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Exercise training promotes cardioprotection through oxygen-sparing action in high fat-fed mice

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There has been a dramatic transition from physical activity to sedentary lifestyle during the last century. This has resulted in an epidemic increase in the prevalence of metabolic syndrome, obesity, and diabetes, all of which increase the risk of developing heart failure, angina, acute myocardial infarction, and dying from an acute myocardial infarction (2).

Diabetes-related cardiac complications are due to increased coronary artery disease as well as the development of a specific diabetic cardiomyopathy characterized by ventricular dysfunction in the absence of coronary artery disease or hypertension (24). Although the pathogenesis of diabetes/obesity-related cardiomyopathy is multifactorial and complex, decreased cardiac efficiency seems to play an essential role and is an early hallmark of the diabetic heart (5, 9, 22, 36).

Physical training is a well-documented measure to reduce the development of obesity/diabetes, as well as an effective prevention and treatment of cardiovascular disease (12, 34, 40). Aerobic capacity [maximum oxygen uptake (\(V\dot{O}_2\max\))] has been found to be the best predictor of both cardiac and all-cause deaths among patients with cardiovascular disease (35). Whereas cardioprotective effects of exercise have been well documented in young healthy animals (18, 38, 39), the effects of exercise on ischemic injury in diabetic/obese animal models are sparse.

We have previously demonstrated that exercise training reverses oxygen wasting in hearts from diet-induced obese mice subjected to a dietary regime that led to diabetic and systolic ventricular dysfunction, as well as concentric remodeling (20). Exercise training also improved mechanical efficiency and counteracted the development of ventricular dysfunction and remodeling (20). The aim of the present study was to examine whether exercise has an oxygen-sparing effect in an obese model with less severe ventricular dysfunction and to examine whether this will increase the tolerance to ischemia-reperfusion injury.

RESEARCH DESIGN AND METHODS

Animals. C57BL/6J male mice (5 to 6 wk) were purchased from Charles River Laboratories (Wilmington, MA). Obesity was induced by feeding the mice a high-fat diet (HFD 58V8, TestDiet, UK) (48), containing 46% of calories from fat, 36% of calories from carbohydrates (primary sucrose, maltodextrin, and dextrin) and 18% calories from protein. Lean control mice were given a standard chow diet (58Y2, TestDiet, UK) containing 10% of calories from fat, 72% calories from carbohydrates, and 18% calories from protein. The local authority of the National Animal Research Authority in Norway approved the experiments, and mice were treated in accordance to the
guidelines on accommodation and care of animals formulated by the European Convention for the Protection of Vertebrate Animals for Experimental and Other Scientific purposes. All mice received chow and drinking water ad libitum and were housed at 23°C on a reversed light-dark cycle so that the training occurred during the dark period since mice are nocturnal.

**Exercise protocol and determination of aerobic capacity.** Following 8 wk of high-fat feeding, HFD mice were assigned to sedentary lifestyle (HFDSED, n = 18) or high-intensity treadmill running 5 days/wk for 10 wk (HFDHIT, n = 20) as previously described by Hafstad et al. (20). The exercise protocol was 10 bouts of 4-min, high-intensity, treadmill running at 25° inclination, corresponding to 85–90% of VO2max interspersed by 2 min active rest. Sedentary lean mice (CON, n = 10) were included as controls. Aerobic capacity, determined as VO2max, was assessed by running mice on a treadmill in a metabolic chamber (Columbus Instruments, Columbus, OH) and defined as the point at which O2 reached its peak (despite increased running speed) and CO2 continued to increase. VO2max was measured in the two groups of HFD mice before the exercise protocol started to confirm equal aerobic capacity.

**Glucose tolerance.** Following a 4-h fast, blood was collected from the saphenous vein before and after intraperitoneal administration of a glucose solution (1.3 g/kg), and blood glucose concentration was measured with a glomerometer (FreeStyle Lite, Alameda, CA). Plasma insulin was analyzed using commercial kits from DRG Diagnostics (Marburg, Germany), and homeostatic model assessment (HOMA) was calculated from the product of fasting blood glucose (in mmol/l) and insulin (in μU/ml) and then divided by 22.5 (33). Plasma glucose was also measured in blood samples taken in fed mice on the day of death.

**Transthoracic echocardiography.** Echocardiography was measured by Vevo 770 VisualSonics (Toronto, Canada) during isoflurane (2%) anesthesia. The heart was imaged in the two-dimensional, parasternal, short-axis view, and an M-mode echocardiogram of the midventricle was recorded at the level of papillary muscles. A single operator imaged all mice. Heart rate and the end-diastolic and end-systolic internal dimensions of the left ventricle (LV) were measured from the M-mode image. LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVEDS) were recorded with parasternal long-axis B-mode echocardiography, which allowed the following calculations: fractional shortening (in %) = [(LVEDD − LVEDS)/LVEDD] × 100 and ejection fraction (in %) = (stroke volume/LV end-diastolic volume) × 100, as indexes of systolic LV function.

**Ex vivo cardiac function, substrate utilization, and efficiency.** Assessment of myocardial substrate utilization, LV mechanical function, and myocardial oxygen consumption (MV02) were done in isolated perfused working hearts using a modified Krebs-Henseleit bicarbonate buffer supplemented with 5 mM glucose and 0.5 mM palmitate. Myocardial glucose and fatty acid oxidation rates were measured using radiolabeled isotopes as previously described (19). Intraventricular volumes and pressures were determined by inserting a 1.0-Fr micromanometer-conductance catheter inserted into the LV, and MV02 was measured using fiber-optic oxygen probes (45). Steady-state values of stroke work (SW), the pressure-volume area (PVA), and MV02 were obtained at several workloads (21). Hearts were paced at a rate ~10% above their endogenous heart rate during steady-state measurements. The relationship between SW and MV02 was used to evaluate changes in mechanical efficiency. An evaluation of LV mechanoenergetics was performed by regression analysis of the relationship between PVA and MV02, where work-independent MV02 (the y-intercept) and work-dependent MV02 (the inverse slope of this relationship) can be identified (21).

**Analysis of myocardial reactive oxygen species and collagen content.** At the end of perfusion, myocardial reactive oxygen species (ROS) content was measured in LV tissue stained with dehydro-ethidium (15-μm cryosections) as previously described (20). Quantitative analysis of myocardial collagen content was performed by HPLC analysis of myocardial hydroxyproline using the AccQ-Fluor reagent kit (Waters, Milford, MA) as previously described (30) with some modifications (1). Briefly, cardiac tissue samples (5 mg dry wt) were hydrolyzed in 6 M HCl at 110°C for 16 h, subsequently dried under vacuum, and redissolved in the AccQ-Fluor borate buffer. Derivatization was initiated by addition of the AccQ-Fluor reagent at 55°C and terminated after 10 min. The samples were finally subjected to HPLC using a 20 × 3.9-mm Sentry Guard column (Nova-Pak C18 bonded silica), connected to a 150 × 3.9-mm AccQ-Tag reverse-phase column (both from Waters) according to the manufacturer’s instructions. Derivatized hydroxyproline was detected by fluorescence after excitation at 250 nm and recording of emission at 395 nm. Elution of hydroxyproline was verified and quantified by coelution with known amounts of derivatized hydroxyproline standards (Fluka, Buchs, Switzerland). The relation of myocardial hydroxyproline contents to myocardial collagen has been previously reported (1).

**Real-time quantitative PCR.** Real-time quantitative PCR analysis was performed on LV tissue samples using an ABI PRISM 7900 HT Fast real-time thermal cycler as previously described (20).

**Infarct size.** In a separate experimental protocol, the effect of exercise on MV02 and ischemic susceptibility in isolated reversegrade (Langendorff)-perfused hearts from HFD mice was examined. The hearts were paced, and intraventricular pressure developments were recorded using a fluid-filled balloon inserted into the LV. A small cannula was inserted into the LV (apex) to drain any remaining perfusate. During the preischemic stabilizing period, the balloon was deflated, and unloaded MV02 was measured. The volume of the balloon was then increased to reach an end-diastolic pressure of 5–10 mmHg. The hearts were subsequently subjected to 30 min of global ischemia and 90 min of reperfusion. At the end of reperfusion, hearts were frozen (~20°C) and cut into 1-mm-sized transverse slices using a heart slicer (Zivic Instruments, Pittsburgh, PA). Viable cardiac tissue was stained using a 1% 2,3,5-triphenyl-2H-tetrazolium chloride solution for 6 min at 37°C. Infarct size was calculated using ImageJ software (National Institutes of Health, Bethesda, MD).

**Statistical analysis.** Data are expressed as means ± SE. Differences between groups were analyzed using one-way analysis of variance with multiple comparisons versus HFDSED (Holm-Sidak method as post hoc test). Where normality test failed (Shapiro-Wilk test), a non-parametric test with Bonferroni correction by Dunn’s was used.

### RESULTS

The effect of HFD and exercise on obesity and glucose tolerance. Sedentary mice fed a HFD for 20 wk (HFDSED) developed marked obesity and displayed a 39% higher body weight compared with the lean controls (CON) (Table 1). The

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<th>CON</th>
<th>HFDSED</th>
<th>HFDHIT</th>
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<tbody>
<tr>
<td>n</td>
<td>23</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>29.9 ± 0.4*</td>
<td>34.3 ± 0.8</td>
<td>36.6 ± 0.3*</td>
</tr>
<tr>
<td>Tibia length, cm</td>
<td>1.82 ± 0.01</td>
<td>1.82 ± 0.01</td>
<td>1.82 ± 0.01</td>
</tr>
<tr>
<td>Heart weight, mg</td>
<td>134 ± 3</td>
<td>141 ± 4</td>
<td>156 ± 3*</td>
</tr>
<tr>
<td>Perirenal fat weight, g</td>
<td>0.2 ± 0.1*</td>
<td>1.1 ± 0.1</td>
<td>0.7 ± 0.1*</td>
</tr>
<tr>
<td>Epididymal fat weight, g</td>
<td>0.5 ± 0.1*</td>
<td>2.0 ± 0.1</td>
<td>1.1 ± 0.1*</td>
</tr>
<tr>
<td>Liver weight, g</td>
<td>1.1 ± 0.0</td>
<td>1.6 ± 0.1</td>
<td>1.2 ± 0.0</td>
</tr>
<tr>
<td>Insulin, μU/ml</td>
<td>0.60 ± 0.05*</td>
<td>2.01 ± 0.32</td>
<td>1.10 ± 0.08*</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>6.1 ± 0.2*</td>
<td>8.6 ± 0.4</td>
<td>8.2 ± 0.4</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>9.2 ± 0.6*</td>
<td>14.7 ± 1.0</td>
<td>10.9 ± 0.8*</td>
</tr>
<tr>
<td>FFA, mmol/l</td>
<td>305 ± 47*</td>
<td>634 ± 56</td>
<td>486 ± 57</td>
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</table>

Values are means ± SE; n, number of mice. CON, control mice fed normal chow; HFDHIT, mice fed high-fat diet and subjected to high-intensity training; HFDSED mice fed high-fat diet and kept sedentary; Fasted and Fed, fasted or fed mice, respectively; FFA, free fatty acids. *P < 0.05 vs. HFDSED.
increased body weight was accompanied by visceral obesity (increased perirenal and epididymal fat) and enlarged liver (Table 1). HFDSED mice also displayed reduced aerobic capacity (8%, Fig. 1A), reduced running speed at VO2max (15.4 ± 0.45 vs. 17.4 ± 0.5 m/min, P < 0.05, HFDSED and CON, respectively), and impaired glucose tolerance as found based on an intraperitoneal glucose tolerance test (Fig. 1C), as well as an increased HOMA (Fig. 1B). HFD mice subjected to high-intensity training (HIT) for 10 wk (HFDHIT) showed a 13% increase in aerobic capacity (Fig. 1A) and a marked increase in running speed at VO2max (24.3 ± 0.9 vs. 15.4 ± 0.4 m/min, P < 0.05, in HFDHIT and HFDSED, respectively). HIT also reduced body weight, visceral obesity, and fed plasma glucose (Table 1), as well as improved glucose homeostasis, as indicated by a decreased area under the curve for the glucose tolerance test (Fig. 1, C and D) and by a reduced insulin and HOMA (Fig. 1B).

The effect of HFD and exercise on LV mechanical and energetic function. Sedentary HFD mice did not display altered heart weights compared with lean controls. Ten weeks of exercise training did however induce physiological hypertrophy in HFDHIT mice, as indicated by an increased heart weight in HFDHIT mice, as indicated by an increased heart weight (Table 1), without any changes in in the expression of patho-logical hypertrophy markers such as brain natriuretic peptide, atrial natriuretic factor, α-myosin heavy chain, and β-myosin heavy chain (data not shown).

Echocardiographic assessment of HFDSED mice revealed signs of diastolic dysfunction [increased ratio of early transmitral filling velocity to early mitral annular velocity (E/E')], whereas changes in fractional shortening or ejection fraction were not found (Table 2). In accordance with in vivo function, isolated perfused working hearts from HFDSED mice showed mild diastolic dysfunction as indicated by increased LV end-diastolic pressure and increased relaxation time constant (Table 3). Furthermore, isolated hearts did not display signs of systolic function or LV concentric remodeling.

Exercised HFD mice displayed improved in vivo diastolic function (E/E') with no changes in LV volumes or fractional shortening (Table 2). Similarly, end-diastolic pressures were also reduced in isolated perfused hearts from HFDHIT mice (Table 3).

Measurement of SW and MV_O2 at different workloads revealed a parallel upward shift of the SW-MV_O2 relationships (Fig. 2A) in hearts from HFDSED mice, indicating reduced mechanical efficiency in these hearts. By analyzing the relationship between total mechanical energy (PVA) and MV_O2 for work-independent processes (increased y-intercept of this relationship), the slope of this relationship (the work-dependent MV_O2) was not changed, indicating unaltered contractile efficiency. These mecanohenergetic changes were accompanied by a switch in myocardial substrate preference toward fatty acid oxidation (Fig. 3, A and B).

HIT was found to normalize mechanical efficiency (Fig. 2A) due to a reduction of the work-independent MV_O2 (Fig. 2B). Exercise training, however, did not alter contractile efficiency.

### Table 2. Cardiac function assessed by transthoracic echocardiography of CON, HFDSED, and HFDHIT mice

<table>
<thead>
<tr>
<th></th>
<th>CON</th>
<th>HFDSED</th>
<th>HFDHIT</th>
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<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>510 ± 14*</td>
<td>472 ± 13</td>
<td>467 ± 14</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>4.06 ± 0.08</td>
<td>4.24 ± 0.09</td>
<td>4.28 ± 0.07</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>2.75 ± 0.14</td>
<td>2.89 ± 0.11</td>
<td>3.01 ± 0.10</td>
</tr>
<tr>
<td>FS, %</td>
<td>0.07 ± 0.03</td>
<td>0.09 ± 0.04</td>
<td>0.07 ± 0.04</td>
</tr>
<tr>
<td>EF, %</td>
<td>78.9 ± 3.3</td>
<td>60.2 ± 2.5</td>
<td>56.2 ± 3.4</td>
</tr>
<tr>
<td>E/E'</td>
<td>5.9 ± 1.1*</td>
<td>3.14 ± 1.3</td>
<td>28.5 ± 1.5*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of mice. LVESD, left ventricular end-systolic diameter; LVESD, left ventricular end-diastolic diameter; FS, fractional shortening; EF, ejection fraction; E/E', ratio of early transmitral filling velocity to early mitral annular velocity. *P < 0.05 vs. HFDSED.

### Table 3. Ex vivo heart function in CON, HFDSED, and HFDHIT mice

<table>
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<th></th>
<th>CON</th>
<th>HFDSED</th>
<th>HFDHIT</th>
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<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>437 ± 9</td>
<td>416 ± 03</td>
<td>453 ± 07</td>
</tr>
<tr>
<td>CO, ml/min</td>
<td>15.5 ± 0.7</td>
<td>14.4 ± 0.4</td>
<td>14.4 ± 0.4</td>
</tr>
<tr>
<td>CF, ml/min</td>
<td>4.0 ± 0.3</td>
<td>3.8 ± 0.2</td>
<td>3.7 ± 0.2</td>
</tr>
<tr>
<td>LVEDV, μl</td>
<td>54 ± 5</td>
<td>52 ± 3</td>
<td>54 ± 4</td>
</tr>
<tr>
<td>LVESV, μl</td>
<td>90 ± 4</td>
<td>89 ± 4</td>
<td>88 ± 5</td>
</tr>
<tr>
<td>LVDP, mmHg</td>
<td>10.0 ± 1.1*</td>
<td>12.7 ± 0.6</td>
<td>10.1 ± 0.9*</td>
</tr>
<tr>
<td>LVDP, mmHg</td>
<td>6.35 ± 2.4</td>
<td>60.2 ± 1.0</td>
<td>61.6 ± 1.8*</td>
</tr>
<tr>
<td>dP/dt_min, mmHg/s</td>
<td>−4,402 ± 401</td>
<td>−3,772 ± 164</td>
<td>−3,848 ± 208</td>
</tr>
<tr>
<td>dP/dt_max, mmHg/s</td>
<td>4,565 ± 236</td>
<td>4,391 ± 160</td>
<td>4,507 ± 186</td>
</tr>
<tr>
<td>τ, ms</td>
<td>16.4 ± 1.6*</td>
<td>22.5 ± 1.2</td>
<td>21.4 ± 1.4</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of mice. CO, cardiac output; CF, coronary flow; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVDP, left ventricular end-diastolic pressure; LVDP, left ventricular developed pressure; dP/dt_min and dP/dt_max, minimum and maximum first derivative of left ventricular pressure, respectively; τ, relaxation time constant. *P < 0.05 vs. HFDSED.
The oxygen-sparing effects were accompanied by an amelioration of the diet-induced changes in myocardial substrate utilization, as well as myocardial superoxide and collagen content. The effect of HFD and exercise training on infarct size. As oxygen demand would be particularly unfavorable under conditions of limited oxygen availability, it is reasonable to suggest that diabetes/obesity-related myocardial oxygen wasting may contribute to increased susceptibility to ischemia-reperfusion injury. Increased oxygen consumption for noncontractile processes was demonstrated in hearts from sedentary HFD mice before the induction of ischemia, and subsequently infarct size following global ischemia was 34% higher in hearts from these mice compared with control mice. HIT ameliorated the HFD-induced increase in unloaded $\dot{MV}_O^2$, and this was accompanied by a marked reduction of infarct size in these hearts.

**DISCUSSION**

In this study, using a mouse model that mimics the clinical condition of prediabetes with mild diastolic dysfunction, we suggest that exercise training improves cardiac efficiency due to its oxygen-sparing effect. In addition, the study showed for the first time that exercise training of obese mice reduces infarct size in hearts subjected to ischemia-reperfusion.
showed increased infarct size. Although the literature supports that long-term HFD feeding is associated with increased infarct size (29, 49), there are also studies reporting reduced infarct size following obesogenic diets (13, 41). Factors such as differences in age, diet composition, and feeding period, as well as ex vivo perfusion conditions (i.e., energy substrate composition), may contribute to some of these discrepancies.

HIT, which started following induction of obesity (i.e., 8 wk after start of a high-fat feeding) and lasted for 10 wk, resulted in improved aerobic capacity (assessed as VO$_{2 \max}$), ameliorated obesity, and improved glucose homeostasis. The systemic effects were similar to those previously reported by Hafstad et al. (20), using the same exercise regime.

In the study by Hafstad et al. (20), exercise also improved LV mechanical efficiency, which was accompanied by prevention of development of systolic dysfunction and concentric remodeling. The present study demonstrates that the exercise-induced improvement of efficiency also occurred in a model without cardiac systolic dysfunction and remodeling. This finding suggests that exercise-mediated beneficial mechanenergetic effects is independent of the beneficial effects on LV remodeling and systolic function. We have previously demonstrated that HIT also had oxygen-sparing effects in hearts from lean mice (19). A limitation of the present study, however, is the lack of HIT lean mice, which prevent us from directly comparing the effect of exercise on obese versus lean mice.

The oxygen-sparing effect was accompanied by improved diastolic function, and one might speculate that the increased cardiac efficiency is causally related to the improved diastolic function. In accordance with this view, a recent study by Lin et al. (27) reported reduced oxygen consumption in hearts from obese patients subjected to dietary weight loss. The authors argued that the reduced oxygen consumption could independently predict improved LV relaxation (23), which in turn implies that myocardial oxygen consumption may be mechanistically important in determining cardiac relaxation. Plausible explanations to these observations could be improved myocardial Ca$^{2+}$ handling as well as reduced obesity-induced fibrosis.

In accordance with Hafstad et al. (20), we also found exercise training to decrease the diet-induced elevation in cardiac ROS content. ROS content is a result of the balance between ROS formation (mitochondrial and nonmitochondrial) and the antioxidant capacity. Although still not fully elucidated, it is generally accepted that the diabetic heart exhibits both decreased endogenous antioxidant capacity and increased ROS formation (3, 6, 20). Long-term endurance exercise may potentially reduce ROS production due to systemic effects (improved insulin signaling, reduced inflammatory status, alteration of plasma lipids, and reduced activity of the renin-angiotensin system), which may dampen the activation of ROS-producing enzymes. In addition, exercise training has also been reported to improve endogenous antioxidant capacity of the heart (17, 20).

The underlying mechanisms related to the increased oxygen consumption in hearts from obese/diabetic models are not fully elucidated, and accordingly, we can only speculate about mechanisms responsible for exercise-induced reduction in MVo$_2$. First, exercise was found to reduce fatty acid oxidation, and as fatty acids are less energetically efficient substrates compared with glucose (31), this shift in metabolism may contribute to the decreased MVo$_2$. It should be noted, however, that, stoichiometrically, this can only account for a minor decrease in oxygen utilization, and other mechanisms are therefore also important. Exercise-induced amelioration of diabetes/obesity-related changes in Ca$^{2+}$ handling may play an important role. Reduced exercise-induced oxygen cost for Ca$^{2+}$ handling may include futile cycling of Ca$^{2+}$ due to a reduced sarcoplasmic reticulum (SR) Ca$^{2+}$ leak, enhanced synchronization of SR Ca$^{2+}$ release, and improvement of SR Ca$^{2+}$ ATPase (SERCA2a) function (46). In addition, exercise-mediated improvement of SERCA2a may lead to a more energetically efficient Ca$^{2+}$ handling, since there is less reliance on sarcoplasmal Ca$^{2+}$ transport (43). As Ca$^{2+}$ handling proteins are sensitive to the intracellular redox environment (14, 16), the exercise-induced, oxygen-sparing effect may be related to ROS-mediated changes in Ca$^{2+}$ handling. Finally, ROS-mediated mitochondrial uncoupling may lead to inefficient mitochondrial ATP production (32); therefore, reduced cardiac oxidative stress may also underlie the beneficial effect of exercise on mitochondrial efficiency (20).

Several studies have shown exercise to be associated with decreased mortality in patients with obesity and diabetes (4). Although exercise has been reported to induce cardioprotection and improve ischemic tolerance in nondiabetic hearts through a range of molecular mechanisms (18, 38), studies in diabetic and/or obese animal models are few (7, 37). In a type 1 diabetic model, Broderick et al. (7) have reported that 10 wk of continuous, moderate-intensity, treadmill running improved postschematic function in isolated perfused rat hearts subjected to ischemia-reperfusion. In a recent report by Pons and colleagues (37), decreased infarct size following treadmill running was demonstrated in a genetic model of severe obesity (ob/ob) mice that underwent in situ coronary artery occlusion followed by 24 h of reperfusion. However, it should be noted that this was an in vivo study using a model of genetic obesity lacking the gene encoding for leptin, a hormone shown to be proinflammatory and plays a role in the regulation of immunity (26, 47).

As decreased efficiency is particularly disadvantageous under conditions of reduced oxygen availability, it is reason to suggest that exercise-induced amendments of cardiac efficiency could reduce susceptibility to ischemic injury. In accordance with this, the present study demonstrated for the first time that myocardial oxygen-sparing effects following exercise are associated with decreased infarct size. Increased oxidative stress in the diabetic heart is believed to be an important contributor to the observed increase in ischemic sensitivity, and interventions that improve myocardial redox status have been suggested to reduce mitochondrial permeability transition pore opening and decrease ischemic susceptibility in diabetic hearts (44). Exercise-induced decrease in cardiac oxidative stress may therefore contribute to cardioprotection against ischemic injury observed in the present study.

**Conclusion.** In the present study, we used an animal model of diet-induced obesity closely related to the etiology of human obesity (10, 11, 28), where diabetic cardiomyopathy is displayed by a mechanical inefficiency and a mild LV diastolic dysfunction. For the first time, we have shown that exercise training in high-fat-fed mice reduced the infarct size in ex vivo hearts subjected to ischemia-reperfusion. We also found that exercise reduced obesity-induced myocardial oxygen wasting.
and improved diastolic function. We therefore conclude that exercise is a practical and sustainable countermeasure that provides cardioprotection in the obese/diabetic heart, likely due to the exercise-mediated oxygen-sparing effect.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


