Heart conditioning as healthy medicine:

Clinical trials.

Andrew Ying-Siu Lee, MD,PhD.

There is consistent evidence among diverse models and species that brief ischemia/reperfusion applied in a remote tissue or organ confers cytoprotection against ischemia/reperfusioninjury.

In remote ischemic conditioning (RIC), mild and transient episodes of ischemia with reperfusion in one vascular bed, tissue or organ confers overall protection and render remote tissues and organs resistant to ischemia/reperfusion injury.

RIC by repeated brief inflation/deflation of a blood pressure culf protects against endothelial dysfunction and myocardial injury in percutaneous coronary interventions, coronary artery bypass grafting and reperfused acute myocardial infarction. Moreover, a number of studies documented RIC-induced attenuation of ischemia/reperfuion injury in brain, lungs, liver, kidney, intestine, skin and other tissues[1].

Botker et al. reported that RIC performed before percutaneous coronary intervention increased myocardial salvage in patients with acute and evolving myocardial infarction[2].Zografos et al investigated the effect of RIC on myocardial injury in patients undergoing percutaneous coronary intervention. They found that RIC significantly reduced periprocedural troponin I release and the incidence of PCI-related myocardial infarction[3].

Thielmann et al. reported that RIC provided perioperative myocardial protection and improved the prognosis of patients undergoing elective CABG surgery[4].Hausenlogy et al investigated the effect of RIC on myocardial injury in patients undergoing coronary artery bypass graft surgery. They found that RIC significantly reduced ovrall serum troponin I release after surgery[5].

RIC remains a potential treatment modality for the reduction of myocardial injury in defined settings, which is also suggested in the 2014 ESC/EACTS guidelines on myocardial revascularization[6].
RIC reduced systolic blood pressure by >6mmHg, of the diastolic blood pressure > 3 mmHg, and of the pulse pressure by 3mmHg, with some evidence for a delayed effect in the ensuing days following RIC. Therefore RIC could be considered a therapeutic adjunct to the pharmacological management of hypertension. Also RIC could be considered as the sole therapeutic maneuver for the management of prehypertension, along with prescription of low salt, DASH diet and exercise[7].

RIC has antiarrhythmic effect on atrial fibrillation. Candillio et al observed a significant reduction in the incidence of new-onset atrial fibrillation after cardiac surgery by 54%[8]. Han et al demonstrated that RIC reduced the incidence of early recurrent atrial fibrillation after catheter ablation[9]. Slagsvold et al observed a postoperative reduction in atrial fibrillation after bypass surgery in the remote ischemic preconditioning groups[10]. Furthermore, Kosiuk et al investigated the impact of RIC on electrophysiologic parameters related to nonvalvular paroxysmal atrial fibrillation. They reported that RIC reduced the inducibility and substanability of atrial fibrillation, which is possibly mediated by changes in electrophysiological properties of the atria. Therefore, RIC may be used as a simple noninvasive procedure to reduce atrial fibrillation burden[11].

RIC induced protection against the increase inplatelet reactivity in patients with stable coronary artery disease, thereby reducing the thrombogenic burden[12].

RIC also have neuroprotective effects in human. The safety and feasibility of RIC in patients with aneurysmal subarachnoid hemorrhage have been confirmed[13]. Preclinical and clinical studies have provided evidence of benefits when apply RIC in the prevention, treatment and recovery of stroke[14]. Chronic RIC may promote neural repair for stroke recovery, including neurogenesis, angiogenesis, axon regeneration, synaptogenesis and remyelination[15]. Although the effects of RIC mainly focused on ischemic vascular disease, intracerebral hemorrhage shares similar pathophysiologic responses such as endothelial dysfunction, impaired cerebral autoregulation,

mitochondrial dysfunction, or proinflammatory state[16]. Therefore, the therapeutic benefits of RIC on ischemic stroke may also be applied in hemorrhagic stroke.

RIC also protects against kidney injury. About 30% of patients develop acute kidney injury after cardiac surgery. Zarbock et al confirmed that RIC reduced the rate of acute kidney injury after cardiac surgery inhigh-risk patients. RIC could thus represent a simple and promising strategy to provide protection to the kidney and improve postoperative outcomes[17].

RIC may affect immune cells and reduce the inflammatory response[18]. RIC improve mitochondrial function against oxidative stress, modify autophagy regulation, and increase cerebral and cardiovascular blood flow and collateral circulation[19].

RIC increased myocardial salvage in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention. This beneficial effects was substained long-term after 3.8 years[20]. RIC reduced major adverse cardiac and cerebral events after elective percutaneous coronary intervention at 6 months. This beneficial effects was sustained long-term after 6 years[21].

Recently, chronic heart conditioning, the daily use of RIC for a period of weeks, is investigated.

It is well established that oxidative stress and inflammation is pivotal in the process of post-myocardial infarction remodeling[22,23]. Remote conditioning, when delivered daily for 10 days, reduced neutrophil adhesion, phagocytosis, and proinflammatory cytokine responses[24].

Seven days RIC leads to bilateral adaptation of the brachial artery endothelial function and forearm skin microcirculation in healthy, young men[25].

Wei et al[26] investigated the effect of chronic, repeated remote conditioning on infarct size and long-term remodeling after myocardial infarction in rats. They reported that chronic conditioning, when delivered daily for 28 days, reduced adverse left ventricular remodeling and improved survival after myocardial infarction, associated with attenuated myocardial inflammatory responses and oxidative stress.

Chen et al[27] investigated the effect of chronic conditioning, when delivered daily for 6 weeks, on heart rate variability and cardiac function in patients with mild heart failure. They reported that chronic conditioning improved cardiac function and heart rate variability in heart failure patients.

Shyu and Lee[28] investigated the effect of remote heart conditioning as healthy strategy, when delivered daily for one year, on the cardiovascular function in patients with heart failure. They reported that a one-year course of remote heart conditioning treatment as healthy regimen could improve cardiovascular function in patients with heart failure, supporting widespread use of remote heart conditioning in the daily lives of these patients.

Lee et al[29]. investigated RIC as healthy strategy in management of patients with cardiomegaly. They reported that RIC, when delivered daily for one year, reduced heart dimension in cardiomegaly patients without any adverse effects, supporting the widespread use of heart conditioning in the daily lives of these patients. Ventricular reverse remodeling was also observed, probably accounts for the reversion of cardiomegaly.

RIC may also reverse valvular heart disease. Lee et al[30] reported an 82-year-old man with severe aortic stenosis. He denied surgical or transcatheter aortic valve replacement, and prefer conservative medical treatment. RIC as an adjunctive management was also applied. After 27 months, to our surprise, follow-up transthoracic echocardiography showed aortic valve area of cm^2. Ventricular reverse remodeling was also observed, probably accounts for the reversion of aortic stenosis.

There are three hypotheses linking the protective effects of heart conditioning: 1. Neural hypothesis: Preconditioning of organs remote from the heart generate the release of endogenous substances such as adenosine, bradykinin or calcitonin gene-related peptides which activate local afferent neural pathways terminating at the heart and mediate cardioprotection[31].
1. Humoral hypothesis: Endogenous substances generated in the organs remote from the heart enter the blood stream, and activate specific myocardial receptors that eventually recruit intracellular pathways of cardioprotection[32].
2. Systemic hypothesis: Peripheral transient ischemia is able to cause a systemic suppressionof inflammatory and apoptotic pathways[33].

REFERENCES

1. Heusch G, Botker HE, Przyklenk K et al. Remote ischemic conditioning. JACC 65:177-95.
2. Botker HF, Kharbanda R, Schmidt MR et al. Remote ischemic conditioning before hospital admission, as a complelment to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomized trial. Lancet 2010;375:727-34.
3. Zografos TA, Katritsis GD, Tsiafoutis I et al. Effect of one-cycle remote ischemic preconditioning to reduce myocardial injury during percutaneous coronary intervention. Am J CArdiol 2014;113-17.
4. Thielmann M, Kattenbery E, Kleinbongard P et al. Cardioprotective and prognostic effects of remote ischemic preconditioning in patients undergoing coronary artery bypass surgery: a dingle centre randomized, double-blind, controlled trial. Lancet 2013;382:597-604.
5. Hausenloy D, Mwamure PK, Venugopal V et al. Effect of remote ischemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomized controlled trial. Lancet 2007;370:575-9.
6. Windecker S, Kolh P, Alfonso F et al. 2014 ESC/EACTS guidelines on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular interventions (EAPCI). Eur Heart J 2014;35:2541-619.
7. Madias JE. Effect of serial arm ischemic preconditioning sessions on the systemic blood pressure of a normotensive subject. Medical Hypotheses 2011;76:503-6.
8. Candilio L, Malik A, Ariti C et al. Effect of remote ischemic preconditioning on clinical outcomes in patients undergoing cardiac bypass surgery: a randomized controlled clinical trial. Heart 2015;101:185-92.
9. Han R, Liu X, Zheng M et al. Effect of remote ischemic preconditioning on left atrial remodeling and prothrombotic response after radiofrequency catheter ablation for atrial fibrillation. Pacing ClinElectrophysiol 2018;41:246-54

10. Slagsvold KH, Rognmo D, Hoydal M, Wisloff U, Wahba A. Remote ischemic preconditioning preserves mitochondrial function and influences myocardial microRNA expression in atrial myocardium during coronary bypass surgery. Cir Res 2014;114:851-9.
11. Kosiuk J, Langehan K, Stegmann C et al. Effect of remote ischemic preconditioning on electrophysiological parameters in nonvalvular paroxysmal atrial fibrillation: The RIPPAE randomized clinical trial. Heart rhythm 2019: :1-7.
12. Battipaglia I, Scalone G, Milo M, Franco AD, Lanza A, Crea F. Upper arm intermittent ischemia reduces exercise-related increase of platelet reactivity in patients with obstructive coronary artery disease. Heart 2011;97:1298-1303.
13. Koch S, Katsnelson M, Dong C, Perez-Pinzon M. Remote ischemic preconditioning after subarachnoid hemorrhage: a phase Ib study of safety and feasibility. Stroke 2011;42:1387-91.
14. Landman TRJ, Schoin Y, Warle MC et al. Remote ischemic preconditioning as an additional treatment for acute ischemic stroke. Stroke 2019;50(7):1934-9.
15. Yu W, Ren C, Ji X. A review of remote ischemic preconditioning as a potential strategy for neural repair poststroke. CNS NeurosciTher 2023;29(2):516-24.
16. Aronowski J, Zhao X. Molecular pathophysiology of cerebral hemorrhage: secondary brain injury. Stroke 2011;42:1781-6.
17. Zarbock A, Schmidt C, Aken HV et al. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery. A randomized clinicl trial. JAMA 2015;313:2133-41.
18. Konstantinov IE, Arab S, Kharbanda RK et al. The remote ischemic preconditioning stimulus modifies inflammatory gene expression in humans. Physiol Genomics 2004;19(1):143-50.
19. Hess DC, Blauenfeldt RA, Andersen G et al. Remote ischemic preconditioning – a new paradigm of self-protection in the brain. Nat Rev Neurol 2015;11:698-710.
20. Sloth AD, Schmidt MR, Munk K et al. Improved long-term clinical outcomes in patients with ST elevation myocardial infarction undergoing remote ischemic preconditioning as an adjunct to primary percutaneous coronary intervention. Eur Heart J 2014;35:168-75.

21. Davies WR, Brown AJ, Watson W et al. Remote ischemic preconditioning improves outcome at 6 years after elective percutaneous coronary intervention: The CRISP stent trial long-term follow up. Cir CardiovasInterv 2013;6:246-51.
22. Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. Cir 2002;53:31-47.
23. Hori M, Nishida K. Oxidative stress and left ventricular remodeling after myocardial infarction. Cardiovas Res 2009;81:457-64.
24. Shimizu M, Saxena P, Konstantinov IE et al. Remote ischemic preconditioning decreases adhesion and selectively modifies functional responses of human neutrophils. J Surg Res 2010;158:155-61.
25. Jones H, Hopkins N, Bailey TG et al. Seven day remote ischemic preconditioning improves local and systemic endothelial function and microcirculation in healthy humans. Am J Hypertension 2014;27:918-25.
26. Wei M, Xin P, Li S et al. Repeated remote ischemic postconditioning protects against adverse left ventricular remodeling and improves survival in a rat model of myocardial infarction. Cir Res 2011; 108:1220-5.
27. Chen L, Zhou Q, Jin H et al. Effects of remote ischaemic conditioning on heart rate variability and cardiac function in patients with mild ischaemic heart failure. Heart Lung Cir 2018;27:477-83.
28. Shyu MY, Lee AYS. Heart conditioning as healthy strategy in the management of heart failure.
29. Lee WWH, Lee DWC, Lee AYS. Heart conditioning as healthy strategy in the management of cardiomegaly.
30. Lee DWC, Lee WWH, Lee AYS. Heart conditioning as healthy strategy in the management of aortic stenosis: case report.
31. Zhao ZQ, Corvera JS, Halkos ME et al. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. Am J Physiol Heart Cir Physiol 2003;285:H579-88.
32. Przyklenk K, Bauer B, Ovize M et al. Regional ischemic preconditioning protects remote virgin myocardium from subsequent sustained coronary occlusion. Cir 1993:87:893-9
33. Peralta C, Fernande L, Panes J et al. Preconditioning protects against systemic disorders associated with heaptic ischemia-reperfusion through blockade of tumor necrosis factor-induced P-selectin up-regulation in the rat. Hepatology 2001;33:100-13.