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Repeat remote ischaemic pre-conditioning for improved cardiovascular function in humans: A systematic review

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ABSTRACT

Background: Single exposure to remote ischaemic pre-conditioning (RIPC) has been shown to be effective in reducing major adverse events during cardiac surgery. We evaluated the efficacy of repeated exposure RIPC to elicit improvements in cardiovascular function.
Methods: A systematic search was conducted up until May 1st, 2015, using the following databases: EMBASE, PubMed (Medline), Web of Science and the Cochrane Central Registry of Controlled Trials (CENTRAL). Data was extracted and synthesized from published studies of repeat RIPC.
Results: Data from seven studies showed evidence of improvements in vascular function and anti-hypertensive effects of systolic, diastolic and mean arterial blood pressure following repeat RIPC. Currently existing work justifies a systematic review but not data pooling of individual study data. Repeat RIPC has also produced evidence of improvements in endothelial dependent vasodilation, but not non-endothelial dependent vasodilation, cutaneous vascular conductance or cardiorespiratory fitness.
Conclusion: Repeated RIPC exposure has produced evidence of improvements in endothelial dependent vasodilation, ulcer healing and blood pressure but no benefit in non-endothelial dependent vasodilation, cutaneous vascular conductance or cardiorespiratory fitness. The optimal delivery of RIPC remains unclear, but at least 3 or preferably 4, 5 min exposures appears to be most beneficial, at least for reducing blood pressure. Aside from those undertaking cardiac surgery, other study populations with endothelial dysfunction may benefit from repeat exposure to RIPC.

1. Introduction

Remote ischaemic pre-conditioning (RIPC) relates to short sequences of ischaemia, usually 4–5 min, of repeated blood pressure cuff inflation and deflation on a limb. Short periods of ischaemia trigger cellular signalling pathways that protect against a subsequent longer period of ischaemia, such as during percutaneous coronary intervention (PCI). RIPC is an effective technique for protecting the heart against ischaemia reperfusion injury because short periods of ischaemia triggers cellular signalling pathways that protect against a subsequent longer period of ischaemia.

The RIPC process usually involves 3–4 cycles of 5 min of cuff inflation at 200 mm Hg, interspersed with 5 min of deflation, total exposure lasts about 35 min [1]. RIPC has become increasingly attractive because it is relatively simple to administer and is non-invasive and safe. Moreover RIPC can be administered during natural waiting periods as patients enter theatre for cardiac surgery. RIPC has been used in both upper and lower limbs and the primary use has offer cardio-protection for those undergoing percutaneous coronary revascularization [2]. RIPC has also been found to reduce acute kidney injury in those exposed to contrast media [3,4] and reduce, in acute cases, infarction size by administering RIPC during transport to the medical centre prior to cardiac surgery [5]. More recent work has examined the cumulative effects of repeated RIPC treatments to manage blood pressure [6], improve endothelial function and blood flow [7].

The effects of RIPC extend beyond the tissues exposed to cuff occlusion, with recent reports suggesting a neuroprotective effect that improves tolerance to cerebral ischaemia [8]. RIPC induces sustained neuroprotection attenuating adenosine 5′-monophosphate-activated protein kinase [9]. RIPC may therefore improve impaired cognitive function in those with known cardiovascular or metabolic disease [10]. The exact mechanism via which RIPC exerts benefits remains unknown but may be related to changes with the autonomic nervous system and diffusible factors [6].

Meta-analyses examined the benefits of a single exposure (3–4 cycles) to ischaemic pre-conditioning for people undertaking PCI, reductions in measures of myocardial infarct size and prevalence of acute kidney injury [11,12]. The benefits of single RIPC exposure appears however to be bi-phasic with a short initial window of protection in the first 12 h, followed by a period of no protection and finally a longer window of protection lasting as long as 72 h after exposure [6]. Recent work has therefore intuitively examined the potential benefits of

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repeated sessions of remote RIPC, administered over weeks or months, for improving several aspects of cardiovascular health. Repeated RIPC exposure serves possibly two purposes; first the 'topping up' of RIPC protection during the unprotected period; second, repeated RIPC may provide a cumulative protective effect that cannot be achieved with a single exposure. To date only a handful of studies of repeated sessions of remote RIPC exist and the primary outcome measures have been varied. The efficacy of this new approach therefore has yet to be fully explored.

The aims of this work were to conduct a systematic review, and where appropriate, meta-analysis, to (i) examine the effects of repeated exposure to bouts of remote RIPC on a range of cardiovascular health indicators; and (ii) relate the findings to established thresholds of clinical significance.

2. Methods

2.1. Search strategy

To identify potential studies, systematic searches were carried out using the following databases: EMBASE, PubMed (Medline), Web of Science and the Cochrane Central Registry of Controlled Trials (CENTRAL). The search was supplemented by scanning the reference lists of eligible studies. The search strategy included the key concepts of: *repeat remote ischaemic preconditioning*, *remote ischaemic conditioning*, *ischaemic preconditioning*, *physiological ischaemia training*, *limb occlusion and cuff inflation*. All identified papers were assessed independently by two reviewers. A third reviewer was consulted to resolve disputes. Searches of published papers were conducted up until January 7th, 2016.

2.2. Inclusion/exclusion criteria

Any trial designs of repeated, remote ischaemic pre-conditioning, of at least 7 days duration, were included. Study populations included were adults (>18 years) without known cardiac disease. There were no language restrictions. Animal studies and review papers were excluded. Studies that included participants who were treated by other pharmaceutical or surgical modalities such as coronary artery bypass grafting were excluded. Authors were contacted to be given the opportunity to provide missing data or to clarify if data was duplicated in multiple publications. Incomplete data, or data from an already included study, were excluded. Studies that included interventions other than repeat remote ischaemic pre-conditioning were excluded.

2.3. Participants/population

This systematic review analysed published studies of both male and female adults (≥18 years) with and without known coronary artery disease. Studies of non-repeat RIPC treatment modalities and interventions were excluded.

2.4. Intervention(s), exposure(s)

This systematic review considered all trials where participants were exposed to repeat, remote ischaemic pre-conditioning. More specifically all published trials where the intervention of expanding a blood pressure cuff or medical tourniquet in a remote limb was carried out on a repeated basis.

2.5. Comparator(s)/control

The systematic review and meta-analysis utilised studies that compared repeat remote ischaemic conditioning with control or repeated sham remote ischaemic conditioning.

2.6. Outcome(s)

The primary outcomes discussed will be:

1. Blood pressure.
2. Blood flow.
3. Endothelial progenitor Cell (EPC) concentrations.
4. Other benefits e.g. wound healing.

2.7. Search results

Initially 792 papers were identified by database searching, a further 20 potential papers were by scrutinizing reference lists of identified papers. Of the 812 papers found, 102 were review articles, 703 were not RIPC trials in humans. Only 7 human trials of repeat RIPC exposure were found.

2.8. Strategy for data synthesis

A descriptive analysis of extracted data was undertaken.

3. Results

Data from eight published studies were extracted and synthesized. 4 were cases studies [6,13–15], 3 were RCT's [7,16,17] and 1 cohort study [18]. Study duration varied from 1 to 8 weeks. Repeat RIPC protocols varied from 1 to 4 cycles of 5 min occlusion, cuff inflation was similar across studies 200–220 mm Hg, and frequency of administration was 1 or 2 times daily. Details of programme characteristics are described in Table 1. A lack of sufficiently similar outcome measures between studies precluded data pooling for meta-analyses.

3.1. Blood pressure

Four case studies reported variable changes in systolic and diastolic blood pressures after repeat RIPC [6,13–15]. These 4 studies, all by the same author, each used repeated, periodic, blood pressure measures to confirm the findings. Madias reported 6 mm Hg and 3 mm Hg falls in systolic and diastolic pressure, respectively, with twice daily repeat RIPC [13]. Madias and Koulouridis slightly refined his methods and noted a short-lived fall of 5 mm Hg in SBP [15]. In 2015, Madias reported a 6.1 mm Hg reduction in SBP, a 3.7 mm Hg change in pulse pressure, but no significant change in DBP, after twice daily, 15-min repeat RIPC sessions for 10 days [6]. Madias's later work in 2015 showed no change in SBP, DBP, pulse pressure and heart rate; this study used once-daily repeat RIPC sessions [14]. Kimura et al.'s work was the only RCT to report blood pressure and they showed no change after 4 weeks repeat RIPC, but they only measured blood pressure during the experiment and not at other times [16]. The works of Madias and Kimura provide conflicting evidence of a sustained reduction in blood pressure. The 7-day study of repeat RIPC by Jones et al. reported a 5 mm Hg reduction in mean arterial pressure in the intervention arm 8 days post-intervention, but again ambulatory blood pressures were not recorded [18].

3.2. Vascular function

Kimura et al. reported that repeat RIPC augments endothelium-dependent vasodilation and also production of nitric oxide [16]. Serum levels of vascular endothelial growth factor (VEGF) were increased by 33.9% and this correlated with an improvement in endothelial progenitor cells after repeat RIPC intervention. An increase in endothelial progenitor cells by 23.9% was also reported.

Similarly Jones et al. [18] reported improved flow-mediated dilatation (FMD) and cutaneous vascular conductance in their 7-day study of repeat RIPC. The same authors showed sustained improvement in FMD at 8 weeks, but did not report improved cutaneous vascular