Right ventricular metabolic adaptations to high-intensity interval and moderate-intensity continuous training in healthy middle-aged men

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Heiskanen MA, Leskinen T, Heinonen IH, Löyttyniemi E, Eskelinen JJ, Virtanen K, Hannukainen JC, Kalliokoski KK. Right ventricular metabolic adaptations to high-intensity interval and moderate-intensity continuous training (MICT) on RV glucose and fat metabolism. Twenty-eight untrained, healthy 40–55 yr-old men were randomized into HIIT (n = 14) and MICT (n = 14) groups. Subjects performed six supervised cycle ergometer training sessions within 2 wk (HIIT session: 4–6 × 30 s all-out cycling/4-min recovery; MICT session: 40–60 min at 60% peak O2 uptake). Primary outcomes were insulin-stimulated RV glucose uptake (RPGU) and fasted state RV free fatty acid uptake (RVFFAU) measured by positron emission tomography. Secondary outcomes were changes in RV structure and function, determined by cardiac magnetic resonance. RPGU decreased after training (−22% HIIT, −12% MICT, P = 0.002 for training effect), but RVFFAU was not affected by the training (P = 0.74). RD end-diastolic and end-systolic volumes, respectively, increased +5 and +7% for HIIT and +4 and +8% for MICT (P = 0.002 and 0.005 for training effects, respectively), but ejection fraction mildly decreased (−2% HIIT, −4% MICT, P = 0.034 for training effect). RV mass and stroke volume remained unaltered. None of the observed changes differed between the training groups (P > 0.12 for group × training interaction). Only 2 wk of physical training in previously sedentary subjects induce changes in RV glucose metabolism, volumes, and ejection fraction, which precede exercise-induced hypertrophy of right ventricle; high-intensity interval training; moderate-intensity continuous training; metabolism; PET imaging

NEW & NOTEWORTHY
This is the first study to investigate the effects of exercise training on the right ventricular metabolism of healthy subjects using positron emission tomography. Only 2 wk of either high-intensity interval or moderate-intensity continuous training induces changes in right ventricular glucose metabolism, volumes, and ejection fraction in previously sedentary men.

EXERCISE-INDUCED HYPERTROPHY of the left ventricle (LV), so-called athlete’s heart, is generally associated with excellent health outcomes. Right ventricle (RV) has remained less studied, and for a long time it was considered merely as “a passive conduit” (8, 14, 42). Recently, RV adaptations to exercise training have gained increased research interest. While previous studies concerning the effects of training on the RV have reported balanced hypertrophy with the LV (21, 35–37), other studies have reported RV dysfunction following intense endurance exercise (3, 9, 10, 25, 26, 40). A recent meta-analysis further confirmed that prolonged intense exercise leads to reduction of RV function, while LV function remains unaffected (6), underlining the need for further studies specifically on RV adaptations.

As an alternative for traditional moderate-intensity continuous training (MICT), high-intensity interval training (HIIT) has recently gained a lot of attention as a time-efficient exercise method for modern, busy people. Many studies have shown that the health-enhancing benefits traditionally associated with high-volume endurance training can be achieved by considerably smaller volumes of HIIT (12, 33, 43). For instance, only six sessions of HIIT within 2 wk have been shown to increase exercise capacity and induce similar metabolic adaptations in skeletal muscles as six sessions of MICT (7, 11). On the other hand, a recent meta-analysis showed that HIIT is not only tolerated but even seems to be superior to MICT in improving cardiovascular fitness in patients with lifestyle-induced cardiometabolic disease (43). However, previous studies on the RV adaptations to HIIT in healthy subjects are scarce, and it is completely unknown whether HIIT and MICT have similar or different effects on RV.

Cardiac function is strongly tied to cardiac metabolism because, without sufficient fuel, the heart is not able to fulfill the circulatory demands. Cardiac metabolism can be measured non-invasively using positron emission tomography (PET). However, RV metabolism has been studied previously using PET only in the context of diseases, such as pulmonary artery hypertension and heart failure (2, 22, 23, 28, 44). These studies indicated that RV glucose utilization is increased when the workload of the RV increases due to a disease. Based on the previous studies on diseased populations, it is speculated that multiple imaging modalities, including nuclear imaging of myocardial metabolism, may provide complementary information about RV adaptations to exercise training (4, 8). Previous cross-sectional PET studies on LV metabolism have shown decreased LV glucose uptake (LVGU) in the trained state (27, 38), whereas no differences in LV fatty acid uptake have been observed between different fitness levels (16, 38, 41). The decrease in LV glucose metabolism correlated negatively with LV mass and appeared to be associated with reduced myocardial work in athletes, possibly because of myocardial hypertrophy or the use of alternative substrates, such

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as fatty acids and lactate (27, 38). The responses of RV metabolism to exercise may also present important adaptations to physical training. Yet, to date, there are no PET studies on the effects of exercise training to RV metabolism, even though RV may undergo even larger remodeling than LV in response to physical exercise (6). The lack of such studies on healthy subjects may be due to low tracer count statistics, which can lead to poor visualization of RV (4).

In this work, we applied PET imaging to study the effects of 2 wk of HIIT or MICT on the RV metabolism in previously sedentary, middle-aged men. Glucose utilization was studied during euglycemic hyperinsulinemic clamp, which mimics the metabolic environment after a meal when glucose metabolism is at its highest during normal daily life. Free fatty acid uptake was measured at fasted state, corresponding to the highest fat metabolism rate in normal life. These metabolic conditions enable better visualization of the myocardium, as well as standardization of metabolic milieu. For instance, euglycemic hyperinsulinemic clamp leads to superior image quality compared with fasting or oral glucose loading conditions (19).

Accompanying changes in RV structure and function were assessed by cardiac magnetic resonance (CMR). Although RV has shown to differ from LV (17, 45), we hypothesized that hyperinsulinemic clamp leads to superior image quality compared with fasting or oral glucose loading conditions (19). Accompanying changes in RV structure and function were assessed by cardiac magnetic resonance (CMR). Although RV has shown to differ from LV (17, 45), we hypothesized that these metabolic conditions enable better visualization of the myocardium, as well as standardization of metabolic milieu. For instance, euglycemic hyperinsulinemic clamp leads to superior image quality compared with fasting or oral glucose loading conditions (19).

Study design. This study was a parallel-group randomized controlled trial with 1:1 allocation ratio conducted at the Turku PET Centre (Turku, Finland). The study flow is illustrated in Fig. 1. The present study is a part of a larger study entitled The Effects of Short-Term High-Intensity Interval Training on Tissue Glucose and Fat Metabolism in Healthy Subjects and in Patients with Type 2 Diabetes (NCT01344928). The study was conducted according to the Declaration of Helsinki, and the study protocol was approved by the ethical committee of the Hospital District of Southwest Finland, Turku (decision 95/180/2010 §228).

Subjects. The participants were recruited with advertisements in local newspapers, through personal contacts, and using electronic and traditional bulletin boards. Before the study, subjects were interviewed and thoroughly examined by a medical doctor, including ECG and oral glucose tolerance test. A candidate was accepted to the study if the following criteria were fulfilled: male sex, age 40–55 yr, body mass index 18.5–30 kg/m², nonsmoking, and no exercise on regular basis [twice a week or less, peak oxygen uptake (VO₂peak) ≤ 40 mJ/kg⁻¹.min⁻¹]. A candidate was excluded if he had a condition that could potentially endanger the subject’s health during the study or interfere with the interpretation of the results (7, 17, 18). Finally, 28 participants fulfilled the criteria. Written, informed consent was obtained from all subjects before the beginning of the study. Randomization was performed in two phases. First, random permuted block for 24 subjects with 1:1 allocation ratio was generated. Because of some unsuccessful PET measurements due to technical problems, another random permuted block of four subjects (2 HIIT, 2 MICT) was generated. Therefore, final group sizes were n = 14 for HIIT and n = 14 for MICT. Subjects were informed about the groups to which they belonged after the screening. Given the nature of the interventions, no blinding was used.

Training interventions. The training interventions consisted of six exercise sessions within 2 wk (7, 18). Each session was performed in supervised laboratory conditions. The HIIT training consisted of 4–6 × 30 s of all-out cycling efforts with 4 min of recovery (Monark Ergomedic 828E, Monark, Vansbro, Sweden). The number of bouts was increased from four to five, and further to six after every other session. The participants were familiarized with HIIT during screening phase (2 × 30-s bouts). Each bout started with 5-s acceleration to maximal cadence without any resistance, followed by a sudden increase of the load (7.5% of whole body weight in kilograms) and maximal cycling for 30 s. The MICT group cycled (Tunturi E85, Tunturi Fitness, Almere, The Netherlands) for 40–60 min at the intensity of 60% of peak workload. The duration of cycling was increased from 40 to 50 min and further to 60 min after every other session.

Outcome measures. Full details of the protocols used to determine the outcome measures of this study have been described elsewhere (17) and are briefly summarized here. No blinding was used in the image analyses.

The primary outcome of the study was to determine the effects of HIIT and MICT on RV metabolism [RV glucose uptake (RVGU) and RV free fatty acid uptake (RVFFAU)] using PET. The PET imaging was performed with GE Advance PET/CT scanner (General Electric Medical System, Milwaukee, WI). RVFFAU was studied at the fasted state using 14(R)-[18F]fluoro-6-thia-heptadecanoic acid ([18F]FTHA) [155 MBq (SD 9)] as a tracer (39). On a separate day, RVGU was measured using 2-deoxy-2-[18F]fluoro-d-glucose ([18F]FDG) [157 MBq (SD 10)] during euglycemic hyperinsulinemic clamp at the fasted state (5, 17). PET image raw files were corrected for attenuation, dead time, and decay. Images were reconstructed using 3D-Ordered-Subsets Expectation Maximization procedure and analyzed using Carimas software (version 2.9, www.turkupetcentre.fi/carimas). Volumes of interest were drawn manually over the entire RV free wall, as shown in Fig. 2. Fractional tracer uptake rate was calculated from tissue and plasma time activity curves by graphical analysis (29). No corrections were performed for partial volume effects. RVGU and RVFFAU were obtained by multiplying the fractional tracer uptake rate with the plasma glucose and free fatty acid concentration during the scanning, respectively.
As secondary outcomes, exercise-induced adaptations of RV structure and function were assessed by CMR using a Philips 1.5T Gyroscan Intera CV Nova Dual MR scanner (Philips Medical Systems, Best, The Netherlands) using previously described imaging parameters (17). Image analysis was performed with Philips Extended MR WorkPlace version 2.6.3.5 (Philips Medical Systems) following the established guidelines (32). Briefly, the endo- and epicardial contours were traced so that RV trabeculations were included into the blood volume and the interventricular septum was excluded from the RV analysis. RV parameters derived from CMR included ejection fraction (RVEF), end-diastolic volume (RVEDV), end-systolic volume (RVESV), stroke volume (RVSV), and mass.

Body composition was measured by bioimpedance monitor (InBody 720; Mega Electronics, Kuopio, Finland) (7, 17). Whole body insulin-stimulated glucose uptake rate (M-value) was measured during euclycemic hyperinsulinemic clamp, as described in detail previously (7, 17). VO2 peak was determined by a maximal exercise test on a cycle ergometer (Ergoline 800s; VIASYS Healthcare). As previously described (7, 17, 18), the test started at 50 W, and the load was increased by 30 W every 2 min until exhaustion. Ventilation and gas exchange were measured (Jaeger Oxycon Pro; VIASYS Healthcare) and reported as the mean value per minute. The peak respiratory exchange ratio was ≥1.15, and peak blood lactate concentration immediately and after 1 min was ≥8.0 mmol/l for all subjects. Also, peak heart rate was within 10 beats of the reference value (220 – age) for all except one subject. The highest 1-min mean value of oxygen consumption was defined as VO2 peak.

Statistical analysis. Normal distribution of the variables was tested using Shapiro-Wilk test and evaluated visually. Logarithmic transformations were performed for variables RVEDV and RVESV to achieve normal distribution. The analyses for primary and secondary outcomes were carried out using intention-to-treat approach and hence included all of the randomized subjects. Statistical analyses were performed using hierarchical mixed linear model with compound symmetry covariance structure, including one within-factor (training; before and after intervention), one between-factor (group; HIIT and MICT), and interaction term (training × group). Missing data points were accounted for by restricted maximum likelihood estimation within the linear mixed models. Hence, model-based means and 95% confidence intervals are reported. Sample size was calculated for the whole study (NCT01344928) based on its primary outcome (skeletal muscle glucose uptake): a total of 24 subjects (12/group) were calculated to give 90% power of detecting a 20% unit difference in insulin-stimulated glucose uptake in quadriceps femoris muscle (estimated increase in HIIT 40% vs. estimated increase in MICT 20%, SD 15) with a level of significance at 5%. All statistical tests were performed as two-
RIGHT VENTRICULAR METABOLIC ADAPTATIONS TO TRAINING

Table 1. Numbers of completed and uncompleted experiments in the study

<table>
<thead>
<tr>
<th></th>
<th>HIIT</th>
<th>MICT</th>
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<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Subjects who participated at</td>
<td></td>
<td></td>
</tr>
<tr>
<td>least in one measurement</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>RVGU, completed</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Missing because</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued intervention</td>
<td>1†</td>
<td>1†</td>
</tr>
<tr>
<td>Technical problem in clamp</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Physiological problem</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Premasurement was not done</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>RVFFAU, completed</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Missing because</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued intervention</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Technical problem in tracer production or PET scan</td>
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<td>1</td>
</tr>
<tr>
<td>Physiological problem</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Premasurement was not done</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>CMR, completed</td>
<td>14</td>
<td>13</td>
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<tr>
<td>Missing because</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued intervention</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Technical problem in CMR</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Values are nos. of subjects. HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; Pre, measurements before the intervention; Post, measurements after the intervention; RVGU, right ventricular glucose uptake; RVFFAU, right ventricular free fatty acid uptake; CMR, cardiac magnetic resonance imaging. *Subject had a transient decrease in blood pressure during the PET scan. †Subject had a mild fever. ‡Subject had forgotten to fast.

RESULTS

Subject characteristics. Recruitment occurred between March 2011 and February 2013, and all the subjects were from the Southwest Finland region. One participant from both groups discontinued the trial during the training interventions due to personal reasons (HIIT) and exercise-induced hip pain (MICT). Hence, 13 subjects in both groups finalized all of their assigned training sessions and underwent follow-up measurements. Some of the imaging measurements were unsuccessful, as detailed in Table 1. The exercise groups were well matched at baseline (Table 2). No changes occurred in body mass, body mass index, or resting heart rate (HRrest) after training. VO2peak and whole body glucose uptake (M-value) were improved after both training modes, as described previously (7, 18), indicating that only 2 wk of exercise induce health-enhancing changes.

RV metabolism. RVGU decreased after training (−22% HIIT, −12% MICT, P = 0.002 for the training effect) but not differently between the groups (P = 0.42 for training × group interaction) (Table 3). The individual responses are shown in Fig. 3. RVFFAU was different between the groups (P = 0.020 for group effect), and it remained unchanged after training (Table 3), although individual responses of RVFFAU varied a lot in both groups (Fig. 3). The changes in RVGU or RVFFAU did not correlate with changes in RV structural and functional parameters, age, or any of the whole body parameters presented in Table 2. Plasma glucose, free fatty acid, and insulin concentrations during the RVGU and RVFFAU measurements were not altered by either of the training modes (Table 4).

RVGU reproducibility. RVGU was measured by two independent observers. The interobserver Pearson’s correlation was 0.97 for baseline RVGU and 0.97 for training-induced differences in RVGU. Furthermore, Bland-Altman plots for baseline measurements and training-induced differences showed good reproducibility of RVGU (Fig. 4).

RV structure and function. Results derived from CMR are presented in Table 3. RVEDV and RVESV increased +5 and +7% for HIIT and +4 and +8% for MICT, respectively (P = 0.002 and 0.005 for training effect, respectively). In contrast, RVEF mildly decreased after training (−2% HIIT, −4% MICT, P = 0.034). However, none of these changes were different between the training groups. RV mass and RVSV did not change significantly by training (Table 3). The changes in RVEDV correlated positively with the changes in RVESV (r = 0.81, P < 0.001) and RV mass (r = 0.41, P = 0.043). The change of RVEF correlated negatively with the changes in RVEDV (r = −0.64, P = 0.001) and RVESV (r = −0.94, P < 0.001) and positively with the changes in RVSV (r = 0.46, P = 0.020). No associations were found between the changes in RV parameters and any of the whole body parameters, such as VO2peak and HRrest.

DISCUSSION

In this study, we investigated, for the first time, the effects of exercise training on the RV metabolism using PET and showed that RVGU decreased after both HIIT and MICT, whereas fat metabolism remained unaltered in previously untrained middle-aged men. CMR-derived RVEDV and RVESV increased, but RVEF mildly decreased, after 2 wk of training. RV mass and RVSV remained unaltered.

Table 2. Characteristics and training adaptations in the HIIT and MICT study groups

<table>
<thead>
<tr>
<th></th>
<th>HIIT</th>
<th>MICT</th>
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<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Age*, yr</td>
<td>47 (45, 50)</td>
<td>48 (45, 51)</td>
</tr>
<tr>
<td>Height*, cm</td>
<td>180 (177, 182)</td>
<td>179 (176, 181)</td>
</tr>
<tr>
<td>Body weight*, kg</td>
<td>83.1 (78.2, 88)</td>
<td>84.1 (79.2, 89.1)</td>
</tr>
<tr>
<td>BMI*, kg/m²</td>
<td>25.9 (24.5, 27.2)</td>
<td>26.4 (25, 27.7)</td>
</tr>
<tr>
<td>VO2peak*, ml/kg⁻¹min⁻¹</td>
<td>34.7 (32.4, 37.1)</td>
<td>33.7 (31.4, 35.9)</td>
</tr>
<tr>
<td>M-value*, μmol·kg⁻¹min⁻¹</td>
<td>38.2 (30.1, 46.4)</td>
<td>31.9 (23.1, 40.7)</td>
</tr>
<tr>
<td>HRrest, beats/min</td>
<td>59 (55, 62)</td>
<td>63 (60, 67)</td>
</tr>
</tbody>
</table>

Values are means [95% confidence interval (CI)]. BMI, body mass index; VO2peak, peak oxygen uptake; M-value, whole body insulin-stimulated glucose uptake; HRrest, heart rate at rest. *Previously published results (7). †Statistically significant training effect (P < 0.05).
RVGU. RVGU was measured during euglycemic hyperinsulinemic clamp using FDG-PET imaging, which enabled clear visualization of the RV free wall. RVGU was decreased by 22% in the HIIT group and 12% in the MICT group without significant difference between the training protocols. The reduction of RVGU was not associated with CMR-derived changes in RV structural and functional parameters or with the changes in the whole body parameters. For instance, even though baseline RVGU has been shown to be age associated (17, 30), the exercise-induced decrease of RVGU was not related to age in the present study. However, the finding of decreased RVGU corresponds to the results obtained in a previous cross-sectional study showing decreased insulin-stimulated LVGU in the trained state (38).

Table 3. Right ventricular metabolic, structural, and functional adaptations

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Group</th>
<th>Training</th>
<th>Training × Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVGU, μmol·100 g⁻¹·min⁻¹</td>
<td>11.6 (9.8, 13.4)</td>
<td>9.0 (7.2, 10.9)</td>
<td>12.8 (10.9, 14.8)</td>
<td>11.2 (9.2, 13.2)</td>
<td>0.17</td>
<td>0.002</td>
<td>0.42</td>
</tr>
<tr>
<td>RVFFAU, μmol·100 g⁻¹·min⁻¹</td>
<td>1.5 (1.3, 1.8)</td>
<td>1.5 (1.2, 1.8)</td>
<td>2.0 (1.7, 2.3)</td>
<td>1.9 (1.5, 2.3)</td>
<td><strong>0.020</strong></td>
<td>0.74</td>
<td>0.76</td>
</tr>
<tr>
<td>RVEDV, ml</td>
<td>196 (183, 210)</td>
<td>205 (192, 220)</td>
<td>187 (175, 200)</td>
<td>194 (181, 208)</td>
<td>0.26</td>
<td><strong>0.002</strong></td>
<td>0.65</td>
</tr>
<tr>
<td>RVESV, ml</td>
<td>92 (82, 102)</td>
<td>98 (88, 109)</td>
<td>88 (79, 98)</td>
<td>95 (85, 105)</td>
<td>0.59</td>
<td><strong>0.005</strong></td>
<td>0.94</td>
</tr>
<tr>
<td>RV EF, %</td>
<td>53 (50, 55)</td>
<td>52 (49, 54)</td>
<td>53 (50, 55)</td>
<td>51 (49, 54)</td>
<td>0.78</td>
<td><strong>0.034</strong></td>
<td>0.51</td>
</tr>
<tr>
<td>RV SV, ml</td>
<td>104 (98, 109)</td>
<td>107 (101, 112)</td>
<td>99 (94, 105)</td>
<td>99 (93, 105)</td>
<td>0.13</td>
<td>0.14</td>
<td>0.12</td>
</tr>
<tr>
<td>RV mass, g</td>
<td>31 (29, 34)</td>
<td>32 (29, 34)</td>
<td>32 (30, 35)</td>
<td>32 (30, 35)</td>
<td>0.56</td>
<td>0.43</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Values are model-based means (95% CI). RVGU, RV glucose uptake; RVFFAU, RV free fatty acid uptake; RVEDV, RV end-diastolic volume; RVESV, RV end-systolic volume; RV EF, RV ejection fraction; RV SV, RV stroke volume. Group P value indicates group main effect (HIIT vs. MICT). Training main effect indicates whether there is mean change between Pre and Post measurements. Training × Group interaction describes whether mean changes are different between the study groups. Values in bold are significantly different.

Fig. 3. Individual responses for RVGU (A) and RVF-FAU (B). Thick lines indicate model-based means (HIIT in black, MICT in gray). Solid thin lines with solid circles indicate individual responses to HIIT, and dashed thin lines with open circles, individual responses to MICT.
It is known that exercise increases insulin sensitivity and enhances glucose uptake in skeletal muscles (7, 34, 38), but, interestingly, myocardium, both LV and RV, seems to be affected by training to the opposite direction. Decreased myocardial glucose utilization was also discovered in mice in a study concerning effects of long-term spontaneous exercise (24). Monleon and colleagues (24) suspected that the decrease of myocardial glucose uptake could result from increase in myocardial fatty acid oxidation rate or exercise-induced bradycardia, but neither of these was confirmed by their experiments. In the present study on humans, RVFFAU remained unaltered, and, as [18F]FTHA traces not only uptake, but also β-oxidation in the myocardium (39), it can be assumed that also RV free fatty acid oxidation rate remained unaltered. However, in the present study, RVGU was measured during euglycemic hyperinsulinemic clamp and RVFFAU without the clamp in the fasting state. Therefore, the results of these two PET measurements are not directly comparable, although both represent the state where the specific substrate utilization is at its highest in normal daily living conditions. Furthermore, in the present study, HRrest remained unaltered after 2-wk-long training intervention.

Takala et al. (38) found that, along with decreased LVGU, myocardial perfusion and oxygen consumption in LV were also decreased in endurance athletes at rest, suggesting that exercise reduces workload in the heart muscle tissue. Furthermore, LVGU of athletes correlated negatively with LV mass and positively with LV rate-pressure product that estimates the LV myocardial work (27). Thus it may be that heart muscle becomes more economical as a response to exercise training, and the same amount of work can be performed with less fuel. However, we did not find correlation between RVGU and RV mass, suggesting that RV metabolism is altered first and RV hypertrophy requires longer training time to occur. Unfortunately, workload of the RV was not measured in the present study, as it would have required invasive procedures, which were not deemed suitable for these healthy subjects.

The main finding of the present study, namely decrease of RVGU after the training, seems to be a positive adaptation to training compared with opposite shift of increasing glucose metabolism in the disease state, which is thought to result from increased myocardial workload due to disease (2, 22, 23, 28, 44). In a recent review regarding physiological and pathophysiological changes in RV of athletes (4), authors speculated whether nuclear imaging could provide the means to differentiate these two conditions. Interestingly, our results suggest that the measurement of insulin-stimulated RVGU may indeed have this potential. However, further studies will be needed to investigate the mechanisms of reduced RVGU and its possible association with RV work to determine whether measurement of RVGU could be used in clinical situations.
RVFFAU. No changes were observed in RVFFAU after either of the training interventions. Unfortunately, some of the RVFFAU measurements were unsuccessful, which may have reduced power to detect training-induced alterations in RVFFAU. However, the result of unchanged RVFFAU is in line with the previous cross-sectional LV study on monozygotic twins, where no difference in LV free fatty acid uptake (LVFFAU) was found when comparing monozygotic twin brothers with higher and lower physical activity and fitness (16). Also, no difference in LVFFAU was observed in another study between endurance athletes and sedentary men (38, 41). Interestingly, while the group means of RVFFAU in both the HIIT and MICT groups were unaltered by the training, the individual responses varied a lot from subject to subject (Fig. 3). Substantial variation in fatty acid β-oxidation index was also previously found by Turpeinen et al. (41), which seemed to be random and was not explained by variables such as maximal exercise capacity or size of the heart. Our laboratory showed previously that, at the baseline, RVFFAU of the subjects of the present study was associated with V̇O₂peak and heart rate so that better physical fitness was related to smaller RVFFAU (17). In the present study, there was a statistically significant difference in RVFFAU between the training groups (Table 3), even though V̇O₂peak and heart rate were not different between the groups. It is possible that also RVFFAU is affected by unknown random components, which may explain the difference between the training groups. After the training intervention, V̇O₂peak was increased for both groups, while heart rate remained the same, and their associations with RVFFAU were lost.

RV structure and function. We utilized CMR to study the effects of training on the RV structure and function. Both RVEDV and RV ESV increased, whereas RVEF mildly decreased by both training modes. These cardiac changes did not correlate with the changes in V̇O₂peak after the 2 wk of training in the sedentary subjects. Rather, the adaptations of the RV volumes and the RVEF may be a response to an increased blood plasma volume, which has been shown to occur rapidly when starting exercise training (13). However, the findings of the present study mirrored those observed in the large CMR study, where RV volumes of endurance athletes were increased and RVEF was decreased compared with nonathletes (31). Hence, reduction of RVEF seems to be a physiological consequence of RV dilation, and it may be that more optimal pumping capacity is achieved by higher RVEDV at the cost of somewhat reduced RVEF (4), at least at the resting state.

As our laboratory previously showed, the RVEF in these subjects was directly proportional with the RVGU at baseline (17), implying that the lower RVEF is related to the lower RVGU. In the present study, both of these decreased after the training. On the other hand, in different diseases, markedly lower RVEF is associated with increase of RVGU (23, 28, 44). Thus, while mildly reduced RVEF may be a positive adaptation to exercise training, providing more optimal stroke volume, in more severe form it may also be associated with disease, making it difficult to distinguish between physiological and pathophysiological adaptations, especially in athletes (4). For instance, RVEF of 45% is a common cutoff in echocardiography for arrhythmogenic RV cardiomyopathy, the cutoff which is relatively often met, especially in elite athletes (31). Thus measurement of RVGU could provide complementary information to CMR results for diagnostic purposes, but further studies are required to confirm this.

As expected, no changes in RV mass or RV SV occurred after 2 wk of training. The RV mass was mildly increased in a study where previously untrained men trained for 6 mo, using either endurance or resistance training (37). In a study of cardiac remodeling after 1 yr of intense endurance training in previously sedentary subjects, RV mass, RV EDV, and RV SV increased, even relatively more compared with the LV (1). Hence, RV volumes and RVEF seem to respond rapidly to exercise training, while increases in its mass and RV SV require a longer time to occur.

Strengths and limitations. Strengths of our study include measurement of RV metabolism using PET, which enables quantitative assessment of RVGU and RVFFAU. Because the PET measurements were performed in the conditions with the highest substrate uptake (insulin clamp for RVGU and fasted state for RVFFAU), the RV free wall was clearly visualized. Hence, this study shows that measurement of RV metabolism is feasible in the context of exercise physiology, and it is not restricted only to patients with increased RVGU with higher tracer count statistics. The secondary outcomes involving RV structure and function were determined by CMR, regarded as the gold standard for RV measurements (15). The CMR images were analyzed following established guidelines (32), making the results comparable to other CMR studies. Finally, the exercise interventions used in this study were well controlled without variation between subjects in their implementation.

Our study has some limitations. As we measured RVGU and RVFFAU in different metabolic conditions, the results of these studies cannot be directly compared. Furthermore, the third important substrate for myocardial metabolism is lactate, but its uptake was not measured in our study. Therefore, we cannot make complete conclusions about the relative changes in the utilization of different substrates based on this study. Unfortunately, some of the PET measurements were unsuccessful, and especially the postexercise FTHA-PET measurements were burdened with technical problems. Even though the missing values were accounted for by the restricted maximum likelihood estimates in linear mixed models, the power to detect differences was decreased. Nevertheless, the current result that RVFFAU was not altered by training corresponded to the earlier observations of unchanged LVFFAU (16, 38, 41). Finally, the purpose of our study was to investigate the initial responses to short-term HIIT and MICT, but the responses to prolonged training remain unclear and warrant further studies. In the present study, none of the observed changes were statistically different after HIIT and MICT. It may be that, for previously sedentary subjects, both forms of exercise provide rapid stimulus for changes in RVGU, volumes, and RVEF. Longer exercise interventions could shed more light on the question of whether chronic cardiac adaptations are different after HIIT and MICT, or do their effects simply overlap, as seems to be the case in skeletal muscle metabolic adaptations (20).

Conclusions. Only 2 wk of either HIIT or MICT decreases RVGU in previously sedentary middle-aged men, along with increase in RV volume and mild reduction of RVEF, the changes which appear to precede exercise-induced RV hypertrophy. While the physiological explanation for reduced RVGU remains unsettled, it seems to be a positive adaptation...
to exercise compared with increased RVGU in diseased heart. Further studies with longer exercise intervention durations and also in athletes with various training backgrounds are needed to understand the underlying mechanisms and significance of altered RVGU in the trained state.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS


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