

## Remote Ischemic Conditioning and the Long Road to Clinical Translation

### Lessons Learned From ERICCA and RIPHeart

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#### Remote ischemic preconditioning and outcomes of cardiac surgery

Hausenloy et al  
*N Engl J Med.* 2015;373:1408–1417.

#### A multicenter trial of remote ischemic preconditioning for heart surgery

Meybohm et al  
*N Engl J Med.* 2015;373:1397–1407.

**R**emote ischemic conditioning (RIC) is the phenomenon whereby brief episodes of peripheral ischemia-reperfusion, typically applied to  $\geq 1$  limbs by inflation–deflation of a standard blood pressure cuff, increase the tolerance of the myocardium to a sustained ischemic episode. Compelling pre-clinical evidence of infarct size reduction with RIC, together with promising results from small, proof-of-concept phase II trials, has yielded cautious optimism that RIC may be the long sought-after cardioprotective strategy capable of attenuating morbidity and mortality in patients having a spontaneous or planned period of prolonged cardiac ischemia. Progress toward clinical translation may, however, be hindered by the recent release of 2 eagerly anticipated phase III trials. ERICCA (Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Graft Surgery) and RIPHeart (Remote Ischaemic Preconditioning for Heart Surgery), both published in the *New England Journal of Medicine* and both designed to assess major adverse cardiac and cerebrovascular events after cardiac surgery in RIC-treated cohorts versus sham controls, concluded that RIC had no benefit on clinical outcomes.

#### Rationale: RIC in Cardiac Surgery

In the 2 decades since the first report of the phenomenon of “preconditioning at a distance,”<sup>1</sup> RIC has evolved from

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Commentaries are edited by Aruni Bhatnagar & Ali J. Marian.

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DOI: 10.1161/CIRCRESAHA.115.308102.)

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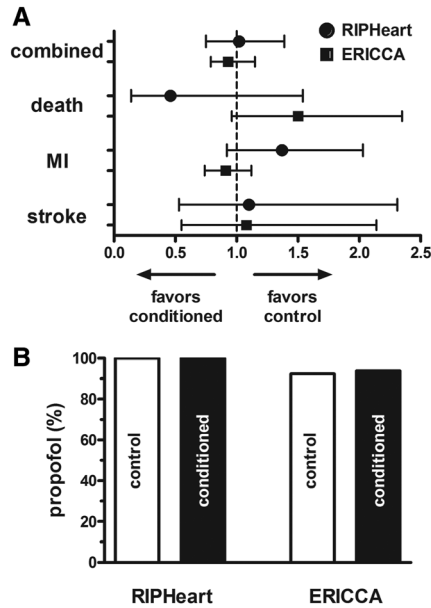
*Circulation Research* is available at <http://circres.ahajournals.org>

DOI: 10.1161/CIRCRESAHA.115.308102

theoretical concept<sup>2</sup> to preclinical investigation<sup>3</sup> to multiple phase II clinical trials in patients undergoing cardiac surgery or percutaneous coronary intervention.<sup>4–6</sup> RIC has largely been investigated as a pretreatment before planned ischemic events, including elective coronary artery bypass grafting (CABG), and is particularly well suited to the controlled surgical environment. Among the phase II trials that focused on CABG in adult patients and provided the foundation for ERICCA and RIPHeart, the primary end point was postoperative release of cardiac enzymes: ie, well-established surrogate markers of cardiomyocyte damage that have been associated with increased perioperative morbidity and mortality and attributed to ischemia-reperfusion injury.<sup>6,7</sup> Most (but not all) of these proof-of-concept studies provided encouraging evidence of a significant attenuation in plasma concentrations of creatine kinase and/or cardiac troponins after surgery in patients randomized to receive RIC when compared with controls.<sup>4–6</sup>

ERICCA is the largest clinical trial to date evaluating RIC in cardiac surgery. Higher-risk patients (those with a European System for Cardiac Operative Risk Evaluation  $\geq 5$ ) undergoing elective CABG with or without concomitant valve surgery were randomly assigned to receive either a standard RIC stimulus (four 5-minute manual inflations of a sphygmomanometer, positioned on the upper arm, to a pressure  $\geq 200$  mm Hg; n=801) or time-matched simulated sham inflations (n=811). Clinical outcome was assessed by quantifying the composite end point of cardiovascular death, nonfatal myocardial infarction, additional coronary revascularization, or stroke within 12 months of surgery. In addition, postoperative cardiac troponin release—the mainstay of the previous phase II trials—was among the secondary end points included in the protocol.<sup>8</sup> RIPHeart also focused on patients undergoing elective cardiac surgery but, in contrast to ERICCA, enrolled lower-risk patients, was not limited to CABG, and compared the composite end point of all-cause death, nonfatal myocardial infarction, stroke, or acute renal failure at hospital discharge or 14 days post surgery. Cohorts were randomized to receive the same standard RIC stimulus utilized in ERICCA, applied to either the patient’s upper arm (n=692) or, for the sham control group, to an artificial arm positioned under the surgical drape (n=693).<sup>9</sup> As in ERICCA, measurement of plasma troponin concentrations during the initial days after surgery was included as a secondary end point.<sup>8,9</sup>

Contrary to expectations, the favorable effects of RIC on cardiac enzyme release reported in the majority of phase II studies were not corroborated in ERICCA or RIPHeart. Moreover, in both trials, there was no evidence of a difference in composite clinical outcomes in RIC-treated groups versus



**Figure.** **A**, Hazard ratios (ERICCA: Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Graft Surgery) and odds ratios (RIPHeart: Remote Ischaemic Preconditioning for Heart Surgery) with their 95% confidence intervals for the studies' primary end points. The odds ratios were adjusted for EuroSCORE, the presence of diabetes mellitus, treatment with statin-lowering drugs, and treatment center. In RIPHeart, the combined end point (defined as death, myocardial infarction [MI], stroke, or acute renal failure) was assessed at hospital discharge or 14 d post surgery. In ERICCA, the combined end point (defined as cardiovascular death or major adverse cardiac and cerebral events) was assessed at 12 mo. **B**, Proportion of patients who received propofol. In RIPHeart, 100% received propofol per protocol; in ERICCA, >90% of patients in each group received propofol.

controls ( $P=0.58$  and  $P=0.89$ , respectively; Figure [A]).<sup>8,9</sup> These data have, not surprisingly, stirred debate on the future of this cardioprotective phenomenon<sup>10,11</sup>: Do ERICCA and RIPHeart herald the end of the long road to clinical translation for RIC? Based on the unequivocally neutral findings of these landmark phase III trials, should RIC be abandoned as a cardioprotective strategy?

### Disappointing but Predictable?

The acknowledged weaknesses of previous phase II studies include (1) the fact that conclusions on the potential cardioprotective efficacy of RIC were based exclusively on attenuated release of creatine kinase and cardiac troponins, combined with (2) uncertainty regarding the relationship between the observed  $\approx 10\%$  to  $40\%$  reductions in cardiac enzyme release during the initial 2 to 3 days after surgery and longer-term morbidity and mortality.<sup>12</sup> In this regard, ERICCA and RIPHeart, and their shift in focus from surrogate end points to quantitative assessment of clinical outcomes, represent an important advance in the field of RIC and cardioprotection. Nonetheless, despite their more robust study design, the aspect of ERICCA and RIPHeart that merits scrutiny is not the failure of RIC to attenuate the incidence of longer-term major adverse events; these results are predictable, given the lack of short-term benefit. Rather, the germane issue is why,

in contrast to most previous smaller studies, RIC was not associated with a favorable reduction in cardiac enzyme release.

Although it is possible that the discrepancy may be a consequence of statistical type 1 errors in earlier positive trials, we propose that the outcomes of ERICCA and RIPHeart are more likely explained by (1) our overall lack of understanding of the temporal and physiological requirements for RIC-induced cardioprotection; (2) our limited knowledge of the mechanisms of RIC; and (3) our failure to capitalize on the little mechanistic insight that is available. With regard to the first issue, recent dose-response studies conducted using young adult male mice demonstrated that the standard RIC stimulus (four 5-minute periods of limb ischemia, interspersed with 5 minutes of reperfusion) yielded a significant infarct-sparing effect, with no added benefit provided by increasing the number of ischemia-reperfusion cycles.<sup>13</sup> However, there is no evidence to establish that this algorithm is effective (and optimal) for all patients and all applications. Is the standard stimulus equally appropriate for CABG (as implied by the outcome of the majority of phase II studies), the  $\approx 50\%$  of patients in ERICCA who underwent CABG combined with valve surgery, and the  $\approx 50\%$  of patients in RIPHeart who underwent valve repair/reconstruction or other surgical procedures?<sup>8,9</sup> Is there leeway in the standard RIC stimulus, or do variations in timing (including prolongation of the intervening period between the RIC stimulus and the onset of sustained myocardial ischemia, typically on the order of minutes in preclinical studies, to a mean of 1.5–2 hours in ERICCA and RIPHeart<sup>8,9</sup>), and violations in the RIC algorithm (as occurred in  $\approx 10\%$  of patients in RIPHeart<sup>9</sup>) have a significant influence on outcome? Although these specific questions remain unresolved, emerging data argue against the concept that, for RIC, one-size-fits-all. In addition to the possible confounding effect of diabetes mellitus and other comorbidities,<sup>14</sup> there is evidence that the magnitude of cardioprotection achieved with RIC is proportional to the ischemic burden.<sup>6,15,16</sup> Specifically, in patients undergoing CABG, recent retrospective analysis revealed that RIC evoked significant reductions in troponin I release with cross-clamp times  $>57$  minutes, but had no effect with ischemic durations  $\leq 56$  minutes.<sup>16</sup> Accordingly, in cohorts undergoing elective cardiac surgeries, with cross-clamp times as short as 18 minutes in the ERICCA trial,<sup>8</sup> and in which myocardial ischemia-reperfusion injury may have already been blunted by cardioplegia, hypothermia and, in subsets of patients, volatile anesthetics and opioids, the scope for improvement with RIC may have been modest at best.

Although all of the aforementioned factors may have had mitigating effects, we posit that a common component in the design of both studies—specifically, the use of propofol in the anesthetic regimen—may have acted as a negative confounder, thereby diluting or obscuring the effect of RIC on study outcomes. That is, propofol may have (1) attenuated RIC-induced cardioprotection,<sup>17</sup> possibly by precluding the activation/phosphorylation of signal transducer and activator of transcription 5 (STAT5: the sole kinase identified to date to be associated with RIC-induced cardioprotection in human myocardium<sup>18,19</sup>), and (2) conferred protection in control subjects, potentially via dual activation of the phosphoinositide 3-kinase/Akt and janus kinase 2/STAT3 pathways.<sup>20</sup> Indeed,  $>90\%$

of subjects in ERICCA and 100% of patients in RIPHeart received propofol<sup>8,9</sup> (Figure [B]).

### Lessons Learned and Proposed Next Steps

ERICCA and RIPHeart have, without question, dealt a blow to both cardioprotection in general and RIC in particular. Some investigators and clinicians may, based on these neutral outcomes, conclude that RIC has no clinical utility. In contrast, we propose that ERICCA and RIPHeart have delivered 4 critical lessons: (1) the danger of working blind, moving forward in the design and execution of clinical protocols without a firm physiological and mechanistic understanding of RIC-induced cardioprotection; (2) acknowledgment that, for RIC, one size probably does not fit all; (3) the need for attention to detail in all aspects of study design and execution, including choice of appropriate patient cohorts and specific clinical applications, as well as identification and consistent delivery of the optimal RIC algorithm(s); and (4) the importance of heeding the still-limited insights that have been obtained from both positive and negative preclinical studies and phase II trials.

These lessons underscore the need to address the gaps in knowledge, and pursue RIC in populations most likely to realize substantial benefit. In this regard, RIC may show greater promise in patients undergoing percutaneous coronary intervention for ST-segment-elevation myocardial infarction,<sup>15</sup> particularly in cohorts with anterior wall infarctions and thus large volumes of at-risk myocardium: ie, a population in which treatment is logistically more challenging, but the outcomes are not confounded by the effects of propofol (or cardioprotection caused by cardioplegia, hypothermia, etc) and the scope for meaningful reward with RIC is high. Thus, rather than abandoning RIC, we advocate that the failed outcomes of ERICCA and RIPHeart “. . . should be our teacher, not our undertaker.” Denis Waitley.

### Disclosures

Drs Garratt and Przyklenk serve as advisors to LifeCuff, Inc. Dr Whittaker reports no conflicts.

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JOURNAL OF THE AMERICAN HEART ASSOCIATION



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*Circ Res.* 2016;118:1052-1054

doi: 10.1161/CIRCRESAHA.115.308102

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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