

Angiotensin II receptor blockade attenuates the deleterious effects of exercise training on post-MI ventricular remodelling in rats

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Abstract

Objectives: The effects of exercise training on LV remodelling following large anterior myocardial infarction (MI) remains controversial. Blockade of the renin–angiotensin system has been shown to prevent ventricular dilation and deleterious remodeling. We therefore tested, in a rat model of chronic MI, whether any potentially deleterious effects of exercise on post-MI remodelling could be ameliorated by angiotensin II receptor blockade. **Methods:** Male Wistar rats underwent coronary ligation or sham operation. Treatment with losartan (10 mg/kg/day) began 1 week post-MI and moderate treadmill exercise (25 m/min, 60 min/day, 5 days/week) was initiated 2 weeks post-MI. Systolic and diastolic pressure–volume relationships were measured in isolated, red-cell perfused, isovolumically beating hearts 8 weeks post-MI. Morphometric measurements were performed in trichrome stained cross sections of the heart. Five groups of animals were compared: sham ($n=13$), control MI (MI; $n=11$), MI plus losartan (MI–Los; $n=13$), MI plus exercise (MI–Ex; $n=10$) and MI plus exercise and losartan (MI–Ex–Los; $n=12$). **Results:** Infarct size (% of left ventricle, LV) was similar among the infarcted groups [MI=43±4%, MI–Los=49±2%, MI–Ex=45±1%, MI–Ex–Los=48±2% (NS)]. Exercise, losartan and exercise+losartan treatments all attenuated LV dilation post-MI to a similar degree. Exercise training increased LV developed pressure in both untreated and losartan treated hearts ($P<0.05$ vs. other MI groups). In addition, exercise resulted in additional scar thinning in untreated hearts, while no additional scar thinning was seen in post-infarct hearts receiving both losartan and exercise. **Conclusions:** Following large anterior MI, losartan attenuated LV dilation and scar thinning. In untreated animals, exercise decreased dilation, but also contributed to scar thinning. Therefore, exercise concurrent with blockade of the renin–angiotensin system may provide optimal therapeutic benefit following large anterior MI. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Myocardial infarction (MI) causes acute and chronic transformation of the necrotic infarct zone and subsequent compensatory hypertrophy of the non-infarct tissue, leading to global alterations and cavity dilation that have collectively been termed ‘ventricular remodelling’ [1,2]. Current treatment of patients post-MI often includes exercise training as an element of cardiac rehabilitation [3]. The effects of exercise training on left ventricle (LV) remodelling post-MI, however, have remained controver-

sial in clinical studies. In an early study of patients with extended anterior myocardial infarction, Jugdutt et al. [4] showed an increase in LV dilation and a decrease in regional and global cardiac function following exercise. In contrast, other studies have shown no detrimental effect of exercise post-MI [5,6]. The ELVD trial, a more extensive, recent investigation of patients with large anterior MI and reduced ejection fractions, reported that exercise training attenuated LV dilation and increased systolic function [7]. The medical treatment of patients enrolled in these studies was similar, with one remarkable exception — level of treatment with angiotensin-converting enzyme inhibitors (ACE inhibitors). Earlier studies, which showed deleterious

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effects of post-MI exercise training, used minimal ACE inhibitor therapy [4], while in more recent studies [6,7], extensive ACE inhibitor therapy was utilized, in up to 100% of patients. Post-MI exercise training in experimental studies, in which no ACE inhibition therapy was used, have repeatedly shown deleterious results on LV remodeling, including an increase in cellular hypertrophy, left ventricular dilation, further scar thinning, and ultimately, a reduction in survival [8–11], with the exception of one study [12]. ACE inhibition might confound the results of these exercise trials, since post-MI, it improves cardiac systolic and diastolic performance, reduces hypertrophy and ventricular dilation, and prolongs survival in both experimental and clinical studies [1,13–17]. Similar effects have also been shown with angiotensin II receptor blockers in both experimental [18–20] and clinical studies [21].

We therefore hypothesized that post-MI treadmill exercise would exacerbate deleterious remodeling, and the addition of angiotensin type-1 (AT_1) receptor blocker, losartan, in conjunction with exercise training would result in an attenuation of this unfavorable exercise effect. We utilized a rat model of post-infarct rehabilitation that closely mimics current clinical procedures of treadmill exercise and AII intervention therapy, to examine left-ventricular dilation and function, as well as morphometric elements of ventricular remodeling.

2. Methods

2.1. Animals and experimental myocardial infarction

Male Wistar rats 200–250 g (Charles River Laboratories), housed one per cage under a 12 h light–dark cycle, received a constant diet of laboratory chow (Purina) and water. Rats were anesthetized with sodium pentobarbital (35 mg/kg, i.p.), intubated, and mechanically ventilated using a Harvard apparatus rodent ventilator. Following left thoracotomy, the left large marginal coronary artery was ligated approximately 2 mm below the left atrium with a 5-0 Ethilon silk suture. Successful ligation was confirmed by observation of pallor of the left ventricular free wall and bulging of the left atrium. Sham-operated animals underwent an identical procedure without tying the suture. All animal handling and protocols were approved by the Institutional Animals Care and Use Committee at Boston University School of Medicine and strictly adhere to the regulations of the National Society for Medical Research.

2.2. Experimental groups and mortality

A total of 66 rats were used, 13 animals as sham operated controls and 53 rats underwent coronary ligation. Seven animals died within 48 h of occlusion, yielding a peri-infarct mortality rate of 13%. The remaining 46 rats were randomized to the following groups: myocardial

infarction without treatment (MI, $n=10$), infarction with exercise treatment (MI–Ex, $n=10$), infarction with losartan treatment (MI–Los, $n=13$), and infarction with both exercise and losartan treatment (MI–Ex–Los, $n=13$). Four rats died before the end of the protocol (MI 1; MI–Ex 1; MI–Los 0; MI–Ex–Los 2).

2.3. Drug and exercise protocol

Losartan treatment (10 mg losartan/kg body weight/day) was initiated, 1 week post-infarction, similarly to previous studies performed with ACE-inhibitors [20]. The drug was added to the drinking water, with careful monitoring of water consumption and body weight to ensure proper drug dosage. The exercise protocol was initiated 2 weeks after infarction. The rats were initially exercised on a rodent treadmill at 0.5 km/h for 35 min. The speed and duration of running were increased in 0.20 km/day and 5 min/day increments until animals were exercising at 1.5 km/h for 1 h. The rats were then exercised 5 days/week for 5 subsequent weeks.

2.4. Whole heart perfusion protocol

Hemodynamic studies were performed in an isolated erythrocyte perfused heart, as described by Eberli et al. [22] Briefly, rats were anesthetized with 35 mg/kg sodium pentobarbital (i.p.) and the hearts excised, weighed, secured on an aortic perfusion cannula, and retrogradely perfused.

The perfusate consisted of cow erythrocytes resuspended in calcium free Krebs–Henseleit buffer (Krebs–Henseleit buffer contained NaCl 118 mM, KCl 4.7 mM, KH_2PO_4 1.2 mM, $MgSO_4$ 1.2 mM, $NaHCO_3$ 25 mM, glucose 5.5 mM, lactate 1 mM, palmitic acid 0.4 mM, Gentamycin 0.2 mg/dl, and 4 g% bovine serum albumin at a final hematocrit of 40%. $CaCl_2$ was added to the perfusate to a final ionized calcium concentration of 1.2 mM. Accurate final ionic concentrations were ensured using a Nova 6 electrolyte analyzer (Nova Biomedical). The erythrocyte perfusate was pumped (Digi Staltic pump, Masterflex) through capillary tubing into an enclosed cylinder with 77% N_2 , 20% O_2 , and 3% CO_2 . A final P_{O_2} of 140–160 mmHg and a pH of 7.35 to 7.4 were attained and confirmed using a blood gas analyzer (BG3, Instrumentation Laboratory).

The heart's coronary perfusion was maintained at a constant pressure of 80 mmHg. Coronary perfusion pressure was recorded by a pressure transducer (Gould-Statham P23dB, Gould Oxnard, CA, USA) fastened to the aortic cannula via a sidearm. The left atria was incised and a small plastic drain was inserted through the apex of the left ventricle for venting of Thebesian drainage. A second drain was inserted into the right ventricle, via the pulmonary artery, for collection of coronary venous effluent. Copper electrodes attached to an electrical stimulator

(model 59 stimulator, Grass Instrument, Quincy, MA, USA) were secured to the sides of the left ventricle and hearts were paced at 5 Hz. A collapsed balloon custom-made from non-compliant, flexible polyvinyl chloride film connected to a short polyethylene tube was inserted in the left ventricle via the left atrium. The balloon was connected to a pressure transducer (Gould-Statham P23dB, Gould Oxnard) for constant monitoring of left ventricular pressure.

2.5. Pressure–volume analysis

After an equilibration period of 30 min, the LV balloon was inflated to an end-diastolic pressure of approximately 40 mmHg and emptied to ensure proper adhesion of the balloon in the ventricular cavity. Active pressure–volume relationships were then generated. From a balloon volume of zero, the balloon was filled in increments of 0.05 ml and subsequent pressures recorded.

Diastolic pressure–volume curves were generated using a model derived by Fletcher et al. [23] End-diastolic pressures, at incremental volumes were plotted and a best-fit exponential curve ($P = b \cdot e^{kV}$) generated for each rat (DELTA GRAPH PRO 3). The volumes at a given pressure were averaged for animals in each group, and a final pressure–volume exponential relationship obtained.

Contractile function was assessed by developed pressure–volume analysis, wherein developed pressure was plotted versus LV end-diastolic volume. The developed pressures at given diastolic volumes were averaged for hearts within each group, and a final contractile function relationship was determined.

2.6. Histology and infarct size measurement

After the pressure–volume experiments, the heart was arrested in diastole by an infusion of 1 ml of high concentration potassium chloride with the LV balloon in place and filled to a final distending pressure of 5 mmHg. The hearts were then flushed with 2 ml of saline and perfusion fixed with 200 ml of 10% buffered formalin acetate (Fisher Scientific). The tissue was processed for paraffin embedding and sections (6- μ m thick) from each of six equally spaced levels (base through apex) were stained with trichrome and picosirius red.

The sections were photographed and infarct size was determined as the mean percent of epicardial and endocardial circumference (IMAGE 1.49, NIH, Wacom) occupied by scar tissue averaged for all of the ventricular levels.

Using a standard desk projector, slides from the mid-ventricular levels were projected at a magnification of 20 \times and left ventricular septal and infarct wall thickness was measured.

Collagen content in the non-infarcted mid-septal region and the infarcted free wall was measured from picosirius

red stained sections using a published image-analysis method [24].

2.7. Assessment of pulmonary congestion

At sacrifice, lungs were extracted, weighed, and placed in an oven at 55°C. After 72 h, the lungs were again weighed and the lung wet/dry ratio calculated, as an indirect assessment of pulmonary congestion.

2.8. Statistics

Statistical analysis of pressure–volume relationships and wall stress curves was conducted using a repeated measures two-factor analysis of variance (ANOVA). If an overall ANOVA indicated a significant difference, individual pairs were compared using the least significant difference method. Animal characteristics were analyzed with a one-factor ANOVA. All data are presented as mean \pm S.E.M.

3. Results

3.1. Animal characteristics

Body mass increased in all groups during the protocol, though infarcted animals that underwent exercise training gained the least weight. MI caused a significant increase in heart weight/body weight ratio in all MI groups, suggesting similar levels of overall myocardial compensatory hypertrophy. In addition, infarction resulted in increased lung wet/dry ratios; however, the increase was only significant in MI–Ex rats (Table 1).

3.2. Diastolic pressure–volume relationships

Fig. 1 shows the left ventricular diastolic pressure–volume curves, normalized for body weight. All rats that underwent MI (MI, MI–Ex, MI–Los, MI–Ex–Los) exhibited ventricular dilation and a rightward shift of the diastolic pressure–volume curve, placing the sham curve significantly ($P < 0.05$) leftward of all other groups. In addition, the untreated MI group experienced the greatest ventricular enlargement, and shifted significantly ($P < 0.05$) rightward of all other groups. Thus, both exercise and losartan attenuated ventricular dilation post-MI, though no additional benefit was seen with combined treatment.

3.3. LV Developed pressure

MI resulted in a reduction in developed pressure over a range of diastolic volumes in all groups relative to sham animals. Exercise post-MI increased left ventricular de-

Table 1
Animal characteristics^a

Group	No. of rats	Body weight (g)		Heart weight (g)	Heart wt./ body wt. (g/kg)	Lung wet/ lung dry
		Initial	8 weeks post-MI			
Sham	13	236±6	543±17	1.82±0.07	3.38±0.16	4.17±0.17
MI	9	235±9	519±15	2.20±0.16**‡§	4.23±0.26**	4.31±0.23
MI-Ex	9	230±5	466±10**†	1.81±0.05	3.95±0.13*	5.29±0.60*
MI-LOS	13	237±3	494±11**	2.01±0.09	4.08±0.17**	5.14±0.44
MI-Ex-LOS	11	238±5	473±11**†	1.88±0.07	4.01±0.25*	4.55±0.30

^a Wt., weight; MI, post-MI controls; MI-Ex, post-MI rats treated with exercise; MI-LOS, post-MI rats treated with losartan; MI-Ex-LOS, post-MI rats treated with exercise and losartan.

* $P < 0.05$ vs. sham; ** $P < 0.01$ vs. sham; † $P < 0.05$ vs. MI; ‡ $P < 0.05$ vs. MI-Ex; § $P < 0.05$ vs. MI-Ex-LOS.

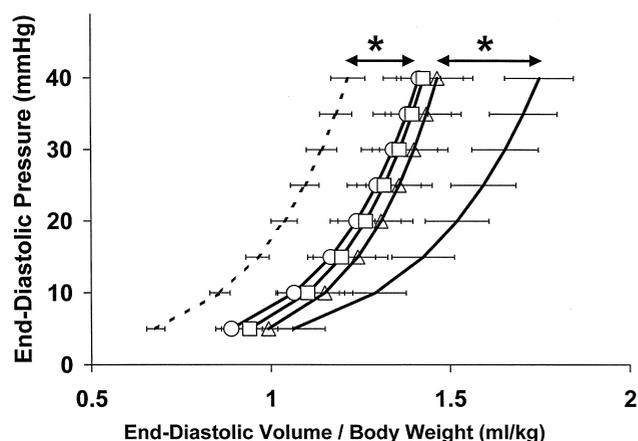


Fig. 1. Diastolic pressure–volume relationship for Sham (---), MI (—), MI-Ex (⊖), MI-LOS (Δ) and MI-Ex-LOS (⊕) hearts. MI resulted in ventricular dilation in all animals, shifting all MI groups significantly rightward of sham animals. Infarcted hearts receiving exercise, losartan, or exercise plus losartan therapy had reduced cavity dilation and a leftward shift in the P - V curve relative to infarcted control animals; * $P < 0.05$.

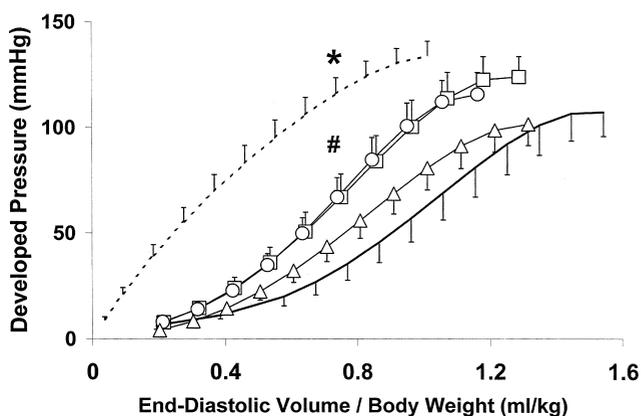


Fig. 2. Developed pressure–volume relationship for Sham (---), MI (—), MI-Ex (⊖), MI-LOS (Δ) and MI-Ex-LOS (⊕) hearts. MI resulted in diminished contractile function in all MI hearts relative to sham animals (* $P < 0.05$). Exercise training augmented LV developed pressures in untreated and losartan treated hearts relative to infarcted control hearts and losartan treated hearts (# $P < 0.05$).

veloped pressures in both untreated and losartan treated hearts relative to control MI hearts (Fig. 2).

3.4. Morphometry and cardiac fibrosis

Infarct size was large in all infarcted animals, with no significant difference among groups. Mid-septal wall thickness, an assessment of compensatory hypertrophy, was also similar for all infarct groups. Furthermore, infarction caused an increase in cardiac fibrosis in the non-infarct and infarct zone compared to the sham group, though collagen content in the scar region was lower in the losartan-treated animals. Infarct thickness, however, was only reduced in exercise trained animals relative to control and exercise + losartan treated animals (Table 2). Therefore post-MI exercise training induced further scar thinning.

4. Discussion

We tested in a rodent model of chronic infarction how treadmill exercise training affects post-MI remodelling and whether exercise in conjunction with AT_1 receptor antagonist losartan, attenuates deleterious remodelling. We found that AT_1 receptor blockade, similarly to ACE inhibition, decreased LV dilation post-infarction, and exercise training resulted in a comparable attenuation of ventricular dilation. Combination therapy of both exercise and AT_1 receptor blockade, however, had no additive effect on ventricular dimensions. Furthermore, post-MI exercise increased LV developed pressure over a range of diastolic volumes, as well as resulted in additional scar thinning and pulmonary congestion. Concurrent losartan treatment, however, attenuated exercise-induced increases in scar thinning.

4.1. Exercise training

Previous studies of exercise in infarcted rats have generally shown an increase in ventricular enlargement [8,9,11], with only one study describing a decrease in LV dilation [12]. It was therefore unexpected that treadmill exercise initiated 2 weeks after infarction would attenuate

Table 2
Morphometry and fibrosis^a

Group	Infarct (%)	Septal thickness (mm)	Thinnest region of infarct (mm)	Fibrosis (%)	
				Septum	Infarct zone
Sham	N/A	1.63±0.08	N/A	2.67±0.14	2.7±0.6
MI	45.8±3.8	1.71±0.15	0.96±0.17	3.39±0.22	76.0±2.2**†§
MI-Ex	44.1±1.6	1.83±0.11	0.59±0.04†§	3.14±0.35	76.2±2.6**†§
MI-LOS	50.7±2.5	1.59±0.08	0.85±0.08	3.37±0.31	66.8±1.3**
MI-Ex-LOS	46.2±3.0	1.76±0.07	0.96±0.08	4.15±0.29**	61.7±2.8**

^a N/A, not applicable; MI, post-MI controls; MI-Ex, post-MI rats with exercise; MI-LOS, post-MI rats treated with losartan; MI-Ex-LOS, post-MI rats treated with exercise and losartan.

***P*<0.01 vs. sham; †*P*<0.05 vs. MI; ‡*P*<0.05 vs. MI-Los; §*P*<0.05 vs. MI-Ex-Los.

LV dilation. The deviation from previous exercise studies may be due to multiple factors, of which mode of exercise might be the most important. Previous studies have generally employed swimming as the exercise regimen. Swimming is a very different, less quantifiable mode of exercise stimulus. It often results in transient hypoxia and hypothermia, as well as undo stress, all which could potentially influence experimental results [25]. We attempted to use an exercise protocol that best simulates current cardiovascular exercise rehabilitation for humans post-MI, namely, low intensity endurance exercise. Previous studies employing treadmill exercise training in rats post-MI have shown no detrimental effect on infarct size and aneurysm expansion [26]. Also, exercise initiated early after infarction has been suggested to cause a more deleterious effect [8], while onset of training after infarct healing has occurred, resulted in more favorable remodelling [12]. Furthermore, the moderate nature of our exercise regimen might have contributed to its final beneficial effect. Increases in mid-septal fibrosis, wall thickness and heart weight associated with intense exercise, especially swimming exercise [27], were not seen in this study. Our study therefore suggests that relative late onset of a moderately intense treadmill exercise regiment is beneficial for overall post-MI dilation, although it may still cause scar thinning [12]. We speculate that the effects of exercise on LV dilation may be influenced by beneficial adaptations of the peripheral and coronary vasculature, resulting in vasodilation and a decrease in vascular resistance [28,29]. Furthermore, exercise has also been shown to attenuate catecholamine release and increases vagal tone [30–32].

In this study, exercise also improved contractile function following MI, causing greater developed pressures over a range of diastolic volumes, relative to infarcted control rats. Though elevated contractile function is believed to generally be beneficial post-infarction, augmented developed pressure, without additional compensatory hypertrophy, would suggest that exercise treated hearts generated greater systolic wall stress. We previously estimated mid-ventricular wall stress according to Laplace's Law (wall stress∝pressure·chamber radius/wall thickness), using pressure–volume relationships and mid-ventricular

mean radius and wall thickness dimensions, and indeed found exercise treated hearts to have elevated systolic wall stresses [33]. The elevated systolic stress in the exercise groups did not deleteriously affect ventricular dilation during the 6-week observation period.

4.2. Losartan

In this study, coronary ligation resulted in large anterior-lateral infarction of ~45% of the LV and subsequent ventricular dilation. AT₁ receptor blockade resulted in a reduction of LV dilation. While other studies have reported that AT₁ antagonists decreased mortality and fibrosis, as well as increased capillary density in post-MI hearts to a similar extent as ACE inhibition therapy, this study may be the first to report a similar attenuation of overall left ventricular remodelling [13,20,21,34]. While these results cannot definitively determine whether an ACE inhibitor or AII antagonist acts more favorable on LV remodelling, they, along with others, do suggest that AII antagonists may be of similar beneficial value as ACE inhibitors upon post-MI hemodynamics and remodelling.

The mechanism by which AII-antagonists exert their effects on post-MI remodelling is not well understood. The beneficial effects of ACE inhibition on left ventricular remodelling have been attributed to an attenuation of tissue and circulating levels of angiotensin II and/or inhibition of bradykinin breakdown [18,19,35–38]. Indeed, most of the beneficial effects of ACE inhibitors on post-MI remodelling can be blocked by inhibition of the kinin system [35–38]. If the kinin pathway contributes substantially to the beneficial effects of ACE inhibition on post-MI remodelling, it was unclear what effect, if any, selective AT₁ blockade may have on post-MI remodelling.

The possible mechanisms by which losartan influenced LV remodelling post-MI include a reduction in afterload and preload, as well as, direct cardiac effects. Though we did not measure in vivo cardiac pressures in this investigation, preliminary studies in non-infarcted rats proved a therapy with losartan (at 10 mg/kg body weight/day) was sufficient to cause a reduction in systolic pressures (data not shown). Furthermore, similar doses, as

well as smaller doses, of losartan were found to decrease blood pressure in previous described post-MI rat studies [18–20]. Therefore, it appears likely that losartan caused a reduction in afterload and that this attenuation of afterload might beneficially contribute to LV remodelling [18]. Losartan, through induction of natriuresis and diuresis, has also been shown to reduce in vivo left ventricular diastolic pressures, thereby reducing preload in post-MI hearts and possibly causing some of the beneficial effects of AII antagonism [18,19,34].

Furthermore, the beneficial effect of losartan might also be in part due to direct cardiac effects [18]. AT₁ receptor antagonists enact their direct cardiac effects via a combination of blockade of the AT₁ receptor and an unhindered stimulation of the angiotensin type-2 (AT₂) receptor. Blockade of the AT₁ receptor results in increased plasma renin and circulating angiotensin II levels [39], and an increase in AII will activate AT₂ receptors, which are already upregulated post-MI [40]. Liu et al., showed that the processes mediated by AT₂ receptors are important for the beneficial effects of AT₁ receptor blockade and suggested that indirect AT₂-mediated activation of nitric oxide, other autocooids, and the kinin system, might be involved [18].

We found a significant reduction in cardiac fibrosis in the infarcted portion of the LV with losartan treatment in both the exercise and non-exercise groups. As previously seen with ACE inhibition [41], this effect did not cause additional scar thinning, and did not influence the overall favorable effect on LV remodelling. Septal fibrosis did not appear to be altered by losartan treatment, and was even slightly elevated in hearts treated with losartan and exercise. The differential effect of losartan treatment on infarcted and non-infarcted portion of the LV might be related to tissue specific alterations of the renin–angiotensin system post-MI. Tissue AII levels and AT₁-receptor mRNA expression were reported to be increased to a greater extent in the infarcted than in the non-infarcted portion of the LV [40,42].

Furthermore, in accordance with previous work [19,38] but in contradiction to finding by Smits et al. [43] we did not find a significant reduction in heart weight with losartan treatment. This might be due to differences in drug dosage and method of application. Smits et al. infused 15 mg/kg/day of losartan subcutaneously, whereas, 10 mg/kg/day was delivered orally in our study. Whether the prevention of cardiac hypertrophy resulted from a more pronounced hemodynamic change or from a dose dependent anti-trophic effect of the AII antagonist remains unclear.

4.3. Combination of exercise and losartan

In this study exercise and losartan independently attenuated LV dilation post-MI, though the combination of the two interventions had no additive beneficial effects on

cavity dimensions. Furthermore, exercise training augmented contractile function post-MI in both untreated and losartan treated hearts. In addition, exercise therapy, in the absence of losartan, resulted in the greatest amount of pulmonary congestion and scar thinning. AII receptor blockade therapy in conjunction with exercise therapy, however, attenuated the increase in pulmonary congestion and scar thinning. Therefore, the combination of exercise and losartan appears to provide the most beneficial therapy on post-MI ventricular remodeling. Concurrent losartan treatment with exercise would still provide the neuro-humoral [30–32] and vasculature benefits [28,29] of exercise training, while reducing deleterious elevations in wall stress.

Though we attempted to mimic clinical episodes of infarction and cardiac rehabilitation, including drug and moderate exercise therapy, the prognostic and therapeutic implications of these results need to be examined with caution. Nevertheless, our study suggests that even following a large anterior infarction, moderate endurance training does not adversely affect overall remodeling. In addition, blockade of the renin–angiotensin system, an indispensable part of post-MI therapy, in conjunction with exercise training might make the latter safer and more beneficial [7].

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