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**Cardiac remodeling and physical training post myocardial infarction**

Garza MA *et al.* Post-myocardial infarction and physical training

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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

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**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](#_ENREF_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](#_ENREF_2),[3](#_ENREF_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](#_ENREF_4),[5](#_ENREF_5)]. Significant improvements in exercise capacity were noted with no major complications in patients with moderate or severe LV dysfunction[[4](#_ENREF_4),[6](#_ENREF_6),[7](#_ENREF_7)]. Post-MI training reverses skeletal muscle metabolic derangements[[8](#_ENREF_8),[9](#_ENREF_9)], increases maximal cardiac output[[6](#_ENREF_6),[10](#_ENREF_10),[11](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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**

Left ventricular (LV) remodeling is the process by which ventricular size, shape, and function are regulated by mechanical, neurohormonal, and genetic factors[[16](#_ENREF_16),[17](#_ENREF_17)]. After acute myocardial infarction (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](#_ENREF_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](#_ENREF_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](#_ENREF_7),[17](#_ENREF_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](#_ENREF_19)].

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

Circulating AngII is markedly increased following MI. AngII 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](#_ENREF_20)]. AngII 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](#_ENREF_21)]. AngII is also generated in the infarcted heart and regulates tissue structure in an autocrine and paracrine manner. All the components for AngII generation including angiotensinogen, renin, and ACE, are present in the infarcted heart[[24](#_ENREF_24),[25](#_ENREF_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](#_ENREF_26)]. Pharmacological intervention with ACE inhibitor or AngII receptor antagonist significantly attenuates cardiac fibrosis, and improves cardiac function and survival[[27](#_ENREF_27),[28](#_ENREF_28)].

Acute physical exercise stimulates renin release and activates renin-angiotensin system[[29](#_ENREF_29),[30](#_ENREF_30)]with an elevation of aldosterone[[31](#_ENREF_31)], whereas chronic exercise training attenuates renin-angiotensin system at resting condition[[32](#_ENREF_32)]. A study on patients with MI has demonstrated that the resting plasma AngII reduced by 26% after 4 mo of exercise training[[32](#_ENREF_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](#_ENREF_33)].

In a previous study[[34](#_ENREF_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, angiotensin converting enzyme (ACE), Angiotensin II (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](#_ENREF_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](#_ENREF_36),[37](#_ENREF_37)]. In a subsequent study[[38](#_ENREF_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](#_ENREF_35),[38](#_ENREF_39)]. 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](#_ENREF_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](#_ENREF_40)]; 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](#_ENREF_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](#_ENREF_4),[6](#_ENREF_6),[7](#_ENREF_7),[40-45](#_ENREF_41)]. However, careful inspection of these studies indicate that after small MI, exercise has no detrimental effect[[7](#_ENREF_7),[41](#_ENREF_42)], or even improves[[4](#_ENREF_4),[43](#_ENREF_44),[44](#_ENREF_45),[46](#_ENREF_47)] LV geometry and function, independent and irrespective of whether exercise was started late (1 year)[[4](#_ENREF_4),[44](#_ENREF_45)] or early (< 2 mo)[[7](#_ENREF_7),[41](#_ENREF_42),[43](#_ENREF_44)] after MI. Conversely, in patients with large MI (encompassing 35% to 50% of LV mass), exercise had either no[[42](#_ENREF_43)], or a beneficial[[4](#_ENREF_4)] effect on ejectionfraction (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](#_ENREF_6),[7](#_ENREF_7),[41](#_ENREF_42)], or even a detrimental[[40](#_ENREF_41),[47](#_ENREF_48)] 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](#_ENREF_46),[48](#_ENREF_49)], or even blunts[[49-51](#_ENREF_50)] LV dilation and hypertrophy. Contrarily, exercise started < 1 wk after moderate to large MI resulted in variable outcomes with beneficial[[52](#_ENREF_53)], no[[53](#_ENREF_54),[54](#_ENREF_55)], or detrimental[[55](#_ENREF_56),[56](#_ENREF_57)] 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](#_ENREF_46),[48-50](#_ENREF_49)], whereas early exercise studies used swimming[[51-55](#_ENREF_52)]. 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](#_ENREF_58),[58](#_ENREF_59)].

Amazingly, in a recent study of evaluating 8-wk of volunteerexercise, de Waard *et al*[[59](#_ENREF_60)] 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/dtP30 from 5295 ± 207 to 5794 ± 207 mmHg/s, and reduced pulmonary congestion. Additionally, this study also provided novel information regarding myocardial Ca2+ handling after MI, debunking the previously held notion that exercise sensitizes myofilaments to the effects of Ca2+[[59](#_ENREF_60)]. A study from our group[[34](#_ENREF_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 in sedentary rats. These finding suggest that exercise training does not cause LV dilation and preserves LV function.

**POST-MI EXERCISE AND MYOCARDIAL CONTRACTION**

Ca2+ 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 Ca2+ sensitivity of the myofilaments[[60](#_ENREF_61)]. As a result, the authors attributed the increased post-MI Ca2+ sensitivity to reduced protein kinase A-mediated troponin I (TnI) phosphorylation[[60](#_ENREF_61)]. Similarly, increased myofilament Ca2+ 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](#_ENREF_60)], which differs from previous studies relying on simultaneous measurements of FS% and Ca2+ fluorescence in unloaded myocytes to estimate myofilament Ca2+ 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 Ca2+ 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](#_ENREF_52)]. Thus, data from de Waard et al 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 Ca2+ transient amplitude was not found to be altered by exercise. Furthermore, basal Ca2+ was reduced by exercise, altogether suggesting that exercise decreases myofilament Ca2+ sensitivity[[59](#_ENREF_60)].

Dysregulation of cardiac ß-adrenergic receptor (ß-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 ß-AR signaling are mainly attributed to ß1-AR downregulation and desensitization/uncoupling of both ß1 and ß2-AR’s. It has been reported that exercise after MI increases ß1-AR, as evidenced by a 48% increase in ß1-AR protein, and a 36% increase in cAMP levels, and improves ß-AR signaling[[59](#_ENREF_60),[61](#_ENREF_62)], 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](#_ENREF_63)]. The isoform α-MHC elicits two to three times faster actin-activated ATPase activity and actin filament sliding velocity than the isoform MHC-ß[[63](#_ENREF_64),[64](#_ENREF_65)]. 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](#_ENREF_66)]; in fact, in the absence of TH, the α-MHC gene is not transcribed[[62](#_ENREF_63)]. Triiodothyronine (T3), the active cellular form of TH, mediates its actions upon binding to thyroid hormone receptors (TRs)[[66](#_ENREF_67),[67](#_ENREF_68)].

After MI, T3 levels are significantly reduced in patients[[68](#_ENREF_69)]; 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](#_ENREF_70)]. In experimental post-MI rat models, following the decrease of serum T3, significant downregulation of α-MHC and the concomitant upregulation of MHC-ß are observed in the LV non-infarcted myocardium, along with changes in TR isoforms at the mRNA level[[68](#_ENREF_69),[70](#_ENREF_71),[71](#_ENREF_72)]. 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](#_ENREF_63),[63](#_ENREF_64),[72](#_ENREF_73),[73](#_ENREF_74)]. Interestingly, endurance exercise has been reported to favorably reverse MHC α- to ß- cardiac isoform shifts after MI at both gene and protein levels[[74](#_ENREF_75),[75](#_ENREF_76)], which in turn, may be associated with preserved cardiac functioning, attenuated LV remodeling, and increased myofibril function[[76](#_ENREF_77)]. Recent evidence by our group[[75](#_ENREF_76)] indicated that post-MI exercise training significantly increase cardiac expression of α-MHC and decrease cardiac expression of MHC-ß without changing serum T3 levels. Similarly, unpublished data from our group recently revealed that moderate-intensity treadmill exercise training markedly increased TRα-1 and TRß-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](#_ENREF_78)]. 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 (O2-), hydroxyl (OH-), and peroxynitrite (ONOO-), have an unpaired electron[[78](#_ENREF_79)]. These ROS serve as signaling molecules when in low concentrations; however, they elicit harmful oxidative stress when produced in excess[[79](#_ENREF_80)]. ROS can directly damage the lipids of cell membranes, proteins and both nuclear and mitochondrial DNA resulting in serious or mortal cellular injury[[80](#_ENREF_81)]. 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)[[82](#_ENREF_82),[83](#_ENREF_83)]. SOD catalyzes the dismutation of superoxide (O2-) to hydrogen peroxide (H2O2). Catalase and GPX further metabolize H2O2 to water and oxygen. The non-enzymatic group includes a variety of biologic molecules, such as vitamins E and C[[81](#_ENREF_82),[82](#_ENREF_83)]. 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](#_ENREF_84),[84](#_ENREF_85)]. Heart failure subsequent to myocardial infarction is associated with oxidative stress in both infarcted and noninfarcted myocardium[[83](#_ENREF_84),[85](#_ENREF_86),[86](#_ENREF_87)]. Researchers have identified a membrane-based NAD(P)H oxidase as a major source of O2- in the heart[[87](#_ENREF_88)]. 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](#_ENREF_89)]. Furthermore, progressive decrease in antioxidant enzymes, SOD, catalase[[89](#_ENREF_90)], and glutathione (an antioxidant)[[90](#_ENREF_91)] 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](#_ENREF_92)].

There is growing evidence that chronic exercise training adaptively bolsters the activity of protective antioxidant enzymes such as catalase, SOD, GPX[[93](#_ENREF_93)], glutathione reductase (GR)[[93](#_ENREF_94)], and antioxidant glutathione content[[94](#_ENREF_95),[95](#_ENREF_96)] 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](#_ENREF_97)]. In contrast, the muscle Mn-SOD gene expression of untrained rats was significantly decreased after an acute bout of exercise[[96](#_ENREF_97)]. Exercise training also resulted in significant increase in SOD activity in the left ventricle (LV) of normal rats[[97](#_ENREF_98),[98](#_ENREF_99)]. 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](#_ENREF_100)]. 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](#_ENREF_101)].

Inconsistent findings have been reported on the effect of post-MI exercise training on ROS and antioxidants. Yamashita *et al***[**[**101**](#_ENREF_102)**] and Brown *et al*[**[**102**](#_ENREF_103)**] 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**](#_ENREF_104)**,**[**104**](#_ENREF_105)**] and** only certain cardiac antioxidant enzyme activities (*i.e.*, SOD) were enhanced in the exercise trained animals[[97](#_ENREF_98),[101](#_ENREF_102),[105](#_ENREF_106)]**.** 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**](#_ENREF_107)**] 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 AngII 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 AngII (AngII) stimulates NAD(P)H oxidase activity, which promotes ROS production[[107](#_ENREF_108),[108](#_ENREF_109)]. Thus, exercise training may improve antioxidant capacity and attenuate oxidative stress by attenuating RAAS[[35](#_ENREF_35),[38](#_ENREF_38),[106](#_ENREF_107)].

**MYOCARDIAL APOPTOSIS AND EXERCISE TRAINING**

Loss of cardiomyocytes is an important mechanism in the development of myocardial remodeling and cardiac failure[[109](#_ENREF_110)]. After MI, apoptotic cardiomyocyte death occurs in the infarcted myocardium as well as the surviving portions of the heart[[110](#_ENREF_111),[111](#_ENREF_112)]. Myocyte apoptosis not only occurs at early phase (7 d) of MI[[112](#_ENREF_113),[113](#_ENREF_114)], but also progresses to late phase (up to 6 mo) in myocardium remote from the area of ischemic damage[[114](#_ENREF_115),[115](#_ENREF_116)], contributing to CHF[[116](#_ENREF_117)]. ROS have proven to be powerful mediators of myocyte apoptosis[[117](#_ENREF_118),[118](#_ENREF_119)]. Treatment of cardiac myocytes with O2- or H2O2 induces apoptosis, suggesting a mechanism of ROS as an initial pathogenic event[[119](#_ENREF_120)]*.* Enhanced pro-apoptotic Bax expression coexists with oxidative stress and apoptosis in the infarcted heart[[120](#_ENREF_121)], whereas oxidative stress activates pro-apoptotic enzymes, caspase-9 and caspase-3, resulting in cardiac apoptosis and ventricular dysfunction[[117](#_ENREF_118)]. *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](#_ENREF_122),[122](#_ENREF_123)].

Siu *et al*[[98](#_ENREF_99)] 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](#_ENREF_100)]. 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](#_ENREF_124)]. Although compensatory angiogenesis can be observed in both the ischemic and infarcted heart, previous studies have demonstrated that angiogenesis may be inadequate[[124](#_ENREF_125),[125](#_ENREF_126)]; in fact, recent evidence suggests that impaired angiogenesis may lead to maladaptive left ventricular (LV) remodeling, promoting the transition from adaptive cardiac hypertrophy to LV dilation and dysfunction[[61](#_ENREF_62),[126](#_ENREF_127)].

Exercise, through increased vascular shear stress, potentiates a powerful angiogenic stimulus[[127](#_ENREF_128)]. The pro-angiogenic effect of exercise has previously been demonstrated in healthy swine hearts[[128](#_ENREF_129)]. A study conducted by Leosco *et al*[[61](#_ENREF_62)] 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](#_ENREF_130)], which represent critical molecular mechanisms by which exercise triggers angiogenesis[[130](#_ENREF_131)]. In addition, exercise-induced upregulation of VEGF in patients with heart failure has also been documented[[132](#_ENREF_133)]. 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](#_ENREF_134),[134](#_ENREF_135)], which likely contributes to arterial dysfunction[[135](#_ENREF_136),[136](#_ENREF_137)]; 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](#_ENREF_138)].

**EXERCISE-BASED CR IN PATIENTS WITH HEART DISEASE**

Previously, four meta-analyses[[138-141](#_ENREF_139)] 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](#_ENREF_143)] 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](#_ENREF_143)]. 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](#_ENREF_3)]. In a stratified analysis, treatment effects were consistent regardless of study periods, duration of CR, or time beyond the active intervention[[3](#_ENREF_3)]. Additionally, Exercise-based CR had favorable effects on cardiovascular risk factors, including smoking, blood pressure, body weight, and lipid profile[[143](#_ENREF_144)].

**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](#_ENREF_29),[30](#_ENREF_30)], ACE, AngII, and aldosterone[[31](#_ENREF_31),[34](#_ENREF_34)]. The attenuation of AngII, in turn, reduces cardiac fibrosis[[34](#_ENREF_34)] and aldosterone secretion[[32](#_ENREF_32),[34](#_ENREF_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](#_ENREF_39)]. Studies show that physical training significantly improves ß-adrenergic receptor, cAMP[[59](#_ENREF_60),[61](#_ENREF_62)], and favorably reverses MHC α- to ß-cardiac isoform shifts[[74](#_ENREF_75),[75](#_ENREF_76)], attributing to improvement in myocardial contractility. In addition, post-MI physical training may enhance antioxidant enzyme capacity and attenuate oxidative stress[[97](#_ENREF_98),[101](#_ENREF_102),[105](#_ENREF_106)]. 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.

**REFERENCES**

1 **Gheorghiade M**, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. *Circulation* 1998; **97**: 282-289 [PMID: 9462531 DOI: 10.1161/01.CIR.97.3.282]

2 **Kokkinos PF**, Choucair W, Graves P, Papademetriou V, Ellahham S. Chronic heart failure and exercise. *Am Heart J* 2000; **140**: 21-28 [PMID: 10874259 DOI: 10.1067/mhj.2000.106916]

3 **Lawler PR**, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. *Am Heart J* 2011; **162**: 571-584.e2 [PMID: 21982647 DOI: 10.1016/j.ahj.2011.07.017]

4 **Giannuzzi P**, Temporelli PL, Corrà U, Tavazzi L. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) Trial. *Circulation* 2003; **108**: 554-559 [PMID: 12860904 DOI: 10.1161/01.CIR.0000081780.38477.FA]

5 **Naughton J**, Dorn J, Oberman A, Gorman PA, Cleary P. Maximal exercise systolic pressure, exercise training, and mortality in myocardial infarction patients. *Am J Cardiol* 2000; **85**: 416-420 [PMID: 10728943 DOI: 10.1016/S0002-9149(99)00765-1]

6 **Dubach P**, Myers J, Dziekan G, Goebbels U, Reinhart W, Vogt P, Ratti R, Muller P, Miettunen R, Buser P. Effect of exercise training on myocardial remodeling in patients with reduced left ventricular function after myocardial infarction: application of magnetic resonance imaging. *Circulation* 1997; **95**: 2060-2067 [PMID: 9133516 DOI: 10.1161/01.CIR.95.8.2060]

7 **Giannuzzi P**, Tavazzi L, Temporelli PL, Corrà U, Imparato A, Gattone M, Giordano A, Sala L, Schweiger C, Malinverni C. Long-term physical training and left ventricular remodeling after anterior myocardial infarction: results of the Exercise in Anterior Myocardial Infarction (EAMI) trial. EAMI Study Group. *J Am Coll Cardiol* 1993; **22**: 1821-1829 [PMID: 8245335 DOI: 10.1016/0735-1097(93)90764-R]

8 **Adamopoulos S**, Coats AJ, Brunotte F, Arnolda L, Meyer T, Thompson CH, Dunn JF, Stratton J, Kemp GJ, Radda GK. Physical training improves skeletal muscle metabolism in patients with chronic heart failure. *J Am Coll Cardiol* 1993; **21**: 1101-1106 [PMID: 8459063 DOI: 10.1016/0735-1097(93)90231-O]

9 **Tyni-Lenné R**, Gordon A, Europe E, Jansson E, Sylvén C. Exercise-based rehabilitation improves skeletal muscle capacity, exercise tolerance, and quality of life in both women and men with chronic heart failure. *J Card Fail* 1998; **4**: 9-17 [PMID: 9573499 DOI: 10.1016/S1071-9164(98)90503-6]

10 **Coats AJ**, Adamopoulos S, Radaelli A, McCance A, Meyer TE, Bernardi L, Solda PL, Davey P, Ormerod O, Forfar C. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation* 1992; **85**: 2119-2131 [PMID: 1591831 DOI: 10.1161/01.CIR.85.6.2119]

11 **Hambrecht R**, Niebauer J, Fiehn E, Kälberer B, Offner B, Hauer K, Riede U, Schlierf G, Kübler W, Schuler G. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *J Am Coll Cardiol* 1995; **25**: 1239-1249 [PMID: 7722116 DOI: 10.1016/0735-1097(94)00568-B]

12 **Schuler G**, Hambrecht R, Schlierf G, Grunze M, Methfessel S, Hauer K, Kübler W. Myocardial perfusion and regression of coronary artery disease in patients on a regimen of intensive physical exercise and low fat diet. *J Am Coll Cardiol* 1992; **19**: 34-42 [PMID: 1729343 DOI: 10.1016/0735-1097(92)90048-R]

13 **Galli M**, Marcassa C, Bolli R, Giannuzzi P, Temporelli PL, Imparato A, Silva Orrego PL, Giubbini R, Giordano A, Tavazzi L. Spontaneous delayed recovery of perfusion and contraction after the first 5 weeks after anterior infarction. Evidence for the presence of hibernating myocardium in the infarcted area. *Circulation* 1994; **90**: 1386-1397 [PMID: 8087949 DOI: 10.1161/01.CIR.90.3.1386]

14 **Fletcher GF**, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Piña IL, Rodney R, Simons-Morton DA, Williams MA, Bazzarre T. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation* 2001; **104**: 1694-1740 [PMID: 11581152 DOI: 10.1161/hc3901.095960]

15 **Suaya JA**, Shepard DS, Normand SL, Ades PA, Prottas J, Stason WB. Use of cardiac rehabilitation by Medicare beneficiaries after myocardial infarction or coronary bypass surgery. *Circulation* 2007; **116**: 1653-1662 [PMID: 17893274 DOI: 10.1161/CIRCULATIONAHA.107.701466]

16 **Remes J**. Neuroendocrine activation after myocardial infarction. *Br Heart J* 1994; **72**: S65-S69 [PMID: 7946807]

17 **Sutton MG**, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. *Circulation* 2000; **101**: 2981-2988 [PMID: 10869273 DOI: 10.1161/01.CIR.101.25.2981]

18 **White M**, Rouleau JL, Hall C, Arnold M, Harel F, Sirois P, Greaves S, Solomon S, Ajani U, Glynn R, Hennekens C, Pfeffer M. Changes in vasoconstrictive hormones, natriuretic peptides, and left ventricular remodeling soon after anterior myocardial infarction. *Am Heart J* 2001; **142**: 1056-1064 [PMID: 11717612 DOI: 10.1067/mhj.2001.119612]

19 **Hoogsteen J**, Hoogeveen A, Schaffers H, Wijn PF, van Hemel NM, van der Wall EE. Myocardial adaptation in different endurance sports: an echocardiographic study. *Int J Cardiovasc Imaging* 2004; **20**: 19-26 [PMID: 15055817 DOI: 10.1023/B: CAIM.0000013160.79903.19]

20 **Colucci WS**. Molecular and cellular mechanisms of myocardial failure. *Am J Cardiol* 1997; **80**: 15L-25L [PMID: 9412539 DOI: 10.1016/S0002-9149(97)00845-X]

21 **Kim S**, Ohta K, Hamaguchi A, Omura T, Yukimura T, Miura K, Inada Y, Wada T, Ishimura Y, Chatani F. Role of angiotensin II in renal injury of deoxycorticosterone acetate-salt hypertensive rats. *Hypertension* 1994; **24**: 195-204 [PMID: 8039844 DOI: 10.1161/01.HYP.24.2.195]

22 **Sun Y**, Zhang JQ, Zhang J, Ramires FJ. Angiotensin II, transforming growth factor-beta1 and repair in the infarcted heart. *J Mol Cell Cardiol* 1998; **30**: 1559-1569 [PMID: 9737942 DOI: 10.1006/jmcc.1998.0721]

23 **Sun Y**, Zhang J, Zhang JQ, Ramires FJ. Local angiotensin II and transforming growth factor-beta1 in renal fibrosis of rats. *Hypertension* 2000; **35**: 1078-1084 [PMID: 10818068 DOI: 10.1161/01.HYP.35.5.1078]

24 **Sun Y**, Weber KT. Angiotensin II receptor binding following myocardial infarction in the rat. *Cardiovasc Res* 1994; **28**: 1623-1628 [PMID: 7842454]

25 **Sun Y**, Zhang JQ, Zhang J, Lamparter S. Cardiac remodeling by fibrous tissue after infarction in rats. *J Lab Clin Med* 2000; **135**: 316-323 [PMID: 10779047 DOI: 10.1067/mlc.2000.105971]

26 **Sun Y**, Weber KT. Angiotensin-converting enzyme and wound healing in diverse tissues of the rat. *J Lab Clin Med* 1996; **127**: 94-101 [PMID: 8592101 DOI: 10.1016/S0022-2143(96)90170-5]

27 **Pfeffer MA**, Braunwald E, Moyé LA, Basta L, Brown EJ, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992; **327**: 669-677 [PMID: 1386652 DOI: 10.1056/NEJM199209033271001]

28 **Linz W**, Wiemer G, Schmidts HL, Ulmer W, Ruppert D, Schölkens BA. ACE inhibition decreases postoperative mortality in rats with left ventricular hypertrophy and myocardial infarction. *Clin Exp Hypertens* 1996; **18**: 691-712 [PMID: 8781754 DOI: 10.3109/10641969609081775]

29 **Staessen J**, Fagard R, Hespel P, Lijnen P, Vanhees L, Amery A. Plasma renin system during exercise in normal men. *J Appl Physiol (1985)* 1987; **63**: 188-194 [PMID: 3305466]

30 **Wade CE**, Claybaugh JR. Plasma renin activity, vasopressin concentration, and urinary excretory responses to exercise in men. *J Appl Physiol Respir Environ Exerc Physiol* 1980; **49**: 930-936 [PMID: 7002889]

31 **Convertino VA**, Keil LC, Greenleaf JE. Plasma volume, renin, and vasopressin responses to graded exercise after training. *J Appl Physiol Respir Environ Exerc Physiol* 1983; **54**: 508-514 [PMID: 6339451]

32 **Braith RW**, Welsch MA, Feigenbaum MS, Kluess HA, Pepine CJ. Neuroendocrine activation in heart failure is modified by endurance exercise training. *J Am Coll Cardiol* 1999; **34**: 1170-1175 [PMID: 10520808 DOI: 10.1016/S0735-1097(99)00339-3]

33 **Liu JL**, Irvine S, Reid IA, Patel KP, Zucker IH. Chronic exercise reduces sympathetic nerve activity in rabbits with pacing-induced heart failure: A role for angiotensin II. *Circulation* 2000; **102**: 1854-1862 [PMID: 11023943 DOI: 10.1161/01.CIR.102.15.1854]

34 **Wan W**, Powers AS, Li J, Ji L, Erikson JM, Zhang JQ. Effect of post-myocardial infarction exercise training on the renin-angiotensin-aldosterone system and cardiac function. *Am J Med Sci* 2007; **334**: 265-273 [PMID: 18030183 DOI: 10.1097/MAJ.0b013e318068b5ed]

35 **Xu X**, Wan W, Powers AS, Li J, Ji LL, Lao S, Wilson B, Erikson JM, Zhang JQ. Effects of exercise training on cardiac function and myocardial remodeling in post myocardial infarction rats. *J Mol Cell Cardiol* 2008; **44**: 114-122 [PMID: 17980387 DOI: 10.1016/j.yjmcc.2007.10.004]

36 **Fraccarollo D**, Galuppo P, Hildemann S, Christ M, Ertl G, Bauersachs J. Additive improvement of left ventricular remodeling and neurohormonal activation by aldosterone receptor blockade with eplerenone and ACE inhibition in rats with myocardial infarction. *J Am Coll Cardiol* 2003; **42**: 1666-1673 [PMID: 14607457 DOI: 10.1016/j.cardiores.2005.03.001]

37 **Fraccarollo D**, Galuppo P, Schmidt I, Ertl G, Bauersachs J. Additive amelioration of left ventricular remodeling and molecular alterations by combined aldosterone and angiotensin receptor blockade after myocardial infarction. *Cardiovasc Res* 2005; **67**: 97-105 [PMID: 15949473]

38 **Xu X**, Wan W, Ji L, Lao S, Powers AS, Zhao W, Erikson JM, Zhang JQ. Exercise training combined with angiotensin II receptor blockade limits post-infarct ventricular remodelling in rats. *Cardiovasc Res* 2008; **78**: 523-532 [PMID: 18252761]

39 **Kramer CM**, Lima JA, Reichek N, Ferrari VA, Llaneras MR, Palmon LC, Yeh IT, Tallant B, Axel L. Regional differences in function within noninfarcted myocardium during left ventricular remodeling. *Circulation* 1993; **88**: 1279-1288 [PMID: 8353890 DOI: 10.1161/01.CIR.88.3.1279]

40 **Kubo N**, Ohmura N, Nakada I, Yasu T, Katsuki T, Fujii M, Saito M. Exercise at ventilatory threshold aggravates left ventricular remodeling in patients with extensive anterior acute myocardial infarction. *Am Heart J* 2004; **147**: 113-120 [PMID: 14691428 DOI: 10.1016/S0002-8703(03)00521-0]

41 **Otsuka Y**, Takaki H, Okano Y, Satoh T, Aihara N, Matsumoto T, Yasumura Y, Morii I, Goto Y. Exercise training without ventricular remodeling in patients with moderate to severe left ventricular dysfunction early after acute myocardial infarction. *Int J Cardiol* 2003; **87**: 237-244 [PMID: 12559545 DOI: 10.1016/S0167-5273(02)00251-6]

42 **Sullivan MJ**, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction. Hemodynamic and metabolic effects. *Circulation* 1988; **78**: 506-515 [PMID: 3409495 DOI: 10.1161/01.CIR.78.3.506]

43 **Koizumi T**, Miyazaki A, Komiyama N, Sun K, Nakasato T, Masuda Y, Komuro I. Improvement of left ventricular dysfunction during exercise by walking in patients with successful percutaneous coronary intervention for acute myocardial infarction. *Circ J* 2003; **67**: 233-237 [PMID: 12604873 DOI: 10.1253/circj.67.233]

44 **Ehsani AA**, Biello DR, Schultz J, Sobel BE, Holloszy JO. Improvement of left ventricular contractile function by exercise training in patients with coronary artery disease. *Circulation* 1986; **74**: 350-358 [PMID: 3731425 DOI: 10.1161/01.CIR.74.2.350]

45 **Musch TI**, Moore RL, Leathers DJ, Bruno A, Zelis R. Endurance training in rats with chronic heart failure induced by myocardial infarction. *Circulation* 1986; **74**: 431-441 [PMID: 3731431 DOI: 10.1161/01.CIR.74.2.431]

46 **Giallauria F**, Acampa W, Ricci F, Vitelli A, Torella G, Lucci R, Del Prete G, Zampella E, Assante R, Rengo G, Leosco D, Cuocolo A, Vigorito C. Exercise training early after acute myocardial infarction reduces stress-induced hypoperfusion and improves left ventricular function. *Eur J Nucl Med Mol Imaging* 2013; **40**: 315-324 [PMID: 23224706 DOI: 10.1007/s00259-012-2302-x]

47 **Kushner EC**. Exercise training after anterior Q wave myocardial infarction: importance of regional left ventricular function and topography. *J Am Coll Cardiol* 1989; **13**: 1451 [PMID: 2765017 DOI: 10.1016/0735-1097(89)90328-8]

48 **Libonati JR**. Exercise and diastolic function after myocardial infarction. *Med Sci Sports Exerc* 2003; **35**: 1471-1476 [PMID: 12972864 DOI: 10.1249/01.MSS.0000084420.77802.DA]

49 **Orenstein TL**, Parker TG, Butany JW, Goodman JM, Dawood F, Wen WH, Wee L, Martino T, McLaughlin PR, Liu PP. Favorable left ventricular remodeling following large myocardial infarction by exercise training. Effect on ventricular morphology and gene expression. *J Clin Invest* 1995; **96**: 858-866 [PMID: 7635980 DOI: 10.1172/JCI118132]

50 **Zhang LQ**, Zhang XQ, Musch TI, Moore RL, Cheung JY. Sprint training restores normal contractility in postinfarction rat myocytes. *J Appl Physiol (1985)* 2000; **89**: 1099-1105 [PMID: 10956356]

51 **Wisløff U**, Loennechen JP, Currie S, Smith GL, Ellingsen Ø. Aerobic exercise reduces cardiomyocyte hypertrophy and increases contractility, Ca2+ sensitivity and SERCA-2 in rat after myocardial infarction. *Cardiovasc Res* 2002; **54**: 162-174 [PMID: 12062372 DOI: 10.1016/S0008-6363(01)00565-X]

52 **Oh BH**, Ono S, Rockman HA, Ross J. Myocardial hypertrophy in the ischemic zone induced by exercise in rats after coronary reperfusion. *Circulation* 1993; **87**: 598-607 [PMID: 8425304 DOI: 10.1161/01.CIR.87.2.598]

53 **Alhaddad IA**, Hakim I, Siddiqi F, Lagenback E, Mallavarapu C, Nethala V, Mounce D, Ross PL, Brown EJ. Early exercise after experimental myocardial infarction: effect on left ventricular remodeling. *Coron Artery Dis* 1998; **9**: 319-327 [PMID: 9812181]

54 **Hochman JS**, Healy B. Effect of exercise on acute myocardial infarction in rats. *J Am Coll Cardiol* 1986; **7**: 126-132 [PMID: 3941199 DOI: 10.1016/S0735-1097(86)80269-8]

55 **Gaudron P**, Hu K, Schamberger R, Budin M, Walter B, Ertl G. Effect of endurance training early or late after coronary artery occlusion on left ventricular remodeling, hemodynamics, and survival in rats with chronic transmural myocardial infarction. *Circulation* 1994; **89**: 402-412 [PMID: 8281676 DOI: 10.1161/01.CIR.89.1.402]

56 **Kloner RA**, Kloner JA. The effect of early exercise on myocardial infarct scar formation. *Am Heart J* 1983; **106**: 1009-1013 [PMID: 6637761 DOI: 10.1016/0002-8703(83)90645-2]

57 **Flaim SF**, Minteer WJ, Clark DP, Zelis R. Cardiovascular response to acute aquatic and treadmill exercise in the untrained rat. *J Appl Physiol Respir Environ Exerc Physiol* 1979; **46**: 302-308 [PMID: 422445]

58 **Bernstein D**. Exercise assessment of transgenic models of human cardiovascular disease. *Physiol Genomics* 2003; **13**: 217-226 [PMID: 12746466 DOI: 10.1152/physiolgenomics.00188.2002]

59 **de Waard MC**, van der Velden J, Bito V, Ozdemir S, Biesmans L, Boontje NM, Dekkers DH, Schoonderwoerd K, Schuurbiers HC, de Crom R, Stienen GJ, Sipido KR, Lamers JM, Duncker DJ. Early exercise training normalizes myofilament function and attenuates left ventricular pump dysfunction in mice with a large myocardial infarction. *Circ Res* 2007; **100**: 1079-1088 [PMID: 17347478 DOI: 10.1161/01.RES.0000262655.16373.37]

60 **van der Velden J**, Merkus D, Klarenbeek BR, James AT, Boontje NM, Dekkers DH, Stienen GJ, Lamers JM, Duncker DJ. Alterations in myofilament function contribute to left ventricular dysfunction in pigs early after myocardial infarction. *Circ Res* 2004; **95**: e85-e95 [PMID: 15528471 DOI: 10.1161/01.RES.0000149531.02904.09]

61 **Leosco D**, Rengo G, Iaccarino G, Golino L, Marchese M, Fortunato F, Zincarelli C, Sanzari E, Ciccarelli M, Galasso G, Altobelli GG, Conti V, Matrone G, Cimini V, Ferrara N, Filippelli A, Koch WJ, Rengo F. Exercise promotes angiogenesis and improves beta-adrenergic receptor signalling in the post-ischaemic failing rat heart. *Cardiovasc Res* 2008; **78**: 385-394 [PMID: 18093988 DOI: 10.1093/cvr/cvm109]

62 **Nadal-Ginard B**, Mahdavi V. Molecular basis of cardiac performance. Plasticity of the myocardium generated through protein isoform switches. *J Clin Invest* 1989; **84**: 1693-1700 [PMID: 2687327 DOI: 10.1172/JCI114351]

63 **Krenz M**, Robbins J. Impact of beta-myosin heavy chain expression on cardiac function during stress. *J Am Coll Cardiol* 2004; **44**: 2390-2397 [PMID: 15607403 DOI: 10.1016/j.jacc.2004.09.044]

64 **Herron TJ**, McDonald KS. Small amounts of alpha-myosin heavy chain isoform expression significantly increase power output of rat cardiac myocyte fragments. *Circ Res* 2002; **90**: 1150-1152 [PMID: 12065316 DOI: 10.1161/01.RES.0000022879.57270.11]

65 **Klein I**, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med* 2001; **344**: 501-509 [PMID: 11172193 DOI: 10.1056/NEJM200102153440707]

66 **Dillmann WH**. Biochemical basis of thyroid hormone action in the heart. *Am J Med* 1990; **88**: 626-630 [PMID: 2189306 DOI: 10.1016/0002-9343(90)90530-Q]

67 **Brent GA**. The molecular basis of thyroid hormone action. *N Engl J Med* 1994; **331**: 847-853 [PMID: 8078532 DOI: 10.1056/NEJM199409293311306]

68 **Pantos C**, Mourouzis I, Saranteas T, Paizis I, Xinaris C, Malliopoulou V, Cokkinos DV. Thyroid hormone receptors alpha1 and beta1 are downregulated in the post-infarcted rat heart: consequences on the response to ischaemia-reperfusion. *Basic Res Cardiol* 2005; **100**: 422-432 [PMID: 16133716 DOI: 10.1007/s00395-005-0545-4]

69 **Hamilton MA**, Stevenson LW, Luu M, Walden JA. Altered thyroid hormone metabolism in advanced heart failure. *J Am Coll Cardiol* 1990; **16**: 91-95 [PMID: 2358611 DOI: 10.1016/0735-1097(90)90462-X]

70 **Kinugawa K**, Yonekura K, Ribeiro RC, Eto Y, Aoyagi T, Baxter JD, Camacho SA, Bristow MR, Long CS, Simpson PC. Regulation of thyroid hormone receptor isoforms in physiological and pathological cardiac hypertrophy. *Circ Res* 2001; **89**: 591-598 [PMID: 11577024 DOI: 10.1161/hh1901.096706]

71 **Pantos C**, Mourouzis I, Xinaris C, Kokkinos AD, Markakis K, Dimopoulos A, Panagiotou M, Saranteas T, Kostopanagiotou G, Cokkinos DV. Time-dependent changes in the expression of thyroid hormone receptor alpha 1 in the myocardium after acute myocardial infarction: possible implications in cardiac remodelling. *Eur J Endocrinol* 2007; **156**: 415-424 [PMID: 17389455 DOI: 10.1530/EJE-06-0707]

72 **Yue P**, Long CS, Austin R, Chang KC, Simpson PC, Massie BM. Post-infarction heart failure in the rat is associated with distinct alterations in cardiac myocyte molecular phenotype. *J Mol Cell Cardiol* 1998; **30**: 1615-1630 [PMID: 9737947 DOI: 10.1006/jmcc.1998.0727]

73 **Rafalski K**, Abdourahman A, Edwards JG. Early adaptations to training: upregulation of alpha-myosin heavy chain gene expression. *Med Sci Sports Exerc* 2007; **39**: 75-82 [PMID: 17218887 DOI: 10.1249/01.mss.0000240324.08406.3d]

74 **Ojamaa K**, Kenessey A, Shenoy R, Klein I. Thyroid hormone metabolism and cardiac gene expression after acute myocardial infarction in the rat. *Am J Physiol Endocrinol Metab* 2000; **279**: E1319-E1324 [PMID: 11093920]

75 **Wan W**, Xu X, Zhao W, Garza MA, Zhang JQ. Exercise training induced myosin heavy chain isoform alteration in the infarcted heart. *Appl Physiol Nutr Metab* 2014; **39**: 226-232 [PMID: 24476479 DOI: 10.1139/apnm-2013-0268]

76 **Hashimoto T**, Kambara N, Nohara R, Yazawa M, Taguchi S. Expression of MHC-beta and MCT1 in cardiac muscle after exercise training in myocardial-infarcted rats. *J Appl Physiol (1985)* 2004; **97**: 843-851 [PMID: 15133008 DOI: 10.1152/japplphysiol.01193.2003]

77 **Morkin E**, Pennock GD, Spooner PH, Bahl JJ, Goldman S. Clinical and experimental studies on the use of 3,5-diiodothyropropionic acid, a thyroid hormone analogue, in heart failure. *Thyroid* 2002; **12**: 527-533 [PMID: 12165118 DOI: 10.1089/105072502760143935]

78 **Sorescu D**, Griendling KK. Reactive oxygen species, mitochondria, and NAD(P)H oxidases in the development and progression of heart failure. *Congest Heart Fail* 2002; **8**: 132-140 [PMID: 12045381 DOI: 10.1111/j.1527-5299.2002.00717.x]

79 **Dröge W**. Free radicals in the physiological control of cell function. *Physiol Rev* 2002; **82**: 47-95 [PMID: 11773609 DOI: 10.1152/physrev.00018.2001]

80 **Lefer DJ**, Granger DN. Oxidative stress and cardiac disease. *Am J Med* 2000; **109**: 315-323 [PMID: 10996583 DOI: 10.1016/S0002-9343(00)00467-8]

81 **Dhalla AK**, Singal PK. Antioxidant changes in hypertrophied and failing guinea pig hearts. *Am J Physiol* 1994; **266**: H1280-H1285 [PMID: 8184905]

82 **Vaziri ND**, Lin CY, Farmand F, Sindhu RK. Superoxide dismutase, catalase, glutathione peroxidase and NADPH oxidase in lead-induced hypertension. *Kidney Int* 2003; **63**: 186-194 [PMID: 12472782 DOI: 10.1046/j.1523-1755.2003.00711.x]

83 **Heymes C**, Bendall JK, Ratajczak P, Cave AC, Samuel JL, Hasenfuss G, Shah AM. Increased myocardial NADPH oxidase activity in human heart failure. *J Am Coll Cardiol* 2003; **41**: 2164-2171 [PMID: 12821241 DOI: 10.1016/S0735-1097(03)00471-6]

84 **Keith M**, Geranmayegan A, Sole MJ, Kurian R, Robinson A, Omran AS, Jeejeebhoy KN. Increased oxidative stress in patients with congestive heart failure. *J Am Coll Cardiol* 1998; **31**: 1352-1356 [PMID: 9581732 DOI: 10.1016/S0735-1097(98)00101-6]

85 **Yücel D**, Aydoğdu S, Cehreli S, Saydam G, Canatan H, Seneş M, Ciğdem Topkaya B, Nebioğlu S. Increased oxidative stress in dilated cardiomyopathic heart failure. *Clin Chem* 1998; **44**: 148-154 [PMID: 9550572]

86 **Nakamura K**, Kusano K, Nakamura Y, Kakishita M, Ohta K, Nagase S, Yamamoto M, Miyaji K, Saito H, Morita H, Emori T, Matsubara H, Toyokuni S, Ohe T. Carvedilol decreases elevated oxidative stress in human failing myocardium. *Circulation* 2002; **105**: 2867-2871 [PMID: 12070115 DOI: 10.1161/01.CIR.0000018605.14470.DD]

87 **Mohazzab-H KM**, Kaminski PM, Wolin MS. Lactate and PO2 modulate superoxide anion production in bovine cardiac myocytes: potential role of NADH oxidase. *Circulation* 1997; **96**: 614-620 [PMID: 9244234 DOI: 10.1161/01.CIR.96.2.614]

88 **Fukui T**, Yoshiyama M, Hanatani A, Omura T, Yoshikawa J, Abe Y. Expression of p22-phox and gp91-phox, essential components of NADPH oxidase, increases after myocardial infarction. *Biochem Biophys Res Commun* 2001; **281**: 1200-1206 [PMID: 11243862 DOI: 10.1006/bbrc.2001.4493]

89 **Hill MF**, Singal PK. Right and left myocardial antioxidant responses during heart failure subsequent to myocardial infarction. *Circulation* 1997; **96**: 2414-2420 [PMID: 9337218 DOI: 10.1161/01.CIR.96.7.2414]

90 **Usal A**, Acartürk E, Yüregir GT, Unlükurt I, Demirci C, Kurt HI, Birand A. Decreased glutathione levels in acute myocardial infarction. *Jpn Heart J* 1996; **37**: 177-182 [PMID: 8676544]

91 **Nakagami H**, Takemoto M, Liao JK. NADPH oxidase-derived superoxide anion mediates angiotensin II-induced cardiac hypertrophy. *J Mol Cell Cardiol* 2003; **35**: 851-859 [PMID: 12818576 DOI: 10.1016/S0022-2828(03)00145-7]

92 **Ji LL**. Antioxidants and oxidative stress in exercise. *Proc Soc Exp Biol Med* 1999; **222**: 283-292 [PMID: 10601887]

93 **Smolka MB**, Zoppi CC, Alves AA, Silveira LR, Marangoni S, Pereira-Da-Silva L, Novello JC, Macedo DV. HSP72 as a complementary protection against oxidative stress induced by exercise in the soleus muscle of rats. *Am J Physiol Regul Integr Comp Physiol* 2000; **279**: R1539-R1545 [PMID: 11049834]

94 **Leeuwenburgh C**, Hollander J, Leichtweis S, Griffiths M, Gore M, Ji LL. Adaptations of glutathione antioxidant system to endurance training are tissue and muscle fiber specific. *Am J Physiol* 1997; **272**: R363-R369 [PMID: 9039030]

95 **Watkins H**, Rosenzweig A, Hwang DS, Levi T, McKenna W, Seidman CE, Seidman JG. Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy. *N Engl J Med* 1992; **326**: 1108-1114 [PMID: 1552912]

96 **Oh-ishi S**, Kizaki T, Nagasawa J, Izawa T, Komabayashi T, Nagata N, Suzuki K, Taniguchi N, Ohno H. Effects of endurance training on superoxide dismutase activity, content and mRNA expression in rat muscle. *Clin Exp Pharmacol Physiol* 1997; **24**: 326-332 [PMID: 9143782 DOI: 10.1111/j.1440-1681.1997.tb01196.x]

97 **Powers SK**, Criswell D, Lawler J, Martin D, Lieu FK, Ji LL, Herb RA. Rigorous exercise training increases superoxide dismutase activity in ventricular myocardium. *Am J Physiol* 1993; **265**: H2094-H2098 [PMID: 8285249]

98 **Siu PM**, Bryner RW, Martyn JK, Alway SE. Apoptotic adaptations from exercise training in skeletal and cardiac muscles. *FASEB J* 2004; **18**: 1150-1152 [PMID: 15132982 DOI: 10.1096/fj.03-1291fje]

99 **Linke A**, Adams V, Schulze PC, Erbs S, Gielen S, Fiehn E, Möbius-Winkler S, Schubert A, Schuler G, Hambrecht R. Antioxidative effects of exercise training in patients with chronic heart failure: increase in radical scavenger enzyme activity in skeletal muscle. *Circulation* 2005; **111**: 1763-1770 [PMID: 15809365 DOI: 10.1161/01.CIR.0000165503.08661.E5]

100 **Adams V**, Linke A, Kränkel N, Erbs S, Gielen S, Möbius-Winkler S, Gummert JF, Mohr FW, Schuler G, Hambrecht R. Impact of regular physical activity on the NAD(P)H oxidase and angiotensin receptor system in patients with coronary artery disease. *Circulation* 2005; **111**: 555-562 [PMID: 15699275 DOI: 10.1161/01.CIR.0000154560.88933.7E]

101 **Yamashita N**, Hoshida S, Otsu K, Asahi M, Kuzuya T, Hori M. Exercise provides direct biphasic cardioprotection via manganese superoxide dismutase activation. *J Exp Med* 1999; **189**: 1699-1706 [PMID: 10359573 DOI: 10.1084/jem.189.11.1699]

102 **Brown DA**, Jew KN, Sparagna GC, Musch TI, Moore RL. Exercise training preserves coronary flow and reduces infarct size after ischemia-reperfusion in rat heart. *J Appl Physiol (1985)* 2003; **95**: 2510-2518 [PMID: 12937028]

103 **Brown DA**, Lynch JM, Armstrong CJ, Caruso NM, Ehlers LB, Johnson MS, Moore RL. Susceptibility of the heart to ischaemia-reperfusion injury and exercise-induced cardioprotection are sex-dependent in the rat. *J Physiol* 2005; **564**: 619-630 [PMID: 15718263 DOI: 10.1113/jphysiol.2004.081323]

104 **Lennon SL**, Quindry JC, Hamilton KL, French JP, Hughes J, Mehta JL, Powers SK. Elevated MnSOD is not required for exercise-induced cardioprotection against myocardial stunning. *Am J Physiol Heart Circ Physiol* 2004; **287**: H975-H980 [PMID: 15031126 DOI: 10.1152/ajpheart.01208.2003]

105 **Somani SM**, Frank S, Rybak LP. Responses of antioxidant system to acute and trained exercise in rat heart subcellular fractions. *Pharmacol Biochem Behav* 1995; **51**: 627-634 [PMID: 7675835 DOI: 10.1016/0091-3057(94)00427-K]

106 **Xu X**, Zhao W, Wan W, Ji LL, Powers AS, Erikson JM, Zhang JQ. Exercise training combined with angiotensin II receptor blockade reduces oxidative stress after myocardial infarction in rats. *Exp Physiol* 2010; **95**: 1008-1015 [PMID: 20660022 DOI: 10.1113/expphysiol.2010.054221]

107 **Gupta M**, Sueblinvong V, Raman J, Jeevanandam V, Gupta MP. Single-stranded DNA-binding proteins PURalpha and PURbeta bind to a purine-rich negative regulatory element of the alpha-myosin heavy chain gene and control transcriptional and translational regulation of the gene expression. Implications in the repression of alpha-myosin heavy chain during heart failure. *J Biol Chem* 2003; **278**: 44935-44948 [PMID: 12933792 DOI: 10.1074/jbc.M307696200]

108 **Griendling KK**, Sorescu D, Ushio-Fukai M. NAD(P)H oxidase: role in cardiovascular biology and disease. *Circ Res* 2000; **86**: 494-501 [PMID: 10720409 DOI: 10.1161/01.RES.86.5.494]

109 **Anversa P**, Cheng W, Liu Y, Leri A, Redaelli G, Kajstura J. Apoptosis and myocardial infarction. *Basic Res Cardiol* 1998; **93** Suppl 3: 8-12 [PMID: 9879436 DOI: 10.1007/s003950050195]

110 **Edwards JG**, Bahl JJ, Flink IL, Cheng SY, Morkin E. Thyroid hormone influences beta myosin heavy chain (beta MHC) expression. *Biochem Biophys Res Commun* 1994; **199**: 1482-1488 [PMID: 8147894]

111 **Kajstura J**, Cheng W, Reiss K, Clark WA, Sonnenblick EH, Krajewski S, Reed JC, Olivetti G, Anversa P. Apoptotic and necrotic myocyte cell deaths are independent contributing variables of infarct size in rats. *Lab Invest* 1996; **74**: 86-107 [PMID: 8569201]

112 **Bialik S**, Geenen DL, Sasson IE, Cheng R, Horner JW, Evans SM, Lord EM, Koch CJ, Kitsis RN. Myocyte apoptosis during acute myocardial infarction in the mouse localizes to hypoxic regions but occurs independently of p53. *J Clin Invest* 1997; **100**: 1363-1372 [PMID: 9294101 DOI: 10.1172/JCI119656]

113 **Li B**, Li Q, Wang X, Jana KP, Redaelli G, Kajstura J, Anversa P. Coronary constriction impairs cardiac function and induces myocardial damage and ventricular remodeling in mice. *Am J Physiol* 1997; **273**: H2508-H2519 [PMID: 9374791]

114 **Sam F**, Sawyer DB, Chang DL, Eberli FR, Ngoy S, Jain M, Amin J, Apstein CS, Colucci WS. Progressive left ventricular remodeling and apoptosis late after myocardial infarction in mouse heart. *Am J Physiol Heart Circ Physiol* 2000; **279**: H422-H428 [PMID: 10899082]

115 **Baldi A**, Abbate A, Bussani R, Patti G, Melfi R, Angelini A, Dobrina A, Rossiello R, Silvestri F, Baldi F, Di Sciascio G. Apoptosis and post-infarction left ventricular remodeling. *J Mol Cell Cardiol* 2002; **34**: 165-174 [PMID: 11851356 DOI: 10.1006/jmcc.2001.1498]

116 **Olivetti G**, Abbi R, Quaini F, Kajstura J, Cheng W, Nitahara JA, Quaini E, Di Loreto C, Beltrami CA, Krajewski S, Reed JC, Anversa P. Apoptosis in the failing human heart. *N Engl J Med* 1997; **336**: 1131-1141 [PMID: 9099657 DOI: 10.1056/NEJM199704173361603]

117 **Cesselli D**, Jakoniuk I, Barlucchi L, Beltrami AP, Hintze TH, Nadal-Ginard B, Kajstura J, Leri A, Anversa P. Oxidative stress-mediated cardiac cell death is a major determinant of ventricular dysfunction and failure in dog dilated cardiomyopathy. *Circ Res* 2001; **89**: 279-286 [PMID: 11485979 DOI: 10.1161/hh1501.094115]

118 **Hare JM**. Oxidative stress and apoptosis in heart failure progression. *Circ Res* 2001; **89**: 198-200 [PMID: 11485969]

119 **von Harsdorf R**, Li PF, Dietz R. Signaling pathways in reactive oxygen species-induced cardiomyocyte apoptosis. *Circulation* 1999; **99**: 2934-2941 [PMID: 10359739 DOI: 10.1161/01.CIR.99.22.2934]

120 **Zhao W**, Lu L, Chen SS, Sun Y. Temporal and spatial characteristics of apoptosis in the infarcted rat heart. *Biochem Biophys Res Commun* 2004; **325**: 605-611 [PMID: 15530436 DOI: 10.1016/j.bbrc.2004.10.064]

121 **Oskarsson HJ**, Coppey L, Weiss RM, Li WG. Antioxidants attenuate myocyte apoptosis in the remote non-infarcted myocardium following large myocardial infarction. *Cardiovasc Res* 2000; **45**: 679-687 [PMID: 10728389 DOI: 10.1016/S0008-6363(99)00400-9]

122 **Sia YT**, Lapointe N, Parker TG, Tsoporis JN, Deschepper CF, Calderone A, Pourdjabbar A, Jasmin JF, Sarrazin JF, Liu P, Adam A, Butany J, Rouleau JL. Beneficial effects of long-term use of the antioxidant probucol in heart failure in the rat. *Circulation* 2002; **105**: 2549-2555 [PMID: 12034664 DOI: 10.1161/01.CIR.0000016721.84535.00]

123 **Anversa P**, Beghi C, Kikkawa Y, Olivetti G. Myocardial infarction in rats. Infarct size, myocyte hypertrophy, and capillary growth. *Circ Res* 1986; **58**: 26-37 [PMID: 3943155 DOI: 10.1161/01.RES.58.1.26]

124 **Karam R**, Healy BP, Wicker P. Coronary reserve is depressed in postmyocardial infarction reactive cardiac hypertrophy. *Circulation* 1990; **81**: 238-246 [PMID: 2137045 DOI: 10.1161/01.CIR.81.1.238]

125 **Fernández-Hernando C**, Ackah E, Yu J, Suárez Y, Murata T, Iwakiri Y, Prendergast J, Miao RQ, Birnbaum MJ, Sessa WC. Loss of Akt1 leads to severe atherosclerosis and occlusive coronary artery disease. *Cell Metab* 2007; **6**: 446-457 [PMID: 18054314 DOI: 10.1016/j.cmet.2007.10.007]

126 **Shiojima I**, Sato K, Izumiya Y, Schiekofer S, Ito M, Liao R, Colucci WS, Walsh K. Disruption of coordinated cardiac hypertrophy and angiogenesis contributes to the transition to heart failure. *J Clin Invest* 2005; **115**: 2108-2118 [PMID: 16075055 DOI: 10.1172/JCI24682]

127 **Egginton S**. Invited review: activity-induced angiogenesis. *Pflugers Arch* 2009; **457**: 963-977 [PMID: 18704490 DOI: 10.1007/s00424-008-0563-9]

128 **White FC**, Bloor CM, McKirnan MD, Carroll SM. Exercise training in swine promotes growth of arteriolar bed and capillary angiogenesis in heart. *J Appl Physiol (1985)* 1998; **85**: 1160-1168 [PMID: 9729595]

129 **Bloor CM**. Angiogenesis during exercise and training. *Angiogenesis* 2005; **8**: 263-271 [PMID: 16328159 DOI: 10.1007/s10456-005-9013-x]

130 **Iemitsu M**, Maeda S, Jesmin S, Otsuki T, Miyauchi T. Exercise training improves aging-induced downregulation of VEGF angiogenic signaling cascade in hearts. *Am J Physiol Heart Circ Physiol* 2006; **291**: H1290-H1298 [PMID: 16617130 DOI: 10.1152/ajpheart.00820.2005]

131 **Prior BM**, Yang HT, Terjung RL. What makes vessels grow with exercise training? *J Appl Physiol (1985)* 2004; **97**: 1119-1128 [PMID: 15333630 DOI: 10.1152/japplphysiol.00035.2004]

132 **Gustafsson T**, Bodin K, Sylvén C, Gordon A, Tyni-Lenné R, Jansson E. Increased expression of VEGF following exercise training in patients with heart failure. *Eur J Clin Invest* 2001; **31**: 362-366 [PMID: 11298785 DOI: 10.1046/j.1365-2362.2001.00816.x]

133 **Devaux C**, Iglarz M, Richard V, Mulder P, Henrion D, Renet S, Henry JP, Thuillez C. Chronic decrease in flow contributes to heart failure-induced endothelial dysfunction in rats. *Clin Exp Pharmacol Physiol* 2001; **31**: 302-305 [PMID: 15191402 DOI: 10.1111/j.1440-1681.2004.03997.x]

134 **Vercauteren M**, Remy E, Devaux C, Dautreaux B, Henry JP, Bauer F, Mulder P, Hooft van Huijsduijnen R, Bombrun A, Thuillez C, Richard V. Improvement of peripheral endothelial dysfunction by protein tyrosine phosphatase inhibitors in heart failure. *Circulation* 2006; **114**: 2498-2507 [PMID: 17101854 DOI: 10.1161/CIRCULATIONAHA.106.630129]

135 **Xu Y**, Henning RH, Lipsic E, van Buiten A, van Gilst WH, Buikema H. Acetylcholine stimulated dilatation and stretch induced myogenic constriction in mesenteric artery of rats with chronic heart failure. *Eur J Heart Fail* 2007; **9**: 144-151 [PMID: 16828577 DOI: 10.1016/j.ejheart.2006.05.003]

136 **Xu Y**, Henning RH, Sandovici M, van der Want JJ, van Gilst WH, Buikema H. Enhanced myogenic constriction of mesenteric artery in heart failure relates to decreased smooth muscle cell caveolae numbers and altered AT1- and epidermal growth factor-receptor function. *Eur J Heart Fail* 2009; **11**: 246-255 [PMID: 19147448 DOI: 10.1093/eurjhf/hfn027]

137 **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. *J Mol Cell Cardiol* 2010; **48**: 1041-1049 [PMID: 20153335 DOI: 10.1016/j.yjmcc.2010.02.005]

138 **Oldridge NB**, Guyatt GH, Fischer ME, Rimm AA. Cardiac rehabilitation after myocardial infarction. Combined experience of randomized clinical trials. *JAMA* 1988; **260**: 945-950 [PMID: 3398199 DOI: 10.1001/jama.1988.03410070073031]

139 **O'Connor GT**, Buring JE, Yusuf S, Goldhaber SZ, Olmstead EM, Paffenbarger RS, Hennekens CH. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* 1989; **80**: 234-244 [PMID: 2665973 DOI: 10.1161/01.CIR.80.2.234]

140 **Bobbio M**. Does post myocardial infarction rehabilitation prolong survival? A meta-analytic survey. *G Ital Cardiol* 1989; **19**: 1059-1067 [PMID: 2695384]

141 **Jones DA**, West RR. Psychological rehabilitation after myocardial infarction: multicentre randomised controlled trial. *BMJ* 1996; **313**: 1517-1521 [PMID: 8978226 DOI: 10.1136/bmj.313.7071.1517]

142 **Taylor RS**, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, Skidmore B, Stone JA, Thompson DR, Oldridge N. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med* 2004; **116**: 682-692 [PMID: 15121495 DOI: 10.1016/j.amjmed.2004.01.009]

143 **Myers J**, Gianrossi R, Schwitter J, Wagner D, Dubach P. Effect of exercise training on postexercise oxygen uptake kinetics in patients with reduced ventricular function. *Chest* 2001; **120**: 1206-1211 [PMID: 11591562 DOI: 10.1378/chest.120.4.1206]

144 **La Rovere MT**, Bersano C, Gnemmi M, Specchia G, Schwartz PJ. Exercise-induced increase in baroreflex sensitivity predicts improved prognosis after myocardial infarction. *Circulation* 2002; **106**: 945-949 [PMID: 12186798 DOI: 10.1161/01.CIR.0000027565.12764.E1]

145 **Marchionni N**, Fattirolli F, Fumagalli S, Oldridge N, Del Lungo F, Morosi L, Burgisser C, Masotti G. Improved exercise tolerance and quality of life with cardiac rehabilitation of older patients after myocardial infarction: results of a randomized, controlled trial. *Circulation* 2003; **107**: 2201-2206 [PMID: 12707240 DOI: 10.1161/01.CIR.0000066322.21016.4A]

146 **Zheng A**, Moritani T. Influence of CoQ10 on autonomic nervous activity and energy metabolism during exercise in healthy subjects. *J Nutr Sci Vitaminol (Tokyo)* 2008; **54**: 286-290 [PMID: 18797149]

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**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](#_ENREF_32)] 1999 | Treadmill walk | 40%-70% of peak oxygen uptake (VO2) | 30-45 min | 3 times/wk | 4 mo | Plasma RAAS | Reduced Resting AngII, Aldosterone, vasopressin, and atrial natriuretic peptide |
| Myers *et al*[[143](#_ENREF_144)] 2001 | Outdoor walking at an elevation of 3500 ft, in addition to cycling | 60-70% of peak VO2 | 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](#_ENREF_145)] 20021 | Graded exercise (cycling, calisthenics) | Adjusted to 75% of the heart rate at peakVO2 | 30 min | 5 times/wk | 1 mo | BRS, LVEF | BRS improved by 26%, while LVEF remained unchanged |
| Marchionni *et al*[[145](#_ENREF_146)] 20032 | 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](#_ENREF_147)] 20081 | 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 diameter, left ventricular ejection fraction | Exercise training prevented ventricular remodeling to a certain extent |
| Giallauria *et al*[[46](#_ENREF_47)] 2013 | Bicycle ergometer | 60%-70% of peak VO2 | 30 min | 3 times/wk | 6 mo | dipyridamole  rest gated myocardial perfusion single photon emission computed  tomography | Improved peak oxygen consumption, myocardial perfusion and LV function. |

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

**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](#_ENREF_77)] 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](#_ENREF_35)] 2008 | Treadmill running | 16m/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](#_ENREF_60)] 2007 | Voluntary treadmill exercise training | N/A | N/A | 5 d/wk | 8 wk | LV fractional shortening, Ca2+ sensitivity, PLB, SERCA | Voluntary exercise improved LV and cardiomyocyte shortening, attenuates global LV dysfunction. |
| Wan *et al*[[34](#_ENREF_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](#_ENREF_107)] 2010 | Treadmill running | 16 m/min @ 5% grade | 50 min | 5 d/wk | 8 wk | SOD, GPx, MnSOD | Exercise training combined with AngII receptor blockade reduced oxidative stress. |
| Yengo *et al*[[144](#_ENREF_145)] 2012 | Treadmill running | 15% grade, 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.