ERICCA and RIPHeart: two nails in the coffin for cardioprotection by remote ischemic conditioning? Probably not!

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Brief episodes of ischaemia/reperfusion in peripheral organs or limbs render the heart and other parenchymal organs more resistant to subsequent injury by more prolonged periods of ischaemia and reperfusion.1 Such remote ischaemic conditioning (RIC) has not only been demonstrated in experimental animals, but is also operative in humans. In proof-of-concept studies, RIC reduced infarct size in patients undergoing elective interventional2 or surgical coronary revascularization,3–5 as evidenced by reduced cardiac biomarker (creatine kinase, troponin I or T) release, and this effect translated into improved short-term6 and long-term4,6 clinical outcomes which were, however, analysed only as secondary endpoints from studies with reduced infarct size as primary endpoint. Also in patients suffering an acute myocardial infarction, RIC before interventional reperfusion still reduced infarct size, as evidenced by SPECT imaging,7 or improved salvage, as evidenced by MRI,8 and this protection again translated into improved short-term8 and long-term clinical outcomes,9 again analysed as secondary endpoints only. Recently, it was shown that in patients with acute myocardial infarction, RIC was induced by four cycles of 5 min blood pressure cuff inflation/5 min deflation on the upper arm after induction of anaesthesia and before skin incision.14 The primary endpoint was a composite of cardiovascular death, myocardial infarction, coronary revascularization, and stroke after 12 months; among the secondary endpoints was perioperative myocardial injury, as reflected by the area under the curve of hs-troponin T over 72 h. The results were neutral for both the composite primary endpoint and for hs-troponin T release; only the 6 min walk test revealed a benefit for RIC.

RIPHeart is a multi-centre phase III trial, in which 1403 patients underwent cardiac surgery under propofol anaesthesia, ischaemic cardiac arrest, and cardiopulmonary bypass with blood or crystalloid cardioplegia. As in ERICCA, RIC was induced by four cycles of 5 min blood pressure cuff inflation/5 min deflation on the upper arm after induction of anaesthesia and before skin incision.15 The primary endpoint was a composite of all-cause mortality, non-fatal myocardial infarction, new stroke and acute renal failure until hospital discharge; among the secondary endpoints were troponin I or T to reflect perioperative myocardial injury.15 The results were neutral for both the composite primary endpoint and for troponin release. Neither ERICCA nor RIPHeart raised a safety concern.

ERICCA and RIPHeart are certainly seen as a setback or the cardioprotection field, and as such they add to the disappointment of the recent CIRCUS trial which, in contrast to a prior phase II trial,16 reported no benefit for cyclosporine A when given before PCI in patients with acute myocardial infarction, in terms of both creatine kinase release and clinical outcome.17 CIRCUS has been critically discussed elsewhere, and it appeared that there were major differences in the trial design (e.g. time from onset of symptoms, use of direct stenting) and notably in the drug vehicle between the two trials that may have accounted for the divergent results.18

The unequivocal merit of both ERICCA and RIPHeart is the primary endpoint of clinical outcome rather than surrogate biochemical or imaging markers to assess the impact of cardioprotection. Both trials addressed the scenario of cardiac surgery, so that their
neutral outcome contradicts prior trials on RIC in cardiac surgery, but not those on RIC in elective or primary PCI and in thrombolysis, where no surgical insult and no anaesthesia was involved. In both, ERICCA and RIPvHeart not only was the primary endpoint neutral, but they did also not confirm the presence of immediate cardioprotection by RIC in terms of reduced cardiac troponin release.

Given the lack of immediate protection, as reflected by troponin release, the lack of benefit in clinical outcome is not surprising and almost expected. In ERICCA, there was a small, but significant reduction in hs-troponin T release in patients with a complete dataset, but not in the entire cohort when data were inter- and extrapolated. Also, in a contemporary single-centre study from the ERICCA lead authors institution, RIC according to the ERICCA protocol reduced hs-troponin T significantly and improved short-term clinical outcome; these discrepancies in regard to the troponin release data raise concern on protocol adherence throughout all participating centres. The lack of immediate protection from perioperative myocardial injury in the multi-centre phase III trials ERICCA and RIPvHeart is most likely not simply the correction of a type I false-positive error in the positive prior phase II trials. In fact, there are major methodological differences between some of the original positive phase II and the negative phase III trials. The positive original phase II trials studied patients undergoing elective coronary artery bypass grafting without valve surgery, whereas about 50% of patients in ERICCA had additional valve surgery, and about 25% of patients had combined coronary bypass grafting and valve surgery, and another approximately 25% in RIPvHeart had isolated valve surgery. Valve surgery causes additional traumatic myocardial injury, whereas the protection by RIC is confined to ischaemia/reperfusion injury, and thus any protection from ischaemia/reperfusion injury by RIC is diluted in patients also undergoing valve surgery. However, reduced hs-troponin T release with RIC was also reported in a prior phase II trial where 36–39% patients had additional valve surgery.

The most plausible explanation for a lack of protection is the use of propofol anaesthesia in more than 90% of patients in ERICCA and all patients per-protocol in RIPvHeart. In fact, propofol is no more cardioprotective than isoflurane—a classical volatile anaesthetic which is recommended as a first choice in patients at risk of myocardial ischaemia—per se, but specifically abrogates the protection (reduced troponin I release) by RIC in patients undergoing elective coronary artery bypass grafting. Abrogation of protection by RIC with propofol anaesthesia has meanwhile been confirmed, and the use of propofol rather than volatile anaesthesia appears to be a common denominator of all studies that failed to see protection with RIC. This information on propofol was public in late 2011, and it is unfortunate and difficult to understand why the authors of ERICCA and RIPvHeart did not modify their trial design accordingly, in particular since the lead authors of ERICCA were also the lead authors of a consensus paper which concluded that inadequate consideration of prior information from pre-clinical and clinical studies in the trial design is a major reason for failure of translation of cardioprotection to patient benefit and since the lead authors of RIPvHeart are anaesthesiologists.

At this point, it would therefore be premature to abandon cardioprotection by RIC, not only for use in acute myocardial infarction where the type of anaesthesia is no issue and the available studies are positive, but also in cardiac surgery until we have evidence of benefit or lack thereof from RIC in trials in which isoflurane is the anaesthetic of choice. While RIC is easily feasible, safe, and inexpensive, its use may require certain modifications of routine procedures such as avoidance of propofol. And even if not every patient benefits from RIC because of confounding conditions, there may still be many who do, given the prevalence of coronary artery disease and its various clinical features.

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References


