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Review

Remote ischaemic preconditioning as a method for perioperative cardioprotection: Concepts, applications and future directions

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HIGHLIGHTS

- Remote ischaemic preconditioning (RIPC) may reduce perioperative risk.
- Its mechanism is thought to involve neural and humoural elements.
- Multiple proof of concept studies has shown benefits in a range of interventions.
- Convincing benefits regarding patient important outcomes are lacking.
- Results from large-scale clinical trials are awaited.

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ABSTRACT

Remote ischaemic preconditioning (RIPC) is a phenomenon whereby brief episodes of non-lethal ischaemia in one organ or tissue can render a distant organ or tissue resistant to subsequent longer ischaemic insults. It represents an exciting perioperative risk reduction strategy as it allows cardioprotection (and organ protection in general) from injuries that are caused by multiple mechanisms. Several proof of concept studies show benefits in cardiovascular interventions and in a variety of other procedures. However convincing and consistent evidence of benefits in patient important outcomes is lacking but may emerge with the completion of large scale studies. This article aims to provide a concise review of the origins and concepts of RIPC. It will revisit the biological theories of RIPC and the clinical applications thus far. The article concludes by discussing the current status of multi-centre cardiovascular RIPC research and the future challenges that investigators must overcome.

1. Introduction to ischaemic preconditioning and remote ischaemic preconditioning

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide and its prevalence is increasing [1]. There is increased perioperative risk when patients have CAD [2] and furthermore the risk profile of those who are undergoing coronary surgery is worsening [3]. Given that an estimated 234 million surgical procedures are performed annually worldwide [4], the global burden of perioperative cardiac disease is increasing and therefore it is crucial that efforts are made to reduce perioperative risk for those with CAD.

Cardioprotection refers to a wide range of strategies that aim to reduce perioperative cardiac risk. The common goal of cardioprotective techniques is the initiation of endogenous mechanisms that can reduce the effects of myocardial ischaemia-reperfusion injury [5]. To date, several strategies have been used to reduce perioperative cardiac risk in humans: risk assessment, prophylactic revascularisation, pharmacological cardioprotection and myocardial conditioning techniques. Myocardial conditioning is a broad concept that refers to both direct and remote ischaemic preconditioning, perconditioning and post conditioning. Unfortunately, not all of these risk reduction strategies have had success. Perioperative cardiac risk assessment is theoretically attractive as it identifies patients who need optimisation of comorbidities prior to elective surgery but hard evidence of its effectiveness is lacking [6].

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Pharmacological methods of inducing cardioprotection have been disappointing [5] with the exception of using beta blockade for high risk procedures [2]. Prophylactic coronary revascularisation was shown to be often ineffective [7–10] and is only occasionally recommended [11,12]. However, there have been convincing preliminary results in relation to some of myocardial conditioning techniques.

Ischaemic preconditioning (IPC) is a phenomenon whereby brief periods of ischaemia in an organ or tissue can confer resistance against subsequent more sustained ischaemic insults [13]. This counterintuitive idea was first demonstrated in a canine model in 1986 – Murry et al. found that, following sustained coronary occlusion, myocardial infarcts were smaller in dogs that had been preconditioned when compared with dogs who did not undergo preconditioning [14]. The preconditioning stimulus used was a series of intermittent short duration coronary occlusions. Since then, there have been several proof of concept trials of IPC in human cardiothoracic surgery and meta-analysis has found evidence of benefits in terms of reductions in arrhythmia rates, inotrope requirements and intensive care unit length of stay [15]. Evidence is lacking regarding the effects of IPC on harder clinical outcomes such as MI and mortality rates. Unfortunately, as IPC involves directly interfering with coronary blood flow (giving rise to ischaemia and the possibility of causing plaque rupture), the potential for widespread use is limited – its only practical role is likely to remain in elective cardiac surgery or elective percutaneous coronary intervention (PCI).

Subsequently, evidence confirmed that episodic intermittent ischaemia of distant tissues can induce cardioprotection – this became known as remote ischaemic preconditioning (RIPC). It was first demonstrated in 1993 when Przyklenk et al. showed that applying a preconditioning stimulus to the circumflex coronary artery in dogs resulted in smaller infarcts in the left anterior descending coronary artery (LAD) distribution following LAD occlusion [16]. Consequent studies found that animal skeletal muscle [17,18], renal [19] and mesenteric [20] ischaemia had attenuating effects on induced myocardial infarct sizes and that tourniquet induced leg ischaemia reduced reperfusion arrhythmias [21]. In humans, it is unlikely that transient renal or mesenteric ischaemia can become a viable cardioprotective mechanism due to the risks inherent in the application of the stimulus. However, as tourniquet induced limb ischaemia has an attractive risk profile, there have been multiple small trials in humans undergoing major cardiovascular surgery and PCI using cuff induced limb ischaemia as the preconditioning stimulus. Meta-analyses of these trials have consistently shown biochemical evidence of reduced myocardial injury although firm clinical outcomes data are lacking [22–29]. Notable a recent meta-analysis on RIPC in PCI found a benefit in terms of reduced incidence of periprocedural myocardial infarction [30]. The remainder of this article focuses on the underlying mechanisms of RIPC, its current status and uncertainties and views on future RIPC research directions.

2. Methods used in this review

Literature published in English from 1st January 1986 to 30th January 2014 on ischaemic preconditioning and remote ischaemic preconditioning in surgery was obtained by electronic search of Medline. The search strategy: ([ischaemic preconditioning OR ischaemic preconditioning OR remote ischaemic preconditioning OR remote ischaemic preconditioning] AND surgery) yielded 2742 studies. Relevant studies were examined by 1 author (DH) and additional articles were identified by cross-referencing and citation mapping. This literature obtained formed the basis of the article.

3. Underlying mechanisms of RIPC

Despite compelling evidence of reduced infarct sizes in animal models and reduced biochemical evidence of myocardial injury in humans, the exact mechanism underlying cardioprotection via RIPC remains unclear. Several theories exist although none of these has been fully accepted – it is likely that no single mechanism is uniquely responsible but rather that several complementary pathways exist [13]. Proposed mechanistic components are initiation via a trigger at the site of the ischaemic stimulus, communication between the remote site and the myocardium and lastly the induction of cardioprotection at the heart (Fig. 1) [31]. Evidence suggests that IPC, RIPC and the postconditioning techniques share common mechanistic components [13,31].

Proposed remote trigger molecules include adenosine, bradykinin, opioids, endocannabinoids and others while the final effect is thought to culminate in a strong cardioprotective and antiapoptotic response in the heart [13,31]. Evidence implicates prevention of opening of the mitochondrial permeability transition pore (mPTP) in the final antiapoptotic step – opening of the mPTP during myocardial reperfusion is thought to initiate programmed cell death via cellular energy depletion [32]. Pharmacologically preventing mPTP closure has been shown to dramatically reduce infarct size in animal studies [32] and in humans mPTP closure inhibition with ciclosporin was shown to reduce infarct size in a small study [33].

Neural, humoural and systemic communication theories have been suggested [13]. The neural hypothesis proposes that remote neurotransmitter release activates a neural link to the myocardium. Support for this comes from studies that found that the ganglion blocker hexamethonium attenuated the preconditioning effect [20,34]. The humoural hypothesis suggests that circulating cardioprotective factors are released during remote site reperfusion and subsequently act on the myocardium – studies have shown that a preconditioning effect can be transferred via a blood transfusion to a non-preconditioned animal [35–37]. The final theory proposes that preconditioning can induce a systemic anti-inflammatory response with alteration of gene expression [13].

Overall, though progress in identifying mechanistic components has been slow, it is important that efforts to identify the mechanisms continue – it may be possible to target these pathways pharmacologically. Furthermore, more biological knowledge would help researchers optimise the physical preconditioning stimulus and clarify other areas where uncertainty exists.

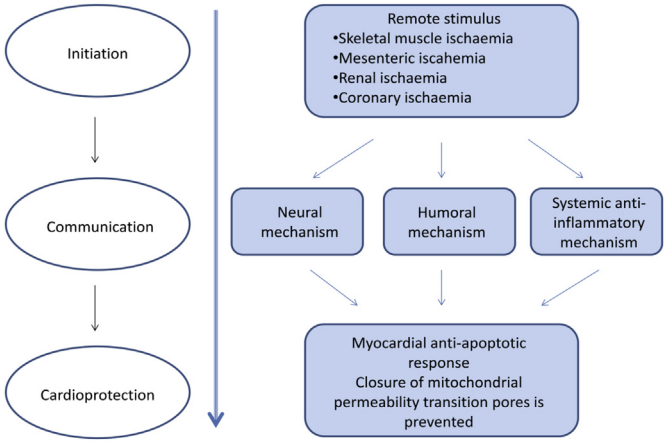

Fig. 1. Proposed mechanisms of remote ischaemic preconditioning.

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4. Overview of the applications of RIPC in interventions on humans

At this stage, much of the experimentation in humans has been explanatory and has aimed to demonstrate "proof of concept" rather than practicality. In general, numbers of included patients have been small and there has been a focus on biochemical outcomes rather than patient important outcomes. There is uncertainty relating to many methodological issues and as further studies emerge it is likely that it will be possible to determine the optimal approaches, thereby allowing future multi-centre evaluation with a focus on clinical outcomes. With further research and increasing sample sizes, it is likely that a measure of the true effect of RIPC on clinical outcomes will emerge.

5. RIPC in human cardiac surgery, percutaneous coronary intervention and major vascular surgery

Clinical trials have evaluated RIPC in coronary artery bypass graft (CABG) surgery [38–53], cardiac valvular surgery [53–56] and congenital cardiac defect surgery in children [57–63]. Cardiac surgery has seen considerably more proof of concept studies than any other type of intervention; it is likely that several factors account for this. Firstly, it is probably a reflection of the fact that most cardiac surgery is performed electively and is therefore suitable for RIPC. Secondly, research on cardioprotection and initial IPC research were dominated by cardiothoracic surgery and this translated to interest in RIPC. A final reason for the dominance of cardiac surgery in RIPC research is that induced myocardial ischaemia is often an integral component of cardiac surgery and this makes cardioprotective strategies attractive.

Most of the cardiac surgery studies used cardiac injury biomarkers as primary outcomes and pooling these results via meta-analysis has confirmed a statistically significant benefit at cardiac biomarker level. This biomarker reduction is both consistent and plausible. As there is mounting evidence for the prognostic significance of isolated cardiac biomarker elevations [64], it is likely that RIPC may indeed have the ability to alter short and long term prognosis for patients undergoing cardiac surgery. However, at present the evidence for benefits in patient important outcomes is not convincing. Two meta-analyses that pooled cardiac surgery and PCI found statistical evidence of reduced MI rates with RIPC [25,29] but another review that excluded the PCI studies did not find this significance [23]. It is likely that a more refined measure of the true effect of RIPC will emerge as international studies with larger sample sizes are completed. Interestingly, evidence has also emerged suggesting that RIPC may reduce the incidence of acute kidney injury in patients undergoing cardiac surgery [44] – this further underlines the biological plausibility of achieving organ protection with RIPC.

Several studies have evaluated RIPC in emergency [65,66] and elective PCI [67–72]. The results are variable – some studies [65,66,68,70,71] found RIPC to be beneficial in terms of myocardial injury biomarker levels but other studies did not find such a benefit [67,69]. Surprisingly, one trial found RIPC to be associated with cardiac enzyme elevation although this trial had the limitation of a small sample size [69]. A study on RIPC in elective PCI found that RIPC was able to reduce the incidence of contrast induced acute kidney injury [72]. In relation to emergency PCI, a major challenge is timely administration of the RIPC stimulus in the setting of acute MI – one of the studies initiated RIPC during transit [65] and another initiated RIPC shortly before PCI commenced [66]. The trials have shown that this difficulty can be overcome and that benefits are likely to exist. A meta-analysis of RIPC in PCI found reduced incidence of periprocedural myocardial infarction there was notable clinical heterogeneity among the studies [30]. The challenge is to evaluate clinical outcomes in an adequately powered study. Long term clinical outcomes follow up data is available the CRISP Stent trial [73] – interestingly, RIPC was associated with a lower major adverse cardiac and cerebral event rate at 6 years.

Trials have also evaluated RIPC in the setting of major vascular surgery: open abdominal aortic aneurysm (AAA) repair [74–76], endovascular aneurysm repair (EVAR) [77] and carotid endarterectomy [78]. There were two AAA repair trials where iliac artery cross-clamping served as the preconditioning stimulus [74,75]. The larger of these [74] ($n = 82$) found a significant reduction in levels of cardiac troponin I, myocardial infarction rates and renal impairment rates with the RIPC intervention and the other study ($n = 40$) focused on biochemical markers of renal injury and could not confirm a benefit with RIPC [75]. 4 patients in the RIPC arm of this trial developed acute lower limb ischaemia requiring operative intervention – this has raised concerns about the suitability of iliac cross-clamping as the preconditioning stimulus. The third AAA RIPC study used the upper limb for the stimulus [76], considering the negative experiences with iliac cross clamping in the prior two studies. In this study ($n = 62$) RIPC reduced markers of pulmonary and intestinal injury and it also reduced markers of systemic inflammatory response but there was no difference in clinical outcomes. The study on EVAR procedures found biochemical evidence of reduced renal injury with RIPC but no difference in renal impairment or clinical outcomes [77]. Inflation of a cuff around the thigh served as the stimulus and there were no lower limb ischaemic events, which may suggest that non invasive lower limb arterial occlusion is better than arterial clamping. RIPC in carotid endarterectomy was also evaluated [78] using a thigh tourniquet (without lower limb adverse events) but without a demonstrable effect of RIPC on cardiac or neurological outcomes.

Overall, the trials in major cardiovascular surgery and PCI have had promising results. The feasibility of using RIPC in these groups has been established and the remaining challenge is to apply RIPC in larger studies with a focus on patient important outcomes. It appears as though upper limb tourniquet induced ischaemia might be the best approach for these patients given the likelihood of co-existing chronic occlusive lower limb arterial disease and the possibility for acute ischaemia when arteries are occluded via clamping.

6. RIPC in other types of intervention

Animal models have confirmed a neuroprotective role for RIPC and IPC – studies found that preconditioning rodents with leg ischaemia reduced stroke size following middle cerebral artery occlusion [79,80] and that direct rodent brain ischaemia was also protective [81,82]. However, there are few studies on such neuroprotection in humans. A non-significant benefit in preservation of saccadic latency (a measure of neurologic function) was shown with RIPC in the carotid endarterectomy study mentioned above [78]. A study evaluating the effect of RIPC on spinal cord ischaemia-reperfusion injury on patients undergoing cervical decompression procedures found that RIPC reduced levels of neurological injury biomarkers [83]. There is also some evidence for a protective effect of direct brain ischaemia in humans – during berry aneurysm clipping, episodic and short-lived direct brain ischaemia was shown to have a beneficial effect on local pH and blood oxygen content [84]. A study on carotid stenting found that episodes of neurological dysfunction induced by angioplasty balloon inflation did not recur following repeated inflations [85], giving further support to the idea that neuroprotection can be achieved via conditioning.

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RIPC has also been applied in plastic surgery. In reconstructive flap microsurgery, proof of concept studies confirmed that IPC and RIPC can reduce ischaemia-reperfusion injury and improve flap outcomes [86,87]. IPC was first shown to be effective in this area in 1992 [88] and multiple in vivo animal studies followed [86]. Limb ischaemia was shown to be as effective as direct flap ischaemia in further animal work that followed [89,90]. Although experimental data are promising, preconditioning has not achieved much clinical use in plastic surgery in humans to date; reasons for this are probably the increased operative time required and other practical difficulties. It follows that randomised clinical data are lacking and this is a target for the future.

In relation to liver surgery, IPC has been shown to reduce the severity of ischaemic injury in murine models of hepatic ischaemic [91,92]. However, clinical benefits of IPC in human hepatectomy surgery have not materialised. A Cochrane review of IPC in elective liver resections found no benefit with IPC other than reduced blood transfusion requirements [93]. Another review found no clinical benefit but found that IPC reduced liver injury biomarker level, a finding that is of uncertain significance [94]. Further high quality studies are needed in this area.

7. Ongoing trials

There are several ongoing multi-centre trials investigating RIPC in major cardiovascular surgery. We are hopeful that definitive evidence of benefits in clinical outcomes will emerge with the completion of these trials.

The Remote Ischaemic Preconditioning for Heart Surgery study (RIPHeart-Study) is a multi-centre clinical trial in Germany that is currently recruiting patients who are undergoing surgery with a need for cardiopulmonary bypass [95]. It aims to recruit 2070 adults including both high and low risk categories (high risk means Euroscore $\geq$5). The intervention comprises 4 cycles of 5 min of cuff induced upper limb ischaemia with 5 min of reperfusion between each inflation. Another key design feature is robust blinding of surgical and anaesthetic teams, data collectors, analysis teams and the endpoint committee. This is achieved with a sham arm – only the person applying the intervention knows the treatment allocation. Furthermore, a total intravenous anaesthetic regimen is being used to eliminate the potential preconditioning effect of volatile anaesthetics [96]. Cardiopulmonary bypass management in the trial is standardised [95]. The primary outcome is a composite of all-cause mortality, non-fatal myocardial infarction, any new stroke, and/or acute renal failure until hospital discharge (up to a maximum of 14 days after surgery). The expected control group primary event rate for this is estimated as 12% and the investigators think that RIPC might reduce the event rate to 8%.

The effect of remote ischaemic preconditioning on clinical outcomes in patients undergoing coronary artery bypass surgery (ERICCA) trial is a multi-centre trial in the United Kingdom that is currently recruiting high risk (Euroscore $\geq$5) patients who are undergoing coronary artery bypass graft surgery ± valve surgery [97]. The trial aims to recruit 1610 adults and it uses a similar RIPC intervention to the RIPHeart-Study. The blinding strategy in ERICCA is robust and uses an adjustable valve on the cuff rather than a sham arm. In contrast to the RIPHeart-Study, volatile anaesthetic agents may be used in ERICCA which will probably increase external validity although it may dilute the treatment effect. The primary outcome is a composite of cardiovascular death, non-fatal myocardial infarction, coronary revascularisation and stroke at one year. The control group event rate is predicted to be 20% and the RIPC group event rate is estimated to be 14.6%. The higher event rates reflect the exclusion of patients with Euroscore $\leq$5.

The Renal Protection Against Ischaemia Reperfusion in Transplantation (REPAIR) trial [98] is another multi-centre trial. It has completed recruitment (406 patients randomised) and published results are awaited. It aimed to determine the effect of RIPC on renal function after renal transplantation using estimated glomerular filtration rate (eGFR) at one year as the primary outcome. It also will report on some clinical outcomes at 2–5 years using registry follow up. There were 4 arms in the trial – control, early RIPC, late RIPC, combined early and late RIPC. Early RIPC was performed immediately pre-operatively and late RIPC was performed 24 h before operations. Dual RIPC involved both. The stimulus was 3 cycles of 5 min of cuff induced arm ischaemia with 5 min reperfusion and routine anaesthetic practices were used.

8. Uncertainties and unresolved questions

Though the potential of RIPC is great, there are many barriers that researchers must overcome. The unanswered questions largely fall into two categories: the mechanistic pathway and practical application issues.

We have examined theories on the biological basis for RIPC and IPC in a prior section of this article and it is clear that sustained research efforts are needed. Knowledge of the involved pathways would enhance and focus future applications of preconditioning and might enable pharmacological initiation of preconditioning cardioprotective pathways.

There are many methodological uncertainties for RIPC researchers and it is important that efforts are made to elucidate these in order to increase research efficiency and facilitate comparisons between studies. Firstly, the optimal preconditioning stimulus has not been established. While undoubtedly skeletal muscle is the most attractive tissue to use for the stimulus, there is uncertainty regarding the optimal duration and number of ischaemia-reperfusion cycles. Furthermore, both upper and lower limbs are options. Theoretically, the increased muscle bulk in the lower limb is advantageous – one cardiac surgery study found that RIPC induced by both leg and arm ischaemia reduced myocardial injury compared to the control group but that RIPC induced by arm ischaemia only did not reduce myocardial injury [56]. However there were acute ischaemic complications with invasive lower limb arterial occlusion in one of the vascular trials mentioned above [75]. To our knowledge, there have been no serious cuff related lower limb or upper limb RIPC complications. Nonetheless, it is probably reasonable for researchers to use the upper limb only as it is rarely affected by peripheral vascular disease (PVD) and has been successfully used in many clinical studies to date, establishing both feasibility and efficacy. In the absence of firm evidence, we propose that researchers use 3 or 4 cycles of 5 min ischaemia with 5 min reperfusion – there has been a tendency for negative results in a short stimulus time [51] and in studies that used 10 min ischaemic episodes [75,77,78].

There is also vagueness regarding the optimal target populations for intervention with RIPC. It is worth highlighting that RIPC induced protection is not absolute – prolonged ischaemia is always lethal and major insults are likely to surmount any cardioprotection. The challenge is to focus efforts on procedures with relatively cardiac high event rates as such patients will benefit maximally and such trials are likely to yield positive results at feasible sample sizes.

Lastly, it is important to reiterate that future studies on RIPC in major cardiovascular interventions should focus on patient important outcomes. In cardiovascular surgery, benefits in surrogate outcomes have been confirmed consistently by meta-analyses – the only way to advance is by shifting towards clinical outcomes where conclusions are less certain.

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9. Conclusion

RIPC is a novel, cost effective and widely available protective phenomenon that has the potential to reduce ischaemia reperfusion injury in major cardiovascular interventions and in many other procedures. Though knowledge gaps exist, particularly in relation to biological mechanisms and some methodological issues, RIPC research has advanced considerably over recent years. The main challenges for the future are to clarify the mechanistic pathways and to demonstrate tangible benefits in patient important outcomes.

Ethical approval

This is a narrative review therefore there was no requirement for ethical approval.

Role of the funding source

This work was performed without funding.

Author contribution

Donagh A Healy – design, literature search, data extraction, writing, revision and approval of the final draft.

Mary Clarke Moloney – design, writing, revision and approval of the final draft.

Seamus M McHugh – writing, revision and approval of the final draft.

Pierce A Grace – writing, revision and approval of the final draft.

Stewart R Walsh – design, writing, revision and approval of final draft.

Conflicts of interest statement

All authors report that there are no conflicts of interest, financial or otherwise.

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