial perfusion at rest and repetitive demand ischemia may be important mechanisms associated with the development of viable dysfunctional myocardium. The ideal animal model of myocardial hibernation should exhibit chronically and severely reduced contractile function distal to a coronary stenosis in the absence of infarction, and show inotropic reserve in response to isoproterenol, accompanied by histological evidence characteristic of hibernating myocardium (Camici et al., 1997). Functional recovery after reversal of the stenosis or discontinuation of the ischemic stimuli would support the relevance of the model in the clinical context of myocardial hibernation.

Because of the technical difficulty in producing chronic partial coronary stenosis several investigators have used models of "short-term hibernation" (Schulz et al., 1992, 1993; Chen et al., 1996) studying the effects of constant flow hypoperfusion for 90 min (Schulz et al., 1993) to 24h (Chen et al., 1996). Although these models are very useful in identifying factors with potential relevance in hibernation they do not simulate the effects of chronic ischemic cardiomyopathy in humans. Chronic partial coronary stenosis models that reduce the coronary flow reserve may be more relevant to the clinical context of myocardial hibernation. Liedtke and co-workers have proposed a porcine model (Liedtke et al., 1995) where a physiologically significant stenosis that reduced flow reserve but not resting flow induced reversible regional dysfunction after four days. Recently several laboratories (Mills et al., 1994; Fallavollita et al., 2001a) have used chronic partial Left Anterior Descending (LAD) coronary occlusion for several months, in order to simulate myocardial hibernation. Using this model Fallavollita and Canty demonstrated severe regional dysfunction, reduced resting subendocardial flow and

markedly decreased subendocardial flow reserve associated with mild non-progressive fibrotic changes (Lim et al., 1999; Fallavollita et al., 2001a). In addition, there is significant myocyte loss accompanied by evidence of apoptosis (Lim et al., 1999) and reductions in sarcoplasmic reticulum protein expression (Fallavollita et al., 2001b).Alterations in sympathetic innervation are also noted and may contribute to the generation of arrhythmias (Luisi Jr. et al., 2002). A porcine two-vessel occlusion model combining LAD and circumflex coronary artery stenoses has also been described and results in accelerated development of myocardial hibernation and compensated heart failure (Fallavollita and Canty Jr., 2002). A major limitation of chronic stenosis models is the potential development of focal areas of myocardial infarction in the territory at risk (Camici et al., 1997; Kudej et al., 1998). Another approach often used to simulate chronic progressive hypoperfusion is the placement of an ameroid constrictor around the coronary artery. This strategy leads to progressive coronary occlusion causing ultimately complete occlusion of the vessel after 2-4 weeks. Development of infarction is again a major problem. However, some studies suggested that the myocardium distal to the ameroid was characterized by many features of hibernating myocardium (Canty Jr. and Klocke, 1987; Shen and Vatner, 1995).

Development of a reproducible and relevant animal model of hibernating myocardium is a daunting task. The clinical substrate leading to human myocardial hibernation is complex and leads to activation of various pathophysiological processes. It is impossible to mimic this situation with the use of a single animal model: rather our goal should be to develop models that simulate certain important and clinically relevant aspects of ischemic cardiomyopathy. With this concept in mind, we have recently proposed a murine model of repetitive brief (15 min) coronary occlusion followed by reperfusion, leading to a reversible ischemic cardiomyopathy (Dewald et al., 2002), in the absence of infarction, associated with a reactive oxygen-mediated inflammatory response and marked interstitial fibrotic remodeling. This model may prove extremely valuable in studying the mechanisms regulating the development and progression of non-infarctive ischemic cardiomyopathy using transgenic and knockout mice.

Pathogenesis of myocardial hibernation: a mechanistic approach

The absence of a reliable and relevant model has greatly limited our understanding of the mechanisms involved in the pathogenesis of myocardial hibernation. It should be emphasized that hibernating myocardium describes a clinical situation with a complex pathophysiologic substrate; understanding the factors related to its development requires knowledge of the fundamental effects of non-infarctive ischemic insults in the heart.

Persistent myocardial hypoperfusion and brief repetitive ischemic insults (Bolli, 1992; Heusch and Schulz, 2000) are important fundamental mechanisms involved in the pathogenesis of myocardial hibernation. Many investigators view myocardial hibernation as an adaptive response to ischemia, suggesting that "protective" molecular signals reducing contractile function are released in the hypoperfused myocardium. Decreased calcium responsiveness has been demonstrated in a porcine model of short-term hypoperfusion and may play a role in the regional dysfunction associated with hibernation (Heusch et al., 1996). On the other hand, the expression of calcium regulatory proteins (such as sarco(endo)plasmic reticulum $Ca^{(2+)}$-ATPase-SERCA and phospholamban) was not altered in short term low-flow ischemia (Luss et al., 1998). In addition, troponin I proteolysis, which has been found to induce myocardial stunning in mice (Murphy et al., 2000), has not been consistently associated with reversible dysfunction in larger animal models (Thomas et al., 1999). TNF-α and iNOS derived nitric oxide have well characterized effects on contractile function (Mann, 2001; Sawyer and Loscalzo, 2002) and may play a role in the pathogenesis of viable dysfunctional myocardium (Canty Jr., 2000; Kalra et al., 2002), but may also be an important part of the adaptive response necessary to maintain viability in the presence of persistent hypoperfusion (Babal et al., 1997; Sawyer and Loscalzo, 2002). Alterations in adrenergic receptor density may also be important in mediating contractile dysfunction (Shan et al., 2000).

Myocardial hibernation represents a part of the spectrum of ischemic cardiomyopathy (Fig. 2). Whether it is an adaptive process or simply the early stage of a continuous injurious response leading to degeneration and irreversible dysfunction remains unclear. However, the fundamental mechanisms of response to injury probably did not evolve to protect the normal structure of the heart, rather they serve to clear an injured area from damaged cells and to trigger repair mechanisms, ultimately leading to fibrosis. Our recent studies suggested that ischemic cardiomyopathy in the absence of a myocardial infarction is a dynamic continuous process ultimately leading to irreversible injury and dysfunction (Frangogiannis et al., 2002a,b). In the early stages, ischemia-induced signals such as chemokine expression and TGF-ß synthesis and release, may lead to mononuclear leukocyte infiltration and fibroblast accumulation in the interstitial space. Accumulating fibroblasts may undergo phenotypic changes, such as the expression of α-smooth muscle actin and SMemb (embryonic isoform of the smooth muscle myosin heavy chain). Interstitial expression of the matricellular protein tenascin, may have a role in modulating cellular adhesion and cytokinesis, promoting matrix remodeling. At a later stage, and despite the presence of myocardial viability (preserved thickness and 201Tl uptake), the cardiac interstitium becomes a less cellular environment, dominated by extracellular matrix accumulation and

showing lower levels of inflammatory activity. This stage is associated with a lower likelihood of functional recovery, further supporting the need for early revascularization in patients with suspected myocardial hibernation.

It should be emphasized that within a given myocardial segment, areas exhibiting different stages of injury may co-exist. Thus, areas containing hibernating cardiomyocytes may be adjacent to regions with extensive evidence of apoptosis, necrosis and fibrotic remodeling, depending on the local microenvironment (Sawyer and Loscalzo, 2002).

Conclusions and future directions

Hibernating myocardium is an important clinical entity affecting the prognosis of many patients with ischemic cardiomyopathy. Patients with viable dysfunctional myocardium have a better long-term prognosis after revascularization, compared with patients with non-viable myocardium (Pagley et al., 1997). Evidence, however, suggests that viable dysfunctional myocardium (hibernating myocardium) and irreversibly injured myocardium represent different aspects of the spectrum of ischemic cardiomyopathy (Frangogiannis et al., 2002a,b; Sawyer and Loscalzo, 2002). Patients with chronic ischemic heart disease may develop cardiac injury in the absence of a completed myocardial infarction. Chronic hypoperfusion and episodic demand ischemia may play an important role in the progression of the cardiomyopathic process. The molecular signals potentially responsible for downregulating contractile function remain unknown. It appears, however that ischemic insults trigger an inflammatory response (Dewald et al., 2002; Elsasser et al., 2000; Frangogiannis et al., 2002a-c), leading to leukocyte infiltration, fibroblast accumulation and active interstitial remodeling (Frangogiannis et al., 2002b). Chemokines (Gerard and Rollins, 2001) may have a significant role in regulating leukocyte recruitment (Frangogiannis et al., 2002b; Dewald et al., 2002) in the cardiomyopathic heart leading to progressive injury and fibrosis. Progression of fibrotic remodeling may be associated with expression of signals downregulating the inflammatory response, however tissue injury and dysfunction may have already reached an irreversible stage.

We suggest that the inflammatory response (Frangogiannis et al., 1998a-c, 2002c) may play an active role in the development of progressive cardiac fibrosis in dysfunctional segments. Interventions inhibiting this process may have beneficial effects for patients with ischemic cardiomyopathy by preventing irreversible tissue injury. For example the use of chemokine inhibitors in this process may suppress inflammatory leukocyte recruitment decreasing fibrotic remodeling. However, understanding of the specific molecular signals involved in the development and progression of ischemic cardiomyopathy is crucial in order to design strategies that do not interfere with important protective mechanisms, such as collateral vessel formation and angiogenesis.

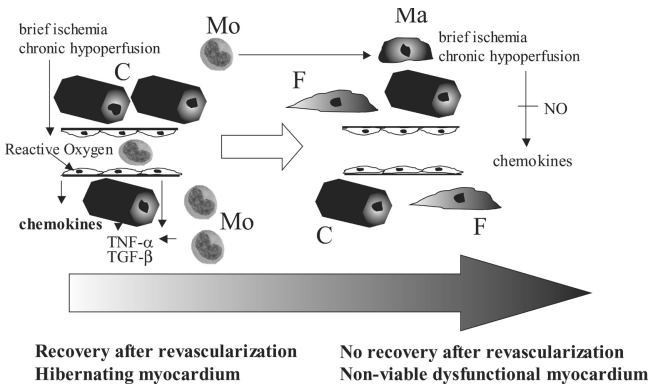

Fig. 2. Involvement of the inflammatory response in the development and progression of ischemic cardiomyopathy. At an early stage, brief repetitive ischemic insults and/or chronic hypoperfusion trigger a reactive oxygen-mediated inflammatory response inducing chemokine expression and monocyte (Mo) recruitment. Factors downregulating cardiomyocyte (C) function (such as TNF-α) may also be induced. This situation represents one end of the spectrum (hibernating myocardium) and is associated with recovery of function after revascularization. However, the injurious process is continuous: long standing inflammatory injury results in monocyte to macrophage (Ma) differentiation and fibroblast (F) accumulation. Fibrotic interstitial remodeling is associated with cardiomyocyte changes such as depletion of contractile material and cytoskeletal protein disorganization. At this stage endogenous mediators (such as nitric oxide) may inhibit ischemia-derived chemokine synthesis downregulating the inflammatory process. However, the presence of extensive, irreversible tissue injury may prevent recovery of function after revascularization.

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