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Exercise Training Reduces Intrathoracic Fat Regardless of Defective Glucose Tolerance

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ABSTRACT

HONKALA, S. M., K. K. MOTIANI, J.-J. ESKELINEN, A. SAVOLAINEN, V. SAUNAVAARA, K. A. VIRTANEN, E. LÖYTTYNIEMI, J. KAPANEN, J. KNUUTI, K. K. KALLIOKOSKI, and J. C. HANNUKAINEN. Exercise Training Reduces Intrathoracic Fat Regardless of Defective Glucose Tolerance. *Med. Sci. Sports Exerc.*, Vol. 49, No. 7, pp. 1313–1322, 2017. **Purpose**: Epicardial (EAT) and pericardial (PAT) fat masses and myocardial triglyceride content (MTC) are enlarged in obesity and insulin resistance. We studied whether the high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) similarly decrease ectopic fat in and around the heart and whether the decrease is similar in healthy subjects and subjects with defective glucose tolerance (DGT). **Methods**: A total of 28 healthy men (body mass index = 20.7–30.0 kg·m^{-2}, age = 40–55 yr) and 16 men with DGT (body mass index = 23.8–33.5 kg·m^{-2}, age = 43–53 yr) were randomized into HIIT and MICT interventions for 2 wk. EAT and PAT were determined by computed tomography and MTC by ^{1}H-MRS. **Results**: At baseline, DGT subjects had impaired aerobic capacity and insulin sensitivity and higher levels of whole body fat, visceral fat, PAT, and EAT ($P < 0.05$, all) compared with healthy subjects. In the whole group, HIIT increased aerobic capacity (HIIT = 6%, MICT = 0.3%; time × training $P = 0.007$) and tended to improve insulin sensitivity (HIIT = 24%, MICT = 8%) as well as reduce MTC (HIIT = −42%, MICT = +23%) (time × training $P = 0.06$, both) more efficiently compared with MICT, and without differences in the training response between the healthy and the DGT subjects. However, both training modes decreased EAT (−5%) and PAT (−6%) fat (time $P < 0.05$) and not differently between the healthy and the DGT subjects. **Conclusion**: Whole body fat, visceral fat, PAT, and EAT masses are enlarged in DGT. Both HIIT and MICT effectively reduce EAT and PAT in healthy and DGT subjects, whereas HIIT seems to be superior as regards improving aerobic capacity, whole-body insulin sensitivity, and MTC. **Key Words:** TYPE 2 DIABETES MELLITUS, MYOCARDIAL FAT CONTENT, EPICARDIAL FAT, PERICARDIAL FAT, CT, H-MRS

Obesity and physical inactivity are major risk factors for the development of insulin resistance and type 2 diabetes mellitus (T2DM), together with its complications. In obesity, excess triglyceride (TG) accumulate not only into the peripheral fat depots but also in and around the internal organs such as liver, muscle, pancreas, and heart (22,42). It has been suggested that the regional fat distribution is independent and an important risk factor for metabolic and cardiovascular diseases as the whole body fat quantity as such (14,42).

The untypical accumulation of TG in and around the heart associates with body adiposity, circulation of nonesterified fatty acid and TG concentrations, insulin resistance, blood pressure, and an increased risk of cardiomyopathy and heart failure (18,22,27,35,45). In the heart, TG can accumulate either inside the myocardium (myocardial triglyceride content [MTC]) or outside the myocardium located between the myocardium and the pericardium (epicardial fat), or between the pericardium and the chest wall (pericardial fat). Both fat depots inside and outside the myocardium have been proposed to have a cardioprotective role by acting as a buffer to protect the myocardium from a high TG load and, in contrast, to act as a rapid energy source when needed (e.g., during intense exercise) (12,15,45). Epicardial and pericardial fat depots

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share some characteristics but also differ regarding anatomy, biochemistry, embryonic cell differentiation, and function and have thus been suggested to be two distinct fat depots (19). Epicardial fat, derived from the splanchnopleuric mesoderm, is not separated from the myocardium by any fascia and shares the microcirculation from the coronary arteries with the myocardium (18). Compared with other fat deposits, epicardial fat has a smaller cell size, a distinct fatty acid composition, and a higher fatty acid and lower glucose metabolism (15). Epicardial fat also secretes defensive cytokines and adipokines (e.g., adiponectin and interleukin-10) and abates vascular tension and thus is not considered harmful under normal physiological conditions (15,45). Pericardial fat is derived from the primitive thoracic mesenchyme, and its blood is supplied by branches of the internal mammary artery (18). The metabolic role of pericardial fat is still unclear, but increased pericardial fat may evolve into a higher risk for metabolic diseases compared with epicardial fat (43).

The mechanisms relating myocardial fats to increased cardiovascular and metabolic risks factors are complex and incompletely studied (8). Under pathological circumstances, such as obesity and T2DM, epi- and pericardial fat masses have been suggested to release adipokines and proinflammatory cytokines, which may lead to the development and progression of atherosclerotic lesions and coronary artery disease (3,15). Increased MTC has been shown to have a positive association with mitochondrial dysfunction and increased oxidative stress, which especially increases the risk of cardiac dysfunctions (27,29).

Exercise training has been shown to reduce MTC (38,39) and epicardial fat (23) accompanied by enhanced left ventricular function (39) in nondiabetic obese individuals. However, the few studies performed with T2DM patients have not revealed promising results. In the study by Schrauwen-Hinderling et al. (40), the 3-month combined endurance and strength training improved insulin sensitivity and the left ventricular ejection fraction but not MTC. Similarly, in the study by Jonker et al. (21), no response was observed in MTC or epicardial fat after 6 months of endurance training in T2DM subjects, although hepatic TG content, visceral fat, and pericardial fat decreased. Overall, the data on the effects of exercise training on MTC are limited. It is also unclear whether exercise training could increase MTC as it occurs in skeletal muscle, which is the phenomenon known as the "athlete's paradox."

Recently, several studies have compared the benefits of high-intensity interval training (HIIT) over moderate-intensity continuous training (MICT). We and others have shown that short-term HIIT induces at least similar improvements in aerobic capacity and insulin sensitivity compared with MICT in healthy middle-age men (9,44,46). Furthermore, for patients with cardiovascular diseases and cardiac dysfunctions, high-intensity aerobic training seems to be the most efficient mode to maximize the cardiac benefits of exercise training (35,38). However, it is unclear whether high-intensity training is an effective method to reduce myocardial ectopic fat accumulation along with improvements in general metabolic health. Thus, the aim of this study was to elucidate whether HIIT and MICT similarly decrease ectopic fat in and around the heart and whether the decrease is similar in healthy subjects and subjects with defective glucose tolerance (DGT). We hypothesized that exercise training reduces ectopic fats in both healthy subjects and subjects with DGT and that MICT reduces these fat depots more than HIIT.

METHODS

The study was a part of a larger study titled "The Effects of Short-Term HIIT on Tissue Glucose and Fat Metabolism in Healthy Subjects and in Patients with Type 2 Diabetes" (NCT01344928). We have previously published several reports from this study (9,10,16,17,24,25,37). The main parameters of the present study, epi- and pericardial fat masses and MTC, have not been published before neither in healthy nor in DGT subjects. Also there are no prior published or accepted reports from the DGT group. The study was performed at the Turku PET Centre, the University of Turku and Turku University Hospital (Turku, Finland), and the Paavo Nurmi Centre (Turku, Finland) between March 2011 and September 2015. The study was approved by the ethical committee of the Hospital District of Southwest Finland (Turku, Finland, decision 95/180/2010 §228) and was conducted according to the Declaration of Helsinki. All participants gave written informed consent.

Subjects and study design. Middle-age physically inactive healthy subjects and subjects with DGT were recruited for the study via newspaper advertisements, personal contacts, and electronic and traditional bulletin boards. The inclusion criteria for healthy subjects (n = 28) were male sex, 40–55 yr old, body mass index (BMI) of 18.5–30 $kg \cdot m^{-2}$, $\dot{V}O_{2peak}$ <40 $mL \cdot kg^{-1} \cdot min^{-1}$, and normal glycemic control (1). The exclusion criteria were as follows: any chronic disease, a medical defect, or injury that interfered with everyday life; a history of eating disorders; a history of asthma; use of tobacco products; use of anabolic steroids, additives, or any other substrates; significant use of alcohol; and current or a history on regular and systematic exercise training of any other condition that in the opinion of the investigator could create a hazard to the participant's safety, endanger the study procedures, or interfere with the interpretation of the study results. For the DGT subjects, the inclusion criteria were the same as in healthy subjects except for a BMI of 18.5–35 $kg \cdot m^{-2}$ and an impaired glucose tolerance according to the criteria of the American Diabetes Association (1), an HbA1c of less than 7.5 $mmol \cdot L^{-1}$, and no insulin treatment in case of T2DM. Of the 16 DGT subjects, 13 had T2DM and 3 had impaired fasting glucose and/or impaired glucose tolerance, and they were regarded as a DGT group. At the screening, three subjects were newly diagnosed with T2DM and had no previous medication. In the other 10 T2DM subjects, the median diabetes duration was 3.5 yr, and they were treated by oral hypoglycemic agents (9 with metformin, 4 with sitagliptin, and 1 with glimepiride). Antidiabetic

treatment was withheld for 72 h, and the subjects were asked to avoid exhausting exercise 48 h before the euglycemic hyperinsulinemic clamp.

The physical examination, oral glucose tolerance test (OGTT), $\dot{V}O_{2peak}$ test, magnetic resonance imaging (MRI) and spectroscopy (MRS), hyperinsulinemic clamp, and computed tomography (CT) were performed as described in Figure 1. After all the pretraining measurements, the subjects were randomly divided into HIIT and MICT training groups within both the healthy and the DGT groups. All the studies were repeated after the training intervention, starting with MRS, MRI, and CT scans at 48 h, a euglycemic hyperinsulinemic clamp at 72 h, and an aerobic fitness and blood sampling at 96 h after the last training session (Fig. 1).

In previous long-term moderate-intensity training studies, epicardial fat has shown a decrease of 9% (23) and pericardial fat a decrease of 20% (21). As the present training intervention was shorter than used in the previous studies, we assumed that the training response would be at a level of 5% per unit (assuming the SD to be 10% per unit). We calculated that a sample size of 34 subjects with decreases of 5% in epi- and pericardial fat masses would give an 80% power of detecting significant change after the training intervention with a level of significance at 5% (two-sided).

Randomization of the healthy subjects was performed in two phases. First, a random permuted block of 24 subjects with a 1:1 allocation ratio was generated. Because of technical problems in the PET studies, another random permuted block of four subjects was also generated. Therefore, the final group sizes were $n = 14$ for the HIIT and $n = 14$ for the MICT in the healthy subjects (totally $n = 28$). Randomization of the DGT subjects ($n = 26$) was performed in blocks of four subjects with a 1:1 ratio. Originally, the DGT group consisted of 26 subjects with T2DM or prediabetes of which 10 were females. As sex has large effect on body adiposity and may also have large effect on epicardial fat, pericardial fat, and MTC and as the healthy group consisted of only males, we decided to leave out the females from the DGT group in the analyses of this

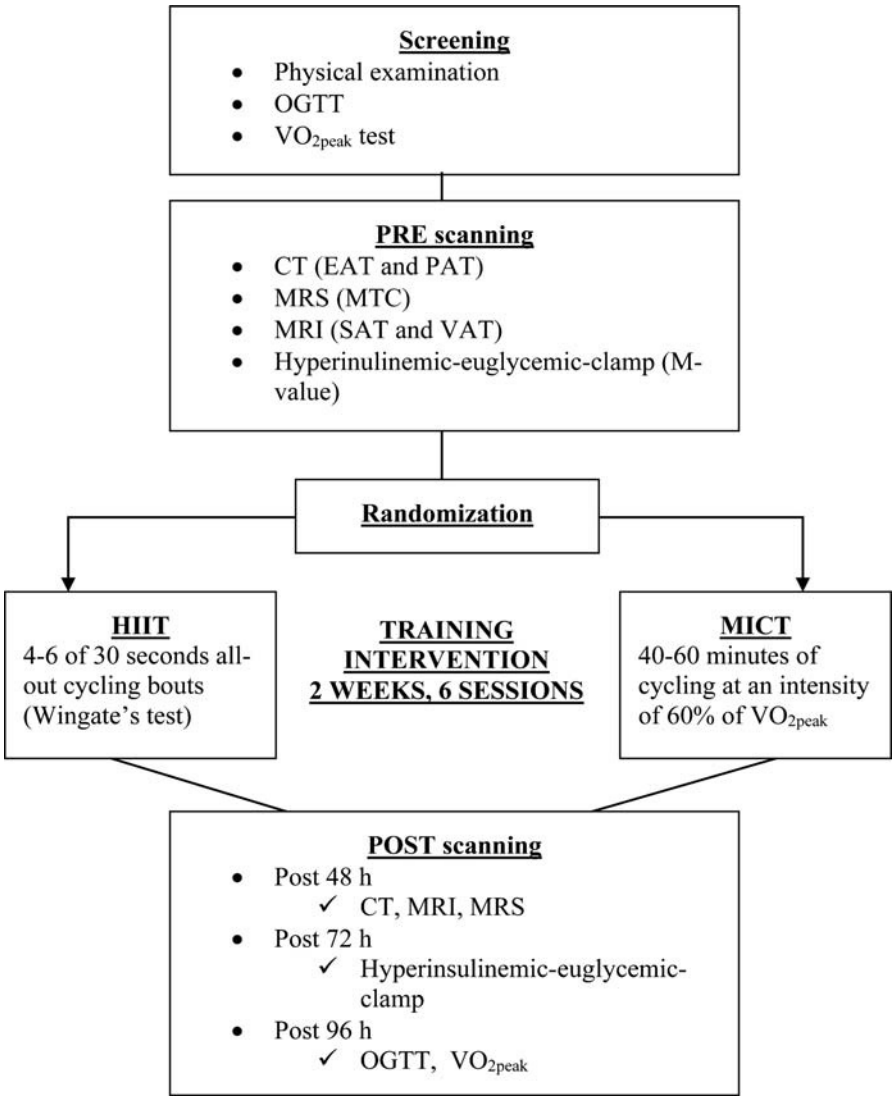

FIGURE 1—The study design. EAT, epicardial fat; PAT, pericardial fat.

report. Thus, the number of subjects in the DGT group was 16 and in the whole study 44; all of the subjects were males.

Euglycemic–hyperinsulinemic clamp. A euglycemic–hyperinsulinemic clamp was performed after a 10-h fast based on the original protocol by Defronzo et al. (7). During the first 4 min, a primed-constant insulin (Actrapid, 100 $U \cdot mL^{-1}$; Novo Nordisk, Bagsvaerd, Denmark) infusion was started at a rate of 40 $mU \cdot m^{-2}$ of body surface area. After the first 4 min, the infusion rate was decreased to 20 $mU \cdot m^{-2}$ for 3 min and then further decreased to 10 $mU \cdot m^{-2}$ for the rest of the clamp. An exogenous glucose infusion was started at 4 min after the beginning of the insulin infusion at a rate of the subject's weight (kg)/0.1 $g \cdot h^{-1}$. The glucose infusion rate was doubled after 10 min and then adjusted based on the blood glucose concentration to maintain it as close to 5 $mmol \cdot L^{-1}$ as possible. Blood samples were collected before the clamp and every 5 min during the first 30 min to adjust the glucose infusion rate. After 30 min, the samples were collected every 5 to 10 min to check the glucose levels. The whole-body glucose uptake (M-value) was calculated from the glucose infusion rate, and the measured glucose values were collected during the study (7).

OGTT. The OGTT was performed after at least 10 h of fasting. Liquid containing 75 g of glucose (Nutrical®; Nutricia Medical, Turku, Finland) was given, and blood samples were taken at the baseline and at 15, 30, 60, 90, 120 min during the test to determine glucose and insulin concentrations for the glycemic status.

$\dot{V}O_{2peak}$ test and bioimpedance analysis. Aerobic capacity was determined with a $\dot{V}O_{2peak}$ cycling ergometer test (ergoline 800 s; VIASYS Healthcare, Germany). The test was performed at the Paavo Nurmi Center (Turku, Finland) approximately 1 wk before the first training session and 96 h after the last training session. The $\dot{V}O_{2peak}$ test was performed as previously described by Kiviniemi et al. (25). Fat percentage was determined using the bioimpedance method (InBody 720; Mega Electronics Ltd., Kuopio, Finland).

Other measurements. Plasma total and HDL cholesterol, TG, and fasting glucose were measured from the venous blood samples with an automatized enzymatic assay and insulin using automatized electrochemiluminescence immunoassay (Cobas 8000; Roche Diagnostics GmbH, Mannheim, Germany). LDL cholesterol concentration was calculated using the Friedewald formula. Blood samples were collected before and 96 h after the last training session.

We also calculated the 10-yr cardiovascular disease risk score, based on age, systolic blood pressure, treatment of hypertension, diabetes, HDL, and total cholesterol using the Framingham risk score (FRS) (5).

Training intervention. Both training interventions took 2 wk and included six supervised training sessions. The duration of the intervention was based on previous studies showing improvements in aerobic fitness and insulin sensitivity after only six training sessions (2,4) and also considering the extremely intense nature of the HIIT intervention. The HIIT sessions consisted of 4–6 × 30 s maximal all-out cycling bouts (Monark Ergomedic 894E; MONARK, Vnasbro, Sweden) with a 4-min recovery between each bout. The number of bouts increased progressively starting with four bouts and increasing by one every other session. The training load was individually determined (healthy 7.5% of whole body weight in kg, DGT 10% of lean body mass in kg). The MICT session consisted of 40–60 min of cycling at a moderate intensity, which was 60% of the $\dot{V}O_{2peak}$ intensity (Tunturi E85; Tunturi Fitness, Almere, Netherlands). The duration of the MICT increased progressively starting with 40 min and increasing by 10 min every other session.

CT. Epi- and pericardial fat volumes were determined using a CT with a 64-row GE Discovery VCT PET/CT scanner (General Electric Medical Systems, Milwaukee, WI) using the fat volume quantification by Mahabadi et al. (28). The fat depots were measured from the calcium score CT images. A gated cine CT was done with a 512 × 512 matrix, and a total of 64 slices were acquired with a rotation time of 0.4 s, 120 kV, and 200 mA. The axial thickness was 2.5 mm. Images were reconstructed with an SD reconstruction algorithm using a display field of view of 25 cm. The data analyst (author SMH) was blinded for the order of before versus after images and analyzed images in random order using a Carimas 2.9 (Turku PET Centre, Finland). First, we outlined the pericardium at each cross section. The fat inside the region of interest was defined as the epicardial fat. Second, we defined the intrathoracic fat, including both epi- and pericardial fat masses, by drawing regions of interests on the thoracic wall. The pericardial fat volume was determined as the difference between the intrathoracic fat and the epicardial fat volume. Finally, the fat volume was defined as pixels within a window of −195 to −45 Hounsfield units (48). Quantification of epi- and pericardial fat masses from the CT scans can be considered to be one of the most accurate methods in use because of its high spatial and temporal resolution and 3-D viewing (6).

MRS. The MTC was determined with a ^{1}H-MRS (Philips Gyroscan Intera 1.5T CV Nova Dual Scanner, with a SENSE body coil; Philips Medical Systems, the Netherlands). This method is based on different chemical shifts of water and fat. The MRS was performed after an 8-h fast. The volume of interests were placed on an interventricular septum using both 4ch and short-axis images. The voxel size was 12 × 10 × 15 mm. The molecular contents of lipids and water were determined using single-voxel proton spectroscopy with a PRESS sequence and using an echo time of 30 ms and a repetition time of 3000 ms. The measurement was triggered by the heartbeat, and a typical triggering delay time was 350 ms. Spectra were collected as a time series with 10 separate measurements done in breath holds. Four spectra were used to calculate the average MTC. The measurement was performed twice, once with water suppression and once without it. Thus, the total number of averages was 40 for the spectrum with water suppression and 40 for the spectrum without water suppression. The data were analyzed using a linear combination of the model spectra software package (LCModel) version 6.3-0C with the LCMgui (34). The results

were corrected as described earlier (26). The data quality was inspected both visually (fit quality and residue) and numerically (fit SD of ≤30%). ^{1}H-MRS evaluation of MTC has been previously validated by Felbliner et al. (11).

MRI. The MRI studies were done to measure the masses of subcutaneous and visceral adipose tissue depots. Scans were done using Philips Gyroscan Intera 1.5T CV Nova Dual scanner (Philips Medical Systems). Whole-body (from head to knee) axial T1-weighted dual fast field echo images (echo time = 2.3 and 4.7 ms, repetition time = 120 ms, slice thickness = 10 mm without gap) were obtained. To measure different adipose tissue masses, the images were analyzed using SliceOmatic software version 4.3 (http://www.tomovision.com/products/sliceomatic.htm). To obtain the weight, the pixel surface area was multiplied by the slice thickness and the density of adipose tissue 0.9196 $kg \cdot L^{-1}$.

Statistical analysis. All the data are presented as mean values (95% confidence interval). Statistical analyses were performed using SAS for Windows (version 9.3; SAS institute Inc., Cary, NC). The normal distribution of the variables was tested using the Shapiro–Wilkin test. Logarithmic transformations were performed for MTC, epicardial fat, M-value, fasting plasma insulin, HDL, and fasting plasma TG, and a square root transformation was performed for visceral and subcutaneous fat to achieve normal distribution in these parameters. The baseline characteristics of the groups were compared by a two-way ANOVA, including the main effect of health status (healthy and DGT), training mode (HIIT and MICT), and their interaction (health status × training mode). Before and after measurements were analyzed using a hierarchical linear mixed model suitable for repeated measurements (PROX MIXED procedure). In the model, the DGT, training mode, and time effects were included as well as all interactions (most important results are seen in Table, Supplemental Digital Content 1, Intervention induced within-group changes and different responses between healthy subjects and subjects with DGT and HIIT and MICT groups, http://links.lww.com/MSS/A863). When a significant interaction was observed, we calculated predetermined contrasts (the Fisher's lease significant difference test) within the model to study more about groupwise differences. Subjects with missing values (drop outs and those with technical problems) are all included in this model. Hence, we report the model-based mean (SAS least square means) values (95% confidence interval) from all the parameters measured before and after the training. We also tested the main results ($\dot{V}O_{2peak}$, M-value, epicardial fat, pericardial fat) using pre-diabetic/diabetic status, whole body fat content, and MTC added as a covariant otherwise using the same method as previously mentioned. Correlation analyses were conducted using Pearson's correlation. P value <0.05 (two-tailed) was considered statistically significant.

RESULTS

At the baseline, the DGT subjects had increased body adiposity, impaired blood lipid values and glucose homeostasis, higher blood pressure, and increased FRS compared with the controls (Table 1). Both interventions improved cholesterol values in both healthy and DGT subjects but did not have any significant effect on glucose homeostasis, nonesterified fatty

TABLE 1. Descriptive statistics and results of two-way ANOVA for baseline characteristics for healthy subjects and subjects with DGT.

	Healthy		DGT		*P*		
	HIIT	MICT	HIIT	MICT	DGT	Training	DGT × Training
N	14	14	9	7	—	—	—
Age (yr)	47 (45–50)	48 (45–51)	47 (44–50)	47 (44–51)	0.8	0.8	0.8
Body mass (kg)	83.1 (77.4–88.8)	84.1 (78.4–89.8)	96.2 (89.1–103.4)	96.5 (88.4–104.5)	**<0.001**	0.8	0.9
BMI ($kg \cdot m^{-2}$)	25.9 (24.4–27.3)	26.4 (25.0–27.8)	29.8 (27.9–31.7)	31.1 (29.1–33.2)	**<0.001**	0.3	0.6
BP systolic (mm Hg)	124 (120–128)	128 (124–132)	133 (128–138)	146 (140–151)	**<0.001**	**<0.001**	0.09
BP diastolic (mm Hg)	78 (75–81)	80 (77–83)	87 (82–91)	88 (83–93)	**<0.001**	0.3	0.9
Body fat (%)	22.2 (19.8–24.7)	22.9 (20.4–25.3)	29.3 (26.0–32.5)	28.4 (24.9–31.8)	**<0.001**	0.9	0.6
Subcutaneous fat (kg)**	3.9 (3.1–4.8)	4.3 (3.5–5.2)	6.4 (5.1–7.9)	5.8 (4.5–7.4)	**<0.001**	0.96	0.4
Visceral fat (kg)**	2.7 (1.9–3.6)	2.5 (1.8–3.3)	4.2 (3.0–5.7)	4.5 (3.1–6.1)	**0.003**	0.99	0.7
Epicardial fat (mL)*	92 (77–110)	78 (64–94)	131 (107–161)	157 (124–199)	**<0.001**	0.98	0.09
Pericardial fat (mL)	157 (123–191)	139 (103–174)	228 (189–267)	211 (167–256)	**<0.001**	0.4	0.9
MTC (%)*	0.42 (0.26–0.68)	0.53 (0.33–0.86)	0.65 (0.35–1.22)	0.48 (0.25–0.89)	0.6	0.9	0.3
Tot cholesterol ($mmol \cdot L^{-1}$)*	5.2 (4.7–5.8)	4.6 (4.2–5.1)	4.5 (4.0–5.2)	4.9 (4.2–5.7)	0.5	0.7	0.1
HDL ($mmol \cdot L^{-1}$)*	1.4 (1.2–1.6)	1.4 (1.2–1.6)	1.2 (1.0–1.4)	1.2 (1.0–1.5)	0.1	0.97	0.9
LDL ($mmol \cdot L^{-1}$)	3.4 (3.0–3.8)	2.9 (2.5–3.3)	2.5 (2.0–3.0)	3.0 (2.4–3.5)	0.1	0.9	0.06
$NEFA_{fS}$ ($mmol \cdot L^{-1}$)*	0.6 (0.5–0.8)	0.7 (0.6–0.9)	0.9 (0.7–1.1)	0.9 (0.6–1.2)	**0.04**	0.5	0.6
TG_{fP} ($mmol \cdot L^{-1}$)*	1.0 (0.8–1.2)	0.9 (0.7–1.1)	1.6 (1.2–2.2)	1.8 (1.3–2.4)	**<0.001**	0.98	0.6
$Glucose_{fP}$ ($mmol \cdot L^{-1}$)	5.3 (5.0–5.7)	5.6 (5.2–6.0)	7.5 (7.1–8.0)	7.0 (6.4–7.5)	**<0.001**	0.5	0.08
$Insulin_{fP}$ ($mmol \cdot L^{-1}$)*	4.7 (3.4–6.5)	4.7 (3.4–6.5)	14.6 (9.7–21.8)	14.4 (9.1–22.8)	**<0.001**	0.99	0.96
HbA1c (%)	5.5 (5.3–5.7)	5.6 (5.3–5.8)	5.7 (5.4–6.0)	5.8 (5.5–6.1)	0.07	0.5	0.95
HbA1c ($mmol \cdot L^{-1}$)	36.6 (34.1–40.0)	37.5 (35.0–40.0)	39.2 (36.1–42.3)	40.2 (36.8–43.8)	0.07	0.5	0.95
M-value ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)*	35.0 (26.9–45.6)	29.5 (22.2–39.2)	14.1 (9.7–20.5)	15.6 (10.8–22.7)	**<0.001**	0.8	0.4
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	34.7 (32.6–36.9)	33.7 (31.5–35.8)	28.0 (25.1–30.8)	30.9 (27.8–33.9)	**0.001**	0.5	0.1
FRS score (%)*	6.1 (5.0–7.5)	6.0 (4.9–7.3)	12.8 (9.8–16.7)	15.5 (11.7–20.6)	**<0.001**	0.5	0.4

The *P* value for DGT describes the difference between healthy ($n = 28$) and impaired glucose tolerance ($n = 16$) groups, and "training" compares all HIIT trained ($n = 23$) to all MICT trained ($n = 21$). DGT × training demonstrates if there is an interaction between the DGT and the training mode. All the data are presented as model based means (95 % confidence interval). The values are LSmeans translated into original unit. Boldfaced values are significantly different between the groups, $P < 0.05$. EXE, exercise mode; BP, blood pressure; NEFA, nonesterified fatty acid; FFA, free fatty acid; fP fasting plasma; fS, fasting serum; HbA1c, glycated hemoglobin.

*Variables with logarithmic transformation to achieve the normal distribution.

**Variables with square transformation to achieve the normal distribution.

acid, or FRS score (see Table, Supplemental Digital Content 1, Intervention induced within-group changes and different responses between healthy subjects and subjects with DGT and HIIT and MICT groups, http://links.lww.com/MSS/A863). HIIT reduced total cholesterol more compared with MICT, but this difference was no longer significant when whole body fat percentage was used as the covariant (training × pre–post P = 0.08). Also, whole body fat percentage (healthy = −4% and DGT = −3%), visceral (healthy = −4% and DGT = −5%) and subcutaneous fat (healthy = −2% and DGT = −1%) masses reduced, but not differently between the groups.

Aerobic capacity was 16% lower in DGT subjects compared with healthy subjects at baseline ($P < 0.001$, Fig. 2A). Training improved aerobic capacity in the whole study population from 31.8 (30.5–33.1) to 32.8 (31.5–34.1) $mL \cdot kg^{-1} \cdot min^{-1}$ (+3%) with no significant differences in the training response between the healthy (+4%) and the DGT (+2%) groups (time $P = 0.003$, time × DGT $P = 0.1$, Fig. 2A). After intervention, the aerobic capacity remained lower in DGT subjects compared with healthy subjects ($P < 0.001$). When studied according to the exercise mode, only HIIT increased the aerobic capacity significantly (HIIT = +6% vs MICT = +0.3%, time × training $P = 0.003$; Fig. 2B). In the whole study group, the aerobic capacity correlated negatively with parameters of body adiposity and positively with insulin sensitivity at the baseline, but not with MTC (see Supplemental Digital Content 2, Pairwise correlations for all measured variables at baseline, http://links.lww.com/MSS/A864).

Before the intervention, the DGT subjects had attenuated insulin sensitivity with 54% lower M-value compared with the controls ($P < 0.001$, Fig. 2C). Exercise training improved insulin sensitivity in the whole study population significantly from 21.9 (18.6–25.7) to 26.1 (22.1–30.9) $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (+17%) with no difference between the healthy (10%) and the DGT (23%) groups (time $P = 0.001$, time × DGT $P = 0.1$) in the training response. After the intervention, the insulin sensitivity stayed lower in DGT compared with the healthy subjects ($P = 0.004$). HIIT tended to improve M-value more than MICT (23% vs 9%; time × training, $P = 0.06$; Fig. 2D). In the whole study group, the M-value correlated positively with aerobic capacity and negatively with the parameters of body adiposity, but not with MTC (see Supplemental Digital Content 2, Pairwise correlations for all measured variables at baseline, http://links.lww.com/MSS/A864). The change in insulin sensitivity correlated inversely with the changes in the whole body fat percentage ($R = -0.38$, $P = 0.02$) and subcutaneous fat ($R = -0.34$, $P = 0.047$).

At the baseline, the DGT subjects had higher epi- and pericardial fat volumes than the healthy subjects (41% and 12%, respectively, both $P < 0.001$; Fig. 3A and B). Training

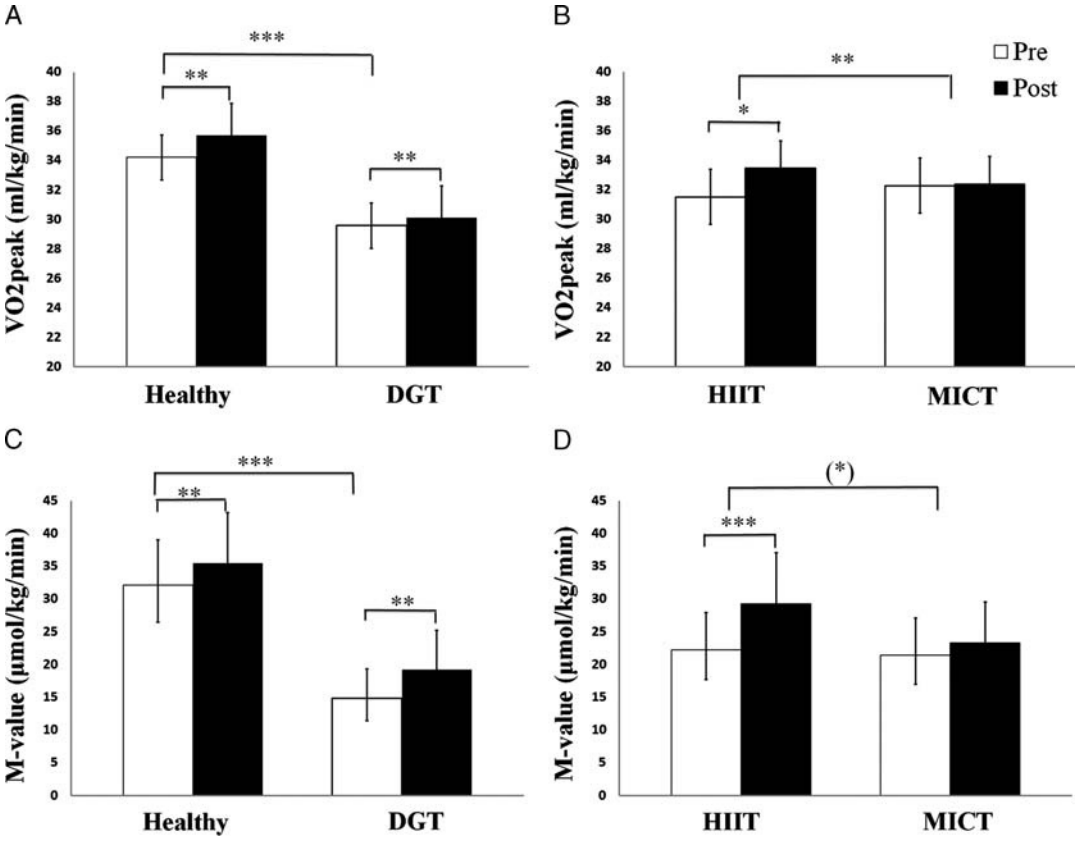

FIGURE 2—Aerobic capacity ($\dot{V}O_{2peak}$) and whole-body insulin sensitivity (M-value) at baseline (white bars) and after the training intervention (black bars) in healthy subjects and in subjects with DGT (A and C) according to the training mode (B and D). All the data are presented as mean values (95% confidence interval). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

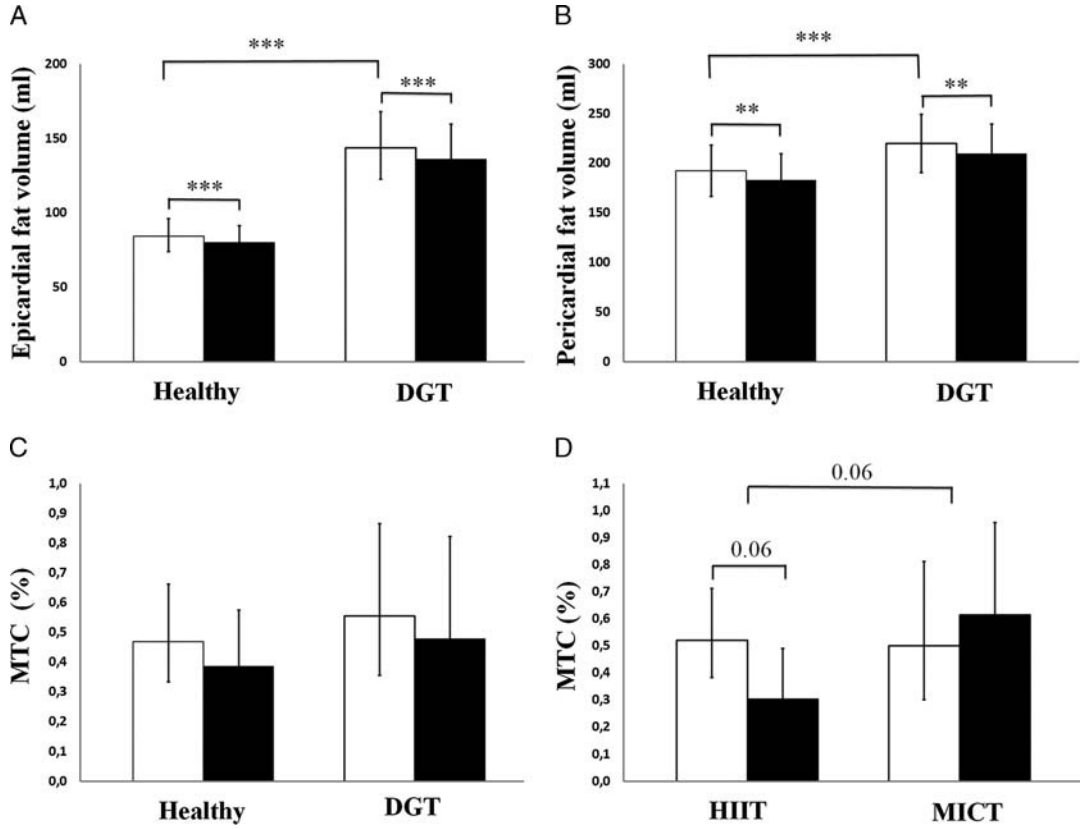

FIGURE 3—Epicardial fat (EAT), pericardial fat (PAT), and MTC at baseline (white bars) and after the training intervention (black bars) in healthy subjects and in subjects with DGT (A, B, and C) and MTC, according to the training mode (D). All the data are presented as mean values (95% confidence interval). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

decreased both epi- and pericardial fat volumes by 5% in both healthy and DGT subjects (time $P < 0.001$, time × DGT $P = 0.8$; Fig. 3A and B). No difference was observed in the training response between the training modes in either epi- or pericardial fat (time × training; $P = 0.8$ and $P = 0.9$, respectively). Both epi- and pericardial fat volumes remained higher in the DGT group compared with the healthy subjects after the 2-wk training (39% and 13%, $P < 0.001$ and $P = 0.01$, respectively). Epi- and pericardial fat volumes correlated positively with each other and with body adiposity but negatively with aerobic capacity and insulin sensitivity (see Supplemental Digital Content 2, Pairwise correlations for all measured variables at baseline, http://links.lww.com/MSS/A864).

No differences were observed in MTC between the healthy and the DGT subjects either at the baseline or after exercise (Fig. 3C). However, the training response tended to be different between the two training modes (time × training; $P = 0.06$) with HIIT tending to decrease MTC ($P = 0.06$, Fig. 3D). Using MTC as the covariant, the different training response between HIIT and MICT in $\dot{V}O_{2peak}$ (time × training $P = 0.10$) and M-value (time × training $P = 0.23$) was no longer significant.

DISCUSSION

The aim of this study was to evaluate whether HIIT and MICT have a similar effect on decreasing the ectopic fat in and around the heart and whether the decrease is similar in healthy subjects and subjects with DGT. We found that both HIIT and MICT effectively reduce epicardial (5%) and pericardial (6%) fat in both healthy and DGT subjects, whereas HIIT seems to be superior in improving aerobic capacity, whole-body insulin sensitivity, and MTC.

Before the intervention, the DGT subjects had higher epi- and pericardial fat volumes than those of the healthy subjects (both $P < 0.001$), but no differences were observed in MTC between these groups. Pericardial fat has been shown to correlate with different metabolic and cardiovascular risk factors, and it has been suggested to be a better marker for cardiometabolic diseases than epicardial fat within a wide range of body adiposity (BMI = 21–40 $kg \cdot m^{-2}$) (43). In the present study, before the intervention, both fat deposits correlated with metabolic risk markers such as visceral adiposity, systolic blood pressure, insulin sensitivity, and aerobic capacity, but only epicardial fat correlated with plasma TG (Figure 1, Supplemental Digital Content 2, Pairwise correlations for all measured variables at baseline, http://links.lww.com/MSS/A864). We also calculated the 10-yr coronary heart disease risk score using the FRS, which has previously shown to be positively correlated with pericardial fat (5). The DGT subjects had a higher FRS at baseline than the healthy subjects ($P < 0.001$), and this remained unchanged by the 2-wk exercise training. In the present study, both epi- and pericardial

fat masses correlated with FRS. Thus, our data suggest that both epi- and pericardial fat masses are relevant correlates for coronary heart disease risk.

In previous exercise training studies, the exercise response on epi- and pericardial fat masses has been studied in obese and T2DM subjects (21,23,47). In obese men, a 4-month intervention decreased epicardial fat on average by 9% (no data regarding pericardial fat or MTC), and this change correlated positively with the reduction in visceral fat (23). In a recent study with morbidly obese subjects, a 12-wk training intervention decreased epi- and pericardial fat masses 7% and 12%, respectively (no data regarding MTC) (47). Jonker et al. (21) showed a 20% decrease in pericardial fat along with a reduction in visceral fat mass, but no change in epicardial fat in T2DM subjects after a 6-month exercise intervention. In the present study, training decreased epi- and pericardial fat volumes in both healthy and DGT subjects (both −5%), thus showing no difference in the training response between the healthy and the DGT groups. Our results also agree with the findings that training induces relatively higher reductions in epicardial fat (−5.3%), pericardial fat (−5.5%), and visceral fat (−4.9%) compared with subcutaneous fat (−1.3%) as previously shown by Kim et al. (23). In addition to these previous results, we now show that this response is rapid as no more than 2 wk of training was needed for these changes. The relatively higher reductions in epi- and pericardial fat masses and visceral fat are probably due to the higher ß-adrenergic receptor density in these fat depots, and thus a higher exercise induced lipolysis compared with subcutaneous fat (14,33). It is also interesting that although epi- and pericardial fat masses have been shown to differ as regards embryologic origin, local circulation, function, and metabolic activity, and that epicardial fat is more similar to visceral fat, our data suggest that exercise training induces a similar mass reduction in each of these deposits (19).

Data on the effect of regular training on MTC are limited to one study showing decreased MTC in overweight men (39), whereas no training responses have been observed in T2DM (21,40). In the present study, we did not observe differences in MTC between healthy and DGT subjects at baseline or in any training responses in either healthy or DGT subjects. However, MTC tended to respond differently to the two different training modes (time × training P = 0.06), HIIT reducing the MTC more efficiently compared with MICT (Fig. 3D). Thus, our data suggest that high-intensity training may be more beneficial in reducing MTC than low- to moderate-intensity training. One explanation for this finding could be that extremely high-intensity training is needed to strain the myocardium to the point of myocardial energy deficit and during the rapid and maximal energy need MTC are mobilized inside the myocyte. In previous exercise training studies showing no change in MTC, moderate-intensity training protocols have been used (21,40). In a recent cross-sectional study, endurance-trained athletes, who usually use different HIIT protocols in training, had a lower MTC than those of healthy male subjects matched for age, BMI, and body fat percentage (38). In the present study, at baseline, MTC correlated with age and FRS but not with other variables.

Subjects with T2DM have higher levels of skeletal muscle intramyocellular lipids (IMCL) compared with healthy subjects in relation to insulin resistance. On the other hand, regular exercise training increases IMCL along with improving insulin sensitivity and aerobic capacity, which is a phenomenon known as the "athlete's paradox." An increase in athlete's IMCL content provides an energy reservoir for rapid energy release during exercise (32). However, whether a similar "athlete's paradox" also occurs in the myocardium is unclear. In a cross-sectional study by Sai et al. (38), MTC was lower in endurance athletes compared with healthy controls. In addition, our present data together with previous exercise training studies (38,39) suggest more of a decrease than an increase in MTC posttraining. The possible differences in the exercise response between MTC and IMCL might be the fact that the myocardium relies on free fatty acid uptake and beta-oxidation at rest and during exercise as well as on the differences in mitochondrial function (41).

Despite the differences at baseline, the 2-wk training demonstrated a similar improvement in both the aerobic capacity (3%) and the insulin sensitivity (16%) of healthy and DGT subjects; both aerobic capacity and insulin sensitivity also remained lower in the DGT subjects after the 2-wk training intervention. Interestingly, HIIT induced a higher increase (6%) in aerobic capacity compared with MICT (0.3%) and also tended to induce a higher response in insulin sensitivity (Fig. 2). HIIT using the Wingate protocol (4) has been shown to be an effective method of improving aerobic capacity in various populations (44,46), but the literature is limited regarding the metabolic health benefits of HIIT in overweight or T2DM subjects (13,31). Recent meta-analysis, including various high-intensity interval training protocols, has indicated that high-intensity exercise may improve insulin sensitivity only in subjects with insulin resistance (20). However, our results indicate that 2 wk training already enhances insulin sensitivity, and for up to 2 wk at least, the enhancement is similar in both healthy and DGT subjects. Currently, the mechanisms of the superior effects of HIIT on aerobic capacity as well as on glucose homeostasis are unclear. It is suggested that the repetition of the marked depletion of the working muscles' glycogen stores during HIIT could be one of the mechanisms behind the effectiveness of HIIT in improving insulin sensitivity (30,36). We studied whether the greater improvements in $\dot{V}O_{2peak}$ and whole-body insulin sensitivity after HIIT could be due to the changes in total body adiposity or observed trend toward the greater decrease in MTC after HIIT than MICT. Using myocardial MTC as a covariant, we indeed found that the difference in training response between HIIT and MICT in $\dot{V}O_{2peak}$ (training × time P = 0.10) and insulin sensitivity (training × time P = 0.23) was no longer significant. This, therefore, suggests that the ability to rapidly reduce MTC could play a role in the superior effects of HIIT to

improve aerobic capacity and glucose metabolism. In the present study, we studied HIIT and MICT responses, and the aim was not to standardize the total amount of work done or energy consumed between the training interventions but rather to compare the two totally different training methods. Both the time spent during the training intervention (time HIIT 15 min vs MICT 300 min) and the average calculated energy consumption during the training sessions (421 vs 2907 kcal, respectively) were much less in HIIT than MICT. However, HIIT leads to higher delayed oxygen consumption for several hours after the training and thus probably also raises the posttraining basal energy metabolism more as compared with MICT. Unfortunately, we did not give any specific diet instructions but only instructed the subjects to maintain their typical diet. Moreover, we were not able to measure 24 h energy consumption and thus evaluate the effect of the possible difference in training-induced energy consumption or intake on the studied parameters.

The major limitation of our study is the relatively small number of subjects, although it is in line with previous exercise training studies with similar technically and financially demanding and detailed designs. Also the fact that DGT group included both subjects with pre-T2DM (n = 5) and T2DM (n = 11) can be considered as a limitation. However, the statistical analyses were performed also as diabetes status (T2DM or prediabetes) as a covariant, with no influence on the outcomes. In the present study, the whole body fat was measured with bioelectrical impedance analysis, which is commonly used in research although it is not as reliably as dual-energy X-ray absorptiometry or MRI. However, the subjects were instructed to prepare for the studies similarly before and after the training intervention and the same BIA machine was used before and after measurement. In addition, all the participants were males, which exclude the possible variation in the results due to menstrual cycles.

CONCLUSION

In conclusion, we have demonstrated that both MICT and HIIT can already, within 2 wk, reduce epi- and pericardial fat masses in middle-age healthy men and in men with DGT. Furthermore, HIIT increases aerobic capacity and tends to improve insulin sensitivity and reduce MTC more effectively compared with MICT. This study suggests that time-saving HIIT training is tolerable and can be recommended as an exercise mode as well as MICT to reduce enlarged myocardial adiposity.

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The authors declare no conflict of interest. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The authors have nothing to disclose. The results of the present study do not constitute an endorsement by the American College of Sports Medicine.

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