Rationale for ischemic conditioning to prevent stroke in patients with intracranial arterial stenosis

Sami Al Kasab, David C Hess¹, Marc I Chimowitz

Abstract:
Intracranial atherosclerotic arterial stenosis (ICAS) is one of the most common causes of stroke worldwide and is associated with particularly a high risk of recurrent stroke. Although aggressive medical management, consisting of dual antiplatelet therapy and intensive control of vascular risk factors, has improved the prognosis of patients with ICAS, subgroups of patients remain at very high risk of stroke. More effective therapies for these high-risk patients are urgently needed. One promising treatment is remote limb ischemic conditioning, which involves producing repetitive, transient ischemia of a limb by inflating a blood pressure cuff with the intention of protecting the brain from subsequent ischemia. In this study, we review the limitations of currently available treatments, discuss the potential mechanisms of action of ischemic conditioning, describe the preclinical and clinical data suggesting a possible role of ischemic conditioning in treating patients with ICAS, and outline the questions that still need to be answered in future studies of ischemic conditioning in subjects with ICAS.

Key words:
Intracranial atherosclerosis, ischemic conditioning, stroke

Introduction

Intracranial atherosclerotic arterial stenosis (ICAS) is responsible for 6–10% of ischemic strokes in whites, 6–29% in blacks, 20–50% in Asians.¹⁻¹⁴ In the US, ICAS causes ~50,000 strokes per year (i.e., 8–10% of the 675,000 ischemic strokes per year)¹⁵ at a cost of $750,000,000 in year 1 and $4.5 billion over the lifetime of these patients.¹⁶ The worldwide burden of ICAS is enormous as it is especially prevalent in Asian, Hispanic, African, and Arabic countries, as well as in India and Pakistan.¹⁻¹² In addition to being a common cause of stroke, ICAS also is associated with a higher risk of recurrent stroke compared with most other cerebrovascular diseases.¹⁷⁻²²

Review of Previous ICAS Trials and Limitations of Current Treatments

The Warfarin Aspirin Symptomatic Intracranial Disease (WASID) stenosis trial showed that aspirin was safer and as effective as warfarin for preventing stroke in subjects with 50–99% ICAS who had a transient ischemic attack or stroke within 90 days before enrollment and that good control of blood pressure (BP) and low-density lipoprotein cholesterol (LDL) were associated with a lower risk of stroke.²³,²⁴ Subjects with 70–99% stenosis whose qualifying event occurred within 30 days before enrollment were at highest risk of stroke.²⁵

In the subsequent stenting and aggressive medical management for preventing recurrent ischemic stroke (SAMMPRIS) trial, subjects with 70–99% stenosis and a qualifying TIA or stroke within 30 days before enrollment were randomized to aggressive medical management (AMM) alone versus AMM plus stenting with the Wingspan stent system. AMM consisted of dual antiplatelet therapy (aspirin and clopidogrel) for 90 days after enrollment followed by aspirin alone in combination with intensive risk factor management (primarily targeting systolic BP (SBP) <140 mmHg and LDL cholesterol <70 mg/dL) and a lifestyle program.²⁶ Enrollment in SAMMPRIS was stopped early because of higher than expected rate of periprocedural stroke in the stenting group (14.7% at 30 days [10.2%, ischemic stroke and 4.5%, hemorrhagic stroke]) and much lower than projected rate of stroke in the medical group. The absolute risk reduction...
from medical therapy alone was 8.9% at 30 days and 9.0% at 3 years, indicating that there was no benefit from stenting beyond the periprocedural period.\textsuperscript{[26,27]}

While the 1-year rate of the primary endpoint (any stroke or death within 30 days of enrollment or stroke in the territory beyond 30 days) in the AMM arm of SAMMPRIS was almost 50% lower than the projected rate, this reduction was driven by particularly a low event rate in subjects whose qualifying event for SAMMPRIS was a TIA (1-year primary endpoint rate of 5.6%).\textsuperscript{[28]} In comparison, the 1-year rate of the primary endpoint in subjects in the AMM arm whose qualifying event for the trial was a stroke was 16.1%.\textsuperscript{[28]} Additional WASID and SAMMPRIS analyses show that subjects with border zone infarcts on baseline imaging had a high frequency of impaired collaterals on cerebral angiography and were at highest risk of recurrent symptomatic infarct during follow-up.\textsuperscript{[29,30]}

Moreover, the recently completed VERITAS study of subjects with vertebrobasilar stenosis showed that impaired blood flow distal to the stenosis also was a strong predictor of recurrent stroke.\textsuperscript{[31]} These findings indicate that hemodynamic factors (impaired distal blood flow and incomplete or absent collaterals) play an important role in the pathophysiology of stroke in ICAS patients and are important therapeutic targets for newer and more effective therapies for high-risk patients. One novel treatment that has emerged as a safe and potentially effective treatment for ICAS is remote limb ischemic conditioning (RLIC).

### Possible Mechanisms of Action of Remote Limb Ischemic Conditioning

While the protective mechanisms of action of RLIC are uncertain, Rassaf et al. recently provided strong evidence that circulating plasma nitrite is a key mediator.\textsuperscript{[32]} Studies using pharmacological blockade and genetic deletion techniques in rats showed that RLIC increased nitrite levels in plasma and confirmed that endothelial nitric oxide synthase-mediated upregulation of nitric oxide (NO) and conversion to nitrite are required for the protective effect.\textsuperscript{[32]} Additional transfer experiments of plasma from healthy human subjects who underwent RLIC identified plasma nitrite as a cardioprotective agent in isolated Langendorff mouse heart preparations exposed to ischemia and reperfusion.\textsuperscript{[32]}

Nitrite provides a storage pool of NO that circulates in the blood associated with red blood cell/hemoglobin and is reduced to NO in areas of hypoxemia, mediating hypoxic vasodilatation, and increased blood flow.\textsuperscript{[33]} Given that impaired collateral flow distal to ICAS was strongly associated with an increased risk of stroke in WASID and SAMMPRIS subjects, some preclinical findings suggest that if RLIC is effective in ICAS patients, the mechanisms may be related to increased plasma nitrite levels and improved cerebral blood flow (CBF). Nitrite also is involved in the nitrosylation of key mitochondria proteins, so increased nitrite levels may also be cytoprotective.\textsuperscript{[32]}

### Rationale for Evaluating Remote Limb Ischemic Conditioning in Subjects with ICAS

The scientific rationale for evaluating RLIC for stroke prevention in patients with ICAS rests on four lines of evidence: (1) Common mechanisms of action between RLIC and exercise, which was the most important predictor of a good outcome in the medical arm in SAMMPRIS; (2) preclinical data of the protective effect of RLIC in animal models of stroke and cardiac injury; (3) results of randomized trials evaluating RLIC in subjects with myocardial ischemia; and (4) two strikingly positive small pilot randomized clinical trials of RLIC in ICAS subjects performed in China.

### Remote limb ischemic conditioning, exercise and stenting and aggressive medical management for preventing recurrent ischemic stroke

Exercise is a powerful cardio- and neuro-protectant that triggers an ischemia-resistant phenotype, similar to RLIC.\textsuperscript{[34–41]}

In a trial of healthy humans, dialysates prepared from plasma of subjects undergoing either vigorous exercise or RLIC were both protective in an isolated rabbit heart preparation and both were blocked by naloxone, suggesting that common humoral mediators of organ protection are shared by exercise and RLIC.\textsuperscript{[41]} In SAMMPRIS, analyses of the impact of risk factor control on outcome showed that 3 factors were associated with significantly lower rates of stroke, myocardial infarction (MI), or vascular death in the AMM group: Achieving targets for (1) SBP (hazard ratio [HR]: 0.53, confidence interval [CI]: 0.31–0.93), (2) LDL (HR: 0.53, CI: 0.30–0.94), and (3) exercise (HR: 0.25, CI: 0.12–0.50).\textsuperscript{[42]} In multivariable analyses, achieving SBP and LDL targets was significant only if exercise was not in the model ($P = 0.047$ and 0.040, respectively). With exercise in the model, only exercise was significant ($P < 0.0001$). Moreover, exercise was the only variable associated with a significantly lower risk of stroke ($HR: 0.22, CI: 0.10–0.50$).\textsuperscript{[42]}

Since RLIC and exercise may share common protective mechanisms, these post hoc data on the protective effect of exercise in SAMMPRIS provide indirect evidence of the potential of RLIC to prevent stroke in patients with ICAS.

### Preclinical evidence

Although there are no animal models for ICAS, RLIC has been studied in a bilateral carotid artery stenosis (BCAS) model in the mouse. Khan et al. placed microcoils around the internal carotid arteries to produce stenosis and on day 7, began daily RLIC using a conditioning device applied to one of the mouse’s hind limbs until day 21.\textsuperscript{[43]} RLIC increased CBF at 21 days, as measured by laser speckle contrast imaging, and CBF remained elevated at 28 days, 1 week after cessation of conditioning. In addition, the mice randomized to RLIC had improved cognition at 28 days as well as less inflammation and reduced damage of the white and gray matter when sacrificed at 28 days compared with mice randomized to sham RLIC.\textsuperscript{[43]}

Other preclinical work using RLIC with acute ischemic stroke models shows that CBF increases within 6–24 h of treatment.\textsuperscript{[44–46]}

Hess et al. tested the hypothesis that upregulation of nitrite might explain the increase in CBF seen after RLIC in the BCAS model.\textsuperscript{[47]} They compared plasma nitrite levels (measured by ozone-chemiluminescence [GE Sievers NOA 280]) at 28 days postcoiling in three groups of mice: Bilateral carotid sham coiling, coiling and sham RLIC, and coiling with RLIC. Coiling alone (sham RLIC) reduced plasma nitrite but coiling with RLIC applied for 2 weeks significantly increased plasma nitrite [Figure 3], which remained elevated 1 week after RLIC was stopped indicating a sustained effect.\textsuperscript{[47]}
Trials of remote limb ischemic conditioning for myocardial ischemia

A meta-analysis of several small randomized cardiac clinical trials of RLIC showed that RLIC reduced the incidence of MI and troponin release. In addition, RLIC effectively reduced myocardial injury when used just once (inflation of the BP cuff to 200 mm Hg for 5 min followed by reperfusion for 5 min, repeated for 4 cycles) in the prehospital setting in ST elevation MI patients before percutaneous coronary interventions (PCIs). In a meta-analysis of 11 small PCI trials, RLIC reduced perioperative MI and acute kidney injury. Moreover, some of these studies showed that just one RLIC treatment before PCI reduced long-term mortality and major cardiac and cerebrovascular events. In one of these studies, 333 patients with a suspected acute ST-elevation MI were randomized to PCI with \( n = 166 \) or without \( n = 167 \) RLIC. RLIC was initiated in the ambulance during transport to the interventional center and was achieved by performing 4 cycles of 5 min inflation followed by 5 min deflation of BP cuff. In the per-protocol analysis of 251 patients fulfilling trial criteria, a major adverse cardiac or cerebrovascular event occurred in 17 (13.5%) of patients in the intervention group compared with 32 (25.6%) patients in the control group (HR: 0.49, 95% CI: 0.27–0.89, \( P = 0.018 \)) during a median follow-up of 3.8 years.

On the other hand, two recent trials that evaluated RLIC treatment just once before cardiac bypass surgery did not show a benefit of RLIC for preventing major vascular events at 90 days or 1 year. However, one possible reason for the lack of benefit of RLIC in these two trials is that propofol, which was used for general anesthesia in most of these subjects (but not in the earlier small cardiac studies), is known to counteract the effects of RLIC.

Pilot trials of remote limb ischemic conditioning in China

The most compelling rationale for further evaluating RLIC in patients with ICAS emerges from two small completed Chinese randomized trials. In the first Chinese trial, subjects aged 18-80 years with TIA or stroke attributed to 50–99% ICAS were randomized to bilateral upper extremity (BUE) conditioning twice daily for 300 days \( n = 167 \). The RLIC group had a significantly lower incidence of new lesions (19.2% in the RLIC group vs. 46.4% in the control group; relative risk 0.41; 95% CI: 0.22–0.77; \( P = 0.003 \)) and significantly smaller median volume of lesions \( P < 0.01 \) than subjects in the control arm who did not undergo RLIC.

Unresolved Research Questions Regarding Remote Limb Ischemic Conditioning

While the results of these preclinical studies, some of the cardiac clinical trials, and the Chinese RLIC clinical trials in subjects with ICAS are encouraging, several key research questions regarding RLIC remain unresolved: (1) What is the optimal duration (in days) and frequency of RLIC for preventing stroke? (2) Is there evidence of potential efficacy of RLIC compared with AMM for preventing stroke? This is an important issue because the medical management in the Chinese trials used standard medical treatment and not the aggressive medical regimen used in SAMMPRIS, which is the new standard of care for patients with ICAS. (3) Are CBF and select biomarkers (vasodilatory, inflammatory, fibrinolytic, and microRNA) valid indicators of the conditioning response? (4) Is RLIC durable, i.e., will any changes in CBF and biomarkers be maintained after RLIC treatment ends? Future studies are needed to address these key questions before a definitive Phase III trial comparing AMM alone versus AMM plus RLIC can be undertaken.

Conclusion

Subgroups of patients with ICAS remain at high risk of recurrent stroke despite AMM. Therefore, more effective therapies for these high-risk patients remain an urgent need. RLIC has promise as a noninvasive treatment option for patients with ICAS; however, further studies are needed before a definitive Phase III trial can be undertaken in the United States comparing AMM alone versus AMM plus RLIC. Since the risk of recurrent stroke in ICAS patients is highest in the first few months after a stroke, a Phase III trial that established the efficacy of RLIC would likely be widely accepted by patients and physicians because RLIC would not have to be used indefinitely (unlike many medications), which is very attractive to patients. In addition, this device could be applied while a subject is performing sedentary activities (e.g., reading, watching television, or listening to music). RLIC devices can record correct use, providing reliable data on treatment adherence in practice, which is difficult to obtain with medications. A positive Phase III trial for RLIC would not only improve the outcome of high-risk patients with
ICAS but also lead to paradigm-shifting treatment of other cerebrovascular diseases (e.g., extracranial carotid stenosis, small vessel disease, vascular cognitive impairment, and subarachnoid hemorrhage).30-31

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. Stroke 1995;26:14-20.
2. Qureshi AJ, Saldañ K, Patel M, Janssen RS, Frankel MR. Stroke in young black patients. Risk factors, subtypes, and prognosis. Stroke 1995;26:1995-8.
3. Weinberg LA. Clinical characteristics of transient ischemic attacks in black patients. Neurology 1991;41:1410-4.
4. Wityk RJ, Lehman D, Krag M, Corejs J, Ahn H, Litt B. Race and sex differences in the distribution of cerebral atherosclerosis. Stroke 1996;27:1974-80.
5. Feldmann E, Danelut N, Kwan E, Ho KJ, Pessin MS, Langenberg P, et al. Chinese-white differences in the distribution of occlusive cerebrovascular disease. Neurology 1990;40:1541-5.
6. Williams AO, Resch JA, Loewenson RB. Cerebral atherosclerosis – A comparative autopsy study between Nigerien Negroes and American Negroes and Caucasians. Neurology 1969;19:205-10.
7. Wang Y, Zhao X, Liu L, Sow YO, Pu Y, Pan Y, et al. Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in China: The Chinese Intracranial Atherosclerosis (CICAS) Study. Stroke 2014;45:663-9.
8. Kumar G, Kailita J, Kumar B, Bansal V, Jain SK, Misra U. Magnetic resonance angiography findings in patients with ischemic stroke from North India. J Stroke Cerebrovasc Dis 2010;19:146-52.
9. Kamal AK, Majeed F, Pasha O, Rehman H, Islam M, Azam I, et al. Clinical, lifestyle, socioeconomic determinants and rate of asymptomatic intracranial atherosclerosis in stroke free Pakistanis. BMC Neurol 2014;14:155.
10. Oludapo O, Olusakin J, Ogun G, Akaneg E. Atherosclerosis of the intracranial carotid arteries in Nigerians: A pilot autopsy study. Niger J Cardiol 2013;10:62-7.
11. Ogha F, Falase A. Intracranial atherosclerotic disease in Nigeria: Any relationship with rising stroke burden in the country? Niger J Cardiol 2013;10:45-6.
12. Moustafa RR, Moneim AA, Salem HH, Shalash AS, Azmy HA. Intracranial steno-occlusive arterial disease and its associations in Egyptian ischemic stroke patients. Stroke 2013;44:538-41.
13. Gorelick PB, Wong KS, Bae HJ, Pandey DK. Large artery intracranial occlusive disease: A large worldwide burden but a relatively neglected frontier. Stroke 2008;39:2396-9.
14. Wong WK. Global burden of intracranial atherosclerosis. Int J Stroke 2006;1:158-9.
15. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Executive summary: Heart disease and stroke statistics-2013 update: A report from the American Heart Association. Circulation 2015;131:434-41.
16. Taylor TN, Davis PH, Toller JC, Holmes J, Meyer JW, Jacobson MF. Lifetime cost of stroke in the United States. Stroke 1996;27:1459-66.
17. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke prevention in atrial fibrillation II study. Lancet 1994;343:687-91.
18. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFIT (European Atrial Fibrillation Trial) Study Group. Lancet 1993;342:1255-62.
19. Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001;345:1444-51.
20. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson CG, Haynes RB, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998;339:1415-25.
21. The APASS Investigators. Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. JAMA 2004;291:576-84.
22. Gorelick PB, Richardson D, Kelly M, Ruland S, Hung E, Harris Y, et al. Aspirin and ticlopidine for prevention of recurrent stroke in black patients: A randomized trial. JAMA 2003;289:2947-57.
23. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Warfarin-aspirin symptomatic intracranial disease trial investigators. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med 2005;352:1305-16.
24. Chaturvedi S, Turan TN, Lynn MJ, Kasner SE, Romano J, Cotsonis G, et al. Risk factor status and vascular events in patients with symptomatic intracranial stenosis. Neurology 2007;69:2063-8.
25. Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation 2006;113:555-63.
26. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 2011;365:993-1003.
27. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): The final results of a randomised trial. Lancet 2014;383:333-41.
28. Waters MF, Hoh BL, Lynn MJ, Kwon HM, Turan TN, Derdeyn CP, et al. Factors associated with recurrent ischemic stroke in the medical group of the SAMMPRIS Trial. JAMA Neurol 2016;73:308-15.
29. Wabnitz AM, Derdeyn CP, Fiorella DJ, Lynn MJ, Cotsonis GA, Liebeskind DS, et al. Infarct patterns in the anterior circulation as predictors of recurrent stroke in the medical arm of SAMMPRIS. Stroke 2016;47:A103.
30. Liebeskind DS, Cotsonis GA, Saver JL, Lynn MJ, Turan TN, Cloft HJ, et al. Collaterals dramatically alter stroke risk in intracranial atherosclerosis. Ann Neurol 2011;69:963-74.
31. Amin-Hanjani S, Pandey DK, Rose-Finnell L, Du X, Richardson D, Thulborn KR, et al. Effect of hemodynamics on stroke risk in symptomatic atherosclerotic vertebralbasilar occlusive disease. JAMA Neurol 2016;73:178-85.
32. Rassaf T, Totzeck M, Hendgen-Cotta UB, Shiva S, Heusch G, Kelm M. Circulating nitrite contributes to cardioprotection by remote ischemic preconditioning. Circ Res 2014;114:1601-10.
33. Liu C, Wajih N, Liu X, Basu S, Janes J, Marvel M, et al. Mechanisms of human erythrocytic bioactivation of nitrite. J Biol Chem 2015;290:1281-94.
34. Curry A, Guo M, Patel R, Liebelt B, Sprague S, Lai Q, et al. Exercise pre-conditioning reduces brain inflammation in stroke via tumor necrosis factor-alpha, extracellular signal-regulated kinase 1/2 and matrix metalloproteinase-9 activity. Neurol Res 2010;32:756-62.
35. Iadecola C, Anrather J. Stroke research at a crossroad: Asking the brain for directions. Nat Neurosci 2011;14:1363-8.
36. Klener RA, Speakman MT, Przyklenk K. Ischemic preconditioning: A plea for rationally targeted clinical trials. Cardiovasc Res 2002;55:526-33.
37. Shinton R, Sagar G. Lifelong exercise and stroke. BMJ 1993;307:231-4.
38. Wannamethee G, Shaper AG. Physical activity and stroke in British middle aged men. BMJ 1992;304:597-601.
39. Zhang F, Wu Y, Jia J. Exercise preconditioning and brain ischemic tolerance. Neurosciience 2011;177:170-6.
40. Zhang Q, Zhang L, Yang X, Wan Y, Jia J. The effects of exercise preconditioning on cerebral blood flow change and endothelin-1 expression after cerebral ischemia in rats. J Stroke Cerebrovasc Dis 2014;23:1696-702.
41. Michelsen MM, Stettrup NB, Schmidt MR, Løfgren B, Jensen RV, Tropak M, et al. Exercise-induced cardioprotection is mediated by a bloodborne, transferable factor. Basic Res Cardiol 2012;107:260.
42. Turan TN, Nizam A, Lynn MJ, Montgomery J, Derdeyn CP, Fiorella D, et al. Relationship between risk factor control and vascular events in the stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) trial. Stroke 2014;45:AW130.
43. Khan MB, Hoda MN, Vaibhav K, Giri S, Wang P, Waller JL, et al. Remote ischemic postconditioning: Harnessing endogenous protection in a murine model of vascular cognitive impairment. Transl Stroke Res 2015;6:69-77.
44. Hoda MN, Hafez SS, Johnson MH, Siddiqui S, Ergul A, et al. Remote ischemic preconditioning is effective after embolic stroke in ovariectomized female mice. Transl Stroke Res 2014;5:484-90.
45. Hoda MN, Siddiqui S, Herberg S, Periyasamy-Thanavas S, Bhatia K, Hafez SS, et al. Remote ischemic preconditioning is effective alone and in combination with intravenous tissue-type plasminogen activator in murine model of embolic stroke. Stroke 2012;43:2794-9.
46. Hoda MN, Fagan SC, Khan MB, Vaibhav K, Chaudhary A, Wang P, et al. A 2 × 2 factorial design for the combination therapy of minocycline and remote ischemic preconditioning: Efficacy in a preclinical trial in murine thromboembolic stroke model. Exp Transl Stroke Med 2014;6:10.
47. Hess DC, Hoda MN, Khan MB. Humoral mediators of remote ischemic conditioning: Important role of eNOS/NO/Nitrite. Acta Neurochir Suppl 2016;121:45-8.
48. Brevvoord D, Kranke P, Kuipers M, Weber N, Hollmann M, Preckel B. Remote ischemic conditioning to protect against ischemia-reperfusion injury: A systematic review and meta-analysis. PLoS One 2012;7:e42179.
49. Botker HE, Kharbanda R, Schmidt MR, Bottcher M, Kalttof AK, Terkelsen CJ, et al. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: A randomised trial. Lancet 2010;375:727-34.
50. Pei H, Wu Y, Wei Y, Yang Y, Teng S, Zhang H. Remote ischemic preconditioning reduces perioperative cardiac and renal events in patients undergoing elective coronary intervention: A meta-analysis of 11 randomized trials. PLoS One 2014;9:e115500.
51. Sloth AD, Schmidt MR, Munk K, Kharbanda RK, Redington AN, Schmidt M, et al. Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention. Eur Heart J 2014;35:168-75.
52. Hoole SP, Heck PM, Sharples L, Khan SN, Duehmke R, Densem CG, et al. Cardiac remote ischemic preconditioning in coronary stenting (CRISP Stent) study: A prospective, randomized control trial. Circulation 2009;119:820-7.
53. Davies WR, Brown AJ, Watson W, McCormick LM, West NE, Dutka DP, et al. Remote ischemic preconditioning improves outcome at 6 years after elective percutaneous coronary intervention: The CRISP stent trial long-term follow-up. Circ Cardiovasc Interv 2013;6:246-51.
54. Meybohm P, Bein B, Brosteaun O, Cremer J, Gruenewald M, Stoppe C, et al. A multicenter trial of remote ischemic preconditioning for heart surgery. N Engl J Med 2015;373:1397-407.
55. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, et al. Remote ischemic preconditioning and outcomes of cardiac surgery. N Engl J Med 2015;373:1408-17.
56. Kottenberg E, Musiolik J, Thiellmann M, Jakob H, Peters J, Heusch G. Interference of propofol with signal transducer and activator of transcription 5 activation and cardioprotection by remote ischemic preconditioning during coronary artery bypass grafting. J Thorac Cardiovasc Surg 2014;147:376-82.
57. Zaugg M, Lucchetti E. Remote ischemic preconditioning in cardiac surgery – Ineffective and risky? N Engl J Med 2015;373:1470-2.
58. Meng R, Asmoro K, Meng L, Liu Y, Ma C, Xi C, et al. Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. Neurology 2012;79:1853-61.
59. Meng R, Ding Y, Asmoro K, Brogan D, Meng L, Sui M, et al. Ischemic conditioning is safe and effective for octo- and nonagenarians in stroke prevention and treatment. Neurotherapeutics 2015;12:667-77.
60. Zhao W, Ma C, Ovbiagele B, Hou B, Sun Y, Feng W, et al. Remote ischemic preconditioning reduces new vascular brain injury early after carotid artery stenting: A randomized controlled trial. Stroke 2016;47:A17.
61. Gonzalez NR, Connolly M, Dusick JR, Bhakta H, Vespa P. Phase I clinical trial for the feasibility and safety of remote ischemic conditioning for aneurysmal subarachnoid hemorrhage. Neurosurgery 2014;75:590-8.