Review

Remote ischemic conditioning for stroke: A critical systematic review

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Abstract

Remote ischemic conditioning (RIC) is the application of brief periods of ischemia to an organ or tissue with the aim of inducing protection from ischemia in a distant organ. It was first developed as a cardioprotective strategy but has been increasingly investigated as a neuroprotective intervention. The mechanisms by which RIC achieves neuroprotection are incompletely understood. Preclinical studies focus on the hypothesis that RIC can protect the brain from ischemia reperfusion (IR) injury following the restoration of blood flow after occlusion of a large cerebral artery. However, increasingly, a role of chronic RIC (CRIC) is being investigated as a means of promoting recovery following an ischemic insult to the brain. The recent publication of two large, randomized control trials has provided promise that RIC could improve functional outcomes after acute ischemic stroke, and that there may be a role for CRIC in the prevention of recurrent stroke. Although less developed, there is also proof-of-concept to suggest that RIC may be used to reduce vasospasm after subarachnoid hemorrhage or improve cognitive outcomes in vascular dementia. As a cheap, well-tolerated and almost universally applicable intervention, the motivation for investigating possible benefit of RIC in patients with cerebrovascular disease is great. In this review, we shall review the current evidence for RIC as applied to cerebrovascular disease.

Keywords

Stroke, remote ischemic conditioning, systematic review

Introduction

Remote ischemic conditioning (RIC) describes the technique of using non-lethal ischemic stimuli in one organ or tissue to protect against lethal ischemic events in a distant organ. Ischemic conditioning (IC) was first demonstrated using isolated dog hearts whereby brief periods of occlusion to the left circumflex artery were found to reduce infarct size when the same artery was subsequently occluded for 40 min, in comparison to non-conditioned hearts.[1] Subsequently, it was shown that brief periods of ischemia applied to the circumflex artery protected against ischemia from a 1 h occlusion of the left anterior descending artery,[2] suggesting that protection via IC is conveyed to a different part of an organ than that supplied by the conditioned artery. This concept was developed when brief periods of occlusion to the mesenteric artery reduced the size of myocardial infarction following prolonged occlusion of a coronary artery.[3] While clearly an interesting phenomenon, it was difficult to imagine this technique translating into clinical practice,

given the perceived danger of occluding blood supply to a major organ. However, cardioprotection was subsequently demonstrated using brief periods of ischemia to skeletal muscle.[4] Thus, we arrive at the paradigm for RIC used today. Brief periods of non-lethal ischemia are applied to a limb, with the aim of inducing ischemic tolerance in a distant organ.

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Figure 1. Different protocols of remote ischemic conditioning. RIC can be given before (RIPreC), during (RIPerC), or after (RIPostC) an ischemic event. Increasingly, RIC is being applied repeatedly over several days, weeks, or even months. This is known as chronic RIC (CRIC).
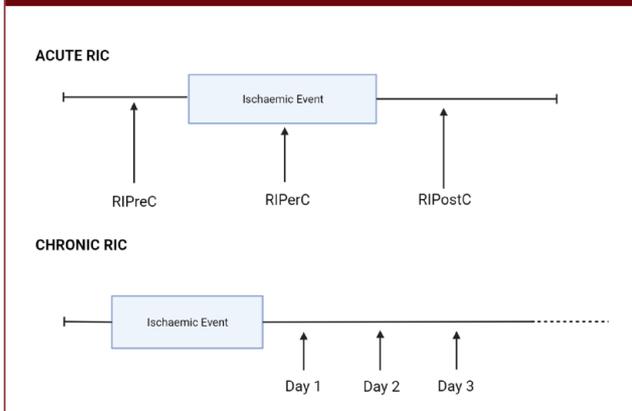
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Several protocols exist for RIC. The stimulus can be given before, during, or after an ischemic event, referred to respectively as remote ischemic preconditioning (RIPreC), remote ischemic perconditioning (RIPerC), and remote ischemic postconditioning (RIPostC; see Figure 1). Ischemia is achieved by the inflation of a blood pressure cuff to supra-systolic pressures in one or multiple limbs. Most administration protocols involve four to five cycles of cuff inflation for 5 min. While early clinical studies predominantly used a single episode of RIC, given around the time of an ischemic event, increasingly, chronic RIC (CRIC) is used. This requires participants to carry out daily RIC as described above for several days, weeks, or even months.

In this review, we shall consider the application of RIC as a cytoprotective strategy in the field of cerebrovascular disease. We shall see how initial studies focused largely on the potential of RIC to protect against ischemia-reperfusion (IR) damage in the acute aftermath of stroke. However, increasingly there is evidence that CRIC promotes recovery of cerebral tissues following ischemic or hemorrhagic insult. A literature search of three databases: OVID Medline, OVID Embase, and PubMed was conducted using the search terms shown in Supplementary Table 1. Titles were screened for relevance by HK. As a narrative review, no inclusion or exclusion criteria were used. References of the articles retrieved using this search strategy were also screened to uncover any important published studies missed by this literature search.

Mechanisms

An extensive review of the mechanisms underpinning RIC is beyond the scope of this article and has been extensively covered elsewhere.[5,6] Nonetheless, an outline of the proposed mechanism of action is necessary if we are to understand the implications of the studies recently published in the field.

How the signal is transmitted from a limb to distant organs and tissues is thought to involve both neural and humoral mechanisms. The role of the nervous system has been demonstrated by the fact that transection of the femoral nerve[7] or cholinergic ganglionic blockade with hexamethonium[8] abrogates the effect of RIC. A great many candidates, acting in parallel (see Figure 2), have been identified as humoral factors involved in the transfer of the RIC signal.[9] Furthermore, both neural and humoral factors appear interdependent; dialysate from hindlimb-conditioned rats to the hearts of naïve rats confers cardio protection, but femoral nerve transection of the donor rats, or treatment of naïve hearts with hexamethonium abrogates this protection.[10] It is understood that RIC confers at least two windows of protection. An acute window of protection starts from the time of conditioning until 6 h after RIC.[11] Next a chronic window confers protection from ischemia to a conditioned subject from 12 to 24 h after RIC until some 72 h later.[11,12]

Protection from cerebrovascular ischemia during the acute phase is thought to be mediated by suppression of apoptosis[13] and upregulation of autophagy[14] via modulation of intracellular protein kinase pathways. In the context of cerebrovascular disease, this is thought to provide protection from IR damage that may follow an acute ischemic stroke (AIS).[15] Regarding the chronic window of protection, RIC induces multiple changes in *de novo* protein synthesis that can affect an organ or tissue's ability to recover from an ischemic event. RIC can modulate the inflammatory milieu of ischemic areas of the brain[16] and modify the immune response to ischemia.[17] In addition to this, RIC may increase blood supply to areas that have suffered an ischemic event. It does this through improving endothelial function,[18] increasing cerebral blood flow,[19] promoting angiogenesis,[20] increasing pro-angiogenic factors such as vascular endothelial growth factor (VEGF),[21] and endothelial production of nitric oxide.[22]

Animal studies

Acute ischemic stroke

A recent review demonstrates that animal models of RIC and stroke have repeatedly shown that IC is able to reduce infarct size and improve early neurological outcome when given as RIPreC, RIPerC, or RIPostC.[23] Of concern, this review found significant publication bias, suggesting neutral or negative animal studies are not known.[23] Neurological score in the long term (60 days) also improved in rats that received RIPostC immediately after stroke onset compared to control rats or rats that received RIPostC 6 h after ictus.[24] A small number of animal studies have investigated the effect of CRIC on outcomes after stroke. In one study, RIPerC alone improved outcomes at 7 but not 14 days; whereas RIPerC + RIPostC (daily for 14 days)

Figure 2. Schematic representing the mechanisms of action for RIC. Brief ischemia is applied to a limb via the inflation of a blood pressure cuff. Release of autacoids at the site of the stimulus causes transmission of the signal to nuclei in the CNS via sensory afferents. Humoral factors are then released, which lead to effects in the target organ, These effects are varied and include regulation of apoptosis and autophagy via intracellular protein kinase pathways and more delayed effects on *de novo* protein synthesis that modify immune, inflammatory, and vascular responses during ischemic insults.
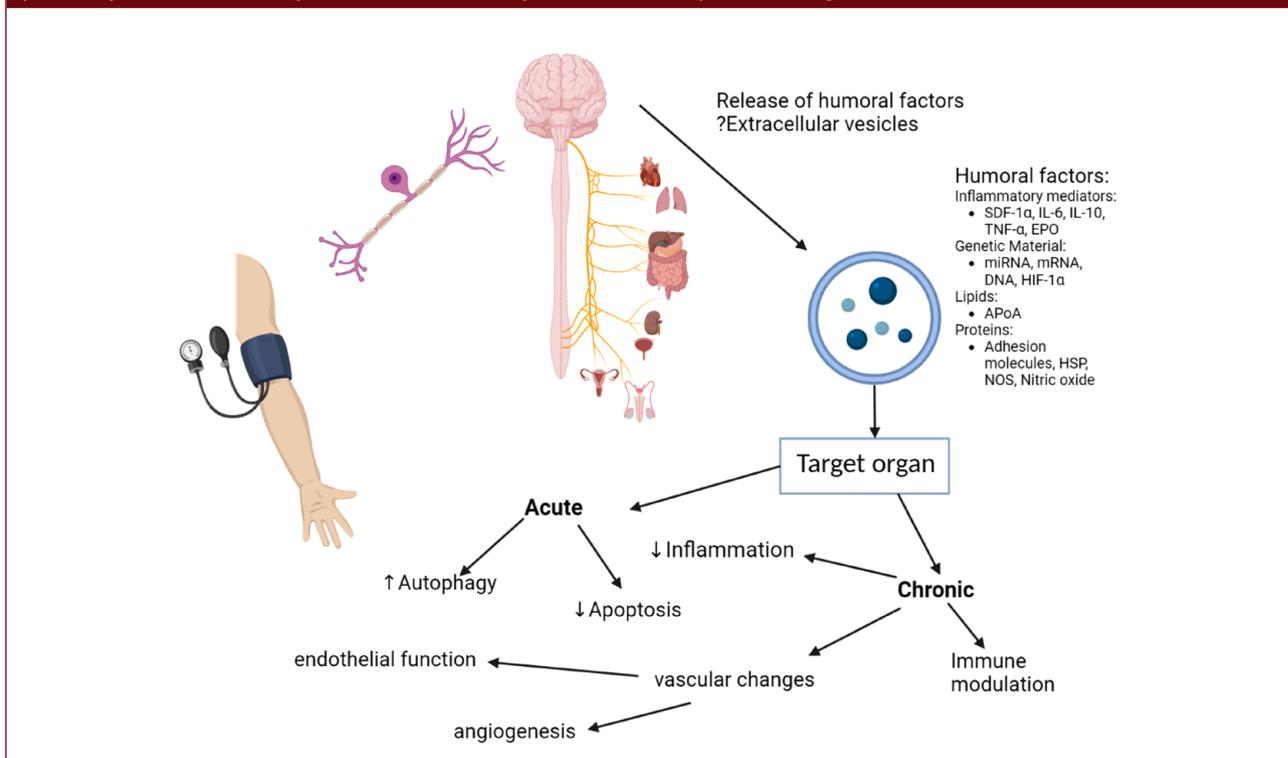
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resulted in improved infarct size and neuroscore at day 14.[25] Furthermore, RIPostC starting 12–24 h after onset (acute) compared to very delayed (5 days) RIPostC for 10 days produced smaller infarct sizes in the acute group. Interestingly, the delayed group showed significantly better neurological deficit scores at 84 days potentially mediated through angioneurogenesis.[26] Therefore, RIC outside the time frame where it can reduce IR damage may improve long-term outcomes. With less rigid time constraints, this has enormous potential for clinical application in a wide variety of circumstances.

Hemorrhagic stroke

In a model of parenchymal IC hemorrhage of the MCA, RIPreC reduced perihematoma edema following autologous blood infusion to rat brains 3 days after conditioning.[27] Furthermore, daily RIPostC improved hematoma resolution and neurological outcome 6 days after collagenase-induced intracerebral hemorrhage (ICH).[28] This effect was associated with an increase in anti-inflammatory monocytes and was abrogated by depletion of myeloid cells or a knockout of AMPK-1α.

Limited study has also been made of the application of RIC as a neuroprotective strategy in subarachnoid hemorrhage (SAH). Delayed cerebral ischemia typically occurs at days 4–14,[29] and so there is a window following diagnosis during which IC can be given to protect against ischemia. In one preclinical study, repeated bilateral hindlimb conditioning, starting immediately after induced SAH and continuing for 3 days, improved neurological function, and reduced neuronal apoptosis.[30]

Human studies

Remote ischemic per-conditioning

With animal studies showing clear benefits of RIC in AIS models, an increasing number of human trials have been performed. Initially, these were limited to studies involving less than 100 patients. Early data suggest RIC is safe in acute stroke, including when given around the time of intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT).[31–35]

The first proof-of-concept study into the clinical application of RIPerC in stroke used pre-hospital RIC delivered

by paramedics and examined the effect on infarct size, infarct growth, and modified Rankin scale (mRS) in patients who received alteplase.[36] They found no difference between RIC and control groups in their pre-specified study outcomes, although a retrospective voxel-wise analysis of magnetic resonance (MR) images adjusted for baseline perfusion showed a reduced risk of infarction in the RIC group. Further limitations included early dose discontinuation due to short ambulance transit times and no measures of pre-hospital severity scores. However, there were significantly more patients with transient ischemic attack (TIA) in the RIC group suggesting that RIC may have had an effect before baseline measurements were taken.

Recently, RESCUE BRAIN, (n = 188) found no effect of RIC on infarct volume or mRS when applied within 6 h of symptom onset of patients who received recanalization therapy.[37] While a high-quality study, the small sample size limits interpretation. RIC is prone to multiple factors that may attenuate its effects, for example, age and diabetes.[38] Moreover, recanalization does not always result in the restoration of blood flow (possibly due to the "no-reflow" phenomenon),[15] lowering the incidence of IR injury. Alternatively, the optimum dose and method of administration of RIC is yet to be determined. It may be that for clinical benefits to be seen, RIC needs to be repeated in the days after stroke. Other small underpowered studies have shown inconsistent effects on infarct volume. A study in patients who were not eligible for revascularisation therapy found no evidence of infarct size reduction,[39] while one trial administering RIC within 72 h reported a reduction in infarct size.[40]

Importantly, the REmote iSchemic conditioning In patients with acute STroke (RESIST) trial[41] was presented at the European Stroke Organisation Conference in May 2023 with full publication awaited at the time of writing. The investigators enrolled 1500 participants within 4 h of onset in a pre-hospital setting, of which 737 were ischemic stroke, 165 ICH (n = 165) and the remainder stroke TIA (10.5%) or mimic. Randomized 1:1 to single limb RIC or sham, 80% received 7 days of twice daily treatment (20% 1 day of treatment); no differences were found between treatment and control groups in the primary outcome, shift in mRS.

Remote ischemic post-conditioning

A recent meta-analysis found that in 11 small trials (total n = 713) of RIPostC in patients with AIS, including those in receipt of thrombolysis,[42] National Institutes of Health Stroke Scale (NIHSS) scores were significantly improved. In addition, although effects were mild and statistical significance was not reached, there was a trend toward improvement in mRS.[43] The authors report a low degree of heterogeneity between these studies; however, meaningful trial differences do exist, in particular, the timing of RIC

application relative to stroke onset, the frequency and number of cuff inflation/deflation cycles, the maximum cuff pressures, the total dose of RIC administered and the site of application (arm versus leg; unilateral versus bilateral).

The RICAMIS trial assessed RIPerC + RIPostC (n = 1893) across 55 hospitals in China;[44] where patients within 48 h of AIS and NIHSS scores of 6–16, excluded if thrombolysed or received mechanical thrombectomy, received 10–14 days of daily RIC to bilateral upper limbs or control (standard care). Functional independence (mRS < 2) at 90 days was significantly more likely in the RIC group (67.4% versus 62%, unadjusted odds ratio (OR) 1.27, (95% confidence interval (CI): 1.05–1.54); $p = 0.02$; adjusted OR 1.41 (95% CI: 1.14–1.74); $p = 0.002$), with no significant differences observed in secondary outcomes which included: (1) early neurologic deterioration, (2) change in NIHSS score compared with randomization at 12 days, (3) stroke or other vascular events within 90 days, and (4) death from any cause. The fact that RIC here was started up to 48 h after the onset of symptoms implies that the functional improvement was mediated by neurorepair, rather than protection from IR damage. The exact time frame of IR damage following reperfusion has not been exactly quantified in humans, but there is evidence that breakdown of the blood–brain barrier and expansion of the lesion occur within 12 and 24 h of reperfusion, respectively.[45,46] Thus, in a cohort of patients who were not verified to achieve recanalization of the infarcted artery and in whom RIC was started on average 24 h after symptom onset, it is likely that any improvement was mediated by enhancement of recovery rather than protection from IR injury.

In the context of one large positive phase III trial (RICAMIS) and the neutral phase III RESIST trial, the benefit of RIPerC/RIPostC after AIS remains in doubt. Further research is needed, such as the UK-based Remote Ischemic Conditioning After Stroke Trial 3 (RECAST-3 trial, ISRCTN registration 63231313). Trials in AIS need to consider higher doses of RIC using bilateral limbs over a longer treatment period.

Carotid endarterectomy

Procedures such as carotid endarterectomy or stenting provide a period of more predictable stroke risk and therefore a target for neuroprotective therapies. In a proof-of-concept, phase II RCT in 189 patients with symptomatic or asymptomatic carotid artery stenosis (≥ 70%), 2 weeks of daily CRIC before stenting was associated with significantly lower incidence of silent infarcts on magnetic resonance imaging (MRI) within the first 6 months post-surgery compared to both control and sham arms.[47] Conversely, an Iranian study of 74 participants, using a single session of RIPreC immediately before stenting (also confounded by including both symptomatic and asymptomatic stenoses) found no significant difference between the number of

silent infarcts in those who received RIC and those who did not[48] (40.5% RIC vs 51.4% control, $p = 0.35$). Moreover, a meta-analysis of RIPreC in vascular and endovascular surgery (including carotid endarterectomy) found no improvement in mortality, cardiovascular events or neurological dysfunction when RIC was used prior to surgery. Thus, the use of repeated (i.e. CRIC) rather than single-dose RIC, potentially inducing an ischemic tolerance and targeting athero-inflammation, may be significant in inducing a treatment effect.

Recurrent ischemic stroke

CRIC has been used with the aim of reducing stroke recurrence in cases of symptomatic intracranial atherosclerosis (ICAS). A small RCT (n = 103) showed a reduced rate of stroke recurrence over 300 days between those treated with daily RIC compared to those treated with standard medical therapy.[49] These results are, however, subject to bias as 34% were excluded from analysis post randomization due to loss/refusal to follow-up or intracranial stent placement. The same research group demonstrated similar results in patients aged 80–95 in a separate study of 79 participants.[50] While encouraging, the reported risk of stroke recurrence in the control group of 26.7% is high when compared to 12.5% in the medically managed patients in the Stenting vs Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study.[51]

Using RIC for secondary prevention of stroke was the subject of the recent, large, multi-center "RICA" trial.[52] A total of 3033 patients with symptomatic ICAS received 12 months of daily RIC or sham, to both upper limbs within 15 or 30 days of TIA or stroke, respectively, and followed up for a median of 3.5 years. The primary outcome of time to first non-fatal or fatal ischemic stroke (16.9% vs 19%) was not significantly different between groups (hazard ratio 0.87, (95% CI: 0.74–1.03; $p = 0.12$), although the secondary outcome of composite cardiovascular events was significantly lower in the RIC group (hazard ratio 0.82 (95% CI: 0.71–0.95; $p = 0.089$). This well-conducted large trial with low loss-to-follow-up (4%) was unfortunately affected by treatment compliance with only 46.5% of patients more than 50% compliant with the study intervention in the first year, dropping to 21% when the intervention became voluntary. Future trials concentrating on improving treatment adherence are warranted.

Hemorrhagic stroke

There has been one small proof-of-concept study investigating the role of RIC in ICH. In the "RICH 1" trial, RIPostC appeared safe and well-tolerated in a study of 40 patients who received daily RIC for 7 days after ICH.[53] This pilot study did not reveal significant differences in hematoma volume but did reveal a significantly increased rate of hematoma resolution in the RIC group. Further trials in this population are needed to determine mechanisms of action and whether RIC is beneficial in this setting.

SAH and RIC has been more extensively studied due to high risk of ischemic stroke from subsequent vasospasm. Several studies have shown that RIC appears to be a safe and feasible intervention in SAH.[54–56] RIC does not significantly alter coagulation profiles in those that have suffered SAH.[57] A matched cohort analysis has suggested a benefit of RIC in SAH, with RIC increasing the chance of good outcomes (mRS 0–2) at discharge.[58] How this is being achieved is the subject of a recent study,[59] which demonstrated a clinically significant reduction in vasospasm in patients who received RIC after SAH (7.4% RIC vs 66.8% sham RIC). Larger trials are needed to determine if these mechanisms can improve clinical endpoints.

Vascular dementia

Cerebral small vessel disease is the most common cause of vascular dementia and is a major contributor to mixed dementia.[60] A few studies have examined the effect of CRIC on vascular dementia. In one study, CRIC reduced white matter hyperintensities (WMHs) on MRI over the course of 1 year, which was correlated with a mild improvement in visuospatial and executive functioning as measured by Montreal Cognitive Assessment (MOCA).[61] CRIC over 6 months in a cohort of patients with more severe dementia (Mini Mental State Examination (MMSE) score: 10–26) improved visuospatial perception and spatial orientation.[62] Furthermore, it has been shown that CRIC in the setting of ICAS is associated with fewer WMHs on MRI and improved cognition as measured by MOCA and MMSE.[63] These studies are limited by their small size and relatively short follow-up intervals; when considering dementia and cognitive impairment, one year is a relatively short duration of study. However, they do at least serve as proof-of-concept.

Hypertension

There has been a small but increasing volume of interest in the application of RIC to the field of hypertension. A meta-analysis has found that CRIC significantly lowers mean arterial pressure and diastolic blood pressure, with a non-significant trend toward lowering systolic blood pressure.[64] Acute RIC, meanwhile, did not result in any lasting reduction in blood pressure. The preliminary findings of CRIC as a means of reducing blood pressure, therefore, add to the body of evidence that CRIC might be an effective intervention in improving vascular health, possibly mediated by its effects on inflammation, angiogenesis, and endothelial function.

Cardiovascular disease

The concept of RIC was first developed investigating possible interventions for coronary artery occlusion and its review in this space is beyond the scope of this article. Nonetheless, differences in stroke and cardiac populations are vital to consider if we are to learn from RIC in other conditions. The definitive "CONDI-2/ERIC-PPCI" study[65] found that a single session of RIC prior to primary percutaneous coronary intervention did not improve cardiac death or hospitalization with heart failure 12 months after ST elevation MI, despite several prior phase II studies indicating that RIC was cardio protective.[66,67] A possible explanation is that patients with ischemic heart disease may be pre-conditioned through effective cardiac treatments. In a rat model of myocardial infarction, rats were treated with opiates, heparin, and a platelet inhibitor. RIC did not confer any additional benefit when given alongside these treatments. Therefore, in the setting of ischemic heart disease, medications that are not routinely used in stroke could attenuate the effects of RIC.[68]

Future directions

There is still a great deal of uncertainty regarding the effective "dose" of RIC. Strategies can be broadly divided into acute RIC, where RIC is given in a single session around the time of cerebrovascular event, or chronic RIC, where RIC is given in multiple sessions over a longer period. Numerous studies are currently in progress with a wide variety of RIC protocols used, ranging from a single episode of RIC to RIC twice daily for a week. These are summarized in Supplementary Table 2. Furthermore, the Remote Ischaemic Conditioning in Stroke Collaboration (RISC) aims to complete an individual participant meta-analysis to understand potential differences in RIC delivery and population subgroups (PROSPERO registration CRD42020197351).

Determining an optimal RIC dose is difficult without an adequate biomarker. RIC can modulate several proteins involved in lipid metabolism, coagulation, immuno-inflammatory responses and endovascular homeostasis;[69] though more work in larger clinical populations and correlated with outcomes is needed to confirm whether proteomic regulation provides a candidate biomarker. Furthermore, RIC has been shown to induce changes in vascular dynamics in stroke patients, such as flow-mediated dilatation[18] and cerebral blood flow;[49,70] offering potential alternative biomarkers of effect.

Compliance has been variably reported across different studies and there is a clear divide between compliance with RIC protocols that last a matter of days compared with those requiring the participant to carry on the intervention for months or even years. When RIC is delivered for a period of 2 weeks or less, compliance has been reported as 78–97%,[32,33,71,72] although the exception to this is the RECAST-2 trial, which found a significant decline in compliance at 48 h in both RIC and sham when patients were transferred from hospital to a rehabilitation facility.[35] This may reflect differing healthcare practices in different countries. Even if we find an effective dose of RIC, it is of no use if the protocol is so demanding that patients cannot comply with it. Future work should focus on finding the minimum effective dose and monitoring compliance with this regime.

Conclusion

The paradigm of IC is a promising intervention in the field of cytoprotection. The fear is, that like so many previous neuroprotective strategies, RIC will fail to translate from pre-clinical studies to beneficial outcomes in clinical trials. However, recent evidence from the RICAMIS and RICA trials is encouraging. Further study of this cheap and easily applicable intervention is, therefore, warranted. Despite this, there remain large gaps in our understanding of the mechanisms and therefore the optimum dose and delivery of RIC. Research for a reliable biomarker of RIC efficacy to help determine the ideal RIC strategy should be promoted. Furthermore, we must ensure RIC is tolerable to the populations in whom it shall be applied.

Declaration of conflicting interests

Funding

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Supplemental material

Supplemental material for this article is available online.

References

1. Murry CE, Jennings RB and Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; 74: 1124–1136.
2. Przyklenk K, Bauer B, Ovize M, Kloner RA and Whittaker P. Regional ischemic "preconditioning" protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 1993; 87: 893–899.

3. Gho BC, Schoemaker RG, van den Doel MA, Duncker DJ and Verdouw PD. Myocardial protection by brief ischemia in noncardiac tissue. *Circulation* 1996; 94: 2193–2200.

4. Birnbaum Y, Hale SL and Kloner RA. Ischemic preconditioning at a distance: reduction of myocardial infarct size by partial reduction of blood supply combined with rapid stimulation of the gastrocnemius muscle in the rabbit. *Circulation* 1997; 96: 1641–1646.

5. Heusch G. Molecular basis of cardioprotection signal transduction in ischemic pre-, post-, and remote conditioning. *Circ Res* 2015; 116: 674–699.

6. Abbasi-Habashi S, Jickling GC and Winship IR. Immune modulation as a key mechanism for the protective effects of remote ischemic conditioning after stroke. *Front Neurol* 2021; 12: 746486.

7. Yu C and Liu J. Protective effect of ischemia preconditioning of lower limbs on brain ischemia-reperfusion injury via neural pathways. *Sichuan Da Xue Xue Bao Yi Xue Ban* 2014; 45: 216–220.

8. Malhotra S, Naggar I, Stewart M and Rosenbaum DM. Neurogenic pathway mediated remote preconditioning protects the brain from transient focal ischemic injury. *Brain Res* 2011; 1386: 184–190.

9. Tsibulnikov SY, Maslov LN, Gorbunov AS, et al. A review of humoral factors in remote preconditioning of the heart. *J Cardiovasc Pharmacol Ther* 2019; 24: 403–421.

10. Pickard JM, Davidson SM, Hausenloy DJ and Yellon DM. Co-dependence of the neural and humoral pathways in the mechanism of remote ischemic conditioning. *Basic Res Cardiol* 2016; 111: 50.

11. Zhao H, Xiong LZ, Dong HL, et al. Protective effect of remote ischemic preconditioning against focal cerebral ischemia/reperfusion injury in rats. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2007; 19: 340–342.

12. Bolli R, Li QH, Tang XL, et al. The late phase of preconditioning and its natural clinical application—gene therapy. *Heart Fail Rev* 2007; 12: 189–199.

13. Cheng Z, Li L, Mo X, et al. Non-invasive remote limb ischemic postconditioning protects rats against focal cerebral ischemia by upregulating STAT3 and reducing apoptosis. *Int J Mol Med* 2014; 34: 957–966.

14. Guo H, Zhao L, Wang B, et al. Remote limb ischemic postconditioning protects against cerebral ischemia-reperfusion injury by activating AMPK-dependent autophagy. *Brain Res Bull* 2018; 139: 105–113.

15. Nour M, Scalzo F and Liebeskind DS. Ischemia-reperfusion injury in stroke. *Interv Neurol* 2013; 1: 185–199.

16. Pradillo JM, Fernández-López D, García-Yébenes I, et al. Toll-like receptor 4 is involved in neuroprotection afforded by ischemic preconditioning. *J Neurochem* 2009; 109: 287–294.

17. Liu ZJ, Chen C, Li XR, et al. Remote ischemic preconditioning-mediated neuroprotection against stroke is associated with significant alterations in peripheral immune responses. *CNS Neurosci Ther* 2016; 22: 43–52.

18. Hyngstrom AS, Nguyen JN, Wright MT, et al. Two weeks of remote ischemic conditioning improves brachial artery flow mediated dilation in chronic stroke survivors. *J Appl Physiol* 2020; 129: 1348–1354.

19. Hoda MN, Siddiqui S, Herberg S, et al. Remote ischemic perconditioning is effective alone and in combination with intravenous tissue-type plasminogen activator in murine model of embolic stroke. *Stroke* 2012; 43: 2794–2799.

20. Liang D, He XB, Wang Z, et al. Remote limb ischemic postconditioning promotes motor function recovery in a rat model of ischemic stroke via the up-regulation of endogenous tissue kallikrein. *CNS Neurosci Ther* 2018; 24: 519–527.

21. Ueno K, Samura M, Nakamura T, et al. Increased plasma VEGF levels following ischemic preconditioning are associated with downregulation of miRNA-762 and miR-3072-5p. *Sci Rep* 2016; 6: 36758.

22. Kroll J and Waltenberger J. A novel function of VEGF receptor-2 (KDR): rapid release of nitric oxide in response to VEGF-A stimulation in endothelial cells. *Biochem Biophys Res Commun* 1999; 265: 636–639.

23. Weir P, Maguire R, O'Sullivan SE and England TJ. A meta-analysis of remote ischaemic conditioning in experimental stroke. *J Cereb Blood Flow Metab* 2021; 41: 3–13.

24. Ren C, Yan Z, Wei D, Gao X, Chen X and Zhao H. Limb remote ischemic postconditioning protects against focal ischemia in rats. *Brain Res* 2009; 1288: 88–94.

25. Ren C, Wang P, Wang B, et al. Limb remote ischemic perconditioning in combination with post-conditioning reduces brain damage and promotes neuroglobin expression in the rat brain after ischemic stroke. *Restor Neurol Neurosci* 2015; 33: 369–379.

26. Doeppner TR, Zechmeister B, Kaltwasser B, et al. Very delayed remote ischemic post-conditioning induces sustained neurological recovery by mechanisms involving enhanced angioneurogenesis and peripheral immunosuppression reversal. *Front Cell Neurosci* 2018; 12: 383.

27. He Y, Karabiyikoglu M, Hua Y, Keep RF and Xi G. Ischemic preconditioning attenuates brain edema after experimental intracerebral hemorrhage. *Transl Stroke Res* 2012; 3: 180–187.

28. Vaibhav K, Braun M, Khan MB, et al. Remote ischemic post-conditioning promotes hematoma resolution via AMPK-dependent immune regulation. *J Exp Med* 2018; 215: 2636–2654.

29. Pluta RM, Hansen-Schwartz J, Dreier J, et al. Cerebral vasospasm following subarachnoid hemorrhage: time for a new world of thought. *Neurol Res* 2009; 31: 151–158.

30. Hu X, Lv T, Yang SF, Zhang XH and Miao YF. Limb remote ischemic post-conditioning reduces injury and improves long-term behavioral recovery in rats following subarachnoid hemorrhage: possible involvement of the autophagic process. *Mol Med Rep* 2018; 17: 21–30.

31. England TJ, Hedstrom A, O'Sullivan S, et al. RECAST (Remote Ischemic Conditioning After Stroke Trial): a pilot randomized placebo controlled phase II trial in acute ischemic stroke. *Stroke* 2017; 48: 1412–1415.

32. Zhao W, Che R, Li S, et al. Remote ischemic conditioning for acute stroke patients treated with thrombectomy. *Ann Clin Transl Neurol* 2018; 5: 850–856.

33. Che R, Zhao W, Ma Q, et al. Rt-PA with remote ischemic postconditioning for acute ischemic stroke. *Ann Clin Transl Neurol* 2019; 6: 364–372.

34. He YD, Guo ZN, Qin C, et al. Remote ischemic conditioning combined with intravenous thrombolysis for acute ischemic stroke. *Ann Clin Transl Neurol* 2020; 7: 972–979.

35. England TJ, Hedstrom A, O'Sullivan SE, et al. REmote ischaemic Conditioning after Stroke Trial 2 (RECAST-2): a pilot randomised controlled phase II trial evaluating remote ischaemic conditioning (RIC) after hyperacute stroke. *Int J Stroke* 2018; 13: 14.

36. Hougaard KD, Hjort N, Zeidler D, et al. Remote ischemic perconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial. *Stroke* 2014; 45: 159–167.

37. Pico F, Lapergue B, Ferrigno M, et al. Effect of in-hospital remote ischemic perconditioning on brain infarction growth and clinical outcomes in patients with acute ischemic stroke: the RESCUE BRAIN randomized clinical trial. *JAMA Neurol* 2020; 77: 725–734.

38. Tyagi S, Singh N, Virdi JK and Jaggi AS. Diabetes abolish cardioprotective effects of remote ischemic conditioning: evidences and possible mechanisms. *J Physiol Biochem* 2019; 75: 19–28.

39. Poalelungi A, Tulbă D, Turiac E, Stoian D and Popescu BO. Remote ischemic conditioning may improve disability and cognition after acute ischemic stroke: a pilot randomized clinical trial. *Front Neurol* 2021; 12: 663400.

40. Li Y, Liang K, Zhang L, Hu Y, Ge Y and Zhao J. Upper limb ischemic postconditioning as adjunct therapy in acute stroke patients: a randomized pilot. *J Stroke Cerebrovasc Dis* 2018; 27: 3328–3335.

41. Blauenfeldt RA, Hjort N, Gude MF, et al. A multicentre, randomised, sham-controlled trial on REmote iSchemic conditioning In patients with acute STroke (RESIST)–Rationale and study design. *Eur Stroke J* 2020; 5: 94–101.

42. An JQ, Cheng YW, Guo YC, et al. Safety and efficacy of remote ischemic postconditioning after thrombolysis in patients with stroke. *Neurology* 2020; 95: e3355–e3363.

43. Lu M, Wang Y, Yin X, Li Y and Li H. Cerebral protection by remote ischemic post-conditioning in patients with ischemic stroke: a systematic review and meta-analysis of randomized controlled trials. *Front Neurol* 2022; 13: 905400–905400.

44. Chen HS, Cui Y, Li XQ, et al. Effect of remote ischemic conditioning vs usual care on neurologic function in patients with acute moderate ischemic stroke: the RICAMIS randomized clinical trial. *JAMA* 2022; 328: 627–636.

45. Warach S and Latour LL. Evidence of reperfusion injury, exacerbated by thrombolytic therapy, in human focal brain ischemia using a novel imaging marker of early blood-brain barrier disruption. *Stroke* 2004; 35: 2659–2661.

46. Zhou Y, He Y, Yan S, et al. Reperfusion injury is associated with poor outcome in patients with recanalization after thrombectomy. *Stroke* 2023; 54: 96–104.

47. Zhao W, Meng R, Ma C, et al. Safety and efficacy of remote ischemic preconditioning in patients with severe carotid artery stenosis before carotid artery stenting: a proof-of-concept, randomized controlled trial. *Circulation* 2017; 135: 1325–1335.

48. Asadi M, Hooshmandi E, Emaminia F, et al. Safety and efficacy of remote ischemic preconditioning in patients with severe carotid artery stenosis before carotid artery stenting: a proof-of-concept, randomized controlled trial. *Curr J Neurol* 2022; 21: 119–124.

49. Meng R, Asmaro K, Meng L, et al. Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. *Neurology* 2012; 79: 1853–1861.

50. Meng R, Ding Y, Asmaro K, et al. Ischemic conditioning is safe and effective for octo- and nonagenarians in stroke prevention and treatment. *Neurotherapeutics* 2015; 12: 667–677.

51. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med* 2011; 365: 993–1003.

52. Hou C, Lan J, Lin Y, et al. Chronic remote ischaemic conditioning in patients with symptomatic intracranial atherosclerotic stenosis (the RICA trial): a multicentre, randomised, double-blind sham-controlled trial in China. *Lancet Neurol* 2022; 21: 1089–1098.

53. Zhao W, Jiang F, Li S, et al. Safety and efficacy of remote ischemic conditioning for the treatment of intracerebral hemorrhage: a proof-of-concept randomized controlled trial. *Int J Stroke* 2022; 17: 425–433.

54. Koch S, Katsnelson M, Dong C and Perez-Pinzon M. Remote ischemic limb preconditioning after subarachnoid hemorrhage: a phase Ib study of safety and feasibility. *Stroke* 2011; 42: 1387–1391.

55. Raval RN, Small O, Magsino K, et al. Remote ischemic preconditioning in subarachnoid hemorrhage: a prospective pilot trial. *Neurocrit Care* 2021; 34: 968–973.

56. Gonzalez NR, Connolly M, Dusick JR, Bhakta H and Vespa P. Phase I clinical trial for the feasibility and safety of remote ischemic conditioning for aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2014; 75: 590–598; discussion 598.

57. Xu Y, Qi M, Wang N, et al. The effect of remote ischemic conditioning on blood coagulation function and cerebral blood flow in patients with aneurysmal subarachnoid hemorrhage. *Neurol Sci* 2020; 41: 335–340.

58. Laiwalla AN, Ooi YC, Liou R and Gonzalez NR. Matched cohort analysis of the effects of limb remote ischemic conditioning in patients with aneurysmal subarachnoid hemorrhage. *Transl Stroke Res* 2016; 7: 42–48.

59. Sangeetha RP, Venkatapura RJ, Kamath S, et al. Effect of remote ischemic preconditioning on cerebral vasospasm, biomarkers of cerebral ischemia, and functional outcomes in aneurysmal subarachnoid hemorrhage (ERVAS): a randomized controlled pilot trial. *Brain Circ* 2021; 7: 104–110.

60. Román GC, Erkinjuntti T, Wallin A, Pantoni L and Chui HC. Subcortical ischaemic vascular dementia. *Lancet Neurol* 2002; 1: 426–436.

61. Wang Y, Meng R, Song H, et al. Remote ischemic conditioning may improve outcomes of patients with cerebral small-vessel disease. *Stroke* 2017; 48: 3064–3072.

62. Liao Z, Bu Y, Li M, et al. Remote ischemic conditioning improves cognition in patients with subcortical ischemic vascular dementia. *BMC Neurology* 2019; 19: 206.

63. Zhou D, Ding J, Ya J, et al. Efficacy of remote ischemic conditioning on improving WMHs and cognition in very elderly patients with intracranial atherosclerotic stenosis. *Aging* 2019; 11: 634–648.

64. Baffour-Awuah B, Dieberg G, Pearson MJ and Smart NA. The effect of remote ischaemic conditioning on blood pressure

response: a systematic review and meta-analysis. *Int J Cardiol Hypertens* 2021; 8: 100081.

65. Hausenloy DJ, Kharbanda RK, Møller UK, et al. Effect of remote ischaemic conditioning on clinical outcomes in patients with acute myocardial infarction (CONDI-2/ERIC-PPCI): a single-blind randomised controlled trial. *Lancet* 2019; 394: 1415–1424.

66. Crimi G, Pica S, Raineri C, et al. Remote ischemic post-conditioning of the lower limb during primary percutaneous coronary intervention safely reduces enzymatic infarct size in anterior myocardial infarction: a randomized controlled trial. *JACC Cardiovasc Interv* 2013; 6: 1055–1063.

67. Prunier F, Angoulvant D, Saint Etienne C, et al. The RIPOST-MI study, assessing remote ischemic perconditioning alone or in combination with local ischemic postconditioning in ST-segment elevation myocardial infarction. *Basic Res Cardiol* 2014; 109: 400.

68. He Z, Davidson SM and Yellon DM. The importance of clinically relevant background therapy in cardioprotective studies. *Basic Res Cardiol* 2020; 115: 69.

69. Song S, Guo L, Wu D, et al. Quantitative proteomic analysis of plasma after remote ischemic conditioning in a rhesus monkey ischemic stroke model. *Biomolecules* 2021; 11: 1164.

70. Guo ZN, Guo WT, Liu J, et al. Changes in cerebral autoregulation and blood biomarkers after remote ischemic preconditioning. *Neurology* 2019; 93: e8–e19.

71. Li XQ, Tao L, Zhou ZH, Cui Y, Chen HS and RICAMIS Protocol Steering Group. Remote ischemic conditioning for acute moderate ischemic stroke (RICAMIS): rationale and design. *Int J Stroke* 2020; 15: 454–460.

72. Li YJ, Liang KK, Zhang L, Pan R, Hu YM and Zhao JH. Remote ischemic post-conditioning may improve post-stroke cognitive impairment: a pilot single center randomized controlled trial. *J Stroke Cerebrovasc Dis* 2020; 29: 105217.