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EDITORIAL COMMENT

Post-Conditioning for Cardioprotection During Reperfusion Therapy

Too Good to Be True?*

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Reperfusion Injury

The extent of myocardial salvage from reperfusion therapy in ST-segment elevation myocardial infarction (STEMI) may be limited by microvascular dysfunction and lethal reperfusion injury (1,2). Reperfusion injury is the phenomenon that describes myocardial and vascular damage occurring as a direct consequence of the restoration of blood flow to the ischemic tissue. Cellular mechanisms that promote reperfusion injury are incompletely understood (3). Recent evidence suggests that opening of the mitochondrial permeability transition pore, a nonselective high conductance channel of the inner mitochondrial membrane, may represent a final common pathway by which various upstream

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triggers cause cell death (4). The channels are closed during the initial ischemic insult. However, experimental data suggest that the pores open almost immediately upon the establishment of reperfusion, which results in the collapse of the mitochondrial membrane potential and uncouples oxidative phosphorylation, leading to depletion of adenosine triphosphate and cell death. It is possible to inhibit reperfusion injury in animal models using a variety of pharmacological and nonpharmacological strategies. In contrast, translation into clinical practice has been disappointing with nearly all human studies of adjunctive therapies for modifying reperfusion injury failing to demonstrate cardioprotective benefits (5). Understandably, this has raised doubt about the clinical relevance of the concept.

Ischemic Pre-/Post-Conditioning

Cardiac ischemic pre-conditioning is a mechanical intervention described 2 decades ago in which several brief cycles of ischemia-reperfusion of the heart, before the lethal ischemic insult, appears to activate endogenous protective mechanisms against reperfusion injury (6). However, its clinical application has not been feasible because of the need to initiate pre-conditioning before the onset of STEMI. Interest in the field has been rekindled by the demonstration in animals that application of brief cycles of ischemia-reperfusion to the heart at the time of reperfusion may also be effective, and this form of modified reperfusion has been called post-conditioning (7). The mechanisms by which post-conditioning operates are not known but they probably involve several triggers and mediators. Endogenous opiates may represent such a trigger that inhibits mitochondrial permeability transition pore opening. Despite its promise, post-conditioning of the heart is limited by the fact that it can only be applied after the patient reaches the cardiac catheterization laboratory. A potential solution to this problem is remote ischemic post-conditioning in which ischemia-reperfusion of a distant tissue or organ may confer cardioprotection (8).

In this issue of *JACC: Cardiovascular Interventions*, Rentoukas et al. (9) present data from a single center trial of remote ischemic "periconditioning" among 96 patients with STEMI subjected to primary percutaneous coronary intervention (PCI). Patients were randomized to 1 of 3 strategies: 1) adjunctive periconditioning; 2) adjunctive periconditioning and morphine; or 3) neither. Periconditioning was the preferred term for the intervention as it was performed before (on average 8 min) reperfusion rather than at the time of reperfusion. Three cycles of 4 min of forearm ischemia followed by 4 min of reperfusion were performed. The primary end point (proportion of patients with complete ST-segment resolution 1 h after PCI, defined as ≥80% reduction in the cumulative ST-segment shift on the 12-lead electrocardiogram) was more often achieved in the 2 groups with periconditioning than with the control group. The administration of morphine within 5 min of PCI, in conjunction with periconditioning, did not lead to a higher frequency of the primary end point compared to periconditioning alone, though there was a trend in that direction. The percentage of ST-segment resolution (a secondary end point) was significantly higher in those with combined periconditioning and morphine therapy than in those receiving periconditioning alone. Peak troponin levels, which appeared to have been measured as part of the clinical practice rather than at pre-defined time intervals to calculate an area under the curve, showed lower values in the 2 periconditioning groups. However, there was no significant difference in the peak troponin levels between the 2 active treatment arms. In summary, the findings of this trial

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provide "proof of concept" for the cardioprotective effects of remote post-conditioning as an adjunctive therapy during mechanical reperfusion in humans.

Several important aspects of the trial design deserve closer attention. First, only patients presenting within 6 h of symptom onset were included. The mean duration of ischemia was a little over 2 h in each group. This is relevant because most previous studies investigating cardioprotective strategies have not focused on patients with short ischemic times. It is possible that there is an optimal window for cardioprotection because patients who present very early (e.g., <2 h) and receive effective reperfusion therapy have small infarcts and gain little additional benefit from adjunctive therapies, whereas those presenting late (e.g., >6 h) sustain large infarcts and may have little potential for myocardial salvage (2). Thus, the results of the trial cannot be applied to patients with prolonged symptom onset to presentation times. Second, periconditioning was initiated within 10 min of reperfusion. Whether such an intervention would be more or less effective if initiated at an earlier time point, for example, during transport in the ambulance, is an important question that cannot be addressed by the study by Rentoukas et al. (9). However, preliminary data from a randomized trial among 333 patients suggest that prehospital forearm remote post-conditioning performed during transportation in the ambulance may indeed increase myocardial salvage following primary PCI (10). Third, high-risk patients were excluded and therefore the results cannot be extrapolated to patients in cardiogenic shock or moderate-to-severe renal failure, among others. Fourth, as acknowledged by the investigators, surrogate end points (ST-segment resolution and peak troponin level as a marker of infarct size) were used, and whereas these correlate with clinical outcomes, the sample size of the study was insufficient to evaluate the influence of remote post-conditioning on "hard" end points. Fifth, PCI was performed very efficiently with a mean door-to-balloon time of <60 min, which confirms that post-conditioning need not delay reperfusion therapy, and that the results cannot be extrapolated to patients with prolonged door-to-balloon times. Finally, the trial does not provide any convincing evidence that opiates mediate post-conditioning. Ideally, an opiate antagonist such as naloxone should be used to investigate the role of the opiate receptors, but this is not feasible in STEMI due to the need for administering opiates for pain relief.

Conclusions

There is accumulating evidence that post-conditioning or periconditioning, either performed directly in the heart or remotely, may confer clinically meaningful benefits. However, our enthusiasm must be tempered because the human data are derived from small, single center studies. If the effect is real, the magnitude of the benefit is remarkably large (35% relative reduction in infarct size) in an era in which it is increasingly difficult to demonstrate additional benefits of new therapies beyond current management due to relatively small infarct size and low mortality of patients with STEMI enrolled in clinical trials. If the field is to move forward, large multicenter clinical trials of cardiac and remote post-conditioning that have adequate statistical power to detect a reduction in clinical end points must be performed. The obvious challenge is how to fund these trials because there is limited incentive for industry support without intellectual property rights. On a positive note, the sample size needed may be reasonable given the magnitude of the cardioprotective effect seen in the preliminary studies, though one cannot help but wonder if it is too good to be true!

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