International Journal of Surgery 12 (2014) 1093–1099

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

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 humoral elements.
- Multiple proof of concept studies have shown benefits in a range of interventions.
- Convincing benefits regarding patient important outcomes are lacking.
- Results from large-scale clinical trials are awaited.

ARTICLE INFO

Article history:
Received 30 January 2014
Accepted 11 August 2014
Available online 21 August 2014

Keywords:
Remote ischaemic preconditioning
Ischaemic preconditioning
Cardioprotection
Cardiac surgery
Percutaneous coronary intervention

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 postconditioning. 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 for its effectiveness is lacking

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http://dx.doi.org/10.1016/j.ijsu.2014.08.352
1743-9191/

[6]. 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 the 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]. Notably 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 ischemic preconditioning OR remote ischaemic preconditioning OR remote ischemic 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. The 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, humoral 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 humoral 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.

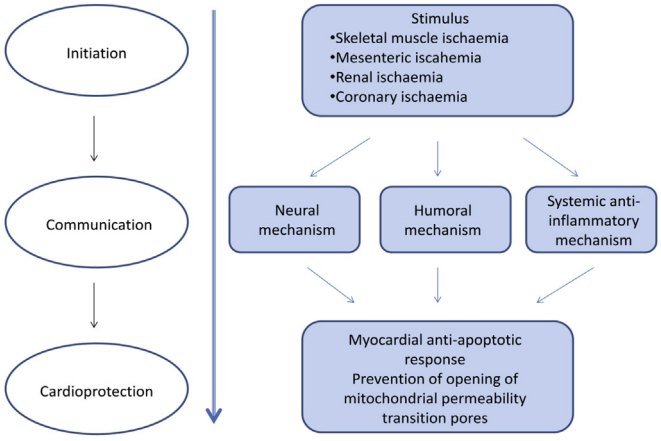

Fig. 1. Proposed mechanisms of remote ischaemic preconditioning.