EDITORIAL COMMENT

Postconditioning

Old Wine in a New Bottle?*

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Infarct size is the decisive determinant of the extent and severity of remodeling (1) and of the prognosis of patients after myocardial infarction (2). Timely reperfusion is the only way to reduce ultimate infarct size. However, reperfusion comes at a price and induces injury per se. The immediate and full restoration of coronary blood flow results in arrhythmias, contractile dysfunction (stunning), and microvascular impairment. Although previously debated (3,4), it is now clear that there also is irreversible reperfusion injury through apoptosis and necrosis (5,6). The mechanisms of reperfusion injury relate to the excess formation of free radicals (7), to calcium overload, and finally to hypercontracture (6,8).

To attenuate reperfusion injury, staged/controlled reperfusion with retarded restoration of full coronary blood flow and perfusion pressure (9–11) or modification of the reperfusate (e.g., maintenance of acidic pH [12], inhibition of sodium–calcium exchange [13], contractile blockade [14], addition of antioxidants [15]), has been proposed for many years. Recently, the pharmacologic activation of reperfusion injury salvage kinase (RISK) pathways also has been documented to attenuate irreversible reperfusion injury (16). How and where in the signal transduction cascade the various maneuvers to attenuate reperfusion injury converge mechanistically, remains to be defined.

Preconditioning does not reduce ultimate infarct size but delays the development of infarction so that with timely reperfusion, the actual infarct size is reduced. Preconditioning has provided a powerful paradigm for the experimental analysis of the signal transduction cascade (17), both of cardiomyocyte death and protection from it. However, the clinical exploitation of the preconditioning phenomenon has been rather disappointing thus far (18), largely because preconditioning must be instituted briefly before an ischemic event, which is not possible in daily life, and also because in cardiac surgery, where it would be feasible, alternative powerful protective interventions are already being used (e.g., opioids, inhalation anesthetics, cardioplegia).

Postconditioning was originally described by Zhao et al. (19) as the reduction of infarct size by several cycles of coronary occlusion/reperfusion after a sustained ischemic insult in dogs and subsequently in rats (20). The catchy term “postconditioning,” which refers to preconditioning and implies likewise an underlying signal transduction cascade, appears justified because a very similar protocol of brief cycles of ischemia/reperfusion is used following, rather than preceding (as in preconditioning), a sustained ischemic insult. However, this does not exclude that postconditioning is merely an easy and effective method of staged/controlled reperfusion (see the preceding text). Again, the mechanistic relationships of staged reperfusion maneuvers, the activation of reperfusion salvage kinase pathways, and the complex signal transduction cascade of preconditioning need to be defined in detail.

In this issue of the Journal, Yang et al. (21) confirm the original observation of postconditioning in another species (i.e., rabbits), and then carefully define the magnitude and time frame of the observed protection with triphenyltetrazolium chloride staining of infarct size as a robust end point. The reduction in infarct size under these controlled conditions, consistent with the original previous study by Zhao et al. (19) in dogs, is indeed impressive, i.e., by approximately 40%, albeit somewhat less than with preconditioning. Importantly, the authors proceed to identify the signaling elements of postconditioning that are shared by preconditioning (i.e., the KATP-channel) (17) and those that are possibly different from those of preconditioning but are shared by the reperfusion salvage kinase pathway (i.e., extracellular signal-regulated kinases) (16) by use of selective antagonists. The analysis of signal transduction in postconditioning will require more studies, particularly in larger mammals that sometimes differ in that respect from rodents but are closer to humans (17).

In contrast to preconditioning, postconditioning appears to be easily feasible in patients with impending acute myocardial infarction who undergo interventional reperfusion. Of course, the potential of postconditioning must be rigorously tested in clinical trials, first for its safety and feasibility and then subsequently for its efficacy and therapeutic potential. It will be mandatory in such clinical trials to carefully control for confounding variables—as done in the above experimental studies—such as the size of the area at risk, the duration of the preceding ischemic insult, and collateral status. Neglect of these confounding variables has probably contributed to the failure of translation of experimentally validated principles of cardioprotection to the clinical arena (e.g., adenosine receptor activation, sodium–proton exchange inhibition) in the past.

In conclusion, to answer the hypothetical question posed in the title of this comment, postconditioning is possibly an old wine (i.e., staged reperfusion), but a very good one, and it comes in a very practical new bottle that may facilitate its widespread distribution.

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REFERENCES


