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.

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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 briefer 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 studies6-11 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 minutes12 or 2 hours13 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.14 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.15 Reimer et al.16 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.17 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;15-18 and this decline is associated with the accumulation of metabolites of ATP such as adenosine, hypoxanthine andinosine, 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.19 Resynthesis of ATP in the myocardium appears to occur, in part, by “salvage pathways,” i.e., from nucleotide precursors,20 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 thrombolysis21 or operative treatment,22 or in whom an effort is made to limit myocardial infarct size by pharmacologic means.23 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.24 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 com-
pensatory mechanisms and the effects of additional
therapeutic interventions.

Severe myocardial ischemia occurs in the course of
many cardiac operations, even when cardioplegic so-
lutions 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 in-
traaortic balloon counterpulsation and the administra-
tion of inotropic agents often tides the patient over
until left ventricular performance improves sufficiently
to sustain the circulation. However, when these meth-
ods 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 ne-
cessity for such prolonged support does not preclude a
successful long-term return of ventricular function, as
long as tissue necrosis is limited. Techniques for dis-
tinguishing stunned from irreversibly injured myocar-
dium 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 in-
farction 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 occur-
r ing 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 elec-
trocardiographic 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 pector-
is, since it is believed that while angina may be
uncomfortable, it has no prolonged adverse conse-
quences. Perhaps this practice should be reconsidered
in the light of the observations on postischemic depre-
sion 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 ex-
periencing coronary spasm and that which occurs dur-
ing 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 coro-
nary occlusion is prevented by a residual subtotal oc-
clusion. Even brief bouts of ischemia impair left ven-
tricular performance, although certainly not for as long
as do 15-minute periods of total occlusion.

Can the myocardium become chronically, even per-
manently stunned as a consequence of repetitive epi-
isodes 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 recov-
ery 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 demon-
stration of “contractile reserve,” i.e., of myocardial
asynnergy at rest that is reversible, impels a reexamina-
tion 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 chronical-
ly stunned. The presence of such contractile reserve is
a favorable prognostic sign insofar as improved myo-
cardial function after coronary revascularization is
concerned.

Third, postmortem examination of the hearts of pa-
tients with ischemic cardiomyopathy often reveals loss
by infarction of only moderate quantities of myocar-
dium. 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 attrib-
utable to severe, widespread, postischemic stunning of
the myocardium. Some patients with ischemic cardio-
mypathy who exhibit reversible ischemia demonstrated
by thallium-201 scintigraphy (but which is unasso-
ciated with angina pectoris) show marked im-

Improvement in left ventricular function, in the basal state, after coronary revascularization. This observation, too, is consistent with the hypothesis that before operation, myocardium that was frequently ischemic was chronically stunned, but recovered with time.

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