“Delaying the postconditioning intervention for even a few minutes while changing balloon catheters, or while allowing balloons to remain deflated beyond the period of time suggested by the algorithm, may abrogate the cardioprotective advantage of postconditioning,” from Kin et al.1

The ability of the myocardium to protect itself under lethal ischemic conditions—so-called ischemic conditioning—is a remarkably robust and reproducible experimental phenomenon demonstrable via direct measure of infarct size in virtually all animal models tested.2 Despite inferences from the analysis of surrogate end points in clinical studies, eg, biomarker elevation, ST-segment shift, anginal discomfort (either preceding or accompanying ischemia), there are as yet no clinical studies directly assessing infarct size reduction consequent to preconditioning, as originally described by Murry et al3 in a canine model. Given the impossibility and implausibility of predicting exactly when an acute myocardial infarction will occur in humans and the necessity for the preconditioning stimulus to be applied before the ischemic insult, it is clear that preconditioning human myocardium imminently facing infarction will likely not be achievable. However, this is a needlessly harsh refutation of the existence and other potential clinical benefits of ischemic preconditioning in humans.4 The initial report of ischemic postconditioning in a canine ischemia-reperfusion model in 20033 was met with rapid uptake by the clinical community,5 no doubt reflecting the obvious concern of John Ioannidis, namely “Why most discovered true associations are inflated.”6 Is the current uncertainty regarding the existence or extent of the benefit of postconditioning in humans simply a matter of inadequately powered studies and inflated early estimates of the true effect?7

The present study from Han et al8 provides some answers to the above, but, as with so many other studies in this area, it raises other unsettling questions. These authors screened 3916 patients presenting with ST-elevation myocardial infarction within 12 hours of symptom onset in 17 percutaneous coronary intervention (PCI) centers. Seven hundred (17.9%) of these patients were eligible, enrolled, and randomly assigned (Web-based system, stratified by center and infarct artery) in a 1:1 fashion to a postconditioning treatment arm or a conventional primary PCI treatment arm. The study sample was arrived at by hypothesizing a 12.5% absolute increase in the primary end point—the rate of complete ST-segment resolution (>70% by procedure completion) in the preconditioning arm—and an expected rate of complete ST-segment resolution of 50% in the conventional PCI arm. Although the postconditioning protocol itself was standardized and consistent with many of the postconditioning protocols used in other studies (low-pressure balloon inflation for 1 minute × 4 separated by 1 minute of deflation/reperfusion), the trial was designed to be as real world as possible and allowed considerable operator discretion in the use of thrombus aspiration, predilation before stenting, use of glycoprotein IIb/IIIa inhibitors, etc. The authors state that, in the postconditioning arm, the postconditioning protocol was initiated “immediately (within one...
minute) after restoration....of coronary flow (without regard to method of restoration)....” The study sample is robust in size (>90% prestudy power to detect the specified treatment effect), similar to a majority of primary PCI trials in terms of age and sex distribution (although the frequency of current smoking is high) and symptom onset to reperfusion time. Importantly, the methods for establishing antegrade flow (94% had Thrombolysis in Myocardial Infarction [TIMI] 0 flow before PCI) were equally distributed between treatment arms and include wire passage, thrombus aspiration, and predilation ballooning. The primary end point—complete ST-segment resolution by procedure end—was virtually identical in each arm: 40.5% in the postconditioning arm and 41.5% in the conventional PCI group (absolute difference, −1.0%; 95% confidence interval, −8.4% to 6.4%). For secondary end points of postprocedural TIMI flow grade and myocardial blush grade, the differences between treatment arms were not statistically significant nor were rates of adverse clinical outcomes at 30 days. In other words, a neutral study, or was it?

That ρ=not significant only tells us that the authors failed to find the prespecified difference under the null hypothesis, not that a difference does not exist. The study was well powered at >90% to find a difference should one exist. The 95% confidence interval for the difference in primary end point rates is tight and excludes the expected 12.5% increase in extent of ST-segment resolution in the postconditioning arm. The numerical differences in myocardial blush grade and TIMI flow favoring postconditioning are not statistically significant. The unfavorable (to postconditioning) numerical difference in the incidence of hard clinical outcomes is a bit concerning but, again, not statistically significant. What, if any, hidden biases or confounding should be considered before we accept the P=not significant at face value?

Postrandomization events, when selectively applied, will undermine best efforts to maintain parity between treatment arms. The frequency of thrombus aspiration, ≈50% in each group, although perhaps real world, confounds interpretation of the primary end point. Whereas controversy still surrounds the ultimate clinical benefit of thrombus removal, in general, during primary PCI, there is more agreement regarding the effect of thrombus aspiration on the rate of ST-segment recovery, the primary end point of this study. That the rate of thrombus aspiration was similar between treatment arms is of little comfort, because the use of this adjunct was not randomly assigned. Thus, confounding by indication (“I think this lesion needs thrombus aspiration; therefore I will aspirate”) is a very real limitation to this study and, given the extent of use of aspiration, could well bias this study’s results toward the null notwithstanding the competing effect of postconditioning on the rate of ST-segment resolution. Further clouding this important issue is the recent demonstration of a disconnect between cardiac magnetic resonance–determined final infarct size and the extent of ST-segment resolution during primary PCI with the use of thrombus aspiration. Probably the most important concern, reflected in the opening quotation, regards the use of such adjunctive measures, the time required to perform such maneuvers, and the very likely possibility of mitigating, if not abrogating, activation of salvage-signaling pathways. This translational departure from the original report from Kin et al1 would mitigate against detection of postconditioning’s effect on the rate of ST-segment resolution, myocardial perfusion, and the extent of myocardial salvage. The key to postconditioning’s beneficial effects (at least in animals) is intermittent, gradual restoration of antegrade coronary flow within the first several minutes of reperfusion.6 Only intermittent balloon inflation–deflation cycles can accomplish this during primary PCI, although it should be recognized that the optimal number and duration of such cycling has yet to be determined.

Other difficulties, beyond the scope of this editorial, continue to plague this area of research. The magnitude of benefit conferred by postconditioning in humans is confined to a modest, albeit statistically significant, effect on biomarker and scintigraphic estimates of infarct size without persuasive evidence for improved clinical outcomes.11 In addition to the sine qua non of early and gradual reperfusion, the benefit of postconditioning is highly dependent on the area at risk and the total ischemic time. A beneficial postconditioning effect is most apt to be manifest with anterior infarcts and total ischemic times <3 hours (both with <50% prevalence in the current trial).11 The importance of the latter cannot be exaggerated given the many variables beyond our control in a patient experiencing an out-of-hospital myocardial infarction.17 The current literature suggests little window for improvement in the extent of myocardial salvage with primary PCI occurring beyond 3 hours of total ischemic time.16 The flip side of that sobering observation is the possibility of reducing the extent of the reperfusion injury by identifying the optimal means of induction of postconditioning.

Thus, although this trial remains the largest reported attempt to identify a postconditioning effect in patients undergoing primary PCI, further improvement in trial conduct, patient selection, and clinical, nonsurrogate outcomes assessment are necessary for effective translation of this still potentially clinically relevant cardioprotective phenomenon.

Disclosures

None.

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References


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