Cardiac Adaptation to Ischemia

Ischemic Preconditioning Increases Myocardial Tolerance to Subsequent Ischemic Episodes

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It has long been recognized that a brief episode of myocardial ischemia causes reversible myocyte injury, "reversible" being defined by the fact that early restoration of arterial flow prevents infarction and permits eventual restoration of normal myocardial structure, function, and metabolism. However, numerous studies during the last 15 years1-5 have revealed that complete recovery is not immediate; in a variety of experimental models, profound metabolic and functional abnormalities may persist for hours or days after as little as 5-15 minutes of coronary occlusion. For example, a 15-minute episode of coronary occlusion in dogs results in 1) increases in tissue water and potassium content that persist for at least 1 hour,1 2) substantial loss of adenine nucleotides, 1 which are not fully resynthesized for as long as 4 days,2,3 and 3) postischemic contractile dysfunction that may persist for 2-4 days. The latter phenomenon, first reported by Heyndrickx et al4 and later termed "myocardial stunning" by Braunwald and Klomer,5 has been the subject of extensive study. The pathogenesis of stunning remains incompletely elucidated, but there is substantial evidence that it is due to a defect in calcium homeostasis,6,7 the underlying cause of which includes free radical-mediated injury.8

The recognition that a single brief episode of ischemia may cause prolonged depletion of adenine nucleotides initially raised the concern that recurrent brief episodes of ischemia, for example in patients with angina pectoris, might have cumulative effects, producing progressively worsening metabolic and functional deficits and perhaps even lethal myocyte injury. However, this concern was not substantiated by experimental results. For example, we observed8 of extensive study. The pathogenesis of stunning remains incompletely elucidated, but there is substantial evidence that it is due to a defect in calcium homeostasis,6,7 the underlying cause of which includes free radical-mediated injury.8

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extraction data from another seven, who were undergoing elective coronary angioplasty. The effects of two sequential 90-second occlusions of the anterior descending artery, separated by 5 minutes of reperfusion, were compared. The second episode of ischemia caused less chest pain and less ST segment elevation in all 19 patients, and less myocardial lactate production in the group of seven patients, than did the first episode. These changes were associated with reduced cardiac vein flow from the ischemic region, suggesting that the apparently lesser severity of ischemia was not due to increased collateral flow but indeed reflected an adaptation to myocardial ischemia. Although these data are necessarily indirect, they provide strong evidence that the phenomenon of ischemic preconditioning observed in animal models also occurs in humans with atherosclerotic heart disease.

The phenomenon of ischemic preconditioning has been confirmed to exist in dogs by other investigators and has been reported to occur in pigs and rabbits as well. In dogs, the protective effect has been achieved by one or more ischemic episodes ranging from 5 to 15 minutes in duration. The increased tolerance to ischemia results in a prolongation of the reversible phase of injury of myocytes and has also been reported to preserve efferent sympathetic and vagal responses in a subsequent ischemic episode. However, the following limitations have been observed: 1) The protective effect was lost in experimental studies when the test episode of injury was extended to 3 hours, and 2) much of the protective effect was lost if the reperfusion time between the initial preconditioning episode(s) of ischemia and the later test episode was extended to 2 hours.

Repeated brief episodes of ischemia have also been reported to affect myocardial arrhythmogenesis. For example, a 5-minute episode of myocardial ischemia in rats reduced the incidence of ischemia and/or reperfusion arrhythmias caused by a subsequent 5-minute episode of ischemia. This antirhythmic effect has also been termed "ischemic preconditioning." However, in our canine studies one or two 10-minute episodes of ischemia were, paradoxically, associated with an increased incidence of ventricular fibrillation during a later 10- or 40-minute episode of ischemia and/or reperfusion (also K.A. Reimer, C.E. Murry, and R.B. Jennings, unpublished observations, 1986). Thus, it is not known whether the antirhythmic effects of ischemic preconditioning in rats are a manifestation of the increased myocyte tolerance to ischemia that defines ischemic preconditioning in larger animal species.

The cellular protection afforded by preconditioning is associated with a marked slowing of ischemic metabolism during the test episode. This slowing of metabolism involves both the production and utilization of high energy phosphates. In severe ischemia, anaerobic glycolysis is the principal source of new ATP production; in preconditioned ischemic myocardium, the entire glycolytic pathway is slowed. This is reflected by markedly less accumulation in the tissue not only of lactate but also of proximal glycolytic intermediates, including glucose-1-phosphate and glucose-6-phosphate. The slowed rate of glycolysis occurs despite an increased glucose content in the tissue at the onset of the test period of ischemia. Glycogenolysis is correspondingly slowed, although substantial quantities of glycogen are still present in the myocytes at the onset of the test episode of ischemia.

Experimental studies have begun to shed some light on the mechanism of preconditioning, but much remains to be learned. Understanding the mechanism of reduced ATP consumption in preconditioned myocardium requires elucidation of those reactions that account for the utilization of ATP in ischemic myocardium. In aerobic myocardium, mechanical function accounts for the majority of the ATP utilized. The reactions that consume most of the ATP during ischemia are poorly defined, but some ATP surely is expended in feeble attempts of the ischemic myocytes to contract. We postulated if this accounts for a major fraction of ATP utilization in ischemia, preconditioning might simply be a manifestation of stunning; that is, preischemic dysfunction might be translated into a reduced contractile effort and therefore a reduced demand for ATP during the test episode of ischemia. Along similar lines, it has been reported that a brief episode of ischemia resulted in a more rapid onset of contractile failure during a subsequent episode. Confuting our hypothesis is the observation that four 5-minute episodes of coronary occlusion, which was the first preconditioning protocol by which dramatic protection was achieved, cause relatively mild stunning (C.E. Murry, R.B. Jennings, K.A. Reimer, unpublished observation, 1988). Moreover, in a direct study of the link between stunning and preconditioning, we observed that a single 15-minute episode of ischemia caused severe stunning that persisted throughout 2 hours of reperfusion. Marked limitation of infarct size was observed when the test episode of ischemia followed the preconditioning episode after 5 minutes of reperfusion. However, much of the protection was lost when the test occlusion was delayed for 2 hours. Thus, although it is possible that stunning contributes to the reduced metabolic rate of preconditioned myocardium, stunning alone is insufficient to cause preconditioning.

Recent studies have indicated that a major cause of ATP degradation in ischemia is the squandering of ATP by the mitochondrial ATPase and that in "slow heart rate" species, including rabbits and larger mammals, the rate of ATP degradation is modulated by a natural protein inhibitor of the ATPase that binds to the enzyme during mitochondrial acidosis induced by ischemia. The possibility that such inhibition might occur more quickly or more completely during a second episode of ischemia and thereby explain preconditioning is an intriguing hypothesis, but one for which no data yet exists.

Another hypothesis is that the cardiac adaptation to ischemia results from a rapid expression of gene
products analogous to the induction of stress proteins after heat shock. Indeed, synthesis of mRNA for stress proteins has been detected in myocardium within 2 hours after a 15-minute episode of ischemia. However, a genetic mechanism must be consistent with the biology of the preconditioning phenomenon: preconditioning is achieved within a 5-minute reperfusion period and is mostly lost after 2 hours of reperfusion. Thus, whether any such gene expression will prove to be activated and deactivated sufficiently quickly to explain the induction and loss of preconditioning is presently unknown.

It also remains to be established whether the phenomenon of ischemic preconditioning can be exploited therapeutically. For example, it seems likely that the duration of balloon inflation during coronary angioplasty might be safely increased if the procedure is preceded by an initial shorter coronary occlusion. Whether ischemic preconditioning might increase the cardiac tolerance to ischemic cardiac arrest during cardiac surgery and thereby serve as an adjunct to other means of cardioplegia is unknown, but the possibility is surely worth investigating in experimental models. Whether it will become possible to induce ischemic tolerance in patients with angina pectoris is also unknown; answering this question will most likely depend on elucidation of the underlying cellular mechanism of ischemic preconditioning.

References

16. Lange R, Ware J, Kloner RA: Absence of a cumulative deterioration of regional function during three repeated 5 or 15 minute coronary occlusions. Circulation 1984;69:400–408
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