Hibernating Myocardium

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Heusch, Gerd. Hibernating Myocardium. Physiol. Rev. 78: 1055–1085, 1998.—Decreased myocardial contraction occurs as a consequence of a reduction in blood flow. The concept of hibernation implies a downregulation of contractile function as an adaptation to a reduction in myocardial blood flow that serves to maintain myocardial integrity and viability during persistent ischemia. Unequivocal evidence for this concept exists in scenarios of myocardial ischemia that lasts for several hours, and sustained perfusion-contraction matching, recovery of energy and substrate metabolism, the potential for recruitment of inotropic reserve at the expense of metabolic recovery, and lack of necrosis are established criteria of short-term hibernation. The mechanisms of short-term hibernation, apart from reduced calcium responsiveness, are not clear at present. Experimental studies with chronic coronary stenosis lasting more than several hours have failed to continuously monitor flow and function. Nevertheless, a number of studies in chronic animal models and patients have demonstrated regional myocardial dysfunction at reduced resting blood flow that recovered upon reperfusion, consistent with chronic hibernation. Further studies are required to distinguish chronic hibernation from cumulative stunning. With a better understanding of the mechanisms underlying short-term hibernation, it is hoped that these adaptive responses can be recruited and reinforced to minimize the consequences of acute myocardial ischemia and delay impending infarction. Patients with chronic hibernation must be identified and undergo adequate reperfusion therapy.

I. INTRODUCTION: THE CONCEPT OF MYOCARDIAL HIBERNATION AND ITS EVOLUTION

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. In the context of coronary artery disease, myocardial hibernation refers to an adaptive reduction of myocardial contractile function in response to a reduction of myocardial blood flow. 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 (95, 96). Whereas the term hibernation was initially borrowed from zoology as a paradigm to characterize the endogenous cardiac protection during ischemia, recent studies indicate that the serum of truly hibernating animals indeed contains a substance with opioid-like activity that acts to preserve the myocardial ultrastructure and to improve the functional recovery from ischemia when given to nonhibernating animals (24).

Diamond et al. (51) were the first in 1978 to use the word hibernation in the introduction to an experimental study on postextrasystolic potentiation in ischemic dog myocardium. Somewhat vaguely, they concluded from the “sometimes dramatic improvement in segmental left ventricular function after coronary bypass surgery” that “ischemic noninfarcted myocardium can exist in a state of function hibernation.” Surprisingly, these authors never used the word hibernation again, when subsequently studying patients with improved wall motion after coronary revascularization (170). In the early 1980s, Rahimtoola (161, 162) systematically reviewed the results of coronary bypass surgery trials and identified patients with coronary artery disease and chronic left ventricular dysfunction that improved upon revascularization. Based on these findings, he first proposed the pathophysiological concept of “hibernating myocardium.” In that context, he more precisely used the term hibernating myocardium to characterize a situation of “a prolonged subacute or chronic stage of myocardial ischemia . . . in which myocardial contractility and metabolism and ventricular function are reduced to match the reduced blood supply,” that 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” (162). Shortly thereafter, the concept of hibernating myocardium was further popularized by Braunwald and Rutherford (30), 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 (33, 72, 73, 215, 217; for review, see Ref. 91). Consequently, mechanical function appeared to “downregulate” depending on the amount of blood flow that was available. To describe this phenomenon, Ross (169) introduced the term perfusion-contraction matching. Such perfusion-contraction matching could be sustained for a period of 5 h of moderate ischemia in conscious, chronically instrumented dogs with eventual full recovery of contractile function upon reperfusion (137).

With reference to sustained perfusion-contraction matching, as demonstrated in experimental studies over several hours, Ross (169) 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 concept of myocardial hibernation was gained from studies demonstrating the recovery of metabolic markers during ongoing persistent ischemia (63, 157).

The concept of hibernating myocardium has subsequently stimulated discussion on myocardial ischemia and its definition in general. Rahimtoola (162) had already postulated that hibernating myocardium may not be “ischemic in the strict sense of the word.” With reference to hibernating myocardium, Hearse (89) 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 biochemically ischemia (“a condition in which coronary blood flow is inadequate to permit the maintenance of a steady-state metabolism”).

More recently, the concept of myocardial hibernation has been challenged. Vanoverschelde et al. (213) accepted the existence and adaptive nature of short-term hibernation but questioned the existence of perfusion-contraction matching over prolonged periods of time (chronic hibernation), since baseline flow in some studies both in patients with coronary artery disease and left ventricular dysfunction and in animal models with chronic coronary stenoses appeared to be not reduced to a sufficient extent to explain the observed reduction of contractile function (213).

The present review therefore also distinguishes short-term hibernation from chronic hibernation and characterizes their essential features separately. Such distinction between short-term hibernation and chronic hibernation is certainly arbitrary in the sense that it uses laboratory hours rather than pathophysiology as criterion. Within the framework of this review, all experimental studies where the history of the observed contractile dysfunction is more or less known are discussed under short-term hibernation, and all clinical studies where the history of contractile dysfunction is not known are discussed under chronic hibernation. Also, for comparison, hibernation is contrasted with acute ischemia, stunning, and ischemic preconditioning. Both short-term hibernating and stunned myocardium are characterized by revers-
ible contractile dysfunction. However, in short-term hibernating myocardium, blood flow is still reduced, whereas in stunned myocardium, blood flow is fully or almost fully restored (22, 23). Both short-term hibernation and ischemic preconditioning are cardioprotective phenomena. However, short-term hibernation is an adaptation to an ongoing blood flow reduction with absence of infarction. Ischemic preconditioning is the delay of infarct size development resulting from the temporal sequence of one or more short episodes of ischemia and reperfusion preceding a prolonged and severe ischemic insult (146).

II. ACUTE ISCHEMIA

A. Development of Contractile Dysfunction in Acute Ischemia

Upon acute coronary artery occlusion, contractile function in the ischemic region rapidly ceases. In chronically instrumented, conscious dogs, within a few cardiac cycles systolic segment shortening and systolic wall thickening are reduced (hypokinesis), later abolished (akinesis), and within 30 s to 2 min replaced by paradoxic systolic segment lengthening and systolic wall thinning (dyskinesis, bulging) (206, 207). Electrophysiological changes in the surface electrocardiogram (ECG) occur only after the loss of systolic wall excursion, and changes in the local subendocardial ECG occur even later than those in the surface ECG (17). Thus loss of regional contractile function is a rapid, sensitive, and important consequence of regional myocardial ischemia.

B. Relation of Flow and Function During Acute Ischemia

Because the microsphere technique requires steady-state conditions, regional myocardial blood flow data are available for no earlier than 2–3 min after the onset of ischemia, and therefore, no information exists on the relation of regional flow and function during this initial time. With acute coronary occlusion, there may be a transient state of imbalance between blood flow (the major determinant of energy supply) and contractile function (the major determinant of energy demand). However, even during the initial few minutes, the discharge of blood from the vascular capacitance into the microcirculation may serve to match flow and function. After a few minutes of ischemia, there is a consistent relation between the reduced regional myocardial blood flow and reduced function (Fig. 1) (33, 72, 73, 215, 217). The relationship between subendocardial blood flow and systolic wall thickening is particularly close (72), because the inner layers contribute most to transmural wall thickening (74). All these studies demonstrate that during steady-state ischemia, reductions in regional myocardial blood flow are associated with proportionate reductions in regional myocardial function. The paradigm of an imbalance between supply and demand therefore appears to no longer apply as soon as a steady state of reduced regional myocardial blood flow and reduced function has developed.

The relationship between regional myocardial blood flow and function during ischemia varies with the hemodynamic situation. During exercise in conscious dogs with different degrees of coronary stenosis, the relationship between systolic wall thickening and subendocardial or transmural myocardial blood flow is shifted. There is a higher blood flow for a given level of function during exercise as compared with resting conditions, but when myocardial blood flow is normalized for heart rate, i.e., expressed as blood flow per beat rather than blood flow per minute, the relationships at rest and during exercise are again superimposable (73). Similarly, in anesthetized pigs with constant-flow coronary hypoperfusion, the relationship between systolic wall thickening and subendocardial blood flow per minute is shifted to lower function values at increased heart rate; however, the relationships of systolic wall thickening and subendocardial blood flow per beat are superimposable and independent of heart rate (Fig. 2) (97). Such normalization to heart rate appears appropriate, since systolic wall thickening characterizes a representative single cardiac cycle, and therefore, blood flow should also be normalized to a single cardiac cycle. In fact, there is no study in the literature that shows a reduction in systolic wall thickening without a concomitant decrease in subendocardial blood flow per beat during myocardial ischemia. In a study designed to examine the sensitivity of systolic wall thickening for detecting ischemia, dogs with a subcritical coronary stenosis were subjected to treadmill exercise; with a slight reduction in systolic wall thickening, they had increased subendocardial blood flow per minute from the respective values at rest but decreased subendocardial blood flow per beat (120). Thus it appears that subendocardial blood flow per beat determines regional function of ischemic myocardium.

When equating perfusion-contraction matching, however, with an energetic supply-demand balance, a few caveats should be noted. Whereas regional blood flow is certainly the major determinant of oxygen supply as oxygen extraction is close to maximal and subject to little variation, anaerobic glycolysis may contribute to energy supply during myocardial ischemia (113, 153, 175). On the other hand, systolic wall excursion (segment shortening
or wall thickening) does not account for wall tension, and wall tension even in akinetic myocardium may be surprisingly high (78) and contribute substantially to energy demand during ischemia.

C. Mechanisms of Acute Ischemic Contractile Dysfunction

Adenosine 5'-triphosphate is well accepted to be the ultimate source of energy for the contractile process. Understandably then, the effect of acute myocardial ischemia on the concentration of ATP has been proposed as the mechanism of acute ischemic contractile dysfunction (88; see Table 1). A causal link between the appearance of regional ischemic contractile dysfunction and the loss of regional myocardial ATP, however, has never been proven experimentally. In the inner myocardial layers of anesthetized swine, the ATP concentration is reduced within 15 cardiac cycles after an acute reduction in myocardial blood flow; however, contractile dysfunction occurs even more rapidly, within the first few cardiac cycles (7).

Activation of ATP-dependent potassium channels by an ischemia-induced decrease in the myocardial ATP concentration, by an increase in the intracellular proton or lactate concentrations, or by activation of adenosine A1 receptors could increase potassium efflux, thereby reducing action potential duration and subsequent calcium influx into the myocyte (150). Decreased intracellular calcium concentration could then reduce contractile function and ATP consumption. Indeed, blockade of ATP-dependent potassium channels abolished the hypoxia-induced reduction of global left ventricular function in saline-perfused rat hearts (46). In contrast, in anesthetized swine in situ, blockade of ATP-dependent potassium channels prevented the ischemic reduction of action potential duration but did not alter ischemic contractile dysfunction or the myocardial ATP concentration (188).

Apart from changes in the absolute concentration of myocardial ATP, decreases in the phosphorylation potential or the free energy change of ATP hydrolysis could be responsible for the decrease in contractile function. Indeed, the reduction in phosphorylation potential (41) or free energy change of ATP hydrolysis (104, 134) correlates well with the onset of contractile dysfunction, both in isolated, saline-perfused hearts and in regional ischemic myocardium.

Other mediators proposed to play a role in the development of early ischemic contractile dysfunction are a decrease in the intracellular pH (101) or a disturbance in the calcium handling of the sarcoplasmic reticulum (112, 115). Decreased perfusion pressure reduces the calcium transient in isolated ferret hearts over a range of pressures (80–60 mmHg) that are not yet associated with alterations in pH and high-energy phosphates (Fig. 3) (109), and a collapse of the coronary arteries has also been suggested to be responsible for the decrease in contractile function early during ischemia in isolated, saline-perfused ferret hearts at 27°C (111). In contrast, in isolated, blood-perfused rat hearts at 37°C, the time course of development of contractile failure did not relate to that of coronary vascular collapse but did to that of metabolic processes, as reflected by oxygen consumption (71).

Apart from or in addition to the reduced calcium transient, the accumulation of P, resulting from the ischemic breakdown of myocardial creatine phosphate and ATP is a possible candidate responsible for the early ischemic decrease in contractile function (117, 143). The increase in the concentration of P, could reduce contractile...
function by direct binding to contractile proteins (171), by inhibition of the myofibrillar ATPase activity (181), and/or by desensitization of myofibrils for calcium (107).

The ultimate mechanism of acute ischemic contractile dysfunction still remains unclear.

III. SHORT-TERM HIBERNATION

A. Relation of Flow and Function During Short-Term Hibernation

In chronically instrumented, conscious dogs, a reduction in subendocardial blood flow by ~50% associated with a decrease in regional systolic wall thickening by 40% was maintained for 5 h without the development of necrosis at the site where function was measured, although some necrosis was noted in the papillary muscle.

Regional contractile function recovered during reperfusion, but full recovery required 7 days (Fig. 4) (137). The relationship of flow and function during the prolonged (5 h) coronary stenosis was identical to that during a brief (few minutes) coronary stenosis, clearly indicating sustained perfusion-contraction matching.

Such sustained perfusion-contraction matching has become a hallmark of short-term hibernating myocardium (see Table 2). Interestingly, however, no subsequent study established and compared flow-function relationships during acute and more prolonged ischemia. Instead, perfusion-contraction matching was assumed to be present when perfusion and function measurements at consecutive time points could be plotted along the same relationship (34, 55, 100, 106, 189) or when the reductions in flow and function were roughly proportionate and stable (38, 182), and no necrosis was noted at the end of the experiment. Proportionate reductions in flow and function are not only seen with coronary hypoperfusion at rest, but also after sustained stress-induced ischemia when a combination of atrial pacing and intravenous norepinephrine was superimposed on mild resting hypoperfusion in anesthetized pigs. These findings, together with the lack of necrosis, indicate that the myocardium may also adapt to stress-induced ischemia (20). Not only the amount, but also the source of blood flow, may determine the level of perfusion-contraction matching. Anesthetized dogs subjected to 3-h partial coronary stenosis had better contractile function during ischemia than dogs with complete coronary occlusion and extensive collateralization, at almost identical subendocardial blood flow and in the absence of irreversible morphological injury (159).

Phenomenologically, the formal contraction pattern of ischemic myocardium, i.e., the extent of postejction wall thickening, also appears to provide information to help to distinguish irreversibly damaged from viable hibernating myocardium (168). The extent of postejction wall thickening at the end of a 90-min ischemic period in anesthetized pigs correlated inversely with the extent of necrosis and positively with myocardial creatine phosphate concentration, the dobutamine-recruitable inotropic reserve, and functional recovery upon reperfusion. Thus greater postejction wall thickening suggested that the
hypoperfused myocardium was hibernating rather than irreversibly damaged.

In some experimental studies, attempts have been made to investigate hibernation for longer than a few hours by subjecting dogs or pigs to either a prolonged partial coronary artery stenosis for a duration ranging from 1 day to 32 wk (25, 37–40, 62, 122, 123, 140, 142) or a progressive narrowing of the coronary artery by use of an ameroid constrictor (34, 195). Most of these studies, however, failed to continuously monitor myocardial blood flow and contractile function over the entire time period of coronary hypoperfusion.

Liedtke and co-workers (25, 122, 123) used anesthetized pigs with measurements and placement of a coronary cuff occluder that reduced peak coronary blood flow velocity during an initial surgery and repeated measurements during a second surgery, 4–7 days later. Regional contractile function was reduced at the time of the second surgery, but in the single study in which flow data with microspheres were reported, the stenosis did not reduce resting flow, both during the first and the second surgeries (122). In contrast, studies in anesthetized, closed-chest pigs with a chronic (≥1 mo) fixed coronary stenosis revealed proportionate reductions in regional myocardial blood flow and oxygen consumption (142) and in regional myocardial blood flow and contractile function (62, 140) as compared with a nonstenotic reference region. Consecutive regional myocardial blood flow and function measurements are available from studies in anesthetized pigs with a coronary cuff occluder adjusted to reduce flow to 40–60% of baseline for 24 h (37, 38), and more recently also for 7 days and 4 wk in a number of pigs (39, 40). These consecutive measurements during early ischemia and after 24 h or 4 wk coronary stenosis indicate proportionate reductions in resting flow and function. However, because the pigs recovered from the initial surgery and were reanesthetized for the repeat study, major alterations in systemic hemodynamics and consequently in re-
FIG. 4. Systolic wall thickening (normalized to control conditions, means ± SD) during 5-h partial coronary stenosis and 7-day reperfusion in chronically instrumented conscious dogs. There is recovery of function back to control values, indicating maintenance of myocardial viability. * P < 0.05, ** P < 0.01 vs. control. [From Matsuzaki et al. (137).]

Systolic myocardial blood flow and function throughout the period of coronary stenosis cannot be excluded. In fact, variations in coronary blood flow between 25 and 50% of control were reported in a subset of pigs (37). Consecutive regional myocardial blood flow and function measurements are also available from two studies in conscious, chronically instrumented animals during the progressive development of a coronary ameroid stenosis (34, 195). In one study in dogs (34), there was a dissociation between almost normal subendocardial blood flow and reduced contractile function before coronary occlusion, consistent with the idea that repetitive episodes of ischemia had occurred, resulting in myocardial stunning. After complete coronary occlusion, however, regional myocardial blood flow and function were once more closely matched, i.e., reduced in a proportionate fashion before they finally returned to normal (34). Also, in pigs (195), regional myocardial blood flow at the maximum reduction of systolic wall thickening (by ~60% from baseline) after the ameroid constrictor implantation was not reduced significantly, although subendocardial blood flow was lower than in the contralateral reference area (0.92 ± 0.10 vs. 1.07 ± 0.12 ml·min⁻¹·g⁻¹). Interestingly, in this study, episodes of spontaneous excitement were observed, resulting in contractile dysfunction with subsequent prolonged recovery. The authors therefore proposed that hibernation is not the consequence of a persistent reduction of blood flow, but a manifestation of repetitive stunning (195).

This particular study was provocative because it refuted the idea that chronic hibernation exists at all, much less as an adaptive response to persistent hypoperfusion. Rather, Shen and Vatner (195) proposed that chronic dysfunction in a setting of coronary artery disease is a manifestation of cumulative stunning, an idea that has received widespread interest. This paper, however, has some limitations worth considering. 1) In this study, blood flow and function were not continuously monitored, and therefore, the history of the contractile dysfunction observed remains unknown. 2) Anecdotal episodes of excitement with subsequent dysfunction were reported, but they were neither systematically followed nor induced in a controlled fashion. 3) Interestingly, this same laboratory has previously reported that no prolonged dysfunction persists after such short (<2 min) episodes of ischemia, even with complete coronary occlusion in conscious dogs (154), and stunning in conscious pigs is even less pronounced than in conscious dogs (196). 4) Most importantly, this study did not reproduce the morphological phenotype of hibernating myocardium (see sect. III), as published in a follow-up paper (194). Microinfarcts surrounded by only a small rim of cardiomyocytes with characteristic features of hibernation were found. Therefore, in this particular study, the observed contractile dysfunction may have indeed been the result of repetitive stress-induced ischemia with subsequent microinfarcts and cumulative stunning, but the methodological power to exclude persistent ischemia as a cause of hibernation is clearly lacking.

Only two studies with controlled hypoperfusion and continuous monitoring of flow and function over 24 h are available, both so far only in abstract form. In one study in conscious pigs (116), a reduction in blood flow by 40% reduced systolic wall thickening by 70%. Surprisingly,

TABLE 2. Characterization of short-term hibernating myocardium

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<th>Characterization</th>
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<tr>
<td>Sustained balance between the reduced regional myocardial blood flow and the reduced contractile function (sustained perfusion-contraction matching)</td>
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<td>Recovery of metabolic parameters (creatine phosphate, lactate, ΔG) during persistent ischemia</td>
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<td>Recruitable inotropic reserve at the expense of metabolic recovery</td>
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<td>Recovery of contractile function during reperfusion</td>
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<td>Lack of necrosis</td>
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upon post mortem examination, the hypoperfused tissue was a mixture of patchy necrosis with reduced blood flow and normal myocardium with normal blood flow (116). However, episodes of excitement cannot be excluded in conscious pigs continuously under study for 24 h, and such episodes of excitement have been shown to result in microinfarcts by this same laboratory, even with normal resting flow (194). In another study in anesthetized pigs (189), coronary blood flow was reduced by 45%, and this reduction in flow was maintained for 24 h. Perfusion-contraction matching was maintained for 90 min, but thereafter, contractile function was further reduced, despite constant flow. Apparently, with ischemia of longer than 90-min duration, additional factors acted to reduce contractile function. However, the close matching between myocardial contractile function and oxygen consumption was maintained, still supporting the concept of metabolic adaptation to prolonged ischemia (189).

B. Recovery of Function After Short-Term Hibernation

In isolated, saline-perfused rat hearts subjected to global hypoperfusion for 2 h, there was almost complete recovery of developed pressure and rate-pressure product at 15-min reperfusion (174, 175). In isolated, saline-perfused rabbit hearts that were subjected to an initial 10-min no-flow and subsequent 4-h low-flow ischemia, there was also almost complete recovery of developed pressure at 60-min reperfusion (64, 65, 211). In isolated, blood-perfused piglet hearts subjected to 2-h reduction of coronary inflow by 90%, there was again almost complete recovery of left ventricular systolic pressure and the rate-pressure product at 30- and 60-min reperfusion (56, 151).

In contrast to the above studies, all in vivo models of regional short-term hibernation in anesthetized pigs (94, 100, 152, 182) and dogs (159, 222) as well as in chronically instrumented pigs (37, 38) and dogs (137, 197) were invariably characterized by severe stunning during reperfusion. When full recovery of regional contractile function was followed, it required 7 days in conscious dogs with a preceding 5-h coronary stenosis (137) and again 7 days in conscious pigs with 24-h coronary stenosis (37, 38). The difference in time course of functional recovery points to important differences in models of short-term hibernation, with almost immediate recovery in isolated hearts subjected to global ischemia as compared with slow recovery in in situ hearts subjected to regional ischemia.

C. Metabolism of Short-Term Hibernating Myocardium

1. Substrate metabolism

A modest reduction in coronary perfusion was associated with modestly decreased left ventricular peak pressure, dP/dt, and myocardial oxygen consumption, but no lactate production in isolated saline-perfused rat hearts (106). However, these measures were only obtained during 10-min steady-state conditions and not over a longer duration of ischemia. In anesthetized pigs within the first 5 min of an acute coronary inflow reduction, coronary venous pH and lactate extraction were reduced and coronary venous PCO₂ increased, but these parameters gradually returned toward control values during 180 min of continued moderate ischemia (Fig. 5) (63). 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 (58) or anesthetized open-chest pigs with regional short-term hibernation of up to 7 days duration (6, 37, 39, 94, 177, 182). Recovery of pH during sustained ischemia has also been confirmed (177).

In an isolated, blood-perfused piglet heart model of short-term hibernation, however, there was no attenuation of lactate production over 2 h of prolonged moderate hypoperfusion (55, 56). In one of those two studies, cardiac glycogen content after 2 h of moderate hypoperfusion was unchanged (55), whereas it was significantly reduced in the other one, at an equivalent level of hypoperfusion (56). In the in situ porcine model of short-term hibernation, cardiac glycogen content was somewhat (albeit not significantly) reduced during 90 min of moderate hypoperfusion with ~50% of baseline transmural flow (182). The inability to metabolically adapt to sustained moderate ischemia may be peculiar to the isolated piglet heart, in contrast to pig hearts in situ (202), again pointing to im-
portant differences in models of short-term hibernation. 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, Ref. 145), and its functional consequences [contribution to ATP production and preservation of ventricular function (58) or contribution to acidosis and reduction of ventricular function] are not entirely clear at present. Glucose uptake is enhanced with 24-h coronary hypoperfusion in anesthetized pigs (37, 38) and in pigs with chronic coronary stenosis and a persistent reduction in regional myocardial blood flow (62, 140). Attenuation of lactate production over time is consistent with but does not prove metabolic recovery secondary to downregulation of contractile function and energy requirements.

Amino acids contribute to myocardial substrate metabolism in short-term hibernation; their content is reduced by 50–70% during 90-min moderate coronary hypoperfusion. 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 positron emission tomography (PET) measurements during prolonged myocardial ischemia (183).

In pigs with a coronary stenosis for 4 days, regional blood flow and myocardial oxygen consumption remained normal, suggesting a situation of repetitive stunning rather than hibernation (122). In this setting, fatty acid oxidation was decreased and glucose utilization was increased (122). Reduced uptake of fatty acids and increased uptake of glucose have previously been reported in myocardial stunning after 20 min and 3 h of sustained ischemia in dogs (190, 191), but not with four cycles of 5-min ischemia and 15-min reperfusion in anesthetized pigs (86).

2. Energy metabolism

Technically, all current information on energetics in short-term hibernation is derived from biopsy-based biochemical measurements or from nuclear magnetic resonance (NMR) spectroscopy. Neither of these techniques can distinguish between cardiomyocytes and other cells in the heart. Nuclear magnetic resonance spectroscopy permits kinetic analyses and measurement of changes in the free cytosolic concentrations, but only biochemical measurements provide data on absolute tissue contents. Thus the two techniques complement each other.

Modest proportionate reductions in both coronary perfusion by ∼50% and contractile function by ∼30% were not associated with decreases in ATP and the creatine phosphate-to-P$_i$ ratio (106, 180). However, these measures were only obtained during step changes in perfusion pressure of 10–106 or 30-min duration (180) and not over a longer duration of ischemia.

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 (149). Decreased ATP content over time was also observed during continued myocardial ischemia in isolated rat (174), rabbit (113), and piglet (55) hearts and in anesthetized pig (6, 157, 182) and dog (222) 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. 6) (157), whereas regional myocardial blood flow and contractile function were persistently reduced (6, 55, 157, 174, 182, 222). It is not clear why in one study in open-chest pigs lactate production was attenuated over time, but creatine phosphate content did not recover (177).

In a more complex approach, simultaneous measurements of ATP, creatine phosphate, creatine, and P$_i$ contents in freeze-clamped, saline-perfused guinea pig hearts permitted the calculation of the free energy change of ATP hydrolysis (76). 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 during 60-min hypoperfusion. Similarly, in a porcine model of regional short-term hibernation, sequential biopsy-based measurements of ATP, creatine phosphate, creatine, and P$_i$ revealed a decrease in the free energy change of ATP hydrolysis during early ischemia with a subsequent recovery during continued 90-min ischemia (134).
Several explanations for the recovery of creatine phosphate content and the restoration of an energetic balance have been offered. 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 (175). 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 (6). Also, attenuation of lactate production during prolonged hypoperfusion is inconsistent with an important role of glycolytic ATP production for the recovery of creatine phosphate (6, 177, 182). Thus glycolytic ATP production may be necessary (but nevertheless insufficient) to allow metabolic adaptation to ischemia.

Alternatively, in isolated, saline-perfused rabbit hearts, NMR spectroscopy revealed a recovery of creatine phosphate content and an attenuation of the reduction in the free energy change of ATP hydrolysis during 45-min severe hypoperfusion that could be related to open-system kinetics and a loss of adenine nucleotides through metabolism to and loss of adenosine (113). However, this explanation did not hold for moderate hypoperfusion, where there was no recovery of creatine phosphate content, in contrast to in situ preparations where only moderate ischemia can be sustained over longer periods of time without the development of necrosis (6, 182, 186). Whereas during the first few hours of ischemia loss of adenine nucleotides may be involved in the maintenance of an energetic balance, both ATP and creatine phosphate content were normal as compared with that in a remote reference region in pigs with chronic coronary stenosis and persistent reductions in regional myocardial blood flow and function (140).

A specific inhibition of myofibrillar creatine kinase during prolonged moderate ischemia is also unlikely, because mitochondrial creatine kinase is more sensitive to ischemia and >2 h of total coronary occlusion is required before total creatine kinase activity is reduced (21). In an isolated, saline-perfused rat heart model of short-term hibernation, the creatine kinase equilibrium was maintained, as indicated by an unchanged ratio of the pseudo first-order rate constants of the forward and reverse creatine kinase reaction (174). Also, the increased energy utilization associated with a rapid breakdown of creatine phosphate during inotropic stimulation of short-term hibernating myocardium (94, 182) indicates a steady state of the creatine kinase reaction.

Therefore, 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 loss of adenine nucleotides 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 (176).

D. Inotropic and Coronary Reserve in Short-Term Hibernating Myocardium

Although baseline contractile function is depressed, the hypoperfused myocardium retains its responsiveness to an inotropic challenge (Fig. 7) (182). When, after 85–90 min of sustained moderate regional ischemia (reduction of transmural blood flow by ~50%) in anesthetized pigs, dobutamine was infused selectively into the ischemic region, contractile function transiently increased, although regional blood flow remained reduced. Thus an energy reserve was available in the ischemic myocardium that was not used to maintain baseline function, but could be recruited to transiently increase contractile function during an inotropic challenge. These results strongly suggest that the decrease in contractile function secondary to a reduction in myocardial blood flow was not simply the consequence of a reduced energy supply, but rather reflected an active adaptive process of the myocardium. Imposement of an inotropic stimulus on the short-term hibernating myocardium disrupted this 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 (38). Similarly, positive inotropic responses of porcine regional short-term hibernating myocardium were observed in response to postextrasystolic potentiation and intracoronary calcium (56, 94). In the latter case, enhanced regional contraction was again associated with increased lactate production and decreased creatine phosphate content (94).

Persistent inotropic reserve in response to dobutamine was observed in the 1-wk coronary stenosis model in pigs which probably reflects cumulative stunning rather than hibernation (25). Persistent inotropic reserve in response to isoproterenol was also observed in conscious pigs with chronic aneroid constriction and normal resting flow at the time of the study, again a situation probably characterized by repeated stunning rather than hibernation (194). However, 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 (Fig. 8), with increased wall thickening at lower doses and contractile dysfunction at higher doses, and was associated with increased net lactate production (38). Importantly, this is the only study that not only demonstrated persis-
tence of inotropic reserve at the expense of metabolic recovery, but also recovery of contractile function after removal of the stenosis over 7 days. Recently, with the use of the same model, 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 (127).

A similar disruption of the developing metabolic balance after prolonged moderate ischemia is also observed upon a chronotropic challenge (6). Increasing heart rate by atrial pacing in this particular study, however, increased the severity of ischemia and reduced regional myocardial blood flow, function, and creatine phosphate content and increased lactate production. Because the
severity of ischemia was increased, the observed metabolic deterioration during pacing does not demonstrate active adaptation of energy demand during the preceding more moderate ischemia as conclusively as that during the imposition of an inotropic challenge at an unchanged blood flow.

In the studies by Liedtke and co-workers (25, 122), reactive hyperemia was reduced after placement of the stenosis during the initial surgery, but it had recovered toward control values by the time of the repeat study 4–7 days later, again suggesting that this is a model of cumulative stunning rather than hibernation. An attenuated but persistent coronary reserve, elicited by adenosine (62, 142) or carbocromen (34), was found in the final study after chronic, fixed coronary stenosis in pigs (62, 142) or progressive ameroid stenosis in dogs (34). The persistence of flow reserve was not surprising in the study in dogs in which resting flow and function had completely recovered back to baseline (34). There was little subendocardial flow reserve in one study with a chronic fixed coronary stenosis in pigs (62) but substantial flow reserve in another study when adenosine was coadministered with phenylephrine to avoid a decrease in perfusion pressure (142). To explain the persistence of coronary reserve at reduced resting flow, the authors speculated that subendocardial flow reduction caused subendocardial contractile dysfunction which, in turn, constrained subepicardial contractile function by tethering, leading finally to a reduction of subepicardial blood flow (142).

E. Limits of Short-Term Hibernation

The development of a delicate balance between regional myocardial blood flow and function during early ischemia is disturbed by subsequent unfavorable alterations in supply and demand. When in anesthetized pigs after 5 min of ischemia, at a blood flow reduction compatible with the development of myocardial hibernation over 90 min, energy supply was further reduced by a further reduction of myocardial blood flow, necrosis developed, as indicated by lack of triphenyltetrazolium chloride (TTC) staining (Fig. 9). The lower limit of transmural myocardial blood flow compatible with the development of short-term myocardial hibernation over 90 min coronary hyperperfusion corresponded to ~50% of baseline in this experimental setting; the lower limit of subendocardial blood flow corresponded to 25% of baseline (Fig. 9) (186). Also, a further increase in energy demand by continuous inotropic stimulation with dobutamine for 85 min induced necrosis (Fig. 10) (186). Thus both a further reduction in energy supply by an increasing severity of ischemia and an enhanced energy expenditure by continuous inotropic stimulation can impair the development of short-term myocardial hibernation and precipitate myocardial infarction. Whether or not infarction is indeed precipitated depends on the severity and duration of flow reduction (see above) as well as on the strength and duration of the inotropic and/or chronotropic challenge. With a protocol of only mildly reduced baseline flow and only 30-min atrial pacing and intravenous norepinephrine in anesthetized pigs, the myocardium was still able to adapt, and no infarction occurred (20).

F. Mechanisms of Short-Term Hibernation

The mechanisms responsible for the development of short-term myocardial hibernation remain largely unclear at present. There were no alterations in the β-adrenoceptor density or affinity in anesthetized pigs with regional short-term hibernation for 90 min (186). However, more detailed analyses of the adrenergic signal transduction cascade are lacking.

1. ATP-dependent potassium channels

As mentioned in section II C, the ischemia-induced activation of ATP-dependent potassium channels might increase potassium efflux, thereby reducing action potential duration and subsequently calcium influx into the cardiomyocyte. Decreased intracellular calcium concentration could then reduce contractile function and ATP consumption, leading to the new equilibrium between supply and demand that characterizes myocardial hibernation. Indeed, the monophasic action potential duration shortens during hypoxia (46) and ischemia (188), and this shortening of action potential duration is prevented by blockade of ATP-dependent potassium channels with glibenclamide. However, blockade of ATP-dependent potassium channels with glibenclamide during 2-h low-flow ischemia in isolated piglet hearts and 90-min low-flow ischemia in isolated rabbit hearts had no effect on the proportionate reductions in ventricular function and coronary perfusion and on the recovery of function, ATP and creatine phosphate content during reperfusion (151). Glibenclamide also failed to alter contractile function, metabolic parameters, or myocardial viability in an in situ porcine model of regional short-term hibernation (188). Consequently, activation of ATP-dependent potassium channels appears, therefore, not to be involved in the development of short-term myocardial hibernation (151, 188). However, two recent studies indicated that it is not the sarcolemmal but the mitochondrial ATP-dependent potassium channels and the mitochondrial redox state that are important in cardioprotection (77, 124). It therefore seems important to study such mitochondrial ATP-dependent potassium channels also in hibernation.

2. Adenosine

Endogenous adenosine that is released during ischemia 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 high-energy phosphates and the increase in intracellular calcium concentration, thereby preserving myocardial viability during ischemia. However, a role for endogenous adenosine in the development of hibernation has been excluded. Adenosine receptor antagonism with 8-sulfophenyltheophylline in isolated piglet hearts subjected to 2 h of low-flow ischemia had no effect on the proportionate reductions in ventricular function and coronary perfusion and on the recovery of function, ATP, and creatine phosphate content during reperfusion (151). Also, in an in situ model of regional short-term hibernation, contractile function, metabolic parameters, and myocardial viability were not altered by increased catabolism of endogenous adenosine by infusion of adenosine deaminase (188).

3. Calcium transient and responsiveness

The calcium transient during short episodes (~10 min) of moderate coronary hypoperfusion is either unchanged (67) or slightly decreased, in proportion to the reduction in perfusion pressure (109, 110, 130). Measurements of intracellular calcium kinetics are not available for more prolonged coronary hypoperfusion. However, isolated adult rat cardiomyocytes maintained viability during 48-h hypoxia, and this adaption was associated with reduced calcium transients and contractile function (200).

In a porcine model of regional short-term hibernating myocardium, 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 (Fig. 11) and 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 (94). The source and nature of the factor(s) that decreases calcium responsiveness in short-term hibernating myocardium.
are not clear at present. In this respect, it was proposed that hypoxic endothelial cells release an as yet unidentified factor that inhibits the contraction of isolated adult rat cardiomyocytes without any effect on the calcium transient (193).

The expression of calcium regulatory proteins (sarcoplasmic calcium ATPase, phospholamban, calsequestrin, and troponin inhibitor) is not altered during 90-min short-term hibernation in anesthetized pigs (126). In biopsies from human hibernating myocardium, phospholamban expression on the mRNA and protein level was even markedly decreased, excluding a significant involvement of the sarcoplasmic reticulum in the reduced excitation-contraction coupling (47). Thus, whereas most studies on the mechanisms of hibernation have been negative so far, calcium transient and calcium responsiveness are decreased in short-term hibernation, and these findings fit well into the concept that a biochemical signal reduces contractile activity and, in consequence, energy expenditure. However, which biochemical signal reduces calcium transient and calcium responsiveness is not clear at present.

G. Events Triggering the Development of Short-Term Hibernation

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 (65). 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 (65) and intracellular (211) pH, and the contractile quiescence was attributed to a faster development of myocardial acidosis. During reperfusion after 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 (65) and intracellular (211) 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 72-kDa heat shock protein, but a cause-effect relationship was not at all established (64). In other studies, 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 (184). 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. These studies might also serve as models of hibernating myocardium after an acute myocardial infarction where an initial total coronary artery occlusion of short duration is followed by spontaneous or therapeutic thrombolysis, however with a persistent coronary stenosis.

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 (100). 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 (5). Thus both an initial intense stimulus of severe flow reduction and a gradually developing moderate flow reduction appear able to facilitate an adaptive response of the myocardium. In any case, the development of hibernation appears to require a triggering event, be that an initial episode of severe ischemia with profound metabolic alterations or a slow, gradual increasing intensity of ischemia. The lack of such a triggering event may be the reason why not all hearts hibernate (93).

H. Short-Term Hibernation Versus Ischemic Preconditioning

Ischemic preconditioning, i.e., the delay of infarct size development resulting from prolonged and severe myocardial ischemia by one or more preceding short episodes of ischemia and reperfusion (146), is the most powerful cardioprotective maneuver known so far. Myocardial ATP and creatine phosphate contents remain somewhat higher in preconditioned hearts than in hearts subjected to prolonged ischemia without ischemic preconditioning (108, 147). Also, glycolysis and lactate production have been reported to be attenuated in ischemic preconditioned hearts (9, 219), although this remains controversial (102). As discussed in section III, a brief episode of no-flow myocardial ischemia without intermittent reperfusion increased the tolerance to sustained low-flow ischemia. Activation of ATP-dependent potassium channels and endogenous adenosine are involved in the infarct size-reducing effect of ischemic preconditioning (185, 187), but not in short-term myocardial hibernation (188). The observed reduction in infarct size by the initial period of no-flow ischemia, like in classical ischemic preconditioning (185), was abolished by blockade of ATP-dependent potassium channels with glibenclamide (184). Therefore, this cardioprotective effect relates to ischemic preconditioning rather than to myocardial hibernation. This view is also supported by the fact that the protection provided by the initial short episode of no-flow ischemia is associated with increased expression of 72-kDa heat shock protein (64), which is also associated with ischemic preconditioning (132, 221). On the other hand, expression of heat-shock proteins may simply be an epiphenomenon.

Despite certain similarities between ischemic preconditioning and myocardial hibernation, those two cardioprotective phenomena appear to be different in nature.

I. Short-Term Hibernation Versus Stunning

Hibernation and stunning, although often confused, are clearly different phenomena (23, 129). Both the short-term hibernating and the stunned myocardium are characterized by reversible contractile dysfunction. In short-term hibernating myocardium, blood flow is still reduced, whereas in stunned myocardium, blood flow is fully or almost fully restored by reperfusion (22, 23). Interestingly, in a recent study in chronically, instrumented conscious dogs, proportionate reductions of regional contractile function and myocardial oxygen consumption persisted into the reperfusion period after 2 h of partial coronary stenosis and were also observed after a protocol of 15 repetitive 2-min complete coronary occlusions with 8-min reperfusion each (197).

To distinguish short-term hibernating from stunned myocardium, regional myocardial blood flow must be measured (23). Alternatively, the metabolic changes associated with an inotropic challenge must be analyzed. The recruitment of an inotropic reserve in short-term hibernating myocardium was at the expense of metabolic deterioration (94, 182), whereas in stunned myocardium, no metabolic deterioration occurred during inotropic stimulation (4, 8, 81). In addition, whereas prolonged inotropic stimulation can cause infarction in short-term hibernating myocardium (186), it does not cause necrosis in stunned myocardium (178). Thus distinction of hibernation and stunning is possible, and it is therefore mandatory that this distinction is done in all pertinent studies.

J. Morphology of Short- Term Hibernating Myocardium

The ultrastructure of reversibly injured myocardium quickly recovers upon reperfusion, and the structural restoration precedes its functional recovery. Therefore, stunned myocardium is characterized by virtually normal morphology (179). No necrosis and only minimal structural abnormalities were seen in the studies by Liedtke and co-workers (25, 122, 123), supporting the idea that this model represents cumulative stunning rather than hibernation. With chronic coronary stenosis for 24 h, minimal patchy necrosis (1–6% of the area at risk) was found with TTC staining and histology in a minority of pigs (37, 38), and findings were similar when the stenosis was maintained for 7 days or 4 wk in a few pigs (39, 40). Electron microscopy revealed loss of myofilaments and sarcomeres and an increased number of glycogen deposits (37). No necrosis but patchy fibrosis and a more generalized increase in connective tissue (to ~2-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 1 mo (62, 140, 142). These morphological alterations are similar to those seen in goats with chronic atrial fibrillation, apart from the interstitial fibrosis that is not seen with chronic atrial fibrillation (13).

The coronary microcirculation exhibits hypertrophy of the smaller microvessels and atrophy and reduced protein synthesis of larger microvessels (142). In the study
in conscious pigs with a chronic ameroid constrictor and no reduction in regional blood flow at the time of peak dysfunction, 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 (194).

Thus it appears that loss of myofilaments, increased amounts of glycogen deposits, and increased connective fibrotic tissue are characteristic of those preparations that definitely or most likely had persistent reductions in regional myocardial blood flow and function. These regional morphological alterations were also associated with a typical left ventricular remodeling response, as reflected by an increase in left ventricular volume and muscle mass (39). Repetitive stress-induced ischemia either induces no morphological alterations (122) or, when too frequent and/or severe, patchy necrosis (194).

Characteristic features of apoptosis, i.e., programmed necrotic cell death, have been observed in rat and rabbit cardiomyocytes in settings of myocardial ischemia and reperfusion (69, 82, 103). No increase in the expression of proapoptotic proteins (Fas, Bak) was found with 90-min regional short-term hibernation in pigs (45), but 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 (40). The apoptosis had a patchy distribution and was predominantly seen in the subendocardium (affecting ~10% of the subendocardium at risk). Apoptosis was seen already with 24-h coronary stenosis, and the incidence of apoptosis was not further increased with 7-day or 4-wk coronary stenosis. The incidence of apoptosis correlated to the severity of coronary hypoperfusion and was higher in pigs that also had patchy infarction than in pigs without infarction (40). 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 this is entirely speculative at present (92).

### IV. CHRONIC HIBERNATION

#### A. Clinical Scenarios With Chronic Hibernation

Hibernation over months or years (chronic hibernation), as initially proposed by Rahimtoola (162), is a state of chronic contractile dysfunction in patients with coronary artery disease that is fully reversible upon reperfusion and can only be inferred from clinical studies. Clinical syndromes consistent with the existence of myocardial hibernation include unstable and stable angina (27, 35, 66, 163, 172), acute myocardial infarction (36, 144, 163), left ventricular dysfunction and/or congestive heart failure (3, 125), and the anomalous left coronary artery from the pulmonary artery (ALCAPA) syndrome (166, 167, 198) (Table 3).

Not surprisingly, data on the prevalence of hibernating myocardium in patients with coronary artery disease are scanty. This is primarily due to the fact that the concept is relatively new and is not even unanimously accepted. Research groups that are more active in the field have developed their own, customized diagnostic and therapeutic approach to hibernation, and there is certainly a positive selection bias in groups with an interest in hibernation. Consequently, to increase objectivity, the diagnosis of hibernation should always be confirmed retrospectively by a documented improvement in ventricular function after revascularization. Unfortunately, unless and until validated standardized procedures for the recognition of dysfunctional but still viable myocardium are made routinely available, it will be almost impossible to obtain data on the prevalence and relevance of hibernation in patients with coronary artery disease.

With these caveats in mind, based on the existing data, it appears that hibernation may be more common in unstable than in stable angina (163). In 41 patients studied 5–21 days after an acute myocardial infarction, 78% had reduced regional contractile function and blood flow, associated with increased glucose uptake (perfusion-metabolism mismatch) in at least one myocardial area on PET scanning, indicative of hibernating myocardium, and 32% of these patients had a large area of perfusion-metabolism mismatch (1). Likewise, 69% of patients with an acute myocardial infarction had a further reduction in the perfusion deficit using technetium sestamibi tomography between 5 wk and 7 mo after the infarction, associated with improved wall motion and suggestive of hibernating myocardium (75).

In a group of 50 coronary bypass surgery candidates with a severe left anterior descending artery stenosis or occlusion with or without regional dysfunction, a principal component analysis identified 18 patients (i.e., 36%) with hibernating myocardium, characterized by low regional ejection fraction, moderately decreased resting flow, and, most importantly, significant recovery after revascularization (199). In patients with myocardial infarction, areas with reduced perfusion at rest and preserved glucose utilization, consistent with hibernation, are more frequently found shortly after the acute event and

### Table 3. Clinical conditions of myocardial hibernation

<table>
<thead>
<tr>
<th>Unstable and stable angina</th>
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</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>Congestive heart failure and/or LV dysfunction</td>
</tr>
<tr>
<td>ALCAPA syndrome</td>
</tr>
</tbody>
</table>

LV, left ventricular; ALCAPA, anomalous left coronary artery from pulmonary artery.
become less frequent with increasing time thereafter (70). About 11% of the patients referred for cardiac transplantation have been suggested to have hibernating myocardium (164). In a total of 635 patients screened over 5 yr, 165 had signs of viability on the basis of rest-201 thallium redistribution. Of these, only 55 had a positive low-dose dobutamine test; this would suggest an incidence of ~ 10% (R. Ferrari, personal communication) (93). However, it is possible that the prevalence of hibernation would be higher when using a high-dose dobutamine test.

Although part of the original definition and currently the best retrospective proof of hibernation, the use of recovery of function upon revascularization as the criterion of hibernation may nevertheless underestimate the prevalence of hibernation. Tethering to infarcted areas may prevent the recovery of function in reperfused myocardium, and long-term changes in contractile or other regulatory proteins may require gene therapy rather than or in addition to revascularization.

Thus the available data on the prevalence of hibernation vary substantially. The awareness of the possible existence of the phenomenon as well as the eventual availability of simple standard methods for its identification will most likely prove that hibernation is more common than currently recognized. Also, whereas the prevalence of hibernation in patients with coronary artery disease may not appear impressive at present, coronary artery disease per se is frequent and the leading cause of death in developed countries.

B. Relation of Flow and Function in Chronic Hibernation

When proposing the concept of hibernation, Rahimtoola (161, 162) reasonably assumed that the observed reduced regional contractile function that recovered upon revascularization must have reflected reduced resting blood flow (161, 162). More recently, this idea was challenged, and chronic hibernation was proposed not to result from chronic hypoperfusion, but from repeated episodes of ischemia and subsequent cumulative stunning (214). This as well as several other more complex patterns of flow and function in chronically dysfunctional myocardium have previously been hypothetically proposed by Bolli (23) (Fig. 12). The issue of hibernation versus cumulative stunning as the underlying mechanism of chronic yet reversible contractile dysfunction in patients with coronary artery disease has been and continues to be a matter of intense debate (165, 213).

Consistent with the original concept of Rahimtoola (161, 162), qualitative studies using thallium scintigraphy (99, 160), 82Rb PET (135), or 13NH3 PET (125, 205, 208) demonstrated reduced regional myocardial perfusion at rest in patients with chronic regional contractile dysfunction which subsequently improved upon revascularization. Nuclear techniques, however, have certain limitations in terms of defining hibernation. Thallium and technetium sestamibi uptake closely correlate with the morphological integrity of the myocardium (48, 128, 141), and thallium reinjection identifies more or less the same viable and nonviable regions as glucose uptake measured with 18fluorodeoxyglucose (18FDG) PET (27). On the other hand, tracer uptake in these studies does not depend solely on perfusion; thus it is always normalized to a reference region that may or may not be normal and is subject to the partial volume effect, i.e., underestimates true regional activity in areas with reduced myocardial wall thickness. Therefore, the issue of perfusion-contraction...
TABLE 4. PET data on resting myocardial blood flow in patients with hibernating myocardium

<table>
<thead>
<tr>
<th>No. of Patients With HM</th>
<th>Function Measure</th>
<th>Flow Tracer</th>
<th>MBF in Region with Normal Function, ml·min⁻¹·g⁻¹</th>
<th>MBF in Region with HM, ml·min⁻¹·g⁻¹</th>
<th>Criteria for HM</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 (wMI)</td>
<td>WMS Echo</td>
<td>H2¹⁵O</td>
<td>0.97 ± 0.22 (P &lt; 0.001)</td>
<td>Functional recovery</td>
<td>de Silva et al. (40)</td>
<td></td>
</tr>
<tr>
<td>22 (wMI)</td>
<td>WMS Echo</td>
<td>¹³NH₃</td>
<td>0.83 ± 0.20 (P &lt; 0.01)</td>
<td>Functional recovery</td>
<td>Czernin et al. (43)</td>
<td></td>
</tr>
<tr>
<td>16 (woMI)</td>
<td>WMS CV</td>
<td>¹³NH₃</td>
<td>0.77 ± 0.26 (P &lt; 0.05)</td>
<td>Functional recovery</td>
<td>Sambuceti et al. (172)</td>
<td></td>
</tr>
<tr>
<td>17 (woMI)</td>
<td>WMS CV</td>
<td>¹³NH₃</td>
<td>0.95 ± 0.27 (P &lt; 0.01)</td>
<td>Functional recovery</td>
<td>Vanoverschelde et al. (214)</td>
<td></td>
</tr>
<tr>
<td>17 (w/woMI)</td>
<td>WMS CV</td>
<td>¹³NH₃</td>
<td>0.97 ± 0.18 (P &lt; 0.001)</td>
<td>Functional recovery</td>
<td>Grandin et al. (83)</td>
<td></td>
</tr>
<tr>
<td>14 (wMI)</td>
<td>WMS Echo</td>
<td>¹³NH₃</td>
<td>1.00 ± 0.24 (P &lt; 0.01)</td>
<td>Preserved FDG uptake</td>
<td>Marzullo et al. (136)</td>
<td></td>
</tr>
<tr>
<td>15 (wMI)</td>
<td>WMS Echo</td>
<td>¹³NH₃</td>
<td>0.83 ± 0.26 (P &lt; 0.01)</td>
<td>Preserved FDG uptake</td>
<td>Brunelli et al. (31)</td>
<td></td>
</tr>
<tr>
<td>17 (w/woMI)</td>
<td>WMS Echo</td>
<td>H2¹⁵O</td>
<td>0.85 ± 0.36 (P &lt; 0.02)</td>
<td>Functional recovery</td>
<td>Conversano et al. (42)</td>
<td></td>
</tr>
<tr>
<td>24 (w/woMI)</td>
<td>WMS Echo</td>
<td>¹³NH₃</td>
<td>0.82 ± 0.22 (NS)</td>
<td>Functional improvement</td>
<td>Gerber et al. (79)</td>
<td></td>
</tr>
<tr>
<td>30 (wMI)</td>
<td>WMS RNV</td>
<td>H2¹⁵O</td>
<td>0.92 ± 0.25 (NS)</td>
<td>Functional recovery</td>
<td>Marinho et al. (133)</td>
<td></td>
</tr>
<tr>
<td>7 (woMI)</td>
<td>WMS Echo</td>
<td>H2¹⁵O</td>
<td>1.02 ± 0.23 (P = 0.066)</td>
<td>Functional improvement</td>
<td>Mäki et al. (138)</td>
<td></td>
</tr>
<tr>
<td>18 (w/woMI)</td>
<td>REF RNV</td>
<td>¹³NH₃</td>
<td>0.93 ± 0.13 (P &lt; 0.005)</td>
<td>Functional improvement</td>
<td>Shivalkar et al. (199)</td>
<td></td>
</tr>
<tr>
<td>12 (5) (w/woMI)</td>
<td>WMS Echo</td>
<td>¹³NH₃</td>
<td>0.73 ± 0.23 (0.81 ± 0.26) (P = 0.004)</td>
<td>PET mismatch, inotropic reserve</td>
<td>Sun et al. (204) and Rahimtoola (165)</td>
<td></td>
</tr>
<tr>
<td>7 (woMI)</td>
<td>WMS Echo</td>
<td>H2¹⁵O</td>
<td>0.81 ± 0.14 (P = 0.16)</td>
<td>Functional improvement</td>
<td>Mäki et al. (139)</td>
<td></td>
</tr>
<tr>
<td>30 (wMI)</td>
<td>WMS CV</td>
<td>¹¹C acetate</td>
<td>1.04 ± 0.27 (P &lt; 0.001)</td>
<td>Improvement with revascularization in flow and function</td>
<td>Wolpers et al. (220)</td>
<td></td>
</tr>
</tbody>
</table>

MBF, myocardial blood flow; HM, hibernating myocardium; w/woMI, with/without myocardial infarction; WMS, wall motion score; CV, contrast ventriculography; REF, regional ejection fraction; RNV, radionuclide ventriculography; Echo, echocardiography; PET, positron emission tomography; FDG, fluorodeoxyglucose.

Matching in patients with chronic regional contractile function can only be resolved with absolute rather than relative regional myocardial blood flow and function data. More recently, absolute regional myocardial blood flow data are available from PET studies using either ¹³NH₃ or H₂¹⁵O as flow tracers (Table 4). The majority of these studies clearly indicate a significant reduction in resting regional myocardial blood flow in those dysfunctional areas classified as hibernating myocardium as compared with intra-individual normal remote areas, with an average reduction in blood flow from baseline by 20–30%. Vanoverschelde et al. (214) observed a significant 19% reduction in resting blood flow in dysfunctional versus remote reference regions of the individual patients (Fig. 13), but they surprisingly reasoned that the observed dysfunction was not secondary to reduced resting blood flow, because blood flow was not significantly different in collateral-dependent myocardium of two subgroups of patients with and without contractile dysfunction (214). Subsequently, Marinho et al. using H₂¹⁵O (133) and Gerber et al. using ¹³NH₃ (79) observed no significant reduction in resting blood flow in the dysfunctional area, both as compared with that in a remote reference region and as compared with normal flow values obtained from healthy volunteers. Clearly, in both studies, the observed reduction in regional contractile function appeared to be out of proportion to the observed changes in regional blood flow at rest, consistent with cumulative myocardial stunning rather than hibernation. In the study by Sun et al. (204), also no significant reduction in resting blood flow in the dysfunctional area as compared with that in the remote reference region and as compared with normal flow values in healthy volunteers was reported. However, in a critical reanalysis, Rahimtoola (165) demonstrated a significant reduction in resting blood flow as compared with that of the remote reference region when using data from those...
When weighing the controversial PET data on regional myocardial blood flow at rest, two critical limitations of any PET flow measurement must be emphasized. 1) The available normal blood flow values from healthy volunteers vary widely $[1.02 \pm 0.26 \text{ ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}, n = 19 (42); 1.02 \pm 0.25 \text{ ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}, n = 25 (133); 0.88 \pm 0.22 \text{ ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}, n = 6 (79); 0.68 \pm 0.16 \text{ ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}, n = 12 (204)]$, and the subjects’ ages also varied widely. In an individual patient, with reference to the reported broad range of normal flow values in volunteers, a 50% reduction in resting blood flow will go undetected. Also, the argument forwarded by Camici et al. (32) that even in the 10% minority of patients who had reduced blood flow at rest (133) this was within the range of normal flow as measured with microspheres (80) is not correct, because the myocardial sample size in the microspheres measurements was far smaller (0.2 g) than in the PET measurements (>> 1 g), and blood flow inhomogeneity, as measured with microspheres, decreases with increasing sample size. Therefore, the comparison to an intraindividual reference region is preferable, even if a certain hyperemia there cannot be excluded. 2) Positron emission tomography flow measurements lack sufficient transmural resolution, and the lack of respiration and/or cardiac motion-gated measurements greatly enhances this problem. As a consequence, an observed 20% reduction in transmural blood flow in regions with chronic contractile dysfunction may well translate to a reduction in subendocardial blood flow as great as 40%, and subendocardial blood flow is the primary determinant of transmural wall function (72).

Apart from these technical concerns related to flow measurements with PET, only one of the above studies provided blood flow data after revascularization, and in this study, there was improvement in flow in areas with improved function (220). Also, in all of the above but one single study (199), wall motion scores were used, and no absolute data on regional contractile function were reported. To resolve the controversial issue of perfusion-contraction matching in chronically dysfunctional myocardium, quantitative data on both regional myocardial blood flow and contractile function before and after revascularization, and possibly with better transmural resolution than currently available are required.

### C. Metabolism in Chronic Hibernation

Information on energy metabolism in patients with chronic hibernation, e.g., from biopsies taken during operative revascularization or from NMR spectroscopy, is not available.

Preserved metabolic activity in chronically dysfunctional myocardium was initially demonstrated in a more or less qualitative fashion from $^{18}$FDG uptake using PET (15, 27, 125, 135, 201, 205, 208). More recently, however, also quantitative data on glucose utilization during a stan-
dardized hyperinsulinemic euglycemic clamp have become available. In such studies, the glucose utilization of healthy volunteers varied from $0.50 \pm 0.18$ (204) or $0.53 \pm 0.11$ (79) to $0.71 \pm 0.14$ (133) $\mu$mol $\cdot$ min$^{-1} \cdot$ g$^{-1}$. Interestingly, in those two studies that observed no reduction in myocardial blood flow at rest, the glucose utilization of dysfunctional myocardium was lower than that in healthy volunteers (79, 133), although not different from that in a remote reference region of the individual patients in one study (133). In contrast, in studies with a reduction in resting blood flow in the dysfunctional myocardium, glucose utilization was not different from that of myocardium in healthy volunteers (204) as well as not different from that of a remote reference region (83, 138, 204). Also, the free fatty acid uptake in regions with chronic dysfunction but preserved viability was not different from that of remote reference regions (139).

During recruitment of inotropic reserve with intravenous dobutamine in the dysfunctional region, glucose utilization, as measured by $^{18}$FDG PET, was increased, whereas it was decreased in normal myocardium (204). In addition, increased anaerobic glycolysis with a significant reduction of net lactate uptake and even net production in some patients, as measured from the arteriocoronary venous differences, was seen in hibernating myocardium during recruitment of inotropic reserve with intracoronary dobutamine (Fig. 14) (98).

An overall measure of oxidative metabolism is derived from the clearance kinetics of $[^{11}]$C-acetate using PET. The rate constant of acetate clearance in areas with chronic hibernation was reduced (42, 43, 214), largely in relation to the reduced blood flow (42, 87). 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 (87).

D. Coronary Reserve and Inotropic Reserve in Chronic Hibernation

Quite consistently, coronary reserve, i.e., the ratio of myocardial blood flow during dipyridamole-induced hyperemia to resting blood flow, was reduced in those chronically dysfunctional areas that had reduced blood flow at rest (136, 172, 214). Recruitment of vasodilator reserve with dipyridamole can also result in improved wall motion score in a number of dysfunctional segments, along an upsloping flow-function relationship (210). A significant inverse relationship between the degree of contractile dysfunction and coronary reserve prompted Vanoverschelde et al. (214) to propose that repeated episodes of ischemia might occur in myocardium that is not capable of increasing its blood flow sufficiently and that repeated episodes of ischemia might induce cumulative stunning.

Also quite consistently, persistent inotropic reserve, i.e., improved regional wall motion in response to dobutamine, was reported from a number of studies in patients with chronic hibernation (79, 87, 98, 201, 204). The recruitment of inotropic reserve was associated with increased oxidative metabolism, as evident from the increased rate constant of $[^{11}]$C-acetate clearance (87), increased glucose utilization (204), and increased anaerobic glycolysis, as evident from reduced net lactate uptake (Fig. 14) (98). Those dysfunctional myocardial regions that responded to dobutamine with increased function also had persistent adenosine-recruitable coronary reserve (201), and the increase in function with dobutamine was associated with increased flow (119, 204). Persistent inotropic reserve, however, is also observed in chronically dysfunctional myocardium with normal perfusion (79) and, unless associated with metabolic deterioration, does not distinguish hibernating from stunned myocardium.

E. Morphology in Chronic Hibernation

Morphological alterations affect the cardiomyocytes and the interstitial space (Table 5). In 1981, before the phenomenon of hibernation was recognized, Flameng et al. (68) already described typical alterations in the morphology of myocardium 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 were
characteristic findings and have been confirmed in a number of studies since then (Fig. 15) (11, 12, 60, 61, 192, 199, 214). The sarcoplasmic reticulum was reduced (11, 68). Also, numerous small doughnut-like mitochondria were consistently observed (11, 60, 61). Loss of contact sites between the inner and outer mitochondrial membranes was taken to indicate reduced oxidative phosphorylation and mitochondrial creatine kinase activity (16). The contractile proteins myosin, the thin filament complex, titin, and α-actinin are reduced (60, 61, 192), and the distribution of titin within the cardiomyocytes is altered (11, 12). The cytoskeleton, consisting of desmin, tubulin, and associated proteins such as vinculin, is disorganized, and these proteins in part accumulate (60, 61). Decreased connexin43 content and reduced gap junction size may predispose to arrhythmias and contribute to impaired excitation-contraction coupling (105).

The interstitial space is characterized by an increased amount of fibrosis (Fig. 16) (10, 61, 68, 192, 214). Cellular particles sequestered into the extracellular space form cellular debris, and the number of macrophages and fibroblasts is increased (60). Extracellular matrix and structural proteins, i.e., all collagens and fibronectin, are increased (10, 28, 60, 61).

Borgers and co-workers emphasized the dedifferentiated phenotype of hibernating myocardium, since α-smooth muscle actin, cardiotin, and titin were found to be expressed in patterns resembling an embryonic phenotype (12, 29), and proposed contractile unloading as the underlying mechanism (28). Somewhat in contrast, J. Schaper and co-workers (60, 61, 192) 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. In correlation to the degree of dysfunction, however, the amount of cardiomyocytes with degeneration and the extent of fibrosis were increased and affected >50% of the myocardium that was morphologically studied (29, 61, 68, 199). The severity of morphological alterations surprisingly did not correlate with the degree of hypoperfusion and wall motion abnormalities and also not with the functional outcome after surgical revascularization in one study (192). On the other hand, the extent of fibrosis (ranging from 10 to 70% of the biopsy specimen) was the major determinant of postoperative functional recovery in the study by Shivalkar et al. (199) and by Elsässer et al. (61). Importantly, in the recent study by Elsässer et al. (61), clear evidence of apoptosis was found in dysfunctional myocardium recovering after surgical revascularization, using both electron microscopy and in situ labeling with terminal deoxynucleotidyl transferase (61), similar to a recent experimental study with hibernating myocardium in pigs with chronic coronary artery stenosis (40). Therefore, these authors emphasized the progressive diminution of the chance for complete structural and functional recovery after restoration of blood flow and the need for early revascularization.

In conclusion, the morphology of hibernation is characterized by signs of atrophy, most notably of the contrac-

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**TABLE 5. Morphological features of chronic hibernation**

<table>
<thead>
<tr>
<th>Cardiomyocyte alterations</th>
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<tbody>
<tr>
<td>Loss of myofilaments (myosin, thin filament complex, titin)</td>
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<tr>
<td>Loss of sarcoplasmic reticulum</td>
<td></td>
</tr>
<tr>
<td>Numerous small, doughnut-like mitochondria</td>
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<tr>
<td>Disorganization of cytoskeleton (desmin, tubulin, vinculin)</td>
<td></td>
</tr>
<tr>
<td>▼Sequestration of cellular particles into extracellular space</td>
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</tr>
<tr>
<td>Atrophy and apoptosis</td>
<td>Also increased number of glycogen deposits</td>
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<table>
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<tr>
<th>Interstitial alterations</th>
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<tbody>
<tr>
<td>Increased amount of matrix and structural proteins (fibronectin and all collagens)</td>
<td></td>
</tr>
<tr>
<td>▼Increased number of macrophages and fibroblasts</td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
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tile myofibrils, similar to skeletal muscle wasting with prolonged quiescence, degeneration, most notably in the interstitial space, and possibly dedifferentiation.

F. Diagnosis of Chronic Hibernation

In principle, residual viability in chronically dysfunctional myocardium of patients with coronary artery disease, which may reflect either hibernating or stunned myocardium or some combination thereof, can be assessed by scintigraphy using either thallium or technetium sestamibi, by PET measurements of perfusion ($^{13}$NH$_3$, H$_2^{15}$O) and metabolism ($^{18}$FDG, $^{11}$Cacetate), and by echocardiography with an inotropic challenge. The value of the respective diagnostic procedures can only be judged with respect to the prediction of recovery of regional contractile function and patients' prognosis (26, 53).

Thallium and technetium sestamibi accumulation are dependent on myocardial blood flow, but also on membrane integrity. A significant inverse relation between the amount of fibrosis and tracer uptake was found for both thallium (48) and technetium sestamibi (44, 128, 141). The reversibility of wall motion abnormalities is well predicted by thallium scintigraphy, in particular when used in a redistribution/reinjection protocol (54, 99, 158, 160, 212). The positive predictive value for contractile recovery in areas with thallium uptake was 69%, and the negative predictive value in areas without thallium uptake was 90% in a review of 13 studies involving 378 patients (26). In a pooled analysis of seven studies, thallium reinjection imaging had an average sensitivity of 86% and an average specificity of 47% for functional improvement after revascularization (19).

Thallium rest-redistribution imaging in eight studies had an average sensitivity of 90% and an average specificity of 54% for functional improvement after revascularization (19). Technetium sestamibi scintigraphy had an average sensitivity of 81% and an average specificity of 60% in seven studies.

The reversibility of wall motion abnormalities is also well predicted by PET techniques (49, 87, 135, 199, 208), and a number of pertinent studies on PET measurements of myocardial perfusion and metabolism have been discussed above. The positive predictive value for contractile recovery in areas with a mismatch between $^{18}$FDG uptake and myocardial blood flow was 82%, and the negative predictive value in areas without mismatch was 83% in a review of six studies involving 146 patients (26). In a pooled analysis of 12 studies, FDG-PET imaging had an average sensitivity of 88% and an average specificity of 73% for functional improvement after revascularization (19).

Recruitment of inotropic reserve is a hallmark of short-term hibernation (38, 182). Such recruitment of inotropic reserve can be clinically monitored by dobutamine echocardiography. A positive, sometimes biphasic (2, 148, 173) response to dobutamine predicts functional recovery upon revascularization (15, 18, 87, 118, 148, 158, 160, 212). The positive predictive value for functional recovery in areas with a positive response to dobutamine echocardiography was 83%, and the negative predictive value was 81% in a review of 15 studies involving 402 patients (26). In a pooled analysis of 16 studies, low-dose dobutamine echocardiography had an average sensitivity of 84% and an average specificity of 81% for functional improvement.
after revascularization (19). Interestingly, lack of a positive response to low-dose dobutamine with a decrease in regional function at high-dose dobutamine also predicts a significant improvement of regional wall motion after percutaneous transluminal coronary angioplasty (2). However, dobutamine echocardiography, in particular when using a prolonged ramp protocol and when higher doses of dobutamine are required (2), is not without risks for the patient (165, 186).

Upon direct comparison, it appears that thallium scintigraphy and PET techniques identify more or less the same regions as viable or nonviable (15, 27). Also, thallium scintigraphy and dobutamine echocardiography yield largely concordant information on viability (158, 160, 212). Given the end point of contractile recovery, it is not surprising that dobutamine echocardiography appears to have greater specificity to predict functional recovery (19, 158, 160, 212), whereas thallium scintigraphy appears to have greater sensitivity (19, 160). Also, dobutamine echocardiography has a higher false-negative rate than PET (155).

It must be emphasized that the above diagnostic tests identify viable, dysfunctional myocardium in patients with coronary artery disease but do not distinguish chronic hibernation from cumulative stunning. Such a distinction requires flow measurements or the analysis of metabolism during inotropic stimulation. Only those dysfunctional areas with reduced myocardial blood flow at rest on quantitative PET flow measurements (see sect. iv B) or those with a positive response to dobutamine in combination with impaired aerobic metabolism (98) can unequivocally be identified as hibernating myocardium. The distinction between chronic hibernation and cumulative stunning may not be that important, however, clinically because revascularization is mandatory in any event. Definitely, patients with multivessel coronary disease and severe left ventricular dysfunction who have signs of maintained viability on thallium scintigraphy (156) or PET imaging of flow and glucose uptake (85) have better postoperative outcome and prognosis than those who have not.

G. Therapy of Chronic Hibernation

Currently, the therapy of chronically hibernating myocardium is reperfusion. Surgical revascularization of chronically dysfunctional myocardium in patients with coronary artery disease is long known to be capable of improving regional wall motion, left ventricular pump function, and clinical status (3, 36), and a review of the results of large randomized coronary bypass surgery trials actually led Rahimtoola to introduce the concept of hibernation (Fig. 17) (161, 162). Also, the presence of hibernating myocardium is associated with an adverse prognosis (52, 59, 121, 218), and its revascularization is associated with improved prognosis (52, 59, 84, 121, 156, 216). In patients with severe coronary artery disease and severe chronic ischemic cardiomyopathy, coronary revascularization is actually a reasonable alternative to cardiac transplantation, in particular given the shortage of donor hearts (57, 114, 125). The recovery of contractile function after coronary revascularization may be almost immediate and detected intraoperatively (209) or occur early after revascularization (2). However, it is important to realize that the improvement in both perfusion and contraction in an area with infarction may not always be immediate upon revascularization, but may require several months in a number of patients (75).

V. CONCLUSIONS AND PERSPECTIVES

Clearly, the myocardium can adapt to prolonged moderate ischemia for several hours. Such short-term hibernation is entirely consistent with the concept of hibernation, and it is characterized by 1) sustained perfusion-contraction matching, 2) recovery of contractile function during reperfusion, and 3) lack of necrosis. In addition, 4) recovery of energy and substrate metabolism, and 5) the potential for recruitment of inotropic reserve at the expense of metabolic recovery have become characteristic features of short-term hibernation. Apart from reduced calcium responsiveness, the underlying mechanisms of short-term hibernation are currently unclear. Several studies demonstrated profound spatial heterogeneity of myocardial blood flow distribution during normal conditions (14, 50, 203), and it was hypothesized that small areas with low perfusion may also have low energy demand secondary to a state of “physiological hibernation” in the absence of ischemia (203). Although such perfusion inhomogeneities at the microvascular level are intriguing and thought provoking, their functional relevance is still questionable, since with integration of 1 g of myocardium or more, little inhomogeneity of blood flow measurements is left.

For future studies on short-term hibernation, experimental models with quiescent isolated cardiomyocytes are, almost by definition, inappropriate. The “lowest acceptable denominator” for the study of short-term hibernation is the isolated perfused heart (93). The limitations of this preparation include denervation, lack of extracardiac hormonal stimuli, buffer perfusion, and usually global rather than regional ischemia. A particular problem is that isolated hearts appear to exhibit no metabolic recovery during prolonged ischemia (202). Therefore, the mechanisms underlying short-term hibernation are probably best studied in acute, large-animal in situ models with regional ischemia, exhibiting all of the above criteria and permitting measurements of flow and mechanical function with good spatial resolution. Also, carefully focused studies in transgenic animals may help to identify the underlying mechanisms. It is expected that, with better understanding of the underlying mechanism(s) of short-term
Fig. 17. Paradigmatic ventriculography of a patient with left anterior descending coronary artery (LAD) occlusion and hibernating myocardium. Eight months after revascularization, regional contractile function and ventricular ejection fraction (EF) are restored to normal. LVEDV, left ventricular end-diastolic volume. [From Rahimtoola (161).]

Almost all of the existing studies on short-term 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, such 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 (162). Also, morphological alterations in such animal models with chronic coronary stenosis are remarkably similar to those found in patients with chronic hibernation. The existence of cumulative stunning secondary to repeated episodes of stress-induced ischemia 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 (23), but has not been systematically investigated and, above all, does not exclude the existence of hibernation in other studies. To resolve such controversies, studies in conscious, chronically instrumented animals with a chronic coronary stenosis and continuous monitoring of flow and function with the stenosis and after its removal are required.

Chronic hibernation in patients will always be a hypothetical condition, insofar as the natural history of the observed dysfunction is never known. The majority of quantitative data available, however, indicate reduced blood flow at rest in the dysfunctional region as compared with an intraindividual remote reference region, consistent with the original concept of hibernation. However, it must be acknowledged that reduced blood flow at rest does not exclude superimposed episodes of stress-induced ischemia, resulting in stunning. In most patients with chronic ischemic dysfunction, there will also be an admixture of some necrotic/fibrotic tissue.

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. 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...
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