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REVIEW

Heart Conditioning and Heterochronic Parabiotic Models as Healthy Strategies

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Abstract
In heterochronic parabiotic model, there is reversion of aging and age-related diseases. Blood or plasma exchange, as well as implementation of young (or healthy) factors and removal of old (or unhealthy) factors, can also produce this phenomenon. Heart conditioning produces cardioprotective (or healthy) factors, in analogy to the heterochronic parabiosis. This may imply a possible healthy strategy for humans, leading to reversion of aging and age-related diseases.

Keywords Heart conditioning · Heterochronic parabiosis · Healthy strategies

Heart Conditioning Model as Healthy Strategy

Myocardial Ischemia

In coronary artery disease (also known as ischemic heart disease), there is coronary occlusion leading to myocardial ischemia. Briefly, transient, physiological myocardial ischemia produces adaptive or compensatory mechanisms. Severe, sustained, pathophysiological myocardial ischemia produces maladaptive or decompensatory mechanisms. Both compensatory and decompensatory mechanisms involve neurohormonal activation, heart remodeling, and other events like oxidative stress, autophagy, endothelin, nitric oxide, inflammatory mediators, and growth factors.

Activation of the adrenergic nervous system and the renin-angiotensin system is the primary neurohormonal activation. Briefly, transient and physiological activation of the sympathetic nervous system results in increased heart rate, myocardial contractility, and cardiac output. However, severe, sustained, and pathophysiological activation of the sympathetic nervous system has adverse effects on cardiac myocyte biology, leading to loss of cardiac function [1–3]. Physiological activation of the renin-angiotensin system leads to vasoconstriction, cell growth, aldosterone secretion, and catecholamine release, which maintains short-term cardiovascular homeostasis [4, 5]. Pathophysiological activation of the renin-angiotensin system is maladaptive, leading to fibrosis of the heart, kidney, and other organs, contributing to reduced vascular compliance and increased ventricular stiffness [4, 5]. Thus, compensatory activation of the adrenergic nervous system and the renin-angiotensin system improves cardiac output through increased retention of salt and water, peripheral arterial vasoconstriction, increased contractility, and activation of inflammatory mediators involved in cardiac repair and remodeling.

Heart remodeling affects the biology of the cardiac myocyte, and the geometry and architecture of the heart, occurring in response to physiological or pathophysiological myocardial ischemia [4, 6]. In compensatory mechanisms, hypertrophy reduces the increased tension and helps maintain cardiac output, which is essentially beneficial and improves muscular economy [7]. In decompensatory mechanisms, heart remodeling is characterized by progressive ventricular dilatation, myocardial hypertrophy, fibrosis, and deterioration of cardiac performance [8].

Reactive oxygen species are normal byproducts of aerobic metabolism. In the heart, reactive oxygen species can modulate the activity of a variety of intracellular proteins and signaling pathways, including essential proteins involved in myocardial contractility such as ion channels and myofilament proteins, as well as signaling pathways

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involved in myocyte growth. Oxidative stress in the heart may be due to reduced antioxidant capacity or the increased production of reactive oxygen species secondary to mechanical strain of the myocardium, neurohormonal activation, or inflammatory cytokines (tumor necrosis factor, IL-1). Excessive reactive oxygen species in the heart lead to contractile dysfunction, stimulate myocyte hypertrophy and apoptosis, modulate fibroblastic proliferation and collagen synthesis, and trigger increased matrix metalloproteinase abundance and activation [9].

Thus, briefly, transient, physiological myocardial ischemia is a stress to the heart. It can trigger compensatory adaptations to maintain cardiovascular homeostasis and normal cardiovascular function, at the molecular, cellular, structural, tissue, and organ levels.

Types of Heart Conditioning

Ischemic Preconditioning

Ischemic preconditioning was first observed in dogs by Murry et al. in 1986 [9]. Briefly (5-min) repeated ischemic occlusions of the circumflex coronary artery before sustained occlusion resulted in reduction in infarct size. I have also observed that briefly (5-min) ischemia followed by sustained ischemia attenuated the latter ischemia–reperfusion-induced cardiac arrhythmias and decreased contractility in the isolated rat heart (unpublished data, 1986). It is well-established that ischemic preconditioning is a biphasic phenomenon, with a first window of protection developing within minutes of a briefly ischemic insult lasting only 1 to 2 h and a second window of protection developing between 12 and 24 h and lasting for 3 to 4 days [9–11]. The mechanisms of the two phases of ischemic preconditioning are different. The first phase is caused by quick modification of pre-existing proteins; the second phase requires synthesis of new proteins. It seems that the beneficial and protective effects within the second window are at least as powerful as those of the first window of protection [12].

Ischemic preconditioning has been reproducibly well demonstrated in all animal species studied as well as humans [9, 13, 14]. Ischemic preconditioning is protective against postischemic contractile dysfunction [15], ischemia- and reperfusion-induced ventricular arrhythmias [16, 17], apoptosis [18], and infarct injury [9, 13, 14]. This shift of the heart to a preconditioned phenotype with briefly, transient, physiological myocardial ischemia is recognized as a significant progress in the field of myocardial protection.

Ischemic Postconditioning

Ischemic preconditioning with briefly coronary occlusion and reperfusion before a sustained period of coronary occlusion with reperfusion ameliorates the ischemia–reperfusion injury. Ischemic postconditioning with repetitive briefly coronary occlusion during early reperfusion of myocardial infarction reduces infarct size.

Remote Ischemic Preconditioning

Remote ischemic preconditioning with briefly ischemia and reperfusion of a distant organ protects the myocardium. All these conditioning protocols involve a complex signal cascade of sarcolemmal receptor activation, intracellular enzyme activation, and inhibition of death signaling in mitochondria [19, 20].

Pharmacological Conditioning

Instead of using ischemia, pharmacological conditioning (preconditioning mimetic) makes use of a pharmacological agent for protection against ischemia–reperfusion injury. Several drugs that potentially play a role in the mechanism of ischemia–reperfusion injury have been assessed, such as adenosine, nicorandil, erythropoietin, diazoxide, and cyclosporine. However, the results are disappointing. Currently, ischemic conditioning is more powerful compared with pharmacological conditioning [19].

Cardioprotection in Patients

It is possible that ischemic preconditioning occurs naturally in humans. Pre-infarct angina may resemble ischemic preconditioning. Patients who had previous angina or angina that occurred prior to myocardial infarction had lower in-hospital death, severe heart failure, or shock [21]. The beneficial and protective effects of pre-infarct angina may be related to ischemic preconditioning.

Ischemic conditioning has been successfully used in patients with coronary artery disease. Ischemic preconditioning improved clinical outcomes in patients undergoing percutaneous coronary intervention [22] and cardiac surgery [23]. Ischemic postconditioning reduced infarct size and other measures of reperfusion injury in patients with myocardial infarction [24–27].

Ischemic remote conditioning commonly uses intermittent inflation of a standard blood pressure cuff to 200 mmHg, with three to four 5-min inflation separated by 5-min reperfusion periods [28]. In patients undergoing percutaneous coronary intervention or cardiac surgery, remote conditioning reduced cardiac injury and major adverse cardiac and cerebrovascular events [29–32]. Moreover, remote preconditioning and postconditioning were found

to be effective in reducing stroke severity in animal studies [33–37].

Signal Transduction

An abundance of cardioprotective signaling events has been identified in myocardial ischemia. There are three hierarchical levels of signal transduction: triggers, intracellular mediator cascade, and effectors. Triggers are molecules such as adenosine, bradykinin, and opioids that are formed and released from cardiomyocyte during myocardial ischemia. The sarcolemmal receptor activation initiates intracellular cascade of enzyme, mostly protein kinase, which acts on the effectors such as mitochondria or cytoskeleton that stabilize the jeopardized cardiomyocyte and prevent cardiomyocyte death [20, 21, 23]. Nitric oxide, protein kinase activation, and mitochondria appear to be important elements in all forms and signal pathway of cardioprotection involved in ischemic conditioning [20, 21, 34].

Heart conditioning is the most attractive method of inducing cardioprotection, as it is both safe and easily feasible. Remote ischemic preconditioning protocols use arm or leg ischemia and reperfusion rather than coronary manipulation [30–33]. Exercise is an independent factor in cardioprotection. It diminishes cardiovascular risk by enhancing lipid metabolism, reducing obesity and increasing insulin sensitivity [38]. Exercise protocols can initiate ischemic preconditioning, and attenuated ischemic injury during percutaneous coronary intervention [39]. Nitric oxide is a trigger and mediator of ischemic preconditioning [40–44]. The intravenous administration of nitric oxide donor, nitroglycerin, has been shown to protect human myocardium against myocardial ischemia [45].

To recapitulate, by briefly, transient, physiological myocardial ischemia which is a stress to the heart, compensatory adaptations are produced, which intend to maintain cardiovascular homeostasis and normal cardiovascular functions, at the molecular, cellular, structural, tissue, and organ levels. Therefore, the heart can already be conditioned and protected, as evidenced by the beneficial and protective effects observed following the subsequent sustained myocardial ischemia and/or reperfusion. Heart conditioning exerts protective effects not only on the heart, but also on remote organs such as the brain, lung, kidney, or gut, against injuries associated with ischemia and other insults, including toxicants, hemorrhagic shock/resuscitation, and iodinated radiocontrast media [46]. Furthermore, it is speculated that, similar to heart conditioning, the other body system may likewise be stressed, conditioned, and protected. Hence, evidence that conditioning exists in humans may provide a major impetus to the development of modalities or strategies for maintaining the body in a continuously conditioned and protected state, preferably regularly and indefinitely. The response of the body to environmental changes is the basis of homeostasis. The human body is able to recruit various protective, adaptive, compensatory mechanisms in order to maintain homeostasis and normal function in responses to a variety of aggression or stressors. It is becoming increasingly clear that conditioning of the heart and other body system is stressors which initiate compensatory adaptations so as to maintain cardiovascular and body homeostasis, and is a key feature of successful healthy strategies.

Heterochronic Parabiotic Model as Healthy Strategy

Heterochronic Parabiosis

In 1878, Claude Bernard first pointed out that the living parts of living organisms exist in the fluids which bathe them (the internal environment or extracellular fluid) and that all vital mechanisms depend on stable internal environment or homeostasis [38, 39].

Pairing two animals in parabiosis to test for systemic or circulatory factors (extracellular fluid) from one animal affecting the other has been used in scientific studies for at least 150 years. A variation on the technique, heterochronic parabiosis (Fig. 1), whereby two animals of different ages are joined together to test for systemic regulators or factors of aspects of aging or age-related diseases, also has a century-long scientific history.

Parabiosis refers to the condition in which two living animals are joined surgically and develop a single, shared circulatory system. In this technique, animals are connected surgically, often along the adjacent flanks, to create shared circulation arising from the newly formed vascular anastomosis. Heterochronic parabiosis, the parabiotic pairing of two animals of different ages, provides an experimental system to test for systemic effects on the process of cell and tissue aging, the development of age-related diseases, or other age-related parameters including organismal longevity. It has been shown that parabiosis to healthy animals could extend the lifespan of animals that would otherwise die earlier due to disease or lethal treatment of some sort such as irradiation [40–42]. Parabiosis to a healthy partner was shown to extend the lifespan of mice with muscular dystrophy [43]. Diabetic animals (which normally show impaired healing after skin wounding) exposed to circulating factors found in normoglycemic animals showed an accelerated rate of wound closure, enhanced angiogenesis, and an increased recruitment of inflammatory cells thought to be important in repair of the wound site in diabetic mice following parabiosis [44]. These and other comparable studies have stimulated interest in the possibility that the dysfunctions associated with aging might likewise be rescued

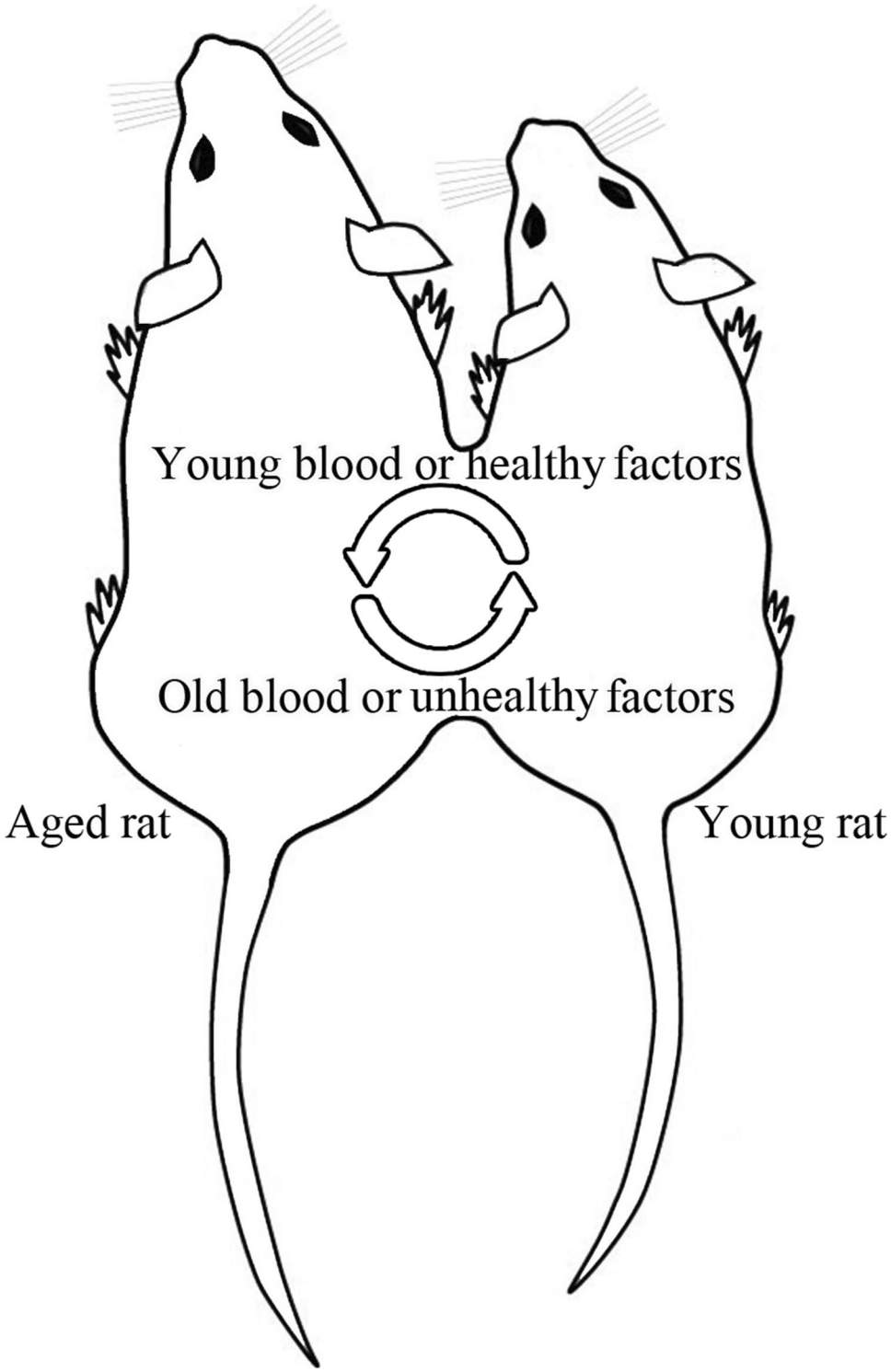

Fig. 1 Heterochronic parabiosis: Young rat giving young or healthy blood or factors to the old rat, whereas old rat giving old or unhealthy blood or factors to the young rat simultaneously. In the old parabiont, therefore, there is implementation of healthy factors, at the same time removal of unhealthy factors

or reversed by parabiosis to a healthy, younger partner, and that lifespan itself might be amenable to prolongation by heterochronic parabiosis. Previous reports that used heterochronic parabiosis to study the physiology of aging and regulation of lifespan and provide evidence of the benefit to the older parabiont in terms of both longevity and tissue function were published since 1950 [45, 47–51]. When exposed to youthful influences, aged stem cells adopted to a more youthful potential, whereas when exposed to the influences of an aged systemic milieu, young stem cells lost regenerative potential [52–54]. In aged animals, young blood through heterochronic parabiosis improved stem cell

function in the muscle [52, 53], the liver [53], spinal cord [55], and brain [55]. In young animals, exposing to an old systemic environment could inhibit myogenesis [53] and neurogenesis [54].

In 1972, Ludwig and Elashoff found that old organism in the heterochronic pairing lived longer in response to the young environment compared to the age-matched isochronic control animals [50]. Later, this model is used to investigate the physiology of aging and stem cells in different tissues and organ systems. Conboy et al. used heterochronic parabiosis and found that the young systemic environment could activate molecular signaling pathways in hepatic or muscle stem cells of the old parabiont leading to increased proliferation and tissue regeneration [52]. Ruckn et al. reported that recovery from experimentally induced demyelination in the central nervous system was enhanced in old mice that were exposed to a young systemic environment [55]. Salpeter et al. showed that the decline in pancreatic beta cell proliferation in old mice could be reversed in old parabionts paired with young mice [56]. Loffredo et al. demonstrated that age-related heart hypertrophy with loss of normal cardiac function was reversible upon exposure of an aged animal to a youthful systemic environment through heterochronic parabiosis [57]. Huang et al. demonstrated that a young blood environment could not only enhance autophagy in elderly kidneys but also mitigate apoptosis and inflammation in aged kidney, thereby slowing injury progression of kidney tissues and improving kidney aging [58]. Sidorenko et al. showed that there was a decline of the immune response in the young parabiont, whereas the low immune response in the old parabiont remained unchanged [50].

The systemic milieu is a complex reservoir of tissues, immune cells, and circulating molecules or factors that is surprisingly not well understood in terms of its communication across organ systems. A main question at the time is whether transmissible, humoral factors present in one animal have a physiological effect on its adjacent partner. Are circulatory factors or cells in a young organism protective against age-related diseases, and vice versa, are factors or cells in the old organism predisposing or promoting diseases in a younger organism?

Pregnancy as Parabiotic Model

When the circulatory systems of two animals of different ages are connected in a heterochronic parabiotic model, the older partner undergoes rejuvenation [45]. Pregnancy might be considered as a specific form of parabiosis in which an aged organism (mother) is tightly joined to a young organism (fetus). Obviously, their bloodstreams do not mix together, but it does not exclude the possibility of the regulatory factor exchange. Recent studies have shown that pregnancy might have beneficial effects on the physiological state of many organs and on maternal longevity in general. It has been shown that pregnancy enhanced the regeneration of the liver [59] and muscle [60] in mice. Moreover, pregnancy protected against cardiac ischemic injury in the rat [61]. In patients with cardiomyopathy, heart functions were restored spontaneously in 50% of pregnant women and those who had recently given birth [62, 63]. One form of central nervous system damage called multiple sclerosis is caused by neuroinflammatory diseases. Multiple sclerosis is characterized by inflammation that targets myelin and oligodendrocytes in the central nervous system, causing demyelinated lesions that can lead to neuron damage and loss. The pregnancy in multiple sclerosis (PRIMS) study demonstrated a lower relapse rate of multiple sclerosis during pregnancy [64]. In addition, there was a decreased risk of multiple sclerosis in multiparous compared with nulliparous women [64]. Analysis of 15,000 twins revealed that the lifespan of twins with children (both men and women) was longer than that of their childless brothers or sisters [65].

Blood Exchange

Rebo et al. used a heterochronic blood exchange system which removes the influence of shared organs, adaptation to being joined, and so on [66]. They demonstrated that the blood exchange enhanced old muscle repair without inhibition of young, and old hepatogenesis was improved and fibrosis and adiposity were decreased, while young hepatogenesis became diminished. Old blood is far more inhibitory to neurogenesis than that young blood is rejuvenative. Most surprisingly, the onset of the influence of heterochronic blood exchange on myogenesis, hepatogenesis, and neurogenesis occurs within a few days.

Exchange transfusion is a routine strategy for the management of several diseases, such as sickle cell disease and hemolytic disease of newborns [67]. Plasmapheresis is used in the treatment of thrombotic thrombocytopenic purpura, Guillain–Barre syndrome, and so on [68]. These extracorporeal blood manipulations are approved and can provide a feasible modality to investigate aging and age-related diseases in humans.

Many studies have demonstrated that exposure to young blood improves the function of various aged tissues, including the skeletal muscle, liver, and brain [69, 70]. Still other studies have described the activity of specific youth-associated proteins that partially recapitulate the anti-aging activity of young blood, including GDF11 [71], TIMP2 [72], oxytocin [73], and osteocalcin [74]. These studies argue that development of blood-based therapies is a prudent strategy for limiting aging and aging-associated dysfunction.

Early studies utilized a parabiotic model in which old rats were surgically connected to young to uncover evidence suggestive of young blood's influence on the lifespan in aged animals [45, 48]. Later, the role of young blood in aging across many tissues is investigated. Brack et al. demonstrated reduced age-related muscle fibrosis with increased Wnt signaling following young blood exposure [53]. Subsequent studies also reported the skeletal muscle stem cell regeneration phenotype using either heterochronic parabiosis [75] or a blood exchange model [66]. Loffredo et al. reported that aged mice sharing young blood via parabiosis exhibited reduced age-related cardiac hypertrophy and decreased ventricular myocyte size [57]. Age-related decreases in pancreatic B-cell proliferation were reverted towards youthful levels after sharing young blood [55], and parameters of kidney aging were also improved in aged parabionts sharing young blood [58]. Bone healing in aged mice was improved when sharing young blood [76]. Old parabionts exposed to young blood exhibited increased neurogenesis [53] and improved hippocampal synaptic plasticity [77].

Plasma Exchange

The role of young plasma is also investigated. For example, young mouse plasma increased hippocampal synaptic plasticity markers and long-term potentiation, memory, and anxiety-related behavior in aged mice [77]. Aged rats treated with young plasma exhibited improvements in liver regeneration and other parameters associated with liver aging [78]. Treatment of aged immunodeficient mice with human umbilical cord plasma improved hippocampal synaptic plasticity and cognitive performance, suggesting that plasma possesses rejuvenating activity regardless of species [79]. Moreover, human umbilical cord plasma improved dementia-like pathology and cognitive performance in mice [80].

Those early heterochronic parabiosis and plasma transfer studies motivated the approach to simply transfer blood products from young individuals to elderly subjects suffering from age-related disease. The Plasma for Alzheimer's Symptom Amelioration (PLASMA) study evaluated the feasibility and safety of treating Alzheimer's disease subjects with plasma from young adults (18–30 years of age), and found that the treatment produced minimal, if any, benefits [81].

Young and Old Factors

The role of factors present in the blood is investigated. Young mice treated with recombinant CCL11 or B2M (proteins elevated in old blood) exhibited impaired memory and reduced hippocampal neurogenesis [53, 69]. On the contrary, proteins enriched in young plasma that decline with advancing age such as GDF11 have been reported to improve cardiac hypertrophy, muscle regeneration, cerebrovascular integrity, and neurogenesis [70, 75, 76]. Oxytocin is elevated in young blood and is sufficient to improve age-related declines in muscle regeneration [71]. Systemic administration of growth hormone-releasing hormone ameliorates age-related cognitive decline in animals and humans [69, 72, 73]. TIMP2 is elevated in young mouse blood and human umbilical cord plasma, which increases synaptic plasticity and improves learning and memory in aged mice [79]. Osteocalcin improves memory and anxiety-like behavior in aged mice [74]. These results suggest that multiple young (healthy) and old (unhealthy) factors play distinct roles in mediating the effects of young and old blood within specific organs, respectively. The systemic factors profoundly influence tissue and organ aging and age-related diseases, and reverse structural and molecular aspects of aging and age-related diseases. However, it is difficult to identify all healthy and unhealthy factors.

The Advantageous Cycle

In the heterochronic parabiotic model, the old parabiont receives young blood or healthy factors from the young parabiont, and at the same time gives old or unhealthy blood to the young parabiont, thus removing the old or unhealthy factors relatively. I propose that this advantageous cycle with implementation of healthy factors and removal of unhealthy factors simultaneously (Fig. 2) may modulate the unhealthy or old cell and give rise to a healthy or young cell, leading to reversion of aging and age-related diseases, as shown by the above findings.

Heart Conditioning and Heterochronic Parabiotic Models as Healthy Strategies

So far, it is almost impossible to apply pairing, frequent blood or plasma exchange transfusion, supply of all healthy factors, and removal of all unhealthy factors as healthy strategies for humans.

It is well-known that stress elicits the release of factors in the systemic circulation and locally within central and peripheral tissues [82]. Lately, it is demonstrated that the aforementioned heart conditioning produces cardioprotective or healthy factors. It has been shown that plasma from animals subjected to heart conditioning may be used to transfer cardioprotection to other animals and between species, suggesting a protective (or healthy) factor in the circulation [83–86]. The common connection or mechanism of heart conditioning and heterochronic parabiosis is the

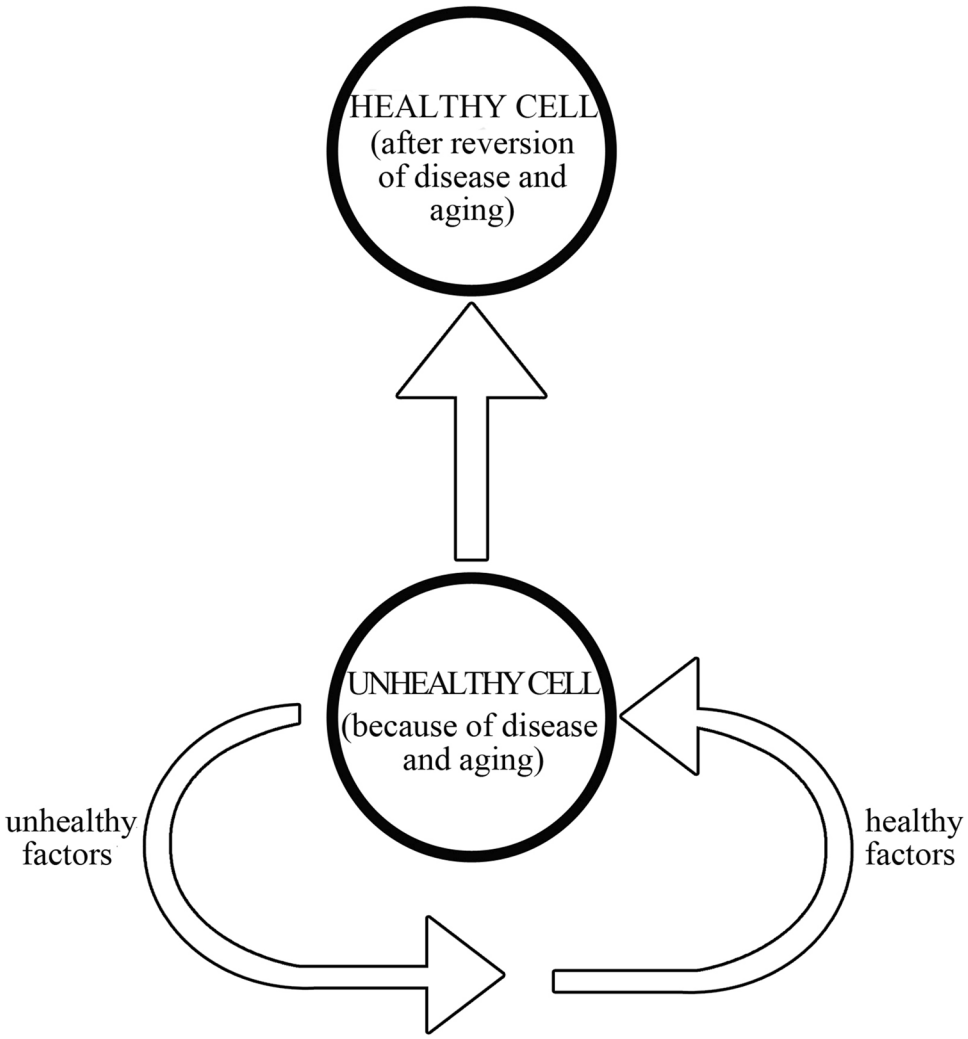

Fig. 2 An advantageous cycle with implementation of healthy factors (such as conditioning of heart and body systems, healthy diet, and regular exercise) and removal of unhealthy factors (such as stop smoking, alcohol, drug abuse, and stress) simultaneously, leading to reversion of aging and age-related diseases

extracellular fluid. Heart conditioning is a hormetic stress eliciting the release of factors in the extracellular fluid. The pairing of old and young animals (heterochronic parabiosis) is the exchange of factors in the extracellular fluid. Both involve the extracellular fluid. Heart conditioning is a stress to the heart. The stressed heart cells elicit compensatory adaptations, which maintain body homeostasis and internal environment — that is, the extracellular fluid, also referred to as the systemic milieu or factors. Utilizing briefly, transient, physiological myocardial ischemia, heart conditioning produces adaptive or compensatory mechanisms, which involve neurohormonal activation [3, 4], heart remodeling [4], and other events like oxidative stress [87], endothelin, nitric oxide, inflammatory mediators, and growth factors. These mechanisms implement healthy factors such as activation of adrenergic nervous system and the renin-angiotensin system [3, 4], and activation of inflammatory mediators involved in cardiac repair and remodeling [87], and affect the biology of the cardiac myocyte [3], synthesis of protective proteins [12], intracellular enzyme activation [19], inhibition of death signaling in mitochondria [19], nitric oxide [19], and so on. At the same time, these mechanisms remove unhealthy factors such as reactive oxygen species [3] and ischemia–reperfusion injury [9], reduce infarct size [18] and apoptosis [18], and enhance autophagy [4]. Therefore, conditioning of the heart or body system can induce adaptive, defense, or compensatory mechanisms with implementation of healthy factors and removal of unhealthy factors simultaneously, leading to conditioning and protective effects in health and function of various organs and tissues such as the brain, heart, lung, gut, kidney, liver, and muscle. Furthermore, Table 1 summarizes the beneficial effects of heart conditioning and heterochronic parabiotic models on cardiac function. The outcomes and results are similar, relatively. Therefore, heart conditioning and heterochronic parabiosis are correlated.

Table 1 Benefits of heart conditioning and heterochronic parabiotic models on cardiac function

Study	Design	Outcomes	Results
Murry et al., 1986 [10]	Ischemic preconditioning; dogs	Histology	Reduction in histologic infarct size
Sumeray and Yellon, 1998 [14]	Ischemic preconditioning; isolated rat heart	Histology	Reduction in histologic infarct size
Schott et al., 1990 [15]	Ischemic preconditioning; pigs	Histology	Reduction in histologic infarct size
Cave and Hearse, 1991 [16]	Ischemic preconditioning; isolated rat heart	Aortic flow	Improve heart contractile function
Shiki and Hearse, 1987 [17]	Ischemic preconditioning; isolated rat heart	Arrhythmias	Reduce ischemia-induced arrhythmias
Vegh et al., 1992 [18]	Ischemic preconditioning; rats and dogs	Arrhythmias	Reduce ischemia-induced arrhythmias
Kloner et al., 1995 [22]	Ischemic preconditioning; patients with acute myocardial infarction	Creatine kinase levels; clinical events	Reduction in infarct size, in-hospital complications, and death
Leslay and Beach, 2003 [23]	Ischemic preconditioning; patients undergoing cardiac catheterization	Clinical events	Reduction in in-hospital complications and death
Walsch et al., 2008 [24]	Ischemic preconditioning; patients undergoing cardiac surgery	Clinical events	Reduction in arrhythmias, inotropic requirements, and intensive care unit stay
Hansen et al., 2010 [25]	Ischemic preconditioning; patients undergoing cardiac catheterization	Creatine kinase levels; left ventricular ejection fraction	Reduction in infarct size; improvement in left ventricular ejection fraction
Khan et al., 2014 [26]	Ischemic postconditioning; patients undergoing cardiac catheterization	Creatine kinase levels; imaging; left ventricular ejection fraction	Reduction in myocardial injury, improve left ventricular function
Staat et al., 2005 [27]	Ischemic postconditioning; patients undergoing cardiac catheterization	Creatine kinase levels; imaging	Reduction in infarct size
Yang et al., 2007 [28]	Ischemic postconditioning; patients undergoing cardiac catheterization	Creatine kinase levels; imaging	Reduction in infarct size, with long-term protection
Thielmann et al., 2013 [30]	Remote ischemic preconditioning; patients undergoing cardiac surgery	Troponin levels; all-cause mortality over 1.54 years	Reduction in infarct size; improve prognosis
Hode et al., 2009 [31]	Remote ischemic preconditioning; patients undergoing cardiac catheterization	Troponin levels; clinical events	Reduction in infarct size and in-hospital complications and improve prognosis
Davis et al., 2013 [32]	Remote ischemic preconditioning; patients undergoing cardiac catheterization	Troponin levels; clinical events	Reduction in infarct size and short- and long-term complications
Crimi et al., 2013 [33]	Remote ischemic preconditioning; patients undergoing cardiac catheterization	Creatine kinase levels; imaging	Reduction in infarct size
Loffredo et al., 2013 [64]	Heterochronic parabiosis; rats	Histology	Regress in cardiac hypertrophy; reduce cardiomyocyte size
Xiao et al., 2013 [68]	Pregnancy as parabiotic model; rats	Polymerase chain reactions; western blot; immunofluorescent staining	Protect against cardiac ischemia injury; activate cardiac progenitor cells
Felker et al., 2000 [75]	Pregnancy as parabiotic model; patients with cardiomyopathy	Retrospective analysis	Restore heart function
Katsimpardi et al., 2014 [71]	Heterochronic parabiosis; growth differentiation factor 11 in plasma; rats	Histology; imaging	Induce vascular remodeling; reverse cardiac hypertrophy

Conclusion

In the heart conditioning model, there is physiological myocardial ischemia which is a stress to the heart, producing adaptive or compensatory mechanisms, as well as cardioprotective or healthy factors in the circulation, maintaining homeostasis with beneficial and protective effects. I have also observed ischemic preconditioning in the isolated rat heart. I suggest that heart conditioning can be utilized as a healthy strategy.

In the heterochronic parabiotic model, there is reversion of aging and age-related diseases. I suggest that this involves the supply of young blood or healthy factors, and removal of old blood or unhealthy factors simultaneously. However, it is difficult to identify all healthy and unhealthy factors. I further suggest that conditioning of the heart (and other body system) can produce protective or healthy factors in the circulation, leading to reversion of aging and age-related diseases, compatible to the heterochronic parabiotic model.

Author Contribution The author contributed in the research, data collection, and manuscript preparation.

Data Availability Not applicable.

Code Availability None.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The author declares no competing interests.

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