Prior exercise improves survival, infarct healing, and left ventricular function after myocardial infarction

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Prior exercise improves survival, infarct healing, and left ventricular function after myocardial infarction. J Appl Physiol 107: 928–936, 2009; doi:10.1152/japplphysiol.91281.2008.—We investigated the effects of voluntary wheel running before or after an acute myocardial infarction (MI) on survival, left ventricular (LV) remodeling and dysfunction and whether exercise before and after MI provides superior protection compared with either exercise intervention alone. After 2 wk of voluntary wheel running or sedentary housing, MI was induced in C57Bl/6 mice, after which exercise was stopped (EX-MI-SED and SED-MI-SED groups, where EX is exercise and SED is sedentary) or continued (EX-MI-EX and SED-MI-EX groups) for a period of 8 wk. Exercise after MI in SED-MI-EX mice had no effect on survival, the area of infarction, and global LV remodeling, but attenuated fibrosis and apoptosis in the remote myocardium and blunted LV dysfunction and pulmonary congestion compared with SED-MI-SED mice. Exercise before MI in both EX-MI-SED and EX-MI-EX mice decreased post-MI mortality compared with both SED-MI-SED and SED-MI-EX mice. Furthermore, limited exercise groups, the infarct area was thicker, whereas interstitial fibrosis and apoptosis in the remote LV myocardium were blunted. In contrast, the ameliorating effects of either pre-MI or post-MI exercise alone on LV dysfunction were lost in EX-MI-EX mice, which may in part be related to the increased daily exercise distance in the first week post-MI in EX-MI-EX versus SED-MI-EX mice. In conclusion, exercise before or after MI blunted LV dysfunction, whereas only exercise before MI improved survival. These findings suggest that when regular physical activity fails to prevent an acute MI, it can still act to improve cardiac function and survival after MI.

Cardiac function; infarct healing; remodeling

Physical inactivity has been proposed to be an independent risk factor for cardiovascular disease (4, 48). Indeed, prospective epidemiological data have indicated that moderate (e.g., walking) and vigorous exercise in healthy subjects are associated with substantial reductions in the incidence of cardiovascular events (23, 31). 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 (44). Furthermore, there is evidence that exercise initiated after a cardiac event, such as myocardial infarction (MI), ameliorates left ventricular (LV) remodeling and dysfunction (8, 14, 22, 27, 36, 37, 49, 52) and improves clinical outcome (35, 43).

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 have suggested that prior exercise can precondition the myocardium, thereby protecting the heart against irreversible damage produced by ischemia-reperfusion in rats (5, 39, 50, 51) and dogs (10). In addition, prior exercise may modulate postinfarct remodeling independent of any myocardial preconditioning effect. Thus, two studies in rats using permanent coronary artery ligation [in which preconditioning cannot limit acute myocardial necrosis (33, 46)] showed that infarct size and, likely as a consequence, LV remodeling were reduced by prior swim training (17, 32). In contrast, studies into the effects of prior exercise by treadmill running on LV remodeling after MI have not been performed to date. Consequently, the present study was undertaken to test the hypothesis that daily exercise started 2 wk before an acute MI is associated with improved survival and attenuated LV remodeling and dysfunction after MI. For this purpose, we used voluntary free wheel running as a mode of exercise, which has negligible effects on LV geometry and function per se but attenuates LV and cardiomyocyte dysfunction when initiated after MI produced by a permanent coronary artery ligation (8).

**METHODS**

Experiments in the present study complied with the National Institutes of Health Guide for Care and Use of Laboratory Animals (NIH Pub. No. 86-23, Revised 1996) and were approved by the Erasmus MC Animal Care Committee.

**Animals**

A total of 186 wild-type C57Bl/6 mice of either sex (~12 wk old) were entered into the study and were randomly assigned to one of six experimental groups. After 2 wk of voluntary wheel running or sedentary housing, MI was induced, after which exercise was stopped (EX-MI-SED and SED-MI-SED groups, where EX is exercise and SED is sedentary) or continued (EX-MI-EX and SED-MI-EX groups) for 8 wk. Sham-operated mice (SED-SH-SED and SED-SH-EX groups, where SH is sham operation) were used as controls.

**Exercise**

Mice were exposed to voluntary wheel running while daily running distances were recorded (8). The followup period of 8 wk was chosen as we have previously shown that this regimen resulted in a ~30% increase in skeletal muscle citrate synthase activity and blunted LV dysfunction after MI (8). The pre-MI exercise period of 2 wk was arbitrarily chosen. However, based on the positive results in pilot experiments of the EX-MI-SED group, the 2-wk time period was used for the remainder of the study. EX-MI mice were allowed to run until the morning of surgery. After surgery, all mice were placed back into their cage after 1–2 h of monitored recovery to allow the SH-EX and MI-EX groups to exercise the first night after surgery.
**Experimental Procedures**

All experimental procedures have previously been published in detail (8, 45). In brief, mice were weighed, sedated with 4% isoflurane, intubated, and pressure-controlled ventilated with O2:N2 [1:2 (vol/vol)] containing ∼2.5% isoflurane for anesthesia. MI was produced by permanent ligation of the left anterior descending coronary artery with a 7-0 silk suture (B.Braun). This location of the ligation creates an area at risk that comprises almost half of the LV, of which ∼90% has become infarcted 24 h later, representing 40–45% of the LV (8). SH animals underwent the operation without infarct induction.

Eight weeks after the induction of MI or SH, hemodynamic measurements were performed under anesthesia. M-mode LV echocardiography (Prosound SSD-4000, ALOKA) was performed, LV diameters at end diastole and end systole were measured, and LV fractional shortening was calculated (8, 45). A 1.4-Fr microcatheter pressure transducer catheter (SPR-671, Millar Instruments) was inserted into the right carotid artery and advanced into the LV for measurements of LV pressure and its first derivative (dP/dt) (8, 45).

Immediately after these measurements, mice were killed, and right ventricular (RV) and LV weights, tibial length, and lung fluid weights were determined (8). The LV of a subset of mice that were randomly selected from each group was fixed overnight in freshly prepared 4% paraformaldehyde in PBS, embedded in paraffin, and used for histological analysis (see below). The operator was blinded to the experimental group during the analysis.

**Morphometric Analysis of the Infarct Region**

The LV was cut along the long axis into 4-μm sections, and Masson’s trichrome staining was used for the analysis of the infarct region (8). The infarct region was demarcated as the blue-green-stained area of the LV. Endocardial infarct circumference was demarcated, and its length was determined. The minimal infarct thickness was measured at the shortest distance between the endocardium and epicardium. The infarct area was demarcated, and the total surface area was measured. Within the infarct area, the thickness of the subendocardial rim of the myocardium and the infarct thickness were each measured at four sites evenly spaced along the infarct area and then averaged. The operator was blinded to the experimental group during the analysis.

**Morphometric Analysis of the Remote NonInfarct Region**

Capillary density. Capillaries were detected using lectin staining. Briefly, short-axis LV paraffin sections were deparaffinized, cleared, and hydrated to Tris-buffered saline (pH 7.4) using a descending series of ethanol. Sections were treated with proteinase-K for 1–2 min with a diaminobenzidine commercial kit (Dako). Sections were washed, counterstained with hematoxylin, dehydrated with graded ethanol solutions, cleared in xylene, and mounted. Capillaries were detected as brown endothelial cells, and capillary density was determined as the number of vessels per millimeter squared.

Cardiomyocyte cross-sectional area and collagen content. Paraffin-embedded LV sections (4 μm thick) were stained with Masson’s trichrome for the analysis of collagen content and cardiomyocyte cross-sectional area (CSA) measurements within the remote noninfarcted myocardium (8). Four fields were randomly selected in two sections of eight mice per group and photographed using an Olympus BH 20 microscope (Olympus) at a magnification of ×400. Within each field, segments representing connective and muscle tissue were identified and manually traced with a digitizing pad and computer image-analysis software (Clemex Vision PE 3.5) to calculate the traced area. Collagen content was calculated in each field as the sum of all connective tissue areas divided by the sum of all connective tissue and muscle areas and averaged for each animal. Cardiomyocyte CSA was measured by tracing the outline of cardiomyocytes showing the nucleus in each field and averaged for each animal.

**Apoptosis.** To localize DNA degradation in the remote noninfarcted LV, we used the In Situ Cell Death Detection Kit (Roche Diagnostics), which is a modification of the 3’-terminal deoxyribonucleotide transferase (TdT)-mediated DUTP nick-end labeling (TUNEL) assay. In brief, paraffin-embedded sections were deparaffinized, cleared, and hydrated to PBS (pH 7.4) using a descending series of ethanol. Sections were treated with proteinase-K for 30 min at 37°C, washed in PBS, treated with the TUNEL reaction mixture, and incubated in the dark for 1 h at 37°C, followed by washing in PBS. Both positive (DNaseI-treated sections) and negative controls (no TDT included in the reaction mixture) were included. Sections were covered with Vectashield including 4’,6-diamidino-2-phenylindole and immediately photographed using fluorescence microscopy. TUNEL-positive cells emitted red fluorescence, and all nuclei were blue. Apoptosis was determined as the number of TUNEL-positive nuclei per 10² nuclei.

**Statistics**

Data were analyzed using two-way ANOVA followed by post hoc testing with the Student-Newman-Keuls test. Survival was analyzed by the Kaplan-Meier method and log-rank (Mantel-Cox) test. Significance was accepted when P < 0.05. Data are means ± SE.

We tested for sex differences and consistently found across all groups that females were characterized by ∼30% lower body weight, ∼5% smaller tibia length, and ∼50% lower post-MI mortality (all P < 0.05 by ANOVA). However, we did not observe statistically significant sex differences with respect to the effects of pre-MI and/or post-MI exercise on post-MI survival, LV dysfunction (fractional shortening and pulmonary congestion), or LV remodeling (LV end-diastolic diameter and LV weight/tibia length). Consequently, we pooled male and female mice for the final analysis.

**RESULTS**

**Survival and Exercise**

SED-MI-SH mice demonstrated 60% survival compared with SED-SH-SH mice (Fig. 1A), which significantly improved to 83% in EX-MI-SH mice, where exercise was started 2 wk before MI. In contrast, exercise started after MI had no significant effect on survival. After the induction of MI, SED-MI-EX mice initially ran significantly shorter distances per day compared with either SED-SH-EX or EX-MI-EX mice, in which exercise had already been started 2 wk before MI and continued after the induction of MI (Fig. 1B). Thus, over the 8-wk post-MI phase, SED-MI-EX mice ran a total distance of only 313 ± 23 km compared with 402 ± 28 km in SED-SH-EX and 456 ± 35 km in EX-MI-EX mice (both P < 0.05 vs. SED-MI-EX mice).

**Global LV Remodeling and Function**

MI resulted in marked LV remodeling and dysfunction. Thus, SED-MI-SH mice exhibited significant LV hypertrophy and dilatation and lower levels of LV systolic pressure, rate of rise of LV pressure at a LV pressure of 30 mmHg (LVdP/dP0), fractional shortening, and LVdP/dPmin and higher levels...
remodeling but that this exercise regimen improved LVdP/dP30 and fractional shortening and alleviated pulmonary congestion after MI. Similarly, 2 wk of voluntary wheel running before MI (EX-MI-SED group) had no effect on MI-induced LV remodeling, whereas it improved fractional shortening and ameliorated pulmonary congestion. In contrast, the beneficial effects of each exercise regimen on MI-induced LV dysfunction appeared to be partly lost when post-MI exercise was added to pre-MI exercise. Thus, in EX-MI-EX mice, LV dilation was slightly aggravated, whereas fractional shortening and LVdP/dP30 were lower (all \( P < 0.05 \)) and pulmonary congestion tended to be increased (\( P = \) not significant) compared with SED-MI-EX mice. As a result, LV fractional shortening, LVdP/dP30, and RV and lung fluid weights were not significantly different between EX-MI-EX and SED-MI-SED mice (Fig. 2).

**Infarct Remodeling**

Exercise after MI had no effect on infarct remodeling, as reflected by an unchanged total infarct area and infarct length and unchanged minimal and average infarct thickness (Figs. 3 and 4, A–C). In contrast, exercise before MI resulted in increased infarct thickness, and hence total infarct area, irrespective of whether mice continued to exercise after MI. Furthermore, the subendocardial rim of the myocardium within the infarct area was thicker, particularly in the EX-MI-SED group but also in the EX-MI-EX group (Fig. 4D).

**Remodeling of the Remote Myocardium**

Cardiomyocyte CSA. The CSA of myocytes in the remote surviving myocardium was increased after MI by 35% (Figs. 5B and 6A). Exercise after MI had no effect on cardiomyocyte size in either SH or MI hearts. In contrast, in EX-MI-SED mice, cardiomyocyte CSA had increased further compared with SED-MI-SED mice, irrespective of whether exercise was continued or stopped after MI.

**Capillary density.** After MI, capillary density (Figs. 5A and 6B) in the remote noninfarcted myocardium decreased by ~20%, which was the result of cardiomyocyte hypertrophy as the capillary-to-myocyte ratio was similar in SED-MI-SED (1.45 ± 0.20) and SED-SH-EX (1.42 ± 0.22) mice. Exercise after MI had no effect on either capillary density (Fig. 6B) or the capillary-to-myocyte ratio (1.55 ± 0.13 in SED-MI-EX mice). Exercise before MI had also no effect on capillary

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**Table 1. Anatomic and functional data**

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<th></th>
<th>SED-SH-SED</th>
<th>SED-SH-EX</th>
<th>SED-MI-SED</th>
<th>SED-MI-EX</th>
<th>EX-MI-SED</th>
<th>EX-MI-EX</th>
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<td>LV weight, mg</td>
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<td>91 ± 2</td>
<td>113 ± 2*</td>
<td>112 ± 3*</td>
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<tr>
<td>Right ventricular, mg</td>
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<td>32 ± 1*</td>
<td>28 ± 1*</td>
<td>29 ± 1*</td>
<td>33 ± 3*</td>
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<td>540 ± 5f</td>
<td>540 ± 10b</td>
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<td>71 ± 2</td>
<td>71 ± 2</td>
<td>66 ± 2</td>
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<td>LV systolic pressure, mmHg</td>
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<td>82 ± 2</td>
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<td>dP/dt\text{max}, mmHg/s</td>
<td>-7,560 ± 360</td>
<td>-7,470 ± 470</td>
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<td>-5,490 ± 430*</td>
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<td>Relaxation time constant, ms</td>
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<td>13.5 ± 1.1b</td>
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Values are means ± SE. SED, sedentary; EX, exercise; SH, sham operation; MI, myocardial infarction; LV, left ventricular. \( * P < 0.05, \) MI-SED groups (SED-MI-SED or EX-MI-SED) vs. the SED-SH-SED group; \( * P < 0.05, \) MI-EX groups (SED-MI-EX or EX-MI-EX) vs. the SED-SH-EX group; \( * P < 0.05 \) vs. the SED-MI-SED group; \( * P < 0.05 \) vs. the SED-MI-EX group; \( * P < 0.05 \) vs. the SED-EX-EX group; \( * P < 0.05 \) vs. the SED-SH-SED group.

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**Fig. 1.** A: Kaplan-Meier survival curves for all six groups. EX, exercise; SED, sedentary; SH, sham operation; MI, myocardial infarction. Numbers of mice that entered the study were as follows: 30 SED-SH-SED, 15 SED-SH-EX, 50 SED-MI-SED, 44 SED-MI-EX, 23 EX-MI-SED, and 24 EX-MI-EX mice. B: daily running distance in SED-SH-EX (n = 15), SED-MI-EX (n = 25), EX-MI-SED (n = 19), and EX-MI-EX (n = 19) mice that survived the entire 8-wk followup period. \( * P < 0.05, \) MI-SED groups (SED-MI-SED or EX-MI-SED) vs. the SED-SH-SED group; \( * P < 0.05, \) MI-EX groups (SED-MI-EX or EX-MI-EX) vs. the SED-SH-EX group; \( * P < 0.05 \) vs. the SED-MI-SED group; \( * P < 0.05 \) vs. the SED-MI-EX group.
density, despite an increase in cardiomyocyte size, which was
due to a commensurate increase in the capillary-to-myocyte
to.

Collagen content. MI increased interstitial collagen content
in the remote myocardium (Figs. 5B and 6C). Exercise (which
slightly reduced collagen content in SH hearts) normalized
collagen content in MI hearts to levels observed in SED-SH-
SED mice. A similar decrease in collagen content was noted in
EX-MI-SED mice. However, combining exercise before and
after MI did not result in a further reduction in interstitial
fibrosis content in EX-MI-EX mice, although in the latter group this failed to reach
statistical significance ($P = 0.066$).

Apoptosis. MI resulted in an increased number of TUNEL-
positive nuclei in the remote myocardium (Fig. 6D). Exercise
(which tended to decrease apoptosis in SH hearts) normalized
the number of TUNEL-positive nuclei in MI hearts to levels
observed in SED-SH-SED hearts. A similar decrease in
TUNEL-positive nuclei was noted in EX-MI-SED and EX-
MI-EX mice, although in the latter group this failed to reach
statistical significance ($P = 0.066$).

**DISCUSSION**

MI results in LV remodeling that serves to restore LV pump
function. However, despite the apparent appropriateness of LV
remodeling to maintain cardiac pump function early after MI,
remodeling is an independent risk factor for the development of
congestive heart failure (28). Recently, we (8) reported that
exercise after MI attenuates LV pump dysfunction in mice. The
present study investigated the impact of 2 wk of voluntary wheel
running before an acute MI on post-MI survival, LV remodeling,
and dysfunction in mice. The main findings were as follows: 1) exercise after MI had no effect on survival and global LV or
infarct remodeling but ameliorated LV dysfunction, interstitial
fibrosis, and apoptosis in the remote myocardium; 2) exercise
before MI, with no exercise after MI, partially attenuated LV
dysfunction, interstitial fibrosis, and apoptosis but also improved
post-MI survival and infarct remodeling; and 3) the combination of
exercise starting 2 wk before MI together with exercise con-
tinued after MI also improved survival and infarct remodeling but
did not improve global LV remodeling or dysfunction. The
implications of these findings will be discussed.
Effects of Voluntary Wheel Running after MI on LV Remodeling and Dysfunction

In agreement with previous findings in our laboratory (8, 45), we observed in the present study that a large MI (comprising ~40% of LV mass) caused 40% mortality in mice, which occurred principally during the first 2 wk post-MI. Eight weeks after the induction of MI, LV remodeling had occurred, as characterized by LV dilation and myocardial hypertrophy, as well as increased interstitial collagen deposition, apoptosis and decreased capillary density in the remote surviving myocardium. MI also produced marked LV dysfunction, as characterized by decrements in LV pump function (fractional shortening) and indexes of systolic (LVdP/dP30) and diastolic (dP/dtmin and τ) function, resulting in pulmonary congestion, as reflected by pulmonary edema and RV hypertrophy (8, 45). LV end-diastolic pressure increased only modestly despite the large MI, which is in agreement with previous observations in mice in our laboratory (8, 9) but contrasts with the marked increases in LV filling pressure that we typically have observed in pentobarbital-anesthetized pigs, which have even smaller (20–25% of the LV) infarct size (47). It could be speculated that the MI-induced increase in LV end-diastolic pressure is blunted due to the fact that we studied the mice under isoflurane anesthesia, which has pulmonary venodilating properties (18) and could have reduced LV filling pressures. Indeed, the increases in lung wet weight and RV hypertrophy, which are less susceptible to the acute hemodynamic effects of anesthetics, strongly suggest that pulmonary congestion was present and that in the awake state LV filling pressures were likely elevated.

The effects of exercise after MI on LV remodeling and dysfunction remain incompletely understood. Several studies in humans have reported contradictory effects of exercise on LV remodeling after MI (12, 14, 20–22, 25, 27, 29, 38, 42). Careful inspection of these studies suggests that after a small MI (ejection fraction > 40%), exercise has no detrimental effect (20, 38) or even improves (14, 22, 27) LV geometry and function, independent of whether exercise was started late, i.e., ~1 yr (14, 22), or early, i.e., <2 mo (20, 27, 38), after MI. In contrast, in patients with a large MI (ejection fraction < 40%), exercise had a beneficial effect on ejection fraction and LV volumes, but only when started late after MI (14, 22). However, when exercise after a large MI is started at a time when LV remodeling is still ongoing (>3–4 mo after MI), the majority of studies have reported that exercise has either no (12, 20, 38, 42) or even a detrimental (25, 29) effect on LV dimensions and/or ejection fraction. Similar to these clinical studies, studies in rats have indicated that exercise started late (>3 wk) after a moderate to large MI (encompassing 35–50% of the LV mass), at a time when infarct healing is complete, does not aggravate (30, 34) or even blunts (37, 49, 52) LV dilation (37) and hypertrophy (30, 34, 37, 49, 52). In contrast, when started <1 wk after a moderate to large MI (1, 18, 19, 24, 26), exercise resulted in variable outcomes with beneficial (18), no (1, 24), or detrimental (19, 26) effects on LV remodeling. These rodent studies lend further support to the concern that early exercise may have detrimental effects on LV remodeling after a large MI, although interpretation is hampered by the fact that late exercise studies in rats have principally used forced treadmill running (16, 22, 34, 37), whereas early exercise studies have predominantly used swimming (1, 19, 24, 49). This is important because the exercise responses to swimming are markedly different from those to treadmill running (2, 3, 16). For example, treadmill running results in marked increases...
In heart rate and cardiac output together with a redistribution of cardiac output toward active skeletal muscle groups (16). In contrast, swimming appears to result in minimal changes in heart rate and cardiac output, so that the increase in skeletal muscle blood flow is principally the result of a redistribution of cardiac output (16). Furthermore, swimming is often accompanied by episodes of submersion, resulting in intermittent hypoxia and diving reflexes (2, 3).

In contrast to these studies using early swim exercise in rats, we observed that exercise through voluntary wheel running (which had negligible effects on LV geometry and function in SH mice) starting gradually early after a large MI [encompassing 40–45% of LV (8)] did not aggravate post-MI mortality, LV remodeling, capillary rarefaction, and cardiomyocyte hypertrophy of the remote myocardium and even reduced myocardial interstitial fibrosis and apoptosis and blunted LV dysfunction and pulmonary congestion (present study and Ref. 8). These observations could be interpreted to suggest that the beneficial effects of exercise initiated early after a large MI depend critically on the exercise mode, i.e., swimming versus running. However, it is clear that future studies are required to investigate in detail the influence of not only the mode but also the intensity and frequency of exercise on LV remodeling and dysfunction initiated either early or late in animals with a large MI.

**Effects of Prior Exercise on LV Remodeling and Dysfunction After MI**

There is a lack of clinical data regarding the effects of prior exercise on outcome after MI. Animal studies have suggested that exercise can precondition the myocardium, thereby protecting the heart against irreversible damage produced by ischemia-reperfusion in rats (5, 39, 50, 51) and dogs (10). In addition, exercise may modulate postinfarct remodeling independent of any preconditioning effect. Thus, two studies in rats using permanent coronary artery ligation reported that 5–7 wk of prior swimming had no effect on post-MI mortality but reduced infarct size and attenuated LV remodeling, as determined at 2 days (32) or 4 wk (17) after the induction of MI. Swimming-induced increases in capillary (32) and arteriolar (17) densities were observed in the remote region, which led 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 the infarct size. Although the myocardial vasculature is known to be enhanced by swimming in young male rats (13), there is no evidence to suggest that collateral vessel growth is stimulated...
by exercise in healthy hearts. Thus, studies pertaining to exercise of healthy dogs, swine, or rats have consistently shown that exercise does not increase the innate collateral blood flow capacity in healthy hearts (13). 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 (17, 32).

In contrast to the findings in rats, we observed that exercise of mice via voluntary wheel running reduced post-MI mortality from ~40% to ~20% and blunted LV dysfunction but did not enhance the vascularity of the remote myocardium or limit infarct size as measured 8 wk later. The mechanism underlying the improved survival remains speculative. First, although we did not determine the occurrence of arrhythmias, we cannot exclude that pre-MI exercise resulted in a reduction in fatal arrhythmias in the early phase after the induction of MI (40). However, mortality in C57Bl/6 mice after permanent coronary artery ligation appears to be principally caused by cardiac rupture of the infarct area within the first 2 wk after MI (7). Interestingly, we observed that infarct thickness was increased, consistent with an 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. Future studies are needed to establish the molecular mechanisms underlying the mitigation of LV dysfunction by pre-MI exercise, which should include an interrogation of possible exercise-induced improvements of intact cardiomyocyte and myofilament function (8).

Combining Exercise Before and After MI

Allowing mice in which voluntary wheel running was started 2 wk before MI to continue running after the induction of MI resulted in similar infarct remodeling, improvements in post-MI survival, and reductions in collagen content of the remote myocardium compared with mice that were exercised before MI but were sedentary housed after MI. In contrast, the mitigating effects of either pre-MI or post-MI exercise on LV dysfunction were principally lost when mice were subjected to voluntary exercise both before and after the induction of MI. Although these observations are difficult to explain, it should be noted that mice that had been adapted to the running wheel for 2 wk before the induction of MI (EX-MI-EX group) ran significantly longer daily distances immediately post-MI (7 km/day during the first week) compared with the initially shorter daily distances in SED-MI-EX mice during the first 4 wk (~2 km/day during the first week). Consequently, it could be speculated that this higher daily exercise load in the immediate post-MI phase offset some of the beneficial effects of post-MI exercise and might also explain why studies in rats and humans have shown variable responses to (forced) exercise early after MI. A limitation of the present study is that our wheel rotation recording system did not allow us to determine whether the mice ran each day at greater speed (intensity) or for longer duration during the early postinfarct period. This is relevant information, as there is evidence that the exercise.
mode and intensity are important determinants of the effects of exercise on LV hypertrophy (15, 41). Future studies should address the influence of mode, intensity, duration, and frequency of early post-MI exercise on LV remodeling and dysfunction in more detail, e.g., by restricting total daily distance of voluntary exercise in EX-MI-EX mice in the very early post-MI phase, allowing a slow progressive increase in daily running distance comparable with that in SED-MI-EX mice.

An interesting observation in the present study was that combined pre-MI and post-MI exercise improved post-MI survival without the concurrent attenuation of global LV remodeling or dysfunction. Conversely, voluntary wheel running starting after MI was associated with improved LV function but did not translate into attenuated LV remodeling or improved survival. Taken together, these observations suggest that neither improved global LV pump function nor attenuated global LV remodeling is required for improved post-MI survival and are consistent with the concept that post-MI mortality in C57Bl/6 mice is principally the result of infarct rupture (which depends on infarct area tissue properties) rather than ventricular arrhythmias [which are influenced by LV geometry (6)] or LV pump failure (7).

Clinical Implications and Conclusions

The beneficial effects of regular physical activity on preventing major cardiac events in healthy individuals and patients with coronary heart disease are now well established (23, 31, 44). The results of the present study show 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 individuals that have an increased risk of MI.

REFERENCES


