The Stunned Myocardium: Prolonged, Postischemic Ventricular Dysfunction

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SUMMARY Myocardial ischemia has, for many decades, been viewed as an all-or-none process that causes myocardial necrosis when prolonged and severe, but whose effects are transient when it is brief or mild. In view of the evidence that the ischemic process may "hit, run, and stun," perhaps our thinking about the consequences of myocardial ischemia should be expanded. According to this formulation, an ischemic insult not of sufficient severity or duration to produce myocardial necrosis may acutely affect myocardial repolarization and cause angina (hit); but these changes wane rapidly (run), when the balance between myocardial oxygen supply and demand has been reestablished. However, the ischemia may interfere with normal myocardial function, biochemical processes and ultrastructure for prolonged periods (stun). The severity and duration of these postischemic changes depend on the length and intensity of the ischemia, as well as on the condition of the myocardium at the onset of the ischemic episode. Furthermore, it is likely that when the myocardium is repeatedly stunned, it may exhibit chronic postischemic left ventricular dysfunction, an ill-defined condition. If prolonged, chronic postischemic left ventricular dysfunction can progress to myocardial scarring and ischemic cardiomyopathy, it may be important to determine how often it can be ameliorated by permanent improvement of myocardial perfusion by surgical treatment.

THE EARLIEST recorded investigation on the effects of coronary artery occlusion on the action of the heart was in 1698, when Chirac ligated a coronary artery in the dog and noted that soon thereafter the heart ceased to beat. Late in the nineteenth century, Porter demonstrated that coronary ligation resulted in a reduction in the systolic ventricular pressure and in its rate of rise as well as in an elevation of diastolic ventricular pressure.


In 1912, Herrick reported that permanent occlusion of a coronary artery caused myocardial infarction. The modern era of research on the physiologic consequences of myocardial ischemia was opened in 1935 by Tennant and Wiggers, who studied the sequential changes in myocardial contraction that occur with brief periods of acute myocardial ischemia in the open-chest dog; they demonstrated that within 60 seconds of coronary occlusion, the ischemic zone changes from a state of active systolic shortening to one of passive systolic lengthening.

As a result of these and many subsequent physiologic and pathologic observations both in experimental animals and in patients, it has been widely believed for more than 40 years that, depending on the duration and severity of myocardial ischemia, there may be two
distinct outcomes: (1) With total coronary occlusion for longer than approximately 20 minutes in the anesthetized dog (the exact duration differs in various species and with the animal's baseline state), myocardial cells in the most severely ischemic subendocardium become irreversibly damaged, reflected in morphologic evidence of necrosis, release into the circulation of cardiac enzymes and failure of return of function despite reperfusion. (2) With brief periods of myocardial ischemia, there is depression of myocardial function, but the injury is reversible since, if flow is restored, there is preservation of normal structure and restoration of metabolism and function. Only recently have we learned that after such brief periods of non-lethal ischemia, the structural, metabolic and functional properties of reversibly injured myocardium remain severely disturbed for days before recovering. Thus, a brief bout of ischemia may stun the heart, but not kill it.

In studies of occlusions of varying durations of a coronary artery in the anesthetized dog, the rate of improvement of function of the ischemic segment is, in general, inversely proportional to the duration of the occlusion. A period of coronary occlusion shorter than 20 minutes is not associated with the development of myocardial necrosis, but when the occlusion is released, the function of the previously ischemic myocardium may remain depressed for several days. In the conscious dog, delayed recovery of function after periods of ischemia of 15 minutes or 2 hours has also been reported; in the latter case, there is, of course, a considerable amount of necrosis. However, in addition to the necrotic tissue, some reversibly injured cells that show delayed recovery of function are probably present. Indeed, over time, the ischemic myocardium that has been salvaged by reperfusion ultimately regains the ability to respond to the stress of exercise with an augmentation of contractility. Furthermore, like systolic function, we have observed that the reduced diastolic compliance, i.e., the upward shift of the ventricle's pressure-volume relation induced by ischemia, also remains abnormal for several days after relief of ischemia but ultimately returns to normal.

After 15 minutes of coronary occlusion, ATP concentrations in the central ischemic zone fall to approximately 50% of normal. Myocardial ATP concentration also remains reduced by an average of 22% after 3 days of reperfusion after a 15-minute coronary occlusion, and like cardiac function it returns to normal by 1 week. Reimer et al. noted that after 4 days of reperfusion following 15 minutes of occlusion of the left circumflex coronary artery of the dog, the ATP concentration of the posterior papillary muscle was still significantly less than the control. Morphologic changes in the myocardium parallel those occurring in function and ATP concentration. After 15 minutes of ischemia, myocardial cells develop wide I bands, suggesting either myocardial relaxation or stretching by adjacent contracting cells, and show depletion of glycogen granules, clumping and margination of nuclear chromatin, and mild intermyofibrillar and mitochondrial edema. However, we did not anticipate the prolonged ultrastructural abnormalities observed in previously ischemic cells salvaged by 3 days of reperfusion; well-delineated vacuoles were present throughout the myocardial cytoplasm, probably representing localized areas of edema in the sarcoplasmic reticulum or mitochondria, or ghosts of lipid droplets. Intermyofibrillar and intermyofilamentous edema and glycogen depletion were also present in some cells. As was the case for cardiac function and ATP concentration, ultrastructural changes were present at 3 days of reperfusion and were resolved by 7 days.

Why is the recovery of cardiac function after a brief episode of ischemia so slow? Myocardial ATP concentration declines rapidly after CP stores are exhausted after experimental coronary occlusion; and this decline is associated with the accumulation of metabolites of ATP such as adenosine, hypoxanthine and inosine, which can be used as precursors in resynthesis. However, since the myocardial cell is permeable to these substances, they are washed out of the ischemic myocardium during reperfusion. Resynthesis of ATP in the myocardium appears to occur, in part, by "salvage pathways," i.e., from nucleotide precursors, and the washout of these substances from the myocardium may contribute to the relatively prolonged period of reduced ATP concentration. Since the recovery of myocardial function parallels the recovery of ATP, it is tempting to speculate that they are causally related, i.e., that myocardial function remains depressed until ATP stores, or at least until the pool of ATP directly related to the contractile process, has returned to normal. However, other factors, including abnormalities in calcium flux, could also be responsible for the prolonged contractile abnormality.

The concept that ischemia stuns the myocardium for prolonged periods may have important clinical implications. It may be particularly relevant to patients with coronary occlusion who undergo early myocardial reperfusion, either by thrombolysis or operative treatment, or in whom an effort is made to limit myocardial infarct size by pharmacologic means. The efficacy of these maneuvers must ultimately be evaluated not only by a demonstration of salvage of threatened myocardium, but perhaps more importantly, by evidence of restoration of function of the salvaged myocardium. If several days are required for complete return to normal function after a 15-minute period of coronary occlusion, restoration of function cannot be expected to occur immediately when reperfusion or other protective interventions are applied after several hours of severe myocardial ischemia. Thus, evaluation of cardiac performance several hours or even days after relief of ischemia may not provide an adequate assessment of eventual function. Indeed, ventriculography has shown no improvement in left ventricular function immediately after successful thrombolytic reperfusion of a coronary artery occluded by a thrombus; however, ventricular function was improved 2 weeks later (Markis JE: personal communication). The assessment of the efficacy of interventions designed to limit myocardial damage after coronary occlusion, therefore, should be delayed, probably for at least 2 weeks after...
the intervention. However, at this time, the results of the assessment could be affected by long-term compensatory mechanisms and the effects of additional therapeutic interventions.

Severe myocardial ischemia occurs in the course of many cardiac operations, even when cardioplectic solutions and regional hypothermia are used; if cardiac function is inadequate to sustain a normal circulation after discontinuation of cardiopulmonary bypass, the combination of mechanical support by means of intraaortic balloon counterpulsation and the administration of inotropic agents often tides the patient over until left ventricular performance improves sufficiently to sustain the circulation. However, when these methods fail to provide sufficient support, more radical methods, such as left ventricular assist devices, may be lifesaving, as long as the myocardium is only stunned and not irreversibly injured. The severe postischemic depression of myocardial function may require days of circulatory support until recovery occurs, and the necessity for such prolonged support does not preclude a successful long-term return of ventricular function, as long as tissue necrosis is limited. Techniques for distinguishing stunned from irreversibly injured myocardium are desirable in order to identify patients who could benefit from prolonged circulatory support. The progressive improvement of left ventricular function in some patients convalescing from acute myocardial infarction may result from the recovery of mechanical performance of stunned, reversibly injured, ischemic myocardium bordering the infarct.

Most important, the concept of myocardial stunning should lead to a reexamination of the consequences of the common episodes of myocardial ischemia occurring in patients with coronary artery disease, whether these are caused by an increased myocardial oxygen demand and/or reduced oxygen supply, and whether they are manifest clinically by angina or only by electrocardiographic changes unaccompanied by chest pain. It has been common practice in patients with ischemic heart disease not to prohibit physical activity that may lead to an occasional attack of angina pectoris, since it is believed that while angina may be uncomfortable, it has no prolonged adverse consequences. Perhaps this practice should be reconsidered in the light of the observations on postischemic depression of left ventricular function.

While most episodes of transient ischemia occurring in patients with chronic coronary artery disease are probably not as severe as that which occurs with 15 minutes of total coronary occlusion in the dog, the ischemia occurring in patients with variant angina experiencing coronary spasm and that which occurs during some episodes of unstable angina may resemble more closely the ischemia observed in the dog model, and recovery of myocardial function may take several days. Indeed, Nixon et al. recently demonstrated that some patients with unstable angina exhibit wall motion disorders during the pain-free period that are restored to normal several days later. However, mild degrees of ischemia produced in the dog by the combination of subtotal occlusion of a coronary artery and cardiac pacing result in full return of function, but only after the ischemic stimulus has been discontinued for more than 1 hour. The return of myocardial function is also delayed after periods of coronary occlusion as brief as 100 seconds, when the reactive hyperemia that occurs normally during reperfusion upon release of the coronary occlusion is prevented by a residual subtotal occlusion. Even brief bouts of ischemia impair left ventricular performance, although certainly not for as long as do 15-minute periods of total occlusion.

Can the myocardium become chronically, even permanently stunned as a consequence of repetitive episodes of myocardial ischemia? Several converging lines of evidence support an affirmative answer. Thus, Ninomiya et al. reported that repetitive episodes of brief (5–15 minutes) bouts of myocardial ischemia, which do not cause death of myocardial cells when they occur singly, may have a cumulative effect and produce myocardial necrosis, indicating that recovery between episodes could not have been complete. Second, for many years it has been considered that the impairment of left ventricular function observed in the basal state in many patients with ischemic heart disease is caused either by previous myocardial necrosis or by the presence of active ischemia. The observation that in many such patients a positive inotropic intervention, such as the infusion of epinephrine, postextrasystolic potentiation or exercise may result in substantial improvement of regional function, as demonstrated by contrast or radionuclide angiography, i.e., the demonstration of "contractile reserve," i.e., of myocardial asynery at rest that is reversible, impels a reexamination of this notion. Obviously, if the myocardium were necrotic, its function could not be improved by any intervention. The depression of myocardial function probably is not caused by active ischemia; patients who respond to inotropic stimulation usually do not have manifestations of this condition, such as anginal pain, transient electrocardiographic changes, lactate production or acute depression of ventricular function. While the contractile reserve of hypokinetic or akinetic myocardium could reside in nonischemic viable cells in the scarred area, an alternative is that it is chronically stunned. The presence of such contractile reserve is a favorable prognostic sign insofar as improved myocardial function after coronary revascularization is concerned.

Third, postmortem examination of the hearts of patients with ischemic cardiomyopathy often reveals loss by infarction of only moderate quantities of myocardium. In such patients with severe, diffuse coronary obstruction, the left ventricle may be markedly dilated and severe heart failure that cannot be explained by necrosis of a critical mass of myocardium may be present. Instead, the heart failure is more readily attributable to severe, widespread, postischemic stunning of the myocardium. Some patients with ischemic cardiomyopathy who exhibit reversible ischemia demonstrated by thallium-201 scintigraphy (but which is unassociated with angina pectoris) show marked im-
provement in left ventricular function, in the basal state, after coronary revascularization.35 This observation too, is consistent with the hypothesis that before operation, myocardium that was frequently ischemic was chronically stunned, but recovered with time.

References
1. Chirac P: De Motu Cordis, Adversaria Analytica, 1698, p 121
2. Porter T: On the results of ligation of the coronary arteries. J Physiol (Lond) 15: 121, 1895
35. Akins CW, Pohost GM, DeSanctis RW, Block PC: Selection of angina-free patients with severe left ventricular dysfunction for myocardial revascularization. Am J Cardiol 46: 695, 1980
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