Myocardial hibernation: adaptation to ischaemia

The concept of hibernation

When severely reduced coronary blood flow persists for more than 20 min, myocardial necrosis begins to develop and contractile function is eventually irreversibly lost. When myocardial ischaemia is more moderate, the myocardium can remain viable for a longer period of time, and although contractile function is reduced, it recovers upon reperfusion. In patients with coronary artery disease, chronic contractile dysfunction, which is reversible upon reperfusion, is termed myocardial hibernation[1].

The term hibernation has been borrowed from zoology and implies that the observed reduction in contractile function is an adaptive and regulatory event acting to preserve viability. The concept of hibernation was developed entirely on clinical grounds, but quickly gained support from experimental studies.

Mechanisms of acute ischaemic contractile dysfunction

Following acute reduction of coronary blood flow, contractile function in the ischaemic region rapidly (within a few cardiac cycles) ceases. However, reduction in myocardial ATP as the underlying mechanism for the rapid reduction in contractile function has been ruled out, since (1) contractile dysfunction occurs prior to changes in myocardial ATP, and (2) the result of myocardial ATP loss should be rigor of the myofibril rather than the observed loss of wall tension. Mechanisms which have been proposed, but not unequivocally proven, include a reduction in the free energy change in ATP hydrolysis, a decreased rephosphorylation rate of cytosolic ADP from creatine phosphate, the development of intracellular acidosis, accumulation of inorganic phosphate or impairment of sarcoplasmic calcium transport kinetics, which again may be pH- or ATP-dependent (for review see[2]).

Transition from an imbalance between supply and demand towards myocardial hibernation

Within the first few seconds following acute reduction of myocardial blood flow, energy demand by the hypoperfused myocardium clearly exceeds the reduced energy supply. However, this imbalance between energy supply and demand is an inherently unstable condition since contractile function and
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Table 1 Characterization of short-term hibernating myocardium

| Balance between the reduced regional myocardial blood flow and the reduced contractile function (perfusion-contraction-matching) |
| Recovery of contractile function during reperfusion |
| Recovery of metabolic parameters (creatine phosphate, lactate) during persistent ischaemia |
| Recruitable inotropic reserve at the expense of metabolic recovery |

Table 2 Characterization of long-term hibernating myocardium

| Decrease in the number of myofibrils and increased collagen network |
| Recovery of contractile function during reperfusion |

thus energy demand rapidly decrease following the onset of ischaemia. In the subsequent steady state condition, the reduction of contractile function is in proportion to the reduction in myocardial blood flow. This situation has been termed perfusion–contraction matching by Ross; perfusion–contraction matching, reflecting a balance between energy supply and demand, is a key feature of short-term myocardial hibernation (Tables 1 and 2).

Metabolism of short-term hibernating myocardium

Within the first 5 min of ischaemia, the myocardial creatine phosphate concentration is reduced, and lactate consumption is reversed to net lactate production. When ischaemia is prolonged to 60–90 min, however, the myocardial creatine phosphate concentration recovers to near control values (Fig. 1), lactate production is attenuated, and regional contractile function is persistently reduced. Apparently, the reduction in regional contractile function during moderate ischaemia permits the partial recovery of ischaemia-induced metabolic alterations.

Recruitment of an inotropic reserve at the expense of metabolic recovery in short-term hibernating myocardium

Although baseline contractile function is depressed, the hypoperfused myocardium retains its responsiveness to an inotropic challenge (Fig. 1). When, after 85 min of ischaemia, dobutamine is infused selectively into the ischaemic myocardium of anaesthetized pigs, contractile function increases, although regional blood flow remains reduced. Thus, energy is available in the ischaemic myocardium which is not used to support baseline function, but permits the increase in contractile function upon an inotropic challenge. However, the increase in contractile function during inotropic stimulation again decreases the myocardial creatine phosphate concentration and increases lactate production (Fig. 1), indicating a renewed supply–demand imbalance.

Mechanisms of short-term hibernating myocardium

The mechanisms responsible for the development of short-term myocardial hibernation remain unclear at present, but suggestions that alterations in β-adrenoceptor density or affinity are the underlying mechanism of such an adaptive process have been excluded.

Ischaemia-induced activation of ATP-dependent potassium channels might increase potassium efflux, thereby reducing action potential duration and subsequently calcium influx into the myocyte. Such decreased intracellular calcium concentration could then reduce contractile function and ATP consumption, thus finally allowing the development of myocardial hibernation. Indeed, monophasic action potential duration shortens during ischaemia, and this shortening is inhibited by blockade of ATP-dependent potassium channels with glibenclamide. However, blockade of ATP-dependent potassium channels neither alters contractile function, metabolic parameters nor myocardial viability. Activation of ATP-dependent potassium channels is therefore not involved in the development of short-term myocardial hibernation.

Increased levels of endogenous adenosine during ischaemia might, through a number of secondary mechanisms, such as inhibition of adenylate cyclase activity, inhibition of norepinephrine release from sympathetic nerve endings or inhibition of L-type calcium channels, attenuate the decrease in myocardial energy-rich phosphates and the increase in

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intracellular calcium concentration, thereby preserving myocardial viability during ischaemia. However, a role for endogenous adenosine in the development of hibernation has been excluded, since neither contractile function, metabolic parameters nor viability are altered by increased catabolism of endogenous adenosine by infusion of adenosine deaminase. Thus, the mechanisms of short-term myocardial hibernation contrast with those of ischaemic preconditioning, in which both adenosine and activation of ATP-dependent potassium channels play an important role.

The reduced regional contractile function in short-term hibernating myocardium is largely based on reduced myocardial calcium responsiveness. In anaesthetized pigs after 90 min of ischaemia, at a time when lactate production is attenuated and the creatine phosphate concentration is restored to a value no longer significantly different from the respective control value, the maximal responses to graded intracoronary calcium infusion and post-extrasystolic potentiation are decreased. However, the relationships between the fractional increases in regional contractile function and dose of added intracoronary calcium and the post-extrasystolic time interval, respectively, are not different, pointing towards decreased maximal force development rather than reduced calcium sensitivity.

Limitations of short-term hibernation
The development of short-term myocardial hibernation is disturbed by unfavourable alterations in supply and demand. When after 5 min of ischaemia, at a blood flow reduction compatible with the development of short-term myocardial hibernation over 90 min, energy supply is further reduced by a further reduction of myocardial blood flow, necrosis develops (Fig. 2). A subendocardial blood flow of 0.17 ml x min$^{-1}$ x g$^{-1}$ (Fig. 2) or a transmural myocardial blood flow of 0.25 ml x min$^{-1}$ x g$^{-1}$ is still compatible with the development of short-term myocardial hibernation.

Likewise, increasing energy demand by continuous inotropic stimulation with dobutamine
induces necrosis\textsuperscript{[8]}. Thus, both the further reduction in energy supply by an increasing severity of ischaemia and an enhanced energy expenditure by continuous inotropic stimulation impair the development of short-term myocardial hibernation and precipitate myocardial infarction.

**Characterization of long-term hibernation**

Whereas short-term hibernation is well characterized in animal experiments, the existence of hibernation over weeks or months (long-term hibernation) can only be inferred from clinical studies. Hibernation, as first defined by Rahimtoola in patients with coronary artery disease, is a state of chronic contractile dysfunction which is fully reversible upon reperfusion. Clinical syndromes consistent with the existence of myocardial hibernation include unstable and stable angina, acute myocardial infarction and left ventricular dysfunction and/or congestive heart failure\textsuperscript{[14]}.

In long-term hibernating myocardium morphological alterations occur. In myocardial biopsies from patients with prolonged contractile dysfunction, which was reversible after bypass surgery, myofibrils are reduced in number and disorganized, but myocardial glycogen content as well as the extracellular collagen network are increased\textsuperscript{[9]}. Thus, despite the fact that the myocardium remains viable during persistent ischaemia and contractile dysfunction is reversible upon reperfusion\textsuperscript{[11]}, there are several morphological alterations. Understandably, full functional recovery following reperfusion can therefore require weeks or even months\textsuperscript{[10]}.

It is still under debate whether chronic contractile dysfunction in patients occurs during persistent ischaemia, i.e. true hibernation exists, or is the result of repetitive episodes of ischaemia and reperfusion, i.e. stunning. In patients with complete occlusion of a major coronary artery but an extensive collateral circulation\textsuperscript{[15]} as well as in animal experiments with a chronic artery stenosis\textsuperscript{[16]}, chronic contractile dysfunction is observed at almost normal resting myocardial blood flows. At almost normal resting blood flow but impaired coronary reserve, repetitive episodes of exercise-induced ischaemia and reperfusion could occur, inducing stunning, which then results in chronic contractile dysfunction. However, these studies do not rule out the existence of true myocardial hibernation, i.e. a situation of chronic contractile dysfunction during persistent ischaemia.

### Identification of hibernating myocardium

In contrast to dysfunctional, irreversibly damaged myocardium, the hibernating myocardium retains an inotropic reserve. To further distinguish hibernating from stunned myocardium, either regional myocardial blood flow must be measured or the metabolic changes associated with an inotropic challenge be analysed. The recruitment of an inotropic reserve in hibernating myocardium is at the expense of metabolic recovery (Fig. 1)\textsuperscript{[7-8]} while in stunned myocardium no metabolic deterioration occurs during inotropic stimulation\textsuperscript{[17]}.

### Therapy of hibernating myocardium

Hibernating myocardium, although exhibiting a number of cardioprotective features, is nevertheless ischaemic and therefore a pathological condition. Thus, the only causal therapy of hibernating myocardium is to restore blood flow to the hypoperfused tissue.

**Perspective**

Currently, the most important question is: can myocardial hibernation be induced or reinforced? This is a challenging therapeutic goal, as it would extend the
time frame for reperfusion interventions in patients with acute ischaemic syndromes. In that respect, short-term myocardial hibernation, i.e. an endogenous cardioprotective mechanism during acute ischaemic syndromes, may be a much more common and important phenomenon than long-term myocardial hibernation.

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References


