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Editorial

Remote Ischemic Preconditioning – Not Ready to Rest in Peace (RIP)?

Helgeson AP[1] and Resar JR[2]*

[1]Division of Cardiology, Johns Hopkins Hospital, USA

[2]Division of Cardiology, Johns Hopkins Hospital, USA

***Corresponding author:** Resar JR, Division of Cardiology, Johns Hopkins Hospital, USA

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Editorial

Ischemic preconditioning was originally recognized in 1986 when Murry discovered that myocardial infarct size was reduced by 75% with transiently ligating a non-culprit coronary artery prior to a prolonged ischemic insult in an adjacent epicardial artery in animal models [1]. More recently, the preconditioning stimulus has been replicated by inflating a blood pressure cuff on the upper extremity for three 5 minute cycles of transient ischemia eliciting a systemic response protecting distant organs exposed to prolonged ischemic insults. This process of remote ischemic preconditioning (RIPC) has evoked incredible enthusiasm in the cardiovascular literature over the past decade. Many proofs of concept trials have shown RIPC to be a simple, inexpensive, and harmless technique to stimulate an innate cardio-protective response to ischemic-reperfusion injury in patients undergoing cardiothoracic surgery or percutaneous interventions. Despite criticism of these early trials for depending on surrogate markers of myocardial injury, including troponin I(cTnI) and CK-MB, in 2013, Thielmann et al enrolled 329 patients undergoing low risk coronary artery bypass surgery and found that RIPC not only reduced to release by 23%, but also provided a 5% absolute risk reduction (ARR) in all cause mortality and a 12.3% reduction in the composite endpoints of cardiac death, all cause mortality, major adverse cardiovascular events (MACCE), and repeat revascularization out to 1 year [2]. This seminal trial brought increased attention to RIPC in cardiac surgery patients and was the first of its kind to show that RIPC improves hard clinical outcomes.

The most recent meta-analysis, published in JACC (01/2015) by Heusch et al, addressed the proposed mechanisms and clinical benefit of RIPC for cardio-protection in cardiac surgery as well as acute myocardial infarction and percutaneous intervention. In the surgical cohort, the spectrum of results ranged from a failure of RIPC to provide protection to the opposite result whereby RIPC led to a 5% reduction in all-cause mortality and 45% reduction in cardiac troponin I (cTnI) release [3]. The heterogeneity in the surgical literature at large called for a large, randomized controlled trial of RIPC. In October of 2015, two large-scale, multi-centered double-blinded, randomized controlled trials of RIPC in cardiac surgery, powered for hard clinical endpoints, ERICCA and RIPHeart, were simultaneously published in NEJM [4,5]. The effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Surgery (ERICCA) trial enrolled 1,612 patients and showed no difference in surrogate endpoints of myocardial or renal injury nor a difference in cardiovascular death, myocardial infarction, revascularization, or stroke at 1 year [4]. RIPHeart, similarly powered for a composite endpoint of death, myocardial infarction, stroke, or acute renal failure, followed 1,385 patients out to discharge (or 14 days) and also found no improvement in the clinical endpoints with RIPC versus a sham protocol, leaving RIPC enthusiasts dumbfounded [5]. Advocates asked, are these two adequately powered trials sufficient for us to close the door on RIPC at large, calling remote ischemic preconditioning itself the sham?

Certainly, the results of RIP-Heart and ERICCA have been disappointing for RIPC advocates; yet, generalizing these results to the entire cardiovascular community seems premature. Before we can close the door on RIPC, the cause of such discrepancies in the literature must be understood. Standardization of clinical trials in surgical cohorts has been riddled with biases, confounders, and heterogeneous outcomes due to the difficulties in controlling patient and procedural variables. As a result, there is a paucity of data supporting pharmacologic or procedural methods of reducing myocardial reperfusion injury during cardiothoracic surgery, explaining the initial excitement for RIPC. In RIPHeart, ERICCA, and preceding surgical studies, procedural characteristics known to increase myocardial injury and adverse outcomes, including procedural length, transfusion requirement, myocardial defibrillation, epinephrine administration, and procedure performed - valve replacement vs CABG - were often excluded in matching the control and intervention arm and further were not corrected for as confounders. When Kleinbongard et al recently evaluated various confounding variables, they found RIPC only provided protection at longer aortic cross-clamp times (>56 minutes), suggesting that the degree of myocardial ischemic-reperfusion injury affects the amount of protection by RIPC [6]. Yet, again, aortic cross clamp time and other variables correlative with the degree of ischemic injury were not analyzed in many of the surgical trials of RIPC, including RIPHeart or ERICCA.

In addition to procedural variables, Kleinbongard evaluated the influence of co-administered medications, including, statins, B-blockers, or ACE/ARB therapy, on the RIPC response, and found no interaction [6]. Yet, there is compelling literature that anesthetic agents, such as propofol, abolish the cardio-protective effects of RIPC by inhibiting signaling pathways known to play a role in the preconditioning stimulus, ultimately nullifying the cardio-protection [7]. A predominance of propofol use, particularly in cardiac surgery yet less in percutaneous intervention, has occurred over the past decade. In RIPHeart and ERICCA, propofol was either standardized as the sole anesthetic or included in > 90% cases. Yet, Thielmann's group avoided propofol due to potential attenuation of the RIPC response. Therefore, while evidence of the benefit of RIPC in cardiac surgery patients, especially following the results of RIPHeart and

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Table 1: Randomized trials of RIPC referenced.

First Author, year (Ref #)	n (control/ RIPC)	Population	Endpoint	Outcome (RIPC vs control)	P value
Thielmann et al., [2]	167/162	CABG	cTnI (AUC at 72 hr) Composite (all-cause mortality, cardiac death, MACCE, stroke, repeat revascularization) at 1.5 year	266 vs 321 ng/ mL (HR 0.83 (0.70-0.97)) 22.1% vs 34.4% (OR 0.38 (0.21-0.70)	p=0.02 p=0.002
Hausenloy et al., [4]	811/801	CABG (+/- valve)	MACCE at 12 month cTnT (AUC at 72 hr)	26.5% vs 27.7% (OR 0.95 (0.79-1.15)) 32.7 vs 36.4 ng hr/mL (OR 0.98 (0.91-1.06))	p=0.58 p=0.63
Meybohm et al., [5]	693/692	Cardiac surgery	Composite (death, MI, stroke, acute renal failure) at discharge/14 days	14.6% vs 14.3% (OR 1.02 (0.75-1.39))	p=0.89
Hoole et al., [8]	98/104	Primary PCI	cTnI, median Composite acute kidney injury, MACCE at 6 month	0.06 vs 0.16 ng/ mL 4 vs 13 events (HR 0.28 (0.12-0.82)	p=0.04 p=0.018

HR: Hazard Ratio (95% confidence interval); OR: Odds Ratio (95% confidence interval)

ERICCA, is weak, there certainly is an argument that unaccounted for confounding procedural variables may explain the heterogeneous results in the literature.

Unlike the inconsistent results in the surgical literature, RIPC has reduced infarct size and myocardial injury in patients undergoing percutaneous coronary intervention (PCI) both in the setting of the ischemic-reperfusion injury of an acute myocardial infarction (AMI) as well as stable coronary artery disease. The Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP) study showed short term reduction in ST deviation, cTnI, and chest pain within the first 24 hours, and additionally revealed a 72% reduction in MACCE at 6 months (HR 0.28 (95% CI, 0.12 to 0.82, p =0.018)) [8]. Recently, 192 of the original 242 CRISP patients were followed out to 6 years evaluating overall MACCE rates, which remained markedly reduced in the RIPC arm with an absolute risk reduction of 13% and number needed to treat=8 to prevent 1 major cardiac event at 6 years [9]. Interestingly, studies in AMI and PCI have shown patients with anterior infarctions, complete occlusions with STEMI, or triple vessel disease attain the greatest benefit from RIPC, again suggesting those at highest risk benefit most from RIPC. Furthermore, there are an increasing number of proofs of concept studies supporting RIPC in reducing contrast-induced acute kidney injury (CI-AKI) for which a dual benefit may exist in this population [10-12].

Certainly, confounders exist in AMI patients and those undergoing elective PCI. Yet, with increased expertise in percutaneous coronary interventions, the procedural technique has largely been standardized, thereby limiting procedural confounding and improving study design in this more homogeneous population. And while the preponderance of the remote ischemic preconditioning literature has been focused in cardiac surgery, the majority of patients today, particularly those experiencing acute myocardial infarctions, are undergoing percutaneous interventions. If history acts as our guide, since the original discovery of RIPC was in animal models of myocardial infarction – perhaps the current focus must again return to the role of preconditioning in acute coronary syndromes (ACS) with percutaneous reperfusion.

In addition to unstable coronary artery disease, up to one-third of patients undergoing elective percutaneous coronary intervention are subject to myocardial injury during the procedure with many small studies suggesting a cardio-protective role of RIPC in this population as well [3,13-17]. Yet, there are no large randomized controlled trials powered for hard clinical outcomes to validate the proof of concept smaller studies of RIPC induced cardio-protection in either ACS or elective PCI patients. As such, can we say "rest in peace" to the concept of remote ischemic preconditioning in these completely different cardiovascular populations based on the results of RIPHeart and ERICCA? Or, shall we carry on our pursuit of larger, well-designed randomized studies of RIPC within a more controlled environment of interventional cardiology? If the question remains whether to continue investigation of an inexpensive, low risk, easily implemented protective technique with adequate pilot data proving benefit, the answer is quite simple, yes.

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