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ORIGINAL PAPER

Strength training attenuates post-infarct cardiac dysfunction and remodeling

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Abstract

Post-myocardial infarction (MI) exercise has been employed to improve cardiac function. However, most studies have focused on endurance training (Et). Although Et has been reported to preserve cardiac function, evidence suggests that Et increases left ventricle (LV) interior dimensions as a result of albumin-induced plasma expansion. In contrast, strength training (St) induces concentric cardiac hypertrophy and improved cardiac function without causing ventricular dilation. Therefore, the purpose of this study was to investigate the effects of St on cardiac function and remodeling in rats with MI. MI was surgically induced in 7-week-old rats via ligation of the coronary artery. Survivors were assigned to two experimental groups, MI-Sed (No exercise; $n=9$), MI-St (St; $n=10$), with a Sham group (no MI, no St; $n=9$). MI-St rats began training 1-week post-MI by climbing a ladder with weights for 10 weeks. Echocardiographic measurements were performed prior to, and following exercise training, while in vivo LV hemodynamic analysis was conducted at the end of the experimental period. Our data revealed that St induced shortening of the LV end-diastolic dimension in the MI-St group compared with the MI-Sed group ($P<0.05$). The peak velocities of contraction ($+dP/dt$ max) and relaxation ($-dP/dt$ max) were significantly greater in the MI-St group than the MI-Sed group ($P<0.05$). These training effects contributed to the improved fractional shortening (%FS). Our results demonstrate that St may be beneficial for post-MI by attenuating LV dilation and concomitant cardiac dysfunction associated with MI.

Keywords Myocardial infarction · Cardiac function · Strength training · Rats

Introduction

Left ventricular (LV) remodeling following myocardial infarction (MI) remains a leading topic of inquiry among cardiovascular researchers. LV remodeling originates as an acute response to a post-MI loss of contractile function, providing adaptive compensation for diminished cardiac performance. Immediately following MI, the acute homeostatic hyperactivity of the sympathetic nervous system (SNS), a systemic delivery of vasoconstrictive hormones via the renin–angiotensin–aldosterone system (RAAS), and activation of the sympathoadrenal system is critical to counteract myocardial systolic dysfunction [1]. The elevated SNS activation increases systemic blood flow while post-MI RAAS influence promotes expansion of plasma volume in an effort to regain adequate blood pressure and cardiac function [2–5].

Although these acute responses occur to counteract the notable reduction of blood pressure [6], chronic SNS and RAAS elevation causes a sodium-induced plasma volume expansion [7], and water retention [8–10]. This maladaptive remodeling contributes to a host of adverse conditions, which include LV dilation, cardiac wall thinning, infarct expansion, and fibrosis, leading to pathologic cardiac hypertrophy [5, 11–14]. Due to an increased risk for developing congestive heart failure after MI [15], a valiant effort has been made to define effective cardiac rehabilitative techniques to attenuate post-MI LV remodeling.

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Exercise-based cardiac rehabilitation has become an important complementary intervention in heart failure. It has proven to lower the risk of mortality and reinfarction when used as a secondary MI preventive technique [16, 17]. Endurance training (Et) exercise studies have revealed beneficial effects on improving cardiac function and attenuating cardiac remodeling [10, 18, 19]. However, possible contraindications may present similar to the compensatory mechanisms of post-MI RAAS-induced plasma volume expansion. In healthy subjects, an increased reliance on aerobic energy metabolism resulting from Et causes alterations in blood composition. These alterations stimulate a compensatory upregulation of serum albumin to transport free fatty acids from adipose tissue to working skeletal muscle [20, 21]. Albeit this transport mechanism is a necessary physiologic component of aerobic respiration in healthy individuals, albumin increases water-binding capacity, promoting blood plasma expansion [22, 23]. Evidence has shown that plasma volume expansion from Et significantly increases volumetric preload to the myocardium and causes LV enlargement [24]. Although it is a physiological Et adaptation in healthy individuals, it may contribute to even greater LV dilation in cardiac patients with an already expanded intravascular volume [25].

In contrast, the hemodynamic condition of the LV that occurs with strength training (St) is pressure-overload, while Et induces volume-overload conditions [24]. In addition, the primary fuel source for St is glucose in contrast to the predominantly free fatty acids used for Et [24, 26]. Thus, St results in concentric cardiac hypertrophy characterized by lateral cardiomyocyte proliferation, parallel addition of sarcomeres, and increased cardiomyocyte thickness, promoting increased LV wall thickness without chamber diameter expansion induced by increased volume [27–29]. The cardiac adaptations induced by concentric hypertrophy include enhanced myocardial contraction force with no parallel effect on albumin-induced plasma volume expansion [30, 31]. Hence, St-induced cardiac hypertrophy is characterized by ventricular wall thickening due to strengthened myocardiocytes without chamber enlargement [24, 26], whereas MI-induced cardiac hypertrophy is categorized by wall thinning due to elongated and weakened myocardiocytes, leading to ventricular dilation [2, 4, 5]. Although strong evidence suggests St elicits beneficial adaptations on cardiac function, these studies, mainly focused on healthy subjects and the effects of St following MI remain to be elucidated.

Therefore, the purpose of this study was to investigate whether post-MI St would beneficially improve cardiac function. We hypothesized that post-MI St would attenuate MI-associated cardiac dysfunction without ventricular dilation.

Methods

Animal model

Six-week-old male Sprague–Dawley rats (185–200 g) were used for this study in accordance with the Institutional Animal Care and Use Committees (IACUC) of the University of Texas at San Antonio. Rats were housed in accordance with institutional procedures and were fed ad libitum using standard laboratory rat chow with free access to tap water. To ensure animals were accustomed to training, all rats were exercised on an 85° inclined rodent ladder for a total of 3 climbs per day for 5 days prior to the induction of MI. This habitual exercise would not cause significant training effects to either the cardiovascular or skeletal systems because the exercise session was very short (only 3 climbs/day) and the intensity was very low (no weights attached). Following the habituating exercise and 2 days of inactivity, MI was induced via surgical ligation of the left anterior descending coronary artery (LAD) [12, 32]. The rats were anesthetized with 2–3% isoflurane oxygen mixture. A left thoracotomy was performed to gently and rapidly exteriorize the heart. Using a 6-0 silk suture the LAD was ligated approximately 2 mm below the left atrium [12]. Sham rats served as non-MI controls and underwent identical surgical procedures without ligating LAD. The animals received Buprenex (0.05 mg/kg s.c.), a pain killer, before waking up from the surgery, and twice a day for the next 2 days after surgery.

Experimental groups

At the end of a 1-week recovery period, echocardiographic (ECHO) assessments were used to determine the percent fractional shortening (%FS) of the experimental groups. Rats with MI were matched by %FS and then randomly assigned to two experimental groups: MI-Sed (MI, no exercise; $n=9$), and MI-St (MI + strength exercise; $n=10$). The Sham group served as a non-MI control group: Sham (no MI, no exercise; $n=9$). Sham and MI-Sed rats remained sedentary throughout the duration of the exercise period. The MI-St group began exercise training the day after %FS randomized group assignment. All rats were sacrificed 48 h following the last training bout of the 10-week exercise protocol. Figure 1 illustrates the experimental flow chart.

Exercise training

Strength training was initiated 1 week after MI for rats assigned to the MI-St group. The strength training protocol was modified from a previous study by Lee et al. [33] and utilized a 1-m ladder with 2-cm grip steps inclined at 85°.

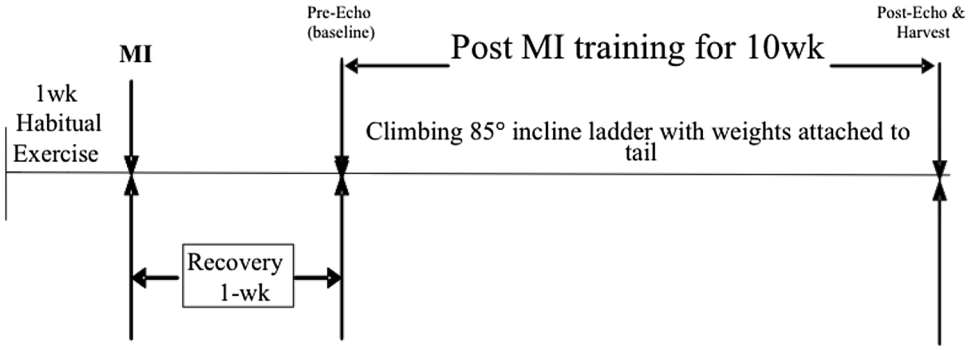

Fig. 1 Experiment flow chart

A cylinder containing premeasured weights was attached to the proximal end of the tail with foam tape (3M Conan) and a Velcro strap [33]. Weight range was determined by a 1 repetition max (1RM) test defined as the heaviest weight lifted the full length of the ladder. Each 1 RM test consisted of 85° ladder climbs using 50–130% g/body weight (BW) with 20% weight increments per climb until a maximally weighted climb was reached. 1 RM tests were performed on week 1 and week 5 post-MI to monitor strength development and effectiveness of the exercise protocol. The 1 RM values were used to formulate a step-periodization program using the following design: a starting climb weight of 50% 1RM, incremental weight increase of 5% per climb, 8–10 climbs per session, with 2 min rest between climbs. Strength training was tolerated well by rats with MI and no mortalities occurred during the 10 weeks of training.

In vivo echocardiographic measurement

ECHO measurements were obtained 1-week post-MI, and after 10 weeks of exercise training using an ECHO system equipped with a 10-MHz transducer (SonoHeart Elite, SonoSite Bothell, WA). Rats were anesthetized with 2–3% isoflurane mixed with oxygen, then a two-dimensional short-axis view of the LV was obtained at the papillary muscle level to identify M-Mode tracings [11]. LV end-diastolic dimension (LVEDd) and LV end-systolic dimension (LVESd) were used to quantify myocardial remodeling. The %FS was calculated as (%FS = [(LVEDd − LVESd)/LVEDd] × 100) [11, 34]. All measurements were averaged over 5 consecutive cardiac cycles.

In vivo hemodynamic measurement

Immediately after ECHO measurements (while anesthetized), each rat was placed on a heated surgical bed and the right carotid artery was exposed. A pressure transducer (Model SPR-838, Millar instruments) was inserted into the right carotid artery and carefully maneuvered inside the LV cavity. Hemodynamic parameters including LV end-systolic pressure (LVESP), LV end-diastolic pressure (LVEDP), aortic systolic pressure, aortic diastolic pressure, and peak velocities of contraction (+ d*P*/d*t* max) and relaxation (− d*P*/d*t* max) were measured and recorded. After measuring, the hearts were harvested and frozen in an isopentane/dry ice mixture and stored at − 80 °C for further analyses.

Determination of infarct percentage

Myocardium samples were sectioned (6 μm) in a cryostat (Lecia CM 1850, Wetzlar, Germany), and stored at − 80 °C until use. Mason's trichrome staining protocol was used to quantify infarct percentage. Images were obtained using a light microscope. Measurements were quantified using Image Pro Plus software (ver. 5, Media Cybernetics). Infarct percentage was determined by measuring the total infarcted epicardial and endocardial lengths then calculated from the myocardium cross-section [35]. We divided the sum of the planimetered endocardial and epicardial infarcted circumferences by the sum of the total LV epicardial and endocardial circumferences. Infarctions qualitatively observed to have a non-transmural infarction were eliminated from the study.

Statistical analysis

Differences in mean parameters among groups (Sham, MI-Sed, and MI-St) were analyzed using a one-way ANOVA. Sigma plot software (version 11.0) was used to perform statistical analysis and graphical representation. An ANOVA with significant F ratios ($P < 0.05$) was followed by Tukey post hoc analysis. Values are expressed as mean ± SEM.

Results

General characteristics

General characteristics for the study population are summarized in Table 1. Infarct percentages among the MI-Sed and MI-groups were comparable, and absolute heart weight (HW, g) of MI-Sed was greater than MI-St ($P < 0.001$). As expected, the total body weight was significantly higher

Table 1 General characteristics

Group	Sham ($n=9$)	MI-Sed ($n=9$)	MI-St ($n=10$)
Infarct size (%)	–	41.0 ± 1.92	39.2 ± 4.41
BW (g)	542.8 ± 10.8	554.4 ± 15.4	472.7 ± 9.8***§
HW (g)	1.44 ± 0.03*	1.66 ± 0.10	1.516 ± 0.04***
HW (g)/BW (kg)	2.65 ± 0.05**	3.00 ± 0.14	3.21 ± 0.05¶

Values are expressed as ± SEM

BW body weight at sacrifice, *HW* heart weight, *HW/BW* ratio of heart weight to body weight

*$P<0.01$ compared to MI groups; **$P<0.001$ compared MI groups; ***$P<0.05$ compared to MI-Sed group; ¶$P<0.001$ compared to MI-Sed; §$P<0.05$ compared to the Sham group

in both the Sham and MI-Sed groups when compared to MI-St ($P<0.05$). Compared to its sedentary counterparts, the lighter body weight of the St group was due to the exercise training. Heart weight normalized by body weight [HW (g)/BW (kg)] showed that both MI groups were significantly heavier compared to the Sham group ($P<0.05$), while MI-St was significantly heavier than MI-Sed ($P<0.001$).

Echocardiography

Doppler ECHO assessment of LV ventricular function (Fig. 2) revealed %FS was significantly higher in the MI-St group when compared to MI-Sed ($P<0.05$). LVEDd (Table 2) was significantly lower for MI-St than MI-Sed ($P<0.05$). In addition, the LV anterior wall systolic thickness (AWST), and diastolic thickness (AWDT) were significantly reduced after MI. The LV posterior wall systolic thickness (PWST) was higher in the MI-St group compared to the MI-Sed group ($P<0.001$), indicative of St-induced increase in LV contractility. It is worth noting that the values of AWST, AWDT, and LV posterior wall diastolic thickness (PWDT) were greater in the MI-St group when compared to the MI-Sed group although they were not statistically significant. These data suggest St attenuates MI-associated cardiac dysfunction and significantly attenuating LV dilation (i.e., LVEDd) and may contribute to an improved myocardial function compared to MI-Sed.

Table 2 Doppler echocardiographic assessment of LV ventricular geometry and function

Group	Sham ($n=9$)	MI-Sed ($n=9$)	MI-St ($n=10$)
LVEDd (cm)	0.83 ± 0.02**	1.16 ± 0.02	1.08 ± 0.01***
LVESd (cm)	0.48 ± 0.03**	0.94 ± 0.03	0.83 ± 0.01
AWDT (mm)	2.51 ± 0.10**	0.40 ± 0.02	0.43 ± 0.04
AWST (mm)	3.75 ± 0.05**	0.50 ± 0.02	0.78 ± 0.01
PWDT (mm)	2.04 ± 0.08	2.29 ± 0.06	2.31 ± 0.07
PWST (mm)	2.94 ± 0.02	2.86 ± 0.10*	3.20 ± 0.08

Values are expressed as ± SEM

LVEDd left ventricular end-diastolic dimension, *LVESd* left ventricular end-systolic dimension, *AWDT* anterior wall diastolic thickness, *AWST* anterior wall systolic thickness, *PWDT* posterior wall diastolic thickness, *PWST* posterior wall systolic thickness

*$P<0.001$ compared to MI-St group; **$P<0.001$ compared to MI groups; ***$P<0.05$ compared to MI-Sed group

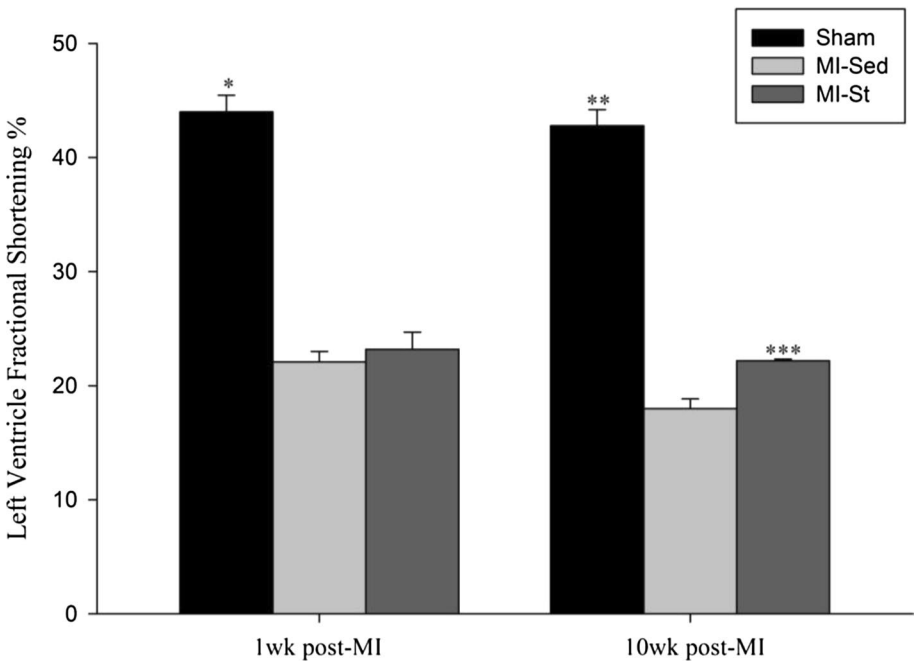

Fig. 2 Left ventricle fractional shortening percentage. Values are expressed as ± SEM. *$P<0.01$ compared to MI groups; **$P<0.001$ compared to MI groups; ***$P<0.05$ compared to MI-Sed group

In vivo hemodynamics

The LVEDP of MI-St was significantly lower when compared to MI-Sed ($P < 0.05$). Mean values for systolic aortic pressure, diastolic aortic pressure, and LVESP were comparable among all groups. Interestingly, the hemodynamic data revealed that + dP/dt max values (Fig. 3) were significantly higher in the MI-St than MI-Sed group ($P < 0.05$). Additionally, the − dP/dt max (Fig. 3) of the MI-Sed group was significantly greater than both Sham and MI-St ($P < 0.05$). Conversely, no significance was found among MI-St when compared to Sham ($P > 0.05$). These data suggest that post-MI St may effectively preserve the rate of contraction and relaxation.

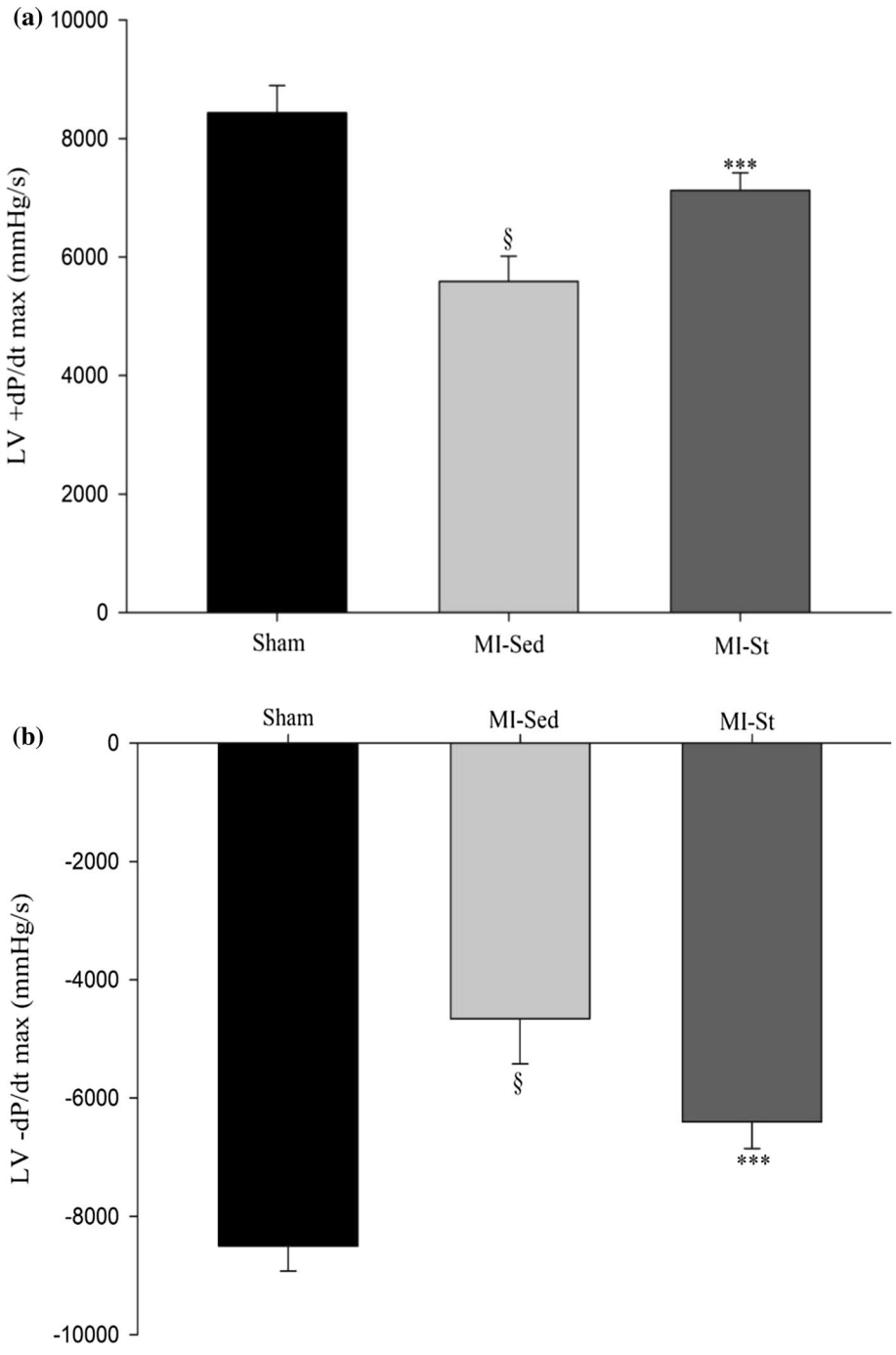

Fig. 3 **a** Peak velocities of contraction, + dP/dt max. §$P < 0.05$ compared to the Sham group; ***$P < 0.05$ compared to the MI-Sed group, **b** peak velocities of relaxation, − dP/dt max. §$P < 0.05$ compared to the Sham group; ***$P < 0.05$ compared to the MI-Sed group

Discussion

The results of the current study demonstrate, for the first time, that St favorably affects post-MI cardiac function. Two novel findings exist within our data. First, post-MI strength training significantly attenuated LV dilation and increased systolic posterior wall thickness in the viable myocardium. Secondly, post-MI St significantly attenuated cardiac dysfunction, as indicated by the improved %FS and maximum rate of contraction and relaxation ($\pm dP/dt$ max).

After MI, the heart undergoes adverse cardiac remodeling characterized by wall thinning and ventricular dilation, leading to impaired cardiac function and heart failure [36]. As expected, the current study showed a significant LV dilation as illustrated by LVEDd and deteriorated cardiac function in the sedentary group over the duration of the studied period. This finding agrees with the consensus that MI causes progressive ventricular dilation [37–39]. In contrast, a shorter LVEDd was observed with MI-St in the current study. This observation is consistent with previous studies reporting unaffected LV chamber volume from St in healthy subjects [24, 40, 41].

It is known that St, in the healthy heart, induces concentric cardiac hypertrophy without ventricular dysfunction, cavity enlargement, or plasma volume expansion [24, 40, 41]. To date, few studies have investigated the effects of St post-MI. A clinical study by Schmid et al. [42] compared post-MI patients trained with Et to those trained with Et + St combined, and reported two key findings. First, the rate pressure product (RPP = heart rate × systolic aortic pressure) was lower with Et + St than with Et alone, without any St-induced effects on ventricular dilation. This suggests the possibility of beneficial post-MI St responses with no opposing LV chamber expansion [42]. Secondly, Schmid et al. [42] deemed dynamic post-MI St to be a safe cardiac rehabilitation exercise prescription for those with mild-to-moderate LV dysfunction (LV ejection fraction < 45% measured during acute coronary event). However, little is known about the effects of St alone (not coupled with Et) following MI, in either humans or animals.

The ratio of HW/BW was markedly increased in the two MI groups compared to Sham. However, contrary to the HW/BW of MI-Sed and based on the significant increase in PWST in the MI-St group compared to the MI-Sed group ($P < 0.05$), our data suggests that St induced an increase in myocardial contractility as a result of the physiological demand from exercise training. Previous studies [11, 12] using a post-MI Et mode demonstrated that after 8 weeks of training, both the cardiac contractility (FS%) and hemodynamic functions were significantly improved compared to their sedentary counterparts. Endurance training-induced enhancement of cardiac function was in part due to the augmented cardiac muscle contractility as illustrated by the shortening of LVESd. However, endurance exercise did not alleviate LVEDd [11, 12]. Interestingly, the current study showed that St not only shortened LVEDd, but also thickened PWST compared to the sedentary group.

It is worth noting that both MI-St and MI-Sed groups had similar cardiac wall thicknesses as illustrated by AWDT and PWDT (Table 2). Thus, MI-St did not induce the expected cardiac concentric hypertrophy as observed in the healthy subjects [24, 26, 43]. The lack of strength training-induced concentric hypertrophy in the infarcted heart may be due to the pathological nature of the wounded heart or the insufficient training intensity/volume employed in the current study. Whether St can induce concentric hypertrophy in the infarcted heart remains to be further elucidated. Nevertheless, the current study provides evidence that post-MI St can preserve cardiac function as effectively as post-MI endurance training [4, 11, 12]. The preserved cardiac function may be attributed to post-MI exercise in general rather than a specific mode of exercise (i.e., strength vs endurance training).

Evidence suggests that exercise training improves LV contractile function and kinetics [11, 44, 45]. In agreement with the previous findings, we found the peak velocities of contraction (Fig. 3a) were markedly increased in MI-St compared with the MI-Sed group ($P < 0.05$). Peak velocity of relaxation (Fig. 3b) remained formidable in the MI-St group, but was significantly diminished in the

Table 3 In vivo hemodynamics

Group	Sham ($n = 9$)	MI-Sed ($n = 9$)	MI-St ($n = 10$)
LVESP (mmHg)	112.0 ± 6.13	105.6 ± 2.04	112.9 ± 3.60
LVEDP (mmHg)	−4.27 ± 1.52	3.69 ± 3.00*#	0.44 ± 0.69
HR (bpm)	319.7 ± 9.20	323.8 ± 11.7	313.0 ± 8.31
Systolic aortic pressure (mmHg)	103.0 ± 2.72	103.8 ± 2.42	106.2 ± 2.59
Diastolic aortic pressure (mmHg)	75.8 ± 1.40	77.4 ± 1.58	79.8 ± 2.33

Values are expressed as ± SEM

LVESP left ventricular end-systolic pressure, *LVEDP* left ventricular end-diastolic pressure, *HR* heart rate

*$P < 0.05$ compared to Sham group; #$P < 0.05$ compared to MI-St group

MI-Sed group compared to Sham ($P < 0.05$). Furthermore, the hemodynamic data (Table 3) demonstrated preserved LVEDP with St comparable to pressures of the Sham group and significantly lower than MI-Sed. Thus, our data demonstrated that post-MI St significantly increased LV posterior wall systolic thickness (Table 2) and peak velocities of contraction and relaxation (Fig. 3) compared to the MI-Sed group. These beneficial St effects preserved cardiac function as illustrated by the fractional shortening (Fig. 2).

The proposed mechanism of exercise training-induced improvement of hemodynamic (peak velocity of contraction and relaxation) and cardiac function includes: enhanced anti-oxidant capacities and attenuated oxidative stress [5, 46, 47], reduced MI-induced elevations of renin–angiotensin–aldosterone system [4], mitigated myocardial fibrosis [11, 12], improved myocardium myosin heavy chain alpha [48], and augmented thyroid hormone receptors (alpha-1 and beta-1) [49]. St not only induces skeletal strength [50], but also preserves cardiac muscle strength as illustrated by improved cardiac function in the present study.

Although our findings may have clinical relevance, there are some notable limitations to the current study. The use of animal St post-MI may be different from human St post-MI, including the method and intensity of the exercise. The measurement of hemodynamic parameters by invasive catheter insertion to the LV may not be applicable in human studies. We did not deploy a reperfusion study of cardiac blood flow in the current experiment model. The sample size was also limited. The comprehensive mechanisms by which the beneficial adaptations occur with post-MI St remain unclear.

In summary, our results suggest that strength exercise training may elicit favorable influences on post-MI cardiac remodeling by improving cardiac function without causing LV dilation. We found that St beneficially attenuated MI-associated cardiac systolic dysfunction (i.e., %FS) and improved cardiac contractility (i.e., $\pm dP/dt$ max). Furthermore, the significant lack of LV diastolic expansion with post-MI St in contrast to Et, could prove vital to successful long-term rehabilitative outcomes. Although our findings may have clinical relevance, the mechanisms by which the beneficial adaptations occur with post-MI St remain unclear. Our results provide a foundation for the direction of future investigation in cardiac rehabilitation surrounding post-MI St techniques, determination of optimal duration and timing of interventions, and better understanding of the mechanisms responsible for beneficial St-induced adaptive responses in the post-MI heart.

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Compliance with ethical standards

Ethical approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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