



A Lexicon of the Heart

Preconditioning

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Myocardium that has been exposed to a brief episode or several episodes of ischemia and reperfusion exhibits a strange and unexpected change in its biology. Unlikely as it may seem, this exposure protects it against the deleterious effects of a prolonged episode of ischemia.

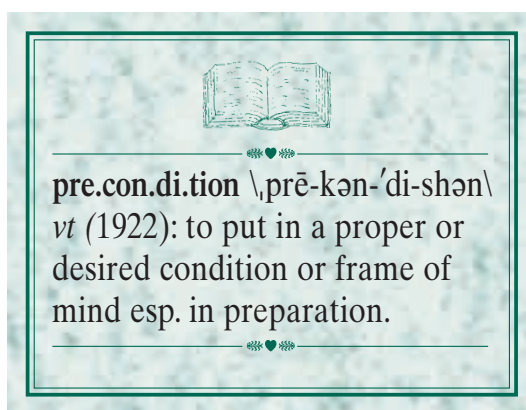
PRECONDITIONING AND CARDIOPROTECTION

In fact, myocardium that has been treated in this way will survive a test episode of ischemia that is sufficiently severe to kill most of the ischemic myocytes in virgin heart. This protective effect is called *preconditioning with ischemia* and is the strongest protective effect so far identified in the treatment of regional ischemia in vivo.

Preconditioning does not prevent myocyte death. Rather, preconditioning allows myocytes to survive in an ischemic state for a longer period of time than virgin myocytes; thus, it delays, but does not prevent myocyte death. In addition, the protection afforded by preconditioning is transient. In the dog heart, the species in

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which the phenomenon was discovered, the protection is about half gone after 120 minutes and is dissipated totally by 180 minutes of reperfusion.¹ However, if the heart is exposed to a second preconditioning episode of ischemia and reperfusion, cardioprotection can be reinstated.²

PRECONDITIONING AND THE HUMAN HEART

There are three lines of indirect evidence supporting the premise that the human heart can also be preconditioned with ischemia.

- The first is intuitive and is the fact that all mammalian hearts so far tested including dogs, pigs, rats, rabbits, and ponies can be preconditioned. The human heart should be no exception to what most investigators assume is a general response of the mammalian heart to ischemia.
- The second is the fact that responses similar to those seen in preconditioned animal hearts are seen in the human

heart when brief periods of ischemia and reperfusion are given to patients undergoing cardiac catheterization prior to angioplasty.³ In such patients, 2 minutes of ischemia followed by reperfusion greatly alters the response of the heart to a second episode of ischemia. Moreover, during the second 2-minute episode of ischemia, the preconditioned bed exhibits the same responses to a test

episode of ischemia as those seen in the preconditioned animal heart, including a reduction both in the degree of ST-segment elevation and in the magnitude of lactate release compared with the changes seen in the initial preconditioning episode of ischemia.

- Finally, repetitive episodes of angina probably precondition the human heart.⁴ The best evidence for this belief comes from the Thrombolysis In Myocardial Infarction (TIMI) 4 trial in which the group of patients that exhibited angina prior to developing myocardial infarction, ie, the presumed preconditioned group, did better than the group that was free of angina.

MOLECULAR MECHANISM OF PRECONDITIONING

It is of interest that the molecular mechanism of preconditioning with ischemia is probably related to the degradation of the adenine nucleotide pool that occurs during ischemia.

Destruction of the pool is associated with the release of adenosine from the ischemic myocytes. Significant adenosine production begins after 10 to 20 seconds of ischemia, ie, shortly after the myocardium converts to anaerobic glycolysis as its chief source of energy. Since energy release during anaerobic metabolism is limited, adenosine diphosphate (ADP), which still has one high-energy phosphate bond, accumulates. The high-energy phosphate bond of ADP is salvaged by a reaction (adenylate kinase) that produces an excess of intracellular adenosine monophosphate (AMP), which is degraded into adenosine. Unlike AMP, adenosine can exit from the myocyte to the extracellular space, where it stimulates myocyte A_1 receptors. These receptors induce a complex set of intracellular signaling reactions that somehow lead to cardioprotection.⁵ These intracellular signaling reactions involve activation of a variety of protein kinases, especially protein kinase C.⁶ When active, these kinases phosphorylate proteins, including enzymes and ion channels with resultant changes in activity. However, it is not clear how these phosphorylations lead to protection.

PRECONDITIONING AS A THERAPEUTIC TOOL

Because the preconditioning effect is transient, it is unlikely that preconditioning with ischemia itself will be useful as a therapeutic tool in patients with severe coronary artery disease because the sequential episodes of ischemia that would be required to maintain the preconditioned state eventually would induce deleterious effects in the treated myocardium. The main negative effect would be depletion of the adenine nucleotide

pool. The depletion would occur because some of the pool is lost with each episode of ischemia and because adenine nucleotide pool resynthesis is very slow in healthy heart tissue. This negative view about the maintenance of the preconditioned state with repetitive episodes of ischemia and reperfusion is based on experimental studies using maximal preconditioning stimuli. Lesser degrees of ischemia such as those seen in angina also precondition, and probably do not result in depletion of the adenine nucleotide pool. However, this idea remains untested. Finally, the use of a single episode of ischemia to precondition may prove useful, eg, to improve the tolerance of the heart to ischemia in patients on pump bypass for cardiac surgery. Here, the aim would be to keep as many of the ischemic myocytes alive during bypass as possible and also to improve their function when coronary flow is restored.

PERSPECTIVES

The important aspect of the above, aside from its intellectual interest, is the possibility that one could develop a drug that would maintain the myocardium of a patient with severe coronary disease in a continuous preconditioned state. The advantage would be increased tolerance to ischemia and a longer time available to intervene if such a patient obstructed a major branch of a coronary artery. Several drugs in the early phase of development have been shown experimentally to be cardioprotective, in fact as protective against infarction as is preconditioning with ischemia. Thus, there is reason to hope that a safe cardioprotective pharmacological agent will be developed.

REFERENCES

- 1. Murry CE, Jennings RB, Reimer KA.** *Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium.* *Circulation.* 1986;74:1124-1136.
- 2. Schwartz LM, Sebbag L, Jennings RB, Reimer KA.** *Duration and renewal of myocardial protection against infarction by ischemic preconditioning in dogs.* *J Mol Cell Cardiol.* 2001. In press. Sept.
- 3. Tomai F, Crea F, Gaspardone A, et al.** *Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K^+ channel blocker.* *Circulation.* 1994;90:700-705.
- 4. Kloner RA, Shook T, Przyklenk K, et al.** *Previous angina alters in-hospital outcome in TIMI-4: a clinical correlate of preconditioning?* *Circulation.* 1995;91:37-45.
- 5. Downey JM, Thornton JD, Van Winkle DM, Stanley AWH, Olsson RA.** *Protection against infarction afforded by preconditioning is mediated by A_1 adenosine receptors in rabbit heart.* *Circulation.* 1990;84:350-356.
- 6. Ytrehus K, Liu Y, Downey JM.** *Preconditioning protects ischemic rabbit heart by protein kinase C activation.* *Am J Physiol.* 1994;266:H1145-H1152.