Response to Myocardial Ischemia as a Regulated Process

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To a great extent, our knowledge of the pathophysiology of myocardial ischemia is based on complete coronary arterial occlusion, with almost total cessation of myocardial blood flow. The resulting sequence of events has been studied in detail, from hemodynamic, metabolic, structural, and therapeutic standpoints. Investigations of the evolution of the process to myocardial necrosis or to recovery after relief of the total occlusion have been essential in guiding new approaches to the management of coronary thrombosis and acute myocardial infarction. However, the severity of that insult does not allow evaluation of some important regulatory processes in the heart that are of interest, especially when chronic coronary stenosis and the "hibernating myocardium" are considered.

This review outlines the relations among myocardial blood flow, mechanical function, and high-energy phosphate metabolism with mild-to-moderate reductions in coronary blood flow. Insights have been gained into the ways in which the heart responds to the challenge of decreased arterial perfusion, and some surprises have been encountered. Observations during ischemia include incomplete dilation of coronary resistance vessels, contractile reserve, and metabolic adjustments. A more complete understanding of these phenomena may ultimately help to explain the apparent downregulation of myocardial function during ischemia. The conclusion can be reached that the heart's response to moderately severe ischemia is controlled and purposeful, contributing to survival of the myocardium.

Myocardial Blood Flow With Graded Ischemia—Incomplete Vasodilation

With constant myocardial metabolic demand, the response of the coronary resistance vessels to a decrease in coronary arterial pressure (CAP) is vasodilation. Judging from animal experiments,1–3 with mild decreases in CAP, this autoregulatory response maintains a relatively constant coronary blood flow, until a mean CAP of approximately 45 to 50 mm Hg is imposed. Any further decrease in CAP is associated with a decrease in coronary flow. Although it might be assumed that flow reserve is then exhausted and further vasodilation is not possible, this proves not to be the case, at least in animals studied acutely. Rather, there is inducible coronary reserve that can be substantial despite flow-limiting stenosis.4–7

The available increase in coronary flow at subnormal CAP can be demonstrated experimentally with intracoronary adenosine or in response to radiographic contrast agent.4–7 Flow reserve is not exhausted until CAP is quite low, if reasonable cardiac loading conditions are present. For example, in our experimental model using the anesthetized pig, some reserve was present almost to the point of cessation of flow when coronary pressure–flow relations were compared with and without adenosine. Inducible coronary flow reserve during ischemia is seen in the distribution of both the left and right coronary arteries.8 It can be shown very soon after the onset of ischemia4 and is demonstrable after 3 hours of continuous ischemia.9 The amount of flow reserve decreases with the severity of the ischemia.

Research by Griggs and Nakamura,10 Hoffman,11,12 Buckberg et al,13 and others,14,15 demonstrated that the subendocardial myocardium is especially vulnerable to acute decreases in CAP. Thus, during ischemia, decreases in subendocardial blood flow are disproportionately large compared with the remainder of the left ventricular wall, and the ratio of subendocardial to subepicardial flow (inner:outer ratio) falls, sensitively reflecting ischemia. The imbalance is exaggerated by excessive myocardial demand, and a fall in the inner:outer ratio can even be provoked without coronary stenosis if metabolic demand is excessive.13 It should follow and has been shown that during ischemia, flow reserve in the subendocardium is less than that in the subepicardial zone.16 Collateral development may ameliorate the inner:outer imbalance somewhat in chronic states.17
Recent research has demonstrated that the anatomic site of vasodilator reserve in ischemia is the coronary arteriole, at least in the subepicardial zone. At higher CAPs with less severe ischemia, the autoregulatory response begins with arteriolar dilation but is aided by dilation of small arteries (more than 150 \(\mu\)M diameter) as CAP decreases to 60 mm Hg. Thereafter, residual vasomotor tone is found to reside in the arterioles, not in the small arteries.\(^\text{18}\) It should be emphasized that these observations were restricted to the epicardial surface of the heart, whereas ischemia is most often severe in the subendocardium.

The presence of vasodilator reserve despite ischemia is both interesting and curious. Because ischemia is associated with abnormalities of contractile function and by definition results from a decrease in coronary blood flow, one might expect stimulation of reserve flow to ameliorate the consequences of ischemia on regional function. However, this does not appear to be the case, at least with acute experimental ischemia. Increased flow to all layers of the left ventricular wall has failed to change mechanical performance of the ischemic segment consistently, if the increased flow is provided at subnormal CAP by the vasodilator adenosine.\(^\text{4}\) Oxygen saturation of coronary venous blood draining the ischemic segment rises as coronary blood flow increases, but significant changes in local oxygen consumption are not seen, at least not during an observation period of 10–15 minutes.

It was reasoned that vasodilator reserve during ischemia might be present to respond to a more physiological stress. However, when pacing-induced tachycardia was superimposed on moderate ischemia at a given CAP, coronary flow did not change, and there was a further decline in function, with no change in the oxygen consumption of the ischemic segment.\(^\text{19}\) Thus, the local oxygen consumption was apparently set at a new level of coronary flow, and available oxygen per beat fell with the tachycardia. Despite this, increased coronary blood flow could be provided by intracoronary adenosine during the tachycardia, although flow reserve was soon exhausted in the subendocardium.

\(\alpha\)-Adrenergic influences appear to be important in maintenance of vasoconstriction during ischemia and could thereby account for flow reserve. A current issue is whether flow reserve reflects activity of \(\alpha\)-receptors with undesirable effects that limit “usable” myocardial blood flow\(^\text{20}\) or whether \(\alpha\)-adrenergic activity is a useful mechanism to maintain the most appropriate transmural distribution of flow and prevention of a “steal” of blood by the subepicardium.\(^\text{21}\)

It is clear that the coronary vessels remain reactive to adrenergic stimulation despite the presumably intense metabolic stimulation present during myocardial ischemia.\(^\text{22}\) This observation strongly argues that adrenergic activity could be responsible for the maintenance of coronary arteriolar tone during moderate ischemia. One interpretation of the presence of vasodilator reserve is that sympathetic vasoconstrictor function, especially in the outer part of the left ventricular wall, helps to maintain the appropriate distribution of flow across the wall to avoid a steal of blood by the subepicardial regions. There is information to support this idea.\(^\text{21,23}\) The merit of this explanation is difficult to judge on the basis of flow data alone, however, without other evidence of benefit to myocardial function or metabolism.

Adrenergic influences on vasodilator reserve are confusing to understand because of apparently conflicting results in the evaluation of \(\alpha_1\) and \(\alpha_2\)-receptors. From one perspective, residual adrenergic tone in myocardial vessels during ischemia has been accounted for predominantly by \(\alpha_1\) activity,\(^\text{20,24}\) and its blockade resulted in increased myocardial flow, oxygen consumption, and mechanical function. Others have found that \(\alpha_2\)-blockade reduced myocardial ischemia and improved mechanical function in ischemia.\(^\text{25}\) However, in another study, \(\alpha_2\) stimulation with clonidine improved coronary flow and myocardial performance during ischemia.\(^\text{26}\) A recent report indicates that \(\alpha_2\)-mediated tone persists in ischemia, and its relief with a blocking agent increases subepicardial flow, whereas subendocardial flow does not change.\(^\text{27}\) In all of the studies of transmural flow distribution, the absolute subendocardial flow is important to interpret, as well as the inner:outer flow ratio. The significance of changes in flow distribution seems most completely interpreted when measurements of mechanical function and regional metabolism are also made.

For the present, we conclude that \(\alpha\)-adrenergic activity (perhaps \(\alpha_1\) and \(\alpha_2\)) can account for some, or perhaps all, residual coronary tone during ischemia. Whether its abolition during a challenge such as exercise is beneficial continues to be controversial.

It is interesting to speculate about mechanisms underlying vasodilator reserve. Hoffman and Spana\(^\text{28}\) suggest three possibilities. First, vasoconstrictor metabolites might be produced during ischemia, or there might be failure of some endogenous vasodilator material to be generated. Because tissue concentrations of adenosine are substantial, failure of generation of adenosine seems unlikely. Second, the vessels that control resistance and must have some residual tone in the presence of vasodilator reserve might be located too far from the source of endogenous metabolites. Third is the possibility of heterogeneity, at a microscopic level.

To address the third mechanism, Coggins et al\(^\text{29}\) studied the distribution of coronary flow to 192 regions of the left ventricle during graded decreases in CAP to evaluate the possibility that heterogeneity of flow distribution could account for flow reserve during ischemia. It was concluded that myocardial ischemia could produce an all-or-none vasodilatory response in the sense that some microregions were ischemic and had maximal vasodilation, whereas others were not ischemic and could demonstrate flow reserve. Increasing ischemia produced more maximally dilated regions and less flow reserve (fewer
nonischemic microregions). This suggests closely coupled regulation between vasomotor tone and local oxygen need in very small myocardial units. The possibility of cyclic distribution of ischemic zones over time—a periodic redistribution of blood flow from microregion to microregion—is a fascinating challenge to evaluate and is suggested by the concept of heterogeneity. A metabolic correlate of flow heterogeneity has been described.30

As mentioned above, many of the observations of myocardial blood flow reserve during ischemia have been made during anesthesia in acute experiments in dogs. Canty points out that a decrease in subendocardial flow begins when CAP falls below 70 mm Hg in such preparations3 (i.e., subendocardial autoregulatory reserve is exhausted at that pressure). In experiments in chronically instrumented dogs, he demonstrated that subendocardial myocardial function began to fall at a lower CAP than had been observed in anesthetized preparations, raising questions about the effects of anesthesia per se on the coronary circulation.3 Furthermore, in a preliminary report, intracoronary adenosine did not produce an increase in subendocardial flow in chronic animals when subendocardial flow had been decreased by approximately 55%.31 It was suggested that presence of endocardial vasodilator reserve could be a product of anesthesia and high sympathetic tone and thus would not be relevant in the natural, conscious state.

However, species differences may be very important in this question. There are considerable preformed collaterals in the dog compared with other animals such as the pig.32–34 Although this would not necessarily change the pressure-flow-function relations of the dog heart studied by the microsphere technique, it raises questions about differences in behavior of the vascular bed. For example, in anesthetized pigs, McFalls et al35 found that the breaks in the myocardial pressure-function, pressure-flow, and pressure-oxygen consumption relations were at approximately 50 mm Hg, considerably less than that reported in anesthetized dogs.34 Other evidence to support the presence of vasodilator reserve comes from research in which an increase in subendocardial flow reserve was demonstrated in awake dogs with ischemia during exercise.24 We believe the evidence suggests that vasodilator reserve is a tenable, physiologically relevant concept.

In summary, during incomplete coronary arterial obstruction, it appears that the overall response of the coronary resistance vessels to ischemia is graded and at most times incomplete, when judged in terms of the maximum possible dilation inducible with drugs in a given region. Adrenergic influence may produce this, at least in part. Whether this is desirable to maintain subendocardial perfusion or is pathologically limiting for cardiac performance is not yet determined. The first of these two possibilities is attractive if one subscribes to the concept of vascular regulation during ischemia. It is interesting that production of pharmacologically increased flow during ischemia has been shown acutely to improve mechanical function only modestly4 or not at all,4 indicating that other factors control function during ischemia beyond simple oxygen availability. The effects of anesthesia and species differences bear further study, as does the possibility that ischemia is heterogeneously distributed throughout a given layer of the ventricular wall, with each tiny zone responding in an all-or-none way.

Mechanical Function and Functional Reserve During Ischemia

In the early days of contrast ventriculography, there were suggestions that myocardial ischemia could decrease the mechanical performance of the left ventricle chronically yet reversibly.36–38 This possibility became evident when return of function followed mechanical myocardial revascularization, in which myocardium that was dysfunctional but not infarcted regained performance.39–47 The return of function can be relatively prompt.48 Such observations led to the idea of the idling or hibernating myocardium, a chronic decrease in local myocardial performance associated with a coronary lesion but no signs of acute ischemia or infarction.49–51

It is now appreciated that myocardial performance during acute ischemia is quantitatively adjusted to blood flow and is not an all-or-none phenomenon. Support for this concept is found in the experimental laboratory with acute and chronic preparations but generally with acute reductions in blood flow only. In a chronic canine preparation, acute reductions in myocardial flow of 10–20% were consistently associated with mildly decreased mechanical performance indicative of a sensitive relation between flow and function. Function did not cease entirely until flow fell about 80% from baseline.52 The work performed by a segment of the left ventricular wall in pigs varied quantitatively and directly with the amount of coronary flow in another early study.53 In our laboratory, a consistent graded relation was demonstrated among CAP, myocardial blood flow, oxygen consumption, and systolic segmental wall thickening during acutely induced ischemia, with a progressive decrease in local function between 55 and 20 mm Hg.35 There is abundant evidence that by some sensitive means, myocardial function decreases in a graded manner in response to decreases in myocardial blood flow.

The next phase in understanding this relation came from the work of Gallagher and colleagues in the laboratory of Ross.54,55 As noted earlier, decreases in myocardial flow are first felt in the subendocardial region. Using systolic thickening measured with ultrasonic crystals as the indicator of segmental function, a systematic relation was found between the distribution of reduced flow across the left ventricular wall and systolic function. When subendocardial flow fell about 18%, systolic wall thickening decreased 13%; functional changes were more or less proportionately depressed with further decreases in
subendocardial flow to 25–35% of control. More severe reductions of subendocardial flow led to dyskinesia. Subepicardial flow did not correlate with function and could be found close to control values with decreases in function greater than 50%. Clearly, subepicardial flow could be made to decrease with severe coronary stenosis, but by this time wall thickening was already considerably reduced.55

The relation between myocardial blood flow and local mechanical function has been recently reviewed in extenso by Ross, who summarized current knowledge. Emphasized in the review was the crucial relation between subendocardial blood flow per beat and local left ventricular wall function. The term “perfusion—contraction matching” was used to describe this relation. The distribution of coronary flow across the left ventricular wall is critical, and the adequacy of myocardial perfusion cannot necessarily be determined by total coronary flow. Thus, McFalls and coworkers in our laboratory showed more severe subendocardial ischemia with unchanged total coronary flow when the vasodilator adenosine was given. The key finding was decreased CAP at a given level of total flow. Thus, one important variable to ensure appropriate flow distribution is the perfusion pressure.

The level of depressed function found in relation to a given decrease in myocardial flow seems to be below that which is obligatory because of reduced oxygen availability (i.e., more function might be produced but is not—active downregulation). Evidence for this comes from studies of contractile reserve during ischemia in patients with coronary artery disease. Postextrasystolic potentiation, a positive inotropic stimulus, occurs in the beat after a premature beat. Abnormally moving left ventricular wall segments have been shown to improve with extrasystolic potentiation, indicative of the presence of contractile reserve in the face of chronic depression of local function.57 Similar improvement in segmentally depressed left ventricular function has been produced by epinephrine.58,59

Crozatier et al.60 suggested that contractile reserve in partial ischemia could be due to heterogeneity of the ischemia (i.e., some cells or regions in the wall may be severely ischemic and others normal). Thus, a relatively spared subepicardial region could respond to stimuli such as postextrasystolic potentiation, whereas the completely ischemic subendocardium could not. The net transmural result would be some response to the inotropic stimulus.

At the cellular level, the controlling mechanisms for mechanical function in the face of ischemia are not fully identified, but several have been postulated to have a regulatory role. The products of ATP hydrolysis or other factors have been assigned a role, such as ADP level, the ratio of phosphocreatine (PCr) to inorganic phosphate, P<sub>O</sub>2, or cellular acidosis.61–64 Recently, CAP (or coronary flow) has been shown to modulate intracellular calcium levels, which in turn may regulate contractile function.65

In summary, there is quantitative matching, probably over extended periods of time, of myocardial flow and local function. The stimulus for the regulation of function downward when flow decreases is not fully known. We suggest that the response of mechanical function is not totally passive once there has been time for the myocardium to actively adjust as discussed below.

**Metabolic Adaptation to Ischemia**

The changes in cardiac energy metabolism in response to decreases in coronary flow or complete coronary occlusion have been well documented. In a variety of models, from isolated hearts to intact working systems, there is a rapid fall in PCr, an increase in the rate of anaerobic glycolysis, a rise in cell lactate content, a fall in cytosolic pH, and accumulation of inorganic phosphate.51.62,66–74

Interestingly, ATP has been thought to fall more slowly, after function has already been depressed. Thus, there appears to be some intervening influence to decrease function before total ATP depletion. If the ischemia is persistent and profound, ultimately there is total utilization of high-energy phosphate and cell death. If the ischemia is less severe, a graded metabolic response occurs, depending on the severity of the flow reduction, and resulting in a new lowered level of cellular ATP content that can remain stable for several hours.75

There are at least two ways of interpreting the changes seen in ischemia, short of total coronary occlusion. In one construct, the level of depression of function is determined by the new rate of production of energy-delivering materials (i.e., PCr and ATP). Thus, function is regulated by oxygen availability. Decreased function is obligatory and passive and is based on the fuel supply. A new ischemic steady state is achieved, which is solely regulated by the rate of ATP synthesis. Lower-than-normal cellular content of PCr and ATP would be expected, but not necessarily depletion. Any increased level of function would result in further loss of high-energy phosphate compounds and depletion of the total adenine nucleotide pool and would probably be a threat to the physiological and anatomic integrity of cardiac cells. In this model, diminished function is essential and passive. The new steady state includes low ATP and PCr levels, low pH, and sustained lactate production. However, there is mounting evidence against this picture as being complete.

An alternative sequence is different in subtle but fundamentally important ways. In this scheme, function is actively downregulated by factors not yet fully identified but probably not continuously related to high-energy phosphate levels. In this scenario, a rapid reduction in mechanical function of the cell prevents profound depletion of high-energy phosphate compounds and the total adenine nucleotide pool. Function is depressed more than would be required by the degree of decreased oxygen delivery. This allows payback of debts that clears lactate from
the cell and allows regeneration of PCr, as reflections of the cell’s energy balance. Evidence suggesting this sequence is outlined subsequently.

The difference between these two sequences is in the achievement of a new steady state of energy balance without accumulating energy debts, such as progressive lactate accumulation and acidosis. Rather, the new steady state is controlled in the cell’s favor, even to the extent that some energy reserves can be reconstituted. It must be emphasized that the findings apply only to moderate decreases in coronary flow. With total coronary occlusion, progressive depletion of all high-energy metabolites ensues, and the cell dies.

Evidence of Metabolic Downregulation and Achievement of a New Steady State of Energy Production

From a series of preliminary experiments in anesthetized pigs, we have concluded that controlled downregulation of energy requirements occurs during moderate myocardial ischemia. Total transmural myocardial lactate blood flow in these studies was reduced by 20–70%, associated with a proportionately greater decrement to the subendocardium. Left ventricular wall function was assessed by the measurement of segmental wall thickening, and periodic, small transmural left ventricular biopsies were obtained, which were analyzed in different layers of the myocardium for lactate, PCr, ATP, and, in some studies, the other adenine nucleotides.

Ischemia produced by incomplete coronary occlusion was associated with a prompt fall in local left ventricular systolic wall thickening, as well as decreases in subendocardial PCr and ATP, by 15 beats. Decreases in the ATP synthesis rate and in the “storage” form of high-energy phosphate (PCr) appear to be promptly associated with changes in function.

When coronary flow was kept constant at the new level, interesting phenomena were observed in other studies. With continuing ischemia, lactate was produced by the myocardium (coronary venous lactate higher than arterial lactate), and tissue content of lactate increased threefold. By 30 and 60 minutes of continuous ischemia, lactate content fell from almost 9 μmol/g during early ischemia to 4.3 and 4.2 μmol/g, respectively (compared with 2.2 μmol/g at baseline). By 60 minutes of ischemia, net lactate production had returned to extraction. There are three ways to interpret these lactate findings (i.e., the demands on myocardial energy metabolism fell, there was depletion of substrate with which to produce lactate in the muscle, or a new energy balance was achieved between synthetic and utilizing processes).

If the demand for myocardial oxygen consumption fell with time, the ischemic state might be lessened, and lactate production could also decrease. Fedele et al found lactate production returning “toward consumption” by 3 hours of ischemia. They also found decreases in regional oxygen consumption with time that were interpreted as reflecting decreased function and a more appropriate matching of oxygen supply and demand. Although we agree that there is a better match of oxygen supply and demand during ongoing ischemia, we have found a rather constant myocardial oxygen consumption over time during ischemia, as well as fairly constant segmental wall function. Thus, we have not been able to explain in our model the decreases in tissue lactate and the return to lactate extraction by decreases in function or metabolic need.

A second explanation for decreasing cellular lactate is depletion of glycogen stores in the cell. To test this idea, ischemia was produced with a 30% decrement in transmural flow (55% decrease in subendocardial flow). After 60 minutes, during which time the early rise in cellular lactate had fallen, heart rate was abruptly increased 50 beats per minute by atrial pacing while a constant, low CAP was maintained. Myocardial lactate promptly rose again, and extraction turned to production. Thus, there were cellular sources of glucose, presumably from glycogen, and carbohydrate depletion of the muscle is an unlikely explanation for the apparently improved lactate balance during the first hour of ischemia.

The third explanation is that cell energy balance improved, as suggested by Fedele et al, but by different means. As noted earlier, PCr falls rapidly at the onset of ischemia, and ATP falls more slowly. It has been known for some time that cellular ATP tends to level off with moderate ischemia, far short of being depleted. This has also been true in our experience. In contrast, PCr follows a different course. After the initial plunge, PCr usually regenerates back to normal levels by 60 minutes. This is a remarkable phenomenon, as PCr can only come by transfer of a phosphate group from ATP via the creatine kinase reaction. Thus, some ATP is used to produce PCr rather than for other purposes.

The regenerated PCr was not sequestered in the cell, as its level fell again, with imposition of the new supply-demand imbalance produced by tachycardia. Given a turnover rate of ATP of two to four times per minute (approximately 10–20 μmol ATP min⁻¹ · g myocardium), the accumulation of 6–8 μmol PCr/g in 60 minutes is not a large amount. However, the regeneration of PCr has significance. If mechanical function were not actively downregulated, then one would assume that any ATP synthesized would be immediately used, and cellular ATP levels would decline, or at best level off, and no ATP would be “shunted” to make PCr. This assumes no transport problems or changes in the creatine kinase reaction. Thus, the slight excess amount of ATP that allows PCr regeneration can be interpreted as a marker of a relatively precise, regulated balance between the supply of ATP and demand.

A related issue would be why ATP does not rise, compared with PCr, as a reflection of the enhanced energy balance in favor of supply. Here, other factors come into play. There is relatively rapid depletion of
the adenine nucleotides ADP and AMP when ischemia occurs.80,81 Thus, there may be a limitation to the accumulation of ATP, based on substrate deficiencies, as the de novo synthetic pathways for the adenine nucleotides are very slow and costly in energy consumption.

Thus, we interpret the regeneration of PCr and the decrease in cellular lactate during continued moderate ischemia to reflect a balanced supply-demand and energy state, with function downregulated by some, as yet incompletely identified, factors to a level that prevents cellular high-energy phosphate depletion. The initial trigger may be decreased ATP availability, but high-energy phosphate levels appear to be dissociated from mechanical function later, when function is at a level consistent with but not exceeding energy supply.

**Other Evidence of a Regulated Response to Ischemia**

The matching of oxygen demand to supply is well documented by numerous workers. For example, the review cited earlier on perfusion-contraction matching is based on the concept,56 and an additional report from the Ross laboratory suggests the following sequence.82 With coronary narrowing and inadequate flow, transient ischemic imbalance occurs between supply and demand. The state is believed to be brief, followed by decreased contractile behavior to reestablish a supply-to-demand balance to prevent progressive ischemia. This sort of reasoning raises new questions about the definition of ischemia. Left unanswered was whether the process was regulated or passive.

The notion of actively controlled matching of supply and demand is supported by the research of Marshall et al.83 In a study of increased contractile demand without increased coronary flow, myocardial high-energy phosphate content was preserved, and contractile performance remained low, at a level the cell could “afford.” Dissociation between preserved energy stores and lowered mechanical performance was seen in another study, and performance was linked to energy production, with preservation of energy compound levels.84

In a study of myocardial “hibernation” in the piglet heart, relatively preserved ATP stores were associated with depressed function, which would help to prevent cellular injury that would occur with total depletion of high-energy compounds.85

Although this review has focused on incomplete coronary arterial occlusion and the resulting mild-to-moderate ischemic state, additional support for the idea of the response to ischemia as a regulated process comes from relatively brief, repeated total coronary occlusions. As shown by Swain et al86 and Reimer et al,87 the first occlusion results in a decline in high-energy phosphate levels, but subsequent occlusions do not produce further depletion. Thus, the system “ learns” from the first ischemic bout and could therefore be seen as protecting itself from subsequent ones.

The fascinating phenomenon of “preconditioning” of the myocardium also is consistent with the idea of a learned response and regulation. Thus, the sequence of several brief ischemic bouts, followed by sustained complete coronary occlusion, results in a smaller infarction than that produced without the preliminary brief periods of ischemia.88–90 Theoretically, such protection might be afforded by opening of collaterals with repeated ischemic challenges. However, Murry et al90 showed the metabolic changes of preconditioning without much change in collateral blood flow; thus, a primary protective effect in the cell appears likely.

**Conclusion**

There is a danger in applying teleological reasoning to a system as complex as the myocardium and its circulation. Thus, the assignment of purpose to the processes we have reviewed should be interpreted with some caution. Nevertheless, survival of myocardial cells in the face of ischemia is clearly in the interest of survival of the organism. The phenomena we review herein should contribute to an economy that enhances survival.

We propose, therefore, that the cardiac response to ischemia is regulated, perhaps to preserve sufficient energy stores to protect the anatomic and physiological integrity of the cardiac cell. Thus, we find residual coronary vasomotor tone during moderate ischemia as a means to ensure appropriate transmural flow distribution, decreased (downregulated) function despite available high-energy phosphate compounds, and reestablishment of metabolic balance during moderate ongoing ischemia. Other phenomena, such as the “hibernating” myocardium, contractile reserve during chronic ischemia, resistance to depletion of energy stores with multiple bouts of ischemia, and preconditioning, support the concept. A better understanding of the means by which the heart achieves these responses will be fascinating to learn.

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