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REVIEW

Cardiac remodeling and physical training post myocardial infarction

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Abstract

After myocardial infarction (MI), the heart undergoes extensive myocardial remodeling through the accumulation of fibrous tissue in both the infarcted and noninfarcted myocardium, which distorts tissue structure, increases tissue stiffness, and accounts for ventricular dysfunction. There is growing clinical consensus that exercise training may beneficially alter the course of post-MI myocardial remodeling and improve cardiac function. This review summarizes the present state of knowledge regarding the effect of post-MI exercise training on infarcted hearts. Due to the degree of difficulty to study a viable human heart at both protein and molecular levels, most of the detailed studies have been performed by using animal models. Although there are some negative reports indicating that post-MI exercise may further cause deterioration of the wounded hearts, a growing body of research from both human and animal experiments demonstrates that post-MI exercise may beneficially alter the course of wound healing and improve cardiac function. Furthermore, the improved function is likely due to exercise training-induced mitigation of renin-angiotensin-aldosterone system, improved balance between matrix metalloproteinase-1 and tissue inhibitor of matrix metalloproteinase-1, favorable myosin heavy chain isoform switch, diminished oxidative stress, enhanced antioxidant capacity, improved mitochondrial calcium handling, and boosted myocardial angiogenesis. Additionally, meta-analyses revealed that exercise-based cardiac rehabilitation has proven to be effective, and remains one of the least expensive therapies for both the prevention and treatment of cardiovascular disease, and prevents re-infarction.

Key words: Post-myocardial infarction; Exercise training; Myocardial remodeling; Angiotensin Ⅱ; Fibrosis

Core tip: After myocardial infarction, the heart undergoes extensive myocardial remodeling through the accumulation of fibrous tissue in both the infarcted and noninfarcted myocardium, which distorts tissue structure, increases tissue stiffness, and accounts for ventricular dysfunction. There is growing clinical consensus that exercise training may beneficially alter the course of post-myocardial infarction (MI) myocardial remodeling and improve cardiac function. This review

summarizes the present state of knowledge regarding the effect of post-MI exercise training on infarcted hearts.

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INTRODUCTION

Myocardial infarction (MI) is the major cause of heart failure in the adult American population[1]. Annually, 1.5 million Americans suffer from MI, with just over one-third of all cases inflicting serious heart disease and death. Because of this, post-MI treatments have become the major focus of research. There is growing clinical consensus that exercise training may beneficially alter the clinical course of post-MI myocardial remodeling and improve cardiac function[2,3]. Exercise training in post-MI patients with left ventricle (LV) systolic dysfunction has been recommended as a useful adjunct to the existing medical therapy, not only to attain symptomatic and functional improvement but also to prevent the progression of LV dysfunction and its attendant morbidity and mortality[4,5]. Significant improvements in exercise capacity were noted with no major complications in patients with moderate or severe LV dysfunction[4,6,7]. Post-MI training reverses skeletal muscle metabolic derangements[8,9], increases maximal cardiac output[6,10,11] and improves the quality of life in these patients. Exercise training also improves in myocardial perfusion, independent of regressive changes in coronary lesions[12]. The improvement in myocardial blood flow of the infarcted area, even late after acute infarction, may lead to a consistent recovery of both regional and global LV function. Patients with MI experienced an exercise training-induced improvement in myocardial oxygenation and LV function[13].

In recent years, cardiac rehabilitation (CR) has become a multi-disciplinary and multi-faceted intervention aimed at restoring well-being and impeding disease progression in patients with heart disease[14]. This complex intervention involves a variety of therapies, including risk factor education, psychological input, and drug therapy. Nevertheless, international clinical guidelines have consistently identified exercise-based CR as an essential element of therapy.

Despite guidelines recommending the use of CR programs for patients with MI, participation in these programs continues to be low; in fact, it has been reported that only 10% to 20% of patients who survive an acute MI participate in an exercise-based secondary prevention CR program[15]. Indeed, the reason for such low participation is likely multifactorial; additionally, conflicting results regarding the efficacy of experimental research and the absence of large randomized controlled trials with respect to re-infarction likely serve as additional barriers[3]. Therefore, we reviewed the evidence and the mechanisms by which post-MI exercise improves morbidity and mortality, as obtained by means of experimental and clinical studies.

POST-MI LV REMODELING

LV remodeling is the process by which ventricular size, shape, and function are regulated by mechanical, neurohormonal, and genetic factors[16,17]. After acute MI, the abrupt increase in volume overload induces a unique pattern of remodeling in the infarct zone and bordering non-infarct myocardium. The oxygen deprived myocardium experiences a localized inflammatory response *via* neurohormonal activation mediated in part by the migration of neutrophils, monocytes and macrophages[16]. Hypotension and the subsequent decrease in cardiac output stimulate temporary circulatory hemodynamic compensatory mechanisms including increased sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), and natriuretic peptide activity[18].

The induction of cardiomyocyte hypertrophy is a key process during post-MI remodeling that offsets increased volume over load, attenuates progressive dilation, and stabilizes contractile function; thus, post-MI myocyte hypertrophy initially serves as an adaptive, cardiac-preserving response[7,17]. However, over time, chronic neurohormonal activation, myocardial stretch, RAAS activity, and various paracrine and autocrine factors continue to promote eccentric, pathological hypertrophy, progressively deteriorating LV function to the point of failure. Interestingly, compelling evidence has shown that post-MI exercise favorably influences the course of LV remodeling, which accordingly, has attracted much attention[19].

EFFECT OF POST-MI EXERCISE TRAINING ON RAAS AND MYOCARDIAL REMODELING

Circulating angiotensin Ⅱ (Ang Ⅱ) is markedly increased following MI. Ang Ⅱ is a potent stimulant in pathologic myocardial remodeling both as a circulating hormone and as an autocrine/paracrine mediator produced in response to hemodynamic overload[20]. Ang Ⅱ plays a major role in vasoconstriction and aldosterone release. This peptide also serves as a growth factor and stimulates fibrous tissue formation in various[21-23]. Ang Ⅱ is also generated in the infarcted heart and regulates tissue structure in an autocrine and paracrine manner. All the components for Ang

Ⅱ generation including angiotensinogen, renin, and angiotensin converting enzyme (ACE), are present in the infarcted heart[24,25]. Locally generated AngⅡ stimulates transforming growth factor-β1 (TGF-β1) synthesis, which, in turn, enhances proliferation and collagen generation of myofibroblast, and leads to cardiac fibrosis[26]. Pharmacological intervention with ACE inhibitor or AngII receptor antagonist significantly attenuates cardiac fibrosis, and improves cardiac function and survival[27,28].

Acute physical exercise stimulates renin release and activates renin-angiotensin system[29,30] with an elevation of aldosterone[31], whereas chronic exercise training attenuates renin-angiotensin system at resting condition[32]. A study on patients with MI has demonstrated that the resting plasma AngⅡ reduced by 26% after 4 mo of exercise training[32]. The reduction in plasma AngⅡ was accompanied with 32% reduction in aldosterone, 30% reduction in vasopressin, and 27% reduction in atrial natriuretic peptide. An animal study using a pacing-induced heart failure in rabbits also revealed exercise training-induced attenuation of resting plasma AngⅡ[33].

In a previous study[34], we systematically examined the effect of exercise training on RAAS using a rat-MI model. Rats performed a moderate intensity exercise training on a rodent treadmill 1 wk after MI 5 d/wk for 8 wk at 16 m/min, 50 min per session. Our results showed that exercise training significantly attenuated circulating renin, ACE, AngⅡ, and aldosterone compared with sedentary rats with MI. Rats in exercise groups had similar LV end-diastolic diameters (LVEDd) compared with their sedentary counterparts and tended to have smaller LV end-systolic diameters (LVESd), and percent fractional shortening in exercise rats was significantly higher than in sedentary rats. These findings suggest that exercise training normalizes the circulating RAAS and improves LV function without compromising LV dilation.

In a similar study[35], we further evaluated the effect of post-MI exercise training on myocardial fibrosis, cardiac function, and factors inducing adverse remodeling. For the first time, changes caused by exercise training were investigated in type Ⅰ and Ⅲ collagen, matrix metalloproteinase (MMP-1), tissue inhibitor matrix metalloproteinase (TIMP-1), TGF-β1), AngⅡ receptor type 1 (AT1), and ACE at both gene and protein levels after MI. Our results indicated exercise training significantly attenuated the expression of TIMP-1 at both gene and protein level and improved balance between MMP-1 and TIMP-1 (imbalance between the two appear to be responsible for the increased MMP activity observed in congestive heart failure). Training also lowered expression of AT1 receptor protein and reduced ACE mRNA expression as well as ACE binding. In addition, training significantly decreased collagen content, thereby resulting in attenuated cardiac fibrosis. Lastly, exercise training preserved cardiac function.

AngⅡ receptor blockade has been widely used to alleviate detrimental effects associated with elevated RAAS[36,37]. In a subsequent study[38], we investigated the effect of combined exercise training along with AngII receptor blockade on post-MI ventricular remodeling in rats. Losartan (an AngⅡ receptor antagonist) treatment (20 mg/kg per day) was initiated 1-wk post-MI, and administered *via* gastric gavage for 8 wk. The results indicated significantly decreased levels of TIMP-1 in mRNA and protein expression in both trained and losartan treated groups. Exercise trained groups exhibited attenuated expression of AT1 receptor protein, and decreased ACE binding. These findings revealed that exercise training after MI provided beneficial effects on post-MI cardiac function and LV remodeling by the alteration of specific gene and protein expressions that regulate myocardial fibrosis, whereas the combination of both exercise training and losartan treatment improved the effects[35,38]. Tables 1 and 2 summarize both human and animal studies on post-MI physical training.

EARLY *VS* LATE PHASE POST-MI EXERCISE

Post-MI remodeling has been arbitrarily divided into two phases: the early phase, which lasts up to 72 h, and the late phase, lasting beyond 72 h[17]. Generally, adaptive responses that preserve stroke volume are invoked during the early stage, whereas late remodeling primarily involves hypertrophy and alterations in LV architecture in an attempt to distribute increased wall stresses more evenly. Differences in function between adjacent and remote non-infarcted regions are greatest at one week after anterior MI, and persist for a minimum of six months post-MI[39]; it is during this six-month period that systolic function decreases drastically, as the LV undergoes progressive dilatation, eccentric hypertrophy, and the lengthening of non-infarcted segments[17]. Thus, the question of when to begin exercise and at what intensity has proven elusive. Nevertheless, recent evidence offers novel insights and indeed provides an answer to some questions, although, as quality research often does, asks several more.

To date, several studies in humans reported contradictory effects of training on LV remodeling after MI[4,6,7,40-45]. However, careful inspection of these studies indicate that after small MI, exercise has no detrimental effect[7,41], or even improves[4,43,44,46] LV geometry and function, independent and irrespective of whether exercise was started late (1 year)[4,44] or early (< 2 mo)[7,41,43] after MI. Conversely, in patients with large MI (encompassing 35% to 50% of LV mass), exercise had either no[42], or a beneficial[4]

Table 1 Summary of physical training protocols and outcomes in selected human studies

Ref.	Type of exercise	Exercise intensity	Exercise duration	Exercise frequency	Training period	Assessment	Outcome
Braith *et al*[32] 1999	Treadmill walk	40%-70% of peak oxygen uptake (VO_2)	Started with 10-20 min as tolerated and increased to 30-45 min by the 10th wk	3 times/wk	4 mo	Plasma RAAS	Reduced Resting AngII, Aldosterone, vasopressin, and atrial natriuretic peptide
Myers *et al*[143] 2001	Outdoor walking at an elevation of 3500 ft, in addition to cycling	60%-70% of peak VO_2	Two 1-h sessions of walking, 45 min of cycling	5 times/wk	2 mo	Post-exercise oxygen uptake kinetics	High-intensity training did not result in a faster recovery of oxygen debt
La Rovere *et al*[144] 2002[1]	Graded exercise (cycling, calisthenics)	Adjusted to 75% of the heart rate at peak VO_2	30 min	5 times/wk	1 mo	BRS, LVEF	BRS improved by 26%, while LVEF remained unchanged
Marchionni *et al*[145] 2003[2]	Cycling	70%-85% of max heart rate	1 h	3 times/wk	6 mo	Total work capacity, health-related quality of life	Improved total work capacity and health-related quality of life
Zheng *et al*[146] 2008[1]	Bicycle ergometer	75% of peak heart rate	30 min	3 time/wk	6 mo	HR recovery, time to reach anaerobic threshold, left ventricular end-diastolic	Exercise training prevented ventricular remodeling to a certain extent
Giallauria *et al*[46] 2013	Bicycle ergometer	60%-70% of peak VO_2	30 min	3 times/wk	6 mo	diameter, left ventricular ejection fraction dipyridamole rest gated myocardial perfusion single photon emission computed tomography	Improved peak oxygen consumption, myocardial perfusion and LV function

[1]Exercise was part of a comprehensive secondary prevention program; [2]Combination study consisting of Home and Hospital/group participants. RAAS: Renin-angiotensin-aldosterone system; LVEF: Left ventricular ejection fraction; BRS: Baroreflex sensitivity.

effect on ejection fraction (EF) and LV volumes but only when started late after MI. However, when exercise after large MI is initiated at a time when LV remodeling is still ongoing (3 to 4 mo after MI), the majority of studies reported that exercise has either no[6,7,41], or even a detrimental[40,47] effect on LV volume and EF.

Similarly, experimental research using rat models of MI suggests that exercise initiated late (> 3 wk) after moderate to large MI does not aggravate[45,48], or even blunts[49-51] LV dilation and hypertrophy. Contrarily, exercise started < 1 wk after moderate to large MI resulted in variable outcomes with beneficial[52], no[53,54], or detrimental[55,56] effects on LV remodeling. Therefore, these rodent studies further evidence the concern that early exercise after MI may further exacerbate LV remodeling. Importantly, there are a number of concerns with the methodology of these studies. First, exercise experimental studies conducted late after MI predominately used treadmill running[45,48-50], whereas early exercise studies used swimming[51-55]. Since swimming is not a habitual activity for rats, this type exercise mode may markedly elicit both psychological and physiological stress to the animals, which potentially offsetting the beneficial effects of exercise compared to treadmill running[57,58].

Amazingly, in a recent study of evaluating 8-wk of volunteer exercise, de Waard *et al*[59] reported remarkable data addressing the question of exercise training 24 h after MI. As opposed to most humans, mice like to run, and will do so seemingly endlessly when presented the opportunity. During the first week after induction of MI, recovering mice slowly titrated up their daily running activity, reaching distances similar to their sham-operated counterparts towards the end of the study, thus, suggesting that early post-MI exercise training may have positive effect in post-MI recovery and myocardial remodeling. Authors reported that exercise had no effect on survival, MI size, or LV dimensions, but improved LV fractional shortening from 8% ± 1% to 12% ± 1%, LV dP/dt_{P30} from 5295 ± 207 to 5794 ± 207 mmHg/s, and reduced pulmonary congestion. Additionally, this study also provided novel information regarding myocardial Ca^{2+} handling after MI, debunking the previously held notion that exercise sensitizes myofilaments to the effects of Ca^{2+}[59]. A study from our group[34] systematically examined the timing effect of post-MI exercise training. Rats started exercise training at either 1 wk or 6 wk after MI on a treadmill for 8 wk. Rats in exercise groups had similar LVEDd compared with their sedentary counterparts and tended to have smaller LVESd, and percent fractional shortening (%FS) in exercise rats was significantly higher than

Table 2 Summary of physical training protocols and outcomes in selected animal studies

Ref.	Type of exercise	Exercise intensity	Exercise duration	Exercise frequency	Training period	Assessment	Outcome
Hashimoto *et al*[76] 2004	Treadmill running	10 m/min	60 min	5 d/wk	6 wk	Myosin heavy chain isoforms, cardiac wall measurements	Exercise training resulted in a significant increase of α-MHC expression in both anterior and posterior wall, ensuring a beneficial role in the remodeling of the heart
Xu *et al*[35] 2008	Treadmill running	16 m/min @ 5% grade	50 min	5 d/wk	8 wk	TIMP-1, AT1, ACE, collagen volume fraction, MMP	Early exercise training after MI reduces TIMP-1 expression, improves the balance between MMPs and TIMPs, and mitigates the expressions of ACE and AT1 receptor, thus attenuating myocardial fibrosis and preserving cardiac function
De Waard *et al*[59] 2007	Voluntary treadmill exercise training	N/A	N/A	5 d/wk	8 wk	LV fractional shortening, Ca^{2+} sensitivity, PLB, SERCA	Voluntary exercise improved LV and cardiomyocyte shortening, attenuates global LV dysfunction
Wan *et al*[34] 2007	Treadmill running	16 m/min @ 5% grade	50 min	5 d/wk	8 wk	Echo and RAAS	Exercise training improved cardiac function and attenuated RAAS. Early and late exercise training had similar beneficial results
Xu *et al*[106] 2010	Treadmill running	16 m/min @ 5% grade	50 min	5 d/wk	8 wk	SOD, GPx, MnSOD	Exercise training combined with Ang Ⅱ receptor blockade reduced oxidative stress
Yengo *et al*[147] 2012	Treadmill running	15% grade, speed increased from 13 to 24 m/min	Progressively increased to 60 min	6 d/wk	10 wk	Collagen concentration, non-reducible collagen cross-linking in the RV	Exercise training normalized the observed increase in cross-linking, and favorably modifies heart extracellular matrix

RAAS: Renin-angiotensin-aldosterone system; MHC: Myosin heavy chain; TIMP-1: Tissue inhibitor matrix metalloproteinase; AT1: AngII receptor type 1; ACE: Angiotensin converting enzyme; MMP: Matrix metalloproteinase; SOD: Superoxide dismutase; GPX: Glutathione peroxidase.

in sedentary rats. These finding suggest that exercise training does not cause LV dilation and preserves LV function.

POST-MI EXERCISE AND MYOCARDIAL CONTRACTION

Ca^{2+} handling abnormalities can largely explain depressed myocyte contractility in the remodeled myocardium, whereas abnormalities in myofilament function are less well understood. Previously, it was reported in pigs that impaired pump function three weeks after MI could also be attributed to decreased maximal isometric tension in skinned cardiomyocytes in areas remote from the ischemic border zone; as it turns out, the impairment occurred in the context of increased Ca^{2+} sensitivity of the myofilaments[60]. As a result, the authors attributed the increased post-MI Ca^{2+} sensitivity to reduced protein kinase A-mediated troponin I (TnI) phosphorylation[60]. Similarly, increased myofilament Ca^{2+} sensitivity has also been reported in end-stage human heart failure, mediated by decreased TnI phosphorylation.

Although experimentally challenging, investigators from the de Waard study were able to construct a full pCa-force relationships in isometrically contracting myocytes[59], which differs from previous studies relying on simultaneous measurements of FS% and Ca^{2+} fluorescence in unloaded myocytes to estimate myofilament Ca^{2+} sensitivity. Although a much simpler experimental approach, there are various problems associated with this method. First, maximal developed tension cannot be assessed in unloaded myocytes, and any changes in developed tension are ignored when estimating Ca^{2+} sensitivity. Secondly, basal sarcomere length is much shorter in unloaded myocytes (1.8 *vs* 2.2), and cannot be controlled; therefore, even a slight change in basal sarcomere length would confound the result, which in turn, has prompted investigators to wrongly conclude that exercise increases myofilament sensitivity[51]. Thus, data from de Waard *et al*[59] reveals that voluntary exercise training in mice early after MI normalizes myofilament dysfunction, which likely occurred in response to the exercise-induced improvement in unloaded shortening of isolated intact cardiomyocytes, as the Ca^{2+} transient amplitude was not found to be altered by exercise. Furthermore, basal Ca^{2+} was reduced by exercise, altogether suggesting that exercise decreases myofilament Ca^{2+} sensitivity.

Dysregulation of cardiac β-adrenergic receptor (β-AR) signaling represents another important factor leading to the pathological LV remodeling and the progression to heart failure. In the failing myocardium, adverse changes in β-AR signaling are mainly attributed to β_1-AR downregulation and desensitization/uncoupling of both β_1 and β_2-AR's. It has been reported that exercise after MI increases

β_1-AR, as evidenced by a 48% increase in β_1-AR protein, and a 36% increase in cAMP levels, and improves β-AR signaling[59,61], which in turn, may also contribute to improvement in myocardial contractility in patients with MI.

Myosin heavy chain (MHC) acts as the chemical-mechanical transducer of motion in muscle fibers by converting energy from ATP into the sliding myofilaments[62]. The isoform α-MHC elicits two to three times faster actin-activated ATPase activity and actin filament sliding velocity than the isoform MHC-β[63,64]. Thyroid hormone (TH) has profound effects on the cardiovascular system, and is known to critically regulate the expression of MHC isoforms in the myocardium[65]; in fact, in the absence of TH, the *α-MHC* gene is not transcribed[62]. Triiodothyronine (T_3), the active cellular form of TH, mediates its actions upon binding to thyroid hormone receptors (TRs)[66,67].

After MI, T_3 levels are significantly reduced in patients[68]; similarly, decreased serum concentrations of TH have also been observed in patients with chronic heart failure (CHF), which, in part, attributes to impaired cardiac function[69]. In experimental post-MI rat models, following the decrease of serum T_3, significant downregulation of α-MHC and the concomitant upregulation of MHC-β are observed in the LV non-infarcted myocardium, along with changes in TR isoforms at the mRNA level[68,70,71]. These, in addition to other MI-induced alterations in cardiac phenotype, are thought to further contribute to the progressive nature of LV systolic dysfunction, and have been associated with poor prognosis[62,63,72,73]. Interestingly, endurance exercise has been reported to favorably reverse MHC α- to β-cardiac isoform shifts after MI at both gene and protein levels[74,75], which in turn, may be associated with preserved cardiac functioning, attenuated LV remodeling, and increased myofibril function[76]. Recent evidence by our group[75] indicated that post-MI exercise training significantly increase cardiac expression of α-MHC and decrease cardiac expression of MHC-β without changing serum T_3 levels. Similarly, unpublished data from our group recently revealed that moderate-intensity treadmill exercise training markedly increased TRα-1 and TRβ-1 nine weeks after MI. Thus, it is likely that favorable changes in TH target gene transcription may be due to exercise-dependent upregulation of TR isoforms. Nevertheless, studies with experimental models of LV dysfunction and preliminary clinical investigation of patients with CHF reported that the TH analog 3,5-diiodothyroproionic acid elicits improvements in both systolic and diastolic LV function, accompanied by an increase in cardiac output and improved lipid profile[77]. Thus, it is conceivable that the combination of exercise combined with TH treatment could potentiate beneficial results, and warrants further investigation.

POST-MI OXIDATIVE STRESS AND EXERCISE TRAINING

Reactive oxygen species (ROS) including superoxide (O_2^-), hydroxyl (OH^-), and peroxynitrite ($ONOO^-$), have an unpaired electron[78]. These ROS serve as signaling molecules when in low concentrations; however, they elicit harmful oxidative stress when produced in excess[79]. ROS can directly damage the lipids of cell membranes, proteins and both nuclear and mitochondrial DNA resulting in serious or mortal cellular injury[80]. However, the toxicity associated with the excessive ROS can be prevented by antioxidant defense systems that provide a healthy cellular environment. Living cells have both enzymatic and non-enzymatic defense mechanisms to balance the multitude of oxidative challenges presented to them. The enzymatic antioxidant system includes superoxide dismutase (SOD), catalase and glutathione peroxidase (GPX)[81]. SOD catalyzes the dismutation of superoxide (O_2^-) to hydrogen peroxide (H_2O_2). Catalase and GPX further metabolize H_2O_2 to water and oxygen. The non-enzymatic group includes a variety of biologic molecules, such as vitamins E and C[81,82]. Oxidative stress is enhanced by an unbalance between elevated ROS production and diminished antioxidant system.

Excessive oxidative stress has been observed in the myocardium of patients with CHF[83,84]. Heart failure subsequent to myocardial infarction is associated with oxidative stress in both infarcted and noninfarcted myocardium[83,85,86]. Researchers have identified a membrane-based NAD(P)H oxidase as a major source of O_2^- in the heart[87]. An elevated NAD(P)H oxidase expression has been observed in the infarcted rat heart and the extent of NAD(P)H oxidase elevation is negatively correlated with the deteriorated hemodynamic function and ventricular remodeling of the heart[88]. Furthermore, progressive decrease in antioxidant enzymes, SOD, catalase[89], and glutathione (an antioxidant)[90] has also been observed in the infarcted rat heart. These observations suggest that the impaired antioxidant system and/or augmented ROS promote oxidative stress, contributing to the adverse remodeling and dysfunction of the infarcted heart[91].

There is growing evidence that chronic exercise training adaptively bolsters the activity of protective antioxidant enzymes such as catalase, SOD, GPX[92], glutathione reductase (GR)[93], and antioxidant glutathione content[94,95] in skeletal muscles of healthy animals. Nine-weeks of treadmill training markedly elevated manganese-SOD (Mn-SOD, an isozyme of SOD) activity and its protein content both at rest and after an acute exercise bout in the soleus muscle of rats[96]. In contrast, the muscle Mn-SOD gene expression of untrained rats was significantly decreased after an acute bout of exercise[96]. Exercise

training also resulted in significant increase in SOD activity in the LV of normal rats[97,98]. These findings suggest that muscles have the capacity of responding to training in such a manner as to enhance antioxidant system and reduce the accumulation of ROS resulting from enhanced metabolic activity.

In patients with CHF, exercise training enhanced GPX and catalase activities, and mitigated lipid peroxidation in skeletal muscles[99]. Exercise training also downregulated both gene expression and activity of pro-oxidant NAD(P)H oxidase, and decreased vascular generation of ROS in human arterial tissue[100].

Inconsistent findings have been reported on the effect of post-MI exercise training on ROS and antioxidants. Yamashita *et al*[101] and Brown *et al*[102] reported that exercise training resulted in an increase in myocardial SOD content along with improved recovery from ischemia-reperfusion injury. Others, however, reported that exercise training increased cardioprotection without amplifying myocardial SOD content[103,104] and only certain cardiac antioxidant enzyme activities (*i.e.*, SOD) were enhanced in the exercise trained animals[97,101,105]. The variation in the findings of these studies may be due to the differences in the intensity and duration of exercise regimens. A study from our group[106] demonstrated that exercise training increased MnSOD gene expression after MI regardless of losartan treatment. In addition, exercise training together with losartan treatment remarkably enhanced the enzymatic activity of catalase, suggesting an additive effect of exercise training and Ang Ⅱ receptor blockade treatment. But exercise training did not enhance myocardial glutathione peroxidase activity. Our data also revealed that post-MI exercise training notably attenuated MI-induced elevation of plasma thiobarbituric acid reactive substances (TBARS, a marker of lipid oxidation) although cardiac TBARS was not altered.

It has been documented that Ang Ⅱ stimulates NAD(P)H oxidase activity, which promotes ROS production[107,108]. Thus, exercise training may improve antioxidant capacity and attenuate oxidative stress by attenuating RAAS[35,38,106].

MYOCARDIAL APOPTOSIS AND EXERCISE TRAINING

Loss of cardiomyocytes is an important mechanism in the development of myocardial remodeling and cardiac failure[109]. After MI, apoptotic cardiomyocyte death occurs in the infarcted myocardium as well as the surviving portions of the heart[110,111]. Myocyte apoptosis not only occurs at early phase (7 d) of MI[112,113], but also progresses to late phase (up to 6 mo) in myocardium remote from the area of ischemic damage[114,115], contributing to CHF[116]. ROS have proven to be powerful mediators of myocyte apoptosis[117,118]. Treatment of cardiac myocytes with O_2^- or H_2O_2 induces apoptosis, suggesting a mechanism of ROS as an initial pathogenic event[119]. Enhanced pro-apoptotic Bax expression coexists with oxidative stress and apoptosis in the infarcted heart[120], whereas oxidative stress activates pro-apoptotic enzymes, caspase-9 and caspase-3, resulting in cardiac apoptosis and ventricular dysfunction[117]. *In vivo* studies have demonstrated that long-term treatment with the antioxidants, probucol or pyrrolidine dithiocarbamate, attenuates oxidative stress and myocyte apoptosis within noninfarcted myocardium in rats[121,122].

Siu *et al*[98] demonstrated that endurance training downregulated the expression of caspase and Bax, and upregulated Bcl-2 (an anti-apoptotic gene product) in both skeletal and cardiac muscles of healthy rats. These anti-apoptotic effects were associated with elevated protein content of Mn-SOD. A clinical study also revealed that exercise training attenuated skeletal muscle apoptosis along with improved antioxidant capacity in patients with CHF[99]. Accordingly, the data are consistent with the idea that an increased antioxidant capacity and attenuated oxidative stress from exercise training may be involved in reducing pro-apoptotic genes, suggesting that exercise training may attenuate the extent of apoptosis in muscles. However, the influence of post-MI exercise training in myocardial apoptosis remains to be elucidated.

POST-MI EXERCISE AND CARDIAC ANGIOGENESIS

After myocardial infarction (MI), the adequate growth of new capillaries and arterioles, or angiogenesis, represents a critical process in the development of compensatory hypertrophy in the remaining non-infarcted myocardium[123]. Although compensatory angiogenesis can be observed in both the ischemic and infarcted heart, previous studies have demonstrated that angiogenesis may be inadequate[124,125]; in fact, recent evidence suggests that impaired angiogenesis may lead to maladaptive LV remodeling, promoting the transition from adaptive cardiac hypertrophy to LV dilation and dysfunction[61,126].

Exercise, through increased vascular shear stress, potentiates a powerful angiogenic stimulus[127]. The pro-angiogenic effect of exercise has previously been demonstrated in healthy swine hearts[128]. A study conducted by Leosco *et al*[61] reported that exercise induced a significant increase of capillary density in lateral border and remote zones to the infarct site, but not in the area close to the infarcted site. One of our recent studies (unpublished data) confirms that post-MI exercise training induced about 1.5-fold increase in capillary density in the septum

and left ventricle compared to non-exercised heart, suggesting that exercise promotes capillary growth in non-infarcted areas of severely decompensated hearts.

A number of studies clearly demonstrate that exercise activates vascular endothelial growth factor (VEGF) dependent angiogenic pathways[129-131], which represent critical molecular mechanisms by which exercise triggers angiogenesis[130]. In addition, exercise-induced upregulation of VEGF in patients with heart failure has also been documented[132]. Recently, experimental studies have revealed that exercise reactivates angiogenic signaling by increasing VEGF and eNOS phosphorylation by Akt in the heart, increases coronary vascular network and density, and enhances myocardial blood perfusion. Evidence of endothelial dysfunction in peripheral resistance arteries post-MI has also been observed in both experimental and clinical studies[133,134], which likely contributes to arterial dysfunction[135,136]; in this regard, post-MI exercise has been shown to reverse arterial dysfunction by virtue of restored production of nitric oxide (NO) in the endothelial vessel wall mediated by adaptive changes in eNOS, its activation by Akt, and by reduced NAD(P)H oxidase-generated ROS scavenging of NO[137].

EXERCISE-BASED CR IN PATIENTS WITH HEART DISEASE

Previously, four meta-analyses[138-141] of the effects of exercise-based interventions in patients with coronary heart disease reported a statistically significant benefit in patients receiving exercise therapy compared with usual medical care, with a reduction in total and cardiac morality ranging from 20% to 32%. However, randomized controlled trials (RCT) have generally been small and often of questionable methodological quality, raising concerns that the effect of exercise-based CR may be overestimated. In 2004, Taylor *et al*[142] aimed to update the systematic review of the effects of exercise-based CR in patients with coronary heart disease, addressing previous concerns regarding the applicability of this evidence to routine practice.

For the analysis, over 5000 articles were retrieved from a number of search sources, and only 425 full papers were considered for possible inclusion. Studies were excluded for various reasons including nonrandomized design, inappropriate patient groups, inappropriate intervention, the control group received an exercise intervention, inappropriate outcomes, in adequate follow-up, and preliminary results only available in abstract form. After identification of duplicate publications, only 48 eligible studies remained, and were still of poor methodological quality.

Although exercise-based CR was associated with a significant reduction in all-cause mortality and total cardiac mortality, there was no significant difference with respect to re-infarction[142]. Conversely, a recent meta-analyses conducted in 2011 consisting of 34 RCTs (n = 6111) found that patients randomized to exercise-based CR had a significantly lower risk of re-infarction, cardiac mortality, and all-cause mortality[3]. In a stratified analysis, treatment effects were consistent regardless of study periods, duration of CR, or time beyond the active intervention[3]. Additionally, Exercise-based CR had favorable effects on cardiovascular risk factors, including smoking, blood pressure, body weight, and lipid profile[143].

CONCLUSION

Most of the human and animal studies demonstrated that post-MI physical exercise training results in positive effect on myocardial remodeling. These beneficial effects include improved cardiac function, mitigated interstitial myocardial fibrosis, and enhanced physical capacity. As a result, physical exercise training provides good prognosis and improves the quality of life of MI patients. The current literature revealed the mechanism of physical training-induced improvement in post-MI cardiac remodeling. Physical training attenuates renin[29,30], ACE, Ang Ⅱ, and aldosterone[31,34]. The attenuation of Ang Ⅱ, in turn, reduces cardiac fibrosis[34] and aldosterone secretion[32,34], which may ease MI-induced plasma expansion. Physical training also improves the balance between MMP-1 and TIMP-1, which, in turn, reduces cardiac stiffness *via* regulation of collagen accumulation[38]. Studies show that physical training significantly improves ß-adrenergic receptor, cAMP[59,61], and favorably reverses MHC α- to β-cardiac isoform shifts[74,75], attributing to improvement in myocardial contractility. In addition, post-MI physical training may enhance antioxidant enzyme capacity and attenuate oxidative stress[97,101,105]. It is important to note that the existing studies have only investigated the effects of *endurance* exercise on post-MI remodeling; therefore, the effects of post-MI resistance training have yet to be systematically examined to identify a better exercise mode. Furthermore, although majority of the research has shown that post-MI exercise training improves cardiac remodeling and function, the suitable exercise intensity, duration, and the time to start training are yet to be optimized to provide clinically relevant information regarding the pathophysiology of post-MI recovery through physical training.

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