INVITED EDITORIAL

Remote ischemic preconditioning in cardiac surgery: caught between clinical relevance and statistical significance?

Matthias Thielmann

Remote ischemic preconditioning (RIPC), which consists of brief episodes of ischemia/reperfusion of remote organs, has been convincingly demonstrated to protect the heart from myocardial infarction [3, 9, 16, 26]. RIPC also protects other organs such as brain, lung, liver, and kidney [1, 2, 4, 11, 19, 24, 25]. Recently, RIPC has been brought from the bench to the operating theater. It has been shown in several randomized controlled trials (RCTs) that RIPC attenuates the extent of myocardial injury, as measured by a reduced release of biomarkers reflecting myocardial injury, in various cardiac and vascular surgery scenarios such as abdominal aortic surgery [1], congenital cardiac surgery [4], adult heart valve surgery [14] and coronary artery bypass grafting (CABG) [7, 10, 22].

Since a direct link has been established between the extent of perioperative myocardial injury after cardiac surgery and postoperative morbidity and mortality in the short and long term [5, 6, 23], RIPC could represent a promising, new and simple strategy, which could be easily implemented into daily practice without apparent risks, to provide additional protection to the myocardium and improve postoperative myocardial function, and thus favorably impact patient outcomes. This would be particularly useful in light of the increasingly challenging risk profiles of patients referred to cardiac surgery.

While some recent RCTs demonstrate the efficacy of transient upper limb ischemic preconditioning to beneficially impact on postoperative outcomes after CABG surgery with significant reduction of cardiac troponin (I and T) serum concentrations [7, 22], others clearly failed to achieve statistically significant differences, and report no benefit with RIPC despite apparently comparable conditions [12, 15, 18]. These apparent inconsistencies may be due to differences in the design and application of study protocols, which may include inconsistencies in potentially confounding co-morbidities [8, 21], differing inherent protective potential of anesthetic regimens used [17], and variation in the surgical procedures, techniques and protection regimens included. Consistent and conclusive interpretation of available data, which are mostly derived from smaller single-center trials, is additionally made more difficult due to the variation in study endpoints used. These are mostly surrogate parameters which are well known to vary widely, such as markers of myocardial necrosis and/or renal injury, postoperative inotropic support and ventilation time, as well as length of ICU and hospital stay. Currently, there are insufficient data from RCTs to clearly determine whether RIPC before cardiac surgery has an impact not only on these surrogate parameters but also on more robust endpoints such as short- and long-term morbidity and mortality. Fortunately, elective CABG surgery is nowadays a highly standardized procedure, and usually the incidence of major adverse clinical events, particularly in the elective and lower risk profile group, is rather low. Ironically, this means that RIPC is mostly investigated under conditions where it may not exert clinically discernible, relevant effects. There are two primary approaches possible in order

M. Thielmann (✉)
Department of Thoracic and Cardiovascular Surgery,
West-German Heart Center Essen, University Hospital Essen,
Hufelandstraße 55, 45122 Essen, Germany
e-mail: matthias.thielmann@uni-due.de

to increase the likelihood of obtaining statistically significant results from such prospective RCTs. Firstly, by increasing the number of individuals included, or secondly, by selection of individuals with a higher risk profile, to increase the anticipated incidence of clinical events or study endpoints. For this reason, a RCT analyzing the efficacy of RIPC in a 'high-risk' group would be of major importance in establishing the clinical significance of RIPC in cardiac surgery.

The current paper by Young et al. [27] published in the present issue of *Basic Research in Cardiology* presents another negative result arising from a small-scale prospective randomized controlled double-blinded trial, which aimed to analyze the efficacy of RIPC in 'high-risk' adult cardiac surgery with cardiopulmonary bypass. A total of 96 patients (48 in each group) were randomized in a double-blinded 1:1 fashion to receive either a RIPC protocol (applied to an upper limb and inflated to 200 mmHg for 5 min, followed by 5 min of deflation) or to serve as control. Plasma concentrations of high-sensitive troponin T at 6 and 12 h after surgery, as well as the postoperative incidence of acute kidney injury were used as primary study endpoints. Results showed higher *hs*TNT plasma concentrations at 6 and 12 h in the RIPC group. After adjustment for baseline confounders, the difference was found not to be statistically significant at 6 h, but remained significant at 12 h. The incidence of postoperative renal injury did not differ between the two groups. The duration of postoperative noradrenaline support was also increased in the RIPC group. There was no difference between the two groups in ICU-support requirements. The authors concluded that RIPC provided neither myocardial nor renal protection, and that RIPC may in fact worsen postoperative outcomes after 'high-risk' cardiac surgery.

Although the ambitiousness of the authors' randomized controlled study in a smaller cardiac surgical unit at Wellington Regional Hospital is to be credited, their methodology may also reveal why results obtained with some RIPC trials have led to increased confusion, rather than shedding light on the role of RIPC in the clinical practice of cardiac surgery.

Of particular importance before conducting such an ambitious RCT is to define what is meant by 'high-risk' cardiac surgery. 'High-risk' could refer to anticipated complex surgery, with or without intraoperative complications related to prolonged myocardial ischemic time. Equally, it could refer to cases where the surgical trauma is likely to be more extensive, such as in cases of concomitant or redo surgery. 'High-risk' could also refer to the patient, rather than the surgery, who may present an increased risk for perioperative myocardial injury, e.g. due to highly impaired left ventricular ejection fraction or due to a more extensive ischemic heart disease. Unfortunately, all of

these definitions were combined in the study by Young et al. [27].

Of at least equal importance is the that, despite the well-known role of anesthetics in mediating preconditioning on their own, anesthetic regimes are hardly standardized in RIPC trials and information on their use, if any, is often limited to a few words. In the present study, Young et al. used midazolam and fentanyl for induction, but propofol infusion and isoflurane for maintenance of anesthesia during surgery on cardiopulmonary bypass, and hence during myocardial reperfusion as well as for the remainder of surgery. Since RIPC has different effects depending on the background anesthetics, it may make a difference whether propofol or volatile anesthetics are used at induction, during cardiopulmonary bypass, before aortic cross-clamping and/or reperfusion, or in relation to the timing of RIPC. Recent data from our group [13] clearly indicate that the use of RIPC under isoflurane anesthesia, but not under propofol anesthesia, decreased myocardial injury in patients undergoing CABG surgery with cardiopulmonary bypass.

On top of that, in the present study Young et al. include a wide variety of surgical patients, techniques and procedures. Examples of inconsistencies include the inclusion of both cross-clamp and fibrillation cardiac arrest as well as cardioplegic arrest; patients with and without diabetes, with some taking sulfonylurea therapy; and the inclusion of more than 10 different combinations of cardiac surgical procedures, for which the postoperative cardiac troponin concentrations are known to vary widely [20]. This is also reflected by the broad interquartile ranges of several outcome variables in the present paper. Therefore, it is not surprising that a statistical power calculation is lacking because of lack of knowledge about the expected benefits, if any. In spite of including such a heterogeneous patient cohort, the present study seems to be statistically highly underpowered by including only 48 patients (undergoing 11 different surgical procedures) in each group. Moreover, it is obvious that incomplete correction and improper risk adjustment for important confounding variables, although not statistically significant, is present between the two groups.

With regards to the analyzed outcome measures, it is well known that cardiac troponin (I and T) serum concentrations, particularly when myocardial injury is more extensive such as in complex cardiac surgery, rise slowly, with a maximum value reached at least 24 h postoperatively. The time points chosen for troponin measurement in the present study, only 6 and 12 h after surgery, are therefore far too short to identify any significant differences in the postoperative cardiac troponin release, and therefore are clearly failing to compare postoperative myocardial injury within this heterogeneous 'high-risk'

group of patients. It would have been essential to measure and analyze postoperative troponin serum concentrations for at least 24 h (preferably 24, 36 and 48 h) after surgery, and to calculate the area under the troponin curve, for a proper and more precise comparison of postoperative myocardial injury between the two groups.

In conclusion, the present study included 'high-risk' cardiac surgery procedures and/or 'high-risk' patients with many differences in baseline characteristics, co-medication, and type of surgery. By only focusing on 6- and 12-h troponin measurements, the primary study endpoint in this setting does not hit the bull's eye. Improper retrospective adjusting for all of these differences cannot compensate for inadequate sample sizing, and therefore the present study by Young et al. can be described as an explorative study at best.

Conflict of interest None.

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