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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

Table 1
Published studies of repeated exposure to remote ischaemic pre-conditioning.

Study	Design	Weeks	Protocol	Frequency	Comparator	No. participants	Outcome measure
Jones 2014a [18]	Cohort	1	4 × 5 220 mm Hg 5 min reperfusion	1× daily	None	13 healthy	Flow mediated dilatation C vascular conductance Shear Mean arterial pressure
Jones 2014b [7]	RCT	8	4 × 5min 220 mm Hg 5 min reperfusion	3× weekly	Control	18 healthy (9 RIPC)	Flow mediated dilatation Vascular conductance Peak VO_2 Shear Mean arterial pressure
Kimura 2007 [16]	RCT	4	1 × 5 200 mm Hg	6× daily	Control	20 healthy (10RIPC)	Forearm blood flow Endothelial progenitor cells Systolic blood pressure Diastolic blood pressure Heart Rate
Madias 2011 [13]	Case study	3 days RIPC with pre- and post-observation	3 × 5min at 20 mm Hg above SBP with 5 min reperfusion	2× daily	None	1	Repeat blood pressure measures
Madias 2014 [15]	Case study	7 days RIPC with pre- and post-observation	3 × 5min at 20 mm Hg above SBP with 5 min reperfusion	2× daily	None	1	Repeat blood pressure measures
Madias 2015a [6]	Case study	10 days	3 × 5	2× daily	Self	1	Repeat blood pressure measures
Madias 2015b [14]	Case study	10 days	3 × 5	1× daily	Self	1	Repeat blood pressure measures
Shaked 2015 [17]	RCT	6 weeks	3 × 5	Bi-weekly	Sham	40	Diabetic ulcer healing

conductance, brachial artery diameter or shear rate. In contrast to Kimura et al.'s work [16], Jones et al. [18] reported an improvement in endothelial function in both the exposed and contra-lateral arm in their 7-day work. Kimura et al. also reported an increase in Acetylcholine induced forearm blood flow by 35.5% [16].

3.3. Cardiorespiratory fitness

The 8-week study by Jones reported no change in peak VO_2 following repeat RIPC [7].

3.4. Wound healing

The largest RCT to date focussed on wound healing in diabetic patients and showed significant improvements in diabetic foot ulcers [17].

3.5. Effect of study duration and residual effects

It appears that anti-hypertensive and endothelial function benefits are possible with repeated exposure to RIPC within 7 days [18]. The work of Jones et al. suggests that some benefits of repeat RIPC may peak after 1 week but sustained benefits from continued RIPC exposure can be retained for at least 8 days after repeat RIPC exposure [7].

4. Discussion

Our systematic review reveals that few published studies of repeat exposure to RIPC exist to date; however, this intervention shows early promise as a treatment for vascular dysfunction. Insufficient data currently exists to justify data pooling, but individual studies have reported anti-hypertensive effects of systolic, diastolic and mean arterial blood pressure following repeat RIPC. Repeat RIPC has also produced evidence of improvements in endothelial dependent vasodilation, but not non-endothelial dependant vasodilation, cutaneous vascular conductance or cardiorespiratory fitness.

The works of Madias may indicate that twice-daily exposure to RIPC may be required to lower blood pressure [6,14]. Madias' findings are countered by those of Kimura et al. [16], but the former did take numerous repeated, but not ambulatory, blood pressure measurements while the latter relied on a single measurement. The works of Jones et al. [18] support Madias' claim of blood pressure reduction within 7 days [6]. Jones et al.'s 8-week study [7] also support Madias' notion that anti-hypertensive effects are maintained for several days after RIPC exposure has ceased [6]. A possible explanation for conflicting blood pressure findings are that Kimura et al. [16] only used 1 × 5min RIPC bouts, although these were applied 6 times daily, both Jones et al. [7] and Madias and Koulouridis [15] used the 3 or 4 × 5min RIPC protocols and both showed BP reduction whereas Kimura et al. did not. Kimura et al. used more frequent RIPC applications, but it therefore appears that the aggregate repeated exposure of 15–20 min per application is more important than frequency, at least for initiating blood pressure reductions. As Madias used ambulatory measurements, which are usually considered more robust and therefore less likely to show blood pressure reductions, it is unlikely that Kimura et al.'s use of single blood pressure measurements would explain why the former showed reductions but the latter did not. One other possible explanation is that Kimura et al. used a standard 200 mm Hg inflation pressure, while others used 220 mm Hg or 20 mm Hg above systolic pressure. It is possible that subjects in Kimura et al.'s study had either resting systolic pressures elevated above 200 mm Hg or they experienced agonal responses elevating their systolic pressures beyond 200 mm Hg, although this is unlikely.

The study by Shaked et al. [17] showed improved diabetic ulcer healing compared to control in the largest repeat RIPC trial to date. Moreover, the degree of wound granulation increased after just one cycle of treatment in one third of diabetic treated compared to only 19% in the control group. Shaked et al.'s work perhaps opens up the possibility for treatment of peripheral arterial disease with repeat RIPC [19].

Kimura et al.'s work perhaps indicates that exposure to repeated bouts of RIPC improves endothelial function, but not non-endothelial dependent vasodilation, nor vascular smooth muscle performance [16]. Moreover, the improved endothelial function may be due to increased systemic nitric oxide concentrations which are at least partially due to an increase in endothelial progenitor cells. It appears that the vascular shear stress that results from repeat exposure to RIPC causes two events; Firstly, increases in availability of nitric oxide, which may explain initial protection against ischaemic reperfusion injury. Secondly, a delayed increase in the presence of endothelial progenitor cells, some of which differentiate to form haematopoietic cells, explains the second phase of protection against ischaemic reperfusion injury [20,21]. Also, related to hypoxic processes is an increase in VEGF which is up-regulated by HIF-1 alpha and contributes to increasing levels of EPCs and therefore improved capillary density and nitric oxide availability [16].

4.1. Limitations

The major limitation of this work is the small sample sizes in studies, aside from one RCT in diabetic patients, published to date [17]. Another significant limitation is that the protocols for implementing the repeated RIPC across studies varied greatly, although it was also a strength as it enabled characteristics of different protocols to be related to the presence or absence of beneficial changes e.g. reduced blood pressure.

It is unclear whether study size of 18–20 RIPC participants is sufficient to detect changes in blood pressure or other markers of endothelial function. Forty participants was however, sufficient to detect changes in ulcer healing in diabetic patients [17]. In contrast, the 4 case studies in a single individual by Madias provided numerous blood pressure measurements that would be considered robust enough to meet the desired gold standard of ambulatory blood pressure measurement.

The short study durations of the two published RCTs are 4 and 8 weeks [7]. There are several limitations of these published works to date. First, it is unclear whether benefits are intermittent, as studies of single exposure to RIPC have suggested a bi-modal effect with a window 12–24 h after exposure. It is therefore unclear whether a twice-daily approach is optimal for 'closing this window' as Jones et al. [7] used once daily and Kimura et al. six daily RIPC exposures [16]. Second, although Jones et al. reported sustained benefits up to 8 days post-intervention [7], it is unclear exactly how long the benefits of RIPC last.

4.2. Implications for future research

Future work should give consideration to the clinical problems, sample characteristics and methodological issues. The implications for research are that administration of repeated RIPC in large numbers of people is time intensive. One solution to this is commercially available devices but these are costly >US$2K per patient. Manual administration of cuff inflation can also be prone to error as some cuffs leak. In terms of the study populations there does not appear to be safety issues for high risk populations based upon single exposure studies in cardiac and renal patients and a recent repeat RIPC exposure study has reported ulcer healing benefits in diabetes patients [17]. Perhaps the most important message though for future study design is to ensure each RIPC session has at least 3 or preferably 4, 5 min exposures. Compared to 3–4 exposures, a single 5 min exposure appears less beneficial for reducing blood pressure, even if the single exposure is provided several times daily [16].

Until now the focus of single exposure RIPC has been upon those undergoing cardiac surgery and repeat exposure has focused on hypertensive populations. Other populations exhibiting endothelial dysfunction, for example people with diabetes [19] or pulmonary hypertension [22] may benefit most from repeated exposure to RIPC.

Twice daily repeat RIPC administration, separated by 12 h, may 'close' the window of exposure to ischaemic reperfusion injury in those at risk. However, as the timing of RIPC administration is paramount, it appears that only those people undertaking elective cardiac surgery may derive most benefit as the optimal timing of RIPC delivery may not be possible with emergency surgery.

5. Conclusions

Repeated RIPC exposure has produced some evidence of improvements in endothelial dependent vasodilation, ulcer healing and blood pressure but not non-endothelial dependent vasodilation, cutaneous vascular conductance or cardiorespiratory fitness. The optimal delivery of RIPC remains unclear, but compared to 3–4 exposures, a single 5 min exposure appears less beneficial for reducing blood pressure. Aside from those undertaking cardiac surgery, other study populations with endothelial dysfunction may benefit from repeat exposure to RIPC.

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