Myocardial blood flow, oxygen consumption, and fatty acid uptake in endurance athletes during insulin stimulation

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Departments of 1Medicine and 4Clinical Physiology, 2Turku PET Centre, and 3Sports and Exercise Medicine Unit, Paavo Nurmi Centre, University of Turku, FIN-20521 Turku, Finland; and 3Department of Nuclear Medicine, Hokkaido University, Sapporo, 060-8638 Japan

Takala, Teemu O., Pirjo Nuutila, Chietsugu Katoh, Matti Luotolahti, Jörgen Bergman, Maija Mäki, Vesa Oikonen, Ulla Ruotsalainen, Tove Grönroos, Merja Haaparanta, Jukka Kapanen, and Juhani Knuuti. Myocardial blood flow, oxygen consumption, and fatty acid uptake in endurance athletes during insulin stimulation. Am. J. Physiol. 277 (Endocrinol. Metab. 40): E585–E590, 1999.—We have previously demonstrated reduced myocardial glucose uptake rates in hearts of endurance athletes, which could be due to increased use of alternative fuels or reduced energy demands. In the present study myocardial blood flow, oxygen consumption, and free fatty acid uptake were measured with [15O]H2O, [15O]O2, [18F]FTHA, and positron emission tomography (PET) in 9 endurance athletes and 11 sedentary men during euglycemic hyperinsulinemia. Compared with sedentary men, athletes had 33% lower myocardial blood flow, 27% lower oxygen consumption, and 20% lower estimated myocardial work per gram of tissue. Myocardial fatty acid uptake rates were not significantly different in endurance athletes (0.83 ± 0.29) and sedentary men (1.0 ± 0.31 µmol·100 g−1·min−1, P = 0.232). In conclusion, myocardial blood flow and oxygen consumption per unit mass of myocardium are reduced at rest in endurance athletes. This can be explained by reduced energy requirements per gram of tissue due to anatomic and physiological changes of the athlete's heart.

Exercise; positron emission tomography; free fatty acid; myocardial metabolism; skeletal muscle

FREE FATTY ACIDS (FFAs) are the main source of energy in the well-oxygenated myocardium (23, 25, 34) in the fasting state. Myocardial fatty acid utilization rate depends on the availability of exogenous fatty acids and the rate of acetyl-CoA oxidation (29). When plasma glucose and insulin levels are increased, the heart preferentially uses glucose, and fatty acid uptake and oxidation are suppressed (27, 34).

The studies investigating the consequences of endurance training on substrate metabolism in the human heart are sparse (24, 35). We have previously shown that, in contrast to skeletal muscle, myocardial glucose uptake per unit mass of myocardium during euglycemic hyperinsulinemia is lower in endurance athletes than in sedentary men (24). This difference may be explained by the increased use of alternative fuels (such as fatty acids or lactate) or lower energy requirements of the endurance athlete's heart compared with that of the sedentary subject (24). Turpeinen et al. (35) investigated the use of an alternative fuel, free fatty acids, but did not find any alterations in fatty acid uptake in trained men compared with sedentary men. However, their studies were performed during fasting conditions, which prevent the direct comparison between their study (35) and our earlier studies (24).

There is only one study in humans measuring perfusion and oxygen uptake in the athlete's heart (15). In the study by Heiss et al. (15), heart blood flow and oxygen consumption were found to be lower in the endurance athletes than in the sedentary subjects, both at rest and during exercise. Because the oxygen consumption per heart stroke was smaller, they concluded that the myocardium of a trained individual requires less energy at given work than that in the untrained state. However, the morphological and anatomic changes of the heart due to training, which might have profound effects on the metabolic requirements of the myocardial tissue, were not taken into account. Therefore, the true oxygen cost of myocardial work cannot be derived from those data. In studies in animals, myocardial blood flow has been reported to be decreased (3) or increased (19) or unaltered (5) as a result of endurance training.

18F-labeled 14(R,S)-fluoro-6-thia-heptadecanoic acid ([18F]FTHA) is a false long-chain fatty acid (LCFA) substrate and inhibitor of fatty acid metabolism (9). After transport into the mitochondria, it undergoes initial steps of β-oxidation and is thereafter trapped in the cell. The carnitine palmitoyl-transferase I inhibitor POCA decreased mice cardiac [18F]FTHA uptake by ~85% (9). The rate of radioactivity accumulation in the myocardium would, therefore, directly reflect the β-oxidation rate of LCFAAs (9, 32). The tracer has been recently used to study fatty acid metabolism in the human heart with positron emission tomography (PET) (2, 12, 20, 21, 30). Most of the studies have been performed in the fasting state (12, 20, 30). We have recently measured myocardial FFA uptake with [18F]FTHA also, under hyperinsulinemic conditions, and the measured myocardial FFA uptake rates were suppressed in response to insulin (21).

With the previous finding concerning decreased insulin-stimulated glucose uptake in the athlete's heart kept in mind, the purpose of the present study was to more completely elucidate the myocardial substrate metabolism in athletes. Myocardial blood flow, oxygen...
consumption, and FFA uptake were measured with PET in endurance athletes and sedentary men under insulin-stimulated conditions, and these were related to parameters obtained with echocardiography.

METHODS

Subjects. Nine male endurance athletes (triathletes, runners) and eleven healthy sedentary men participated in the study (Table 1). Endurance athletes competed on the national or international level, and they had engaged in regular endurance exercise for more than 10 years. The sedentary group did not exercise regularly. The subjects were healthy, as judged by history, physical examination, and routine laboratory tests, and they were not taking any medications. The nature, purpose, and potential risks of the study were explained to all subjects before written informed consent was obtained. The experimental protocol was reviewed and approved by the Joint Commission of Ethics of Turku University and Turku University Central Hospital.

Study design. All subjects were studied after a 10- to 12-h overnight fast, and they had not exercised for 2 days before the study. Two catheters were inserted, one in an antecubital vein for sampling of arterialized venous blood. Infusions and blood sampling at 2, 5, 10, 15, 20, 25, 30, 40, and 50 min from the start of insulin infusion, and a dynamic scan of 32 min of the thoracic region was performed (Fig. 1). The mean doses of $^{15}$O$^2$CO, $^{15}$O$^2$H$_2$O, $^{15}$O$^2$O$_2$, and $^{18}$F$^2$FTHA were 3,110 ± 243 MBq, 1,640 ± 120 MBq, 3,770 ± 936 MBq, and 178 ± 31.7 MBq, respectively.

Production of $^{15}$O$^2$CO, $^{15}$O$^2$H$_2$O, $^{15}$O$^2$O$_2$, and $^{18}$F$^2$FTHA. For production of $^{15}$O, a low-energy deuteron accelerator, Cyclone 3, was used (Ion Beam Application, Louvain-la-Neuve, Belgium). A natural nitrogen target containing 1% oxygen was used, and radiochemical purity of $^{15}$O$^2$O$_2$ was 97% (6, 33). $^{15}$CO was produced in a conventional way (6). $^{15}$O-labeled water was produced using dialysis techniques in a continuously working water module (7). Sterility and pyrogenicity tests for water and chromatographic analysis for gases were performed to verify the purity of the products. $^{18}$F$^2$FTHA was produced as previously described (20), and the radiochemical purity of the final product was > 98%.

Image acquisition, processing, and corrections. The patients were positioned supine in a 15-slice ECAT 9310/12 tomograph (Siemens/CTI, Knoxville, TN) with a technical in-plane resolution of 6.5 mm and axial resolution of 6.7 mm. To correct for photon attenuation, transmission scanning was performed for 20 min before the emission scans. Two reconstruction methods were applied: 1) median root prior, or MRP (5), in $^{15}$O$^2$CO, $^{15}$O$^2$H$_2$O, $^{15}$O$^2$O$_2$, and $^{18}$F$^2$FTHA studies (full-width half-maximum 8.0 mm), and 2) filtered back projection, or FBP, in $^{18}$F$^2$FTHA studies (full-width half-maximum 9.5 mm). Four (lateral, anterior, septal, and whole left ventricle) regions of interest were drawn on at least four representative midventricular slices, with care taken to avoid myocardial borders.

Calculation of the myocardial blood flow and oxygen consumption. Regional myocardial blood flow (MBF), oxygen extraction fraction (OEF), and oxygen consumption (MMRO$_2$) were quantitated using previously published methods (16–18) and an image analysis package (Dr. View, Asahi-Kasei, Tokyo) with special dedicated software.

Calculation of the regional $^{18}$F$^2$FTHA fractional uptake constant and FFA uptake index. The nonmetabolized fractions of $^{18}$F$^2$FTHA were determined with HPLC from nine blood samples (2, 5, 10, 15, 20, 25, 30, 40, and 50 min from the beginning of the $^{18}$F$^2$FTHA injection), and these were linearly interpolated to correct the plasma input function, as previously described (21). $^{18}$F$^2$FTHA was assumed to be irreversibly trapped, and back flux is considered insignificant. The three-compartment model (31) and graphic analysis according to Patlak and Blasberg (26) were applied to quantitate the fractional uptake constant of $^{18}$F$^2$FTHA (K), from myocardial and metabolite-corrected plasma time-activity curves. The slope of the linear phase of the plot in the graphic analysis is equal to K. The last seven time points (5–32 min) were used to determine the slope by linear regression. The Patlak plots of $^{18}$F$^2$FTHA showed no curvature, indicating metabolic trapping. The residuals of the regressions were stochastically scattered. The regional myocardial FFA uptake indexes were calculated by multiplying K, with the mean serum FFA concentration during $^{18}$F$^2$FTHA PET imaging. $^{18}$F$^2$FTHA uptake was assumed to directly reflect FFA uptake, and no correction factor was applied (i.e., the lumped constant for $^{18}$F$^2$FTHA was assumed to be 1.0) (22).

Infusions and blood sampling. Whole body glucose uptake was quantitated using the euglycemic hyperinsulinemic clamp technique (8). Serum insulin was increased for 170 min using a primed-continuous (7.2 pmol·kg$^{-1}$·min$^{-1}$) infusion of insulin (Velsulin, Novo Nordisk A/S, Bagsvaerd, Denmark). Normoglycemia was maintained with an infusion of 20% glucose on the basis of frequent plasma glucose measurements. Whole body glucose uptake was calculated from the glucose infusion rate during the period of 60–140 min after
Table 2. Circulating substrate concentrations during PET scanning

<table>
<thead>
<tr>
<th></th>
<th>Endurance (Athletes)</th>
<th>Sedentary (Men)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum free fatty acids, µmol/l</td>
<td>60 ± 15</td>
<td>64 ± 14</td>
<td>0.552</td>
</tr>
<tr>
<td>Plasma insulin, pmol/l</td>
<td>395 ± 79</td>
<td>437 ± 65</td>
<td>0.221</td>
</tr>
<tr>
<td>Plasma glucose, mmol/l</td>
<td>5.2 ± 0.6</td>
<td>5.0 ± 0.6</td>
<td>0.418</td>
</tr>
<tr>
<td>Plasma lactate, mmol/l</td>
<td>1.7 ± 0.3</td>
<td>1.3 ± 0.2</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Table 3. Systolic and diastolic blood pressure, heart rate, and rate-pressure product during myocardial blood flow, oxygen consumption, and fatty acid uptake measurements and echocardiography

<table>
<thead>
<tr>
<th>Group</th>
<th>$^{15}$O]H_2O</th>
<th>$^{15}$O]O_2</th>
<th>$^{18}$F]FTHA</th>
<th>Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athlete</td>
<td>111 ± 12†</td>
<td>111 ± 13†</td>
<td>114 ± 15†</td>
<td>121 ± 14</td>
</tr>
<tr>
<td>BPs, mmHg</td>
<td>59 ± 10</td>
<td>58 ± 11</td>
<td>62 ± 11</td>
<td>68 ± 10</td>
</tr>
<tr>
<td>BPD, mmHg</td>
<td>52 ± 10†</td>
<td>53 ± 12†</td>
<td>57 ± 8*</td>
<td>58 ± 9</td>
</tr>
<tr>
<td>HR, beats·min^−1</td>
<td>5,810 ± 1,450†</td>
<td>5,980 ± 1,910†</td>
<td>6,540 ± 1,370*</td>
<td>7,090 ± 1,710</td>
</tr>
<tr>
<td>RPP, mmHg·beats·min^−1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>119 ± 9</td>
<td>122 ± 8</td>
<td>124 ± 10</td>
<td>123 ± 11</td>
</tr>
<tr>
<td>BPs, mmHg</td>
<td>63 ± 9</td>
<td>65 ± 8</td>
<td>65 ± 8</td>
<td>69 ± 8</td>
</tr>
<tr>
<td>BPD, mmHg</td>
<td>62 ± 12</td>
<td>65 ± 14</td>
<td>67 ± 12</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>HR, beats·min^−1</td>
<td>7,430 ± 2,000</td>
<td>7,970 ± 2,290</td>
<td>8,350 ± 1,930</td>
<td>7,740 ± 1,840</td>
</tr>
<tr>
<td>RPP, mmHg·beats·min^−1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BPs and BPD, systolic and diastolic blood pressure; respectively; HR, heart rate; RPP, rate-pressure product; $^{15}$O]H_2O, myocardial blood flow; $^{15}$O]O_2, oxygen consumption; $^{18}$F]FTHA, $^{18}$F-labeled thia-hepta-decanoic acid fatty acid uptake measurements; Echo, echocardiography.

*P ≤ 0.05 vs. sedentary; †0.05 < P < 0.1 vs. sedentary.
and myocardial efficiency were not different between the groups.

MBF and MMRO2. Athletes had 33% lower MBF (73 ± 14 vs. 110 ± 31 ml·min⁻¹·100 g⁻¹, P = 0.003) and 27% lower MMRO2 (8.8 ± 2.3 vs. 12.0 ± 3.8 ml·min⁻¹·100 g⁻¹, P = 0.044, athletes vs. sedentary subjects) compared with sedentary subjects (Fig. 2). OEF was comparable in athletes and sedentary men (68 ± 14 and 62 ± 12%, respectively). Because of increased LV mass in athletes, total LV MBF (183 ± 39 and 222 ± 86 ml/min, athletes and sedentary men) and total LV MMRO2 (22 ± 7 and 24 ± 10 ml/min) were comparable between the groups.

Myocardial fatty acid uptake. Myocardial fractional [¹⁸F]FTHA uptake (K𝑖) rates were not significantly different (0.14 ± 0.04 vs. 0.16 ± 0.03 ml·muscle ml⁻¹·min⁻¹) in the athletes and the sedentary men, respectively. No significant changes were observed either in the calculated fatty acid uptake indexes or total LV fatty acid uptake rates between the athletes and the sedentary men (0.83 ± 0.29 vs. 1.0 ± 0.31 µmol·100 g⁻¹·min⁻¹, P = 0.232, Fig. 2, and 2.1 ± 0.8 vs. 2.0 ± 0.7 µmol·min⁻¹, P = 0.672, respectively).

Associations between myocardial work, MBF and MMRO2, and FFA uptake in the pooled data. The rate-pressure product correlated with total MBF (r = 0.65, P = 0.002) and with total MMRO2 (r = 0.70, P = 0.001). Myocardial work per gram of myocardium was associated with MBF (r = 0.57, P = 0.009), MMRO2 (r = 0.63, P = 0.004), and myocardial FFA uptake index (r = 0.48, P = 0.031). V̇O₂max had negative association with MBF (r = −0.74, P < 0.001) and MMRO2 (r = −0.64, P = 0.004).

**DISCUSSION**

The present study was conducted to investigate the effects of endurance training of several years on myocardial perfusion, oxygen metabolism, and substrate utilization. We have previously shown that insulin-stimu-

Table 4. Cardiac dimensions and hemodynamic parameters

<table>
<thead>
<tr>
<th></th>
<th>Endurance</th>
<th>Sedentary</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular mass, g</td>
<td>251 ± 35</td>
<td>198 ± 40</td>
<td>0.006</td>
</tr>
<tr>
<td>Left ventricular mass/body surface area, gm²</td>
<td>130 ± 13</td>
<td>102 ± 18</td>
<td>0.002</td>
</tr>
<tr>
<td>Posterior wall, diastole, mm</td>
<td>9.7 ± 0.6</td>
<td>8.9 ± 0.8</td>
<td>0.034</td>
</tr>
<tr>
<td>Septum, diastole, mm</td>
<td>10.4 ± 0.8</td>
<td>9.2 ± 0.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Left ventricular diameter, systole, mm</td>
<td>33 ± 4</td>
<td>31 ± 3</td>
<td>0.292</td>
</tr>
<tr>
<td>Left ventricular diameter, diastole, mm</td>
<td>55 ± 3</td>
<td>52 ± 4</td>
<td>0.103</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>101 ± 10</td>
<td>89 ± 15</td>
<td>0.067</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>5.8 ± 1.1</td>
<td>5.6 ± 1.4</td>
<td>0.770</td>
</tr>
<tr>
<td>Heart output work, mmHg·l·min⁻¹</td>
<td>505 ± 134</td>
<td>494 ± 164</td>
<td>0.880</td>
</tr>
<tr>
<td>Myocardial work/tissue, mmHg·l·g⁻¹·min⁻¹</td>
<td>2.0 ± 0.4</td>
<td>2.5 ± 0.6</td>
<td>0.042</td>
</tr>
<tr>
<td>Left ventricular meridional wall stress, kPa</td>
<td>5.7 ± 1.8</td>
<td>5.6 ± 0.8</td>
<td>0.880</td>
</tr>
<tr>
<td>Myocardial efficiency, %</td>
<td>16 ± 4</td>
<td>14 ± 4</td>
<td>0.465</td>
</tr>
</tbody>
</table>

lated myocardial glucose uptake is decreased in the athlete’s heart, suggesting either reduced need for energy or use of alternative fuels, such as FFAs or lactate (24). In the present study, no evidence of enhanced myocardial FFA uptake rates was found. In contrast, myocardial perfusion and oxygen consumption per unit mass of myocardium were reduced in athletes. These changes appear to be associated with the reduction of myocardial work due to anatomic and physiological changes induced by endurance training.

Myocardial blood flow and oxygen consumption. The results of our study are in accordance with the findings by Heiss et al. (15), the only previously published study in humans about heart blood flow and oxygen consumption in endurance athletes. With invasive measurements, they found 20–25% decreased heart blood flow and oxygen consumption in athletes at resting conditions. Because the oxygen consumption per heart stroke was reduced, Heiss et al. suggested that myocardial efficiency is enhanced in the athlete’s heart. However, the morphological and anatomic changes of the heart due to training were not taken into account. Endurance training induces profound changes in left ventricular volumes and wall thickness (13, 22) (Table 4), which are important determinants of myocardial workload.

Results of blood flow studies in animals are controversial. Barnard et al. (3), using exercised dogs and radioactive microspheres, demonstrated reduced coro-
nary flow at rest in trained animals compared with untrained animals. Myocardial blood flow rates were reported to be similar at rest in exercise-trained and untrained pigs (5) or elevated in anesthetized endurance-trained dogs (19). One explanation for such variability in blood flow results in animal studies is the different conditions in which measurements were done (5).

The present study shows that perfusion and oxygen consumption are closely related to the estimates of myocardial work load. This suggests that alterations of myocardial blood flow are reflective of the actual hemodynamic condition and that probably the metabolic requirements are reduced, together with the reduced workload in the athlete's myocardial tissue. Therefore, the results of the present study do not support the idea of reduced oxygen cost of myocardial work in the athlete's myocardium.

Myocardial fatty acid uptake. We did not find significant differences in either fractional [18F]FTHA uptake or calculated FFA uptake indexes in heart between the athletes and the sedentary group. The substrate metabolism was related to myocardial energy requirements. Because of the previous unresolved questions (24), the present study was conducted during insulin stimulation, when myocardial FFA uptake is known to be suppressed (21). During such conditions, FFA utilization was small and contributed only a small fraction of myocardial oxygen consumption. In further studies, it would be important to measure myocardial FFA uptake under conditions in which serum FFA concentrations are not suppressed. On the other hand, our results are in concert with Turpeinen et al. (35), who using [13C]heptadecanoic acid and single photon emission tomography found no alterations in myocardial fatty acid utilization between endurance athletes and untrained men in the fasting state.

[18F]FTHA has been used for the investigation of human myocardial (2, 12, 20, 21, 30) FFA uptake in both the fasting state and during insulin stimulation (21). In the fasting state, its uptake is mainly related to fatty acid β-oxidation (9, 32). However, there are no data available as to whether this holds true also during insulin stimulation. During low serum FFA concentrations, the fraction of FFAs and probably [18F]FTHA undergoing β-oxidation might be smaller. We assumed that the fractional uptake of [18F]FTHA represents that of the natural unlabeled FFAs (i.e., the lumped constant was assumed to be 1.0). Despite these limitations, FFA uptake indexes obtained with [18F]FTHA are in good agreement with the results obtained with other methods (21).

In addition to glucose and FFA, heart is able to utilize lactate as a fuel. The athletes exhibited higher levels during hyperinsulinaemia than the sedentary men. It has been demonstrated that plasma lactate concentrations are determined by the rate of peripheral glucose uptake (37), which is in agreement with the increased whole body glucose uptake rates in the athletes of the present study. The higher plasma lactate concentration in the endurance athletes might have enhanced lactate utilization in the heart (36). Unfortunately, we were not able to directly measure the contribution of lactate on myocardial energy metabolism. On the other hand, the reduced energy requirements and oxygen consumption can be considered to be sufficient to explain the reduced glucose utilization in the athlete's heart.

In conclusion, myocardial oxygen consumption and blood flow per unit mass of myocardium are reduced in endurance athletes compared with sedentary subjects. This can be explained by reduced energy requirements per gram of tissue due to anatomical and physiological changes of the athlete's heart. Myocardial fatty acid uptake is not significantly changed during insulin stimulation. Due to increased left ventricular mass in athletes, total left ventricular oxygen consumption, blood flow and work are similar in the athletes and the sedentary men.

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