Letter to the Editor

An alternative viewpoint for the cardioprotective effects of ischemic preconditioning

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Received: 27 October 2020; Accepted: 16 December 2020; Published: 30 March 2021.

doi: 10.21037/jxym-20-107

View this article at: http://dx.doi.org/10.21037/jxym-20-107

Ischemic preconditioning was originally described by Murry et al. in 1986 (1). They demonstrated that brief ischemic episodes before prolonged ischemia reduced infarct size by 75% in a canine model of ischemia and reperfusion. Despite the potent cardioprotective effects of ischemic preconditioning, its clinical translation remains to be seen because it needs to be implemented before starting prolonged ischemia. It is difficult to implement this except in cases of planned coronary artery bypass surgery or heart transplantation. On the other hand, the potent cardioprotective effects of preconditioning garnered sufficient interest regarding its mechanisms because these might help elucidate the key process in the progression to irreversible ischemic cell injury. The most popular mechanism of the cardioprotective effects of preconditioning is the release of various triggering molecules, such as autacoids, neurohormones, and cytokines, in response to brief episodes of ischemia and reperfusion. The release of such molecules induces phosphorylation/activation of protein kinases, which triggers the initiation of intracellular signal transduction cascades, such as the reperfusion injury salvage kinase system, resulting in the prevention of both mitochondrial permeability transition and resultant cell deaths (2). However, the precise mechanisms of the cardioprotective effects of preconditioning still remain to be investigated. Especially, there is no reasonable explanation, thus far, for the total loss of the cardioprotective effects of preconditioning when subsequent ischemia was prolonged to 3 hours (1).

Apart from the precise molecular mechanisms, a hint for solving the long-standing question seems to lie in another cardioprotective approach that is as potent as preconditioning: temporary contractile activity blockade during reperfusion using 2,3-butanedione monoxime (BDM). Schlack et al. demonstrated that BDM administration immediately before reperfusion reduced infarct size by 73% in a canine model of ischemia and reperfusion (3). The infarct-sparing effect of BDM has been attributed to the prevention of reperfusion-induced hypercontracture. In their experiments, 60-minute ischemia was used instead of 40-minute ischemia. Nevertheless, infarct-size reduction was as robust as that achieved by preconditioning. Both preconditioning and BDM treatment seem to provide the most potent cardioprotection in the in vivo canine model of ischemia and reperfusion. As BDM administration was performed immediately before reperfusion, its infarct-sparing effects can be attributed purely to the prevention of lethal reperfusion injury. Conversely, myocardial necrosis caused by ischemic injury can be estimated to be <30% of the total infarcted myocardium caused by 60-minute ischemia followed by reperfusion in the canines. Looking back to ischemic preconditioning, similar maximum cardioprotection, i.e., 75% infarct-size reduction, is observed after 40 minutes of ischemia followed by reperfusion in the canine hearts. This cannot be attributed to the prevention of myocardial necrosis caused by ischemic injury, which should be <30% of the total amount of myocardial necrosis in 40-minute ischemia. Instead, it might be reasonable to assume that this large infarct-sparing effect (75%) resulted from the prevention of lethal reperfusion injury as in the BDM-treated hearts. Preconditioning, however, seems unlikely to have such potent, direct cardioprotective effects against lethal reperfusion injury. If so, how are...
preconditioned hearts protected? One possible explanation is that lethal reperfusion injury is not prevented, but rather avoided in preconditioned hearts.

The cardioprotective effects of preconditioning were completely lost after a 3-hour ischemic period followed by reperfusion (1), as if an all-or-none mechanism of preconditioning effects was present. In certain specific situations, this may happen (Figure 1). This situation requires an assumption that preconditioning can extend the ischemia duration necessary for lethal reperfusion injury to occur after reperfusion. There is a lag period, which is the difference in the ischemia duration necessary for lethal reperfusion injury to occur after reperfusion between the control and preconditioned hearts. If reperfusion starts during the lag period, a large difference in infarct size will be observed as no lethal reperfusion injury occurs in postconditioned hearts, while a nearly maximum extent of lethal reperfusion injury occurs in control hearts. This difference will be lost if reperfusion starts after the lag period.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was a standard submission to the journal. The article did not undergo
external peer review.

**Conflicts of Interest:** The author has completed the ICMJE uniform disclosure form (available at [http://dx.doi.org/10.21037/jxym-20-107](http://dx.doi.org/10.21037/jxym-20-107)). The author has no conflicts of interest to declare.

**Ethical Statement:** The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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