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Review

Exercise Training after Myocardial Infarction Attenuates Dysfunctional Ventricular Remodeling and Promotes Cardiac Recovery

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Abstract

Recent evidences have shown that exercise training not only plays a necessary role in maintaining cardiac homeostasis, but also promotes cardiac repair after myocardial infarction. Post-myocardial infarction, exercise training has been observed to effectively increase the maximum cardiac output, and protect myocardial cells against necrosis and apoptosis, thus leading to an improved quality of life of myocardial infarction patients. In fact, exercise training has received more attention as an adjunct therapeutic strategy for both treatment and prevention of myocardial infarction. This review summarizes the experimental evidence of the effects of exercise training in ventricular remodeling after myocardial infarction, and tries to provide theoretical basis along with suitable references for the exercise prescription aimed at prevention and therapy of myocardial infarction.

Keywords: exercise training; ventricular remodeling; microRNA; myocardial Infarction

1. Introduction

Cardiovascular disease (CVD) has become one of the most common causes of human mortality throughout the world [1]. Aging populations, fast paced modern lifestyle, poor dietary habits and other socio-psychological factors, are leading towards a constantly and rapidly increasing risk for CVD in young and low-income population [2]. Myocardial infarction, which is one of the most common causes of mortality among CVDs, occurs when narrowing coronary arteries are blocked due to blood clot, cholesterol or fat deposits that prevent blood from flowing into the heart [3,4]. During myocardial infarction, the blockage of blood flow to a part of the heart leads to an insufficiency of oxygen in the myocardium [5,6]. Consequently, the left ventricular wall of the heart becomes thinner and dilates, causing decreased ejection fraction, and finally, the myocardial injury area is filled with scar tissue without any diastolic or systolic functions. Patients with severe myocardial infarction are likely to develop heart failure [7,8]. The prognosis of acute myocardial infarction is closely associated with the size of the infarct area. Without early effective treatment, myocardial infarction will lead to continuous deterioration of the disease process and even death [9]. At present, the most commonly used method for effectively reducing myocardial ischemic injury is the reperfusion therapy [10,11]. However, reperfusion therapy often causes reperfusion injury and triggers ventricular remodeling [11].

For a long time, exercise training was considered as a significant part in maintaining cardiovascular health. It is reported to be an effective intervention for both primary and secondary prevention of cardiovascular diseases in many clinical studies [12–15]. Regular exercise training can increase coronary blood flow by improving vasodilatory functions, thereby reducing myocardial oxidative stress, preventing myocardial cell loss and limiting cardiac fibrosis, which in turn reduce the risk of coronary heart disease, myocarditis, myocardial infarction, and other cardiovascular diseases [16,17].

Additionally, *in vivo* experiments revealed exercise training could delay cardaic aging and reduce aging-related cardiac fibrosis, apoptosis, and necrosis [18,19]. Recent research by several groups have uncovered that exercise training could significantly reduce the occurrence of myocardial ischemia and reperfusion injury, offer protection from dilated cardiomyopathy and hypertrophic cardiomyopathy, by increasing the activity of endothelial nitric oxide synthase (eNOS) - nitric oxide (NO) and phosphoinositide 3-kinase (PI3K) signaling pathways [12,20–23]. Moreover, exercise training was verified to be able to attenuate ventricular remodeling after myocardial infarction [24,25]. Thus, exercise training is increasingly receiving more attention in the context of both prevention and treatment of cardiovascular diseases.

2. Ventricular Remodeling Triggered by Myocardial Infarction

When the ventricular remodeling occurs, mechanical, neurohormonal, or genetic factors would alter the shape, size and function of the ventricles [26,27]. The ventricular volume overload suddenly increases, triggering the process of remodeling in the infarcted area after acute myocardial infarction [28]. Myocardial hypoxia leads to an increased activation of neurohormones by inducing the migration of immune cells such as neutrophils, monocytes and macrophages to the infarct area, resulting in local inflammation [29,30]. One of the key processes in post-infarcted remodeling is inducing cardiomyocyte hypertrophy [31]. Myocardial hypertrophy counteracts the increase in ventricular volume after myocardial infarction, weakening the progressive expansion of the myocardium, and stabilizes the myocardial contractile function [32,33]. Therefore, cardiomyocyte hypertrophy is initially an adaptive and a protective response to the pathological change of myocardial infarction. However, at later stages various paracrine and autocrine factors, chronic neurohormonal activation, renin-angiotensin-aldosterone system activity (RAAS), and myocardial stretching, would continue to stimulate eccentric pathological hypertrophy, gradually leading to left ventricular failure [34–36].

Myocardial infarction also increases the degree of oxidative stress [37]. Low concentration of reactive oxygen species (ROS) is known to play an important role in signal transmission. However, higher ROS concentrations can directly impair cell membrane lipids, nuclear and mitochondrial deoxyribonucleic acid (DNA), as well as proteins thus causing severe and fatal cellular damage [38]. In fact, myocardium of congestive heart failure patients was found with excessive oxidative stress [39]. These observations indicated that a damaged antioxidant system and/or enhanced reactive oxygen species could elevate oxidative stress, resulting in dysfunction and poor remodeling of the infarcted myocardium. In addition, the growth of new capillaries and small arteries after myocardial infarction, or the occurrence of angina pectoris, were key processes of ventricular remodeling [40–42]. Damaged angiogenesis may lead to maladjusted left ventricular remodeling and promote transition from adaptive cardiac hypertrophy to left ventricular dilation and dysfunction [43,44].

3. Improved Ventricular Remodeling Caused by Exercise Training Following Myocardial Infarction

The heart tends to be hypertrophic following stress stimulation, which is generally classified into either physiological hypertrophy or pathological hypertrophy. These two types of cardiac hypertrophy have significant differences in structure, function and molecular mechanism [31, 45]. Pathological hypertrophy is often accompanied by myocardial fibrosis, myocardial cell apoptosis and necrosis, and eventually develops into heart failure [31,40]. However, physiological hypertrophy is an adaptive response induced by long-term standardized exercise training, which does not result in adverse remodeling including myocardial fibrosis. Unlike pathological hypertrophy, physiological hypertrophy is found with a protective effect on the heart [46].

Aerobic exercise training for eight weeks after undergoing surgery for myocardial infarction was revealed to increase the cardiac function in rats with chronic heart failure (CHF), accompanied by reduced cardiac remodeling, left ventricular end-diastolic pressure (LVEDP), left ventricular hypertrophy, and left ventricular collagen volume fraction. These changes could also help reduce the congestion of lungs [25,47]. Similarly, exercise training programs reduced the degree of inflammation in myocardium, which indicated that physical exercise played a key role in controlling chronic systemic inflammation observed during heart failure [48–50]. In another exercise training model involving swimming in rats, researchers observed that compared to the infarct group without exercise training, exercise training reduced left ventricular expansion and thickened the non-infarct wall [24]. Exercise training was also observed to limit undesirable remodeling by weakening ventricular dilation and reducing wall tension in animal models having left ventricular dysfunction post-myocardial infarction [25,51,52]. Additionally, following exercise training abnormal expression of β-myosin was also found to be decreased [53].

Studies have demonstrated that free-wheeling exercise had little effect on the left ventricular geometry and function in mice from the sham-operated group. However, in severe myocardial infarction surgical group, free-wheeling exercise training was able to limit a further increase in post myocardial infarction mortality as well as simultaneously improve left ventricular remodeling, capillaries, and distal myocardial hypertrophy in this group. Moreover, the myocardial interstitial fibrosis and apoptosis were observed to be reduced after exercise training [54].

4. Protective Mechanisms Involved in Ventricular Remodeling due to Exercise Training post —Myocardial Infarction

Myocardial infarction has been accompanied by a variety of processes that lead to heart function damage, including reduced myocardial contractility, unbalanced energy metabolism, increased oxidative stress, escalated apoptosis, altered myocardial microstructure, and rapidly surging inflammatory response [55–59]. Exercise training protects ventricular remodeling and cardiac function through the following mechanisms: (1) regulation of the expression of certain microRNAs (2) adjustment of cardiac function either by improving the balance between metallopeptidase inhibitor 1 (TIMP-1) and matrix metalloproteinase-1 (MMP-1), thereby enhancing myocardial contractility;

or by adjusting collagen accumulation to reduce cardiac rigidity and promote myocardial contractility (3) by regulating the energy metabolism of myocardial cells, such as increasing the level of catecholamines in local areas and in blood, increasing plasma free fatty acid (FFA) levels, increasing mitochondrial synthesis, and increasing adenosine triphosphate (ATP) production (4) through inhibition of oxidative stress of cardiomyocytes by activating PI3K-protein kinase B (PI3K-Akt) signaling pathway, increasing endothelial nitric oxide synthase (eNOS) activity and nitric oxide (NO) production in vascular endothelial cells (5) by enhancing vascular endothelial growth factor (VEGF) dependent angiogenesis pathways through increase in vascular shear stress, including increasing coronary vascular network and density, increasing myocardial blood flow perfusion signals, promoting angiogenesis, and thereby regulating ventricular remodeling (6) by increasing immunosuppressive factor interleukin 10 (IL-10), inhibiting expression of inflammatory factors such as tumor necrosis factor alpha (TNF-α) and interferons alpha (IFN-α), and regulating inflammatory response in the heart [60,61].

4.1 Regulation of miRNA Expression in Cardiac Tissue

MicroRNAs (miRNAs, miRs), regulate protein translation via regulating the stability of messenger RNA (mRNA) to modulate numerous signaling pathways and cellular processes. MiRNAs have been reported to regulate cell-to-cell communication by altering the expression of signaling molecules involved in key biomolecular processes [62,63]. In fact, the study of miRNAs in the context of cardiovascular pathophysiology could provide a new perspective, as they have been observed to play a key role in patients with CVD, such as myocardial infarction, hypertrophy, fibrosis, heart failure, arrhythmia, inflammation and atherosclerosis [64,65]. MiRNAs have also been shown to regulate important processes that can lead to the pathophysiological consequences of acute myocardial infarction, by regulating cardiomyocyte apoptosis, and the formation of new blood vessels after ischemia [66–70]. Cardiac regeneration is also affected by miRNAs that control cardiomyocyte proliferation. In addition, miRNAs could also directly reprogram myocardial fibroblasts into cardiomyocytes to regenerate injured myocardium [71,72].

MiRNAs can not only be used as important targets in the treatment of CVD, but also as important biomarkers indicative of systemic functionality [73,74]. Exercise training was reported to induce changes in specific miRNAs expression levels in heart tissue. In addition, specific circulating miRNAs were observed to be expressed in response to exercise training, along with their corresponding downstream signals [75,76]. Thus, the heart function could be regulated either by knocking down or over-expressing of these miRNAs [77–79].

The first miRNAs that were found and studied in exercise training animal models are three heart-specific miRNAs namely miR-1, miR-133a, miR-133b. In two independent experimental groups, swimming training and interval training of rats, the expression of these miRNAs was downregulated in heart tissues. Another kind of miRNA, highly expressed miR-21 was observed in cardiac fibroblasts during acute myocardial infarction as well as transverse aortic constriction (TAC) and enhanced the mitogen-activated protein kinase-extracellular signal-regulated kinase (MAPK-ERK) signaling pathway by inhibiting false homolog 1 (Spry1) [80]. In another study, myocardial infarction decreased the expression of miR-1 and increased the expression of miR-214. It has been reported that exercise training could prevent myocardial infarction induced reduction of miR-1 expression and increased miR-214 expression. These responses may be associated with the normalization of Ca^{2+} handling and left ventricular compliance in infarcted hearts due to exercise training, thereby promoting cardiac recovery [77,81,82].

Exosomes released during exercise training were proved to contain microRNAs—miR-455, miR-29b, miR-323-5p, and miR-466 that bind to the 3' region of matrix metallopeptidase 9 (MMP9) and downregulates its expression, thereby reducing its harmful effects. Among these miRNAs, miR-29b and miR-455 have shown the highest regulation. On comparison with the non-exercise group, MMP9 activity of the exercise group was significantly reduced [83]. A study with aerobic training using animal model demonstrated that aerobic training could promote an increase in miR-126 expression by indirectly regulating VEGF pathway and directly regulating the mitogen-activated protein kinase (MAPK) and PI3K-Akt-eNOS pathways, which are associated with exercise-induced cardiac angiogenesis [84]. Single left ventricular myocyte dimensions were increased while cell-contraction and relaxation became faster during resistance training. These mechanical adaptations were corelated with the overexpressed expression of sarco/endoplasmic reticulum Ca^{2+}-ATPase 2alpha (SERCA2α), which in turn, has effects in epigenetic modification of decreased miR-214 expression [85]. In addition, miR-17-3p protected against myocardial ischemic-reperfusion injury by metalloproteinase inhibitor 3(TIMP3) and phosphatase and tensin homolog-protein kinase B (PTEN-Akt) pathway which contributed to exercise-induced cardiac growth [25]. Another study found that aerobic training increased miR-29 expression and correspondingly reduced collagen expression levels in heart, resulting in improved left ventricular compliance and had beneficial cardiac effects. This protective effect was verified to be associated with high-performance aerobic training [78,79] (Table 1, Ref. [25,71,78–85]).

4.2 Altering Myocardial Contractility

After myocardial infarction, the infarct myocardium becomes composed of scar tissue without systolic and diastolic function [86,87]. The contractile and diastolic ability

Table 1. Summary of miRNAs regulated during exercise training with a protective role against heart diseases.

Diseases	Exercise	Targets	miRNAs	Regulation Function	References
MI	Running	- SERCA2α	miR-1 ↑ miR-214 ↓	Ca^{2+} handling diastolic function ↑	[71,81,82,85]
AMI/TAC/IRI	Swimming	Spry1	miR-21 ↑	cardiac fibroblasts; cardiomyocyte apoptosis ↓	[80]
-	Swimming/Running	MMP9	miR-455, miR-29b, miR-323-5p, miR-466 ↓	fibrosis ↓	[83]
-	Swimming/Running	MAPK&PI3K-Akt-eNOS pathways	miR-126 ↑	angiogenesis ↑	[84]
IRI	Swimming	TIMP3&PTEN-Akt pathway	miR-17-3p ↑	myocyte proliferation ↑	[25]
Ventricular compliance	Swimming/Running	Collagen gene	miR-29 ↑	cardiac fibroblasts ↓	[78,79]

MI, Myocardial Infarction; AMI, Acute myocardial infarction; TAC, Transverse Aortic Constriction; IRI, Ischemia/Reperfusion Injury; MAPK, Mitogen-Activated Protein Kinase; MMP9, Matrix Metallopeptidase 9; PTEN, Phosphatase and tensin homolog; eNOS, Endothelial Nitric Oxide Synthase; TIMP3, Recombinant Tissue Inhibitors of Metalloproteinase 3; Akt, Protein Kinase B; PI3K, Phosphatidylinositol-3-Kinase.

of the heart muscle is greatly reduced. Exercise training can reduce myocardial fibrosis [81,86]. Exercise training can also improve the balance between matrix metallopeptidase 1 (MMP-1) and tissue inhibitor of metalloproteinases 1 (TIMP-1), thereby reducing the stiffness of the heart by regulating collagen accumulation [18,88–91]. Studies have demonstrated that exercise training notably improves β-adrenergic receptors (β-Ars), reverses the major histocompatibility complex (MHC) α-β-cardiac isotype transition, and improves myocardial contractility [20,92] (Fig. 1).

Exercise training can also improve the myocardial contractility by increasing cardiac Ca^{2+} intake by targeting SERCA2a or SERCA2a regulators/modifiers after myocardial infarction [93,94]. The expression of SERCA2a has been observed to be upregulated by exercise training. This has significant implication with respect to cardiac contractility because SERCA2a regulates the uptake of Ca^{2+} into sarcoplasmic reticulum (SR), and affects cardiac relaxation, Ca^{2+} loading of the SR, and consequently the amount of Ca^{2+} available for release during cardiac myocyte contraction [94,95]. On top of SERCA2a, cardiac excitation-contraction (E-C) coupling is in fact mainly initiated by Ca^{2+} influx through L-type voltage gated $Ca_V1.2$. Calcium channel ($Ca_V1.2$) in cardiomyocytes via Ca^{2+}-induced Ca^{2+} release mechanisms [96], and more importantly, the expression of $Ca_V1.2$. $Ca_V1.2$ channels is reduced in TAC induced cardiac pathological hypertrophy and heart failure [97]. Studies showed that exercise could partially affect heart function by altering calcium channel levels and calcium signaling proteins [98,99].

The heartbeat originates from the sinoatrial node (SA) in the right atrium of the heart. SA acts as the pacemaker and generates regular electrical impulses. Exercise training was found to control the density and activity of several pumps, channels, and processes linked with cardiac action

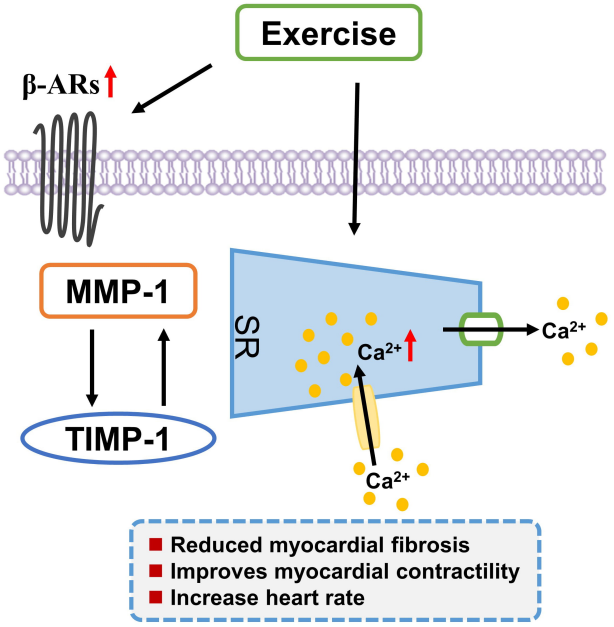

Fig. 1. Exercise training positively regulates calcium homeostasis, improves the balance between MMP-1 and TIMP-1, and enhances the expression of β-adrenergic receptors. MMP-1, matrix metallopeptidase 1; TIMP-1, tissue inhibitor of metalloproteinases 1; SR, sarcoplasmic reticulum; β-ARs, β-adrenergic receptors.

potential (AP) and E-C coupling [100]. In order to meet the energy requirement of exercise, heart rate and myocardial contractility show a corresponding increase [94]. This is a reaction of the autonomic nervous system and hormones, wherein the heart rate increases by acting on SA and enhances the contractility of cardiomyocytes by modulating the components of ion current, pump and E-C coupling [100].

4.3 Enhancement of Cardiomyocyte Energy Metabolism

The heart requires a large amount of energy supplement and needs to constantly produce ATP to maintain its contractile function, ion homeostasis, anabolic processes and signaling transduction [101–103]. The number and size of mitochondria are controlled by the process of mitochondrial fusion and division [104]. Suppressing excessive mitochondrial division is deemed to be good for cardiac function [105]. Exercise training is confirmed to regulate the alterations in fusion and division-related proteins, which can prevent myocardial infarction-induced mitochondrial fusion reduction and division increase [106,107]. About 60% to 70% ATP is used by the heart to promote contraction, while about 30% to 40% of the remaining ATP is used by various ion pumps, especially Ca^{2+}-ATPase in the sarcoplasmic reticulum (SR). Therefore, to a large extent, the cardiac function depends on the production of ATP, and damages in this process will quickly induce contractile dysfunction [108,109]. During exercise, increased circulation and local production of catecholamines result in raised heart rate and muscle strength, which in turn lead to moderations in cardiac metabolism [110,111]. Both epinephrine and norepinephrine can promote the oxidation of endogenous triglycerides. Increase in plasma free fatty acid (FFA) levels during exercise adaptation could be considered sufficient to increase myocardial fat catabolism [112].

The upregulation of neuregulin-1 by exercise training can induce interleukin-1α (IL-1α) and interferon-γ (IFN-γ), which are associated with paracrine cardiac cytokines, as well as pro-repair factors such as angiogenin-2, brain-derived neurotrophic factor and crypto-1 [113,114]. These factors have been shown to contribute to the repair mechanism of the heart. In chronic heart failure, neuregulin-1 has been shown to regulate reverse cardiac remodeling, and it remains elevated during exercise adaptation and further increase glucose absorption and utilization [114]. Other studies have found that exercise training regulates myocardial glycolytic activity due to the expression of kinase 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK2) [115,116]. Insulin-like growth factor 1 (IGF-1) has also been reported to affect cardiac energy requirements and metabolism through its role in muscle strength [47,59,108].

Studies have shown that exercise training can increase the level of circulating extracellular vesicles [117,118]. These vesicles can transfer metabolic enzymes to the recipient cells, thereby changing metabolism of the recipient tissue [119]. The cellular fuel agent AMP-activated protein kinase (AMPK), that senses the levels of AMP and ATP in cells, is activated during exercise. When the energy demand is high, AMPK will be activated to enhance ATP levels by increasing glucose and fatty acid catabolism and simultaneously inhibiting protein synthesis. Metabolites involved in glucose and fat metabolism have also been implicated as regulators of exercise-induced heart growth. In fact, changes in glucose-6-phosphate (G6P) levels in cells has been shown to promote ventricular remodeling by regulating mammalian target of rapamycin (mTOR) signaling [120] (Fig. 2).

4.4 Reduction in Oxidative Stress of Cardiomyocytes

Oxidative stress is the excessive production of reactive oxygen species (ROS) associated with antioxidant defenses, and can affect ventricular remodeling [121]. eNOS, the predominant NOS isoform in vasculature, has a crucial role in many protective effects attributed to exercise. In the presence of its cofactors, electrons from reduced nicotinamide adenine dinucleotide phosphate (NADPH) could be transferred by eNOS to heme site via flavin adenine dinucleotide and flavin mononucleotide. The electrons are used to decrease and activate oxygen and oxidize L-arginine to L-citrulline and NO [122–124]. After four weeks of random wheel running training in mice, circulating adrenaline and norepinephrine levels were found to be increased, and myocardial eNOS and NO production were consequently activated, bestowing a protective effect on ischemic-reperfusion injury [125,126]. Similar studies demonstrate that exercise training increases the expression of β3-adrenoceptor agonist (β3-AR) after myocardial infarction and attenuates oxidative stress of cardiomyocytes by regulating eNOS-NO signaling [127] (Fig. 3).

Exercise training also has a beneficial effect in balancing cardiac nitroso redox by activating ROS scavenging enzymes, like superoxide dismutase [128]. In cardiomyocytes, mitochondria can transfer energy between myofibrils by offering ATP to cell membrane ion pumps. Basal ROS levels in cardiomyocytes of exercise trained mice have been shown to be reduced. In order to promote ventricular remodeling, it is essential to maintain mitochondrial membrane potential, reduce the production of mitochondrial ROS, and protect the redox homeostasis [46,54,127–133].

4.5 Promotion of Angiogenesis to Protect Against Ventricular Remodeling

After myocardial infarction, poorly adapted left ventricular remodeling could occur due to impaired angiogenesis, which can further promote transition from adaptive myocardial hypertrophy to left ventricular dilation and dysfunction. Exercise training has been demonstrated to activate VEGF dependent angiogenesis pathways and increase VEGF expression in the heart [134–137]. After myocardial infarction, exercise training can reverse nitric oxide (NO) induced arterial dysfunction in the endothelial vessel wall [134,138]. NO has several benefits for cardiovascular functions, including vasodilation, inhibition of platelet aggregation and adhesion, reduction of leukocyte and vascular inflammation level, increased angiogenesis, proliferation of vascular smooth muscle cells, and activation of endothelial progenitor cells [139,140]. Follistain like-1 (FSTL1) has

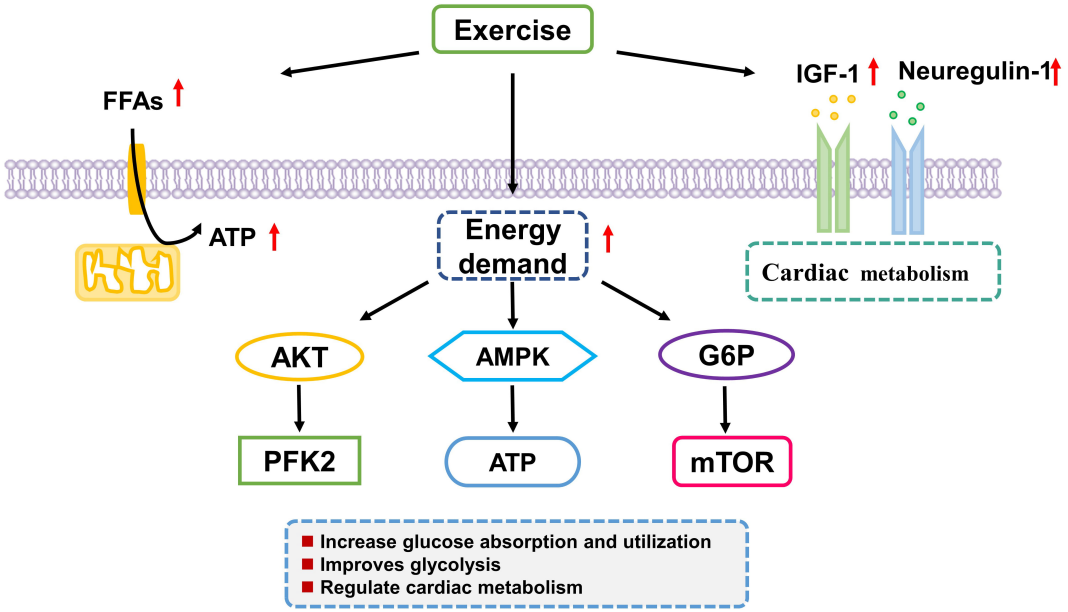

Fig. 2. Exercise training regulates myocardial cells energy metabolism. Exercise training causes adaptations in energy metabolism of the heart including glucose absorption and utilization and glycolysis. Akt, serine/threonine kinase; FFA, plasma free fatty acid; AMPK, AMP Activated Protein Kinase PFK2, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase; ATP, adenosine triphosphate; G6P, glucose-6-phosphate.

Table 2. Summary of pro- and anti-inflammatory cytokines regulated by exercise training following myocardial infarction.

Down-regulation	References	Up-regulation	References
Interleukin-1β	[153,154]	IL-10	[148,149,153,154]
Interleukin-6	[148,149,153,154]	antigen-specific T cells	[156]
Tumor necrosis factor-α	[61,148,149,153,154]	CD8+ T cells	[156]
Nuclear factor κB	[150,151,153,154]		
Interferon-γ	[156]		
Interferon-α	[60,61,155]		
Transforming growth factor-β	[46,138]		
Toll-like receptors 4	[152]		
Toll-like receptors 7	[155]		
Regulatory T cells	[156]		

been reported to play an important role in cardiac protection obtained due to exercise training. Resistance exercise stimulates the skeletal muscle to secrete FSTL1, which binds to the disco-interacting protein 2 homolog A (DIP2A) receptor, and through Smad2/3 signaling promotes myocardial angiogenesis in rats with myocardial infarction [141]. In addition, exercise training upregulates the level of hypoxia-Inducible factor 1-alpha (HIF-1α), triggering angiogenesis promotion through the PI3K-Akt-eNOS and MAPK signaling pathway and protects cardiac function after myocardial infarction [142] (Fig. 3).

4.6 Inhibition of Inflammation

After myocardial infarction, the myocardium activates the innate immune system to initiate tissue repair mechanisms, corelated with significant increase in the levels of different kinds of pro-inflammatory cytokines [143]. This increase in pro-inflammatory cytokines contributes to cardiac remodeling [144,145]. Following an acute pro-inflammatory phase there is an anti-inflammatory response that promotes heart repair [146]. However, the spread of the pro-inflammatory response in the myocardium depends upon the diversity and uniqueness of cardiac pressure. If it is not counteracted by the anti-inflammatory mechanism, this prolonged inflammatory response will turn into chronic inflammation [146,147]. The key feature of this chronic cardiac inflammation is the continued increase in production of pro-inflammatory cytokines in the heart. These pro-inflammatory cytokines have harmful effect on the myocardium and are participated in the transition from myocardial infarction to heart failure [147].

Elevated levels of pro-inflammatory cytokines in circulation and heart are associated with ventricular remodeling, thereby leading to chronic heart failure. Exercise

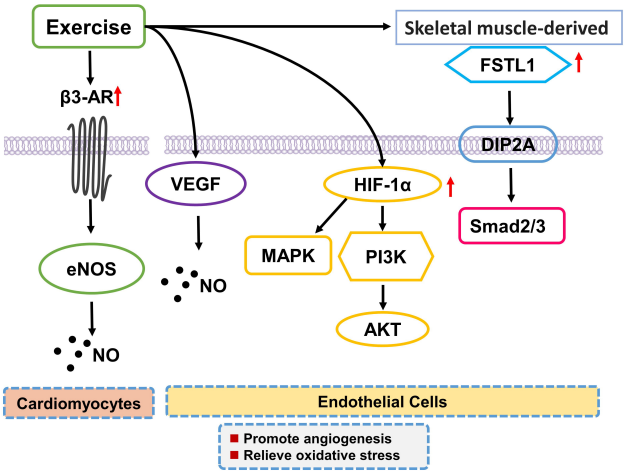

Fig. 3. Exercise training inhibits oxidative stress and promotes angiogenesis. Exercise training increases the expression of β3-AR after myocardial infarction and relieves oxidative stress of cardiomyocytes by regulating eNOS-NO signaling pathway. Exercise training also regulates the VEGF and NO expression and reverses arterial dysfunction in the endothelial vessel wall. In addition, exercise training upregulates the expression of HIF-1α, resulting in angiogenesis stimulation through PI3K-Akt-eNOS and MAPK signaling pathway. Alternatively, exercise training also stimulates skeletal muscle to secrete FSTL1 and promotes myocardium angiogenesis. β3-AR, β-adrenergic receptors; NOS, endothelial nitric oxide synthase; NO, nitric oxide; HIF-1α, hypoxia-Inducible factor 1-alpha; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide-3-kinase; VEGF, vascular endothelial growth factor; Akt, serine/threonine kinase; FSTL1, follistain like-1; DIP2A, disco-interacting protein 2 homolog A.

training can inhibit the expression of inflammatory factors, such as TNF-α and IL-6, and increase the abundance of immunosuppressive factor IL-10 [148,149]. Aerobic exercise training was verified to promote endothelial function through regulation of these mechanisms, such as, reducing the expression of proinflammatory transcription factor nuclear factor kappa B (NF-κB) and mitigation of oxidative stress [150,151]. Downregulation of Toll-like receptor 4 (TLR4), a transmembrane receptor that can induce the production of inflammatory cytokines, also promotes the anti-inflammatory effects induced by exercise training [152]. In both the aerobic exercise group and TLR4 inhibited mice, the expression levels of pro-inflammatory factors namely IL-1β, IL-6, TLR4, NF-κB, and TNF-α were downregulated, and the mRNA expression levels of the anti-inflammatory factor IL-10 was upregulated [153,154]. Previous study showed that exercise induced a reduction in TNF-α and IFN-α production in response to R-848 by Toll-like receptor (TLR-7) [61], and TLR-7 deficiency reduced post-MI scar formation and inflammation [155].

Exercise training can not only protect from myocardial infarction by directly regulating the release of inflammatory factors, but also regulate the activity of immune cells that release inflammatory factors [49,50,53]. Compared to the non-exercise control group, continuous high-intensity aerobic exercise training increased the production of anti-inflammatory factors and the number of regulatory T cells (Tregs), and weakened the production of the cytokine interferon γ (IFN-γ). In addition, aerobic exercise training also inhibited the proliferation of antigen-specific T lymphocytes and reaction of antigen-specific cluster of differentiation 8+ (CD8+) cytotoxic T lymphocytes [156]. Studies have also verified that even after stopping the exercise training for a few weeks, the effect of previously consistent and regulated exercise training still lingers [49]. In addition, many studies have revealed the molecular mechanisms by which aerobic exercise training can protect the heart and the whole body through many factors, including but not limited to TNF-α, TGF-β, IL-1β, IL-6, osteoprotegerin and leptin [49,157]. Cells produce changes in the expression levels of these inflammatory factors and thereby exert exercise-driven cardioprotective effects (Table 2, Ref. [46,60,61,138,143–156]).

However, based on the recent research evidence, the effects of exercise training on the immune system cannot be generalized conclusively. Different studies have showed that the effects of exercise on immune cells are not only inconsistent, sometimes even contradictory, possibly due to differences in test subjects or the intensity of aerobic exercise. Since the metabolism of the body is a complicated process, the effects of exercise training on myocardial infarction are not uniform across various studies [49,153,154,156,158–163]. In addition, the different effects brought by exercise training may be caused by different research individuals, different exercise intensity, and different time [164]. Therefore, it is of great relevance to formulate and prescribe appropriate and customized exercise training based on patient history and nature as well as the degree of the heart disease.

5. Summary

Myocardial infarction is considered the most common emergency in cardiovascular system, with high morbidity and mortality, being one of the leading causes for heart failure, causing a great burden on patients and society. Exercise training has a recognized beneficial effect on the heart, irrespective of its healthy or diseased condition. In addition, exercise training becomes one of effective interventions to reverse cardiac remodeling and improve cardiac function in patients with heart failure. Exercise training can reverse ventricular remodeling after myocardial infarction via multiple mechanisms including regulating the expression of miRNA in cardiac tissues [25,62–69,71–85,134], enhancing myocardial contractility [20,82,86–100], regulating cardiomyocyte energy metabolism [47,101–120], reversing oxidative stress [46,54,121–133], promoting angiogenesis [134–142] and reducing inflammation [49,143–

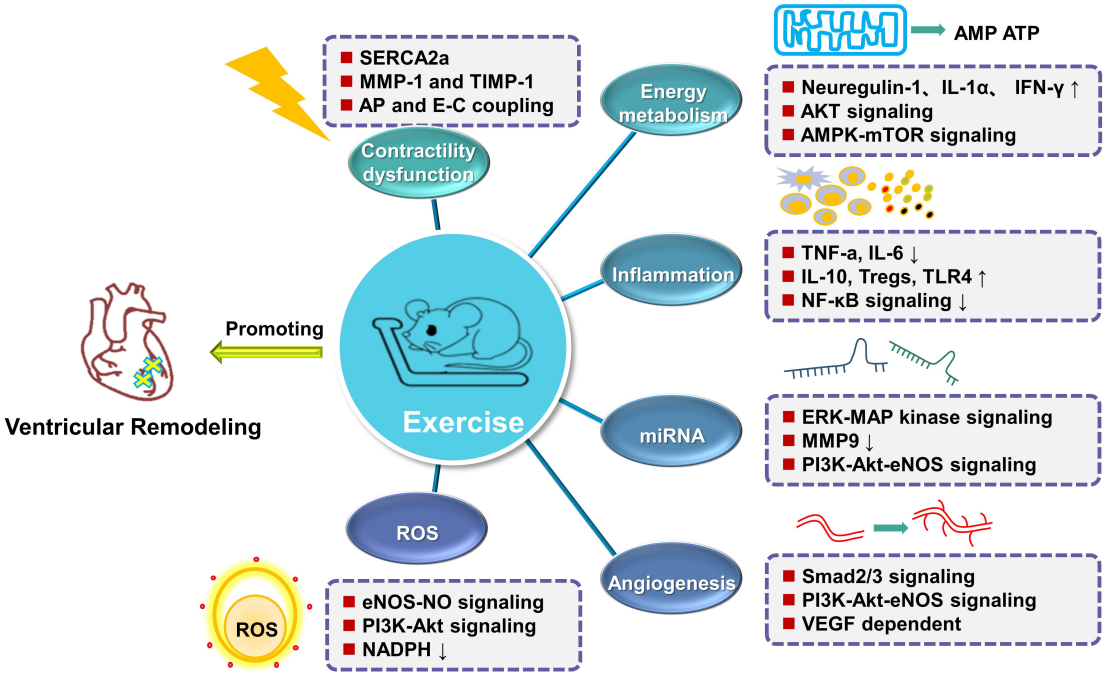

Fig. 4. Summary of protective mechanisms involved in ventricular remodeling observed due to exercise training following myocardial infarction. Exercise training alleviates ventricular remodeling and restores cardiac function by altering microRNAs expression selectively; adjusting Ca^{2+} homeostasis and collagen accumulation to improve myocardial contractility; regulating energy metabolism of myocardial cells; inhibiting oxidative stress of cardiomyocytes; enhancing VEGF dependent angiogenesis pathways, and/or regulating inflammatory response. VEGF, vascular endothelial growth factor.

163]. In this review, several recent evidence regarding the mechanisms involved in executing the protective effects of exercise training post-myocardial infarction have been summarized (Fig. 4).

Although regular physical activity reduces cardiovascular disease, vigorous activity also increases the risk of acute myocardial infarction and sudden cardiac death in susceptible individuals [165–169]. In people with diseased or susceptible hearts, vigorous and high-intensity exercise may increase the risk of worsening cardiovascular function, acute cardiac events, or sudden cardiac death (SCD) in some individuals [170,171]. There is substantial epidemiological, basic science and clinical evidence that habitual physical activity reduces the risk of cardiovascular disease and that the benefits of regular physical activity outweigh the risks [164,165,168]. Research suggests that individuals should do $\geq$30 minutes of moderate-intensity physical activity each day [172]. Individuals who start exercising should start slowly and increase the intensity and duration of the exercise as their tolerance allows. In addition, exercise should be assessed according to AHA/American College of Cardiology and relevant guidelines [173–175]. Further studies are required for investigating the role of organ or tissue cross-talk in exercise mediating cardiovascular protection effects. Several studies have shown that exercise has similar functions to many other drugs, such as protecting chronic heart disease and as a treatment for heart failure [176]. Therefore, combined exercise training and heart medication may result in improvements in cardiovascular disease [177]. Although interaction between exercise and anticoagulant, antiplatelet, angiotensin II receptor blockers, calcium channel blockers and statins have been reported to be involved in protecting against cardiovascular disease [176], the critical aspects of exercise-induced cardioprotection may be changed by the complexity of exercise-drug interactions [177,178]. The combination of drug and exercise can be beneficial in some cases and harmful in others [176,177]. It is necessary to further study the adverse effects.

Author Contributions

JW and JX designed the research study. SL, XM, GL and PG wrote the manuscript. All authors contributed to language changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, *et al*. Executive summary: heart disease and stroke statistics–2012 update: a report from the American Heart Association. Circulation. 2012; 125: 188–197.

[2] Tzoulaki I, Elliott P, Kontis V, Ezzati M. Worldwide Exposures to Cardiovascular Risk Factors and Associated Health Effects: Current Knowledge and Data Gaps. Circulation. 2016; 133: 2314–2333.

[3] Sharma B, Chang A, Red-Horse K. Coronary Artery Development: Progenitor Cells and Differentiation Pathways. Annual Review of Physiology. 2017; 79: 1–19.

[4] Panh L, Lairez O, Ruidavets J, Galinier M, Carrié D, Ferrières J. Coronary artery calcification: from crystal to plaque rupture. Archives of Cardiovascular Diseases. 2017; 110: 550–561.

[5] Lu L, Liu M, Sun R, Zheng Y, Zhang P. Myocardial Infarction: Symptoms and Treatments. Cell Biochem Biophys. 2015; 72: 865–867.

[6] Edupuganti MM, Ganga V. Acute myocardial infarction in pregnancy: Current diagnosis and management approaches. Indian Heart Journal. 2019; 71: 367–374.

[7] Jessup M, Brozena S. Heart failure. The New England Journal of Medicine. 2003; 348: 2007–2018.

[8] Shah AM, Mann DL. In search of new therapeutic targets and strategies for heart failure: recent advances in basic science. Lancet. 2011; 378: 704–712.

[9] Boateng S, Sanborn T. Acute myocardial infarction. Disease-a-Month. 2013; 59: 83–96.

[10] Martínez-Sánchez C, Arias-Mendoza A, González-Pacheco H, Araiza-Garaygordobil D, Marroquín-Donday LA, Padilla-Ibarra J, *et al*. Reperfusion therapy of myocardial infarction in Mexico: a challenge for modern cardiology. Archivos De Cardiologia De Mexico. 2017; 87: 144–150.

[11] Heusch G, Gersh BJ. The pathophysiology of acute myocardial infarction and strategies of protection beyond reperfusion: a continual challenge. European Heart Journal. 2017; 38: 774–784.

[12] McMullen JR, Amirahmadi F, Woodcock EA, Schinke-Braun M, Bouwman RD, Hewitt KA, *et al*. Protective effects of exercise and phosphoinositide 3-kinase(p110alpha) signaling in dilated and hypertrophic cardiomyopathy. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104: 612–617.

[13] Lenk K, Erbs S, Höllriegel R, Beck E, Linke A, Gielen S, *et al*. Exercise training leads to a reduction of elevated myostatin levels in patients with chronic heart failure. European Journal of Preventive Cardiology. 2012; 19: 404–411.

[14] Quindry J, French J, Hamilton K, Lee Y, Mehta JL, Powers S. Exercise training provides cardioprotection against ischemia-reperfusion induced apoptosis in young and old animals. Experimental Gerontology. 2005; 40: 416–425.

[15] Bei Y, Wang L, Ding R, Che L, Fan Z, Gao W, *et al*. Animal exercise studies in cardiovascular research: Current knowledge and optimal design-A position paper of the Committee on Cardiac Rehabilitation, Chinese Medical Doctors' Association. Journal of Sport and Health Science. 2021; 10: 660–674.

[16] Adams V, Reich B, Uhlemann M, Niebauer J. Molecular effects of exercise training in patients with cardiovascular disease: focus on skeletal muscle, endothelium, and myocardium. American Journal of Physiology. Heart and Circulatory Physiology. 2017; 313: H72–H88.

[17] Pina IL, Lin L, Weinfurt KP, Isitt JJ, Whellan DJ, Schulman KA, *et al*. Hemoglobin, exercise training, and health status in patients with chronic heart failure (from the HF-ACTION randomized controlled trial). American Journal of Cardiology. 2013; 112: 971–976.

[18] Kwak H, Kim J, Joshi K, Yeh A, Martinez DA, Lawler JM. Exercise training reduces fibrosis and matrix metalloproteinase dysregulation in the aging rat heart. FASEB Journal. 2011; 25: 1106–1117.

[19] Kwak H, Song W, Lawler JM. Exercise training attenuates age-induced elevation in Bax/Bcl-2 ratio, apoptosis, and remodeling in the rat heart. The FASEB Journal. 2006; 20: 791–793.

[20] Calvert JW, Condit ME, Aragón JP, Nicholson CK, Moody BF, Hood RL, *et al*. Exercise protects against myocardial ischemia-reperfusion injury via stimulation of β(3)-adrenergic receptors and increased nitric oxide signaling: role of nitrite and nitrosothiols. Circulation Research. 2011; 108: 1448–1458.

[21] Nicholson CK, Lambert JP, Chow C, Lefer DJ, Calvert JW. Chronic exercise downregulates myocardial myoglobin and attenuates nitrite reductase capacity during ischemia–reperfusion. Journal of Molecular and Cellular Cardiology. 2013; 64: 1–10.

[22] Ma Z, Qi J, Meng S, Wen B, Zhang J. Swimming exercise training-induced left ventricular hypertrophy involves microRNAs and synergistic regulation of the PI3K/AKT/mTOR signaling pathway. European Journal of Applied Physiology. 2013; 113: 2473–2486.

[23] Owen KL, Pretorius L, McMullen JR. The protective effects of exercise and phosphoinositide 3-kinase (p110alpha) in the failing heart. Clinical Science. 2009; 116: 365–375.

[24] Liu X, Xiao J, Zhu H, Wei X, Platt C, Damilano F, *et al*. MiR-222 is Necessary for Exercise-Induced Cardiac Growth and Protects against Pathological Cardiac Remodeling. Cell Metabolism. 2015; 21: 584–595.

[25] Shi J, Bei Y, Kong X, Liu X, Lei Z, Xu T, *et al*. MiR-17-3p Contributes to Exercise-Induced Cardiac Growth and Protects against Myocardial Ischemia-Reperfusion Injury. Theranostics. 2017; 7: 664–676.

[26] Burchfield JS, Xie M, Hill JA. Pathological Ventricular Remodeling: part 1 of 2. Circulation. 2013; 128: 388–400.

[27] Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. JACC Cardiovasc Imaging. 2011; 4: 98–108.

[28] White HD, Chew DP. Acute myocardial infarction. Lancet. 2008; 372: 570–584.

[29] Peet C, Ivetic A, Bromage DI, Shah AM. Cardiac monocytes and macrophages after myocardial infarction. Cardiovascular Research. 2020; 116: 1101–1112.

[30] Taqueti VR, Mitchell RN, Lichtman AH. Protecting the pump:

controlling myocardial inflammatory responses. Annual Review of Physiology. 2006; 68: 67–95.
[31] Nakamura M, Sadoshima J. Mechanisms of physiological and pathological cardiac hypertrophy. Nature Reviews. Cardiology. 2018; 15: 387–407.
[32] Lazzeroni D, Rimoldi O, Camici PG. From Left Ventricular Hypertrophy to Dysfunction and Failure. Circulation Journal. 2016; 80: 555–564.
[33] Tham YK, Bernardo BC, Ooi JYY, Weeks KL, McMullen JR. Pathophysiology of cardiac hypertrophy and heart failure: signaling pathways and novel therapeutic targets. Archives of Toxicology. 2015; 89: 1401–1438.
[34] Meijers WC, van der Velde AR, Pascual-Figal DA, de Boer RA. Galectin-3 and post-myocardial infarction cardiac remodeling. European Journal of Pharmacology. 2015; 763: 115–121.
[35] Bahit MC, Kochar A, Granger CB. Post-Myocardial Infarction Heart Failure. JACC. Heart Failure. 2018; 6: 179–186.
[36] Navarro P, Moskowitz R, Le Jemtel TH. Inhibition of RAAS–when is it too much? Current Heart Failure Reports. 2004; 1: 57–64.
[37] Dubois-Deruy E, Peugnet V, Turkieh A, Pinet F. Oxidative Stress in Cardiovascular Diseases. Antioxidants. 2020; 9.
[38] Cadenas S. ROS and redox signaling in myocardial ischemia-reperfusion injury and cardioprotection. Free Radical Biology and Medicine. 2018; 117: 76–89.
[39] Tahrir FG, Langford D, Amini S, Mohseni Ahooyi T, Khalili K. Mitochondrial quality control in cardiac cells: Mechanisms and role in cardiac cell injury and disease. Journal of Cellular Physiology. 2019; 234: 8122–8133.
[40] Shimizu I, Minamino T. Physiological and pathological cardiac hypertrophy. Journal of Molecular and Cellular Cardiology. 2016; 97: 245–262.
[41] Xiao Y, Zhao J, Tuazon JP, Borlongan CV, Yu G. MicroRNA-133a and Myocardial Infarction. Cell Transplantation. 2019; 28: 831–838.
[42] Chong SY, Zharkova O, Yatim SMJM, Wang X, Lim XC, Huang C, *et al*. Tissue factor cytoplasmic domain exacerbates post-infarct left ventricular remodeling via orchestrating cardiac inflammation and angiogenesis. Theranostics. 2021; 11: 9243–9261.
[43] Garza MA, Wason EA, Zhang JQ. Cardiac remodeling and physical training post myocardial infarction. World Journal of Cardiology. 2015; 7: 52–64.
[44] Badimon L, Borrell M. Microvasculature Recovery by Angiogenesis after Myocardial Infarction. Current Pharmaceutical Design. 2018; 24: 2967–2973.
[45] Bei Y, Fu S, Chen X, Chen M, Zhou Q, Yu P, *et al*. Cardiac cell proliferation is not necessary for exercise-induced cardiac growth but required for its protection against ischaemia/reperfusion injury. Journal of Cellular and Molecular Medicine. 2017; 21: 1648–1655.
[46] Bernardo BC, Ooi JYY, Weeks KL, Patterson NL, McMullen JR. Understanding Key Mechanisms of Exercise-Induced Cardiac Protection to Mitigate Disease: Current Knowledge and Emerging Concepts. Physiological Reviews. 2018; 98: 419–475.
[47] Weeks KL, Bernardo BC, Ooi JYY, Patterson NL, McMullen JR. The IGF1-PI3K-Akt Signaling Pathway in Mediating Exercise-Induced Cardiac Hypertrophy and Protection. Advances in Experimental Medicine and Biology. 2017; 76: 187–210.
[48] Wang J, Liu S, Li G, Xiao J. Exercise Regulates the Immune System. Physical Exercise for Human Health. 2020; 16: 395–408.
[49] Frodermann V, Rohde D, Courties G, Severe N, Schloss MJ, Amatullah H, *et al*. Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. Nature Medicine. 2019; 25: 1761–1771.
[50] Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nature Reviews. Immunology. 2011; 11: 607–615.
[51] de Waard MC, van Haperen R, Soullié T, Tempel D, de Crom R, Duncker DJ. Beneficial effects of exercise training after myocardial infarction require full eNOS expression. Journal of Molecular and Cellular Cardiology. 2010; 48: 1041–1049.
[52] Xu M, Jiang H, Xiao J. Exercise Protects Sympathetic Stress-Induced Myocardial Fibrosis by Regulating Cytokines. Journal of Cardiovascular Translational Research. 2020; 13: 570–571.
[53] Nunes RB, Alves JP, Kessler LP, Dal Lago P. Aerobic exercise improves the inflammatory profile correlated with cardiac remodeling and function in chronic heart failure rats. Clinics. 2013; 68: 876–882.
[54] van Deel ED, Octavia Y, de Waard MC, de Boer M, Duncker DJ. Exercise Training Has Contrasting Effects in Myocardial Infarction and Pressure Overload Due to Divergent Endothelial Nitric Oxide Synthase Regulation. International journal of molecular sciences. 2018; 19: 1968.
[55] Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodelling. Nature Reviews. Cardiology. 2014; 11: 255–265.
[56] Rodríguez M, Lucchesi BR, Schaper J. Apoptosis in myocardial infarction. Annals of Medicine. 2002; 34: 470–479.
[57] Greenwell AA, Gopal K, Ussher JR. Myocardial Energy Metabolism in Non-ischemic Cardiomyopathy. Front Physiol. 2020; 11: 570421.
[58] Ribeiro Júnior RF, Ronconi KS, Jesus ICG, Almeida PWM, Forechi L, Vassallo DV, *et al*. Testosterone deficiency prevents left ventricular contractility dysfunction after myocardial infarction. Molecular and Cellular Endocrinology. 2018; 460: 14–23.
[59] Bass-Stringer S, Tai CMK, McMullen JR. IGF1–PI3K-induced physiological cardiac hypertrophy: Implications for new heart failure therapies, biomarkers, and predicting cardiotoxicity. Journal of Sport and Health Science. 2020; 10: 637–647.
[60] Steensberg A, van Hall G, Osada T, Sacchetti M, Saltin B, Klarlund Pedersen B. Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. The Journal of Physiology. 2000; 529: 237–242.
[61] Yano H, Uchida M, Nakai R, Ishida K, Kato Y, Kawanishi N, *et al*. Exhaustive exercise reduces TNF-α and IFN-α production in response to R-848 via toll-like receptor 7 in mice. European Journal of Applied Physiology. 2010; 110: 797–803.
[62] Bushati N, Cohen SM. MicroRNA functions. Annual Review of Cell and Developmental Biology. 2007; 23: 175–205.
[63] Ambros V. The functions of animal microRNAs. Nature. 2004; 431: 350–355.
[64] Vegter EL, van der Meer P, de Windt LJ, Pinto YM, Voors AA. MicroRNAs in heart failure: from biomarker to target for therapy. European Journal of Heart Failure. 2016; 18: 457–468.
[65] Chen YT, Wong LL, Liew OW, Richards AM. Heart Failure with Reduced Ejection Fraction (HFrEF) and Preserved Ejection Fraction (HFpEF): The Diagnostic Value of Circulating MicroRNAs. Cells. 2019; 8.
[66] Wang C, Jing Q. Non-coding RNAs as biomarkers for acute myocardial infarction. Acta Pharmacologica Sinica. 2018; 39: 1110–1119.
[67] Mirzavi F, Ebrahimi S, Ghazvini K, Hasanian SM, Hashemy SI. Diagnostic, Prognostic, and Therapeutic Potencies of Circulating miRNAs in Acute Myocardial Infarction. Critical Reviews in Eukaryotic Gene Expression. 2019; 29: 333–342.

[68] Uchida S, Dimmeler S. Long Noncoding RNAs in Cardiovascular Diseases. Circulation Research. 2015; 116: 737–750.
[69] Lucas T, Bonauer A, Dimmeler S. RNA Therapeutics in Cardiovascular Disease. Circulation Research. 2019; 123: 205–220.
[70] Lou J, Wu J, Feng M, Dang X, Wu G, Yang H, *et al*. Exercise promotes angiogenesis by enhancing endothelial cell fatty acid use via liver-derived extracellular vesicle miR-122-5p. Journal of Sport and Health Science. 2021. (in press)
[71] Wojciechowska A, Osiak A, Kozar-Kamińska K. MicroRNA in cardiovascular biology and disease. Advances in Clinical and Experimental Medicine. 2017; 26: 868–874.
[72] Boon RA, Dimmeler S. MicroRNAs in myocardial infarction. Nature Reviews. Cardiology. 2015; 12: 135–142.
[73] Chen L, Heikkinen L, Wang C, Yang Y, Sun H, Wong G. Trends in the development of miRNA bioinformatics tools. Briefings in Bioinformatics. 2019; 20: 1836–1852.
[74] Zhou S, Jin J, Wang J, Zhang Z, Freedman JH, Zheng Y, *et al*. MiRNAS in cardiovascular diseases: potential biomarkers, therapeutic targets and challenges. Acta Pharmacologica Sinica. 2018; 39: 1073–1084.
[75] Improta Caria AC, Nonaka CKV, Pereira CS, Soares MBP, Macambira SG, Souza BSDF. Exercise Training-Induced Changes in MicroRNAs: Beneficial Regulatory Effects in Hypertension, Type 2 Diabetes, and Obesity. International Journal of Molecular Sciences. 2018; 19: 3608.
[76] Domańska-Senderowska D, Laguette M, Jegier A, Cięszczyk P, September A, Brzeziańska-Lasota E. MicroRNA Profile and Adaptive Response to Exercise Training: a Review. International Journal of Sports Medicine. 2019; 40: 227–235.
[77] Wang L, Lv Y, Li G, Xiao J. MicroRNAs in heart and circulation during physical exercise. Journal of Sport and Health Science. 2018; 7: 433–441.
[78] van Rooij E, Sutherland LB, Thatcher JE, DiMaio JM, Naseem RH, Marshall WS, *et al*. Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis. Proceedings of the National Academy of Sciences. 2008; 105: 13027–13032.
[79] Soci UPR, Fernandes T, Hashimoto NY, Mota GF, Amadeu MA, Rosa KT, *et al*. MicroRNAs 29 are involved in the improvement of ventricular compliance promoted by aerobic exercise training in rats. Physiological Genomics. 2011; 43: 665–673.
[80] Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, *et al*. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. Nature. 2008; 456: 980–984.
[81] Wisløff U, Loennechen JP, Currie S, Smith GL, Ellingsen Ø. Aerobic exercise reduces cardiomyocyte hypertrophy and increases contractility, Ca^{2+} sensitivity and SERCA-2 in rat after myocardial infarction. Cardiovascular Research. 2002; 54: 162–174.
[82] Melo SFS, Barauna VG, Neves VJ, Fernandes T, Lara LDS, Mazzotti DR, *et al*. Exercise training restores the cardiac microRNA-1 and -214 levels regulating Ca^{2+} handling after myocardial infarction. BMC Cardiovascular Disorders. 2015; 15: 166.
[83] Chaturvedi P, Kalani A, Medina I, Familtseva A, Tyagi SC. Cardiosome mediated regulation of MMP9 in diabetic heart: role of mir29b and mir455 in exercise. Journal of Cellular and Molecular Medicine. 2015; 19: 2153–2161.
[84] DA Silva ND, Fernandes T, Soci UPR, Monteiro AWA, Phillips MI, DE Oliveira EM. Swimming training in rats increases cardiac MicroRNA-126 expression and angiogenesis. Medicine and Science in Sports and Exercise. 2012; 44: 1453–1462.
[85] Melo SFS, Barauna VG, Júnior MAC, Bozi LHM, Drummond LR, Natali AJ, *et al*. Resistance training regulates cardiac function through modulation of miRNA-214. International Journal of Molecular Sciences. 2015; 16: 6855–6867.
[86] Eskander M, Kern MJ. Invasive Hemodynamics of Myocardial Disease: Systolic and Diastolic Dysfunction (and Hypertrophic Obstructive Cardiomyopathy). Interventional Cardiology Clinics. 2017; 6: 297–307.
[87] von Hafe M, Neves JS, Vale C, Borges-Canha M, Leite-Moreira A. The impact of thyroid hormone dysfunction on ischemic heart disease. Endocrine Connections. 2019; 8: R76–R90.
[88] Jaoude J, Koh Y. Matrix metalloproteinases in exercise and obesity. Vasc Health Risk Manag. 2016; 12: 287-295.
[89] Xu X, Wan W, Powers AS, Li J, Ji LL, Lao S, *et al*. Effects of exercise training on cardiac function and myocardial remodeling in post myocardial infarction rats. Journal of Molecular and Cellular Cardiology. 2008; 44: 114–122.
[90] Radauceanu A, Moulin F, Djaballah W, Marie PY, Alla F, Dousset B, *et al*. Residual stress ischaemia is associated with blood markers of myocardial structural remodelling. European Journal of Heart Failure. 2007; 9: 370–376.
[91] Marín F, Roldán V, Climent V, Garcia A, Marco P, Lip GYH. Is thrombogenesis in atrial fibrillation related to matrix metalloproteinase-1 and its inhibitor, TIMP-1? Stroke. 2003; 34: 1181–1186.
[92] Cao N, Chen H, Bai Y, Yang X, Xu W, Hao W, *et al*. B2-adrenergic receptor autoantibodies alleviated myocardial damage induced by β1-adrenergic receptor autoantibodies in heart failure. Cardiovascular Research. 2018; 114: 1487–1498.
[93] Zhihao L, Jingyu N, Lan L, Michael S, Rui G, Xiyun B, *et al*. SERCA2a: a key protein in the Ca^{2+} cycle of the heart failure. Heart Failure Reviews. 2020; 25: 523–535.
[94] Abi-Samra F, Gutterman D. Cardiac contractility modulation: a novel approach for the treatment of heart failure. Heart Failure Reviews. 2016; 21: 645–660.
[95] Kemi OJ, Ellingsen O, Ceci M, Grimaldi S, Smith GL, Condorelli G, *et al*. Aerobic interval training enhances cardiomyocyte contractility and Ca^{2+} cycling by phosphorylation of CaMKII and Thr-17 of phospholamban. Journal of Molecular and Cellular Cardiology. 2007; 43: 354–361.
[96] Hofmann F, Flockerzi V, Kahl S, Wegener JW. L-type CaV1.2 calcium channels: from in vitro findings to in vivo function. Physiological Reviews. 2014; 94: 303–326.
[97] Hu Z, Wang J, Yu D, Soon JL, de Kleijn DPV, Foo R, *et al*. Aberrant Splicing Promotes Proteasomal Degradation of L-type CaV1.2 Calcium Channels by Competitive Binding for CaVβ Subunits in Cardiac Hypertrophy. Scientific Reports. 2016; 6: 35247.
[98] Uurasmaa T, Streng T, Alkio M, Heinonen I, Anttila K. Short-term exercise affects cardiac function ex vivo partially via changes in calcium channel levels, without influencing hypoxia sensitivity. Journal of Physiology and Biochemistry. 2021; 77: 639–651.
[99] Guizoni DM, Oliveira-Junior SA, Noor SLR, Pagan LU, Martinez PF, Lima ARR, *et al*. Effects of late exercise on cardiac remodeling and myocardial calcium handling proteins in rats with moderate and large size myocardial infarction. International Journal of Cardiology. 2016; 221: 406–412.
[100] Richard S, Leclercq F, Lemaire S, Piot C, Nargeot J. Ca^{2+} currents in compensated hypertrophy and heart failure. Cardiovascular Research. 1998; 37: 300–311.
[101] Neely JR, Morgan HE. Relationship between Carbohydrate and Lipid Metabolism and the Energy Balance of Heart Muscle. Annual Review of Physiology. 1974; 36: 413–459.
[102] Lopaschuk GD, Ussher JR, Folmes CDL, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. Physiological Reviews. 2010; 90: 207–258.
[103] Doenst T, Nguyen TD, Abel ED. Cardiac metabolism in heart failure: implications beyond ATP production. Circulation Re-

search. 2013; 113: 709–724.
[104] Friedman JR, Nunnari J. Mitochondrial form and function. Nature. 2014; 505: 335–343.
[105] Kwong JQ, Molkentin JD. Physiological and pathological roles of the mitochondrial permeability transition pore in the heart. Cell Metabolism. 2015; 21: 206–214.
[106] Guan Y, Drake JC, Yan Z. Exercise-Induced Mitophagy in Skeletal Muscle and Heart. Exercise and Sport Sciences Reviews. 2019; 47: 151–156.
[107] Seo DY, Kwak HB, Kim AH, Park SH, Heo JW, Kim HK, et al. Cardiac adaptation to exercise training in health and disease. Pflugers Arch. 2020; 472: 155-168.
[108] Khan RS, Martinez MD, Sy JC, Pendergrass KD, Che P, Brown ME, *et al*. Targeting extracellular DNA to deliver IGF-1 to the injured heart. Scientific Reports. 2014; 4: 4257.
[109] Suga H. Ventricular energetics. Physiological Reviews. 1990; 70: 247–277.
[110] Zouhal H, Jacob C, Delamarche P, Gratas-Delamarche A. Catecholamines and the effects of exercise, training and gender. Sports Medicine. 2008; 38: 401–423.
[111] Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. Physiological Reviews. 2008; 88: 1009–1086.
[112] Ranallo RF, Rhodes EC. Lipid metabolism during exercise. Sports Medicine. 1998; 26: 29–42.
[113] Nishimune H, Stanford JA, Mori Y. Role of exercise in maintaining the integrity of the neuromuscular junction. Muscle & Nerve. 2014; 49: 315–324.
[114] Odiete O, Hill MF, Sawyer DB. Neuregulin in cardiovascular development and disease. Circulation Research. 2012; 111: 1376–1385.
[115] Gibb AA, Epstein PN, Uchida S, Zheng Y, McNally LA, Obal D, *et al*. Exercise-Induced Changes in Glucose Metabolism Promote Physiological Cardiac Growth. Circulation. 2017; 136: 2144–2157.
[116] Donthi RV, Ye G, Wu C, McClain DA, Lange AJ, Epstein PN. Cardiac expression of kinase-deficient 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase inhibits glycolysis, promotes hypertrophy, impairs myocyte function, and reduces insulin sensitivity. The Journal of Biological Chemistry. 2004; 279: 48085–48090.
[117] Archer AE, Von Schulze AT, Geiger PC. Exercise, heat shock proteins and insulin resistance. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2018; 373: 20160529.
[118] Schweitzer AM, Gingrich MA, Hawke TJ, Rebalka IA. The impact of statins on physical activity and exercise capacity: an overview of the evidence, mechanisms, and recommendations. European Journal of Applied Physiology. 2020; 120: 1205–1225.
[119] Schüttler D, Clauss S, Weckbach LT, Brunner S. Molecular Mechanisms of Cardiac Remodeling and Regeneration in Physical Exercise. Cells. 2019; 8.
[120] Fulghum K, Hill BG. Metabolic Mechanisms of Exercise-Induced Cardiac Remodeling. Frontiers in Cardiovascular Medicine. 2018; 5: 127.
[121] Tsutsui H, Kinugawa S, Matsushima S. Mitochondrial oxidative stress and dysfunction in myocardial remodelling. Cardiovascular Research. 2009; 81: 449–456.
[122] Donato AJ, Morgan RG, Walker AE, Lesniewski LA. Cellular and molecular biology of aging endothelial cells. Journal of Molecular and Cellular Cardiology. 2015; 89: 122–135.
[123] Kojda G, Hambrecht R. Molecular mechanisms of vascular adaptations to exercise. Physical activity as an effective antioxidant therapy? Cardiovascular Research. 2005; 67: 187–197.
[124] Cocks M, Wagenmakers AJM. The effect of different training modes on skeletal muscle microvascular density and endothelial enzymes controlling no availability. The Journal of Physiology. 2016; 594: 2245–2257.
[125] Suvorava T, Cortese-Krott MM. Exercise-Induced Cardioprotection via eNOS: a Putative Role of Red Blood Cell Signaling. Current Medicinal Chemistry. 2018; 25: 4457–4474.
[126] Nosarev AV, Smagliy LV, Anfinogenova Y, Popov SV, Kapilevich LV. Exercise and no production: relevance and implications in the cardiopulmonary system. Frontiers in Cell and Developmental Biology. 2014; 2: 73.
[127] de Waard MC, van der Velden J, Boontje NM, Dekkers DHW, van Haperen R, Kuster DWD, *et al*. Detrimental effect of combined exercise training and eNOS overexpression on cardiac function after myocardial infarction. American Journal of Physiology-Heart and Circulatory Physiology. 2009; 296: H1513–H1523.
[128] Chen C, Wang T, Varadharaj S, Reyes LA, Hemann C, Talukder MAH, *et al*. S-glutathionylation uncouples eNOS and regulates its cellular and vascular function. Nature. 2010; 468: 1115–1118.
[129] Balligand J, Feron O, Dessy C. eNOS activation by physical forces: from short-term regulation of contraction to chronic remodeling of cardiovascular tissues. Physiological Reviews. 2009; 89: 481–534.
[130] Yang L, Jia Z, Yang L, Zhu M, Zhang J, Liu J, *et al*. Exercise protects against chronic β-adrenergic remodeling of the heart by activation of endothelial nitric oxide synthase. PLoS ONE. 2014; 9: e96892.
[131] Jones SP, Greer JJM, van Haperen R, Duncker DJ, de Crom R, Lefer DJ. Endothelial nitric oxide synthase overexpression attenuates congestive heart failure in mice. Proceedings of the National Academy of Sciences of the United States of America. 2003; 100: 4891–4896.
[132] Graham DA, Rush JWE. Exercise training improves aortic endothelium-dependent vasorelaxation and determinants of nitric oxide bioavailability in spontaneously hypertensive rats. Journal of Applied Physiology. 2004; 96: 2088–2096.
[133] Haykowsky M, Scott J, Esch B, Schopflocher D, Myers J, Paterson I, *et al*. A meta-analysis of the effects of exercise training on left ventricular remodeling following myocardial infarction: start early and go longer for greatest exercise benefits on remodeling. Trials. 2011; 12: 92.
[134] Leosco D, Rengo G, Iaccarino G, Golino L, Marchese M, Fortunato F, *et al*. Exercise promotes angiogenesis and improves beta-adrenergic receptor signalling in the post-ischaemic failing rat heart. Cardiovascular Research. 2008; 78: 385–394.
[135] Leosco D, Rengo G, Iaccarino G, Sanzari E, Golino L, De Lisa G, *et al*. Prior exercise improves age-dependent vascular endothelial growth factor downregulation and angiogenesis responses to hind-limb ischemia in old rats. the Journals of Gerontology. Series a, Biological Sciences and Medical Sciences. 2007; 62: 471–480.
[136] Iemitsu M, Maeda S, Jesmin S, Otsuki T, Miyauchi T. Exercise training improves aging-induced downregulation of VEGF angiogenic signaling cascade in hearts. American Journal of Physiology. Heart and Circulatory Physiology. 2006; 291: H1290–H1298.
[137] Gustafsson T, Puntschart A, Kaijser L, Jansson E, Sundberg CJ. Exercise-induced expression of angiogenesis-related transcription and growth factors in human skeletal muscle. The American Journal of Physiology. 1999; 276: H679–H685.
[138] Duncker DJ, van Deel ED, de Waard MC, de Boer M, Merkus D, van der Velden J. Exercise training in adverse cardiac remodeling. Pflugers Archiv. 2014; 466: 1079–1091.
[139] Bohlen HG. Nitric oxide and the cardiovascular system. Comprehensive Physiology. 2015; 5: 808–823.
[140] Förstermann U, Sessa WC. Nitric oxide synthases: regulation

and function. European Heart Journal. 2012; 33: 829–837d.
[141] Xi Y, Hao M, Liang Q, Li Y, Gong D, Tian Z. Dynamic resistance exercise increases skeletal muscle-derived FSTL1 inducing cardiac angiogenesis via DIP2a–Smad2/3 in rats following myocardial infarction. Journal of Sport and Health Science. 2020; 10: 594–603.
[142] Song W, Liang Q, Cai M, Tian Z. HIF-1α-induced up-regulation of microRNA-126 contributes to the effectiveness of exercise training on myocardial angiogenesis in myocardial infarction rats. Journal of Cellular and Molecular Medicine. 2020; 24: 12970–12979.
[143] Bartekova M, Radosinska J, Jelemensky M, Dhalla NS. Role of cytokines and inflammation in heart function during health and disease. Heart Failure Reviews. 2018; 23: 733–758.
[144] Braunwald E. Cardiovascular Medicine at the Turn of the Millennium: Triumphs, Concerns, and Opportunities. New England Journal of Medicine. 1997; 337: 1360–1369.
[145] Valen G. Innate immunity and remodelling. Heart Failure Reviews. 2011; 16: 71–78.
[146] Ionita MG, Arslan F, de Kleijn DPV, Pasterkamp G. Endogenous Inflammatory Molecules Engage Toll-Like Receptors in Cardiovascular Disease. Journal of Innate Immunity. 2010; 2: 307–315.
[147] Mann DL. Stress-activated cytokines and the heart: from adaptation to maladaptation. Annual Review of Physiology. 2003; 65: 81–101.
[148] Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. Journal of Applied Physiology. 2005; 98: 1154–1162.
[149] Abd El-Kader SM, Al-Jiffri OH. Aerobic exercise modulates cytokine profile and sleep quality in elderly. African Health Sciences. 2019; 19: 2198–2207.
[150] Pourheydar B, Biabanghard A, Azari R, Khalaji N, Chodari L. Exercise improves aging-related decreased angiogenesis through modulating VEGF-A, TSP-1 and p-NF-Ƙb protein levels in myocardiocytes. Journal of Cardiovascular and Thoracic Research. 2020; 12: 129–135.
[151] Yu Q, Xia Z, Liong EC, Tipoe GL. Chronic aerobic exercise improves insulin sensitivity and modulates Nrf2 and NF-κB/IκBα pathways in the skeletal muscle of rats fed with a high fat diet. Molecular Medicine Reports. 2019; 20: 4963–4972.
[152] Rodriguez-Miguelez P, Fernandez-Gonzalo R, Almar M, Mejías Y, Rivas A, de Paz JA, *et al*. Role of Toll-like receptor 2 and 4 signaling pathways on the inflammatory response to resistance training in elderly subjects. Age. 2014; 36: 9734.
[153] Boyce BF, Schwarz EM, Xing L. Osteoclast precursors: cytokine-stimulated immunomodulators of inflammatory bone disease. Current Opinion in Rheumatology. 2006; 18: 427–432.
[154] Takayanagi H. Osteoimmunology: shared mechanisms and crosstalk between the immune and bone systems. Nature Reviews. Immunology. 2007; 7: 292–304.
[155] de Kleijn DPV, Chong SY, Wang X, Yatim SMJM, Fairhurst A, Vernooij F, *et al*. Toll-like receptor 7 deficiency promotes survival and reduces adverse left ventricular remodelling after myocardial infarction. Cardiovascular Research. 2019; 115: 1791–1803.
[156] Wang J, Song H, Tang X, Yang Y, Vieira VJ, Niu Y, *et al*. Effect of exercise training intensity on murine T-regulatory cells and vaccination response. Scandinavian Journal of Medicine & Science in Sports. 2012; 22: 643–652.
[157] Zouggari Y, Ait-Oufella H, Bonnin P, Simon T, Sage AP, Guérin C, *et al*. B lymphocytes trigger monocyte mobilization and impair heart function after acute myocardial infarction. Nature Medicine. 2013; 19: 1273–1280.
[158] Oldfield CJ, Duhamel TA, Dhalla NS. Mechanisms for the transition from physiological to pathological cardiac hypertrophy. Canadian Journal of Physiology and Pharmacology. 2020; 98: 74–84.
[159] Brand CS, Lighthouse JK, Trembley MA. Protective transcriptional mechanisms in cardiomyocytes and cardiac fibroblasts. Journal of Molecular and Cellular Cardiology. 2019; 132: 1–12.
[160] Suzuki K, Yamada M, Kurakake S, Okamura N, Yamaya K, Liu Q, *et al*. Circulating cytokines and hormones with immunosuppressive but neutrophil-priming potentials rise after endurance exercise in humans. European Journal of Applied Physiology. 2000; 81: 281–287.
[161] Datta HK, Ng WF, Walker JA, Tuck SP, Varanasi SS. The cell biology of bone metabolism. Journal of clinical pathology. 2008; 61: 577–587.
[162] Li Y, Toraldo G, Li A, Yang X, Zhang H, Qian W, *et al*. B cells and T cells are critical for the preservation of bone homeostasis and attainment of peak bone mass in vivo. Blood. 2007; 109: 3839–3848.
[163] Arron JR, Choi Y. Bone versus immune system. Nature. 2000; 408: 535–536.
[164] Xing Y, Yang SD, Wang MM, Feng YS, Dong F, Zhang F. The Beneficial Role of Exercise Training for Myocardial Infarction Treatment in Elderly. Frontiers in Physiology. 2020; 11: 270.
[165] Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, Estes NAM, *et al*. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. Circulation. 2007; 115: 2358–2368.
[166] Mons U, Hahmann H, Brenner H. A reverse J-shaped association of leisure time physical activity with prognosis in patients with stable coronary heart disease: evidence from a large cohort with repeated measurements. Heart. 2014; 100: 1043–1049.
[167] Siscovick DS, Weiss NS, Fletcher RH, Lasky T. The Incidence of Primary Cardiac Arrest during Vigorous Exercise. New England Journal of Medicine. 1984; 311: 874–877.
[168] Giri S. Clinical and Angiographic Characteristics of Exertion-Related Acute Myocardial Infarction. JAMA. 1999; 282: 1731–1736.
[169] Franklin BA, Thompson PD, Al-Zaiti SS, Albert CM, Hivert MF, Levine BD, et al. Exercise-Related Acute Cardiovascular Events and Potential Deleterious Adaptations Following Long-Term Exercise Training: Placing the Risks Into Perspective-An Update: A Scientific Statement From the American Heart Association. Circulation. 2020; 141: e705–e736.
[170] O'Keefe JH, Franklin B, Lavie CJ. Exercising for Health and Longevity vs Peak Performance: Different Regimens for Different Goals. Mayo Clinic Proceedings. 2014; 89: 1171–1175.
[171] Eijsvogels TMH, Thompson PD, Franklin BA. The "Extreme Exercise Hypothesis": Recent Findings and Cardiovascular Health Implications. Current Treatment Options in Cardiovascular Medicine. 2018; 20: 84.
[172] Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, *et al*. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. JAMA. 1995; 273: 402–407.
[173] Maron BJ, Zipes DP, Kovacs RJ. Eligibility and Disqualification Recommendations for Competitive Athletes with Cardiovascular Abnormalities: Preamble, Principles, and General Considerations: A Scientific Statement From the American Heart Association and American College of Cardiology. Circulation. 2015; 132: e256–261.
[174] Levine BD. Going High with Heart Disease: the Effect of High Altitude Exposure in Older Individuals and Patients with Coronary Artery Disease. High Altitude Medicine & Biology. 2015; 16: 89–96.
[175] Parati G, Agostoni P, Basnyat B, Bilo G, Brugger H, Coca A,

et al. Clinical recommendations for high altitude exposure of individuals with pre-existing cardiovascular conditions: A joint statement by the European Society of Cardiology, the Council on Hypertension of the European Society of Cardiology, the European Society of Hypertension, the International Society of Mountain Medicine, the Italian Society of Hypertension and the Italian Society of Mountain Medicine. European Heart Journal. 2018; 39: 1546–1554.

[176] Dizon LA, Seo DY, Kim HK, Kim N, Ko KS, Rhee BD, *et al*. Exercise perspective on common cardiac medications. Integrative Medicine Research. 2013; 2: 49–55.

[177] Naci H, Ioannidis JP. Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. British Journal of Sports Medicine. 2015; 49: 1414–1422.

[178] Quindry JC, Franklin BA. Cardioprotective Exercise and Pharmacologic Interventions as Complementary Antidotes to Cardiovascular Disease. Exercise and Sport Sciences Reviews. 2018; 46: 5–17.