Current Treatment Options in Cardiovascular Medicine
https://doi.org/10.1007/s11936-024-01054-2

REVIEW

Heart Conditioning as a Healthy Strategy in Adjunctive Treatment of Cardiovascular Disease: Clinical Trials

William Wing-Ho Lee[1] · **David Wing-Ching Lee**[1] · **Andrew Ying-Siu Lee**[1]

Accepted: 31 July 2024

Abstract

Purpose of Review This review highlights the clinical significance and ongoing clinical trials of heart conditioning as a healthy strategy, for reversing disease and aging. This approach is compatible with the heterochronic parabiotic model, as evidenced by reverse remodeling.

Recent Findings Over the past 38 years, research has shown that heart conditioning can enhance cardiovascular functions, as well as prevent and treat various cardiovascular and cerebrovascular diseases. Chronic heart conditioning as a healthy strategy leads to cardiac reverse remodeling, which may contribute to the reversal of cardiac enlargement and heart failure suggesting the reversion of aging and age-related diseases.

Summary Heart conditioning as a healthy strategy may lead to the reversion of disease and aging, serving as a possible adjunctive treatment for cardiovascular diseases.

Keywords Heart conditioning · Heterochronic parabiosis · Reverse remodeling · Healthy strategy

Opinion Statement

Heart conditioning as a healthy strategy has the potential to prevent, treat, and reverse aging and age-related diseases. Therefore, it is a potential adjunctive treatment for cardiovascular diseases through the process of cardiac reverse remodeling.

Introduction

For over a century, parabiotic experiments have demonstrated that there is reversion of disease and aging (healthy strategy)! Heart conditioning, demonstrated 38 years ago, has been proven to improve cardiovascular function, and prevent and treat various cardiovascular and cerebrovascular diseases (another healthy strategy)! Heart conditioning and heterochronic parabiosis are correlated. This may imply a possible healthy strategy for humans, leading to reversion of aging and age-related diseases. Therefore, heart conditioning stands as a promising adjunctive treatment for cardiovascular diseases through the process of cardiac reverse remodeling.

Heterochronic Parabiosis

Since a century ago, parabiotic experiments have shown that there is reversion of disease and aging (healthy strategy)!

Claude Bernard first pointed out in 1878 that the living parts of living organisms exist in the fluids that surround them (the internal environment or extracellular fluid), and that all vital mechanisms depend on a stable internal environment or homeostasis [1].

In 1907, Harrison observed the growth of nerves from the central nervous system of frog embryos cultured in a drop of lymph [2]. In 1910, Burrows successfully cultured tissues from the nervous system, heart, and mesenchymal tissue of chick embryos in plasma [3]. Carrel and Burrows later expanded their research by cultivating tissues and organs in plasma, studying their growth patterns [4]. By 1912, Carrel reported that the lifespan of tissues could be extended indefinitely through secondary, tertiary, and subsequent cultures [5]. These discoveries collectively underscore the importance of extracellular fluid for sustaining life.

For over a century, scientists have been conducting experiments on the effects of pairing two animals in

✉ Andrew Ying-Siu Lee
lee.yingsiu@msa.hinet.net

[1] Department of Cardiology, Jen-Ai Hospital, Tali, Taichung, Taiwan

Published online: 22 August 2024

parabiosis to examine the impact of circulatory or systemic factors (extracellular fluid) from one animal on the other. Additionally, a variant technique known as heterochronic parabiosis, involving the joining of young and old animals, has also been extensively studied to investigate systemic factors related to aging or aging-related diseases.

Parabiosis is the term used to describe the condition in which two living animals are surgically connected and develop a single, shared circulatory system. Research has shown that connecting healthy animals through parabiosis can increase the lifespan of animals that would otherwise succumb to disease or lethal treatments such as irradiation [6–10]. In a heterochronic parabiotic model, joining the circulatory systems of old and young animals leads to rejuvenation in the older partner [11]. Therefore, current work validates the potential for treating or reversing aging and age-related diseases, the age and pathologies of tissues can be rapidly and effectively reversed to a younger and healthier state.

In the following, blood [12] or plasma exchange transfusion [13], as well as the supply of young (or healthy) factors and removal of old (or unhealthy) factors [14], can also induce the phenomenon of heterochronic parabiosis. Thus, it is evident that in heterochronic parabiosis, there is an exchange of extracellular fluid, with the implementation of healthy factors, and the removal of unhealthy factors simultaneously in the old parabiont. This advantageous cycle leads to the reversion of disease and aging, as indicated in all prior experimental findings.

Recently, Ma et al. conducted a study on a single-cell transcriptomic atlas of aged tissues and their rejuvenation through heterochronic parabiosis. Their findings revealed that heterochronic parabiosis successfully revitalized senile adult stem cells and their niches in aged tissues. Additionally, they observed the restoration of youthful transcriptomes in resident hematopoietic stem and progenitor cells, and the reintroduction of rejuvenating factors in aged hematopoietic stem cells helped mitigate the decline in lymphopoiesis [15].

However, humans cannot be conjoined. Therefore, this effective healthy regimen, the only one in the world at this time, was set aside.

Heart Conditioning

For the past 38 years, research has shown that heart conditioning can improve cardiovascular function, as well as prevent and treat various cardiovascular and cerebrovascular diseases (another healthy strategy)!

Stress is a constellation of events, consisting of a stimulus or signal generated by any physical, chemical, or biological factors (stressor), that activates physiological fight or flight systems in the body (stress response) in order to counteract, adapt, and survive, which involve the release of factors in the systemic circulation and locally within central and peripheral tissues [16].

Generally speaking, brief, transient, and physiological stress activates multiple physiological systems such as the cardiovascular, musculoskeletal, neuroendocrine, and immunological systems to enhance body protection or performance. This adaptive response to stress is a crucial survival mechanism in nature, also known as self-curative mechanisms. However, severe, persistent, and pathological stress is maladaptive, and can have numerous adverse effects on health and longevity [17].

Coronary arteries are the blood vessels of the heart. Heart ischemia occurs when blood supply to the heart muscle is reduced owing to occlusion of the coronary arteries. Mild, transient, physiological heart ischemia produces adaptive or compensatory mechanisms. Severe, sustained, pathophysiological heart ischemia gives rise to maladaptive or decompensatory mechanisms.

Ischemic preconditioning was discovered by Murry et al. in 1986. A brief repeated occlusion of the coronary artery before the subsequent sustained occlusion reduces the extent of myocardial infarction [18]. Ischemic preconditioning has been demonstrated in many animal and clinical trials [18–24]. Heart conditioning can protect against postischemic contractile dysfunction, ischemia- and reperfusion-induced arrhythmia, apoptosis, and infarct injury [18–24]. This conditioning role of mild, short, physiological myocardial ischemia is recognized as a significant area of heart protection.

In summary, mild, transient, physiological heart ischemia triggers compensatory adaptations that help maintain cardiovascular homeostasis and normal functions at various levels within the body. This conditioning can protect the heart from subsequent cardiovascular events, reducing the risk of diseases such as sudden death, myocardial infarction, and stroke. A healthy cardiovascular system not only benefits the heart but also impacts other organs, such as the brain, lungs, kidneys, and gut, protecting them from various injuries. This suggests that conditioning may extend to other body systems as well [25]. The concept of conditioning in humans could lead to the development of strategies to keep the heart and other systems continuously protected and conditioned over time.

Heart Conditioning as a Healthy Strategy

Until now, it has been nearly impossible to use pairing, frequent blood or plasma exchange transfusions, the provision of all healthy factors, and the removal of all unhealthy factors as anti-aging strategies or healthy regimens for humans.

Table 1 The advantages of heart conditioning and heterochronic parabiotic models on heart function

Research	Protocols	Results
Murry et al., 1986 [18]	Ischemic preconditioning in dogs	Decrease in histologic infarct size
Sumeray & Yellon, 1988 [19]	Ischemic preconditioning in isolated rat hearts	Reduction in histologic infarct size
Schott et al., 1990 [20]	Ischemic preconditioning in pigs	Decrease in histologic infarct size
Vegh et al., 1992 [21]	Ischemic preconditioning in rats and dogs	Decrease in ischemia-induced arrhythmias
Kloner et al., 1995 [22]	Ischemic preconditioning in patients with acute myocardial infarction	Reduction in infarct size, in-hospital complications and death
Khan et al., 2014 [23]	Ischemic postconditioning in patients undergoing cardiac catheterization	Reduction in myocardial injury, improve left ventricular function
Thielmann et al., 2013 [24]	Remote ischemic preconditioning during cardiac surgery	Decrease in infarct size and improved patient prognosis
Loffredo et al., 2013 [7]	Heterochronic parabiosis in rats	Regression of cardiac hypertrophy and a reduction in cardiomyocyte size
Xiao et al., 2013 [8]	Pregnancy as parabiotic model in rats	Protected against cardiac ischemia injury, and activated cardiac progenitor cells
Felker et al., 2000 [9]	Pregnancy as parabiotic model in patients with cardiomyopathy	Restore heart function
Katsimpardi et al., 2014 [10]	Heterochronic parabiosis in rats	Induce vascular remodeling; reverse cardiac hypertrophy

It is well-known that stress triggers the release of factors in the systemic circulation and locally within central and peripheral tissues [16]. Recently, it has been established that heart conditioning produces cardioprotective or healthy factors. Studies have shown that plasma from animals subjected to heart conditioning can transfer cardioprotection to other animals and even between species, indicating a protective (or healthy) factor in the circulation [26, 27]. The common link or mechanism of heart conditioning and heterochronic parabiosis is "the extracellular fluid." Heart conditioning induces the release of factors in the extracellular fluid, while heterochronic parabiosis involves the exchange of factors in the extracellular fluid. Both processes involve the extracellular fluid. Heart conditioning, as a form of stress on the heart, triggers compensatory adaptations, that help maintain body homeostasis and the internal environment—that is, the extracellular fluid, also known as the systemic milieu or factors. By using mild, transient, physiological heart ischemia, heart conditioning activates adaptive or compensatory mechanisms that involve neurohormonal activation, heart remodeling, and other events such as oxidative stress, endothelin, nitric oxide, inflammatory mediators, growth factors, and more [28–30]. These mechanisms provide healthy factors such as activation of the adrenergic nervous system and the renin–angiotensin–aldosterone system, activation of inflammatory mediators involved in heart repair and remodeling, affect the biology of the heart cell, synthesis of protective proteins, intracellular enzyme activation, inhibition of death signaling in mitochondria, nitric oxide, and so on [28–30]. Simultaneously, these mechanisms help eliminate unhealthy factors such as reactive oxygen species, ischemia–reperfusion injury, decreased infarct size, apoptosis, and enhanced autophagy [18, 31]. Additionally, Table 1 summarizes the beneficial effects of heart conditioning and heterochronic parabiotic models on heart function. The endpoints and results are similar, relatively. Therefore, heart conditioning and heterochronic parabiosis are closely related.

In the context of heterochronic parabiosis, young blood contains proteins with anti-aging and protective properties, such as GDF11, TIMP2, oxytocin, growth hormone-releasing hormone, and osteocalcin. When young rats were given proteins like CCL11 or B2M found in old blood, their memory and brain function deteriorated [32]. In the context of heart conditioning, RIC triggers the release of circulating cardioprotective factors such as nitric oxide, cytokines, chemokines, microRNA, caveolae proteins, and connexin. Additionally, signaling molecules such as adenosine, bradykinin, opioids, reactive oxygen species, interleukin, heat shock protein, connectin, stromal derived factor 1α, and others are involved [33]. Figure 1 illustrates the beneficial cycle involving the implementation of healthy factors and the removal of unhealthy factors simultaneously, resulting in the reversal of disease and aging in heart conditioning and heterochronic parabiotic models. The above findings suggest that an advantageous cycle of healthy and unhealthy factors can have a profound impact on the reversion of disease and aging. This may imply a possible healthy strategy for humans, leading to reversion of aging and age-related diseases [32].

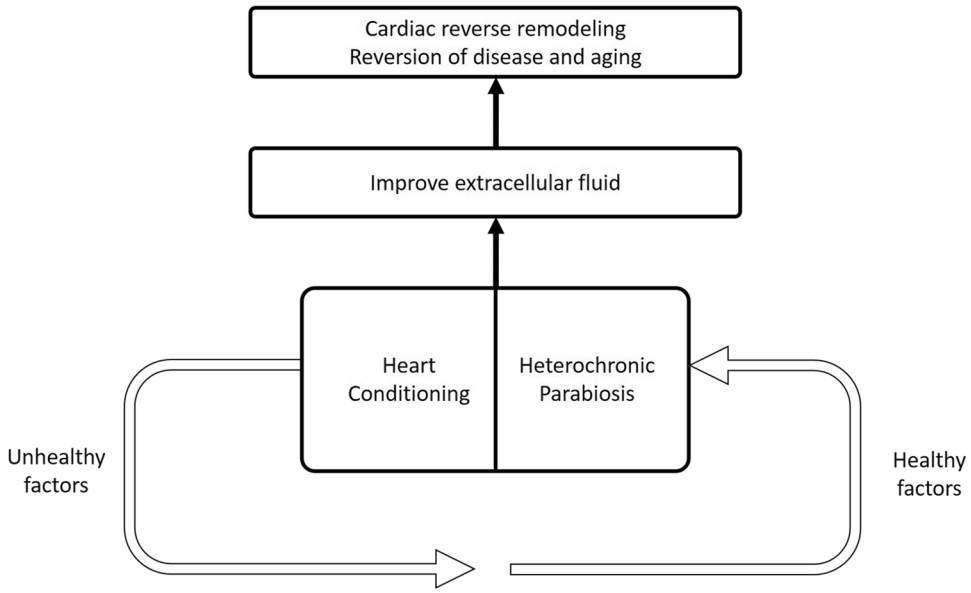

Fig. 1 Beneficial cycle with implementation of healthy factors and removal of unhealthy factors simultaneously, leading to reversion of disease and aging in heart conditioning and heterochronic parabiotic models

Heart Conditioning as a Healthy Strategy in Adjunctive Treatment of Cardiovascular Disease: Clinical Trials

Various models and species have consistently shown evidence that brief periods of ischemia/reperfusion in a distant tissue or organ can offer protection against ischemia/reperfusion injury.

In remote ischemic conditioning (RIC), mild and transient episodes of ischemia followed by reperfusion in a specific vascular bed, tissue, or organ provide overall protection and make remote tissues and organs resilient to ischemia/reperfusion injury.

RIC, achieved through repeated short periods of blood pressure cuff inflation/deflation, has been shown to protect against endothelial dysfunction and myocardial damage during percutaneous coronary interventions (PCI), coronary artery bypass graft surgery (CABG), and reperfused acute myocardial infarction. Additionally, several studies have demonstrated the ability of RIC to reduce ischemia/reperfusion injury in various organs such as the brain, lungs, liver, kidney, intestine, skin, and others [33].

Botker and colleagues discovered that RIC administered prior to PCI resulted in enhanced myocardial salvage for patients experiencing acute or evolving myocardial infarction [34]. On the other hand, Zografos et al. examined the impact of RIC on myocardial damage in patients undergoing PCI. They found that RIC led to a notable decrease in troponin I release during the perioperative period and a reduction in the occurrence of PCI-related myocardial infarction [35].

Thielmann et al. stated that RIC provided perioperative myocardial protection and improved the prognosis of patients undergoing elective CABG [36]. On the other hand, Hausenlogy and collaborators examined the effect of RIC on myocardial injury in patients undergoing CABG. They found that RIC significantly decreased overall serum troponin I release following surgery [37].

RIC remains a potential treatment modality for the reduction of myocardial injury in defined settings, as suggested in the 2014 ESC/EACTS guidelines on myocardial revascularization [38].

RIC has been shown to decrease systolic blood pressure by more than 6 mmHg, diastolic blood pressure by more than 3 mmHg, and pulse pressure by 3 mmHg, with evidence of a delayed impact in the days following RIC. Consequently, RIC may be viewed as a therapeutic adjunct to the pharmaceutical treatment of hypertension. Furthermore, RIC may be regarded as the primary therapeutic intervention for prehypertension management, in conjunction with the recommendation of a low salt, DASH diet, and exercise [39].

RIC exhibits an antiarrhythmic effect on atrial fibrillation (AF). Candillio et al. noted a significant decrease in the occurrence of new-onset AF following cardiac surgery by 54% [40]. Han et al. demonstrated that RIC lowered the occurrence of early recurrent AF after catheter ablation [41]. Slagsvold et al. observed a postoperative decrease in AF following cardiac surgery in the RIC groups [42]. Additionally, Kosiuk et al. examined the influence of RIC on electrophysiologic parameters associated with nonvalvular paroxysmal AF. They found that RIC decreased the inducibility and sustainability of AF, potentially through alterations in the electrophysiological characteristics of the atria. Consequently, RIC could serve as a simple noninvasive approach to alleviate the AF burden [43].

RIC has been shown to provide protection against the rise in platelet reactivity in patients with stable coronary artery disease, consequently lessening the thrombotic burden [44].

RIC has also been shown to have neuroprotective effects in humans. The safety and feasibility of RIC in patients with aneurysmal subarachnoid hemorrhage have been verified [45]. Both preclinical and clinical studies have demonstrated the benefits of applying RIC in the prevention, treatment, and recovery of stroke [46]. Additionally, chronic RIC may facilitate neural repair for stroke recovery, including neurogenesis, angiogenesis, axon regeneration, synaptogenesis, and remyelination [47]. While the effects of RIC have primarily been focused on ischemic vascular disease, intracerebral hemorrhage shares similar pathophysiologic responses, such as endothelial dysfunction, impaired cerebral autoregulation, mitochondrial dysfunction, or a proinflammatory state [48]. Therefore, the therapeutic benefits of RIC on ischemic stroke may also be applicable to hemorrhagic stroke.

RIC provides protection against kidney injury. Approximately 30% of patients experience acute kidney injury following cardiac surgery. Zarbock et al. verified that RIC decreased the incidence of acute kidney injury after cardiac surgery in high-risk patients. Therefore, RIC may serve as a simple and promising strategy to safeguard the kidneys and improve postoperative outcomes [49].

RIC has the potential to impact immune cells and decrease the inflammatory response [50]. Additionally, RIC can enhance mitochondrial function against oxidative stress, modify the regulation of autophagy, and increase cerebral and cardiovascular blood flow as well as collateral circulation [51].

RIC has been shown to improve myocardial salvage in individuals with ST elevation myocardial infarction who underwent primary PCI. This positive impact was maintained over the long term after 3.8 years [52]. RIC also reduced major adverse cardiac and cerebral events after elective PCI at 6 months, and this beneficial effect was sustained long-term after 6 years [53].

Chronic heart conditioning, which involves the regular application of RIC over several weeks, is currently being investigated.

It has been widely recognized that oxidative stress and inflammation play a crucial role in the post-myocardial infarction remodeling process [54, 55]. When administered daily for a period of 10 days, RIC was found to decrease neutrophil adhesion, phagocytosis, and proinflammatory cytokine reactions [56].

Additionally, a week of RIC results in the bilateral adjustment of brachial artery endothelial function and forearm skin microcirculation in young, healthy men [57].

Wei and colleagues [58] examined the impact of chronic, repeated remote conditioning on infarct size and long-term remodeling following myocardial infarction. Their findings indicated that daily delivery of chronic conditioning for 28 days led to a decrease in adverse left ventricular remodeling and an enhancement in survival after myocardial infarction. This was linked to a reduction in myocardial inflammatory responses and oxidative stress.

Chen et al. [59] investigated the effects of long-term heart conditioning, administered daily for 6 weeks, on heart rate variability and cardiac function in patients with mild heart failure. Their findings showed that chronic heart conditioning resulted in improvements in both cardiac function and heart rate variability in these patients.

Shyu and Lee [60] studied the impact of RIC as a healthy strategy, administered daily for a year, on the cardiovascular function of heart failure patients. Their findings suggested that a 1-year course of RIC treatment as a healthy strategy could improve cardiovascular function in heart failure patients through the process of cardiac reverse remodeling, indicating the reversion of disease. These results support the widespread use of RIC in the daily routines of heart failure patients. Additionally, they observed ventricular reverse remodeling, which likely contributed to the reversal of heart failure.

Lee et al. (unpublished data, submitted) investigated the use of RIC as a healthy strategy in patients with cardiac enlargement. Their results showed that daily RIC treatment over 1 year led to a decrease in heart size among patients with cardiomegaly without any adverse effects. This supports the idea of incorporating heart conditioning into the daily routines of these patients. Additionally, the study observed ventricular reverse remodeling, which likely played a role in reversing cardiac enlargement indicating a reversal of the disease.

Chronic or age-related heart diseases can lead to end-stage cardiac enlargement and heart failure, known as cardiac remodeling. Chronic remote cardiac conditioning as a form of healthy medicine can result in cardiac reverse remodeling, which reverses age-related heart diseases. In essence, heart conditioning has the potential to reverse disease and aging, consistent with heterochronic parabiotic experiments, as a form of healthy medicine. The mechanism behind this is that heart conditioning provides external pressure as a stressor, triggering the body's compensatory mechanisms, to release healthy factors such as cardioprotective factors, remove unhealthy factors such as free radicals, improve extracellular fluid, and ultimately lead to cardiac reverse remodeling, reversing disease and aging [33, 60].

The focus of traditional medicine is on treating organs and at the systems level, while healthy medicine focuses on treating cells (through the extracellular fluid). Both approaches are important! From a clinical standpoint, medicine can prevent and treat disease, while healthy medicine can prevent, treat, and reverse disease and aging.

There are three hypotheses that explain the protective effects of heart conditioning:

1. According to the neural hypothesis, preconditioning of organs distant from the heart triggers the release of endogenous substances such as adenosine, bradykinin, or calcitonin gene-related peptides. These substances activate local afferent neural pathways that reach the heart and provide cardioprotection [61].
2. The humoral hypothesis suggests that endogenous substances produced in organs far from the heart enter the bloodstream and stimulate specific myocardial receptors. This activation leads to the recruitment of intracellular pathways that offer cardioprotection [62].
3. Lastly, the systemic hypothesis proposes that peripheral transient ischemia can suppress inflammatory and apoptotic pathways systemically, resulting in cardioprotection [63].

Dr. Zhang Zhongjing from the Eastern Han Dynasty, two millennia ago, outlined the roles of medicine as:

1. treating illnesses;
2. preserving lives; and
3. enhancing vitality to stay healthy without disease and aging. According to Chinese philosophy, life encompasses the stages of birth, aging, illness, and death. Through hormetic stress, heart conditioning, and overall body conditioning, it is possible to reverse the effects of disease and aging, making it an exceptional form of healthcare.

Conclusion

Heart conditioning is stress on the heart, triggering compensatory mechanisms that release healthy factors such as cardioprotective factors and remove unhealthy factors such as free radicals simultaneously. This beneficial cycle results in the reversion of disease and aging, in line with the heterochronic parabiotic model, as evidenced by the reverse remodeling and improvement in cardiac enlargement and heart failure. Therefore, heart conditioning as a healthy strategy is a potential adjunctive treatment modality for cardiovascular diseases through the process of cardiac reverse remodeling.

Key References

- Lee AYS (2023) Heart conditioning and heterochronic parabiotic models as healthy strategy. SN Comprehen Clin Med 5:6.
  - Findings from this study suggest that heart conditioning, in analogy to the heterochronic parabiotic model, leads to reversion of aging and age-related diseases.
- Shyu MY, Lee AYS (2024) Remote ischemic conditioning improves cardiovascular functions in heart failure patients. Cardiol Res. https://doi.org/https://doi.org/10.14740/cr1669
  - Findings from this study suggest that chronic heart conditioning as a healthy strategy leads to reversion of disease and aging by reverse remodeling and improvement in heart failure.

Authors' Contributions WWH Lee search and collected data, drafting and review the manuscript. DWC Lee search and collected data, drafting and review the manuscript. AYS Lee conceptualized this study, review and edited the manuscript.

Funding No funding was received for conducting this study.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval This study was approved by the Ethic Committee of Jen Ai Hospital. Patients completed a written informed consent. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Competing Interests The authors declare no competing interests.

References

1. Bernard C. Les Phenomenes de la Vic. Paris 1878.
2. Harrison RG. Proc Soc Exp Biol Med. 1907;iv:140.
3. Burrows MT. J Am Med Asso. 1910;iv:2057.
4. Carrel A, Burrows MT. Cultivation of tissues in vitro and its technique. J Exp Med. 1911;XIII:387–96.
5. Carrel A. On the permanent life of tissues outside of the organism. J Exp Med. 1912;XV:516–28.
6. Carroll IM, Kimeldorf DJ. Mechanisms of protection against gastrointestinal and hematopoietic radiation lethality by parabiosis. Radiat Res. 1969;39:770–6.
7. Loffredo FS, Steinhauser ML, Jay SM, et al. Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. Cell. 2013;153:828–39.
8. Xiao J, Li J, Xu T, et al. Pregnancy-induced physiological hypertrophy protects against cardiac ischemia-reperfusion injury. Int J Clin Exp Pathol. 2013;7:229–35.
9. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Eng J Med. 2000;342:1077–84.

10. Katsimpardi L, Litterman NK, Schein PA, et al. Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. Science. 2014;344:630–4.
11. Pope F, Lunsford W, McCay CM. Experimental prolongation of the life span. J Chronic Dis. 1956;4:153–8.
12. Rebo J, Mehdipour M, Gathwala R, et al. A single heterochronic blood exchange reveals rapid inhibition of multiple tissues by old blood. Nat Comm. 2016;7:13363.
13. Villeda SA, Plambeck KE, Middeldorp J, et al. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nat Med. 2014;20:659–63.
14. Villeda SA, Luo J, Mosher KI, et al. The aging systemic milieu negatively regulated neurogenesis and cognitive function. Nature. 2011;477:90–4.
15. Ma S, Wang S, Ye Y, et al. Heterochronic parabiosis induces stem cell revitalization and systemic rejuvenation across aged tissues. Cell Stem Cell. 2022;29:990–1005.
16. Dhabhar FS, McEwen BS. Acute stress enhances while chronic stress suppresses immune function in vivo: a potential role for leukocyte trafficking. Brain Behav Immun. 1997;11:286–306.
17. Dhabhar FS. The short-term stress response – Mother nature's mechanism for enhancing protection and performance under conditions of threat, challenge and opportunity. Frontiers Neuroendocrinol. 2018;4:175–92.
18. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation. 1986;74:1124–36.
19. Sumeray MS, Yellon DM. Characterization and validation of a murine model of global ischemia-reperfusion injury. Mol Cell Biochem. 1998;186:61–8.
20. Schott RJ, Rohmann S, Braun ER, Schaper W. Ischemic preconditioning reduces infarct size in swine myocardium. Cir Res. 1990;66:1133–42.
21. Vegh A, Komori S, Szekeres L, Parratt JR. Antiarrhythmic effects of preconditioning in anesthetized dogs and rats. Cardiovas Res. 1992;26:487.
22. Kloner RA, Shook T, Przyklenk K, et al. Previous angina alters in-hospital outcome in TIMI 4: a clinical correlate to preconditioning? Circulation. 1995;91:37–45.
23. Khan AR, Binabdulhak AA, Alastal Y, et al. Cardioprotective role of ischemic postconditioning in acute myocardial infarction: a systemic review and meta-analysis. Am Heart J. 2014;168:512–21.
24. Thielmann M, Kottenberg E, Kleinbongard P, et al. Cardioprotective and prognostic effects of remote ischemic preconditioning in patient undergoing coronary artery bypass surgery: a single-centre randomized, double-blind, controlled trial. Lancet. 2013;382:597–604.
25. Przyklenk K, Whittaker P. Remote ischemic preconditioning: current knowledge, unresolved questions, and future priorities. J Cardiovas Pharmacol Ther. 2011;16(3–4):255–9.
26. Leung CH, Wang L, Nielsen JM, et al. Remote cardioprotection by transfer of coronary effluent from ischemic preconditioned rabbit heart preserves mitochondrial integrity and function via adenosine receptor activation. Cardiovas Drugs Ther. 2014;28(1):7–17.
27. Skyschally A, Gent S, Amanakis G, et al. Across-species transfer of protection by remote ischemic preconditioning with species-specific myocardial signal transduction by reperfusion injury salvage kinase and survival activating factor enhancement pathways. Cir Res. 2015;117(3):279–88.
28. Mann DL. Basic mechanisms of disease progression in the failing heart: the role of excessive adrenergic drive. Prog Cardiovas Dis. 1998;41(suppl 1):1–8.
29. Dell'Italia L, Sabis A. Activation of the rennin-angiotensin system in hypertrophy and heart failure. In Mann DL (ed): Heart failure: a companion to Baunwald's heart disease. Philadephia; Saunders. 2004; pp 129–143.
30. Heusch G. Cardioprotection: chances and challenges of its translation to the clinic. Lancet. 2013;381:166–75.
31. Piot CA, Padmanaban D, Ursell PC, et al. Ischemic preconditioning decreases apoptosis in rat hearts in vivo. Circulation. 1997;96:1598.
32. Lee AYS. Heart conditioning and heterochronic parabiotic models as healthy strategy. SN Comprehen Clinical Med. 2023;5:6.
33. Heusch G, Botker HE, Przyklenk K et al. Remote ischemic conditioning. JACC. 65:177–95.
34. Botker HF, Kharbanda R, Schmidt MR, et al. Remote ischemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomized trial. Lancet. 2010;375:727–34.
35. 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.
36. 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.
37. 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.
38. 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.
39. Madias JE. Effect of serial arm ischemic preconditioning sessions on the systemic blood pressure of a normotensive subject. Med Hypotheses. 2011;76:503–6.
40. 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.
41. 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 Clin Electrophysiol. 2018;41:246–54.
42. 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.
43. 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.
44. 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;97:1298–303.
45. 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.
46. 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.

47. Yu W, Ren C, Ji X. A review of remote ischemic preconditioning as a potential strategy for neural repair poststroke. CNS Neurosci Ther. 2023;29(2):516–24.
48. Aronowski J, Zhao X. Molecular pathophysiology of cerebral hemorrhage: secondary brain injury. Stroke. 2011;42:1781–6.
49. 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 clinical trial JAMA. 2015;313:2133–41.
50. 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.
51. 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.
52. 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.
53. 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 Cardiovas Interv. 2013;6:246–51.
54. Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. Circulation. 2002;53:31–47.
55. Hori M, Nishida K. Oxidative stress and left ventricular remodeling after myocardial infarction. Cardiovas Res. 2009;81:457–64.
56. 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.
57. 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.
58. 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.
59. 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.
60. Shyu MY and Lee AYS. Remote ischemic conditioning improves cardiovascular functions in heart failure patients. Cardiology Res. 2024; https://doi.org/10.14740/cr1669.
61. 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.
62. Przyklenk K, Bauer B, Ovize M, et al. Regional ischemic preconditioning protects remote virgin myocardium from subsequent sustained coronary occlusion. Circulation. 1993;87:893–9.
63. Peralta C, Fernande L, Panes J, et al. Preconditioning protects against systemic disorders associated with hepatic ischemia-reperfusion through blockade of tumor necrosis factor-induced P-selectin up-regulation in the rat. Hepatology. 2001;33:100–13.