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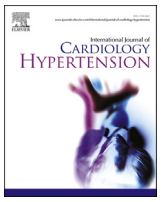

Review Article

The effect of remote ischaemic conditioning on blood pressure response: A systematic review and meta-analysis

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ABSTRACT

Background: Previous work has evaluated the effect of remote ischaemic conditioning (RIC) in a number of clinical conditions (e.g. cardiac surgery and acute kidney injury), but only one analysis has examined blood pressure (BP) changes. While individual studies have reported the effects of acute bouts and repeated RIC exposure on resting BP, efficacy is equivocal. We conducted a systematic review and meta-analysis to evaluate the effects of acute and repeat RIC on BP.

Methods: A systematic search was performed using PubMed, Web of Science, EMBASE, and Cochrane Library of Controlled Trials up until October 31, 2020. Additionally, manual searches of reference lists were performed. Studies that compared BP responses after exposing participants to either an acute bout or repeated cycles of RIC with a minimum one-week intervention period were considered.

Results: Eighteen studies were included in this systematic review, ten examined acute effects while eight investigated repeat effects of RIC. Mean differences (MD) for outcome measures from acute RIC studies were: systolic BP 0.18 mmHg (95%CI -0.95, 1.31; $p = 0.76$), diastolic BP -0.43 mmHg (95%CI -2.36, 1.50; $p = 0.66$), MAP -1.73 mmHg (95%CI -3.11, −0.34; $p = 0.01$) and HR -1.15 bpm (95%CI -2.92, 0.62; $p = 0.20$). Only MAP was significantly reduced. Repeat RIC exposure showed non-significant change in systolic BP -3.23 mmHg (95%CI -6.57, 0.11; $p = 0.06$) and HR -0.16 bpm (95%CI -7.08, 6.77; $p = 0.96$) while diastolic BP -2.94 mmHg (95%CI -4.08, −1.79; $p < 0.00001$) and MAP -3.21 mmHg (95%CI -4.82, −1.61; $p < 0.0001$) were significantly reduced.

Conclusions: Our data suggests repeated, but not acute, RIC produced clinically meaningful reductions in diastolic BP and MAP.

1. Introduction

Uncontrolled hypertension is a major cardiovascular risk factor. People with hypertension have decreased arteriole and capillary density within their tissues. This condition is known as rarefaction and increases peripheral resistance resulting in elevated blood pressure, vessel damage and systemic inflammation [1]. The treatment and management of hypertension is a major public health concern since prevalence continues to rise significantly with age [2–4].

Hypertension treatment options include pharmacological and lifestyle modification interventions [5,6]. However, treatment responses and adherence continue to be variable as management is ongoing [7–9]. Regular exercise participation rates remain low due to financial cost, lack of time and motivation [10–14]. Therefore, identification of a novel, beneficial, time efficient and cost-effective intervention is of great importance.

Remote ischaemic conditioning (RIC) is a simple emerging intervention, requiring minimal time commitment, that has been shown to induce stimulation of angiogenesis within the existing vasculature via the activation of physiological or functional non-pathological processes in the myocardium [15] and the repeated exposure has the potential to modify cardiovascular disease (CVD) risk factors [16].

First shown in 1993 [17], RIC was developed to protect from myocardial injury during coronary artery bypass grafting (CABG). RIC is

Abbreviations: BP, blood pressure; CABG, coronary artery bypass grafting; CI, confidence interval; HR, heart rate; MD, mean difference; VEGF, vascular endothelial growth factor; RIC, Remote ischaemic conditioning; SD, standard deviation; T2DM, type 2 diabetes mellitus.

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usually executed by the application of an inflated blood pressure cuff that elicits repeated brief episodes of ischaemic conditioning alternated with periods of reperfusion (deflated cuff). RIC deprives a vascular bed, tissue or organ of blood flow in order to condition it towards a permanent or prolonged restricted blood flow as a means of protection against future hypoxia [16,18,19]. The application of RIC usually comprises 3–4 repetitions of 5-min cuff inflation at 200 mmHg intermittently spread with 5-min of deflation [16] in either a remote organ [20] or limb [21].

The safety of RIC has been shown in patients with anterior ST-segment elevation myocardial infarction who had reduced enzymatic infarct size with an improved cardiac magnetic resonance imaging (MRI) and ST-segment resolution [22,23]. Pilcher et al. [24] in their systematic review and meta-analysis showed the cardioprotective efficacy of RIC in open cardiac surgery demonstrating a significantly reduced concentration of postoperative troponin. The magnitude of troponin release following cardiac surgery has independently been linked with a high risk of mortality [25,26]. Meng et al. [27] also showed the efficacy and safety of RIC in octo- and non-agenarians with symptomatic intracranial arterial stenosis to prevent stroke occurrence and recurrence.

Single session RIC performed immediately preceding exercise improved athletic performance in both competitive athletes [28] and recreationally active young individuals [29,30]. Similarly, in people with multiple sclerosis a single session of RIC resulted in an immediate improvement in 6-min walk distance [31].

More importantly, the relationship between BP and RIC has received attention following Madias' self-experimentation case study reporting mean reduction in both systolic (>6 mmHg) and diastolic (>3 mmHg) BP at 60 min following acute bouts of RIC as a normotensive, middle-aged adult [32]. Subsequent work by Madias and Koulouridis [33] improving on the initial work of Madias, which may have had minor design flaws [32], confirmed the hypotensive effect of repeated RIC compared to control. Further work showed a sustained BP lowering effect during RIC, which remained for 5–10 days after cessation of therapy [19]. Adopting RIC as an adjunct therapeutic modality for controlling blood pressure may be appropriate.

There have been a number of reviews and meta-analyses that have assessed the clinical outcomes of RIC during cardiac surgery [24–26,34–43]. By including cohort and non-RCTs, previous meta-analyses have provided weaker level evidence. While some individual studies have reported the effects of repeated RIC on resting BP, there has not been a consensus on its efficacy [16] and an updated systematic review using only RCTs in the meta-analysis is indicated as new studies are now available. The aim of this work was to evaluate the effect of acute and repeated exposure RIC on BP.

2. Methods

This systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO) [CRD42020180784] [44].

2.1. Search strategy

A systematic literature search was conducted to identify potential studies for inclusion. PubMed, Web of Science, EMBASE from 1966 up until October 31, 2020 and the Cochrane controlled trials registry were searched. Reference lists from systematic reviews and eligible studies were searched for additional studies. The search strategy included a combination of the following terms: (remote ischaemic preconditioning) or (remote ischaemic conditioning) or (physiological ischaemia training) or (limb occlusion) or (cuff inflation) and (blood pressure) (Supplementary Table S1).

2.2. Inclusion and exclusion criteria

We included RCTs, cohort, crossover studies in adult (over 18 years) humans that investigated blood pressure response after exposing participants to acute or repeated RIC by the application of BP cuff inflation or medical tourniquet in a remote limb. RIC studies that completely prevented blood flow, for repeated ischaemic cycles were included. We included acute studies and studies that assessed the repeated effects of RIC using a minimum intervention duration of one week. We included studies in adult participants, with or without known CVD (i.e. both healthy and diseased adult populations).

We excluded studies that did not report any desired outcome of interest.

Authors were contacted to provide missing data where necessary. Two reviewers (BB, MP) assessed all identified articles independently for eligibility, and two reviewers (GD, NS) were consulted for any disagreement to be resolved.

2.3. Comparisons

We compared data from studies that utilized a "remote ischaemic conditioning intervention group" versus either [non-exposed control, or sham group, or another intervention group] OR a comparison between pre-versus post-remote ischaemic interventions.

2.4. Outcome measures

The outcome measures were change in blood pressure (systolic and diastolic BP, MAP) and heart rate.

2.5. Data extraction

Data was extracted using a data extraction form purposely designed for this review. The extracted data was checked and discussed by all authors. Extracted data from each study included first author's name and year of publication, country, study design, population, participants' baseline characteristics (age, gender proportion and sample size), protocol characteristics, duration and frequency of protocol, change in the desired outcome variables, number of withdrawal participants and intervention compliance.

2.6. Analyses

A descriptive analysis of extracted data was undertaken for all studies included in the review. However, only RCT data was pooled for meta-analyses. The change in means after the intervention were obtained by subtracting the pre-intervention means from the post-intervention means. The change in SD of the corresponding means were calculated adopting the formula [45] for calculating change in means' SD, using a correlation of 0.5 for all studies. A random effects model was used for the pooled analyses. Forest plots was generated to provide visual representation of the effect of RIC on outcome measures. Egger's plots were provided to evaluate the publication bias by visual inspection [46].

Statistical heterogeneity (I^2) was assessed and the values of 25%, 50%, and 75% corresponded to low, moderate, and high degrees of heterogeneity [47]. The level of statistical significance was set at $p < 0.05$ CIs. The meta-analyses were carried out using Review Manager version 5.4, *The Cochrane Collaboration* software package [48].

2.7. Quality assessment

The methodological quality of the included studies was assessed using the JADAD scale [49]. Three domains were assessed based on study description as randomisation (score: 0–2), blinding (score: 0–2), and an account of withdrawals and dropouts (score: 0–1) for a total score of 5. Any study with a total score ≤ 2 or ≥ 3 was described as low or high quality, respectively.

3. Results

The systematic database search identified a total of 6488 records without any filters applied. A total of 1116 records remained after human, clinical and randomised controlled trial filters were applied. An additional 18 records were found in reference lists from systematic reviews and references of papers found in the initial search. After removal of duplicates, 731 articles were screened by title and abstract leaving 183 publications (Fig. 1). Of these, 165 full-text publications were excluded for not meeting inclusion criteria with reasons indicated in the PRISMA flow diagram. Eighteen (10 acute and 8 repeat RIC) studies were deemed eligible for inclusion in the systematic review.

3.1. Study characteristics

Ten **acute RIC exposure studies** [31,50–58] were considered in this systematic review including one cohort study [50]. Nine studies (10 comparisons) were eligible for pooling meta-analytically for acute RIC effect. Three studies [50,51,56] were conducted in healthy individuals, one study each in patients with multiple sclerosis [31] and peripheral artery disease [53], three other studies [52,54,55] were conducted in patients undergoing surgery. One study was conducted in coronary heart disease patients [58] and a crossover study in both healthy adults and patients with coronary heart disease [57]. The duration of the follow-up after RIC application ranged from 10-min to 28 h; while in two studies [51,57], the duration before post-measurement was not clearly described. Acute RIC protocols varied from 3 to 4 cycles with 5-min cuff inflation-induced ischaemia at similar pressure of 200 mmHg or 30–50 mmHg above each participant's predetermined systolic BP across studies. The characteristics of the acute RIC effect included studies are summarized in Table 1.

Eight **repeat RIC exposure studies** [59–66] were considered in this systematic review including two cohort studies [60,65]. Only 5 RCTs [59,61–63,66] were pooled in the meta-analysis for reported repeat RIC effect. Five studies [60–62,65,66] conducted repeated RIC in healthy individuals while three others conducted repeated RIC in patient with chronic heart disease [59], compensated chronic heart failure [64] and type 2 diabetes mellitus (T2DM) [63]. The study duration spanned from one week to 3 months; the frequency of RIC administration ranged from a daily application to 3 times per week. Repeated RIC protocols varied from 3 to 6 cycles with 3- to 5-min cuff inflation-induced ischaemia at similar pressure of 200–220 mmHg across studies. Participants' compliance to RIC protocols varied from 92 to 100% and male subjects were in the majority of included studies. The characteristics of the repeat RIC exposure included studies are summarized in Table 2.

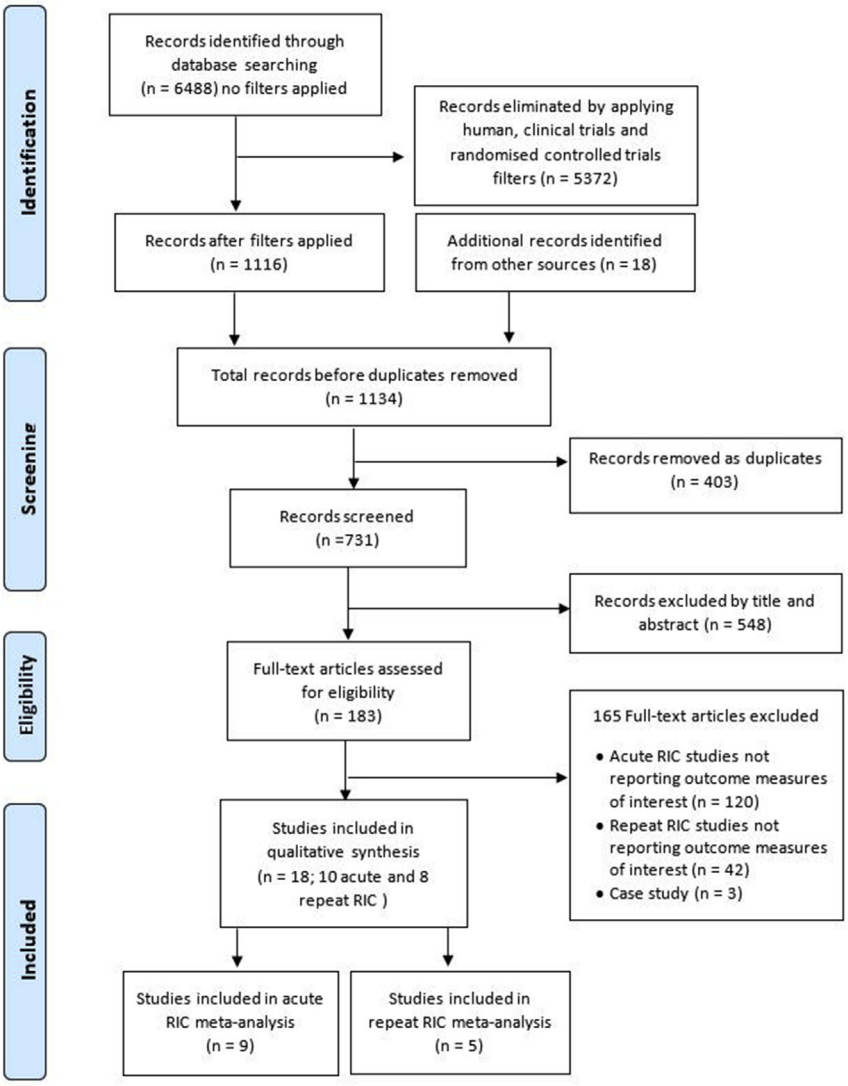

Fig. 1. PRISMA flow diagram.

Table 1
Acute RIC – Characteristics of included studies.

Study/Year/ Country	Design/MA inclusion	Population – Age (yr) – Sex	Outcome measures	Duration before post-measurement	Treatment groups and protocol	Ischaemic pressure and Device[a]	Withdrawal Compliance
Chotiyarnwong 2020 [31] UK	RCT Yes	76 Multiple sclerosis 45.8 31 M; 44 F	6MWT, Borg RPE, gait speed, BP, HR	10 min	RIC = 38 (21 M; 17 F) 3x (5 min cuff inflation x 5 min deflation) unilateral arm	30 mmHg above resting SBP	None
					CON sRIC = 37 (10 M; 27 F) 3x (5 min cuff inflation x 5 min deflation) unilateral arm	30 mmHg below resting DBP	1
Guo 2019 [50] China	Cohort Self-controlled No	50 Healthy adults 34.5 ± 12.0 22 M; 26 F	dCA parameters, MAP, HR, VEGF, GDNF, BDNF, CNF, β-NGF, inflammation-related biomarkers	2 h	RIC = 48 4x (5 min cuff inflation x 5 min deflation), unilateral arm and leg	200 mmHg Automatic BP device	None 2 low coherence
					CON = 48 No intervention		
Incognito 2017 [51] Canada	RCT Yes	37 Healthy men 24 ± 5 37 M; 0 F	MAP, HR, SV, CO, TVC, MSNA	No clear time description	RIC = 21 3x (5 min cuff inflation x 5 min deflation), unilateral left arm	200 mmHg	None
					CON sRIC = 16 3x (5min cuff inflation x 5 min deflation), unilateral left arm	20 mmHg	
Kepler 2019 [52] Estonia	RCT Yes	90 Vascular Surgery 66.5 66 M; 24 F	PWV, AIx, BP, HR, elasticity indices of arteries	20–28 h post-op	RIC = 44 (36 M; 8 F) 4x (5 min cuff inflation x 5 min deflation), unilateral arm	200 mmHg or 20 mmHg above SBP ≥ 180 mmHg	None
					CON sRIC = 46 (30 M; 16 F) 4x (5min cuff inflation x 5 min deflation), unilateral arm	10–20 mmHg	
Kuusik 2019 [53] Estonia	RCT Yes	102 Peripheral artery disease 65.6 81 M; 21 F	PWV, AIx, PP, SVR, BP, HR, elasticity indices of arteries	24 h	RIC = 47 (33 M; 14 F) 4x (5min cuff inflation x 5 min deflation), unilateral arm	200 mmHg or 20 mmHg above SBP ≥ 180 mmHg	7
					CON sRIC = 55 (48 M; 7 F) 4x (5min cuff inflation x 5 min deflation), unilateral arm	20 mmHg	2
Li 2013 [54] China	RCT Yes	62 Abdominal aortic aneurysm repair 64.5 55 M; 7 F	a/A ratio, A-aDO_2 $PaCO_2$, PaO_2, IR, arterial pH, lung compliance, CVP, MAP, HR, biomarkers of intestinal injury, oxidative stress and inflammation	30 min	RIC = 31 (29 M; 2 F) 3x (5min cuff inflation x 5 min deflation), unilateral left arm	200 mmHg	None
					CON = 31 (26 M; 5 F) deflated cuff for 30 min	0 mmHg	
Li 2014 [55] China	RCT Yes	216 Thoracic pulmonary resection under one-lung ventilation 57.5 158 M; 58 F	a/A ratio, A-aDO_2 $PaCO_2$, PaO_2/FiO_2, IR, arterial pH, lung compliance, CVP, MAP, HR, biomarkers of oxidative stress & inflammation, incidence of in-hospital complications	30 min	RIC = 108 (82 M; 26 F) 3x (5min cuff inflation x 5 min deflation), unilateral left arm	200 mmHg Automated cuff-inflator	None
					CON = 108 (76 M; 32 F) deflated cuff for 30 min	0 mmHg Automated cuff-inflator	
		40 Healthy adults	BP, HR, arterial stiffness (Central systolic BP and PWV)	30 min	RIC = 40 3x (5min cuff	200 mmHg	None

(*continued on next page*)

Table 1 (*continued*)

Study/Year/ Country	Design/MA inclusion	Population – Age (yr) – Sex	Outcome measures	Duration before post-measurement	Treatment groups and protocol	Ischaemic pressure and Device[a]	Withdrawal Compliance
Muller 2019 [56] Germany	RCT (Crossover) Yes	25.6 ± 2.8 17 M; 23 F			inflation x 5 min deflation), unilateral leg (right thigh) CON sRIC = 40	40 mmHg	
Xu 2018 [58] China	RCT Yes	17 Coronary heart disease RIC 65.88 ± 4.99 CON 65.25 ± 5.52 6 M; 11 F	BP, HR	No clear time description	3x (5min cuff inflation x 5 min deflation), unilateral right arm None	RIC = 9 3x (5min cuff inflation x 5 min deflation), unilateral leg (left thigh)	Not specified (vascular Doppler revealed no blood flow)
CON = 8 deflated cuff	Unrestricted blood flow						
Zagidulin 2016 [57] Russia	RCT (Crossover) Yes	20 Healthy adults 58.2 ± 2.49 16 M; 4 F	BP, HR and HR variability, oxygen saturation, arterial stiffness, PWV	No clear time description	RIC = 20 3x (5min cuff inflation x 5 min deflation), unilateral arm CON sRIC = 20 3x (5min cuff inflation x 5 min deflation), unilateral arm	50 mmHg above participant's predetermined SBP Participant's predetermined DBP	None
		30 Coronary heart disease 63.9 ± 1.6 21 M; 9 F		No clear time description	RIC = 30 3x (5min cuff inflation x 5 min deflation), unilateral arm CON sRIC = 30 3x (5min cuff inflation x 5 min deflation), unilateral arm	50 mmHg above participant's predetermined SBP Participant's predetermined DBP	None

A-aDO_2: alveolar–arterial oxygen tension difference, a/A ratio: arterial–alveolar ratio, BP: blood pressure, BDNF: brain-derived neurotrophic factor, CNF: ciliary neurotrophic factor, β-NGF: beta-nerve growth factor, CO: cardiac output, CON: control, CVP: central venous pressure, dCA: dynamic cerebral autoregulation, GDNF: glial cell line–derived neurotrophic factor, F: female, HR: heart rate, RI: respiratory index M: male, MA: meta-analysis, MAP: mean arterial pressure, MSNA: muscle sympathetic nerve activity, $PaCO_2$: arterial carbon dioxide partial pressure, PaO_2: arterial oxygen partial pressure, PaO_2/FIO_2: ratio of arterial oxygen partial pressure to fractional inspired oxygen, PD: phase difference, PP: pulse pressure, PWV: pulse wave velocity, RIC, remote ischaemic conditioning; RPE: rate of perceived exertion, 6MWT: 6-min walk test, SV: stroke volume, SVR: systemic vascular resistance, TVC: total vascular conductance, VEGF: vascular endothelial growth factor, yr: years.

[a] All studies used a manual BP cuff (sphygmomanometer) unless stated otherwise. Cuff deflation = reperfusion; cuff inflation = ischaemia.

3.2. Acute RIC exposure

BP parameters and HR were available in all the acute RIC exposure included studies except three studies [50,54,55] that reported only MAP and HR results.

Systolic and diastolic BP data were available in 7 studies [31,51–53,56–58] and 8 comparisons were included in the meta-analysis. There was no significant change in systolic BP (MD = 0.18 mmHg [95%CI -0.95 to 1.31; $p = 0.76$]) and diastolic BP (MD = −0.43 mmHg [95%CI -2.36 to 1.50; $p = 0.66$]). Seven studies reported MAP [31,51–55,58] and there was a significant reduction in MAP with MD -1.73 mmHg (95%CI -3.11 to −0.34; $p = 0.01$). Nine studies (10 comparisons) reported HR; there was no significant change in HR (MD -1.15 bpm [95% CI -2.92 to 0.62; $p = 0.20$]). See Fig. 2 for changes in BP and HR after acute RIC exposure.

3.3. Repeat RIC exposure

Outcome measures of interest were reported by 5 repeat RIC exposure studies [59,61–63,66] and were included in data pooling.

Systolic and diastolic BP data were available in 4 studies [59,62,63,66] with 5 comparisons, totaling 107 participants. Systolic BP was non-significantly reduced with MD -3.23 mmHg (95%CI -6.57 to 0.11; $p = 0.06$); whereas diastolic BP was significantly reduced with MD -2.94 mmHg (95%CI -4.08 to –1.79; $p < 0.00001$). MAP was reported in 3 studies [59,61,63], totaling 73 participants, and significantly reduced with MD -3.21 mmHg (95%CI -4.82 to −1.61; $p < 0.0001$). Only one study [62] (2 comparisons) reported HR; there was no change in MD with −0.16 bpm (95%CI -7.08 to 6.77; $p = 0.96$) (Fig. 3).

Three studies were included in the qualitative synthesis. The cohort study by Banks et al. [65] reported no change in systolic and diastolic BP in healthy adults after 9 days of RIC intervention. A parallel group study conducted by Pryds et al. [64] showed a significant reduction in systolic BP and non-significant reduction in diastolic BP. One cohort study by Jones et al. [60] reported reduced MAP after 7 days of RIC intervention that was sustained 8 days post RIC intervention in healthy men. Two studies reported on HR [64,65] with no significant changes post intervention.

3.4. Sub-analyses

The sub-analysis of all studies – acute versus repeat RIC – showed a non-significant reduction in systolic and diastolic BP and HR. Only MAP was significantly reduced with MD -2.36 mmHg (95%CI -3.41 to −1.31; $p < 0.0001$) (Supplementary Fig. S1).

Table 2
Repeat RIC – Characteristics of included studies.

Study/ Year/ Country	Design/MA inclusion	Population – Age (years) – Sex	Outcome measures	Duration Frequency per week	Treatment groups and protocol	Ischaemic pressure Device*	Withdrawal Compliance
Banks 2016 [65] Canada	Cohort No	10 Sedentary healthy adults 18 - 35 (24 ± 4) 6 M and 4 F	BP, HR, peak VO_2, cardiac and skeletal muscle energetics	9 days Daily	4x (5 min caff inflation x 5 min caff deflation) unilateral right arm	200 mmHg	None 100%
Chen 2019 [59] China	RCT Yes	55 Coronary heart disease 50–70 (64.44 ± 8.28) 31 M and 24 F	BP, MAP, cardiac structure and function, VEGF	3 months 5 days per week 3 months 2 session daily for 5 days per week	RIC = 18 (9 M; 9 F) 3x (3 min cuff inflation x 5 min cuff deflation) bilateral arm IET = 19 (11 M; 8 F) 10x (1 min 40–50% MVC x 1 min rest) bilateral HGT as one session CON = 18 (11 M; 7 F) No exercise but only drug treatment	Not reported 40–50% MVC handgrip dynamometer	Not reported 92%
Herrod 2019 [66] UK	RCT Yes	30 Healthy pre-menopausal sedentary women 20 - 50 (37.9 ± 7.9)	BP, FMD, CPET parameters	4 weeks 3 days per week	RIC = 10 3x (3 min cuff inflation x 3 min cuff deflation) unilateral right arm IET = 10 4x (2 min 30% MVC x 2 min rest) unilateral right arm HGT CON = 10 No intervention	200 mmHg 30% MVC handgrip dynamometer	None 100%
Jones 2014 [60] UK	Cohort No	13 Active healthy men 22 ± 2	FMD, MAP, CVC	7 days Daily	4x (5 min cuff inflation x 5 min deflation), unilateral dominant arm	220 mmHg	None 100%
Jones 2015 [61] UK	RCT Yes	18 Active healthy men RIC 22.4 ± 2.3 CON 26.0 ± 4.8	FMD, MAP, CVC, peak VO_2	8 weeks 3 days per week	RIC = 8 4x (5min cuff inflation x 5 min deflation), unilateral arm CON = 8 No intervention	220 mmHg	2 (1 each group) 96%
Kimura 2007 [62] Japan	RCT Yes	30 Healthy men PC arm 28.1 ± 3.9 CL arm 27.3 ± 4.0	FBF, VEGF, BP, HR, serum lipid profile	4 weeks Daily	$RIC_{PC\ arm}$ = 10 6x (5min cuff inflation x 5 min deflation) per day, preconditioned arm $RIC_{CL\ arm}$ = 10 6x (5min cuff inflation x 5 min deflation) per day, contralateral arm CON = 10 No intervention	200 mmHg 200 mmHg	None 100%
Maxwell 2019 [63] UK	RCT Yes	21 T2DM RIC 58.8 ± 7.4 CON 59.7 ± 9.6 13 M and 8 F	FMD, BP, MAP, $P_{et}CO_2$, partial pressure of end tidal carbon dioxide, MCAv, CbVC	7 days Daily	RIC = 11 (6 M; 5 F) 4x (5min cuff inflation x 5 min deflation), unilateral arm CON = 10 (7 M; 3 F) No intervention	220 mmHg	None 96%
Pryds 2017 [64] Denmark	RCT (parallel group study) No	43 Cardiovascular disease RIC_1 66 ± 9.7 RIC_2 63.1 ± 6.3	LVF, CPET parameters, skeletal muscle function, BP, HR, NT-proBNP	4 weeks Daily	RIC_1 = 22 CIHF (20 M; 2 F) 4x (5 min cuff inflation x 5 min deflation), unilateral RIC_2 = 21 matched CON non-CIHF (17 M; 4 F) 4x (5 min cuff inflation x 5 min deflation) unilateral	Auto RIC device Auto RIC device	None None

Cuff deflation = reperfusion; Cuff inflation = ischaemia.
BP: blood pressure, CPET: cardiopulmonary exercise test, CbVC: cerebral vascular conductance, CIHF: chronic ischaemic heart failure, CL arm: contralateral arm, CVC: cutaneous vascular conductance, FBF: forearm blood flow, FMD: flow-mediated dilatation, HG: handgrip training, IET: isometric exercise training, LVF: left ventricular function, MAP: mean arterial pressure, MCAv: middle cerebral artery velocity, NT-proBNP: N-terminal pro-brain natriuretic peptide, $P_{et}CO_2$: partial pressure of end tidal carbon, PC arm: preconditioned, RIC: remote ischaemic conditioning, T2DM: type 2 diabetes mellitus, VEGF: vascular endothelial growth factor.

For acute RIC, a sub-analysis of healthy patients versus patients receiving hypertension treatment revealed a significant decrease in DBP in the healthy patients (3 studies) with MD -1.6 mmHg (95%CI -2.91 to −0.29; $p = 0.02$); HR decreased in patients receiving hypertension treatment (7 studies) with MD -2.25 bpm (95%CI -4.38 to −0.12; $p = 0.04$) (Supplementary Fig. S2).

For repeat RIC, a sub-analysis of healthy patients versus patients receiving hypertension treatment revealed a significant decrease in SBP and MAP for patients receiving treatment (2 studies) with SBP MD -3.7 mmHg (95%CI -7.42 to 0.02; $p = 0.05$) and MAP MD -3.27 mmHg (95%CI -4.89 to −1.66; $p = 0.05$) (Supplementary Fig. S3).

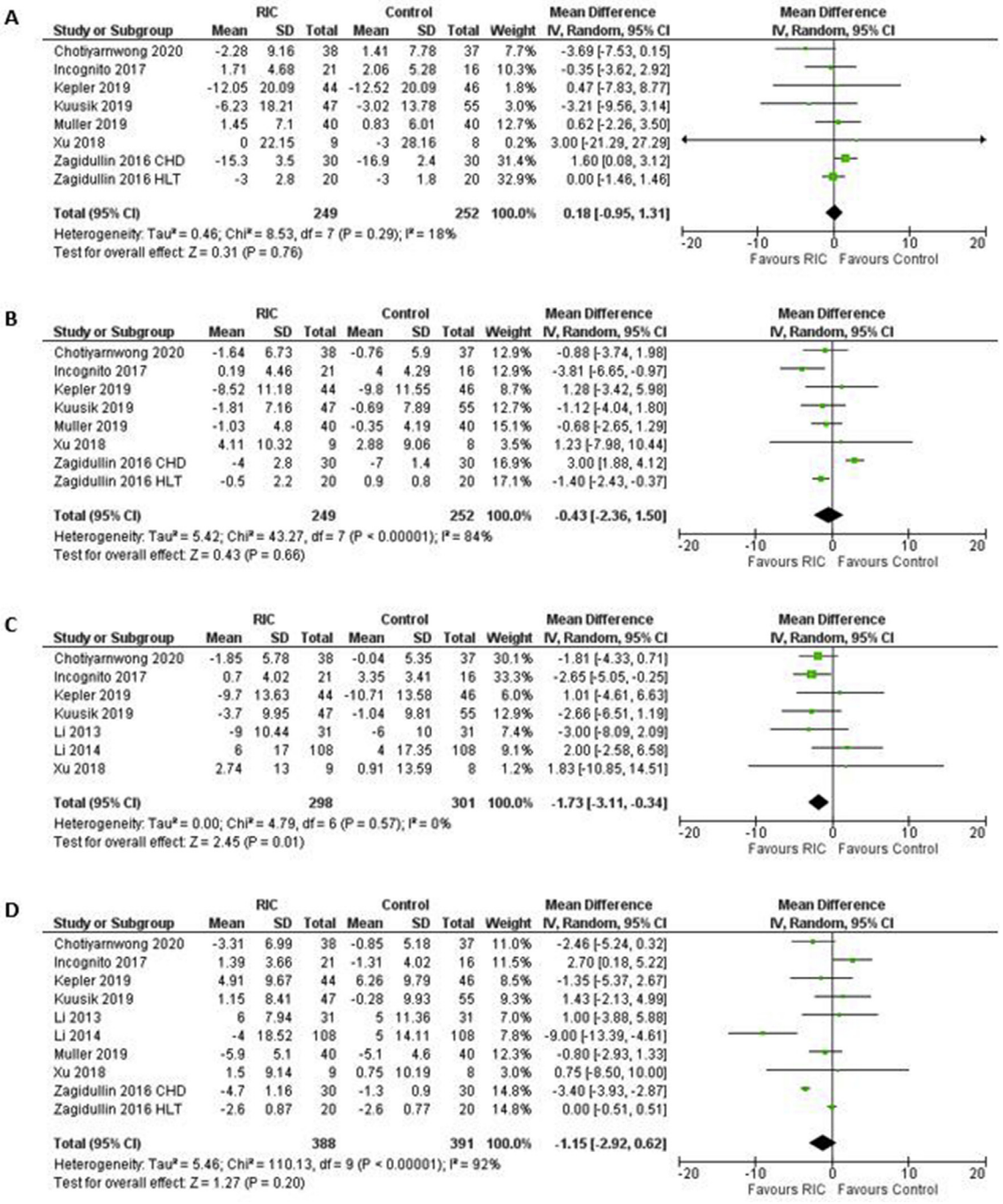

Fig. 2. Changes in systolic and diastolic BP, MAP and HR after acute RIC exposure. Forest plots showing the effects of acute RIC exposure on systolic BP (A), diastolic BP (B), MAP (C) and HR (D). A p-value < 0.05 represents a significant pooled mean difference of overall effect. Horizontal lines across each present 95% CI for each study. The diamond represents the 95% CI for pooled estimates of effect of mean difference. CHD: chronic heart disease group; HLT: healthy group; IV: inverse variance; RIC: remote ischaemic conditioning; SD: standard deviation; Total: number of participants.

3.5. Heterogeneity and publication bias

In general, acute and repeat RIC exposure studies demonstrated a low heterogeneity (I^2 = 0%–18%. Heterogeniety was high in acute RIC exposure studies for diastolic BP (I^2 = 84%) and HR (I^2 = 91%). Egger plots showed minimal evidence of bias (Supplementary Figs. S4 and S5).

3.6. Study quality

The median JADAD scores for acute RIC and repeat RIC exposure included studies were 4 out of a maximum of 5. All trials were of high quality with only two acute RIC exposure studies and two repeat RIC exposure studies not describing the method of randomisation or blinding (Supplementary Tables S2 and S3).

4. Discussion

Our work expands on the previous work of Epps et al. [16] on repeat RIC for improved cardiovascular function. The major findings of this systematic review were: First, the meta-analyses from all studies suggested that acute and repeat RIC exposure decreases MAP; second, repeat RIC exposure has the potential to lower diastolic blood pressure; and

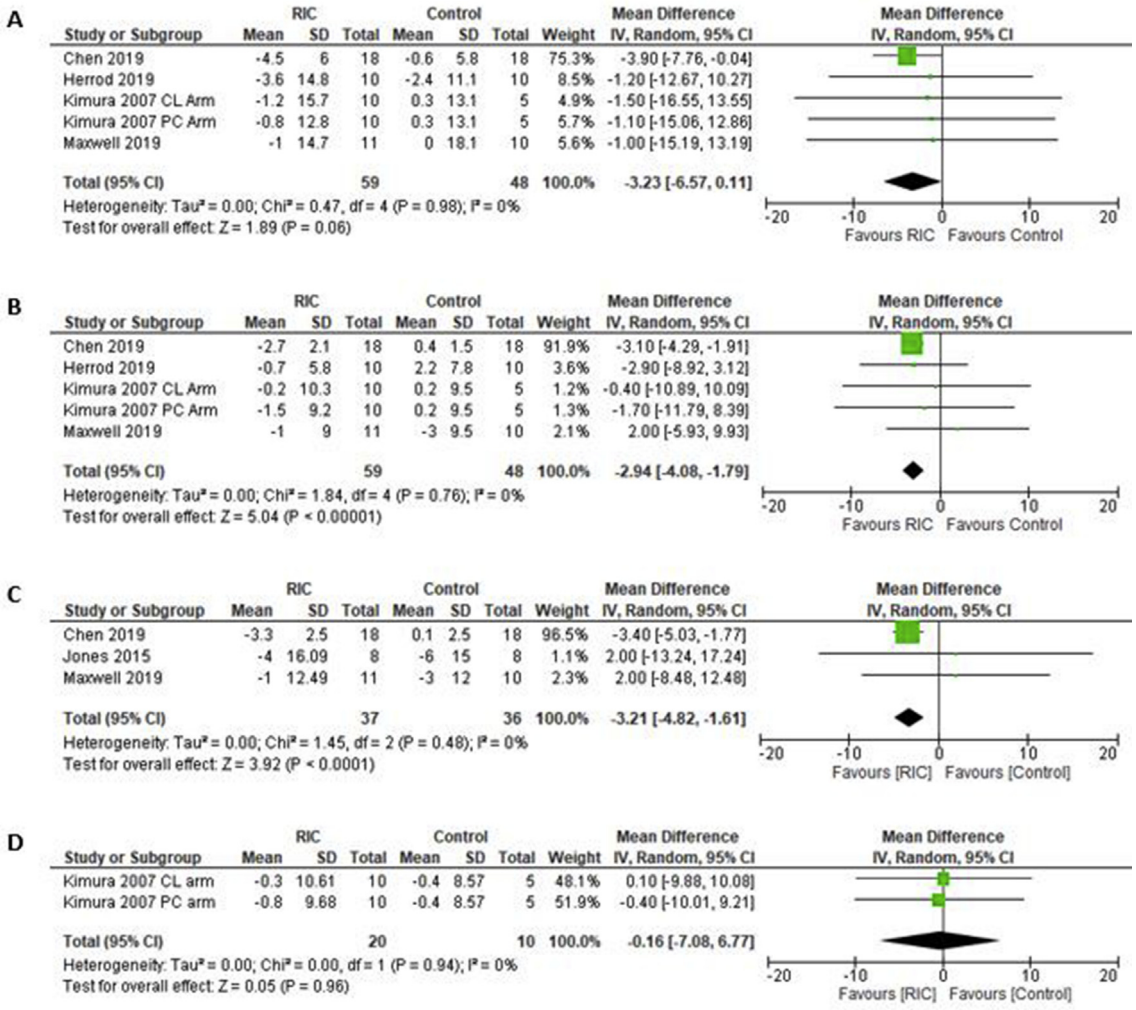

Fig. 3. Changes in systolic and diastolic BP, MAP and HR after repeat RIC exposure. Forest plots showing the effects of repeat RIC exposure on systolic blood pressure (A) and diastolic BP (B), MAP (C) and HR (D). A p-value < 0.05 represents a significant pooled mean difference of overall effect. Horizontal lines across each present 95% CI for each study. The diamond represents the 95% CI for pooled estimates of effect of mean difference. CL: contralateral arm; IV: inverse variance; PC: pre-conditioned; SD: standard deviation; Total: number of participants.

third, relatively fewer studies have been conducted on repeat RIC exposure, compared to acute RIC. This analysis may currently be underpowered due to the limited number of studies and sample sizes included in this meta-analysis.

Our analysis of acute RIC exposure showed that the typical delivery method was 3–4 cycles of 5-min ischaemic periods interspersed with 5-min reperfusion periods in each single session. However, 3 cycles of alternated ischaemic and reperfusion periods per session was adopted in the majority of studies. In contrast, for chronic effects, although our analyses did not clarify the optimal delivery method for repeat RIC exposure, it appears that the majority of the studies adopted four RIC cycles of 5-min (ischaemic period) interspersed with 5-min reperfusion or rest intervals during each session. Sessions were performed either daily or at least 3 days per week in the case of repeat RIC exposure, except in two studies [59,66] which used a 3 times 3-min ischaemia protocol. Preferably, 4 times 5-min exposure appears to be most common application method, at least for lowering blood pressure in people with chronic disease. This intervention shows promise as an adjunct treatment for hypertension management. Despite the relatively few studies, most individual studies have reported anti-hypertensive effects of systolic, diastolic and mean arterial blood pressure following participants' exposure to repeat RIC. The anti-hypertensive effect was sustained for at least one week after cessation of exposure to RIC [60,63].

Repeat remote ischaemic conditioning delivers clinically meaningful blood pressure reductions and has potential as an adjunct therapeutic modality for controlling blood pressure. Repeat RIC is easy to use/apply, appropriate for people with mobility issues, and requires less time commitment (about 35 min per session) than aerobic exercise. Moreover, repeat RIC can be performed anywhere at an individual's convenience providing exceptional flexibility. While RIC has mostly been utilized in a clinical setting, as no adverse events have been reported, there is no obvious reason why individuals cannot obtain a blood pressure cuff and self-administer the RIC protocol. Madias [19], for example, made extensive, self-administered, use of RIC when collecting data for publication.

4.1. *Effect of acute versus repeat RIC outcome responses*

Our meta-analysis showed no significant changes in systolic and diastolic BP or HR following acute RIC exposure but MAP was significantly reduced. It is possible that a single session of RIC is insufficient to reduce blood pressure. It is widely accepted that in the period immediately following physiological stress (e.g. exercise or RIC) there is an acute hypotensive response that can be quite pronounced, but blood pressure often returns to baseline levels within a matter of hours [67]. It is therefore perhaps unsurprising to note that the acute RIC response is

less than that observed from repeated exposure; the acute response is likely to be both more variable and transient, which may explain the higher heterogeneity. In contrast, the accumulated repeat effect confirms the anti-hypertensive benefit of repeat RIC. The magnitude of the reduction is similar to those reported by other exercise modalities (e.g. endurance exercise) [68]. There were observed reductions (~3 mmHg) in systolic and diastolic blood pressure and MAP across the included studies combining both healthy individuals and patients with chronic disease. Some of these patients were treated with anti-hypertension medication which is unlikely to have influenced the magnitude of RIC's pressor effect. For both, acute and repeat RIC, the sub-analyses of healthy versus patients treated with anti-hypertension medication showed mixed results. For healthy individuals DBP decreased with acute but not repeat RIC. For patients receiving hypertension treatment SBP and MAP decreased with repeat RIC. The limited number of studies and patient numbers are most likely responsible. Moreover, exercise training increases an individual's ability to exercise in terms of intensity and duration that may augment the acute response providing more and lasting post-exercise hypotensive effect over time, which explains the possible interaction between acute and chronic exercise [67]. These results show promise for future research to substantiate these benefits.

Overall, repeat RIC significantly reduced diastolic BP and MAP by about 3 mmHg. This should be considered clinically meaningful since a reduction in diastolic BP is beneficial for individuals with isolated elevation of diastolic BP. This is equally important as reducing systolic BP as isolated elevation of diastolic BP is more closely related to end-organ damage [69]. Staley et al. [70] found increased diastolic BP to be associated with the reduction of executive functioning performance in cognitively healthy older adults which highlights increased DBP as a risk factor for neurodegeneration. Also, a higher DBP has been associated with a higher bleeding risk in patients with nonvalvular atrial fibrillation [71]. Although, systolic BP has been known to have greater effect for BP control [72], both systolic and diastolic BP independently influenced cardiovascular outcomes, therefore diastolic BP should not to be overlooked [73].

Qualitative synthesis revealed that there were observed BP reductions in individual repeat RIC studies [60,64], with the exception of the Banks et al. [65] study. Banks et al. [65] reported no change in BP, although they exposed participants to repeated RIC similar to Jones et al. [60] and Maxwell et al. [63] using the 4 × (5 min cuff inflation x 5 min deflation) for a duration of approximately one week with equal frequency. A possible explanation for these conflicting results could be the (1) difference in populations with respect to the gender distribution that was predominantly male compared to Banks et al. [65]; (2) Ischaemic inflation pressure difference applied during the RIC exposure. Both Jones et al. [60] and Maxwell et al. [63] employed 220 mmHg inflation pressure while Banks et al. [65] used the standard 200 mmHg ischaemic inflation pressure; (3) the occurrence of a possible "floor" effect for BP reduction as participants of the Banks et al. study had lower systolic BP at baseline; and (4) method of BP measurement employed since the position (both body and arm) assumed by an individual influences variations in BP measurements [74,75] – the varying distances between the heart level and the arm support of the chair, can be large depending on the height of the person (e.g. it can be larger than 25 cm in tall persons) [75]. BP devices use a different measuring technique (i.e. auscultatory, automated, oscillometric and ultrasound) and the location has an effect on the BP measurement. Although the brachial artery is the standard location for BP measurement, other devices measure pressure at the wrist and fingers. However, it is important to know that at different parts of the arterial tree, systolic and diastolic pressures differ considerably – while systolic pressure rises more in distal arteries, diastolic pressure declines [74]. Regardless, the use of BP monitoring devices may be preferred in certain situations.

4.2. Limitations

The major limitations of this review are (i) the small sample size in the included studies; and (ii) not all studies provided data suitable for pooling. Another significant limitation is the fact that we could not perform sub-analysis to determine the difference in result with regards to the effect of age, population (health and unhealthy), frequency of RIC exposure and duration of study. Although, the protocols for RIC application varied across studies, this allowed the differing protocols characteristics to be related to the presence or absence of beneficial effect on the blood pressure variables. Our study may have been underpowered by the sample size to detect a statistically significant mean reduction difference in systolic blood pressure.

5. Conclusions

The available literature indicates that acute RIC exposure does not alter blood pressure, but repeated RIC may have beneficial anti-hypertensive effects. Our work suggests repeat RIC may be a safe, effective, economical and simple therapy to manage blood pressure, offering venue flexibility and manageable time commitment, for both healthy and clinical individuals that could be adopted as an adjunct treatment modality. Given the limited data availability on the effects of RIC exposure in blood pressure management as well as other cardiovascular variables, more research is warranted.

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Declaration of competing interest

None of the authors declare any conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijchy.2021.100081.

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