

From Preconditioning to Postconditioning: Novel Interventions in the Armory of Salvage of the Ischemic Heart

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Total coronary occlusion without prior development of collateral circulation results in a wavefront of myocardial necrosis, which moves from subendocardium to subepicardium. The early restoration of flow by pharmacological or mechanical means may interrupt the development of necrosis, saving the jeopardized myocardium. Twenty years ago, experimental studies revealed an endogenous defense mechanism, called ischemic preconditioning.¹ Preconditioning is activated by brief ischemic insults separated by short reperfusion intervals applied prior to long ischemia. In a great number of experimental studies, ischemic preconditioning limited the infarct size in every species, independently of the existence of collaterals. Despite the fact that preconditioning is difficult to apply in clinical practice, because of the undefined conditions for proper activation and the unknown time interval between short and long ischemic periods, there is ample evidence that preconditioning exists in humans and may reduce the infarct size.² Preconditioning has also been shown to reduce the incidence of lethal arrhythmias, chest pain, ST elevation, and to confer better post ischemic recovery of the left ventricle.²⁻⁷

Recent experimental studies in dogs revealed a novel protective mechanism of the heart, which has been termed postconditioning.⁵ This mechanism is activated by

several very short ischemic and reperfusion bouts, which are initiated during the first minute of reperfusion after a prolonged period of ischemia. Commencing within the first minute of reperfusion, the application of brief ischemic periods of 10 to 60 seconds, separated by short reperfusion intervals of similar duration, causes a significant decrease of the infarct size in comparison to controls. Both phenomena, preconditioning and postconditioning, are shown in figure 1. This paradoxical protection by an intervention that is applied after the end of sustained ischemia is well explained by the fact that postconditioning is a mechanism that limits the reperfusion injury. It is well known that reperfusion reduces the infarct size, but at the same time significant damage, called reperfusion injury, may occur.^{6,7} This term includes the acceleration of necrosis despite restoration of the flow, post-ischemic mechanical dysfunction (stunning), reperfusion arrhythmias, and endothelial dysfunction.⁶⁻⁸ The rapid generation of free radicals and intracellular calcium accumulation are the predominant factors involved in the development of reperfusion injury.⁶⁻⁹

Myocardial necrosis after reperfusion is due to the increased permeability of the mitochondrial transition pores, which eventually cause mitochondrion and cell death.¹⁰ Postconditioning protects the heart through the activation of specific

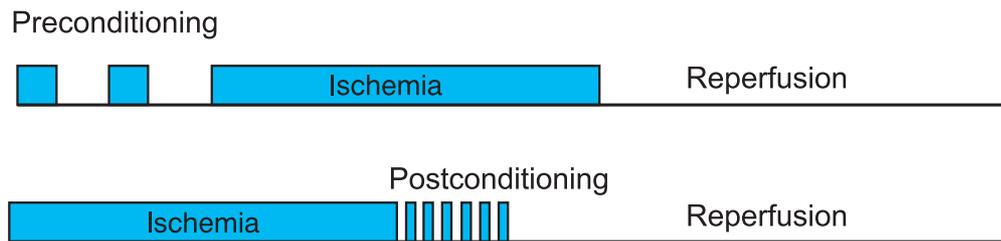


Figure 1. Schematic representation of ischemic preconditioning and postconditioning, with short periods of ischemia and reperfusion before and after long ischemia.

reperfusion injury salvage kinases (RISK),¹¹ which inhibit the mitochondrial permeability transition pore opening. Phosphatidylinositol3 (PI3)-kinase and extracellular signal-regulated kinases (ERKs) belong to the RISK.^{11,12} Mitochondria permeability transition pore opening occurs during the first minute of reperfusion and therefore postconditioning should be applied at that time in order to be effective.¹²⁻¹⁴ Delayed postconditioning, initiated after the first minute of reperfusion, is not effective. RISK levels must remain high for at least 30 minutes after the onset of reperfusion, since there is a risk that mitochondria and heart cells can be destroyed because of irreversible damage.

Postconditioning seems to be more easily applicable than preconditioning in clinical practice.⁸ This is due to the fact that postconditioning stimuli are applied immediately after the restoration of blood flow, whereas preconditioning is activated before prolonged periods of ischemia with unpredictable onset and duration. In other words, the activation of preconditioning in these circumstances may become ineffective. Postconditioning has already been shown to reduce myocardial necrosis in patients with acute myocardial infarction, as was verified by the attenuation of enzyme release into the systemic circulation.¹⁵ Furthermore, a better endothelial response was found under controlled conditions of upper limb ischemia and reperfusion.¹⁶ These are the first indications that postconditioning may be used in clinical practice. Similarities and differences between the two endogenous mechanisms of preconditioning and postconditioning are being investigated by a series of studies that are already in progress. Initial comparisons between the two endogenous mechanisms have shown some differences in the way of activation and the level of protection under similar conditions.¹⁷⁻²¹ However, it is important to note that both pre- and postconditioning may share some common pathways, which include several common intracellular mediators such as PI3, nitric oxide, cyclic guanosine monophosphate, and mitochondrial adenosine triphosphate-sensitive potassium

channels.^{8,11,13,14,22} Common intracellular signaling may facilitate a possible pharmacological development in the future that would protect ischemic and post-ischemic myocardium. The gradual and controlled restoration of the blood flow by postconditioning interventions overcomes the limitations of former experimental studies.^{8,11,23}

It appears that postconditioning is an old wine in a new bottle.²⁴ However, initial experimental enthusiasm is likely to decline with the increase in restrictions emerging from validated everyday practice. The experience acquired from laboratory studies should be treated with extreme caution before it can be introduced into clinical practice. Nevertheless, the easy and effective manner of postconditioning activation carries an optimistic message that this is a feasible intervention that may reduce the infarct size in humans. Current evidence suggests that postconditioning is a novel weapon for the treatment of an evolving myocardial infarction.

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