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Effects of remote ischemic conditioning on cognitive performance: A systematic review

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ABSTRACT

The aging process leads to subtle decline in cognitive function, and in some overt dementia. Like physical activity Remote Ischemic Conditioning (RIC) may ameliorate these changes on cognitive impairment in humans. The purpose of this study was to compared the effects of single, repeated short-term and long-term treatment RIC, and analyze its effect registered as immediate vs. long-term on cognitive performance in humans. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was registered with PROSPERO, number (CRD42021285668). A systematic review was conducted to identify relevant studies through six healthcare science databases (Cochrane, PubMed, EMBASE, EBSCO, Scopus, and Web of Science) up to December 2021. Eligibility criteria included (1) a study sample of participants aged ≥18 years, (2) post-intervention changes on cognitive performance in humans, and (3) this systematic review included only randomized controlled trials of RIC in humans. The quality of the included studies was assessed by GRADEpro tool. A total of 118 articles were initially identified, 35 of which met the inclusion criteria. Based on title/abstract, age and RIC protocol, 14 articles were included in this review: 5 studies investigated the immediate and long-term effect of a single RIC (n = 370 patients), 4 studies examined intermittent short-term RIC (n = 174 patients) and 5 studies evaluated repeated long-term RIC (n = 228 patients). A single preoperative RIC treatment had an immediate effect that disappeared at one week. Short-term RIC showed either a positive or no effects on cognitive function. The majority of studies examining long-term RIC treatment showed improvements in cognitive performance, particularly in very old adults and older patients with cognitive impairments. Single RIC treatment did not show any persisting effect on cognition. However, repeated short term RIC showed some improvement and long-term RIC may improve cognitive performance after stroke or enhance neuropsychological tests in patients diagnosed with vascular dementia. The mixed results might be explained by different RIC treatment protocols and populations investigated.

1. Introduction

The human aging process frequently leads to declines in cognitive function [1]. As part of the normal aging process, middle-aged and older adults may experience subtle memory impairments and attenuated cognitive performance [2]. At the same time, aging increases the risks of chronic diseases such as hypertension, obesity, dyslipidemia, and diabetes, which could lead to stroke, degeneration of white matter regions and local microvascular hypoperfusion in the brain and ultimately vascular dementia [3]. Cognitive function is negatively affected by the above changes, which altogether may impose a significant negative impact on activities of daily living, social engagement and quality of life, especially in older adults [4].

Physical exercise, including resistance training [5], aerobic exercise [6], tai chi [7] and yoga [8] may induce protective effects on brain microcirculation, metabolism and cognitive performance in older adults by stimulating brain-growth factors, diminishing oxidative stress and less white matter damage [9]. Nevertheless, patients that suffer from cognitive impairments may not always be able to handle these types of physical activities.

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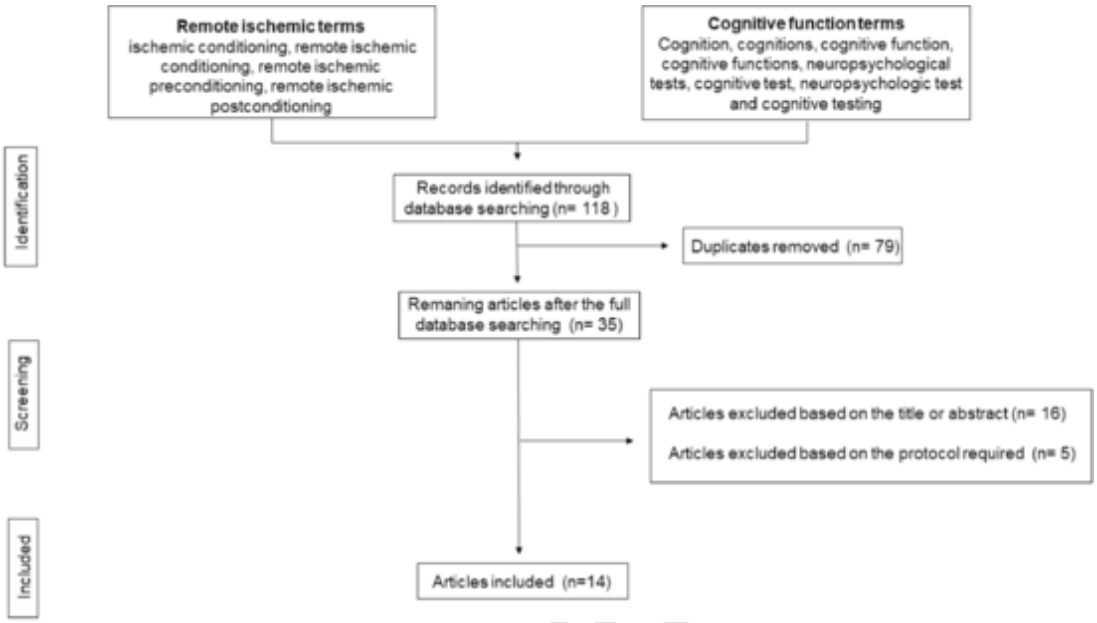

Fig. 1. PRISMA flow diagram.

Remote ischemic conditioning (RIC) shares the physiological effects of physical activity [10–13], and over time, may have the benefit of being administered safely and remotely at home [14]. RIC is a non-invasive and feasible method to stimulate various organs in the human body, such as skeletal muscle [15], heart [16] and brain [17]. Typically, RIC is performed in the form of repeated bouts of brief ischemia followed by reperfusion using a blood pressure cuff. The standard protocol of RIC in humans consists of 3–5 cycles of ischemia of 5 min duration while at rest interspaced by cuff release and limb reperfusion in alternating 5 min intervals [18–20]. A relatively high occlusion pressure (≥200 mmHg) are typically applied to the upper or lower extremity [11].

It has been shown that RIC immediately enhances dynamic cerebral autoregulation in healthy adults [21] and a single RIC pre-operative treatment during cardiac and colon surgery have indicated immediate post-operative improved cognitive tests although lasting no longer than one week (19,14). Long-term studies using repeated bilateral RIC (both arms) for one year have reported a decreased recurrent stroke incidence in high risk patients with intracranial arterial stenosis [22] while 300 days of RIC intervention has been shown to improve cognition in patients with subcortical ischemia and vascular dementia [20].

Based on these reports, it seems that RIC may induce positive effects on cognition. However, the effects of short- and long-term RIC on cognition have not been systematically reviewed. Hence, the aim of this systematic review was to evaluate the short-and long-term effects of RIC on cognitive performance in humans.

2. Methods

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23].

2.1. Protocol and registration

The protocol for this systematic review was published online at International Prospective Register of Systematic Reviews (PROSPERO), number (CRD42021285668).

2.2. Eligibility criteria

2.2.1. Type of studies

Only randomized controlled studies were included.

2.2.2. Type of participants

Women and men aged 18-years or above. Studies were excluded if including systematic reviews, meta-analyses, case series or reports and editorials.

2.2.3. Type of intervention

Studies were included if they investigated the short- and long-term efficacy of RIC in humans, by comparing standardized RIC protocols to sham intervention or performing comparisons to matched control groups. The protocol required in the studies should be described in details providing sufficient information for reproducibility. Also, short-term RIC studies, including single pre-application and short-term RIC treatment (1 to 7 days). The long-term studies included lasted longer than three months.

2.2.4. Outcome measures

Included studies were required to report results of standard cognitive tests used to evaluate the effects of RIC on cognitive performance in humans.

2.3. Search strategy

Studies were retrieved through systematic literature search in MEDLINE via Pubmed, EMBASE via Ovid, CINAHL (including pre CINAHL) via EBSCO, Web of Science, Sports Discus via EBSCO and the Cochrane Central Register of Controlled Trials up to December 2020. The major search terms were (all databases): ("Ischemic Preconditioning"[Mesh] OR (ischaemic OR ischemic OR ischaemia OR ischemia) AND (preconditioning OR preconditionings OR pre-conditioning OR pre-conditionings OR pre conditioning OR pre conditionings) AND “remote ischemic conditioning”, “remote ischemic preconditioning”, “ischemic preconditioning”, (“cognition”[Mesh] OR “cognitions” OR “cognitive function” OR “cognitive functions”) AND (“neuropsychological tests” [Mesh] OR “cognitive test” OR “neuropsychologic test” OR “cognitive

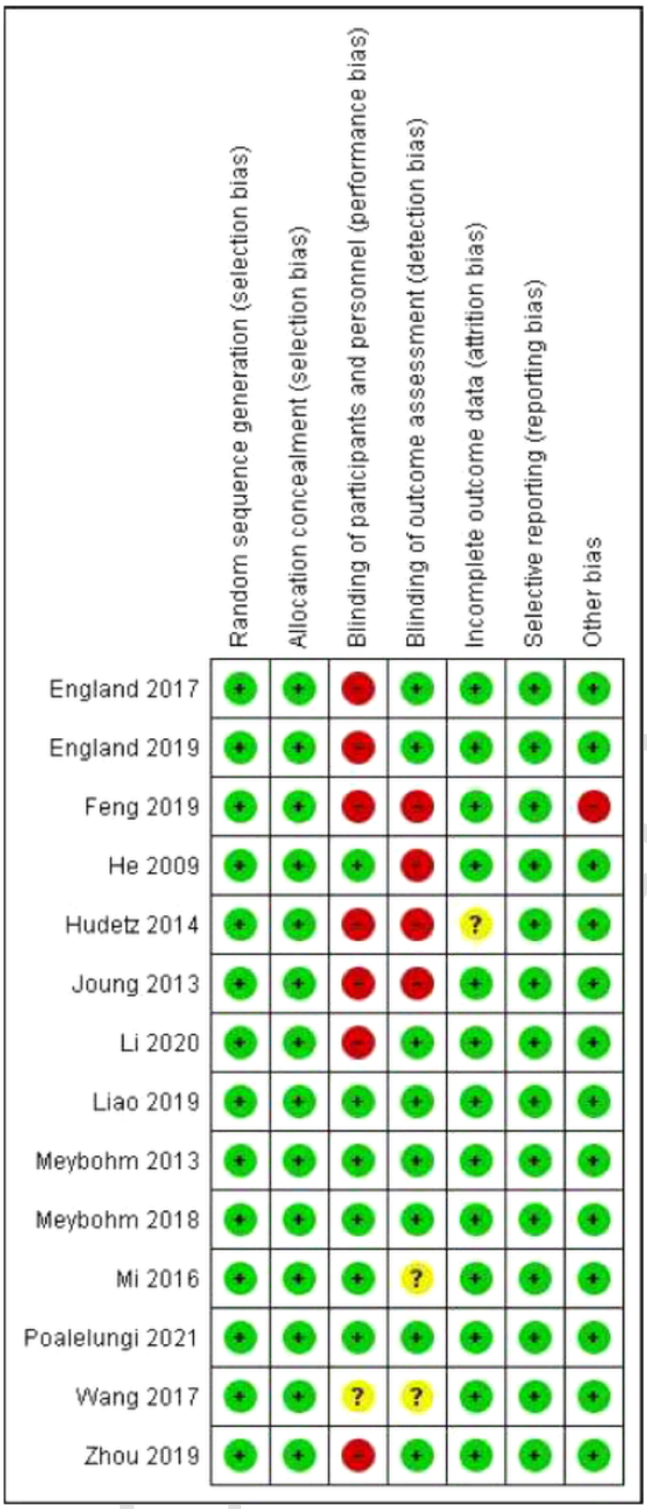

Fig. 2. Summary of risk of bias: review author judgments about each risk of bias item for each included study.

testing") AND ("human"[Mesh] OR "humans"). Only studies published in English language were included

2.4. Study selection

Each article was evaluated by two independent assessors (PA, CS) using a two-stage screening process: (a) summary screening and (b) full-text reading. According to each assessor, a study was considered for full text review based on its title/abstract. Studies that had not met all the inclusion criteria, also had to be excluded by both assessors independently. Any disagreements resulting from this process were settled by consensus.

2.5. Data extraction

The following data were extracted from the included articles: study design (incl. author names, date of publication), clinical population characteristics (age, gender, health status of the study population), trial design, RIC protocol, endpoints and main results.

2.6. Data collection process

Two assessors (PA and SC) screened all titles and abstracts individually. If consensus could not be reached, consensus was sought with a third reviewer (RB) available to assist.

2.7. Risk of study bias

Assessment of study bias was conducted using Cochrane's risk of bias tool [24]. Assessment scores of biases in judgment items included the following: (1) Adequate (A risk of bias that will not have a significant impact on the results), (2) Unclear (Bias that may have a significant impact on the results), and (3) Inadequate (Bias that might have a negative impact on the results). Each study was assessed individually by the principal author (SA) based on 7 explicit criteria (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selecting reporting and anything else). Attrition bias and reporting bias also were considered, as well as selection bias, performance bias, and detection bias.

2.8. Quality assessment

GRADE methodology was used to evaluate the quality of the retrieved evidence (GRADEpro, Version 20. McMaster University, 2014).

3. Results

3.1. Study selection

A total of 118 study articles were identified during the systematic search of the aforementioned databases. On the basis of the title and abstract, 79 publications were excluded (Flow diagram is shown in Fig. 1). Of the remaining 36 articles, 14 met the specific eligibility criteria, including demonstrating sufficient validity and methodological quality.

3.2. Study characteristics

3.2.1. Methodological aspects

All included studies had (a) randomized allocation procedures, and (b) involved either a single or repeated short- or long-term RIC intervention protocols.

3.2.2. Participants

A total of 14 studies with 772 participants were included in the overall analysis, aged over 18-year-old. Studies using a single RIC treatment included patients undergoing colon carcinoma surgery [18] and patients with acute ischemic stroke [25–28], while the remaining studies included patients undergoing vascular surgery [19,29–31]. Repeated short and long-term studies included older patients with subcortical ischemic vascular dementia [20], small-vessel disease–related mild cognitive impairment [32,33], intracranial atherosclerotic stenosis [22] and patients with acute ischemic stroke [34].

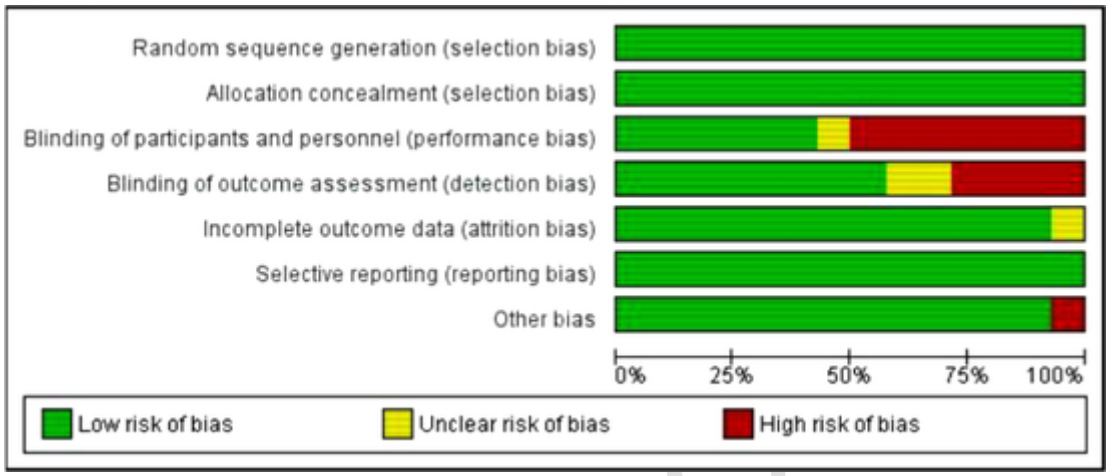

Fig. 3. Bias distribution (%) in each included study.

3.2.3. Outcome variables

Changes related to RIC on cognitive performance were assessed by neuropsychological standard tests. In the included studies, the tests used to evaluate the effects of RIC on cognition were: Mini–Mental State Examination (MMSE), The Montreal Cognitive Assessment (MoCA), Seoul Verbal Learning Test (SVLT), digit span forward test, digit span backward test, trail making test part A, trail-making test part B, digit symbol substitution test (DSST), Modified Telephone Interview for Cognitive Status (TICS-M) and comprehensive neurocognitive test battery.

3.3. Risk of bias of individual studies

Our risk of bias assessments (RoB) for all included studies are presented in Fig. 2. Further, Fig. 3 summarizes RoB expressed as percentage distribution across all studies included. In four studies [18,30,31,34], a high risk of bias was noted for blinded outcome assessment. Additionally, seven studies [22,25,27,28,30,31,34] had high risk bias for blinding of participants and personnel and one study [34] showed high risk bias for other bias. Unclear risk bias were identified in three studies such as incomplete outcome data [30], blinded outcome assessment [32,33] and blinding of participants and personnel [33]. Random sequence generation, allocation concealment, incomplete outcomes data, selective reporting and other bias were considered at low risk of bias in most of the included studies.

3.4. Study quality assessment

According to GRADEpro, single application and intermediate duration RIC treatment RCTs were regarded as moderate-quality evidence. In most short-term studies, outcome assessments and subjects were not blinded. The quality of evidence associated with longitudinal RCTs was also considered to be moderate. The majority of longitudinal RCTs included blinding of both participants and researchers, though cognitive performance was typically considered a secondary outcome (Table 4).

3.5. Effects of short-term RIC on cognitive function

3.5.1. Single preconditioning RIC (pre-RIC) treatment before surgery procedure

Single pre-RIC treatment studies in humans revealed inconsistent but no long-term effects (Table 1). Subtle immediate positive effects were observed in some studies, manifested as retention or enhancement of cognitive test performance [18,30], while other studies were unable to detect any measurable intervention effects [19,29,31] and no significant long-term effects could be detected. Specific study findings are discussed in detail below.

In a randomized, double-blind study, Meybohm et al. [29] evaluated cognitive performance in 180 patients before and 5-to-7 days after cardiac surgery. All patients received propofol (1.5 mg/kg to 6 mg/kg), sufentanil (0.5 mg/kg to 1.5 mg/kg) and rocuronium (0.6 mg/kg). Cognitive dysfunction was assessed by a comprehensive test battery including the domains: memory, motor skills, attention, and executive function. The RIC protocol consisted of four bouts of 5-minutes ischemia (200 mmHg) followed by 5-min cuff release and reperfusion on the upper body. RIC was applied on the arm to allow continuous access to the blood pressure cuff during surgery. According to a summary z-score analysis, there was no significant reduction on post-operative cognition [RIC (1.14 ± 4.02; $p = 0.228$) vs control (2.16 ± 5.30)]. Likewise, no statistically significant difference in the effect of RIC on 5–7 days, postoperatively cognitive function. No effect on cognitive performance was detected after 3 and 12 months follow-up either and RIC did not prevent long-term myocardial dysfunction following cardiac surgery [19,29].

RIC was also investigated by Joung et al. [31] for its effects on postoperative cognitive dysfunction in patients undergoing off-pump coronary artery bypass graft surgery. RIC was applied using 220 mmHg on an upper limb following four cycles of 5 min of ischemia with 5 min of reperfusion prior to coronary artery anastomosis. The patients were also administered by 0.2 mg/kg etomidate intravenously along with continuous infusion of propofol and remifentanil using a target control infusion. An assessment of cognitive status was performed one day before surgery and again seven days after surgery. There were no significant differences between the preoperative compared to postoperative periods on cognitive tests. Moreover, the incidence of postoperative cognitive dysfunction (defined as decreased postoperative test values more than 20% of the baseline values in more than two of the six cognitive function tests that were performed) was not reduced in RIC group (31.4% −11 patients) compared to the control group (28.6% −10 patients).

In contrast, Hudetz et al. [30] examined the effect of acute RIC on cognitive performance in 30 patients after cardiac surgery using cardiopulmonary bypass. A combination of etomidate (0.03 mg/kg), fentanyl (3 to 5 mg/kg), and rocuronium (1 mg/kg) was used to induce anesthesia in the patients. Adopting a RIC protocol used in previous studies (4 cycles of 5 min of ischemia with 5 min of reperfusion between cycles using a blood pressure cuff inflating 200 mmHg on upper limbs before cardiac surgery) [29,31], they showed that patients treated preoperatively by RIC had preserved cognitive tests after surgery at 1-week. Non-treated controls demonstrated a decline in tests in 2 of 3 major neuropsychometric domains, with no difference in delirium scores between groups [30].

Table 1
Effects of single preconditioning RIC (pre-RIC) treatment before surgery procedure.

Authors	Subjects	Trial design	Protocol used	Outcomes and main results
He et al.	RIC: n = 45 (22 W/ 23 M)	Randomized	3 cycles of 5 min of ischemia with	Primary outcome was cognitive test MoCA
(2019)	Age: 68 ± 7	Single-blinded	5 min of reperfusion between cycles	RIC enhanced cognition assessed by MoCA test
	Control: n = 45 (17 W/ 28 M)	Researches masked	Where used: Static on the right upper	First day after surgery (26.87 ± 0.84 vs 25.96 ± 0.85)
	Age: 68 ± 3	Subjects blinded	Period: Once before cardiac surgery	Third day after surgery (27.49 ± 0.66 vs 27.02 ± 0.9)
	Population: PUCS		Cuff pressure used: 200 mmHg	
Hudetz et al.	RIC: n = 15	Randomized	4 cycles of 5 min of ischemia with	Primary outcome was cognitive function assesed by neuropsychometric test
(2014)	Age: 66 ± 6	Single-blinded	5 min of reperfusion between cycles	RIC prevented deterioration of verbal and non-verbal memory
	Control: n = 15	Researches blinded	Where used: Upper limb	One week after surgery only control group declined
	Age: 65 ± 9		Period: Once before cardiac surgery	
	Population: PUCPB		Cuff pressure used: 200 mmHg	
Meybohm et al.	RIC: n = 90	Randomized	4 cycles of 5 min of ischemia with	Primary outcome was postoperative neurocognitive dysfunction
(2013)	Age: 70 (42–86)	Double-blinded	5 min of reperfusion between cycles	No significant change in cognitive function
(2018)	RIC sham: n = 90	Researches blinded	Where used: Upper limb	(pre vs post-operation) between both groups - 1-year follow-up
	Age: 68 (23–83)	Subjects blinded	Period: Once before cardiac surgery	
	Population: CSP	Outcomes blinded	Cuff pressure used (mmHg): RIC:200 / Sham:20	
Joung et al	.RIPC: n = 35	Randomized	4 cycles of 5 min of ischemia with	Cognitive function tests were performed one day
(2013)	Age: 61.1 (7.3)		5 min of reperfusion between cycles	before surgery and again on postoperative day 7
	Control: n = 35		Where used: Upper limb	RIPC did not reduce the incidence of postoperative
	Age: 59.0 (8.3)		Period used: Once after induced anesthesia	cognitive dysfunction (28%) compared to control (31%)
	Population: POPCAB		Cuff pressure used: 200 mmHg	

Abbreviations: R: randomized; RIC: remote ischemic conditioning; PUCS: patients undergoing colon carcinoma surgery; PUOPCAB: patients undergoing off-pump coronary artery bypass graft surgery; PUCPB: patients undergoing elective coronary artery or valve surgery using cardiopulmonary bypass; CSP: cardiac surgery patients; POPCAB: patients who underwent off-pump coronary artery bypass graft surgery; MOCA: The Montreal Cognitive Assessment, SBP: systolic blood pressure.

He at al [18]. detected an immediate effect on cognitive tests in 90 older patients following RIC before colon surgery. The patients were induced to midazolam (0.02 mg/kg) and sufentanil (0.1 mg/kg) intravenously via a peripheral vein, then performed a dorsalis pedis catheterization under local anesthesia using 1% lidocaine. Cognition was assessed seven days post-operatively using the Montreal cognitive assessment (MoCA) tool while their RIC protocol consisted of 3 cycles with 5-minute ischemia applying 200 mmHg cuff pressure to the upper limbs, each separated by 5-minutes of cuff release and reperfusion. Notably, MoCA scores were significantly higher following RIC compared to control treatment on the first (26.87 ± 0.84 vs 25.96 ± 0.85, $P < 0.001$) and third days (27.49 ± 0.66 vs 27.02 ± 0.92, $P = 0.009$) following surgery. There was however no difference between groups seven days after surgery. Further, secondary outcomes showed that RIC reduced serum concentrations of interleukin-1b (IL-1b), tumor necrosis factor-a (TNF-a), and S100B proteins compared with controls ($P < 0.001$), and authors suggested that the observed acute effect could be related to an immediate decrease in inflammation response.

3.5.2. Intermediate duration RIC treatment: until 1-week postconditioning-RIC (post-RIC) treatment after acute ischemic stroke with long-term follow up

Studies using short-term repeated application of RIC treatment (1–7 days) showed no consistent results and reported neutral effects in one study [26–28] but improved long-term cognitive performance in another study [25] (Table 2).

Poalelungi et al. [26] found that RIC might reduce cognitive disability among 40 patients who suffered from acute ischemic stroke. During the first five days of hospitalization, patients were treated with five cycles of 3-min inflation and 5-min reperfusion twice daily (in the mornings and afternoons) with an occlusion pressure of 180 mmHg. After six months, the median difference in MoCA score was −2 in the sham group and −3 in the RIC group, but neither of these differences reached statistical significance.

In addition, England et al. [27] investigated the cognitive performance in 26 acute stroke patients. The patients received 4 cycles of RIC with 5 min reperfusion (20 mmHg above systolic blood pressure) in the nonparetic upper body within 24 h of ictus. At day 90, the secondary outcome was cognitive function measured by MMSE and there were no significant difference on between groups. However, RIC were feasible, well-tolerated without side effects and increase at day 4 heat shock protein 27 (HSP27).

Similarly, England et al. [28] showed that RIC had no effect on cognition in 60 patients with hyperacute stroke. The patients were divided into 3 blocks of increasing RIC dose (20 patients had 4 cycles of cuff inflation and deflation with 20 mmHg above SBP in the non-paretic arm; 20 patients had a second dose one hour after the first dose; and the rest of patients had twice-daily with a total of 8 doses), starting within 6 h of ictus. After three months, cognitive performance had no significant differences between groups using TICS-M test as a secondary outcome (RIC: 23 [20–25] / Sham: 23.5 [21–27]).

In contrast, Li et al. [25] analysed the effects of RIC on cognitive impairments in 48 older patients who had clinical diagnosis of acute supratentorial ischemic stroke. Their RIC protocol involved 4 cycles of RIC with 5 min reperfusion (20–30 mmHg above systolic blood pressure) in the nonparetic arm, performed daily for seven days. Cognitive

Table 2
Effects of intermediate duration RIC treatment: 1-week postconditioning-RIC (post-RIC) treatment after acute ischemic stroke with long-term follow up.

Authors	Subjects	Trial design	Protocol used	Outcomes and main results
Poalelungi et al	RIC: $n = 18$ (7 W/11 M)	Randomized	5 cycles of 3 min of ischemia with	Primary outcome was the difference in infarct volume on day 3–4 / 180
(2021)	Age: 67 ± 6	Double-blinded	5 min of reperfusion between cycles	Slightly larger in the sham group compared to RIC group ($p = 0.4$)
	RIC sham: $n = 22$ (9 W/13 M)	Researches masked	Where used: Non-paretic upper limb	Cognitive function was the secondary outcome
	Age: 64 ± 9	Subjects masked	Period: Twice daily during the first 5 days	MoCA was slightly higher in the RIC group
	Population: PAIS	Outcomes masked	Cuff pressure used (mmHg): RIC:180/Sham: 30	The median difference score for MoCA was −2 in the sham group and −3 in RIC group
Li et al.	RIC:24 (10 W/14 M)	Randomized	4 cycles of 5 min of ischemia with	Primary outcome measure was tolerability and feasibility of RIC
(2020)	Age: 68 ± 5.47	Single-blinded	5 min of reperfusion between cycles	RIC was well tolerated without adverse events and feasible to use
	Sham RIC:24 (8 W/16 M)	Researches masked	Where used: Upper limb	Secondary outcomes were neurological and cognitive function
	Age: 67 ± 6		Period: Daily for 7 days	RIC group improved MOCA and ADAS-cog test
	Population: PPSCI		Cuff pressure used (mmHg): RIC:20–30 < SBP or 30	After 90 and 180 days MOCA test ($p < 0.05$)
				After 180 days ADAS-cog test ($p < 0.05$)
England et al.	RIC:13 (5 W/ 8 M)	Randomized	4 cycles of 5 min of ischemia with	Primary outcome measure was tolerability and feasibility of RIC
(2017)	Age: 74.7 (10.8)	Single-blinded	5 min of reperfusion between cycles	RIC was well tolerated without adverse events and feasible to use
	Sham RIC:13 (4 W/9 M)	Outcomes masked	Where used: Non-paretic arm	Secondary outcome was cognitive function
	Age: 77.7 (10.4)		Period: within 24 h of ictus	After 90 days there were no
	Population: PAIS	Cuff pressure used (mmHg): RIC:20 above SBP/ Sham:30	RIC: 26.5 (3.3) / Sham: 23.2 (5.7)	difference between groups on MMSE
England et al.	RIC:31 (10 W/21 M)	Randomized	4 cycles of 5 min of ischemia with	Primary outcome measure was feasibility of RIC
(2019)	Age: 70.9 (13.4)	Single-blinded	5 min of reperfusion between cycles	RIC was feasible in terms of adherence
	Sham RIC:29 (14 W/15 M)	Outcomes masked	Where used: Non-paretic arm	Secondary outcome was cognitive function
	Age: 73.7 (10.2)		Period: Until day 4 - 3 blocks of increasing RIC dose	After 90 days there were no difference between groups on TICS-M
	Population: PAIS	Cuff pressure used (mmHg): RIC:20 above SBP/ Sham:30	RIC: 23 [20–25] / Sham: 23.5 [21–27]	

Abbreviations: R: randomized; RIC: remote ischemic conditioning; W: women; M: men; PAIS: patients with acute ischemic stroke; PPSCI: patients with post-stroke cognitive impairment; MOCA: The Montreal Cognitive Assessment, MMSE: Mini-mental status examination, TICS-M: Modified Telephone Interview for Cognitive Status; SBP: systolic blood pressure.

performance was listed as a secondary outcome and was assessed by MoCA scores at 90 days and 180 days and both the absolute difference between the groups and the changes in scores from baseline showed significant improvements in the RIC group compared to non-treated controls. By 180 days using Alzheimer's Disease Assessment Scale-cognitive, 75% of patients in the RIC group demonstrated improvements in cognitive test scores versus 45.8% in control group ($P = 0.039$) [25].

3.6. Long-term RIC treatment and cognitive performance

As summarized in Table 3, longitudinal repeated long-term RIC studies generally have reported positive effects on cognitive performance [20,22,33,34], and only one study failed to demonstrate any impact at 1-year follow-up [32]. No studies exceeded one year duration.

Mi et al. [32] assessed the responses of RIC on cognitive performance in a very small study including 17 patients with cerebral small vessel disease (SVD). They used 5 ischemia–reperfusion cycles of RIC on both upper limbs twice a day for 1 year, utilizing pressure at 200 mmHg. Secondary outcomes as MMSE and MoCA scores did not differ significantly between pre- and post-treatment in either group. Although, when compared to control group secondary outcomes showed that the RIC group accelerated mean flow velocity of the left middle cerebral artery assessed by transcranial doppler (57.33 (52.33–61.34) compared to 51.33 (48.83–58.33), respectively), and the post-treatment dizziness handicap inventory score was reduced (18 (13–19) as compared to 34 (21–45), respectively). In addition, the post-treatment volume of the white matter lesions (WMLs) was decreased 4.19 cm^3 (2.96–7.25) vs. 6.06 cm^3 (4.67–10.95).

On the other hand, Wang et al. [35] evaluated cognition using MMSE and MoCA in 30 patients with patients with SVD, applying the same treatment regimen (5 cycles of ischemia followed by reperfusion twice a day for a year, applying pressure of 200 mmHg on both upper limbs). The primary endpoint was change in brain lesions and cognitive tests performance was a secondary endpoint. At 1 year (compared to baseline), the white matter hyperintensities volume in the RIC group was significantly reduced (9.10 ± 7.42 versus 6.46 ± 6.05 cm^3), whereas there was no significant difference in the sham-RIC group (8.99 ± 6.81 versus 8.07 ± 6.56 cm^3). However, at 1-year follow-up both groups improved visuospatial and executive ability evaluated by MoCA test, RIC ($n = 14$) 0.639 versus Control ($n = 16$) 0.191.

Feng at al. [34] analyzed the effects of RIC on neuropsychological evaluation in 86 patients of noncardiac ischemic stroke. The RIC group received 5 cycles of 5 min ischemia with 5 min of reperfusion between cycles with 200 mmHg pressure on upper limb of the side unaffected by the stroke, daily for six months. Patients in the RIC group had significantly higher MoCA scores and lower ADL scores (less disability), as compared to the control group ($P < 0.05$). Moreover, RIC significantly

Table 3
Long-term post-RIC treatment on cognitive test performance.

Authors	Subjects	Trial design	Protocol used	Outcomes and main results
Zhou et al. (2019)	RIC: $n = 30$ Age: 83.5 ± 2.3 Sham RIC: $n = 28$ Age: 84.2 ± 1.6 Population: VEPIAS	Randomized Blinded Researchers masked Period: Twice daily for 300 days	5 cycles of 5 min of ischemia with 5 min of reperfusion between cycles Where used: Bilateral upper arms twice daily RIPC compared to sham group improve MMSE or MoCA Cuff pressure used (mmHg): RIC:200 / Sham:30	The primary outcome was the progression of WMHV RIC prevented the progression of WMHV in two tests Secondary outcomes was cognitive function scores 180-day and 300-day follow-ups (all $p < 0.05$)
Liao et al. (2019)	RIC: $n = 18$ Age:67.6 (7.2) Sham RIC:19 Age: 70.6 (7.4) Population: SIVD	Randomized Double-blinded Subjects masked Researchers masked	5 cycles of 5 min of ischemia with 5 min of reperfusion between cycles Where used: Bilateral upper limb twice daily Period: Ttwice daily over 6 months Cuff pressure used (mmHg): RIC:200 / Sham:60	The primary outcome was changes in neuropsychological tests Only RIC group improved (JLO, HVLTR, COWAT, TMTAB) The secondary outcomes were Hs-CRP, WMLV and DTI There were no significant diferrence between groups
Feng et al. (2019)	RIC: $n = 42$ (28 M / 14 W) Age: 64.16 ± 7.71 Control: $n = 44$ (26 M / 18 W) Age: 63.91 ± 7.61 Population: PNIS	Randomized	5 cycles of 5 min of ischemia with 5 min of reperfusion between cycles Where used: Upper limb of the side unaffected by the stroke Period: Daily for 6 months Cuff pressure used (mmHg): RIC:200	Cognitive function was the primary outcome Patients in the RIC group had significantly higher MoCA scores and lower ADL scores, as compared to the control group ($P < 0.05$) RIC group significantly improved scores in neuropsychological evaluations than control group
Wang et al. (2017)	RIC: $n = 14$ Age: NR Control: $n = 16$ Age: NR	Randomized Double-blinded Subjects blinded Researchers blinded	5 cycles of 5 min of ischemia with 5 min of reperfusion between cycles Where used: Both upper limbs Period: Twilce daily for 1-year	The primary outcome was the change of brain lesions WMHV in the RIC group was significantly reduced (9.10±7.42 versus 6.46±6.05 cm3; $P = 0.020$) Secondary outcomes were changes of cognitive function
Mi et al. (2016)	RIC: $n = 9$ Age: 67.0 (60.0–70.0) Sham: $n = 8$ Age: 59.5 (47.5–66.0) Population: PCSVD	Randomized Double-blinded Subjects blinded Researchers blinded	5 cycles of 5 min of ischemia with 5 min of reperfusion between cycles Where used: Both upper limbs Period: Twice daily for 1-year Cuff pressure used (mmHg): RIC:200 / Sham:50	The primary outcome was the change of brain lesions WMHV in the RIC group was significantly reduced 4.19 (2.96–7.25) vs. 6.06 (4.67–10.95) Secondary outcomes were changes of cognitive function No difference between 2 groups in MMSE and MoCA tests

Abbreviations: RIC: remote ischemic conditioning: RIPC: remote ischemic preconditioning; SIVD: patients with subcortical ischemic vascular dementia; VEPIAS: very elderly patients with intracranial atherosclerotic stenosis; W: women; H: healthy individuals; PVS: patients undergoing vascular surgery, MMSE: Mini-mental State Examination; MoCA: The Montreal Cognitive Assessment; JLO: Judgment of Line Orientation; HVLTR: Hopkins Verbal Learning Test-Revised; COWAT: Controlled Oral Word Association Test; ,TMTAB: Trail Making Test A and B; PPSCI: Patients with post-stroke cognitive impairment; PNIS: patients of noncardiac ischemic stroke; PCSVD: patients with cerebral small-vessel disease–related mild cognitive impairment; ADAS-cog, Alzheimer's disease assessment scale-cognitive; WMHV: white matter hyperintensities volume; Hs-CRP:: high-sensitive C-reactive protein concentration; DTI: diffusion tension imaging metrics of white matter.

improved performance in visuospatial, executive functioning and attention.

Similarly, Zhou et al. [22] reported improved cognitive performance in 58 very old patients (aged 80–90) with intracranial atherosclerotic stenosis in response to 300 days of RIC intervention. The Authors analysed cognitive impairments by MMSE and MoCA testing and performed MRI-based measurements of white matter hyperintensities (WMHs) at 180 and 300 days of RIC exposure, based on a protocol of 5 cycles of alternating 5-minute periods of passive ischemia followed by 5 min of reperfusion applied bilaterally to the upper arms (200 mmHg) [22]. MMSE and MoCA scores increased significantly at 180 and 300 days in RIC compared to sham group. Notably, their RIC protocol contained a higher RIC dose (5 cycles and twice daily) than usually applied, and RIC was applied bilaterally to both arms. Further, RIC prevented progression of WMHs compared to control treatment [22].

Liao et al. [20] investigated the effects of daily RIC intervention for 6 months on cognitive performance in 37 older patients with subcortical ischemic vascular dementia. The authors evaluated cognitive performance in five domains: memory, language, attention, executive function, and spatial orientation. After 6 months, RIC treatment (5 cycles of ischemia/reperfusion with 200 mmHg pressure applied on both upper limbs) showed significant improvements only in the Judgment of Line Orientation (JLO) test (23.10 ± 1.23) compared to control group (18.56 ± 1.23), respectively; ($p = 0.013$) [20], but not in other domains. No correction for multiple comparisons were made.

4. Discussion

To our best knowledge this is the first systematic review to examine the effects of RIC on cognitive performance in humans. Based on the available data, long-term daily repeated RIC treatment may improve

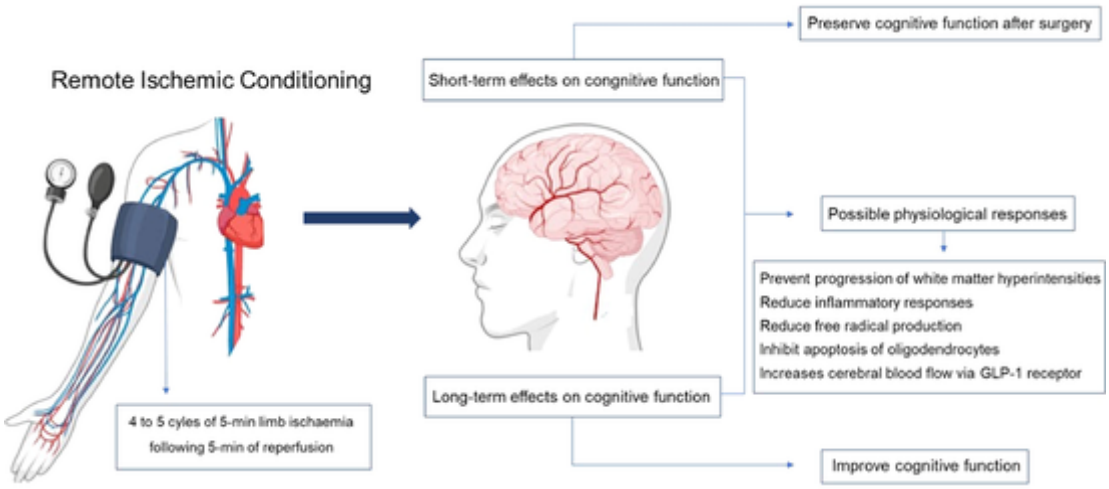

Fig. 4. The physiological effects of remote ischemic conditioning that may related to cognitive functions in humans.

Table 4
Gradepro assessments.

Certainty assessment							Summary of findings		
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%) With RIPC Sham	With RIPC	Impact
Single preconditioning RIC (pre-RIC) treatment before surgery procedure (assessed with: cognitive tests)									
370 (5 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	Single pre-RIC treatment studies in humans revealed inconsistent but no long-term effects		
Intermediate duration RIC treatment: 1-week postconditioning-RIC (post-RIC) treatment after acute ischemic stroke with long-term follow up (assessed with: cognitive tests)									
174 (4 RCTs)	serious[b]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	Studies using short-term repeated application of RIC treatment (1–7 days) showed no consistent results and reported neutral effects in one study but significantly improved MoCA test and significant change in ADAS-cog compared to baseline after acute ischemic stroke. Also, cognitive performance was a secondary outcome in the majority of studies.		
Long-term post-RIC treatment on cognitive test performance (assessed with: cognitive tests)									
228 (5 RCTs)	serious[b]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	Longitudinal repeated long-term RIC studies generally have reported positive effects on cognitive performance, and only one study failed to demonstrate any impact at 1-year follow-up		

CI: confidence interval.
Explanations.
a. Three studies included did not blind outcome assessments and subjects.
b. The cognitive tests were the secondary outcome in most studies.

cognitive performance after 6- 12 months in patients with pre-existing acute or chronic cerebrovascular disease. The effect of short-term RIC (1–7 days) treatment applied in the acute phase after stroke may have an effect on long-term cognitive function, but findings are inconsistent. On the contrary, a single preconditioning RIC treatment before surgery did not show any consistent effect on short term cognitive function and no long-term effects were detected.

These partly conflicting short-and-long-term effects resulting from RIC may be attributed to generally small study samples and in part by (i) type of anesthesia administrated before surgery, (ii) study population (participants without ongoing cerebrovascular disease vs patients with pre-existing acute stroke or vascular dementia), (iii) dose of RIC (minutes of occlusion, single dose vs. repeated once or twice daily for 6 −12 months), (iv) number of RIC cycles used (3 cycles vs 4 cycles vs 5 cycles) and site of occlusion (unilateral vs bilateral). Due to marked between-study variations in these variables, it is challenging to draw any definite conclusions. There seems to be a dose-relationship response and overall, the current findings support the hypothesis that long-term applied daily RIC may activate endogenous protective mechanisms and improve cognitive performance, although this conclusion should be viewed cautiously based on the limited data available.

It is important to highlight that RIC operates as a neural reflex with vagal preganglionic neurons [36] as the nodal point for the reflex [37]. anesthetic agents, especially propofol, are highly sensitive to vagal nerves [38], therefore RIC may be ineffective under general anesthesia. This is relevant as short-term studies administrated this type of anesthesia before surgery and applied RIC without impact on the cognitive performance outcomes.

The effect of short-term RIC treatment after acute ischemic stroke on long-term cognition may be mediated by a reduction of infarct volume, whereas long-term (≥ 6 months) RIC treatment may induce cerebrovascular protection by improved cerebral blood flow resulting from cerebral angiogenesis and microvascular remodeling and microvascular perfusion [39–41]. Previous studies using animal models have shown that chronic limb remote ischemic conditioning (i.e. RIC) can reverse or attenuate white matter damage induced by bilateral carotid artery occlusion-related to vascular cognitive impairment [40,42]. Also, application of daily RIC protocols in patients with cerebral small-vessel disease for 1-year was associated with a substantially lower mean white matter hyperintensities (WMHs) volume compared to the control group [35]. RIC seems to reduce inflammatory responses [39], free radical production [43,44] and downregulate microglial expression while inhibiting

apoptosis of oligodendrocytes [45], all of which may help to enhance the recovery of WMHs resulting from ischemic injury [46]. Recently, it has been shown that RIC may stimulate a hormone glucagon-like peptide-1 (GLP-1), contributing to neuroprotection by improving blood flow to brain tissue surrounding infarcts [47]. This may be a viable way to prevent progressive cognitive decline, dementia, and other neurological diseases caused by persistent reductions of brain perfusion over time [48] (Fig. 4).

A number of limitations with this systematic review may be mentioned. The included studies were all small, and only five out of 14 had cognitive assessment as the primary outcome measure. Further, the studies differed vastly in terms of application methodology and RIC protocols, cognitive assessments and clinical populations, altogether preventing a meaningful meta-analysis. Therefore, this review summarizes general trends based on limited data.

There are several ongoing RIC trials (NCT04109963, NCT03481777 and NCT04168021) focusing on cognitive performance and long-term effects (>3 months) aiming at feasibility and effects of applying RIC as a non-pharmacological, easy applied preventive method in patients at risk for recurrent stroke or development of vascular dementia.

5. Conclusion

Long-term daily RIC treatment may improve cognitive function after 6- 12 months in patients with pre-existing cerebrovascular disease. The effect of short-term RIC and a single preconditioning RIC treatment before surgery is inconsistent and uncertain. RIC is safe, feasible and an attractive future therapy that may reduce the burden of cognitive impairment and dementia. Ongoing studies will add information to our understanding of the neuroprotective mechanisms and long-term effects.

6. Clinical implications

Regular physical activity is recommended life-long to ensure brain health. This may be difficult for various reasons in old age and RIC may be an attractive method as a non-pharmacological therapy, to achieve a similar effect on cognition. RIC may reduce aging-related cognitive decline in humans by enhancing endogenous protective mechanisms and may act as a long-term neuroprotectant. Consequently, RIC represents a promising therapy for preventing and treating cognitive impairments and dementia.

Authors' contributions

AS, AG and BR involved in the concept and data collection. AS, AG, BR analysed the data and drafted the paper. AP, SC and FA reviewed the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest regarding the publication of this manuscript.

Data Availability

Data will be made available on request.

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