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INVITED REVIEW

Exercise training in adverse cardiac remodeling

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Abstract Cardiac remodeling in response to a myocardial infarction or chronic pressure-overload is an independent risk factor for the development of heart failure. In contrast, cardiac remodeling produced by regular physical exercise is associated with a decreased risk for heart failure. There is evidence that exercise training has a beneficial effect on disease progression and survival in patients with cardiac remodeling and dysfunction, but concern has also been expressed that exercise training may aggravate pathological remodeling and dysfunction. Here we present studies from our laboratory into the effects of exercise training on pathological cardiac remodeling and dysfunction in mice. The results indicate that even in the presence of a large infarct, exercise training exerts beneficial effects on the heart. These effects were mimicked in part by endothelial nitric oxide synthase (eNOS) overexpression and abrogated by eNOS deficiency, demonstrating the importance of nitric oxide signaling in mediating the cardiac effects of exercise. Exercise prior to a myocardial infarction was also cardioprotective. In contrast, exercise tended to aggravate pathological cardiac remodeling and dysfunction in the setting of pressure-overload produced by an aortic stenosis. These observations emphasize the critical importance of the underlying pathological stimulus for cardiac hypertrophy and remodeling, in determining the effects of exercise training. Future studies are needed to define the influence of exercise type, intensity and duration in different models and severities of pathological cardiac remodeling. Together such studies will aid in optimizing the therapy of exercise training in the setting of cardiovascular disease.

Keywords Heart failure · Cardiac function · Cardiac remodeling · Exercise · Transgenic mice

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Introduction

Myocardial hypertrophy is a compensatory mechanism by which the left ventricle (LV) adapts to an increased systolic load, which serves to restore LV wall stress to normal levels and maintain cardiac pump function [31, 39]. Clinically, chronic systolic overload of the LV most commonly results from regional loss of myocardial tissue (myocardial infarction [MI]) or elevated impedance to LV outflow (hypertension, aortic stenosis) [44, 80]. Despite the apparent appropriateness of hypertrophic remodeling in response to an increased systolic workload, LV hypertrophy has been shown to be an independent risk factor for the development of angina pectoris, congestive heart failure and sudden death [31, 57, 69]. The mechanisms underlying the progression from LV remodeling to overt heart failure remain incompletely understood [11, 112], but may include perfusion abnormalities [25, 28], loss of cardiomyocytes through apoptosis [77], reduction in contractile function and impaired Ca^{2+} handling of the surviving myocardium [41, 106], and/or alterations in extracellular matrix leading to LV dilation [94].

In contrast to pathological LV remodeling, physiological LV remodeling that is produced by regular dynamic exercise is

associated with a decreased risk for coronary artery disease and heart failure [37], an increased myocardial perfusion capacity [9], and with normal or even increased contractile function in the normal heart [64, 74]. In addition, there is clinical evidence that exercise training has a beneficial effect on disease progression and survival in patients with LV dysfunction [16, 115]. For example, physical conditioning in patients with LV dysfunction results in an increased exercise capacity. The improved exercise capacity was initially ascribed to skeletal muscle adaptations [1], but growing evidence indicates that exercise training may also ameliorate cardiac dysfunction [34–36, 43, 64]. Nevertheless concern has also been expressed regarding potentially detrimental effects of exercise training on cardiac remodeling and function, particularly when started too early after a large MI or in case of strenuous exercise [33, 50, 52, 58, 91].

In this review article, we describe a series of studies in mice [18–21, 27, 101], in which we previously explored the effects of exercise training on pathological LV remodeling and dysfunction produced by a large MI, or by pressure-overload, with a special emphasis on the mechanisms by which exercise exerts its effects.

Experimental models of pathological LV remodeling

Myocardial infarction

In our studies we produce MI by permanent ligation of the proximal left-anterior-descending-coronary-artery (LAD), which results in an infarct area of ~40 % of the LV mass [19, 103]. Eight weeks after induction of MI, LV remodeling occurs, characterized by LV dilation and myocardial hypertrophy, as well as increases in interstitial collagen deposition and apoptosis, and decreases in capillary density in remote surviving myocardium [19–21, 103]. MI also produces marked LV dysfunction, characterized by a pronounced decrease in LV pump function (fractional shortening) and decreases in indices of systolic LV function (dP/dt_{P30}) and diastolic LV function (dP/dt_{min} and the time constant of relaxation, τ), which are associated with pulmonary congestion reflected in pulmonary edema and RV hypertrophy (Fig. 1) [19–21, 103].

Aortic stenosis

For our studies on pressure-overload we apply transverse aortic constriction (TAC) with a suture between the truncus brachiocephalicus and the arteria carotis communis sinistra [73, 87, 101]. A 25G needle is used to induce mild TAC (mTAC) and a 27G needle is used to produce severe TAC (sTAC). Eight weeks of exposure to sTAC results in LV remodeling, characterized by marked LV hypertrophy (reflect in an ~80 % increase in LV mass), capillary rarefaction and interstitial fibrosis [101]. In addition, LV systolic dysfunction is present, characterized by a decrease in fractional shortening and LV dP/dt_{P40} as well as LV diastolic dysfunction, characterized by a reduction in LV dP/dt_{min} and increases in τ and LV end-diastolic pressure. The latter is associated with pulmonary congestion reflected in pulmonary edema and secondary RV hypertrophy. In contrast, mTAC results in ~40 % LV hypertrophy, which is not associated with LV systolic or diastolic dysfunction, reflecting a state of compensated hypertrophy [101].

Exercise training and LV remodeling and dysfunction after MI

In our exercise studies, we exposed mice to an 8-week period of voluntary wheel running. Voluntary exercise is our training method of choice in order to minimize stress factors, which are present during forced running and particularly during swimming [5]. Furthermore, the C57Bl/6 J strain, which is the typical background for our transgenic (Tg) mouse models, is known to perform excellent in voluntary wheel running, while being poor performers during forced treadmill running [5]. Voluntary wheel running, up to 6 km/night, had negligible effects on LV geometry and function in sham operated mice. In mice with a large MI, voluntary wheel running, starting gradually early after MI, did not aggravate post-MI mortality, LV remodeling, capillary rarefaction and cardiomyocyte hypertrophy of remote myocardium [19, 21], and even reduced myocardial interstitial fibrosis and apoptosis, while blunting LV dysfunction and pulmonary congestion (Fig. 1). The mechanism(s) underlying the improvement of LV function likely include the reductions in apoptosis and collagen deposition as well as improvement of cardiomyocyte function. Thus, shortening of isolated cardiomyocytes was increased by exercise [19, 21]. Ca^{2+}-transient amplitude remained unaltered [6, 19], despite a small increase in Sarco-Endoplasmatic Reticulum Calcium ATPase (SERCA2a) expression in exercise-trained mice [21]. However, basal (diastolic) calcium concentrations were reduced by exercise after MI [6, 19], which was likely the result of the slight increase in SERCA2a [21] in conjunction with the increased expression of Na^+/Ca^{2+} exchange [19]. In view of the unchanged Ca^{2+}-transient amplitude, we hypothesized that an exercise-induced normalization of myofilament function could have contributed to the exercise-induced improvement in LV function. Both in our pig and mouse model of MI, we typically observe a reduction in the maximal force generating capacity (F_{max}) and an increase in calcium sensitivity (pCa_{50}) of myofilaments in post-MI remodeled myocardium [19, 106]. Indeed, in trained MI mice, an increase in F_{max} and normalization of pCa_{50} appeared to be principally responsible for the improved isolated myocyte shortening in vitro and global LV fractional shortening in vivo (Fig. 2). We did not investigate the effects of exercise

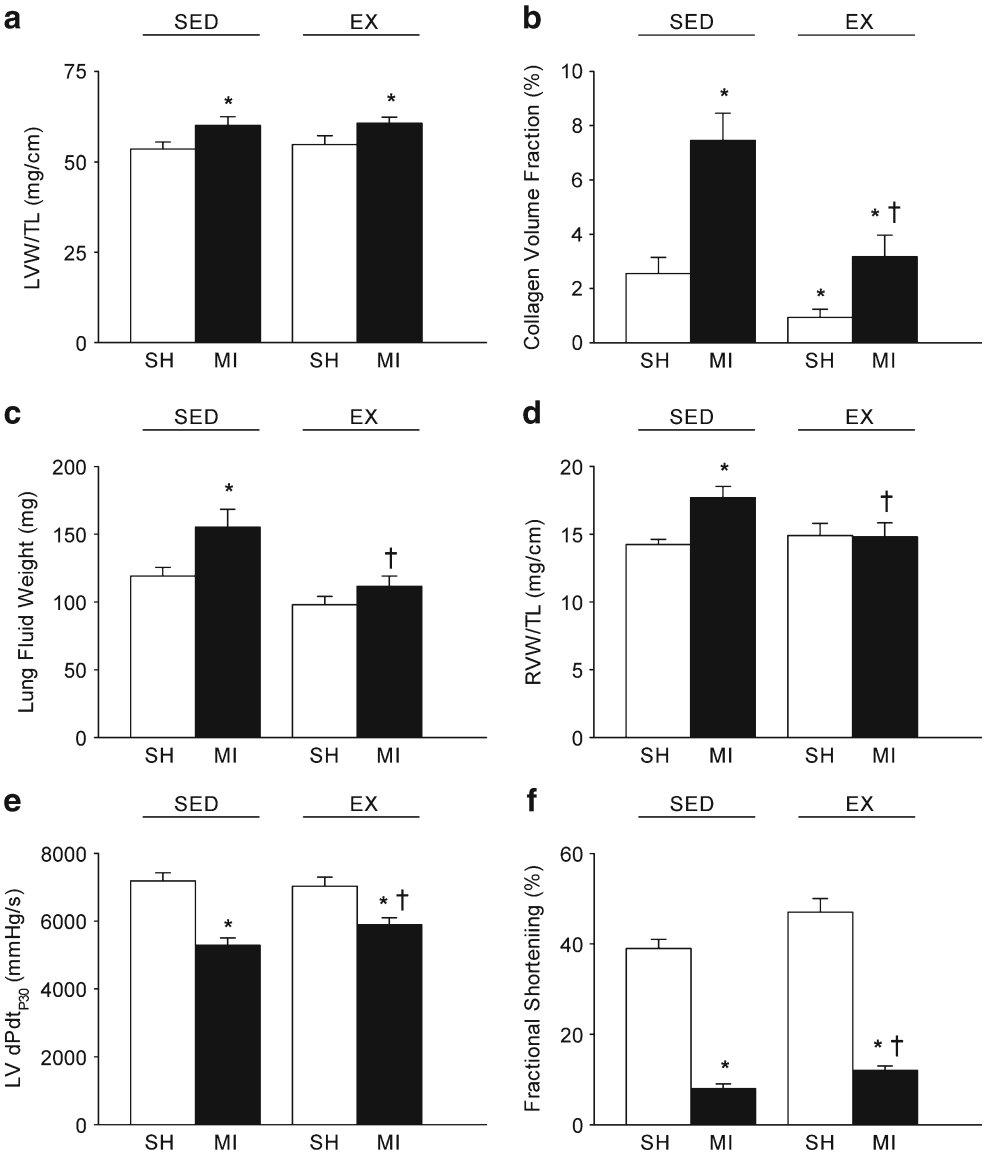

Fig. 1 Effects of MI and exercise on relative LV mass (**a**), collagen content (**b**), lung fluid weight (**c**), relative RV mass (**d**), global LV contractility (dP/dt_{P30}) (**e**), and global LV pump function (fractional shortening) (**f**). *SH* sham operated, *MI* myocardial infarction, *EX* exercise training, *SED* sedentary housed, LVW, LV weight; TL, tibia length, RVW, RV weight. *$P<0.05$ vs. corresponding SH; †$P<0.05$ vs. corresponding SED. Modified from de Waard et al. [19] with permission

on subendocardial versus subepicardial cardiomyocytes in mice, but a subsequent study in rats suggested that the effects of exercise on myofilament dysfunction is transmurally heterogeneous. Thus, not only was the post-MI myofilament dysfunction most pronounced in the remote subendocardium [2, 105], but also was the effect of exercise most pronounced in the subendocardium [2].

Role of nitric oxide signaling in the beneficial effects of exercise training after MI

In view of the critical role of the endothelium in modulating the progression of ventricular and vascular remodeling in heart failure, the beneficial effects of exercise on cardiac function could be due, at least in part, to an exercise-induced increase in expression and activity of endothelial nitric oxide synthase (eNOS) [92], which is the major isoform of NOS that is expressed in coronary vascular endothelium and cardiac myocytes [67]. For example, an increase in nitric oxide (NO) bioavailability has been shown to improve many of the perturbed processes in LV remodeling, including angiogenesis [75], cardiac fibrosis [51], and hypertrophy [86].

For our studies into the role of eNOS in the beneficial effects of exercise in mice with MI, we took a two-pronged approach. First, we investigated whether eNOS overexpression could mimic the effects of exercise training [20, 49], and second we investigated whether eNOS knockout would abrogate the protective effects of exercise [21]. To test the hypothesis that eNOS overexpression mimics exercise training, we investigated the effects of eNOS overexpression on LV remodeling and dysfunction in eNOS Tg mice with a large MI [20, 49]. We found that 10- to 12-fold overexpression of eNOS improved survival, global LV pump function, and

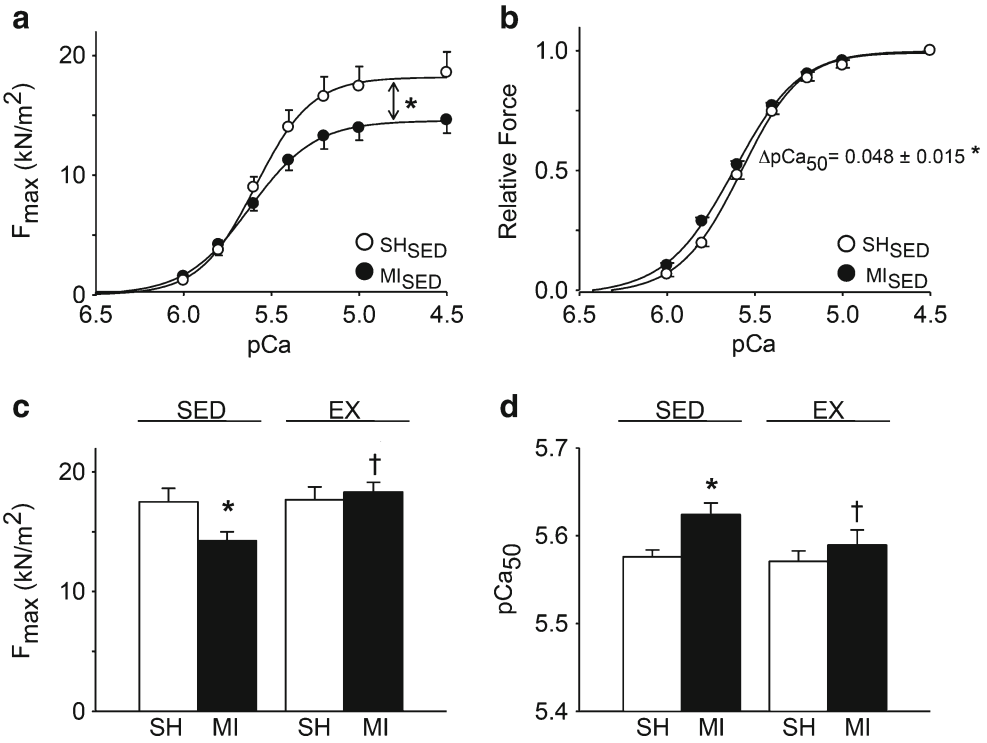

Fig. 2 Absolute (**a**, **c**) and normalized (**b**, **d**) force–pCa curves and bar charts. **a** and **b** The effects of MI in SED mice. **c** and **d** The effects of EX in SH and MI. *SH* sham operated, *MI* myocardial infarction, *EX* exercise training, *SED* sedentary housed. **P*<0.05 vs. corresponding SH; †*P*<0.05 vs. corresponding SED. Modified from de Waard et al. [19] with permission

attenuated LV dilation, myocardial interstitial fibrosis, and pulmonary edema after MI [20, 49]. Conversely, eNOS overexpression did not attenuate cardiac hypertrophy or improved global cardiac contractility and relaxation parameters. Interestingly, all improvements by elevated eNOS expression occurred without significant differences in baseline LV geometry, morphology or function in sham operated mice.

The mechanism underlying the improved cardiac function in eNOSTg mice after MI was probably two-fold. First, the lower systemic vascular resistance and hence lower aortic and LV systolic pressure [102] likely facilitated fractional shortening of the post-MI LV. In addition, a direct effect on the heart is suggested by the observation that cardiomyocyte-specific overexpression of eNOS exerts a beneficial effect on LV structure and function after MI [47]. To further investigate the effects of eNOS overexpression on cardiomyocyte function, we investigated myofilament function and myofilament protein phosphorylation status. Interestingly, we noted that similar to exercise training, elevated eNOS expression increased the F_{max}. However, in contrast to exercise, elevated eNOS expression did not correct the increased myofilament Ca^{2+} sensitivity in MI and had no effect on Myosin Light Chain-2 protein phosphorylation and β_1-adrenergic receptor and SERCA2a protein levels [30]. These findings suggest that in addition to the afterload reduction, an improvement in myofilament F_{max} could have contributed to eNOS overexpression-induced improvement in LV pump function after MI. The mechanism by which eNOSTg increased F_{max} remains to be determined, but it is of interest to note that *S*-nitrosylation of myofilament proteins, including alpha-myosin heavy chain, myosin light chain kinase 1 and myomesin, may be involved in the cardioprotection by ischemic preconditioning against ischemia–reperfusion induced sarcomeric damage in mice [95, 96]. In addition, recent studies showed that oxidative stress may increase myofilament protein *S*-glutathionylation and increase myofilament Ca^{2+} sensitivity [48, 83]. It remains to be investigated whether *S*-nitrosylation of myofilaments is increased and contributes to the eNOS overexpression-enhanced myofilament contractility in our model, and whether this occurs by reducing oxidative stress-induced post-translational modifications of myofilament proteins.

An important part of NO signalling occurs through activation of soluble guanylyl cyclase (sGC), resulting in the production of cGMP. cGMP activates PKG and cGMP/PKG signaling is considered a myocardial brake, by blunting contraction and growth, while promoting relaxation [119]. cGMP signaling is terminated by its breakdown by phosphodiesterases (PDEs). In cardiac tissue, the majority of cGMP breakdown occurs by PDE1 and PDE3 [108]. However, PDE5 has been shown to be upregulated in the myocardium of humans with ischemic cardiomyopathy [84], and is therefore likely to contribute to cGMP breakdown in the diseased myocardium. In mice with MI, inhibition of PDE5, either pharmacologically with sildenafil [88] or by interfering with its expression through adenoviral shRNA [26], improved LV function and reduced LV dilation. These beneficial effects were accompanied by increases in cGMP and increased activity of PKG [61]. Pretreatment with an eNOS inhibitor negated the beneficial

effects of PDE5 inhibition, indicating that these effects were NO dependent [88]. Conversely, overexpression of PDE5 aggravated left ventricular remodeling and dysfunction after MI, while baseline cardiac function and initial infarct size were not different [84]. Ten weeks after MI, both diastolic Ca^{2+} concentrations and the amplitude of the Ca^{2+} transient were increased, while contraction and relaxation were slower in myocytes isolated from PDE5-Tg mice as compared to wild type mice. These data indicate that PDE5 inhibition may be a valuable tool to improve cardiac function after MI. Whether the combination of PDE5 inhibition and exercise training has additional beneficial effects remains to be established.

In order to ascribe the beneficial effects of exercise on cardiac function to an exercise-induced upregulation of eNOS expression and activity, the effects of exercise and eNOS overexpression should be similar. However, whereas the effects of either exercise or eNOS overexpression in sedentary MI mice on LV geometry, collagen content, and LV function were indeed similar, survival in MI mice was improved by eNOS overexpression but not by exercise. Interestingly, mortality in C57Bl/6 J mice after 8 weeks of MI is principally caused by cardiac rupture of the infarct area within the first 2 weeks after MI [13]. It is thus possible that the lower systemic vascular resistance and mean aortic pressure in eNOSTg compared to wild type mice [102] may have prevented cardiac rupture thereby enhancing post-MI survival in eNOSTg mice.

In order to unequivocally demonstrate a critical role for eNOS in the beneficial effects of exercise after MI, it is mandatory to show that the effects of exercise training are absent in eNOS deficient mice. For this purpose, we repeated our studies in wild type ($eNOS^{+/+}$) and eNOS-deficient mice lacking either one ($eNOS^{+/-}$) or both ($eNOS^{-/-}$) functional eNOS alleles [21]. We also included $eNOS^{+/-}$ mice, in view of observations by Kojda et al. [54] that basal levels of eNOS expression and hemodynamics are not different from $eNOS^{+/+}$ mice, but the exercise-induced increase in eNOS expression is selectively abolished [54, 55]. Indeed, we observed not only that basal LV protein levels of eNOS were maintained, but also that aortic blood pressure, as well as systolic and diastolic function, was normal in $eNOS^{+/-}$ mice. In addition, levels of apoptosis and cardiomyocyte cross-sectional area were also similar to $eNOS^{+/+}$ mice. However, we did observe that collagen content was higher in $eNOS^{+/-}$ mice and that, similar to the $eNOS^{-/-}$ mice, capillary densities were lower.

Scherrer-Crosbie et al. [90] reported that 4 weeks after a small MI (resulting in a decrease in fractional shortening from 58±2 % to 44±2 % in $eNOS^{+/+}$ mice), mortality as well as LV remodeling and dysfunction were more pronounced in $eNOS^{-/-}$ compared to $eNOS^{+/+}$ mice. In contrast, we found that mortality, LV remodeling and dysfunction, as well as cardiomyocyte hypertrophy, interstitial fibrosis and increased apoptosis that occurred after a large MI (decreasing fractional shortening from ~40 % to ~10 %) were similar in $eNOS^{+/+}$, $eNOS^{+/-}$ and $eNOS^{-/-}$ mice (Fig. 3) [21]. Our observations are in agreement with the study of Liu et al. [62], in which mortality, LV remodeling and the development of heart failure over a 6-month follow-up period after a large MI (decreasing fractional shortening from ~65 % to ~20 %) were similar in $eNOS^{-/-}$ and $eNOS^{+/+}$ mice. These findings are consistent with the concept that lack of eNOS does not aggravate myocardial remodeling and LV dysfunction after a large MI. These findings suggest that in more chronic (i.e. longer than our 8-week follow-up period) post-MI remodeling an adaptation through compensatory mechanisms has occurred. Such compensatory factors might include prostacyclin [38], nNOS [45, 59, 70] and iNOS [3, 93]. However, we failed to observe compensatory increases in expression of nNOS or iNOS [21]. An explanation for the lack of a compensatory increase is not readily found, but could be related to the genetic background of the $eNOS^{-/-}$ mice. Thus, Sharp et al. [93] previously observed that iNOS upregulation in $eNOS^{-/-}$ depended critically on the strain of mice employed. Future studies are necessary to investigate the exact mechanisms that act to compensate after MI in eNOS deficient mice.

$eNOS^{+/+}$, $eNOS^{+/-}$, and $eNOS^{-/-}$ mice were exposed to either sedentary housing or voluntary exercise training [21]. Although, exercise after MI in $eNOS^{+/-}$ and $eNOS^{-/-}$ mice did not influence LV myocardial hypertrophy, the beneficial effects of exercise on MI-induced LV dilation and LV systolic dysfunction, as observed in $eNOS^{+/+}$ mice, were lost in $eNOS^{+/-}$ and $eNOS^{-/-}$ mice (Fig. 3). Furthermore, the exercise-induced amelioration of LV backward failure that was observed in $eNOS^{+/+}$ mice was lost in $eNOS^{-/-}$ mice and even reversed to aggravated pulmonary congestion in $eNOS^{+/-}$ mice. At the myocardial level, the beneficial effects of exercise in $eNOS^{+/+}$ mice on interstitial fibrosis and apoptosis within non-infarcted remote myocardium were lost in $eNOS^{+/-}$ and $eNOS^{-/-}$ mice [21]. These findings indicate that eNOS is critical for the exercise-induced improvement of LV geometry (both at the macroscopic and microscopic level) and LV function after MI.

Interestingly, $eNOS^{+/-}$ mice which lack only one eNOS allele, appeared to respond even slightly worse to exercise after MI than $eNOS^{-/-}$ mice, as reflected in the exacerbated pulmonary congestion and LV interstitial fibrosis (Fig. 3). Kojda et al. [54] proposed that when two eNOS alleles are present, as in $eNOS^{+/+}$ mice, under basal conditions both are being transcribed at a *submaximal* rate. Exercise thus increases transcriptional activity of both genes. The absence of one eNOS allele results in the opposite allele functioning at near peak transcription rate, so that it cannot be further activated by exercise [55]. It could be speculated that in the complete absence of eNOS expression, other factors, including prostacyclin [38], may be upregulated or increased in $eNOS^{-/-}$ mice and act to compensate for the absence of eNOS, thereby preventing further worsening of cardiac remodeling and function. If one eNOS allele is still functional and results

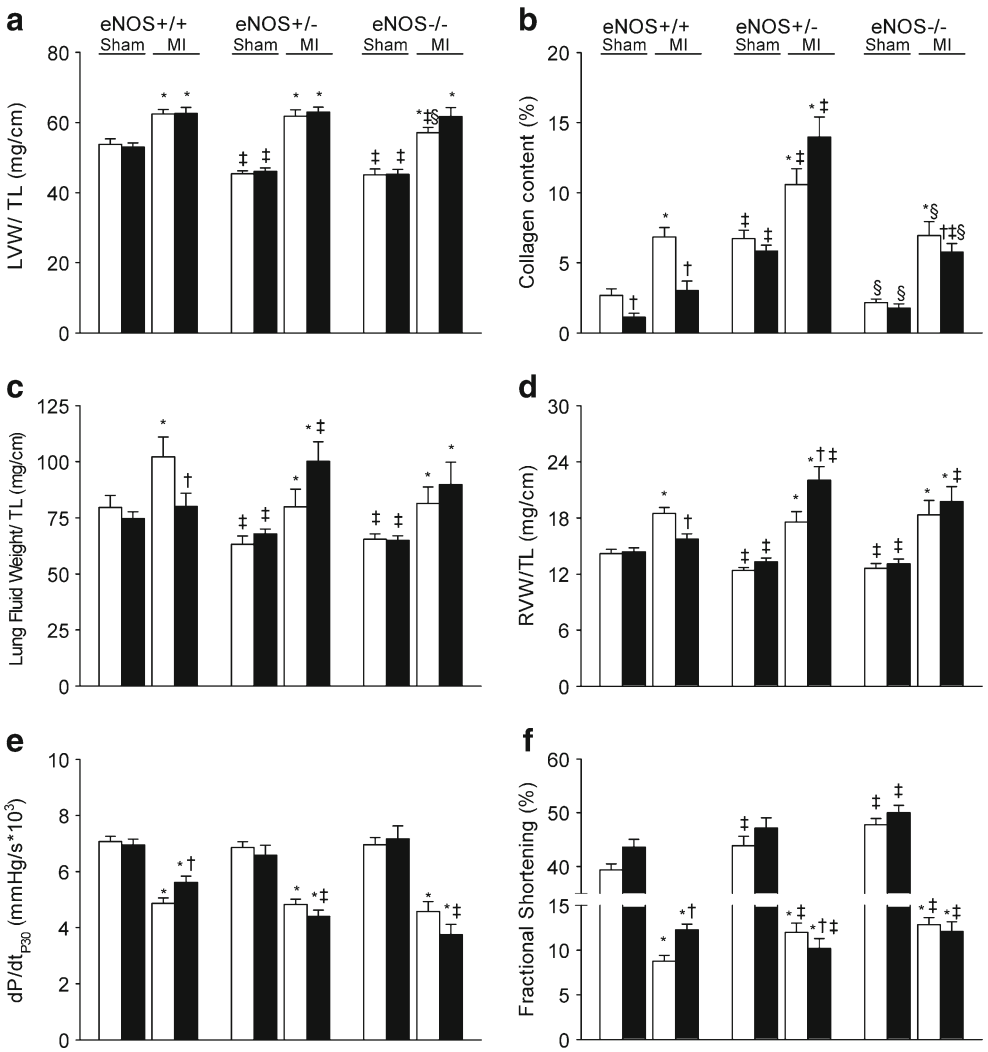

Fig. 3 Effects of MI and exercise in eNOS$^{+/+}$, eNOS$^{+/-}$ and eNOS$^{-/-}$ mice on relative LV mass (**a**), collagen content (**b**), relative lung fluid weight (**c**), relative RV mass (**d**), global LV contractility (dP/dt_{P30}) (**e**) and global LV pump function (fractional shortening) (**f**). LVW, LV weight; TL, tibia length, RVW, RV weight *P<0.05 vs. corresponding sham; †P<0.05 vs. corresponding sedentary; ‡P<0.05 vs. corresponding eNOS$^{+/+}$; §P<0.05 vs. corresponding eNOS$^{+/-}$. *Empty square* sedentary housed; *filled square* exercise. Reproduced from de Waard et al. [21] with permission

in normal basal eNOS expression, such compensatory mechanisms may not occur, leaving the heart more vulnerable to the effects of exercise. Future studies are needed to study the influence of potential compensating factors.

From this study, we could not determine the exact location of eNOS involved in the exercise-induced amelioration of LV dysfunction after MI. First, an exercise-induced increase in vascular eNOS expression in the systemic vascular bed may have contributed to the beneficial effects of exercise on LV function after MI. Indeed, we have previously shown that endothelial eNOS overexpression [107] partly mimicked the beneficial effects of exercise on cardiac function after MI [20]. However, eNOS overexpression could not explain all the effects of exercise, suggesting that in addition to systemic vascular eNOS, cardiac eNOS (in the coronary endothelium and/or cardiomyocytes) also contributed to the beneficial effects of exercise. Indeed, a recent study reported that eNOS in bone marrow-derived coronary endothelial cells is critical for ameliorating pathological cardiac remodeling [2, 26].

The mechanism by which eNOS mediated the beneficial effects of exercise in the heart likely includes reduced fibrosis and apoptosis, possibly as a result of activation of survival pathways and reduced senescence [2, 110]. In addition, the observations in a previous study that the MI-induced myofilament dysfunction was prevented by exercise [19], in conjunction with the observation that exercise blunted MI-induced oxidative stress [21, 98], could be interpreted to suggest that eNOS-derived NO prevented oxidative modifications of myofilaments and thereby contributed to the beneficial effects of exercise on LV function. The exact location of eNOS, as well as the mechanisms involved in the eNOS-mediated exercise-induced amelioration of LV dysfunction after MI, remain the subject of future studies.

Exercise training prior to a myocardial infarction

Physical inactivity has been proposed to be an independent risk factor for cardiovascular disease [8, 109]. Indeed,

prospective epidemiological data indicate that moderate (e.g., walking) and vigorous exercise in healthy subjects are associated with substantial reductions in the incidence of cardiovascular events [40, 65]. The beneficial effects of exercise extend to patients with established coronary heart disease in which regular physical activity also reduces the incidence of cardiac events and all-cause mortality [100]. Furthermore, there is evidence that exercise initiated after a cardiac event, such as MI, ameliorates LV remodeling and dysfunction [19, 29, 36, 53, 79, 81, 111, 118] and improves clinical outcome [78, 99].

In contrast, there is substantially less information available as to whether prior exercise affords any protection in situations where, despite regular exercise, a major cardiovascular event like MI does occur. Animal studies suggest that prior exercise can precondition the myocardium, thereby protecting the heart against irreversible damage produced by ischemia–reperfusion in rats [10, 85, 113, 117] and dogs [22]. In addition, prior exercise may modulate post-infarct remodeling independent of any myocardial preconditioning effect. Thus, two studies in rats using a permanent coronary artery ligation (in which preconditioning cannot limit acute myocardial necrosis) [76, 104] reported that 5–7 weeks of prior swimming had no effect on post-MI mortality, but reduced infarct-size and attenuated LV remodeling, as determined at 2 days [68] or 4 weeks [30] after induction of MI. Swimming-induced increases in capillary [68] and arteriolar [30] densities were observed in the remote region, which lead the authors to speculate (collateral blood flow was not actually measured) that prior exercise may have resulted in increased collateral blood flow to the area at risk thereby limiting infarct size. Although myocardial vascular densities are known to be enhanced in young male rats by swim training [24], there is no evidence to suggest that collateral vessel growth is stimulated by exercise in healthy hearts [9, 60]. Thus, studies pertaining to exercise of healthy dogs, swine or rats have consistently shown that exercise does not increase innate collateral blood flow capacity in healthy hearts [24]. An alternative explanation may be that prior exercise affected healing and remodeling of the infarct area (contracture) thereby leading to a reduction of infarct length [30, 68]. Consequently, we tested the hypothesis that a daily exercise regimen started 2 weeks *prior* to an acute MI is associated with improved survival and blunted LV remodeling and dysfunction after MI [18].

Prior exercise reduced post-MI mortality from ~40 % to ~20 % and attenuated LV dysfunction, but did not enhance capillary density in remote myocardium or limit infarct size as measured 8 weeks later [18]. Mortality in C57Bl/6 J mice after MI appears to be principally caused by cardiac rupture of the infarct area within the first 2 weeks after MI [13]. Interestingly, we observed that infarct thickness was increased (Fig. 4), a finding recently confirmed in rats [9], consistent with exercise-induced modulation of infarct healing and remodeling. Consequently, it could be speculated that the increased infarct thickness acted to reduce systolic wall stress and thereby prevented cardiac rupture, thus enhancing post-MI survival in mice that had been subjected to prior exercise.

The precise mechanism for the blunted LV dysfunction in MI mice exposed to prior exercise was not determined. However, there is evidence that the hearts of exercised animals respond more effectively to stress. For example, rats subjected to 8 weeks of forced treadmill exercise were able to maintain or increase myocardial contractility more effectively in the face of a sustained pressure-overload than sedentary housed animals [23], Importantly, these results suggest that even when regular exercise fails to prevent an acute MI it can still act to improve cardiac function and survival after MI. These observations warrant an even greater emphasis on lifestyle changes in patients with an increased risk of or already established coronary heart disease, and which are at increased risk of encountering an acute MI.

Effects of exercise training in pressure-overload LV hypertrophy

There is ample evidence from both clinical and experimental studies that aerobic exercise training has a beneficial effect on cardiac function and remodeling secondary to ischemic cardiomyopathy [17, 19, 43]. Similarly, the majority of experimental studies in genetic models of systemic hypertension [15, 63, 72] have shown a beneficial effect of regular exercise on cardiac remodeling and function, which is supported by recent clinical studies [7, 82]. In contrast, little is known about the effects of exercise on LV pressure-overload hypertrophy as a result of mechanical obstruction to outflow. This is important because there is an increasing number of patients with (congenital) aortic stenosis that are chronically exposed to LV pressure-overload and which will ultimately require surgery during their adult life [114]. Furthermore, as life expectancy in general is increasing in the western society and since the prevalence of aortic stenosis increases with age, the number of patients suffering from pressure-overload-induced cardiac hypertrophy due to aortic stenosis is inevitably growing [14]. It is therefore imperative to investigate new therapies for the prevention and treatment of cardiac dysfunction in these patients. So far the potentially beneficial effects of exercise on cardiac function and hypertrophy have been insufficiently examined in this group of patients. Several studies recommended patients with pressure-overload hypertrophy to participate only in mild physical training [89, 116] to minimize the increase in workload to the heart during exercise, but solid clinical evidence for such guidelines is lacking. The effects of regular physical exercise in such patients may well be different from that in patients with cardiac hypertrophy due to systemic hypertension. Thus the presence of an aortic stenosis

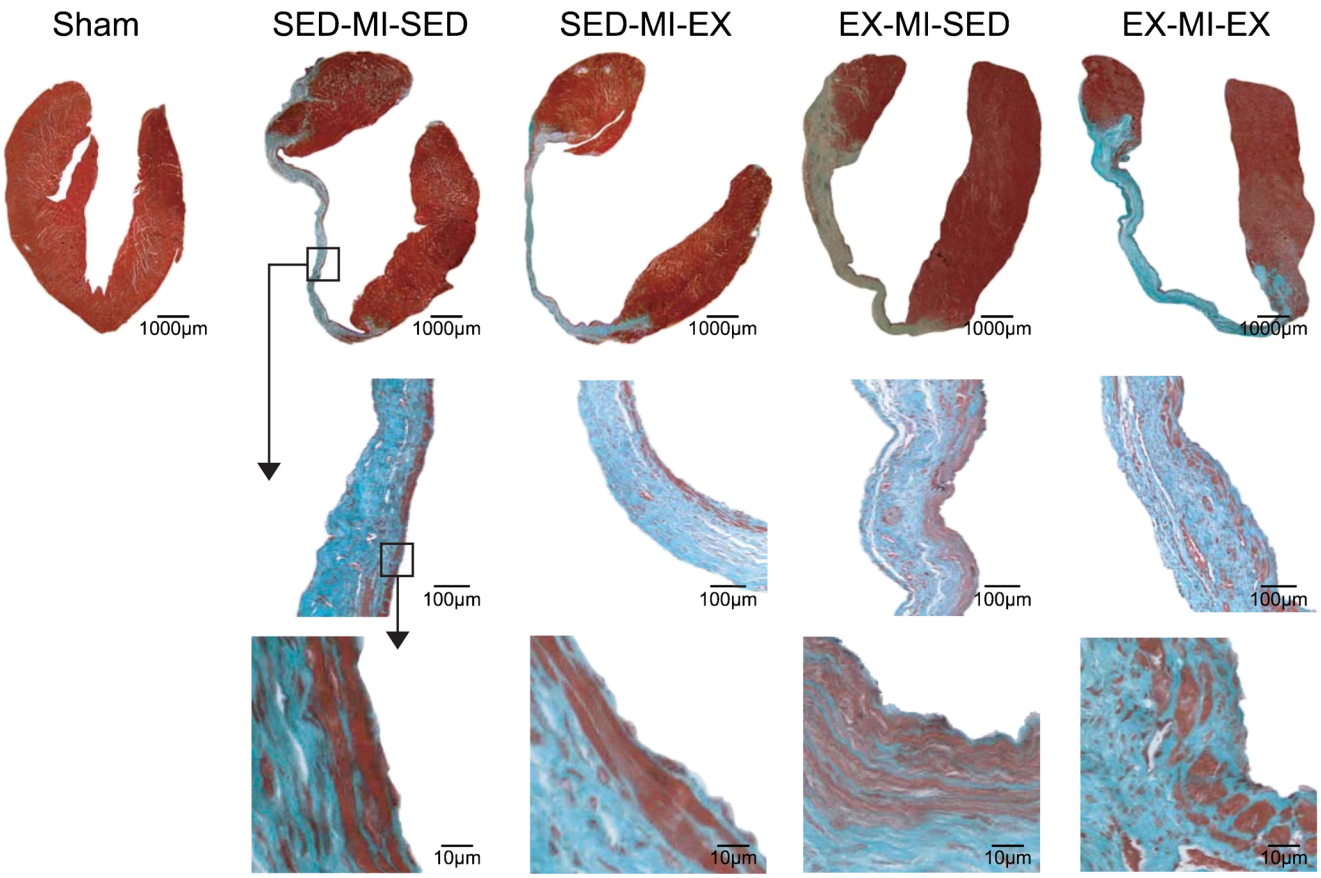

Fig. 4 Macroscopic and microscopic representative examples of the LV infarcted myocardium. Masson's trichrome staining of longitudinal sections of the LV is shown. Red staining represents viable cardiomyocytes, whereas blue-green staining represents collagen. *MI* myocardial infarction, *EX* exercise training, *SED* sedentary housed. Reproduced from de Waard et al. [18] with permission

results in exaggerated LV pressure responses to exercise thereby producing aggravated increases in afterload during each exercise bout [28], which contrasts with the relatively normal LV hemodynamic responses to exercise in case of systemic hypertension [4]. It is therefore possible that exercise training in case of a chronic aortic stenosis does not recapitulate the beneficial effects that are observed in ischemic heart disease or systemic hypertension. In light of these considerations, we investigated the effects of dynamic exercise training on aortic stenosis induced LV hypertrophy and dysfunction. Since the effects of exercise training might depend on the severity of the aortic stenosis, we assessed the effects of exercise in mice subjected to either mTAC or sTAC [101].

Eight weeks of voluntary wheel running had no significant effect on LV hypertrophy and remodeling in either mTAC or sTAC mice. In contrast, while LV function was well maintained by exercise in mTAC mice (not shown), a trend towards aggravated LV dysfunction and backward failure was apparent in sTAC mice when exposed to exercise (Fig. 5). These effects of exercise in sTAC mice could not be explained by alterations in myofilament function, as F_{max} and pCa_{50} were not altered. Interestingly, a decrease in passive stiffness of myofilaments (F_{pas}) was noted, which was however not associated with a reduction in LV end-diastolic pressure. The latter may, at least in part, be related to an increase in collagen-I content in these mice, which may have offset the exercise-induced lowering of passive cardiomyocyte stiffness. Survival rate in TAC mice was not significantly altered by exercise training, but tended to improve with exercise in both mTAC and sTAC mice. This trend towards an improved survival with exercise without improvements in LV function is in agreement with another rodent study of pressure-overload hypertrophy [15] and indicates that exercise could potentially improve survival in models of pressure-overload hypertrophy without beneficial effects on LV function. The results of this study contrast with the beneficial effects of exercise on LV hypertrophy and dysfunction reported for ischemic [43], systemic hypertensive [7, 82] and hypertrophic [56] cardiomyopathy. Similarly, experimental studies in Dahl salt-sensitive or spontaneously hypertensive rats, have generally shown beneficial effects of regular treadmill exercise [15, 63] or swimming [32, 72] on cardiac function, fibrosis, the expression of hypertrophy marker genes and survival although not on LV hypertrophy per se. Only Schultz et al. [91] reported that excessive long-term (up to 16 months) wheel running aggravated cardiac hypertrophy

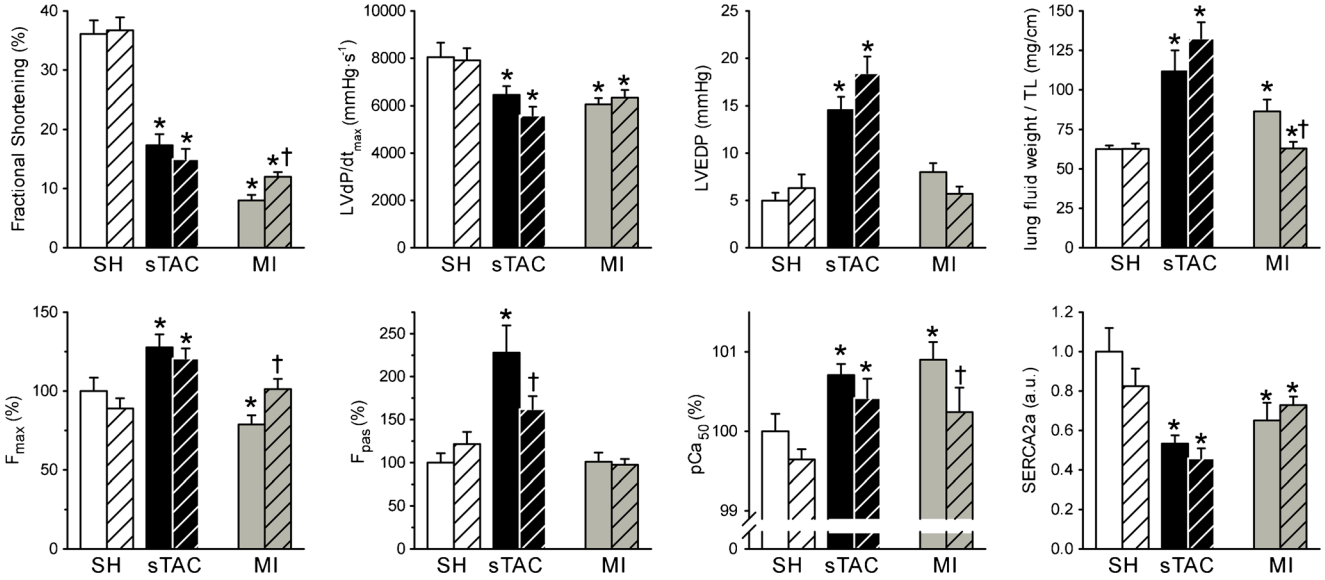

Fig. 5 Comparative data of the effect of exercise on cardiac function and geometry after severe transverse aortic constriction (*sTAC*) and myocardial infarction (*MI*). Solid bars, sedentary mice; hatched bars, exercised mice. *LVEDP* LV end-diastolic pressure, *TL* tibia length; data on myofilament function are normalized to corresponding SH_{SED}. F_{max} maximum force, F_{pas} passive force, pCa_{50} calcium sensitivity, *SERCA2a* Sarco-Endoplasmatic Reticulum Calcium ATP-ase, *SH* sham operated, *TAC* transverse aortic constriction. *$P<0.05$ vs. corresponding SH; †$P<0.05$ vs. corresponding SED. Reproduced from van Deel et al. [101] with permission

and dysfunction, fibrosis and expression of hypertrophy marker genes in spontaneously hypertensive female rats.

An explanation for the contrasting effect of exercise in mice with MI versus mice with TAC is not readily found. However, it should be noted that the effects of exercise training on the development of LV dysfunction and hypertrophy depend at least in part on the mode, frequency and intensity of exercise [43, 91]. For example, dynamic exercise, which exposes the heart to a volume-overload reverses LV remodeling and improves cardiac function in patients with heart failure [43, 71]. In contrast, when static and dynamic exercises are combined (resulting in more pronounced increases in systemic pressure) the beneficial effects of physical training are no longer observed [43]. Since dynamic exercise in the presence of an aortic stenosis will result in exaggerated increases in LV systolic pressures [28], this will likely add a pronounced static component to the exercise response. It is thus possible that the excessive increase in LV systolic workload that occurs in response to acute exercise may have offset the positive effects of the 8-week voluntary wheel running protocol, which we previously observed in mice with a MI [19]. In view of our observations that eNOS overexpression in part mimics the beneficial effects of exercise training in mice with MI [20, 49] it will be of interest to evaluate the effects of eNOS overexpression (i.e., the beneficial molecular effects of exercise, but without the hemodynamic overload) on LV hypertrophy and dysfunction in sTAC mice in future studies. This is particularly interesting since two studies reported that endogenous eNOS afforded protection against TAC-induced LV hypertrophy and dysfunction [12, 46], whereas another study reported that eNOS$^{-/-}$ mice were protected against TAC-induced cardiac pathology through prevention of eNOS-uncoupling and consequent formation of reactive oxygen species [120]. The latter authors proposed that a more promising approach to enhance the NO-cGMP signaling pathway in order to ameliorate LV hypertrophy and dysfunction would be to inhibit cGMP breakdown by inhibition of PDE5. Thus, PDE5 inhibition with sildenafil in sTAC prevented and reversed LV hypertrophy and improved LV diastolic function by preventing dilation and reducing interstitial fibrosis [97]. Future studies are required to determine whether PDE5 inhibition is indeed superior to eNOS overexpression as a therapeutic approach in the treatment of LV hypertrophy and dysfunction.

A recent study in Yucatan miniature swine investigated the effect of mild intensity interval exercise training for 15 weeks in swine in which banding of the ascending aorta was performed 5 weeks earlier [66]. Mild intensity interval training for 15 weeks had no effect on LV hypertrophy in swine with aortic banding, but ameliorated cardiac dysfunction. Thus, exercise training in these swine reduced both end-diastolic volume and end-systolic volume, and increased stroke volume and ejection fraction. Moreover, the rate of relaxation was increased towards control values, and interstitial fibrosis and collagen-1 were reduced, while the more elastic collagen-3 was increased. In contrast to its effects on the extracellular matrix, exercise training did not reverse the increase in cardiomyocyte stiffness. An explanation for the disparate findings regarding the benefit of exercise in swine versus mice with an aortic stenosis is not readily available, but may

involve differences in exercise mode, intensity and/or duration, in conjunction with species differences.

Conclusions and perspectives

Our studies into the effects of exercise training on pathological cardiac remodeling and dysfunction have shown that even in the presence of a large MI, early exercise training exerts a beneficial effect, an observation that is now increasingly recognized in clinical research [42]. The beneficial effects of exercise training on the heart were (in part) mimicked by eNOS overexpression and abrogated by eNOS deficiency, clearly pointing towards the importance of NO-cGMP signaling in the beneficial effects of exercise. Interestingly, exercise prior to an MI was also cardioprotective, likely by improving infarct healing. In contrast to the beneficial effects of training in the setting of an acute MI, exercise tended to aggravate pathological cardiac remodeling and dysfunction in the setting of aortic stenosis, which emphasizes the critical importance of the underlying pathological stimulus for cardiac hypertrophy and remodeling. Future studies are needed not only to further unravel the mechanisms by which exercise training exerts its cardiac effects [64], and how it interferes with the mechanisms of pathological cardiac remodeling [11, 112], but also to better define the influence of exercise mode, intensity and duration on different models and severities of pathological cardiac remodeling. Together such studies will aid in optimizing the therapy of exercise training and exploiting its molecular mechanisms in the setting of cardiovascular disease.

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