Remote Ischemic Preconditioning
No Loss in Clinical Translation

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Cardioprotective and Prognostic Effects of Remote Ischemic Preconditioning in Patients Undergoing Coronary Artery Bypass Surgery: A Single-Center Randomized, Double-Blind Trial
Thielmann et al

During the past 3 decades, several experimental studies have shown that ischemic conditioning reduces myocardial damage by modifying ischemia-reperfusion injury. A recent study in the Lancet indicates that remote ischemic preconditioning translates into clinical benefit in patients undergoing coronary artery bypass surgery. The implications of the study extend to patients undergoing elective and acute coronary angioplasty and beyond.

Adjunctive therapies to reduce myocardial ischemia-reperfusion injury related to cardiac surgery and percutaneous coronary interventions have yet to find their way into clinical practice, mainly because no pharmacological or mechanical cardioprotective strategy has convincingly shown clinically relevant benefit to the patient. That may be about to change. In a recent study by Thielmann et al, 329 low-risk patients undergoing elective isolated on-pump first-time coronary artery bypass grafting (CABG) were randomized to either standard CABG or CABG preceded by remote ischemic preconditioning (RIPC), achieved by 3 cycles of 5-minute upper limb ischemia through inflation of a blood pressure cuff followed by 5-minute deflation. The results indicate that RIPC confers a prognostic benefit to the patient.

The study was conducted as a single-center, double-blind, randomized, controlled trial. The primary end point was perioperative myocardial injury assessed by troponin I release measured at 6, 12, 24, 48, and 72 hours after surgery. The secondary end points comprised all-cause mortality, major adverse cardiac and cerebrovascular events (MACCE), and repeat revascularization at 30 days, 1 year, and at completion of follow-up, ranging from 1 to >4 years with a mean of 1.54 years. The group demographics were well-matched, and there were no significant differences in baseline risk factors.

The authors demonstrated acutely reduced myocardial injury (assessed by troponin I release), as also shown previously by others but, in addition, they also found a reduction in all-cause and cardiac mortality, as well as MACCE in the intervention group during the follow-up period. During the follow-up period, MACCE occurred 23 times in the control group versus 8 times in the RIPC group (P=0.011). The authors observed 11 deaths in the control group and only 3 deaths in the RIPC group (P=0.046). The combined end point (death, MACCE, and repeat revascularization) exhibited a hazard ratio of 0.38 (0.21–0.70) in favor of RIPC. There was no difference between groups regarding the need for revascularization.

The present study is noteworthy because it is the first to show that the reduction in surrogate end points in patients treated with RIPC before CABG translates into clinical benefit. Although several trials have investigated the effect of RIPC in the context of CABG and a recent meta-analysis of these trials indicates that RIPC reduces troponin release in these patients, there is continued skepticism regarding the clinical efficacy of RIPC. In contrast to earlier studies, Thielmann et al conducted a detailed follow-up analysis on clinical end points, albeit these were secondary outcomes in the trial design. Event rates were low because a low-risk population was investigated. Nevertheless, the results prompt optimism about the potential clinical value of RIPC as a cardioprotective strategy. Interestingly, Thielmann et al also found that RIPC reduced the occurrence of sepsis, stroke, and noncardiac deaths, which adds to the speculation that RIPC could confer systemic beneficial effects beyond the organ exposed to ischemia-reperfusion injury.

The work of Thielmann et al is not a stand-alone study. A more recent and larger study by Hong et al did not show any clinical benefit of RIPC combined with remote ischemic post-conditioning in 1280 patients undergoing CABG. The primary end point was a much broader composite of major adverse outcomes than in the study of Thielmann et al and included death, myocardial infarction, arrhythmia, stroke, coma, renal failure or dysfunction, respiratory failure, cardiogenic shock, gastrointestinal complication, and multiorgan failure. Furthermore, the anesthetic regimen included propofol in all patients. Propofol has been shown to interfere with the activation of the signal transducer and activator of transcription 5 (STAT5) pathway and to abrogate the cardioprotection afforded by RIPC in patients undergoing CABG surgery. Finally, the release of myocardial biomarkers was not measured to document a cardioprotective effect. Therefore, the differences in the outcomes of the trials are most likely explained by the consequent use of propofol in the latter. Unfortunately, the lack of biomarker assessment in the trial by Hong et al makes it unclear whether any biological effect was evoked by the RIPC treatment.

Two other important studies supporting the clinical effect of RIPC have recently been published. Davies et al investigated...
the long-term clinical outcomes of 192 patients undergoing elective coronary angioplasty randomized to RIPC or standard treatment. Although their original study showed a significant reduction in troponin release in the RIPC group,\(^{10}\) the follow-up study revealed that this translated into a reduced MACCE rate ≤6 years after the coronary intervention.\(^{11}\) Most recently, Sloth et al\(^{12}\) added further support by demonstrating that the increase in myocardial salvage by remote ischemic conditioning performed in the ambulance during transportation to primary angioplasty also translates into a 35% reduction of MACCE and 52% reduction of all-cause mortality among 333 patients followed-up for up to 4 years after ST-segment elevation myocardial infarction.\(^{13}\)

Although both the original trial and the follow-up analysis by Thielmann et al\(^{2}\) were properly conducted, some limitations remain. The scientific methodology is described clearly and the data quality is sound, with complete follow-up. However, as expected in this population, the event rates are low and, hence, absolute differences in specific event rates are rather small. Although it is the largest study to date to simultaneously document cardioprotection and prognostic benefit, the trial is in fact not sufficiently sized for comparing clinical outcomes. The difference in MACCE and mortality between groups seems real, but the early clinical effects have not been observed in other trials\(^{4,14}\) and require confirmation in large-scale trials.

As in the study by Hong et al,\(^{7}\) an important detail in the present study is the anesthetic regimens used. Propofol was used in 47 RIPC and 32 control patients. Hence, the effect of RIPC may have been even larger if propofol had not been used.\(^{9}\)

The study by Thielmann et al\(^{2}\) and the studies by Davies et al\(^{11}\) and Sloth et al\(^{12}\) share the same limitations of being single-center trials, which are not optimally powered to demonstrate definitive answers about clinical outcome. This is legitimate in the light of the significant improvement in primary outcome in as much as clinical outcome was a prespecified secondary end point. The consistency of the beneficial clinical outcome in all 3 studies adds significant credibility to the clinically relevant beneficial effects of remote ischemic conditioning in relation to cardiac surgery and coronary angioplasty.

The biological effects of RIPC are supported by strong experimental evidence. The organ protection is at least partially mediated by release of endogenous substances into the bloodstream because plasma from RIPC-treated humans is cardioprotective. The same plasma can be dialyzed, and the dialysate applied to a virgin heart achieves cardioprotection equal in strength to cardioprotection in the RIPC-treated animal.\(^{15,16}\) The exact nature of the circulating cardioprotective factors released by RIPC remains unknown. RIPC by transient limb ischemia is dependent on intact neural pathways\(^{17}\) and nitric oxide–sensitive nerve stimulation to release bloodborne, hydrophobic, and small (molecular mass <15 kDa) circulating factor(s)\(^{18-20}\) modify the prosurvival kinase phosphatidylinositol 3-kinase (PI3K)-Akt and the mitogen-activated protein kinase p44/p42 extracellular signal-regulated kinase (ERK)1/2, glycogen-synthase kinase GSK-3β\(^ {21}\) and STAT5 signaling\(^ {22}\) and finally converge at the mitochondrial level to prevent mitochondrial permeability transition pore opening in early reperfusion (Figure).

The exciting findings by Thielmann et al\(^{2}\) and the supporting evidence recently published by other groups add to the increasing, albeit still incomplete, mechanistic insight and strongly suggest that RIPC can be translated into an improvement of clinical outcome. The reduction in noncardiac complications suggests that RIPC, unlike local conditioning, may have more widespread effects not only limited to the heart but also useful as an adjunct for thrombolysis in the treatment of stroke\(^ {23}\) and for prevention of contrast medium-induced nephropathy.\(^ {24}\)

**Figure.** Potential mechanisms underlying the effect of remote ischemic conditioning. IS indicates infarct size; and mPTP, mitochondrial permeability transition pore.
Although the recent evidence of beneficial clinical effects of RIPC is highly promising, it is important to stress that properly sized studies with clinical end points, such as the “Effect of Remote Ischaemic Preconditioning on Clinical Outcomes in CABG Surgery trial” (ERICCA) (ClinicalTrials.gov NCT01247545), the “Remote Ischaemic Preconditioning for Heart Surgery trial” (RIPHeart Study) (ClinicalTrials.gov NCT01067703), and the “Effect of Remote Ischemic Conditioning on Clinical Outcomes in ST-elevation Myocardial Infarct Patients Undergoing Primary PCI trial” (CONDI 2)(ClinicalTrials.gov NCT01857414), are needed to confirm the clinical effect before RIPC is applied as standard adjunctive therapy in patients.

Disclosures

None.

References

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