Myocardial hibernation: a delicate balance

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Heusch, Gerd, Rainer Schulz, and Shahbudin H. Rahimtoola. Myocardial hibernation: a delicate balance. Am J Physiol Heart Circ Physiol 288: H984–H999, 2005. First published November 24, 2004; 10.1152/ajpheart.01109.2004.—The pathophysiology of myocardial hibernation is characterized as a situation of reduced regional contractile function distal to a coronary artery stenosis that recovers after removal of the coronary stenosis. A subacute “downregulation” of contractile function in response to reduced regional myocardial blood flow exists, which normalizes regional energy and substrate metabolism but does not persist for more than 12–24 h. Chronic hibernation develops in response to one or more episodes of myocardial ischemia–reperfusion, possibly progressing from repetitive stunning with normal blood flow to hibernation with reduced blood flow. An upregulation of a protective gene program is seen in hibernating myocardium, putting it into the context of preconditioning. The morphology of hibernating myocardium is characterized by both adaptive and degenerative features.

PATHOPHYSIOLOGY OF HIBERNATING MYOCARDIUM
Concept of Myocardial Hibernation and Its Evolution

In the early 1980s, Rahimtoola (123, 124) systematically reviewed the results of coronary bypass surgery trials and identified patients with coronary artery disease and chronic left ventricular dysfunction that improved on revascularization. Based on these findings, Rahimtoola first proposed the pathophysiological concept of myocardial hibernation to characterize a situation of “a prolonged subacute or chronic state of myocardial ischemia . . . in which myocardial contractility and metabolism and ventricular function are reduced to match the reduced blood supply,” which is “a new state of equilibrium . . . whereby myocardial necrosis is prevented, and the myocardium is capable of returning to normal or near-normal function on restoration of an adequate blood supply” (124).

The term “hibernation” has been borrowed from zoology and implies an adaptive reduction of energy expenditure through reduced activity in a situation of reduced energy supply. Thus, in the concept of myocardial hibernation, the observed reduction of myocardial contractile function is not regarded as the consequence of a sustained energetic deficit but instead as a regulatory event that serves to avoid an energetic deficit and to maintain myocardial integrity and viability (76). It must be noted, however, that the detailed elements of a regulatory circuit in the strict physiological sense were not identified so far. Myocardial hibernation was further popularized by Braunwald and Rutherford (19) who emphasized the need for its recognition and therapy through revascularization.

Initially, the concept of myocardial hibernation was based on clinical observations only. However, the clinical concept of hibernation quickly merged with a number of experimental observations. Also in the early 1980s, several laboratories found that the long-held concept of myocardial ischemia as an imbalance between myocardial blood flow (the major determinant of energy supply) and contractile function (the major determinant of energy demand) was not necessarily correct at the regional myocardial level. In fact, the reduction in regional contractile function was proportionate to the reduction in regional myocardial blood flow (23, 61, 62, 164) (for review see Ref. 80). Consequently, mechanical function appeared to be “downregulated” depending on the amount of blood flow that was available. To describe this phenomenon, Ross (126) introduced the term “perfusion-contraction matching.” Such perfusion-contraction matching could be sustained for a period of several hours of moderate ischemia in conscious, chronically instrumented dogs with eventual full recovery of contractile function on reperfusion (111).

With reference to sustained perfusion-contraction matching, as demonstrated in experimental studies over several hours, Ross (126) defined “short-term hibernation” and distinguished it from “chronic hibernation,” i.e., a hypothetical condition of chronic perfusion-contraction matching. Further experimental evidence for the idea of an adaptive downregulation of contractile function was gained from studies demonstrating the recovery of metabolic markers during ongoing persistent ischemia (54, 122).

The concept of myocardial hibernation has subsequently stimulated discussion on myocardial ischemia and its definition in general. Rahimtoola (124) had already postulated that hibernating myocardium may not be “ischemic in the strict sense of the word.” With reference to hibernating myocardium, Hearse (75) went on to propose a distinction between physiological ischemia (“a condition in which coronary flow is inadequate to permit the organ to perform at a level sufficient to support the body over its full physiological range of activity”) and biochemical ischemia (“a condition in which coronary blood flow is inadequate to permit the maintenance of a steady state metabolism”).
With this historical background, the current pathophysiological focus is on the quantitative relation of myocardial blood flow and contractile function and its temporal stability, the myocardial substrate and energy metabolism, the maintenance of morphological integrity of the myocardium permitting the recovery of contractile function following reperfusion, and finally the potential mechanisms underlying all of the above. Importantly, the vast majority of experimental studies on myocardial hibernation did not assess the recovery of contractile function following reperfusion, which is the hallmark of clinical hibernation, but, if anything, substituted lack of infarction for it.

Quantitative Relation of Flow and Function

Acute (minutes) ischemia. On acute coronary artery inflow reduction, contractile function in the ischemic region is rapidly decreased (73). As soon as a steady state has developed (2–3 min) that permits the measurement of regional myocardial blood flow with the microspheres technique, a consistent relation between the reduced regional contractile function is apparent. Whereas normally subendocardial blood flow is greater than subepicardial blood flow, subendocardial blood flow is reduced to a greater extent than subepicardial blood flow in the presence of a coronary stenosis, such that a modest reduction in transmural blood flow by 20% may well translate to a reduction in subendocardial blood flow as great as 40% (61). Vatner (164) was the first in 1980 to demonstrate a consistent relationship between subendocardial blood flow and subendocardial segment shortening. Gallagher et al. (61, 62) found the relationship between systolic wall thickening and subendocardial or transmural blood flow to be more or less linear and dependent on the hemodynamic situation. It is primarily subendocardial blood flow that governs transmural wall function such that a 50% [anesthetized dog, (42)] to 75% [conscious dog (61)] reduction in subendocardial blood flow results in akinesis, whereas subepicardial blood flow does not correlate to transmural wall function (Fig. 1) (60). Also there is a higher blood flow for a given level of function during exercise than at rest (62). However, when myocardial blood flow is normalized for heart rate, i.e., expressed as blood flow per beat rather than per minute, and thus related to the same temporal reference as contractile function, i.e., one arbitrary average cardiac cycle, the relationships during normo- and hyperperfusion at rest and during exercise (62) and those at different heart rate (84, 86) are superimposable.

When such perfusion-contraction matching in acutely ischemic myocardium is equated with an energetic supply-demand balance, several limitations must be considered. On the supply side, changes in myocardial oxygen extraction and anaerobic glycolytic metabolism may also contribute to supply apart from blood flow. On the demand side, regional wall excursion may underestimate the true regional metabolic demand when the ischemic myocardium still develops wall tension, and indeed even dyskinetic myocardium has a surprisingly high oxygen consumption (21, 66). When an ischemic episode is followed by reperfusion through a stenosis, inflow is normalized to preischemic levels, but there is initially “a redistribution of myocardial blood flow with production of subendocardial ischemia in the presence of a net volume of arterial inflow, which, if properly distributed, would have been adequate to prevent myocardial ischemia” (7).

Subacute (hours) ischemia. With extension of moderate ischemia, defined by a reduction of systolic wall thickening to 60% of baseline to 5 h in chronically instrumented dogs, perfusion-contraction is still maintained (111), and this situation is associated with complete recovery of contractile function following reperfusion and lack of infarction in the previously dysfunctional myocardium. Also, 2 h of moderate coronary stenosis in chronically instrumented dogs induces matched 50% reductions in regional blood flow and contractile function (149, 150). However, when ischemia, defined by a reduction in transmural blood flow to 40% of baseline, is prolonged to 24 h in anesthetized, open-chest pigs with constant flow perfusion, perfusion-contraction matching is lost after more than 90 min, contractile function is progressively reduced without any further reduction in blood flow, and myocardial infarction develops in half of the animals, whereas viability is still maintained in the other half (Fig. 1) (138). In chronically instrumented pigs with 24 h reduction of subendocardial blood flow to 30% of baseline, there is loss of perfusion-contraction matching with associated multifocal patchy necrosis (95). In two other studies in anesthetized, closed-chest pigs with reduction of coronary inflow to 60% by a hydraulic occluder for 24 h, the relation of reduced coronary blood flow to reduced wall thickening appeared to be maintained, but coronary inflow varied substantially during the protocol. Also, some animals developed patchy necrosis (26, 27). It is currently unclear whether or not a small reduction in subendocardial blood flow can progress into hibernation.

Chronic stenosis. In pigs with a hydraulic occluder that reduced resting coronary inflow by 30–40% (28, 29), there were proportionate reductions in coronary inflow and systolic wall thickening (echocardiography) at 7 days (28) and at 4 wk (29), which were associated with patchy necrosis in some pigs (28, 29) and patchy apoptosis in all pigs (29), indicating the
myocardial blood flow at rest was still normal, whereas an stenosis. One to two months after stenosis placement, regional typical time course of adaptation to this chronic coronary persistent reduction in resting flow. Using a model of a chronic a downregulation of contractile function in response to a pig myocardium may exhibit some hyperfunction and increased hibernation (24). Similarly, using an Ameroid constrictor in pigs, Shen and Vatner (148) found decreased systolic wall function to control. They proposed a complex adjustment to progressive coronary stenosis, initially involving stunning as a consequence of episodic, transient ischemia, and subsequently hibernation (24). Similarly, using an Ameroid constrictor in pigs, Shen and Vatner (148) found decreased systolic wall thickening after 3 wk but no decrease in regional blood flow; subsequently, function returned to normal after 5 wk, again with no change in blood flow. They observed occasional episodes of transient excitement followed by stunning and patchy necrosis post mortem in some pigs (147, 148), and Shen and Vatner concluded that the phenotype of hibernating myocardiopathy downregulation of contractile function to fully prevent loss of viable cardiomyocytes. Canty and Klocke (24) implanted an Ameroid constrictor on the left circumflex coronary artery in dogs after ligation of visible, epicardial collateral and followed regional myocardial blood flow and contractile function over 2–4 wk. They observed a temporal pattern of flow-function relationship with function being reduced in excess of blood flow before and at Ameroid closure, then a match of reduced blood flow and function later after Ameroid closure, and finally the return of both blood flow and function to control. They proposed a complex adjustment to progressive coronary stenosis, initially involving stunning as a consequence of episodic, transient ischemia, and subsequently hibernation (24). Similarly, using an Ameroid constrictor in pigs, Shen and Vatner (148) found decreased systolic wall thickening after 3 wk but no decrease in regional blood flow; subsequently, function returned to normal after 5 wk, again with no change in blood flow. They observed occasional episodes of transient excitement followed by stunning and patchy necrosis post mortem in some pigs (147, 148), and Shen and Vatner concluded that the phenotype of hibernating myocardium is the result of cumulative stunning rather than that of a downregulation of contractile function in response to a persistent reduction in resting flow. Using a model of a chronic fixed stenosis, Fallavollita et al. (46, 52) again characterized a typical time course of adaptation to this chronic coronary stenosis. One to two months after stenosis placement, regional myocardial blood flow at rest was still normal, whereas an echocardiographic wall motion score was reduced, associated with increased subendocardial 2-[18F]fluoro-2-deoxy-D-glucose (FDG) uptake, consistent with chronic stunning (46). However, 3–4 mo after stenosis placement, there were both decreased resting blood flow and contractile function, again associated with increased FDG uptake, consistent with hibernation (52). The pattern of both reduced flow and function with increased FDG uptake and a small amount of replacement fibrosis was stable between 3 and 5 mo, supporting the adaptive nature of hibernation rather than progressive deterioration of an unstable situation (50). Hibernating myocardium developed regardless of whether the chronic stenosis was eventually totally occluded or remained patent; however, the inotropic reserve that was recruited by epinephrine depended on coronary reserve and was greater with a patent artery (49). Fallavollita and Canty (46) emphasized the hypothesis of a temporal progression from stunning to hibernation in which reduced resting flow is the result rather than the cause of chronic contractile dysfunction. More recently, these authors showed that the progression to matched decreases in flow and function can occur as early as after 1 wk when a 15-min partial coronary occlusion is followed by reperfusion through a critical stenosis (159).

The combination of multiple Ameroid constrictors with that of a chronic fixed stenosis in dogs over 8 wk initially induced episodic decreases in systolic wall thickening that became more persistent subsequently but no decreases in resting blood flow. Importantly, there was recovery of contractile function with revascularization, and there were only minor morphological changes in some dogs (151). After implantation of multiple Ameroid constrictors in dogs, there was decreased systolic wall thickening but unchanged regional myocardial blood flow at 2 wk, but at the final study after 6 wk there were both regions with proportionate decreases in blood flow and contractile function (perfusion-contraction mismatch) and others with decreased function but without decreased blood flow (perfusion-contraction mismatch). Although no episodes of stunning were documented, these authors also proposed a temporal progression from stunning to hibernation (57). Finally, combined stenoses of the left anterior descending and circumflex coronary arteries also accelerated the development of hibernating myocardium in pigs (47). Taken together, these experimental studies with chronic stenosis may suggest a temporal progression from repetitive ischemia-reperfusion (perfusion-contraction mismatch) to hibernation (perfusion-contraction mismatch).

Clinically, the only available method to measure regional myocardial blood flow quantitatively is positron emission tomography (PET) (15, 22, 133). However, apart from the expensive technical requirements and radiation safety concerns that prevent its widespread and frequent use, PET has serious limitations. PET flow measurements lack sufficient spatial, particularly transmural, resolution, and the lack of respiration- and/or cardiac motion-gated measurements enhances this problem such that the spatial resolution is far less than that of the microspheres technique (i.e., 1–10 g rather than 100 mg of myocardium). Also, the very few reported normal blood flow values from healthy volunteers vary widely, i.e., from 0.68 ± 0.16 (SD) ml·g⁻¹·min⁻¹ (155) to 1.02 ± 0.25 (SD) ml·g⁻¹·min⁻¹ (108), and the variation may be partly related to age (125). In consequence, in an individual patient, a major reduction in resting blood flow may go undetected. An only modest reduction in transmural blood flow by PET in regions with contractile dysfunction may well translate to a much more severe reduction in subendocardial blood flow, and subendocardial blood flow is the primary determinant of transmural wall function (63). It may therefore be more appropriate to compare blood flow in hibernating myocardium to that in a remote region in the same individual patient, although remote myocardium may exhibit some hyperfunction and increased blood flow (65). Finally, PET, as well as the microspheres technique, permits no continuous monitoring of myocardial
blood flow, and most studies only report data at one single time point. Still, with these critical caveats in mind, the vast majority of studies in patients with chronic hibernation revealed a significant reduction in baseline flow, and those who did not show this reduction failed to exclude a significant subendocardial flow reduction (20, 30–32, 53, 67, 69, 71, 88, 92, 106, 108, 110, 112, 113, 118, 120, 121, 125, 127, 152, 155, 156, 162, 163, 166, 167) (Table 1).

In conclusion, hibernating myocardium is characterized by a delicate balance of matched reductions in myocardial blood flow and function. However, the acute perfusion-contraction

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients With HM</th>
<th>Function Measure</th>
<th>Flow Tracer</th>
<th>MBF in Region With Normal Function, ml/min g⁻¹</th>
<th>MBF in Region With HM, ml/min g⁻¹</th>
<th>Criteria for HM</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Silva et al. (32)</td>
<td>12 (w/MI)</td>
<td>WMS, Echo</td>
<td>H₂¹⁵O</td>
<td>0.97±0.02</td>
<td>0.73±0.18†</td>
<td>Functional recovery with revascularization</td>
</tr>
<tr>
<td>Czernin et al. (31)</td>
<td>22 (w/MI)</td>
<td>WMS, Echo</td>
<td>¹³NH₃</td>
<td>0.83±0.20</td>
<td>0.57±0.20‡</td>
<td>Preserved FDG uptake</td>
</tr>
<tr>
<td>Sambuceti et al. (127)</td>
<td>16 (w/oMI)</td>
<td>WMS, CV</td>
<td>¹³NH₃</td>
<td>0.77±0.26</td>
<td>0.66±0.19§</td>
<td>Positive exercise test or dipyridamole Echo</td>
</tr>
<tr>
<td>Vanoverschelde et al. (163)</td>
<td>17 (w/MI)</td>
<td>WMS, CV</td>
<td>¹³NH₃</td>
<td>0.95±0.27</td>
<td>0.77±0.25ół</td>
<td>Functional recovery with revascularization relative FDG uptake increase</td>
</tr>
<tr>
<td>Maes et al. (106)</td>
<td>14 (w/oMI)</td>
<td>WMS, CV</td>
<td>¹³NH₃</td>
<td>0.94±0.11</td>
<td>0.64±0.12*</td>
<td>Preserved FDG uptake</td>
</tr>
<tr>
<td>Grandin et al. (71)</td>
<td>17 (w/woMI)</td>
<td>WMS, CV</td>
<td>¹³NH₃</td>
<td>0.97±0.18</td>
<td>0.77±0.20*</td>
<td>Preserved FDG uptake</td>
</tr>
<tr>
<td>Marzullo et al. (110)</td>
<td>14 (w/MI)</td>
<td>WMS, Echo</td>
<td>¹³NH₃</td>
<td>1.00±0.24</td>
<td>0.42±0.12‡</td>
<td>Preserved FDG uptake</td>
</tr>
<tr>
<td>Brunelli et al. (20)</td>
<td>15 (w/MI)</td>
<td>WMS Echo</td>
<td>¹³NH₃</td>
<td>0.83±0.26</td>
<td>0.65±0.27‡</td>
<td>Preserved FDG uptake</td>
</tr>
<tr>
<td>Conversano et al. (30)</td>
<td>17 (w/woMI)</td>
<td>WMS, Echo, RNV</td>
<td>H₂¹⁵O</td>
<td>0.85±0.36</td>
<td>0.65±0.28ד</td>
<td>Functional recovery with revascularization relative FDG uptake increase</td>
</tr>
<tr>
<td>Gerber et al. (69)</td>
<td>24 (w/woMI)</td>
<td>WMS, Echo</td>
<td>¹³NH₃</td>
<td>0.82±0.22</td>
<td>0.84±0.27ُ</td>
<td>Functional improvement with revascularization preserved FDG uptake</td>
</tr>
<tr>
<td>Marinho et al. (108)</td>
<td>30 (w/MI)</td>
<td>WMS, RNV</td>
<td>H₂¹⁵O</td>
<td>0.92±0.25</td>
<td>0.87±0.31ė</td>
<td>Functional recovery with revascularization preserved FDG uptake</td>
</tr>
<tr>
<td>Mäki et al. (112)</td>
<td>7 (w/MI)</td>
<td>WMS, Echo</td>
<td>H₂¹⁵O</td>
<td>1.02±0.23</td>
<td>0.81±0.27ƒ</td>
<td>Functional improvement with revascularization preserved FDG uptake</td>
</tr>
<tr>
<td>Shivalkar et al. (125, 152)</td>
<td>18 (w/woMI)</td>
<td>REF, RNV</td>
<td>¹³NH₃</td>
<td>0.93±0.13</td>
<td>0.64±0.13§</td>
<td>Functional improvement with revascularization preserved FDG uptake PET mismatch, inotropic reserve</td>
</tr>
<tr>
<td>Sun et al. (125, 155)</td>
<td>12 (5) (w/woMI)</td>
<td>WMS, Echo</td>
<td>¹³NH₃</td>
<td>0.73±0.23 (0.81±0.26)</td>
<td>0.53±0.33ë</td>
<td>Functional improvement with revascularization preserved FDG uptake</td>
</tr>
<tr>
<td>Mäki et al. (113)</td>
<td>7 (w/MI)</td>
<td>WMS, Echo</td>
<td>H₂¹⁵O</td>
<td>0.81±0.14</td>
<td>0.59±0.24</td>
<td>Functional improvement with revascularization preserved FDG uptake</td>
</tr>
<tr>
<td>Wolpers et al. (167)</td>
<td>30 (w/MI)</td>
<td>WMS, CV</td>
<td>¹¹C]Acetate</td>
<td>1.04±0.27</td>
<td>0.73±0.18öl</td>
<td>Improvement with revascularization in flow and function</td>
</tr>
<tr>
<td>Gerber et al. (67)</td>
<td>16 (w/woMI)</td>
<td>WMS, Echo</td>
<td>H₂¹⁵O</td>
<td>0.74±0.06</td>
<td>0.83±0.06а</td>
<td>Functional recovery with revascularization PET mismatch, inotropic reserve</td>
</tr>
<tr>
<td>Fath-Ordubadi et al. (53)</td>
<td>24 (w/MI)</td>
<td>WMS, Echo</td>
<td>H₂¹⁵O</td>
<td>0.89±0.24</td>
<td>0.82±0.26§</td>
<td>Functional recovery with revascularization PET mismatch, inotropic reserve</td>
</tr>
<tr>
<td>Kitsujo et al. (92)</td>
<td>26</td>
<td>WMS, MRI, RNV</td>
<td>¹³NH₃</td>
<td>0.64±0.24</td>
<td>0.63±0.27ε</td>
<td>Functional recovery with revascularization PET mismatch, inotropic reserve</td>
</tr>
<tr>
<td>Pagano et al. (121)</td>
<td>22 (w/MI)</td>
<td>WMS, Echo</td>
<td>H₂¹⁵O</td>
<td>1.02±0.23</td>
<td>1.02±0.24δ</td>
<td>Functional recovery with revascularization PET mismatch, inotropic reserve</td>
</tr>
<tr>
<td>Tawakol et al. (156)</td>
<td>8 (w/woMI)</td>
<td>WMS, Echo</td>
<td>¹³NH₃</td>
<td>1.14±0.52</td>
<td>0.48±0.15δ</td>
<td>Functional recovery with revascularization PET mismatch, inotropic reserve</td>
</tr>
<tr>
<td>Vanoverschelde et al. (162)</td>
<td>19 (w/woMI)</td>
<td>WMS, Echo</td>
<td>¹³NH₃</td>
<td>0.77±0.18</td>
<td>0.82±0.29δ</td>
<td>Functional recovery with revascularization PET mismatch, inotropic reserve</td>
</tr>
<tr>
<td>Pagano et al. (120)</td>
<td>30 (w/MI)</td>
<td>WMS, Echo</td>
<td>H₂¹⁵O</td>
<td>0.95±0.03</td>
<td>0.95±0.03α</td>
<td>Functional recovery with revascularization PET mismatch, inotropic reserve</td>
</tr>
<tr>
<td>Wiggers et al. (166)</td>
<td>11 (w/woMI)</td>
<td>WMS, Echo</td>
<td>¹³NH₃</td>
<td>0.69±0.20</td>
<td>0.59±0.16β</td>
<td>Functional recovery with revascularization PET mismatch, inotropic reserve</td>
</tr>
<tr>
<td>Itoh et al. (88)</td>
<td>7 (w/woMI)</td>
<td>WMS, CV</td>
<td>H₂¹⁵O</td>
<td>1.13±0.32</td>
<td>0.78±0.27β</td>
<td>Functional recovery with revascularization PET mismatch, inotropic reserve</td>
</tr>
<tr>
<td>Nowak et al. (118)</td>
<td>15 (w/MI)</td>
<td>WMS, CV</td>
<td>H₂¹⁵O</td>
<td>0.66±0.02</td>
<td>0.61±0.03adays</td>
<td>Functional recovery with revascularization PET mismatch, inotropic reserve</td>
</tr>
</tbody>
</table>

Values are ± SD. w/woMI, with/without myocardial infarction (MI); WMS, wall motion score; CV, contrast ventriculography; RNV, radionuclide ventriculography; Echo, echocardiography; MRI, magnetic resonance imaging; MBF, myocardial blood flow; HM, hibernating myocardium; FDG, 2-[¹⁸F] fluoro-2-deoxy-D-glucose. P values are compared with MBF with normal function; aP < 0.001; bP < 0.05; cP < 0.01; dP < 0.02; eNS, not significant; fP = 0.036; gP < 0.005; hP = 0.0004; iP = 0.16. Values in parentheses correspond to reanalysis of data for Sun et al.
matching during short-term hibernation is not necessarily sustained over more than several hours. Perfusion-contraction matching in chronic hibernation probably develops from a single or possibly repetitive bouts of stress-induced ischemia and reperfusion in the presence of a severe coronary stenosis. However, because no single study has monitored both flow and function continuously, the actual history of hibernating myocardium remains unclear. It is currently also unclear whether the repetitive ischemia per se and/or the subsequent stunning is essential to induce the phenotype of chronic hibernation.

Metabolism of Hibernating Myocardium

Short-term hibernation. The recovery of the initially disturbed substrate and energy metabolism is taken as evidence for the fact that downregulation of contractile function serves to restore the myocardial energy balance. In anesthetized pigs coronary venous pH and lactate extraction are reduced and coronary venous PCO₂ is increased within a few minutes after acute coronary inflow reduction, but these parameters gradually return toward control values during 180 min of continued moderate ischemia (Fig. 3) (54). An early increase in myocardial lactate production followed by a decline to normal or near-normal levels during sustained moderate ischemia was confirmed in a number of subsequent studies, using blood-perfused isolated rabbit hearts (41) or anesthetized open-chest pigs with regional short-term hibernation of up to 7 days duration (3, 26, 28, 79, 132, 136). Recovery of pH during sustained ischemia was also confirmed (132).

The exact source of lactate production (contribution of glycogen stores or exogenous glucose uptake), the reason for its attenuation [reduced anaerobic glycolysis, augmented glutamate-pyruvate transamination, and clearance of alanine (116)], and its functional consequences [contribution to ATP production and preservation of ventricular function (41) or contribution to acidosis and reduction of ventricular function] are not entirely clear at present time. Glucose uptake is enhanced with 24 h coronary hyperperfusion in anesthetized pigs (26, 27) and in pigs with chronic coronary stenosis and persistent reductions in regional myocardial blood flow and contractile function over months (46, 50). Amino acids contribute to myocardial substrate metabolism in short-term hibernation; their content is reduced by 50–70% during 90 min of moderate coronary hyperperfusion. Such a decrease in amino acid pool size may also affect the calculation of myocardial oxygen consumption from the rate constant of acetate clearance in sequential PET measurements during prolonged myocardial ischemia (137).

With moderate ischemia (myocardial blood flow on the average at 30% of control) over 5 h in anesthetized dogs, myocardial ATP content was initially decreased and then stabilized, in contrast to more severe ischemia (myocardial blood flow on the average at 10% of control) with progressive loss of ATP (117). Decreased ATP content over time was also observed during continued myocardial ischemia in isolated rat (129), rabbit (94), and piglet (38) hearts and in anesthetized pig (3, 122, 136) and dog (168) models of short-term hibernation. In contrast to the steady decline in ATP content and like the attenuation of lactate production over time, the myocardial creatine phosphate content was significantly decreased immediately after the onset of ischemia but gradually recovered over time toward control values (Fig. 4) (122), whereas regional myocardial blood flow and contractile function were persistently reduced (3, 38, 122, 129, 136, 168).

In a more complex approach, simultaneous measurements of ATP, creatine phosphate, creatine, and inorganic phosphate contents in freeze-clamped, saline-perfused guinea pig hearts permitted the calculation of the free energy change of ATP hydrolysis (64). The free energy change of ATP hydrolysis was markedly decreased at 10 min coronary hypoperfusion but, like creatine phosphate content, recovered back to control values.

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**Fig. 3.** Reversal of lactate uptake to net lactate production at 5 min moderate ischemia with recovery over 3 h continued ischemia. *P < 0.05 vs. pre (before stenosis); **P < 0.01 vs. pre; ###P < 0.01 vs. 5 min poststenosis (STNS). (Reproduced with permission from Lipincott Williams and Wilkins; Fedele PA, Gewirtz H, Capone RJ, Sharaf B, and Most AS. Metabolic response to prolonged reduction of myocardial blood flow distal to a severe coronary artery stenosis. Circulation 78: 729–735, 1988.)

**Fig. 4.** Decrease in phosphocreatine (PCr) content at 5 min moderate ischemia and full recovery after 60 min. (Reproduced with permission from Lippincott Williams and Wilkins; Pantely GA, Malone SA, Rhen WS, Anselone CG, Arai A, Bristow J, and Bristow JD. Regeneration of myocardial phosphocreatine in pigs despite continued moderate ischemia. Circ Res 67: 1481–1493, 1990.)
during 60 min of hypoperfusion. Similarly, in a porcine model of regional short-term hibernation, sequential biopsy-based measurements of ATP, creatine phosphate, creatine, and inorganic phosphate revealed a decrease in the free energy change of ATP hydrolysis during early ischemia with a subsequent recovery during continued 90 min ischemia (Fig. 5) (109).

Several explanations for the recovery of creatine phosphate content and the restoration of an energetic balance have been advanced. In isolated, saline-perfused rat hearts the recovery of creatine phosphate content during ongoing moderate low-flow ischemia was only observed in the presence of glycolytic substrate (130). On the other hand, in a porcine model of short-term hibernation, the anaerobic ATP production was insufficient to account for the recovery of creatine phosphate (3). Also, attenuation of lactate production during prolonged hypoperfusion is inconsistent with an important role of glycolytic ATP production for the recovery of creatine phosphate (3, 132, 136). Thus glycolytic ATP production may be necessary (but nevertheless insufficient) to allow metabolic adaptation to ischemia.

The most plausible explanation for the recovery of creatine phosphate content and the free energy change of ATP hydrolysis is indeed a downregulation of contractile function, i.e., energy demand. Glycolytic ATP production and also loss of adenine nucleotides (94) may contribute to the restoration of an energetic steady state but probably play a relatively small role. In support of this view, pharmacological reduction of contractile function by intracoronary lidocaine prevented the decreases in ATP and creatine phosphate otherwise seen during a marked reduction in regional myocardial blood flow in anesthetized pigs (131).

Chronic hibernation. Hibernating myocardium of pigs with 3 mo chronic coronary stenosis is characterized not only by matched decreases in regional myocardial blood flow and function but also by reduced myocardial oxygen consumption and lack of lactate extraction, even during inotropic stimulation (51). Increased glucose utilization is a consistent finding in animals with chronic stenosis and perfusion-contraction matching (50, 52) but also in the preceding situation of chronic stunning and perfusion-contraction mismatch (46, 98). ATP and creatine phosphate contents were normal compared with those in a remote reference region in pigs with chronic coronary stenosis and persistent reductions in regional myocardial blood flow and function (114).

In patients, preserved metabolic activity in chronically dysfunctional myocardium was initially demonstrated in a more or less qualitative fashion from $^{18}$FDG uptake using PET (16, 100, 160). More recently, however, also quantitative data on glucose utilization during a standardized hyperinsulinemic euglycemic clamp have become available. In such studies, preservation of FDG uptake in areas with reduced flow and function was consistently predictive of eventual contractile recovery following reperfusion (68, 93, 162) and of prognosis (1).

Reversibly dysfunctional myocardium also had normal lactate, glycogen, and ATP concentrations in one study (166) but increased lactate and decreased ATP and creatine phosphate in another study (165). The obvious difference was the lack of replacement fibrosis in the former study.

An overall measure of oxidative metabolism is derived from the clearance kinetics of $^{11}$Cacetate using PET. The rate constant of acetate clearance in areas with chronic hibernation was reduced (30, 31, 163), largely in relation to the reduced blood flow (30, 74). Recruitment of inotropic reserve in such hypoperfused, but viable myocardium, was associated with increased oxidative metabolism, as indicated by an increase in the rate constant of acetate clearance (74).

In conclusion, the adaptive nature of hibernation manifests as a recovery of an energetic balance in short-term hibernation and preservation of metabolic activity in chronic hibernation.

Inotropic Reserve in Hibernating Myocardium

Although baseline contractile function is depressed, the hypoperfused myocardium retains its responsiveness to an inotropic challenge (Fig. 6) (136). When, after 85–90 min of reduction of transmural blood flow by about 50% in anesthetized pigs, dobutamine is infused selectively into the ischemic region, contractile function transiently increases, although regional blood flow remains reduced.

Imposition of an inotropic stimulus on the short-term hibernating myocardium disrupts the adaptive process, as indicated by the once more decreased myocardial creatine phosphate content and increased lactate production. An inotropic response of regional short-term hibernating myocardium to dobutamine at the expense of increased lactate production was subsequently confirmed, again in anesthetized pigs (27). Similarly, positive inotropic responses of porcine regional short-term hibernating myocardium were observed in response to postextrasystolic potentiation and intracoronary calcium (39, 79). Enhanced regional contraction was again associated with increased lactate production and decreased creatine phosphate content (79).

A persistent inotropic reserve in response to dobutamine was also apparent in anesthetized pigs with 24 h coronary stenosis and reduced resting flow. The inotropic response to dobutamine was typically biphasic, with increased wall thickening at lower doses and contractile dysfunction at higher doses and was associated with increased net lactate production (27).
Importantly, this is the only study that not only demonstrated persistence of inotropic reserve at the expense of metabolic recovery, but also recovery of contractile function following removal of the stenosis over 7 days. The typical biphasic response to dobutamine was confirmed in pigs with 1 mo coronary stenosis, reduced baseline blood flow, and minimal infarction (154). Recently, an enhancement of the inotropic response to low-dose dobutamine with the addition of nitroglycerin was reported, suggesting that inotropic reserve is in part dependent on coronary reserve (105). In pigs with chronic coronary stenosis, the magnitude of inotropic reserve in response to epinephrine also depended on coronary reserve (49).

With more sustained inotropic stimulation over 90 min in short-term hibernating myocardium of anesthetized pigs, the metabolic deterioration is followed by the development of myocardial infarction (141). In pigs with months of chronic coronary stenosis, minimal patchy necrosis (1–6% of the area at risk) was found with triphenyltetrazolium chloride staining and histology in a minority of pigs (26, 27, 138), and the findings were similar when the stenosis was maintained for 7 days or 4 wk in a few pigs (28, 29). Electron microscopy revealed loss of myofilaments and sarcomeres and an increased number of glycogen deposits (26). No necrosis, but patchy fibrosis and a more generalized increase in connective tissue (to about two-fold of that in the normal remote myocardium), were found in pigs with chronic coronary stenosis and persistently reduced myocardial blood flow for more than a month (52, 114, 115). In conscious pigs with a chronic Ameroid constrictor and no reduction in regional blood flow at the time of peak dysfunc-

**Morphology**

**Short-term hibernation.** No increase in the expression of proapoptotic proteins (Fas, Bak) was found with 90 min of regional short-term hibernation in pigs (10). In chronically instrumented dogs with 2–5 h coronary stenosis and perfusion-contraction matching, there were perinuclear aggregates of disrupted myofibrils associated with areas of glycogen accumulation and heterochromatin clumping adjacent to the inner nuclear envelope (150).

**Chronic hibernation.** With chronic coronary stenosis for 24 h, minimal patchy necrosis (1–6% of the area at risk) was found with triphenyltetrazolium chloride staining and histology in a minority of pigs (26, 27, 138), and the findings were similar when the stenosis was maintained for 7 days or 4 wk in a few pigs (28, 29). Electron microscopy revealed loss of myofilaments and sarcomeres and an increased number of glycogen deposits (26). No necrosis, but patchy fibrosis and a more generalized increase in connective tissue (to about two-fold of that in the normal remote myocardium), were found in pigs with chronic coronary stenosis and persistently reduced myocardial blood flow for more than a month (52, 114, 115). In conscious pigs with a chronic Ameroid constrictor and no reduction in regional blood flow at the time of peak dysfunc-

**Table 2. Characterization of short-term hibernating myocardium**

<table>
<thead>
<tr>
<th>Characterization of Short-Term Hibernating Myocardium</th>
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<tbody>
<tr>
<td>Sustained balance between the reduced regional myocardial blood flow and the reduced contractile function (sustained perfusion-contraction-matching)</td>
</tr>
<tr>
<td>Recovery of metabolic parameters (creatinine phosphate, lactate, ΔG) during persistent ischemia</td>
</tr>
<tr>
<td>Recruitable inotropic reserve at the expense of metabolic recovery</td>
</tr>
<tr>
<td>Recovery of contractile function during reperfusion</td>
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<tr>
<td>Lack of necrosis</td>
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**Fig. 6.** Inotropic stimulation with dobutamine (+DOB) increases contractile function without increasing blood flow and disrupts the recovery of creatine phosphate and lactate consumption. (Reproduced with permission from Lippincott Williams and Wilkins; Schulz R, Guth BD, Pieper K, Martin C, and 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* 70: 1282–1295, 1992.)
tion, post mortem histology revealed multifocal areas of fibrosis, surrounded by only a small rim of cells with myofibrillar lysis and increased amounts of glycogen that were similar to the phenotype of human hibernating myocardium (147).

In pigs with chronic (>24 h) coronary artery stenosis, clear evidence for apoptosis was obtained from both in situ labeling with terminal deoxynucleotidyl transferase and ex vivo demonstration of DNA laddering on electrophoresis (29). The apoptosis had a patchy distribution and was predominantly seen in the subendocardium (affecting about 10% of the subendocardium at risk). Apoptosis was seen already with 24 h of coronary stenosis, and the incidence of apoptosis was not further increased with 7 days or 4 wk coronary stenosis. The incidence of apoptosis correlated with the severity of coronary hypoperfusion and was higher in pigs that had also patchy infarction than in pigs without infarction (29). Apoptotic loss of cardiomyocytes and compensatory hypertrophy characterize the hibernating myocardium of pigs with 3 mo coronary stenosis (Fig. 7) (99). Therefore, programmed death of some cardiomyocytes might contribute to hibernation by shunting the available energy supply to the still viable cardiomyocytes and improve the likelihood of their survival, but presently this is entirely speculative (77).

In 1981, before the phenomenon of hibernation was recognized, Flameng et al. (58) already described in humans typical alterations in myocardial biopsies taken from areas that were dysfunctional and recovered after surgical revascularization. Loss of cardiomyocytes and loss of contractile material within the remaining cardiomyocytes, increased number of glycogen deposits, and increased interstitial fibrosis are characteristic findings and have been confirmed in a number of studies since then (5, 6, 43, 44, 144, 152, 163). The sarcoplasmic reticulum is reduced (5, 58). Also, numerous small doughnut-like mitochondria are consistently observed (5, 43, 44). Loss of contact sites between the inner and outer mitochondrial membranes is taken to indicate reduced oxidative phosphorylation and mitochondrial creatine kinase activity (9). The contractile protein myosin, the thin filament complex titin, and α-actinin are reduced (43, 44, 144), and the distribution of titin within the cardiomyocytes is altered (5, 6). The cytoskeleton, consisting of desmin, tubulin, and associated proteins such as vinculin, is disorganized and these proteins in part accumulate (43, 44). Decreased connexin 43 content and reduced gap junction size may predispose to arrhythmias and contribute to impaired excitation-contraction coupling (90). Autophagic and apoptotic cell death contribute to loss of cardiomyocytes (45).

The interstitial space is characterized by an increased amount of fibrosis (4, 44, 58, 144, 163). Cellular particles sequestered into the extracellular space form cellular debris, and the number of macrophages and fibroblasts is increased (43). Extracellular matrix and structural proteins, i.e., all collagens and fibronectin, are increased (4, 17, 43, 44). The coronary microcirculation distal to a chronic stenosis exhibits hypertrophy of the smaller microvessels and atrophy and reduced protein synthesis of larger microvessels (83, 115).

Two studies by Borgers and colleagues (6, 18) emphasized the dedifferentiated phenotype of hibernating myocardium because α-smooth muscle actin, cardiotin, and titin were found to be expressed in patterns resembling an embryonic phenotype and proposed contractile unloading as the underlying mechanism (17). Somewhat in contrast, Schaper’s laboratory (43, 44, 144) recognized the adaptive nature of some morphological changes and their reversibility up to a certain degree but emphasized the degenerative nature of more severe cardiomyocyte alterations and increased fibrosis. It is somewhat difficult to estimate how much of the dysfunctional, hibernating myocardium was morphologically altered, because all analyses are based on biopsies that are not necessarily representative for the entire hibernating region. It is therefore not surprising that functional recovery inversely correlated with the amount of fibrotic tissue in some (44, 152) but not all (144) studies. Also, a recent study in pigs with chronic regional hibernation noted important alterations in the remote control myocardium, mak-

Fig. 7. Increased number of apoptotic myocytes in chronically hibernating myocardium with compensatory hypertrophy, as reflected by largely unchanged myocyte area but decreased number of myocytes. (Reproduced with permission from Lippincott Williams and Wilkins; Lim H, Fallavollita JA, Hard R, Kerr CW, and Canty JM. Profound apoptosis-mediated regional myocyte loss and compensatory hypertrophy in pigs with hibernating myocardium. Circulation 100: 2380–2386, 1999.)
ing intraindividual comparisons of hibernating and control tissue mandatory (159).

In conclusion, the morphology of myocardial hibernation is characterized by signs of atrophy, most notably of the contractile myofilbrils, and signs of degeneration, most notably in the interstitial space, and possibly dedifferentiation (Table 3).

**Mechanisms Underlying Acute and Subacute Perfusion-Contraction Matching and Metabolic Recovery**

Events triggering the development of short-term hibernation and relation to acute ischemic preconditioning. Hibernation-like metabolic adaptation to a severe sustained (4 h) low-flow ischemia was reported in studies with isolated, buffer-perfused rabbit hearts in which there was a preceding short episode (10 min) of no-flow ischemia (56). In these hearts, the early decline in contractile function was more pronounced and significantly faster than in control hearts that did not have the brief episode of no-flow ischemia. The rapid decline in contractile function during the brief episode of no-flow ischemia was accompanied by a greater decrease in interstitial (56) and intracellular (161) pH, and the contractile quiescence was attributed to a faster development of myocardial acidosis. During reperfusion following the sustained ischemia, only a transient creatine kinase release occurred. On the basis of these findings it was proposed that the development of myocardial hibernation requires an initial period of severe ischemia, during which the rapid decrease in interstitial (56) and intracellular (161) pH, which initiates the decrease in contractile function, facilitates the restoration of the balance between energy supply and energy demand. The protection provided by the initial period of no-flow ischemia was associated with increased expression of heat shock protein 72, but a cause-effect relationship was not established (55). Also in anesthetized pig hearts in situ, infarct size resulting from sustained (90 min) low-flow ischemia was also reduced by a short (10 min) period of no-flow ischemia immediately before the sustained ischemia (139). These experimental studies attributed a potentially important role to an initial stimulus of severe ischemia as being critical to “triggering” the development of a protective state with preserved viability during a subsequent period of sustained, less severe ischemia and would put the phenomenon of short-term hibernation into the context of acute preconditioning (134).

However, in contrast to the above studies, better preservation of coronary venous pH and PCO2 as well as less lactate production and reduced infarct size were demonstrated in anesthetized pigs when a sustained episode of severe ischemia was preceded by a period of gradual but continuous flow reduction (87). Also in anesthetized pigs, a gradual decrease in coronary blood flow was associated with a parallel decrease in regional contractile function, attenuated lactate production, and ATP depletion, suggesting that downregulation of myocardial energy requirements can keep pace with the gradual decline in coronary blood flow (2). Thus both an initial intense stimulus of severe flow reduction and a gradually developing moderate flow reduction can apparently facilitate an adaptive response of the myocardium.

Thus it appears that the temporal development of hibernating myocardium is not really specific and that short-term hibernation is not closely linked to acute ischemic preconditioning. In support of this distinction, adenosine, opioids, and activation of ATP-dependent K-channels, which are decisive to ischemic preconditioning (135, 140, 142), are not involved in porcine short-term hibernation (119, 135, 143).

**Potential mechanisms of short-term hibernation.** The mechanisms responsible for the development of short-term myocardial hibernation remain largely unclear at present. There are no alterations in the β-adrenoceptor density or affinity in anesthetized pigs with 90 min of regional short-term hibernation (141). However, more detailed analyses of the adrenergic signal transduction cascade are lacking.

Endogenous nitric oxide (NO) is also not the biochemical signal for perfusion-contraction matching but sets the level for such matching, i.e., with inhibition of NO synthesis regional myocardial function for any level of blood flow and oxygen consumption is reduced in anesthetized open-chest (78) and in sedated, chronically instrumented pigs (96) subjected to 90 min acute ischemia.

A transient activation of p38 mitogen-activated protein (MAP) kinase during early myocardial ischemia has been found in a porcine model of short-term hibernation (103), and potentially such transient p38 MAP kinase activation could initiate subsequent alterations in gene expression and protein synthesis. However, pharmacological inhibition of p38 MAP kinase activation failed to improve the depressed contractile function in an isolated mouse heart model of short-term hibernation (70).

**Excitation-contraction coupling and short-term hibernation.** In a porcine model of regional short-term myocardial hibernation, after 90 min of ischemia, at a time when lactate production was attenuated and the creatine phosphate content was restored to a value no longer significantly different from the respective control value, the maximal contractile responses to graded intracoronary calcium infusion and to postextrasystolic potentiation were decreased. However, the relationships between the fractional increases in regional contractile function and dose of added intracoronary calcium or the postextrasystolic time interval, respectively, were not different. Thus overall calcium responsiveness of short-term hibernating myocardium was substantially reduced. The reduction of calcium responsiveness was, however, attributable to a decrease in maximal developed force and not to a decrease in calcium sensitivity (Fig. 8) (79). Such decreased calcium responsiveness persists up to 12 h of sustained moderate ischemia when there is no longer perfusion-contraction matching (138). The source and nature of the factor(s) that decrease(s) calcium

### Table 3. Morphological features of chronic hibernation

<table>
<thead>
<tr>
<th>Cardiomyocyte alterations</th>
<th>Interstitial Alterations</th>
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<tbody>
<tr>
<td>Loss of myofilaments</td>
<td>Increased amount of matrix and structural proteins (fibronecetin and all collagens)</td>
</tr>
<tr>
<td>of sarcolemmal reticulum</td>
<td>Increased number of macrophages and fibroblasts (i.e., Fibrosis)</td>
</tr>
<tr>
<td>Loss of connexin</td>
<td></td>
</tr>
<tr>
<td>Numerous small, doughnut-like mitochondria</td>
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<tr>
<td>Disorganization of cytoskeleton</td>
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<tr>
<td>Sequestration of cellular particles into extracellular space (i.e., Atrophy and Apoptosis)</td>
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<tr>
<td>Also: increased number of glycogen deposits</td>
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responsiveness in short-term hibernating myocardium are not presently clear. In this respect, it was proposed that hypoxic endothelial cells release an as-yet-unknown factor that inhibits the contraction of isolated adult rat cardiomyocytes without any effect on the calcium transient (145). The expression of calcium regulatory proteins (sarcoplasmic reticulum calcium-ATPase, phospholamban, calsequestrin, and troponin inhibitor) is not altered during 90 min of short-term hibernation in anesthetized pigs (102, 103), and these proteins continue to have unaltered expression even after 24 h of sustained ischemia, as does heat shock protein 72 (138). Also, there is no troponin I degradation after 1 h of moderate ischemia and reperfusion in pigs (158).

In conclusion, the only mechanistic feature of short-term hibernation, which has been identified so far, is reduced calcium responsiveness. Other than that, the biochemical signal cascade mediating perfusion-contraction matching and metabolic recovery remains to be established.

Mechanisms underlying chronic hibernation and relation to repetitive stunning, delayed preconditioning, coronary microembolization, and inflammation. There is some evidence that acute perfusion-contraction matching, metabolic recovery, and viability cannot always be maintained during sustained moderate ischemia for more than a few hours but that chronic hibernation results from repetitive bouts of ischemia-reperfusion and a temporal progression from perfusion-contraction mismatch to renewed perfusion-contraction matching (see Quantitative Relation of Flow and Function. Chronic stenosis). The mechanisms of such renewed perfusion-contraction matching are as unclear as those of the acute perfusion-contraction matching in short-term hibernation. Theoretically, the chronically reduced contractile function could reduce myocardial energy demand and, through metabolic regulation, reduce coronary blood flow in a causal sequence opposite to that assumed for short-term hibernation. This idea has not been thoroughly tested and would probably require the establishment of relationships of coronary blood flow to both contractile function and oxygen consumption in chronically hibernating myocardium. However, a recent study that induced chronic hibernation through repeated episodes of 90-min coronary stenosis and 12-h reperfusion in chronically instrumented pigs found that the flow-function relationship in chronic hibernation is different from that in normal myocardium, suggesting an alteration of metabolic coronary blood flow regulation (91).

This functional study goes along with morphological studies demonstrating remodeling (decreased lumen, increased wall thickness) of the poststenotic coronary circulation in pigs with chronic stenosis and hibernation (83, 115).

Clearly, ischemia-reperfusion initiates a genetic program of cellular survival (34, 35), which is not expressed at the protein level yet during short-term hibernation but can contribute to chronic hibernation, which develops from repeated episodes of ischemia-reperfusion activating such survival program. One protein that has been identified to have reduced expression and activity in chronically hibernating myocardium is glycogen synthase kinase-3ß, which is possibly not only responsible for the observed glycogen deposits but also involved in cellular survival (91). Interestingly, inhibition of glycogen synthase kinase-ß has also been implicated in opioid-induced cardioprotection (72). Recently, the upregulation of anti-apoptotic (IAP) and cytoprotective genes and proteins (heat shock protein 70 and hypoxia-inducible factor-1-ß) was reported in both a pig model of chronic hibernation and human hibernating myocardium (33). The idea of altered protein expression and activity puts the adaptation of chronic hibernation into the context of delayed preconditioning where enhanced expression and activity of NO synthase and cyclooxygenase have been established and identified as causal for the observed cardioprotection (13, 14). Specifically, enhanced immunoreactivity of inducible NO synthase (iNOS) and cyclooxygenase-2 was also found in hibernating myocardium of humans (8). Interestingly, enhanced iNOS and cyclooxygenase-2 expression are not only common denominators of delayed preconditioning and chronic hibernation but also of inflammation and chronic hibernation. Indeed, a number of studies provided evidence for inflammation in hibernating myocardium. In a chronic mouse model with repeated brief ischemia-reperfusion, absence of infarction, and decreased regional contractile function, there was enhanced expression of chemokines at the mRNA level, extensive macrophage infiltration, and finally replacement fibrosis (36). Recruitment of mononuclear leukocytes and enhanced immunoreactivity of monocyte chemotactic protein-1 was also found in hibernating myocardium of humans (59). Human hibernating myocardium, as identified by a biphasic response to dobutamine and functional recovery after revascularization, also had higher tumor necrosis factor-α (TNF-α) and iNOS...
mRNA than remote control myocardium (89). These features of inflammation in chronically hibernating myocardium are remarkably reminiscent of what is seen in an experimental model of coronary microembolization where progressive contractile dysfunction is induced through an inflammatory signal cascade (153, 157). It therefore appears possible that repeated subclinical plaque fissuring and rupture results in showers of microemboli, which, through an inflammatory signal cascade, contribute to the hibernation phenotype (81). Regardless of whether or not coronary microembolization is the initiating event, the enhanced expression of TNF-α in viable myocardium surrounding a microinfarct is obviously capable of reducing contractile function in a much larger area (40), and this may also be relevant to chronic hibernation, where there is little, but significant, and patchy myocardial infarction and contractile dysfunction of a much larger region (Fig. 9). TNF-α and iNOS serve both a cardioprotective and a detrimental function in myocardial ischemia-reperfusion with an only narrow "therapeutic" window, and therefore myocardial hibernation may result from a delicately balanced expression of these and other factors in a given microenvironment (128).

Apart from its pathogenesis, the phenotype of chronic hibernation, different from short-term hibernation, is characterized by altered adrenergic control. There is a heterogeneous impairment of norepinephrine uptake in pigs with chronic hibernation (101), and there is decreased β-adrenoceptor density in conscious dogs with chronic hibernation (151) and decreased β-adrenoceptor and reciprocally increased α-adrenoceptor density in hibernating myocardium of humans (Fig. 10) (146). However, the causal relation of these observations to the observed contractile dysfunction and its potentially adaptive nature remain unclear.

There is also experimental evidence for reduced calcium responsiveness in chronic hibernation. In isolated cardiomyocytes from pigs with 4–6 wk chronic coronary stenosis, the calcium transient was almost normal, whereas the maximal contractile response to calcium was reduced. Protein levels of sarcoplasmic reticulum-ATPase, phospholamban, and the sodium-calcium exchanger were not reduced, and there was no troponin I degradation in this study (12). In pigs with 3 mo chronic stenosis, sarcoplasmic reticulum-ATPase and phospholamban were reduced at the mRNA and protein level, with no change in calasequestrin and increased heat shock protein 72 (48). It appears possible that the latter study reflected a more advanced state of hibernation than the former, but no changes at all were found for sarcoplasmic reticulum-ATPase, phospholamban, calasequestrin, and heat shock protein 72 expression in human hibernating myocardium (104).

In conclusion, chronically hibernating myocardium may emerge from repetitive ischemia-reperfusion and shares the upregulation of a genetic survival program with delayed preconditioning and inflammatory signs with coronary microembolization. Alterations in adrenergic control and in calcium responsiveness are seen, but their causal role and exact pathogenesis remain to be resolved. Phenomenologically, the similarity of features of chronic hibernation with those of heart
failure, be that of ischemic or nonischemic origin, is obvious: apoptosis, patchy fibrosis, inflammation, and depressed β-adrenergic control.

Hibernation and Arrhythmias

In a recent meta-analysis of 3,088 patients with chronic coronary artery disease and left ventricular dysfunction, patients with evidence of myocardial viability had tremendous benefit from revascularization versus medical therapy in terms of 3.2% versus 16% annual mortality over 25 ± 10 mo follow-up. In contrast, patients without evidence of myocardial viability had intermediate mortality that was not different between revascularization (7.7%) and medical therapy (6.2%) (1). Excess death in the population with hibernating myocardium is to a large extent sudden, presumably arrhythmic death (37).

Both an arrhythmogenic substrate and specific triggering events can contribute to the precipitation of such lethal arrhythmias. Scar formation and a reduction in inhomogeneity of connexin 43 expression in human hibernating myocardium (90) may contribute to alterations in electrical impulse propagation and reentry. However, also the surviving cardiomyocytes contribute to the pathogenesis of arrhythmias. Isolated cardiomyocytes from chronically hibernating myocardium in pigs are hypertrophied and have reduced contraction and striking prolongation of the action potential (12), rendering them potentially prone to afterdepolarization. In a recent retrospective analysis (25), pigs with chronic hibernation had a substantial incidence of sudden death, and ventricular fibrillation was monitored in a number of cases. Obvious triggering stimuli for the initiation of arrhythmias would be sympathetic activation and acute ischemia, but that has not been analyzed in detail yet (82).

In conclusion, hibernating myocardium is prone to develop potentially lethal arrhythmias.

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