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### **CON: Hibernating Myocardium: Adaptation to Ischaemia**

R. Schulz, G. Heusch

Patients with chronic coronary artery disease frequently have ventricular 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 downregulation that serves to maintain myocardial integrity and viability. Experimental studies have indeed demonstrated reduction in regional myocardial function in proportion to the reduction of resting blood flow (perfusion-contraction matching) that recovered upon reperfusion. Furthermore, recovery of energy and substrate metabolism during ongoing ischaemia, the potential for recruitment of inotropic reserve and lack of necrosis are established features of hibernation. Similarly, in most patients, baseline blood flow is reduced in the dysfunctional myocardium. Morphologically, the hibernating myocardium displays features of dedifferentiation, with loss of cardiomyocytes and myofibrils, and of degeneration, with increased interstitial fibrosis. The mechanisms of hibernation, apart from reduced calcium responsiveness, are not clear at present. With the identification of the underlying mechanism(s) of hibernation, it can potentially be recruited and reinforced pharmacologically to delay impending myocardial infarction. *J Clin Basic Cardiol 2000; 3: 143–4.* 

Key words: myocardial ischaemia, ventricular function

Reviewing the results of coronary bypass surgery trials and identifying patients with coronary artery disease and chronic left ventricular dysfunction that improved upon revascularization, Rahimtoola proposed the concept of myocardial hibernation. He suggested that the observed dysfunction was not the result of an ongoing energetic deficit, but an adaptive downregulation of contractile function to preserve myocardial integrity and viability [1]. Shortly thereafter, the concept of myocardial hibernation was further popularized by Braunwald and Rutherford [2] who emphasized the need for its recognition and therapy through revascularization.

At the same time, experiments in chronically instrumented conscious dogs demonstrated that regional myocardial function and blood flow were reduced proportionately during ischaemia [3, 4], ie, there was no imbalance between demand/function and supply/flow, as previously assumed, but a state of perfusion-contraction matching [5] that could be sustained for up to 5 [6] or 24 hours [7] of coronary stenosis without necrosis and with eventual full recovery of function upon reperfusion, again supporting the concept of myocardial hibernation.

#### Energetics and metabolism

In anesthetized pigs with regional ischaemia, metabolic parameters such as myocardial lactate consumption [8], creatine phosphate content [9] and the free energy change of ATPhydrolysis [10], after an initial reduction, recovered towards their pre-ischaemic baseline values during ongoing ischaemia, 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 [11]. Further experimental studies documented the persistence of an inotropic reserve in hibernating myocardium [12] and this primarily experimental finding prompted again clinical studies using stress echocardiography to demonstrate viability of dysfunctional myocardium in patients with coronary artery disease [13–15].

#### Mechanism(s)

The mechanism(s) of the almost immediate down-regulation of contractile function in response to reduction in myocardial blood flow, permitting the development of myocardial hibernation, are currently unclear, but several potential mediators have been excluded (β-adrenoceptors [16], adenosine [17], activation of ATP-dependent potassium channels [17], for review, see [18]). Endogenous nitric oxide is also not involved in the immediate downregulation of baseline contractile function. However, contractile function for any given blood flow and oxygen consumption is lower without than with endogenous nitric oxide. Thus, endogenous nitric oxide contributes to successful hibernation by reducing futile oxygen consumption and maintaining contractile function as high as possible without any additional energetic costs, most probably through preservation of contractile calcium sensitivity [19]. While calcium sensitivity is preserved in short-term hibernating myocardium, calcium responsiveness - due to a decrease in the maximal calcium-activated force - is reduced [20]. The expression of calcium regulatory proteins (SERCA, phospholamban, calsequestrin, troponin inhibitor) is not altered during experimental short-term hibernation [21], suggesting an unaltered intracellular calcium handling. Therefore, the downregulation of contractile function during moderate ischaemia appears to be at the level of the myofilaments themselfs.

#### Morphology

Morphological alterations in animal models with chronic coronary stenosis are remarkably similar to those found in patients with chronic hibernation, ie, the number of myofibrils is reduced while mitochondria and glycogen deposits are increased [22-28]. The interstitium contains cellular debris, increased numbers of macrophages and fibroblasts and increased collagen [24, 25, 28, 29]. Recently, apoptosis was also detected in experimental [30] and human hibernating myocardium [25]. Up to a certain degree these degenerative alterations appear to be reversible [24]. In addition, changes in the distribution of titin and cardiotin have been observed, and together with the expression of alpha-smooth muscle actin in hibernating myocardium, these alterations have been suggested to represent hibernation-induced dedifferentiation of cardiomyocytes [29].

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#### Ischaemia versus stunning

The existence of cumulative stunning secondary to repeated episodes of stress-induced ischaemia in regions with normal blood flow at rest, but reduced coronary reserve, was proposed as an alternative mechanism underlying the observed regional contractile dysfunction in studies with chronic coronary stenosis. This possibility certainly exists, as do other more complex scenarios of flow and function in the setting of coronary stenosis [31], but has not not been systematically investigated and, above all, does not exclude the existence of hibernation in other studies.

Almost all of the existing experimental studies on hibernation over longer than a few hours duration can be criticized because of the limited observation periods and the lack of continuous monitoring of both regional myocardial blood flow and function, so that the history of the observed dysfunction is not known. Clearly, however, reduced blood flow at rest is observed in dysfunctional regions of conscious, chronically instrumented animals with chronic coronary stenosis, consistent with the original concept of Rahimtoola [1]. The majority of quantitative data available in patients, also indicates reduced blood flow at rest in the dysfunctional region as compared to an intraindividual remote reference region, consistent with the original concept of hibernation (for review, see [18]). However, it must be acknowledged that reduced blood flow at rest does not exclude superimposed episodes of stress-induced ischaemia, resulting in stunning. In most patients with chronic ischemic dysfunction, there will also be an admixture of some necrotic/fibrotic tissue.

#### Conclusion

Conceptually, it appears that the process of hibernation involves an initial biochemical signal inducing contractile quiescence and energetic recovery, 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. Clinically, the recognition of viability in chronic dysfunctional myocardium of patients with coronary artery disease and the selection for revascularization is of utmost importance [2]. Given the presence of viable myocardium, the distinction between chronic hibernation and cumulative stunning may be of only academic value, since revascularization is mandatory in any event [32]. Somewhat paradoxically, it appears that therapeutic approaches will aim at mimicking and reinforcing short-term hibernation, but at removing chronic hibernation. A better mechanistic understanding is therefore particularly important for shortterm hibernation.

#### **References:**

- Rahimtoola SH. A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina. Circulation 1985; 72 (Suppl.V): V123–V135.
- 2 Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: evidence for the "hibernating myocardium". J Am Coll Cardiol 1986; 8: 1467–70.
- Gallagher KP, Matsuzaki M, Osakada G, Kemper WS, Ross J Jr. Effect of exercise on the relationship between myocardial blood flow and systolic wall thickening in dogs with acute coronary stenosis. Circ Res 1983; 52: 716–29.
  Gallagher KP, Matsuzaki M, Koziol JA, Kemper WS, Ross J Jr. Regional myocardial
- Gallagher KP, Matsuzaki M, Koziol JA, Kemper WS, Ross J Jr. Regional myocardial perfusion and wall thickening during ischemia in conscious dogs. Am J Physiol 1984;247: H727–H738.
- Ross J Jr. Myocardial perfusion-contraction matching. Implications for coronary heart disease and hibernation. Circulation 1991; 83: 1076–83.

- Matsuzaki M, Gallagher KP, Kemper WS, White F, Ross J Jr. Sustained regional dysfunction produced by prolonged coronary stenosis: gradual recovery after reperfusion. Circulation 1983; 68: 170–82.
- Chen C, Li L, Chen LL, Preda JV, Chen MH, Fallon ST, Weyman AE, Waters D, Gillam L. Incremental doses of dobutamine induce a biphasic response in dysfunctional left ventricular regions subtending coronary stenoses. Circulation 1995; 92:756–66.
- Fedele FA, Gewirtz H, Capone RJ, Sharaf B, Most AS. Metabolic response to prolonged reduction of myocardial blood flow distal to a severe coronary artery stenosis. Circulation 1988; 78: 729–35.
- Pantely GA, Malone SA, Rhen WS, Anselone CG, Arai A, Bristow J, Bristow JD. Regeneration of myocardial phosphocreatine in pigs despite continued moderate ischemia. Circ Res 1990; 67: 1481–93.
- Martin C, Schulz R, Rose J, Heusch G. Inorganic phosphate content and free energy change of ATP hydrolysis in regional short-term hibernating myocardium. Cardiovasc Res 1998; 39: 318–26.
- Bristow JD, Arai AE, Anselone CG, Pantely GA. Response to myocardial ischemia as a regulated process. Circulation 1991; 84: 2580–7.
- Schulz R, Guth BD, Pieper K, Martin C, Heusch G. Recruitment of an inotropic reserve in moderately ischemic myocardium at the expense of metabolic recovery: a model of short-term hibernation. Circ Res 1992; 70: 1282–95.
- Indolfi C, Piscione F, Perrone-Filardi P, Prastaro M, Di Lorenzo E, Sacca L, Condorelli M, Chiariello M. Inotropic stimulation by dobutamine increases left ventricular regional function at the expense of metabolism in hibernating myocardium. Am Heart J 1996; 132: 542–9.
- Skopicki HA, Abraham SA, Weissman NJ, Mukerjee AK, Alpert NM, Fischman AJ, Picard MH, Gewirtz H. Factors influencing regional myocardial contractile response to inotropic stimulation. Analysis in humans with stable ischemic heart disease. Circulation 1996; 94: 643–50.
- Sun KT, Czernin J, Krivokapich J, Lau Y-K, Böttcher M, Maurer G, Phelps ME, Schelbert HR. Effects of dobutamine stimulation on myocardial blood flow, glucose metabolism, and wall motion in normal and dysfunctional myocardium. Circulation 1996; 94: 3146–54.
- Schulz R, Rose J, Martin C, Brodde OE, Heusch G. Development of short-term myocardial hibernation: its limitation by the severity of ischemia and inotropic stimulation. Circulation 1993; 88: 684–95.
- Schulz R, Rose J, Heusch G. Involvement of activation of ATP-dependent potassium channels in ischemic preconditioning in swine. Am J Physiol 1994; 267: H1341– H1352.
- 18. Heusch G. Hibernating myocardium. Physiol Rev 1998; 78: 1055-85.
- Heusch G, Post H, Michel MC, Helm M, Schulz R. Endogenous nitric oxide and myocardial adaption to ischemia. Circ Res 2000; 87.
- Heusch G, Rose J, Skyschally A, Post H, Schulz R. Calcium responsiveness in regional myocardial short-term hibernation and stunning in the in situ porcine heart – inotropic responses to postextrasystolic potentiation and intracoronary calcium. Circulation 1996; 93: 1556–66.
- Lüss H, Boknik G, Heusch G, Müller FU, Neumann J, Schmitz W, Schulz R. Expression of calcium regulatory proteins in short-term hibernation and stunning in the in situ porcine heart. Cardiovasc Res 1998; 37: 606–17.
- 22. Chen C, Chen L, Fallon JT, Ma L, Li L, Bow L, Knibbs D, McKay R, Gillam LD, Waters DD. Functional and structural alterations with 24-hour myocardial hibernation and recovery after reperfusion. A pig model of myocardial hibernation. Circulation 1996; 94: 507–16.
- Ausma J, Schaart G, Thoné F, Shivalkar B, Flameng W, Depré C, Vanoverschelde J-L, Ramaekers F, Borgers M. Chronic ischemic viable myocardium in man: aspects of dedifferentiation. Cardiovasc Pathol 1995; 4: 29–37.
- Elsässer A, Schaper J. Hibernating myocardium: adaptation or degeneration? Basic Res Cardiol 1995; 90: 47–8.
- Elsässer A, Schlepper M, Klövekorn W-P, Cai W, Zimmermann R, Müller K-D, Strasser R, Kostin S, Gagel C, Münkel B, Schaper W, Schaper J. Hibernating myocardium. An incomplete adaptation to ischemia. Circulation 1997; 96: 2920–31.
- 26. Flameng W, Suy R, Schwarz F, Borgers M, Piessens J, Thone F, van Ermen H, de Geest H. Ultrastructural correlates of left ventricular contraction abnormalities in patients with chronic ischemic heart disease: Determinants of reversible segmental asynergy postrevascularization surgery. Am Heart J 1981; 102: 846–57.
- Shivalkar B, Maes A, Borgers M, Ausma J, Scheys I, Nuyts J, Mortelmans L, Flameng W. Only hibernating myocardium invariably shows early recovery after coronary revascularization. Circulation 1996; 94: 308–15.
- Vanoverschelde J-LJ, Wijns W, Depré C, Essamri B, Heyndrickx GR, Borgers M, Bol A, Melin JA. Mechanisms of chronic regional postischemic dysfunction in humans. New insights from the study of noninfarcted collateral-dependent myocardium. Circulation 1993; 87: 1513–23.
- Borgers M, Ausma J. Structural aspects of the chronic hibernating myocardium in man. Basic Res Cardiol 1995; 90: 44–6.
- Chen C, Ma L, Linfert DR, Lai T, Fallon JT, Gillam LD, Waters DD, Tsongalis GJ. Myocardial cell death and apoptosis in hibernating myocardium. J Am Coll Cardiol 1997; 30: 1407–12.
- 31. Bolli R. Myocardial "Stunning" in man. Circulation 1992; 86: 1671-91.
- 32. Marber M. Viewpoint: stunning and longterm perfusion-contraction matching are clinically indistinguishable components of clinical hibernation and separation, even if practical, is unlikely to matter. Basic Res Cardiol 1997; 92 (Suppl. 2): 26–9.

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