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Remote ischemic preconditioning during cardiac surgery. What does the future hold?

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Dear Editor,

Myocardial protection during cardiac surgery has evolved over the past several decades, aiming to attenuate the damage associated with reperfusion-ischemic injury. Since the advent of cardioplegia in the 1950s, countless studies have explored the ideal composition, delivery, and temperature of cardioplegia solutions for protecting the myocardium. With the anesthetic pharmacologic agents, most studies focus on using volatile anesthetics and propofol, which have been shown to help with myocardial protection. One modality that has gathered a lot of interest over the past two decades is remote ischemic preconditioning (RIPC). This technique involves applying a non-invasive blood pressure (NIBP) cuff to an extremity, followed by repeat inflation and deflation, typically before cardiopulmonary bypass. The theory is that temporary ischemia elsewhere can help with myocardial pre-conditioning. In doing so, the myocardium becomes resistant, or at least more tolerant to further episodes of ischemia post-cardiopulmonary bypass. The earliest studies we identified were from the early 2000s, suggesting that brief periods of ischemia can help suppress the transcription of pro-inflammatory genes [1]. These studies also indicated that RIPC adheres to a biphasic model, such that it provides 'early' and 'late' protection, essentially intra-operative and post-operative protection [2]. The notion was initially tested during percutaneous coronary intervention procedures followed by cardiac surgery. Unfortunately, the results have been controversial, with insufficient evidence suggesting routine RIPC use during cardiac surgery.

The two landmark trials looking into RIPC are the Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery (ERICCA) [3] and A Multicenter Trial of Remote Ischemic Preconditioning for Heart Surgery (RIPHeart) [4]. The ERICCA trial randomized 1612 patients undergoing coronary artery bypass graft (CABG) or valve surgery to receive RIPC in the form of inflation/deflation of the NIBP cuff in 5-minute intervals versus sham treatment. The intervention was performed before surgical incision, a total of four times. The primary outcome was adverse cardiac and cerebral events within one year of surgery. The team found no difference between the RIPC and sham treatment groups ($P = 0.58$) [3]. The RIPHeart trial had a similar methodology, randomizing 1403 patients undergoing elective cardiac surgery, including CABG and valve surgery. The primary outcome was myocardial infarction, acute renal failure, stroke, or death before hospital discharge. The team found no protective benefit of RIPC concerning the primary outcome variables ($P = 0.89$) [4]. We must acknowledge that both trials utilized propofol, which is known to attenuate the protective effects of RIPC seen during *in vivo* studies. Lucchinetti *et al.*'s [5] study investigating RIPC and isoflurane use during CABG found that the RIPC group had a higher incidence of arrhythmias and myocardial infarction. At a molecular level, the authors

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postulate that RIPC may even promote transcription of inflammatory genes, thus causing more harm than benefit for the patient [5].

Since January 2024, several studies have re-investigated the utility of RIPC. Law *et al.* [6] demonstrated that RIPC during pediatric cardiac surgery conferred renal protection ($P = 0.037$). Kourtis *et al.* [7] investigated the use of RIPC along with RIPC and ranolazine before percutaneous coronary intervention. Combining the two therapies significantly reduced myocardial markers such as troponin I and creatine kinase-MB. A meta-analysis by Han *et al*. [8] revealed that RIPC use in adult patients undergoing general anesthesia helped reduce the incidence of postoperative cognitive dysfunction. This potentially reveals possible neurological benefits of RIPC that warrant further investigation.

We live in an age where interventional cardiology continues to advance with percutaneous valve replacements and valve repairs; however, we must not neglect the role of conventional cardiac surgery. With that said, research continues to look for the magic bullet concerning ideal myocardial protection. While RIPHeart and ERICCA found no benefit, we have seen several recent trials with promising results. Further research involves observing any difference with an alternative sedation infusion, such as dexmedetomidine instead of propofol. Another approach is comparing different ischemia times; the studies we identified typically used four cycles of 5-minute ischemic periods. While we are skeptical about advocating RIPC use entirely, we believe RIPC should not be written off just yet; there are still variables we can alter and adjust with future trials. Medicine is constantly evolving; for many years, isoflurane was thought to cause coronary steal syndrome. However, this has subsequently been debunked. Perhaps time will enable us to explore RIPC to its fullest extent. Currently, RIPC for cardiac surgery is not universally recommended, but let us see what the future holds.

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