Basic Res Cardiol (2016) 111:48
DOI 10.1007/s00395-016-0564-3

INVITED EDITORIAL

Anaesthetics and remote ischaemic preconditioning: do not stop the music, despite a (yet) unhappy marriage

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Received: 21 May 2016 / Accepted: 1 June 2016 / Published online: 20 June 2016

Remote ischaemic preconditiong (RIPC), at least in the context of cardioprotection during heart surgery, has arrived at an apparent deadlock.

Following numerous laboratory investigations demonstrating smaller areas of myocardial infarction following RIPC (for review, see [6]), proof of principle studies revealing lesser postoperative cardiac troponin concentrations as well as smaller clinical studies both with positive or negative results [3, 11–13], a larger monocentric trial had demonstrated not only significantly decreased postoperative cardiac troponin concentrations but also a significant reduction of all-cause mortality and MACCE rates as secondary end points with intermediate time follow-up [23]. This indicated less myocardial damage following RIPC with repetitive left upper arm ischemia/reperfusion following coronary artery bypass graft (CABG) surgery under isoflurane anaesthesia. Recently, however, two large multicenter studies, the RIPHeart and ERRICA trials, failed to show any positive effects on troponin concentrations and clinical end points, including mortality [4, 16]. This resembles the situation with ischaemic preconditioning by intermittent coronary artery occlusion which never became a clinical routine [7], and leaves behind in reasonable frustration and disappointment both RIPC investigators and their clinician audience.

Accordingly, it is clear now that RIPC is not an all purpose, easily implemented magic drink protecting all cardiac surgical patients and ensuring their longevity like a sip from the Holy Grail. In fact, the area under the curve of postoperative troponin concentrations, while likely reflecting cardiomyocyte injury during aortic cross-clamping and subsequent reperfusion, is unlikely to strictly mirror clinical benefits for a patient and the mechanisms reflecting regional cardiac ischaemia/reperfusion in the awake state, such as during coronary stent interventions. However, it is premature to drop the final curtain in the RIPC theater. Rather, do not stop the music for a variety of reasons.

First, let us not forget that the ultimate goal of RIPC research is not so much the efficacy of organ protection by simply blowing up blood pressure cuffs, perhaps giving physicians a less technical face and a long missed touch to treat by more natural means. Rather, we are only ready for prime time when the unique molecular downstream mechanism(s) of RIPC and their pathways have been solidly identified. Only then will we be able to mimic RIPC pharmacologically and with greater efficacy, likely yielding broad clinical applications. While RIPC mechanisms have not yet been identified in detail and there is evidence for a variety of humoral and neural pathways [1, 6–8, 19], scientific troops are bulleyeing this target closer and closer, effectively encircling potential mechanisms down to the mitochondria. Accordingly, there still is hope for a magic pill or injection, e.g., mitochondrial potassium channel agonists, so stay tuned and listen to the music.

Second, there is reason to look critically at the recent clinical trials and their potential confounders. To this end, it now appears obvious and is widely discussed [8, 11, 12, 14, 24] that anaesthetics may have played a major role in RIPC trial results that address cardiac surgical patients. Currently, RIPC and anaesthetic action in cardiac surgery resembles a (yet) unhappy marriage unable to be divorced.

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On a descriptive level, the first large monocentric trial [23] on RIPC in coronary artery bypass patients had excluded not only diabetics but had relied on isoflurane/sufentanil anaesthesia before, during, and after aortic cross-clamping, i.e., before myocardial ischaemia ensued but also during and after cardiac reperfusion. Technically, this approach requires a dedicated calibrated anaesthetic vaporizer incorporated into the heart–lung-machine oxygenator's gas supply. While this anaesthetic technique stood the test of time for some 60+ years, in many countries, it is now a hassle in terms of certification, maintenance costs, and regulatory affairs that may have led many hospitals to switch to propofol-based intravenous anaesthesia. In fact, and in contrast to the initial trial published in THE LANCET [23], the overwhelming share of patients in the RIPHeart [16] and ERICCA trials [4] had received the intravenous anaesthetic propofol, at least at some points during anaesthesia and surgery, rather than isoflurane or another volatile anaesthetic.

Since a smaller study in coronary artery bypass patients found significantly decreased postoperative cardiac troponin concentrations with RIPC under isoflurane but not under propofol-based anaesthesia, propofol may well interfere with RIPC mechanisms [11, 12].

Furthermore, in diabetics treated with sulfonylurea drugs and anaesthetized by isoflurane anaesthesia, RIPC failed to decrease postoperative cardiac troponin concentrations, whereas RIPC decreased troponin concentrations in non-diabetics [13]. The RIPHeart and ERRICA trials [4, 16] did not exclude diabetics, and this may also explain the apparent absence of RIPC effects in the latter study.

Also, in our positive monocentric RIPC trial [23], we used for the RIPC procedure repetitive ischaemia/reperfusion only of the left arm whereas, apparently, cuff inflation had been randomly switched between the right and left arms in the RIPheart and ERRICA trials [4, 16]. Since it is mainly the left postganglionic sympathetic efferents that project to the left ventricular myocardium and different nerves projecting to the heart can have different regional efferent cardiac effects [2, 5, 9, 17, 20], repetitive left or right arm ischaemia as a tool for RIPC could well have different effects on the heart, if sympathetically mediated mechanisms for cardioprotection by RIPC exist. Thus, apparently minor details of trial design may well have influenced their results. Therefore, further trials addressing these issues are both welcome and required. Accordingly, do not stop the music!

Fourth, whereas our initial trial [23] included only non-diabetic CABG patients undergoing isoflurane/opioid anaesthesia, the RIPHeart and ERRICA trials [4, 16] also included many patients with long-standing valve disease that besides coronary artery surgery also underwent valve surgery with various techniques of cardioplegia.

Fifth, a post hoc analysis of CABG patients undergoing RIPC suggests that decreased troponin release was likely to be evoked by RIPC only if aortic cross-clamp time exceeded 57 min [10]. Thus, while beneficial RIPC effects may not be revealed (and possibly may not be clinically required) with rapid CABG surgery, any beneficial RIPC effects may only become important with more prolonged surgery and, hence, longer aortic cross-clamping. Candidly speaking, a slow surgeon would need RIPC, whereas a fast surgeon deserves it. In any case, given this outlined potpourri of patient cohorts, anaesthetics, and other techniques, its no miracle that no clear cut results have emerged. Therefore, more music is required to understand the tune.

Volatile anaesthetics have genuine cardioprotective aspects independent of RIPC and decrease infarct size after an index ischemia in isolated hearts as well as in animals anaesthetized with other agents. These effects have been labeled "anaesthetic preconditioning" and "anaesthetic postconditioning" when applied before myocardial ischaemia or upon reperfusion, respectively. That patients undergoing cardiac surgery fare better when receiving a volatile anaesthetic-based regimen, and that this may have added effects on top of RIPC has been suggested by meta-analyses [14, 24, 25]. This also raises questions.

First, whatever the mechanisms of RIPC in humans, can RIPC and volatile anaesthetics add up to provide better cardioprotection than either RIPC or volative anaesthetics alone? Conversely, can anaesthetics and propofol in particular mitigate or abolish any potentially beneficial effects of RIPC? Does any of these anaesthetic regimens alter signal transduction differentially, e.g., depending on their effects on nitrite generation [19], effects on microRNAs [15] and other epigenetic mechanisms, cardiomyocyte mitochondrial potassium channels, mitochondrial DNA [18] or even the individual mitochondrial genome [21, 22]? Obviously, an unequivocal answer to these questions is difficult to achieve in humans.

At a minimum, a randomized, prospective study comparing RIPC and no-RIPC in patients receiving either propofol/opioid or volatile anaesthetic/opioid-based anaesthesia is urgently required. Since anaesthesia and RIPC are a (yet) unhappy marriage, unable in principle to ever be divorced, it is prudent, therefore, to select the optimum matching partners both in terms of anaesthetic drugs/RIPC maneuvers used and their respective dosages.

Second, even more efforts are required to study RIPC mechanisms and their signal transduction in humans. If anaesthetics and RIPCS share downstream mechanisms in cardiomyocytes as well as other body systems, study of their interaction may well provide critical insight translatable into the clinics.

Therefore, let us not be discouraged by the negative results of the RIPHeart and ERRICA studies. Rather, see their weaknesses as a chance and potential to learn. In any case, RIPC in humans is important to gain molecular insights. Accordingly, despite a (yet) unhappy marriage, do not stop the music.

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