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Remote Ischemic Conditioning: Challenges and Opportunities

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Abstract

Remote ischemic conditioning (RIC) has been investigated as a promising, safe, and well-tolerated non-pharmacological therapy for cardio-cerebrovascular disease over the past three decades; variable results have been found when it used in cerebrovascular versus cardiovascular disease. For patients with cardiovascular disease, milestone studies suggest that the roles of RIC may be limited. Recently, however, two large trials investigating RIC in patients with cerebrovascular disease found promising results, which may reignite the field's research prospects after its setbacks in the cardiovascular field. This perspectives article highlights several important clinical trials of RIC in the cardio-cerebrovascular disease and describes the many challenges of RIC in clinical translation. Finally, based on the available evidence, several promising research directions such as chronic RIC, timing of initiation, improvement of compliance, and identification of specific biomarkers are proposed and should be investigated before RIC can become applied into clinical practice for patient benefit.

Remote ischemic conditioning (RIC), involving several brief cycles of ischemia and reperfusion to an organ or tissue (such as a blood pressure cuff on the limb), is a promising, safe, and well-tolerated non-pharmacological therapy for cardio-cerebrovascular disease.[1] Recently, two large randomized clinical trials investigating RIC in patients with cerebrovascular disease have been completed, with promising results. One trial investigating RIC in 1,776 patients with moderate ischemic stroke found an improvement in neurological outcomes after 90 days if RIC was initiated within 48 h of stroke onset and performed twice daily for 14 days.[2] The other trial investigated RIC in 3,033 patients with symptomatic intracranial artery stenosis and found that it reduced the cumulative incidence of composite outcome events (including stroke, transient ischemic attack, and myocardial infarction) if performed once daily for 12 months.[3]

RIC may have variable results when used in cerebrovascular versus cardiovascular disease, and the recent findings in cerebrovascular disease may reignite the field's research prospects after its setbacks in the cardiovascular field. In 2015, two large clinical trials investigating RIC in patients undergoing elective cardiac surgery found no significant reduction in major adverse cardiovascular events with RIC performed once before surgical incision.[4, 5] In 2019, a large trial of patients with acute myocardial infarction also found no reduction in major adverse cardiac events at 12-months follow up if RIC was performed once before the primary percutaneous coronary intervention.[6] These three milestone studies suggest that the role of RIC, initially considered one of the most promising cardioprotective therapies, may be limited in the treatment of cardiovascular disease or one time dosing may be inadequate.

RIC, first demonstrated in *Circulation* in 1993 by Przyklenk and colleagues,[7] evolved from ischemic preconditioning, initially described by Murry et al. in 1986.[8] Despite intensive research over the last three decades, it remains unclear why RIC is not proven to benefit patients with cardiovascular disease. Both animal studies and preliminary "proof of concept" clinical studies found that RIC could reduce myocardial infarct size or enzyme levels;[9-11] however, these benefits were not confirmed when translated into clinical outcomes in large clinical trials. Although propofol anesthesia used during cardiac surgery has been suggested as one of the main reasons for the failed translation of RIC for patient benefit,[12] this cannot explain the failed translation in acute myocardial infarction patients who did not receive propofol anesthesia. For acute myocardial infarction, it has been proposed that the failure to translate RIC for patient benefit may be attributed in part to the RIC

stimulus not being optimized and the low-risk well-treated population.[13] To address this, therefore, new ongoing RIC trials are investigating the cardioprotective potential of RIC in higher-risk populations including the RIC-AFRICA trial (which is testing RIC in acute myocardial infarction patients receiving thrombolysis)[14] and the RIP-HIGH trial (which is testing RIC in acute myocardial infarction patients presenting in heart failure, *ClinicalTrials.gov* Identifier: NCT04844931).

Despite 30 years since the conception of RIC, there still remains a lot of unknowns, from the underlying mechanisms to the protocol implementation. The encouraging findings from the two largest clinical trials of RIC in cerebrovascular disease may direct future research into this area and away from cardiovascular disease although we await outcome from the 2 new studies exploring the potential for RIC to have a positive effect in high-risk patients. Based on the available research evidence, the RIC protocol used may be responsible for the failed translation of RIC in cardiovascular disease and the discrepancy between outcomes in cardiovascular and cerebrovascular disease. Long-term, repetitive RIC (i.e., chronic RIC) may be an effective protocol albeit with the recognition that compliance may be an underlying problem (see below); however, more research is required to determine the optimal one, and more efforts are needed to exploring its specific biomarkers, optimal protocol, and etc.

Chronic remote ischemic conditioning

Precursor studies have demonstrated that RIC is effective at reducing serum biomarkers of myocardial injury and infarction size;[15] however, these effects did not translate into improved clinical outcomes.[4-6] Multiple factors may have contributed to the neutral results of these large trials investigating RIC in cardiovascular disease; however, the RIC protocol is likely to be important. Generally, only one treatment of 4 cycles of 5-min ischemia followed by 5-min reperfusion was used in these studies. The protection of one ischemic preconditioning treatment can last for approximately 96 h, with a 12–24 h interval of no protection.[16] The protection induced by one RIC treatment may last 3–4 days; however, the repair of injured tissue often takes much longer; the effects of one RIC treatment in reducing clinical events at several weeks or months later may be not observed.

Several clinical studies of patients with acute ischemic stroke investigated chronic RIC, performed for 1–2 weeks or several months, and found significantly improved functional outcome assessed by National Institute of Health stroke scale or modified Rankin scale.[17] More recently, one large trial

further confirmed the benefits of chronic RIC,[2] and subgroup analysis of another large trial that investigating patients undergoing 12-month RIC treatment found that only patients with ≥50% compliance could benefit for reduced recurrent stroke risk.[3] Chronic RIC demonstrated a sound safety profile, with no severe adverse events reported.[18, 19] Given the protective time window of one RIC treatment and the clinical effects of chronic RIC in patients with cerebrovascular disease, investigating the clinical benefits of chronic or repeated daily RIC might be a better choice.

Improving compliance

The time-consuming nature of RIC treatment is one factor influencing compliance. Currently, the protective window of RIC remains poorly understood, but the protection of ischemic preconditioning, one form of ischemic conditioning that RIC evolving from, has been demonstrated to last for a maximum of 3-4 days, with 12–24 hours of no protection.[16] However, unlike a once-a-day medication, the RIC procedure is performed using pneumatic cuffs or devices and lasts 30 min or more, during which the patient is not able to perform other activities.

Using automated equipment may help improve chronic RIC compliance. Initially, RIC was manually performed using pneumatic limb cuffs placed on the arms, an approach which is both time-consuming and requires extra help from other personnel. To simplify the implementation method of RIC and improve its compliance, dedicated automated devices have been developed and produced by several companies, including CellAegis Devices Incorporated (Canada), Beijing Renqiao Cardiocerebrovascular Disease Prevention and Treatment Research Jiangsu Co., Ltd. (China), and etc. Compared with manual RIC, these devices allow easier operation but do not reduce the treatment time; many patients may still prefer taking medication once a day when compared to chronic RIC.

To further improve RIC compliance, portable and intelligent devices should be developed, but more importantly the RIC protocol should be optimized to speed up the process. Moreover, monitoring the patient's compliance with telemonitoring and incentivizing patients with "gamification" to encourage compliance may help. In addition, further research is required to determine whether RIC treatment time could be reduced to 5 min or less, and whether RIC performed once every four days or once a week is as effective as once or twice daily.

Exploring specific biomarkers and optimal protocols

Currently, the most commonly used protocols are four cycles of unilateral limb ischemia or five cycles of bilateral limbs ischemia for 5 min, each followed by 5 min of reperfusion.[20] These protocols are derived from the first study on ischemic preconditioning conducted over 30 years ago, which induced ischemic preconditioning via four 5-min episodes of ischemia and reperfusion of the coronary artery.[8] However, it remains unclear whether four or five cycles of 5-min ischemia followed by reperfusion is the optimal protocol. The lack of specific molecular biomarkers to monitor the biological effects of RIC makes it difficult to determine the optimum protocol. In animal studies of RIC in myocardial or cerebral infarction, serum biomarkers and infarct size are used to monitor its effects, and in clinical studies specific clinical events are used to evaluate its efficacy.[9, 17, 21]

The potential mechanisms of RIC involve multiple pathways, including humoral, neural, immune, and inflammatory pathways, with multiple genes and proteins involved.[15, 22] In addition, the effects of RIC on increasing cerebral blood flow has also been demonstrated to be an important factor for its neuroprotection.[23] However, the precise molecules through which RIC triggers downstream pathophysiological changes and protective organ and tissue effects remain unknown. Without identifying specific molecules that can measure the protective impact of RIC, it may be difficult to determine the optimal protocol; the best RIC regimen for different diseases and populations may vary, making the task more challenging.

Timing of initiation

Previous studies indicate that 2 weeks of RIC could benefit patients by promoting neurological recovery if initiated within 48 h of onset.[2, 24] However, if starting RIC was extended to within 30 days of symptom onset, it may no longer provide protective neurological effects, even if performed for several months.[3] This suggests that the timing of RIC initiation may be also an important factor that influences its protective effects. In the early phase of cerebral or myocardial infarction, major pathophysiological changes occur which enlarge the infarction size resulting in secondary injuries; during this phase, RIC could provide maximal protective effect.[25]

Due to the safety profile of RIC, it has been used during pre-hospital transport for patients with acute myocardial infarction and suspected stroke, with a reduction in tissue infarction but no improvement

in clinical outcomes.[6, 11, 26] Currently, a multicenter randomized control trial, the Danish RESIST trial (NCT03481777), is investigating RIC initiated prehospital within 4 h of stroke symptom onset and continued during hospital admission for 7 days.[27] The regimen of RIC used in the RESIST trial appears promising, and the trial seems to be a promising study in the field of stroke.

Conclusions

In summary, although animal and clinical research into RIC has been ongoing for 3 decades, and multiple underlying mechanisms of RIC have been identified, the lack of specific molecular biomarkers hinders optimal protocol identification. Although, based on the available evidence, chronic RIC appears to be the most promising regime, early initiation within the acute phase and patient compliance to chronic RIC thereafter are important to achieve desirable outcomes. As a feasible, safe, and noninvasive treatment, RIC could be applied in a variety of clinical settings without requiring specialized personnel. However, significant work remains before RIC can become widely accepted.

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Competing interests

None.

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