High- and Moderate-Intensity Training Normalizes Ventricular Function and Mechanoenergetics in Mice With Diet-Induced Obesity

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Although exercise reduces several cardiovascular risk factors associated with obesity/diabetes, the metabolic effects of exercise on the heart are not well-known. This study was designed to investigate whether high-intensity interval training (HIT) is superior to moderate-intensity training (MIT) in counteracting obesity-induced impairment of left ventricular (LV) mechanoenergetics and function. C57BL/6J mice with diet-induced obesity (DIO mice) displaying a cardiac phenotype with altered substrate utilization and impaired mechanoenergetics were subjected to a sedentary lifestyle or 8–10 weeks of isocaloric HIT or MIT. Although both modes of exercise equally improved aerobic capacity and reduced obesity, only HIT improved glucose tolerance. Hearts from sedentary DIO mice developed concentric LV remodeling with diastolic and systolic dysfunction, which was prevented by both HIT and MIT. Both modes of exercise also normalized LV mechanical efficiency and mechanoenergetics. These changes were associated with altered myocardial substrate utilization and improved mitochondrial capacity and efficiency, as well as reduced oxidative stress, fibrosis, and intracellular matrix metalloproteinase 2 content. As both modes of exercise equally ameliorated the development of diabetic cardiomyopathy by preventing LV remodeling and mechanoenergetic impairment, this study advocates the therapeutic potential of physical activity in obesity-related cardiac disorders. Diabetes 62:2287–2294, 2013

Obesity, sedentary lifestyle, and reduced aerobic capacity are known predictors of heart failure and a major challenge to the health care system of the Western society (1,2). In addition to increasing the risk of cardiovascular disease, obesity and diabetes have been associated with the development of a distinct cardiomyopathy with ventricular remodeling and the progression to cardiac dysfunction (3). Reduced mechanical efficiency is an important hallmark of obesity/diabetic cardiomyopathy (4,5), and recent experimental studies have demonstrated diabetes-related inefficiency to be due to impaired mechanoenergetics, where myocardial oxygen consumption (MVO2) for nonmechanical processes is increased (6,7). Several obesity- or diabetes-induced changes, including increased fatty acid oxidation (4,8,9), impaired calcium handling (10,11), increased oxidative stress (12), and mitochondrial dysfunction (13), are factors that, most likely, contribute to increased MVo2. Although exercise has been reported to induce mitochondrial and cellular adaptations that could potentially influence myocardial oxygen-consuming processes (such as increased antioxidant capacity, reduced oxidative stress, increased mitochondrial efficiency, and improved myocardial Ca2+ homeostasis [10,14,15]), no studies have assessed the consequences of exercise-induced adaptations in terms of left ventricular (LV) mechanical efficiency and mechanoenergetics properties in a model of obesity and insulin resistance.

High-intensity exercise training induces a more pronounced increase in aerobic capacity and more evident cardiovascular adaptations compared with low- and moderate-intensity training (MIT) in healthy subjects (16–18). In a recent study by Tjønna et al. (19), high-intensity training (HIT) was also found to be superior to MIT in reducing cardiovascular risk factors in patients with metabolic syndrome. In addition, we found that high- but not MIT altered myocardial substrate utilization (decrease in fatty acid oxidation and increase in glucose oxidation) and increased mitochondrial respiratory capacity and LV mechanoenergetic properties in hearts from lean mice (18). Based on these findings, we hypothesized that exercise of high intensity would be superior to isocaloric moderate-intensity exercise in counteracting the unfavorable metabolic and functional changes that occur in the heart during obesity.

RESEARCH DESIGN AND METHODS

Mice with diet-induced obesity (DIO mice) were produced by initially feeding male C57BL/6J mice (5–6 weeks; Charles River Laboratories) a high-fat diet (60% kcal from fat, cat. no. 58Y1, TestDiet, London, U.K.) for 9 weeks. The diet was then changed to a palatable Western diet (50% kcal from fat, cat. no. 5A7-1814152; TestDiet), and the mice were subjected to high-intensity interval training (HIT) (DIOHIT) (n = 10), isocaloric moderate-intensity continuous training (MIT) (DIOMIT) (n = 10), or a sedentary lifestyle (DIOsed) (n = 15). Lean control mice fed a standard control diet (10% kcal from fat, cat. no. 58Y2, TestDiet) over the entire period were also included (CON) (n = 15). The experiments were approved by the local authority of the National Animal Research Authority in Norway (identification no. 2348/2010). The mice were treated in accordance with 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 ad libitum and free access to drinking water and were housed at 23°C on a reversed light/dark cycle so that the exercise occurred during the dark period.

Exercise protocol and determination of aerobic capacity. Treadmill running (25° inclination) was performed 5 days/week for 8–10 weeks as previously described by Hafstad et al. (18). Aerobic capacity was assessed as V2max using a metabolic chamber equipped with a treadmill (18). HIT consisted of 10 bouts of 4-min high-intensity running, corresponding to 85–90% of V2max interspersed by 2 min active rest. The interval pace was increased...
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RESULTS

Diet-induced obesity. After 9 weeks on a high-fat diet, C57BL/6J mice showed increased body weight, increased fasting glucose, and reduced glucose tolerance, while aerobic capacity (whole-body \(V_{\text{O2max}}\)) was similar to controls (Supplementary Table 1 and Supplementary Fig. 1). Despite marked changes in myocardial substrate utilization (i.e., increased fatty acid oxidation with a concomitant decrease in glucose oxidation [see Supplementary Fig. 2]), LV function was not impaired (Supplementary Table 1). A significant parallel upward shift of the SW-MVO\(_2\) relationships (Supplementary Fig. 3B) revealed reduced mechanical efficiency as previously reported in hearts from high-fat fed rats (5). In accordance with previous findings (7), we found that the decrease in mechanical efficiency was due to impaired LV mechanoenergetics, where MVO\(_2\) for non-contractile work (the \(y\)-intercept of the MVO\(_2\)-V\(_{\text{O2}}\) relationships) was increased (Supplementary Fig. 3A), while LV contractile efficiency (the inverse slope of the MVO\(_2\)-V\(_{\text{O2}}\) relationships) was unaltered. The increased work-independent MVO\(_2\) was confirmed by a 69% increase in MVO\(_2\) in retrogradely perfused mechanically unloaded hearts (MVO\(_2\) unloaded). This was due to an increase in the oxygen cost for basal metabolism (MVO\(_2\) BM, measured in electrically arrested hearts), as well as in processes related to ECC (MVO\(_2\) ECC, Supplementary Fig. 4).

DIOSED mice continued to gain weight after the next 8–10 weeks so that at the end of the protocol they showed a 43% higher body weight compared with CON mice (Supplementary Fig. 5). The increased body weight was accompanied by visceral obesity (increased perirenal fat) and an enlarged liver with steatosis (Table 1). DIOSED mice also displayed reduced aerobic capacity (Table 1 and Supplementary Fig. 6), reduced glucose tolerance (Table 1 and Supplementary Fig. 7), and increased plasma levels of glucose and free fatty acids (Table 1). Obesity was also associated with increased mRNA expression of tumor necrosis factor-\(\alpha\) (\(t\)n\(f\)a) in perirenal fat, indicative of a low-grade inflammatory state (Table 1). The hearts from DIOSED mice also showed higher work-independent MVO\(_2\) as revealed both by analyzing the PVA-MVO\(_2\) relationships (increased \(y\)-intercept [Fig. 1A]) and by measuring MVO\(_2\) in mechanically unloaded hearts (Fig. 1C). Again, increased MVO\(_2\) was ascribed to increased oxygen cost for BM and ECC (Fig. 1D and E). The impaired mechanoenergetic properties resulted in mechanical inefficient hearts, i.e., a significant upward parallel shift of the MVO\(_2\)-SW relationship (Fig. 1D). The metabolic phenotype with increased myocardial fatty acid oxidation rates and decreased glucose oxidation rates was maintained in DIOSED mice (Fig. 2).

In a follow-up study, assessment of mitochondrial respiration (Fig. 3) showed reduced mitochondrial respiratory capacity (\(Y_{\text{max}}\)) and impaired mitochondrial respiratory coupling (reduced P-to-O ratio) in hearts from DIOSED mice. Obesity was, however, not associated with altered oxygen consumption during state 4 respiration (\(V_{\text{O2 state4}}\)), which may suggest an unchanged proton leak.

Finally, as shown in Table 2, isolated hearts from DIOSED mice showed impaired LV systolic function (i.e., reduced dP/dt\(_{\text{max}}\) and preload recruitable stroke work index [P\(\text{RSWI}\)]) as well as impaired early diastolic function (i.e., increased diastolic relaxation time constant and reduced dP/dt\(_{\text{min}}\)). A leftward shift of the pressure-volume (P-V) loop indicated obesity-induced LV concentric remodeling, and an elevated end-diastolic P-V relationship (D\(\text{FVPR}\)) revealed...
ventricular stiffening (Fig. 4). In concert with the observed changes in LV function, these hearts showed obesity-induced fibrosis (Fig. 5C and Supplementary Fig. 8) and increased myocardial intracellular staining of MMP-2 (Fig. 5A and B). Finally, DHE staining showed myocardial reactive oxygen species (ROS) content (Fig. 6A and B) in the sedentary DIO mice.

**Effects of exercise on obesity and glucose tolerance.** Exercise training reduced weight gain in DIO mice (Supplementary Fig. 6) so that the body weights of the DIOHIT and DIOMit mice at the end of the training protocol were only 14 and 21% above CON mice, respectively (Table 1). Both training protocols also reduced visceral obesity, plasma free fatty acid, liver weight, and steatosis and showed anti-inflammatory action (reduced perirenal fat Tnfα expression) (Table 1). Only HIT significantly improved glucose tolerance (Table 1 and Supplementary Fig. 7). HIT was also superior to MIT in increasing the running pace, while both training protocols increased \( V_{\text{O2max}} \) and citrate synthase activity in skeletal muscle, myocardial lipid and mitochondrial content, and liver triglycerides were measured in 7–8 animals/group. *P < 0.05 vs. DIOSED.

**TABLE 1**
Animal characteristics of CON, DIOSED, DIOMit, and DIOHIT mice

|                      | CON          | DIOSED       | DIOMit       | DIOHIT      |
|----------------------|--------------|--------------|--------------|-------------|
| n                    | 15           | 15           | 10           | 10          |
| Body weightstart (g) | 25.8 ± 0.3*  | 33.6 ± 0.6   | 32.1 ± 0.7   | 33.7 ± 0.4  |
| Body weightend (g)   | 31.2 ± 0.5*  | 44.7 ± 0.6   | 35.0 ± 0.6*  | 38.3 ± 0.7* |
| Heart weight/tibia length (mg/mm) | 7.9 ± 0.2    | 8.0 ± 0.2    | 8.2 ± 0.2    | 9.1 ± 0.2*  |
| Perirenal fat weight (mg) | 384 ± 26*    | 1,168 ± 48   | 755 ± 42*    | 912 ± 59*   |
| Tnfα in perirenal fat | 0.20 ± 0.02* | 1.00 ± 0.10  | 0.52 ± 0.11* | 0.45 ± 0.06*|
| Liver weight (g)     | 1.04 ± 0.03* | 1.87 ± 0.10  | 1.13 ± 0.05* | 1.35 ± 0.08*|
| Triglyceride contentliver (μmol/g) | 46 ± 6*     | 184 ± 8      | 49 ± 8*      | 77 ± 17*   |
| Mitochondrial fractionheart (%) | 35.4 ± 1.6    | 35.1 ± 0.7    | 36.5 ± 0.8   | 39.8 ± 1.4* |
| Lipid contentheart (droplets/mm²) | 3.4 ± 0.9    | 4.9 ± 1.0    | 2.7 ± 0.7    | 1.8 ± 0.4*  |
| CS activityskeletal muscle (IU/g) | 11.0 ± 1.5   | 11.7 ± 0.9   | 17.5 ± 2.2*  | 15.4 ± 1.1* |

Aerobic capacity and running speed

|                      | CON          | DIOSED       | DIOMit       | DIOHIT      |
|----------------------|--------------|--------------|--------------|-------------|
| \( V_{\text{O2max}} \)start (mL/kg^{0.75}/min) | 47.2 ± 0.6   | 45.9 ± 0.9   | 46.02 ± 0.9  | 46.6 ± 0.5  |
| \( V_{\text{O2max}} \)end (mL/kg^{0.75}/min)  | 44.7 ± 0.5*  | 40.2 ± 0.4   | 46.8 ± 0.4*  | 46.8 ± 0.5* |
| Speed at \( V_{\text{O2max}} \)end (m/min)    | 16.3 ± 0.5*  | 14.3 ± 0.3   | 21.2 ± 0.4*  | 26.4 ± 1.6* |

Glucose tolerance/plasma parameters

|                      | CON          | DIOSED       | DIOMit       | DIOHIT      |
|----------------------|--------------|--------------|--------------|-------------|
| Glucose tolerance test (AUC) | 1.014 ± 120*  | 1.561 ± 164  | 1.473 ± 108  | 1.063 ± 58* |
| Glucosefasted (mmol/L) | 6.6 ± 0.3*   | 8.2 ± 0.2    | 7.8 ± 0.2    | 7.4 ± 0.3*  |
| Free fatty acidfed (μmol/L) | 516 ± 46*    | 789 ± 105    | 576 ± 106    | 545 ± 38    |

Data are means ± SEM. mRNA expression of Tnfα was normalized to the expression in DIOSED, citrate synthase (CS), and whole-body \( V_{\text{O2max}} \). The area under curve (AUC) was measured after a standard glucose tolerance test (see Supplementary Data). Glucose tolerance, citrate synthase activity in skeletal muscle, myocardial lipid and mitochondrial content, and liver triglycerides were measured in 7–8 animals/group. *P < 0.05 vs. DIOSED.

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**FIG. 1.** Individual values of M\( \text{VO2} \) in relation to total cardiac work (assessed as PVA) (A) or SW (B) in isolated working hearts from CON (\( n = 13 \)), DIOSED (\( n = 10 \)), DIOMit (\( n = 8 \)), and DIOHIT (\( n = 7 \)) mice at different workloads (preload, 4–10 mmHg; afterload, 40–50 mmHg). The table gives the mean ± SEM values of the y-intercept and the slope of the PVA-M\( \text{VO2} \) relationships (\( r^2 = 0.89 ± 0.01 \)) obtained after mixed-model analysis. M\( \text{VO2} \) was also measured in retrogradely perfused unloaded hearts (paced at 7 Hz) before (M\( \text{VO2 unloaded} \)) (C) and after (M\( \text{VO2 BM} \)) (D) electrical arrest. M\( \text{VO2 ECC} \) (E) was calculated as the difference between M\( \text{VO2 unloaded} \) and M\( \text{VO2 BM} \). Values are means ± SEM. \( n = 8–14 \) in each group; *P < 0.05 vs. DIOSED; wwt, wet weight.
(gastrocnemius) to the same extent (Table 1 and Supplementary Fig. 6).

**Effects of exercise on LV mecanoenergetics.** Both HIT and MIT induced a significant parallel downward shift of the SW-MVO₂ and the PVA-MVO₂ relationships, showing that exercise normalized the obesity-induced mechanical inefficiency (Fig. 1B) by decreasing work-independent MVO₂ (y-intercept [Fig. 1A]). This finding was further supported by the measurements of MVO₂ in mechanically unloaded hearts, which also showed that both training protocols reduced MVO₂ IM, while the reduction in MVO₂ ECC was statistically significant only after HIT (Fig. 1C–E). None of the training protocols altered contractile efficiency (inverse slope of the PVA-MVO₂ relationships [Fig. 1A]). Myocardial ROS content was reduced after both training protocols (Fig. 6A and B) and accompanied by increased mRNA levels of mitochondrial superoxide dismutase (mn-sod) (Fig. 6D). Interestingly, we found a significant (P < 0.001) correlation between ROS content and MVO₂ unloaded (Fig. 6C), suggesting that oxidative stress plays an important role in inducing processes leading to increased MVO₂.

**Effects of exercise myocardial substrate utilization and mitochondrial respiration.** Both MIT and HIT significantly increased absolute and work-adjusted rates of myocardial glucose oxidation (Fig. 2). While absolute rates of fatty acid oxidation were unaltered, work adjustment revealed a significant decrease in fatty acid oxidation rates after MIT and HIT. These findings indicate that both modes of exercise induced a mild change in substrate utilization toward an increased myocardial use of glucose. Exercise was also found to normalize the obesity-induced impairment of mitochondrial capacity (Vₘₐₓ), as well as efficiency (P-to-O ratio). Interestingly, we also found exercise to induce a mild proton leak (Vₒₒₒₒ) without any change in respiratory coupling ratio (Fig. 3).

**DISCUSSION**

Exercise has been shown to reduce cardiovascular risk factors associated with type 2 diabetes (27). The cardiac effects of exercise in obesity/diabetes are, however, not...
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well studied, and to our knowledge, this is the first study addressing the impact of exercise intensity on functional, metabolic, and mechanoenergetic cardiac adaptations in a model of obesity/diabetes. The main findings of the study are that exercise of both high and moderate intensity improved LV mechanical efficiency, by abrogating the obesity-induced increase in $\text{MV}_2$, and that these changes were accompanied by prevention of obesity-induced LV remodeling and dysfunction.

**Obesity/diabetes-induced cardiac phenotype.** The current study used a mouse model of cardiomyopathy induced by 20 weeks’ feeding on high-energy rich diets. As anticipated, we found that 9 weeks on the high-fat diet altered myocardial substrate utilization, reduced LV mechanical efficiency, and impaired mechanoenergetics (4–6,8,28). As LV dysfunction was not evident at this stage, this study shows for the first time that not only altered substrate utilization (8,28) and mechanical inefficiency (4,5) but also LV mechanoenergetic impairment precede development of cardiac dysfunction in obesity/diabetes.

The diabetic cardiac metabolic phenotype persisted in mice kept on a sedentary lifestyle for another 10 weeks. In addition, these hearts developed diastolic and systolic dysfunction and showed a leftward shift of the LV P-V loop indicative of development of concentric remodeling (6,29). In accordance with previous studies on diabetes-induced cardiac remodeling, the hearts exhibited increased fibrosis, impaired metalloproteinase expression, and elevated oxidative stress (12,30). Obesity was also found to reduce mitochondrial maximal respiratory capacity and efficiency (P-to-O ratio)—findings that are in accordance with a recent report by Cole et al. (5) in high-fat fed rats and suggest that decreased respiratory coupling can contribute to the impaired cardiac efficiency observed following obesity.

**Systemic effects of exercise training.** Exercise training is considered a cornerstone in the treatment of insulin resistance and obesity, where the impact of exercise mode and intensity has been suggested to play a decisive role. In lean subjects, high-intensity has been shown to be superior to moderate-intensity exercise training in terms of increased aerobic capacity (16–18). Although the numbers of studies directly examining the effect of isocaloric high- and MIT on aerobic capacity in metabolic disorders are limited, a superior effect of high intensity has been suggested (19,31,32).

In contrast to this view, we found both intensities to equally increase aerobic capacity in this model of obesity and insulin resistance. The ability of subjects on high-fat diets to perform HIT has, however, been questioned (33), and it can therefore not be excluded that diet might have limited the potentiation of aerobic capacity in response to high-intensity exercise in the current study.

While MIT was as effective as isocaloric HIT in reducing obesity, only exercise of high intensity improved glucose...
tolerance. This finding supports a recent pilot study by Tjønna et al. (19) where high-intensity aerobic interval training in patients with metabolic syndrome improved glycemic control to a greater extent than MIT—a response most likely due to exercise-induced adaptations in skeletal muscle (19,31,34).

**Cardiac effects of exercise training.** Despite the notion that exercise training has beneficial effects in patients with cardiovascular disease, its documented effect on ventricular energetics is sparse. Improved LV function and mechanical efficiency have been reported in heart failure patients enrolled in a 5-month endurance and strength-training program (35). In a recent study, we found that only exercise of high, but not moderate, intensity was able to induce metabolic and energetic adaptations in hearts from normal (nonobese) mice (18). Hence, we anticipated that exercise training of high intensity would be superior to moderate intensity in counteracting obesity-induced LV metabolic, energetic, and functional changes. Surprisingly, however, we found both modes of exercise to be equally effective in ameliorating LV mechanical and energetic dysfunction. Exercise improved both LV diastolic and systolic function, and improved LV mechanical efficiency owing to a reduction of the oxygen cost for nonmechanical purposes (i.e., BM and ECC).

The development of both ventricular dysfunction and mechanoenergetic impairments in diabetes/obesity is clearly multifactorial and complex and has been suggested to involve alterations in myocardial substrate utilization and calcium handling, as well as oxidative stress, mitochondrial dysfunction, and structural remodeling (11,12,30,36–38). Many of these processes are likely to be influenced by exercise training, and here we focus on how they may be linked to the exercise-induced improvements of LV mechanoenergetics and prevention of LV dysfunction. It should be noted, however, that owing to the pleiotropic effects of exercise in a model of obesity (both systemic and direct cardiac effects), the current study cannot pinpoint one underlying mechanism leading to the observed cardiac effects, and additional mechanistic studies will be warranted.

First, although obesity-induced increase in myocardial fatty acid supply and/or utilization is believed to contribute to the increased myocardial oxygen consumption (5,7,9,21,36), this change can only partly account for the decrease in O2 consumption (18,39). This study shows, however, for the first time, that exercise abrogated obesity-induced mitochondrial respiratory uncoupling. Surprisingly, the improved mitochondrial efficiency in response to exercise training was accompanied by a mild mitochondrial proton leak during state 4 (oligomycin-inhibited) respiration, which was also recently reported in skinned cardiac fibers from high-fat fed UCP3KO mice (40). Although the role of this proton leak is unclear, there are substantial data suggesting that a mild proton leak will, owing to reduced mitochondrial potential, reduce mitochondrial ROS formation (15,41). Thus, both enhancement of endogenous antioxidant capacity (14,15) and decreased mitochondrial ROS production are candidates for the observed exercise-induced decrease in myocardial oxidative stress.

Diabetes is also associated with impaired myocardial Ca2+ handling, including increased ryanodine receptor (RyR2) Ca2+ leak (10,11), which most likely contributes to the increased oxygen consumption demonstrated in the
present and in previous studies (4–7,9), and exercise has been reported to improve myocardial Ca\textsuperscript{2+} handling in lean and diabetic models (10,31,42,43). In cardiomyocytes from type 2 diabetic mice, exercise training enhanced synchronization of sarcoplasmic reticulum Ca\textsuperscript{2+} release and reduced diabetes-induced RyR2 Ca\textsuperscript{2+} leak (10)—adaptations that could provide oxygen-sparing effects. Although we did not find exercise to induce changes in the gene expression of RyR2 or SERCA, improvements in Ca\textsuperscript{2+} homeostasis can be achieved by posttranscriptional regulation of calcium-handling proteins, as well as by changes in the intracellular redox environment. ROS has been shown to activate RyR2 and inhibit SERCA (44), and it is therefore tempting to suggest that the positive correlation between myocardial ROS and myocardial O\textsubscript{2} consumption is linked to ROS-mediated changes in Ca\textsuperscript{2+} handling, which is supported by the recent study showing changes in MVO\textsubscript{2} to predict improvement of LV relaxation (45). Amelioration of the diabetes-induced myocardial Ca\textsuperscript{2+} dysregulation (10) most likely also plays a key role in the enhancement of systolic and early diastolic LV function in exercised mice, while the decreased fibrosis will reduce LV chamber stiffness and thus improve late diastolic function. Our results are in line with a previous study in the aging heart, where exercise decreased fibrosis and normalized MMP-2 regulation (46). Although the underlying mechanisms of these changes are unclear, the current study suggests that exercise may have exerted such effects through improved inflammatory status and ameliorated oxidative stress, as both ROS and TNF-\alpha can increase the expression of MMP-2 (47,48) and induce fibrosis (49). Future studies are, however, required to address this issue.

In a recent study, substantial weight loss (1 year of dieting) was also found to improve myocardial energetics and diastolic function in obese subjects (50). In the current study, DIO mice already exhibited decreased LV mechanoenergetic features before the start of exercise. As exercise did not reduce body weight but, rather, attenuated weight gain in DIO mice, we suggest that the observed exercise-induced improvements in LV mechanoenergetics are not only a result of decreased obesity per se.

**Conclusion.** The current study demonstrates that prevention of LV dysfunction by exercise training in diet-induced obesity involves restored mechanical efficiency and improved mechanoenergetic properties. These changes are most likely related to improvements in mitochondrial efficiency and capacity, reduction in oxidative stress, and reversal of ventricular remodeling. Despite previous reports of superior effects of HIT compared with MIT with respect to reducing cardiovascular risk factors associated with metabolic disorders, the current study shows that both intensities equally ameliorated the obesity-induced functional and structural changes in the heart, underlining the profound therapeutic potential of physical activity in obesity and diabetes-related cardiovascular disease.

**ACKNOWLEDGMENTS**

This work was supported by the Norwegian Research Council and the Northern Norway Regional Health Authority (Helse Nord RHF, UNIKARD), as well as by the Norwegian Health Association.

No potential conflicts of interest relevant to this article were reported.

A.D.H. designed the study, analyzed data, wrote the manuscript, and reviewed and edited the manuscript. J.L., E.H.-O., and A.C.H. analyzed data and reviewed and edited the manuscript. T.S.L. reviewed and edited the manuscript. E.A. designed the study, analyzed data, wrote the manuscript, and reviewed and edited the manuscript. E.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented in abstract form at the American Heart Association Scientific Sessions, Orlando, Florida, 12–16 November 2011, and at the 10th Annual Meeting of the Society of Heart and Vascular Metabolism, Oxford, U.K., 24–27 June 2012.

The authors acknowledge valuable contributions from Knut Steineins, Ahmed Murtaz Khalid, Martin Hagve, Elisabeth Boerde, Randi Olsen, Sigurd Lindal, and Elin Mortensen (Department of Medical Biology, University of Tromsø).

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