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Remote Ischemic Preconditioning: A Complex Question with an Even More Complex Answer

Sarah A. Schubert, MD and Irving L. Kron, MD

Department of Surgery, Division of Thoracic and Cardiovascular Surgery, University of Virginia, Charlottesville, Virginia

The concept of ischemic preconditioning dates back to the 1980s, when it was discovered that brief periods of ischemia slow rates of adenosine triphosphate (ATP) depletion during subsequent episodes of ischemia and that intermittent reperfusion during ischemic periods can flush out accumulated catabolites.¹ Given that applying ischemia directly to target organs – such as the heart, brain, or kidneys – is impractical outside of an experimental setting, attention turned to the application of remote ischemia – that is, applying an ischemic stimulus in an area away from target organs.² Over the next several years, continued experimentation with remote ischemic preconditioning (RIPC) led to the discovery that even brief induced limb ischemia can reduce myocardial infarct size and prevent endothelial dysfunction.^{3, 4} It is believed that RIPC works by to limit ischemia-reperfusion injury, which is tissue damage induced by an ischemic insult and the subsequent injury that occurs with reperfusion of those tissues.⁵

In spite of the growing understanding of the mechanisms of ischemia-reperfusion injury and the promising *in vitro* results with RIPC, translation of RIPC into clinical outcomes for attenuation of ischemic injury has been inconsistent and variable, especially with regard to clinical outcomes.^{6–8} In their manuscript, “Remote Ischemic Preconditioning in High-risk Cardiovascular Surgery Patients: A Randomized-controlled Trial,” the authors present a valiant attempt to elucidate the complex outcomes of an even more complex process.

The authors report their results of a double-blind trial in which patients undergoing high risk cardiac or vascular surgery procedures were randomized to undergo RIPC or a sham-RIPC treatment (control) prior to their planned surgical intervention. Assuming an event rate of 30%, type I error equal to 0.05, power equal to 0.80, and relative risk reduction of 40% with RIPC, their study was well-powered to detect a difference in outcomes between the cohorts. Their well-validated method of RIPC consisted of three cycles of a blood pressure cuff inflated on the upper arm to a pressure of 200 mmHg for five minutes, followed by five minutes of deflation. The authors found no significant benefit with the addition of RIPC compared to control for patients undergoing high risk surgical procedures. Their primary outcome – a composite measure of all-cause mortality, myocardial infarction, stroke, respiratory failure, acute renal failure, and low cardiac output syndrome – did not differ between either group (control: 34% vs RIPC: 32%, $p=0.73$) or when analyzed as subgroups

of cardiac (42% vs 37%, $p=0.47$) and vascular surgical (16% vs 21%, $p=0.60$) patients. Additionally, they did not observe any differences in biomarkers of ischemic damage or length of hospital stay between the RIPC group and the control group following cardiovascular surgery. With their results, the authors concluded that RIPC confers no benefit in patients undergoing cardiovascular surgery.

The only constant in the literature regarding RIPC is that results are highly variable and that the mechanisms of such protection are incompletely understood. That being said, there are several factors that have been definitively shown to positively or negatively affect the efficacy of RIPC, none of which the authors addressed or controlled for in this study. Given the rather broad inclusion and exclusion criteria and the resultant composition of their study population, their lack of significant clinical benefit with RIPC is therefore not surprising.

First, it is well-known that many medications inhibit ATP-sensitive potassium channel conductance and thus prevent the inhibition of ATP depletion that makes RIPC effective.^{9, 10} Most relevant for this study population, however, are cyclo-oxygenase inhibitors (i.e. aspirin, celecoxib) and sulfonylurea medications (i.e. glyburide, glimepiride). In this study, all of the patients were designated as being “high-risk” cardiovascular surgical candidates. Although the number of patients receiving preoperative aspirin therapy was not reported, it is highly likely that most, if not all, of the patients in this study were on aspirin prior to surgery. The cyclo-oxygenase enzyme is responsible for the production of prostaglandins, which in turn, stimulate conductance of the ATP-dependent potassium channels in the myocyte mitochondrial membrane.¹¹ Inhibition of that enzyme, especially irreversibly with a medication like aspirin, would ostensibly then prevent the increase in ATP-dependent potassium channel opening that is integral to RIPC efficacy.¹² Additionally, sulfonylurea medications function similarly to inhibit these same potassium channels. In fact, glyburide is used in many studies to abolish the cardioprotective effect of RIPC.¹² Even more significantly, Kottenberg et al have shown that RIPC-induced myocardial protection is abolished in sulfonylurea-treated diabetics undergoing coronary revascularization.¹³ Over one-third of the patients in each of this study’s cohorts were diabetics (35% of the RIPC cohort and 36% of the control cohort). Although it is not known whether or not their diabetic patients were on a sulfonylurea, it is likely that some of them were taking that class of medications, which would confound their results and certainly diminish any observable benefit of RIPC.

In addition to the confounding associated with patients’ preoperative medications, commonly used methods of intraoperative anesthesia have well-described effects on ischemia reperfusion injury and even RIPC. Propofol is known to attenuate the beneficial effects of RIPC, and the mechanism of that abolishment has even been elucidated in human studies.^{14, 15} Inhalational anesthetics such as sevoflurane or isoflurane, however, have been shown to attenuate ischemia reperfusion injury and are known to provide some level of myocardial protection, as evidenced by less troponin release in those patients receiving inhalational anesthetics.¹⁶ Despite the evidence that varying anesthetics can affect RIPC in different ways, the authors of this study purposefully did not develop a standard anesthesia protocol. They rationalized their decision so as to make their results “generalizable to cardiovascular surgery where multiple anesthetics can be used over the course of one surgery

and the protocol may vary from site to site.” Although this is a reasonable rationalization, there is extensive evidence that anesthetics confound these processes in a variety of ways, and ignoring these facts diminishes the rest of their cogent, meticulous study design and statistical analysis.

Although the authors conclude that RIPC has no protective benefits for patients undergoing high risk cardiovascular procedures, this is a strong conclusion when their results are considered within the context of existing data, some of which corroborates their findings and some of which does not. The mechanisms of RIPC are not well-understood, and data regarding the efficacy of RIPC for attenuation of ischemia reperfusion injury is mixed. That being said, there are several factors that have been definitively shown to positively or negatively affect the efficacy of RIPC, several of which the authors did not address or control for in this study. Because the clinical benefit of RIPC has yet to be consistently reproduced, the authors should have attempted to control for as many of these factors as possible in order to determine if there is even a marginal benefit with RIPC. Despite the lack of efficacy with this intervention, we applaud the authors for testing their hypothesis with a randomized clinical trial.

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