Relationship between local perfusion and FFA uptake in human skeletal muscle—no effect of increased physical activity and aerobic fitness

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at the whole body level, increased physical activity improves free fatty acid (FFA) metabolism, since endurance training has been shown to enhance whole body lipid oxidation during low- and moderate-intensity exercise. This has been shown to be due to the increased uptake of FFAs to the cells and enhanced use of intramyocellular lipid storages (15, 31, 36). The positive effects of increased physical activity on FFA metabolism are well known in metabolic disorders, but the results in healthy young adults are inconsistent (5, 20, 29, 58). In healthy young adults, skeletal muscle and leg lipid oxidation during low- and moderate-intensity exercise has been either increased (20, 58) or decreased (5). Also, muscle FFA uptake has been similar (29, 58) or enhanced (5, 15, 20, 29, 58) due to endurance training. These divergent results, between whole body and local muscle measurements, can partly be explained by the different methods and physiological state used.

Perfusion regulates skeletal muscle oxygen and nutrient supply at rest and during exercise. It is well known that perfusion distributes heterogeneously, not only between tissues, but also between and within skeletal muscles (10, 25, 32, 45). Similarly, metabolic activity also differs in different tissues and between and within skeletal muscles (30, 41, 45), and it has been suggested that perfusion heterogeneity influences negatively to delivery of nutrients and oxygen in tissues. On the other hand, it is poorly known how well local nutrient and oxygen delivery (perfusion) is matched to the needs of different muscles or muscle areas. Evidently, at the whole body and whole limb level (3, 47), matching is almost perfect. However, few studies examining this between or within muscles have shown poor local match (19, 18, 41, 45, 37, 23).

Matching between delivery (muscle perfusion) and needs (metabolic activity) has previously been studied by correlating different measures of local metabolic activity to local perfusion (19, 18, 23, 37, 41, 45); the correlation between local muscle perfusion and glucose uptake (19) or citrate synthase activity (18) was poor at rest and only moderate during exercise. In recent human studies, relatively good correlation was found between local perfusion and oxygen uptake in different muscles of quadriceps femoris (QF) muscle group (23) and between different regions of QF muscle group in proximal to distal direction (37). However, in smaller regions within the gastrocnemius muscle, the matching between perfusion and oxygen consumption was poorer, even during moderate-intensity exercise in humans (45). Correspondingly, poor correlation

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was found between local skeletal muscle glucose uptake and perfusion at rest and only moderate during exercise in humans (41). However, it is not known how well muscle perfusion is matched to other metabolic parameters, such as muscle FFA uptake within and between muscles in humans. In the present study, we hypothesized that, without the confounding effects of genetic factors, long-term exercise training would decrease skeletal muscle perfusion and FFA uptake heterogeneity and improve muscle FFA uptake. As FFA uptake is only partly dependent on delivery (perfusion) and largely on transporter proteins (28), we also hypothesized that the muscle FFA uptake is not associated with muscle perfusion at rest or during exercise.

To test these hypotheses, we recruited genetically identical monozygotic (MZ) twins discordant for physical activity and aerobic fitness and measured perfusion, oxygen uptake, and FFA uptake in the muscles of QF muscle group at rest and during mild, submaximal, dynamic, one-legged, knee-extension exercise using positron emission tomography (PET). Correlation between perfusion, oxygen uptake, and FFA uptake between the four muscles of QF was measured, as well as correlation between perfusion and FFA uptake between the voxels of PET images.

METHODS

Subject selection. Subjects were recruited from five consecutive twin birth cohorts (born 1975–1979), which were ascertained from the Central Population Register of Finland. They are participating in the ongoing FinnTwin16 study, and there were totally 3,065 twin pairs with both co-twins alive and resident in Finland at their 16th birthday in 1991–1995 when the baseline assessment of the FinnTwin16 study was performed. Their health habits, including numerous questions on physical activity, have been studied by mailed questionnaires four times, and currently the last follow-up was completed in 2002 (26). The subjects were initially selected among the MZ male twins based on the results of this last follow-up. A pair was initially considered suitable into the present study, if the healthy brothers had a marked difference in leisure time physical activity. The criteria for the marked difference were that one brother was sedentary and the other exercised at least two to three times per week or that, if both brothers exercised, the more active brother exercised at least twice as much as the less active brother. The process for subject selection, the inclusion criteria, subject details, and determination of zygosity have been previously described in more detail in our laboratory’s previous report from the same subject group (14). Based on the inclusion and exclusion criteria, a letter of invitation was sent to 26 MZ twin pairs. Thereafter, a more detailed telephone interview regarding the current physical activity was performed, and, as a result, 12 consenting twin pairs were selected to the present study. In the first part of the measurements, 2–8 wk before the PET measurements, the physical activity was studied by a questionnaire of Baekke et al. (4), and a bicycle ergometer test was performed to determine maximum O2 uptake (VO2 max) (14). According to the criteria of significant differences in physical activity and at least 9% difference in VO2 max, nine twin pairs [age 25.9 yr (SD 1.7)] were selected into the second part of the study. The co-twins with higher physical activity and VO2 max constituting the more active group were compared with the less active group with lower physical activity and VO2 max. More active group had 18% (SD 10) higher VO2 max compared with less active group [50.9 (SD 5.1) vs. 43.4 ml·min⁻¹·kg⁻¹ (SD 6.7), P < 0.001]. The amount of physical activity of the preceding year was studied by a questionnaire. The physical activity was divided into conditioning exercise (e.g., running, cross country skiing, strength training, and intensive ball games) and other physical activity (e.g., light walking, gardening, shoveling of snow, and field sports). On average, the more active group had 4.0 (SD 2.9) and the less active group 1.7 (SD 1.5) (P = 0.003) conditioning exercise workouts per week, and the average time per week spent for those were 229 (SD 156) and 98 min (SD 71), respectively (P = 0.013). The times per week spent for other physical activities was on average 4.3 (SD 2.1) in the more active group and 4.4 (SD 4.3) in the less active group (P = 0.96), and the average time per week spent for those were 144 (SD 110) and 157 min (SD 162), respectively (P = 0.77). Within each pair, the more active brother was also more fit. In one pair, both brothers smoked, and in another pair both brothers took snuff regularly.

Before starting any measurements, written, informed consent was obtained after purpose, nature, and potential risks were carefully explained to the subjects. The Ethical Committee of the Hospital District of South-Western Finland had approved the study protocol (191/2003).

Study design. PET studies were performed in 2–8 wk after physical activity questionnaire and VO2 max measurement. All PET studies were performed after the subjects had fasted at least 12 h and abstained from physical exercise other than daily living for 48 h. Caffeine and alcohol were prohibited 12 h before the PET scans. In PET studies, skeletal muscle perfusion using [15O]H2O, oxygen uptake using [15O]O2, and FFA uptake using 18F-labeled 6-thia-heptadecanoic acid ([18F]FTHA) were measured at rest and during submaximal dynamic one-legged, knee-extension exercise (Fig. 1).

Before the PET studies, two catheters were inserted: one into an antecubital vein for saline infusion and injection of the tracers, and the other into the opposite radial artery for blood sampling. The subjects were lying in the same supine position in all three scans, and their right leg was fastened to a dynamometer for exercise (specially designed for this purpose), while the left leg rested in an extended position, as previously described (22, 32). Care was taken to fasten the subjects carefully to the imaging table to limit any movement in the femoral region during the study. After positioning, the one-legged, submaximal, dynamic, knee-extension exercise was started and continued until the end of the study. During all of the PET scans, the left leg was resting while right leg was exercising, and both legs were scanned simultaneously. Five minutes after the start of exercise, skeletal muscle perfusion was measured (40, 46). The measurement was started with an injection of [15O]H2O [1,111 MBq (SD 137)], and dynamic 6-min PET scanning was started simultaneously (6 × 5 s,
for the exercise. The exercise load (more active group: 3.4 kg, SD 2 s). A metronome with sound signal was used to give the proper speed for knee-extension exercise (32) in which one contraction cycle lasted for 1 s, and the relative dispersion (heterogeneity) of muscle perfusion and FFA uptake within each muscle was calculated individually as SD × 100%/mean. Voxel size in the present study was 87 mm³ (in plane 3.6 × 3.6 mm and plane thickness 6.75 mm).

Biochemical analyses. Serum FFA and plasma lactate were both measured by the enzymatic colorimetric methods (ACS-ACOD method, Wako Chemicals USA for FFA, and Roche Diagnostics, Mannheim, Germany for lactate) and analyzed with Roche Modular P800 automatic analyzer (Roche Diagnostics).

Statistical analysis. Statistical analyses were performed using SAS/STAT statistical analysis program package, version 8.02 (SAS Institute, Cary, NC). Normality of variables was assessed by Shapiro-Wilkinson test. In the analysis, the effect of exercise on skeletal muscle perfusion, oxygen uptake, and FFA uptake, as well as relative dispersion of perfusion and FFA uptake, was first tested using ANOVA for repeated-measures with three factors (exercise, group, and muscle). Thereafter, the effect of two other factors (group and muscle) was tested separately for resting and exercising leg. Correlations were calculated using Pearson correlation. P values <0.05 were considered statistically significant. All results are expressed as means (SD).

RESULTS

Skeletal muscle perfusion, oxygen uptake, and FFA uptake were 6–10 times higher in the exercising compared with resting muscles (P < 0.001, Fig. 2). Compared with the less active group, oxygen uptake was higher in the more active group in the exercising muscles (P = 0.05), but similar between the groups in the resting muscles (Fig. 2). No differences were observed in muscle perfusion and FFA uptake in the resting or exercising muscles between the groups (Fig. 2). Perfusion, oxygen uptake, and FFA uptake levels were highest in the VL muscle and lowest in the RF and VL muscles in both the resting and the exercising legs in both groups. Neither exercise nor group had significant effect on the heterogeneity of mean FFA uptake, perfusion, and oxygen uptake between the muscles.

The relative dispersion of perfusion and FFA uptake within the muscles was lower in the exercising compared with the resting muscles (P < 0.001, Fig. 3). No significant differences were observed between the groups. The relative dispersion of both perfusion and FFA uptake was highest in the VL muscle in the exercising leg, but no differences were observed between different muscles in the resting leg (Fig. 3).

Only moderate correlation was found between mean levels of perfusion and oxygen uptake in the QF muscles in both groups at rest (r = 0.67, P = 0.33 in more and r = 0.77, P = 0.23 in less active twins) and during exercise (r = 0.81, P = 0.19 in more and r = 0.74, P = 0.26 in less active twins), while between perfusion and FFA uptake correlation was stronger (at rest r = 0.97, P = 0.03 in more and r = 0.98, P = 0.02 in less active twins and during exercise r = 0.99, P = 0.01 and r = 0.94, P = 0.06, respectively) (Fig. 4). When r was calculated individually (Table 1), mean values were lower compared with the correlations calculated from the group mean values (Fig. 4). Table 1 shows a large variation in individual correlation values between the subjects.

Figure 5 shows an example of the correlation between perfusion and FFA uptake values of each voxel in the whole QF muscle group in a representative twin pair. On average, the correlation was poor at rest (r = 0.28 (SD 0.13) vs. 0.33 (SD 0.21), P = 0.58) and only moderate during
exercise \( r = 0.73 \text{ (SD 0.08)} \) vs. \( 0.74 \text{ (SD 0.10)}, P = 0.92 \) in the more active and less active group, respectively.

**DISCUSSION**

The results of the present study show that long-term history of moderately increased physical activity and aerobic fitness increases skeletal muscle oxygen uptake but not perfusion and FFA uptake during submaximal knee-extension exercise. Skeletal muscle FFA uptake and perfusion are heterogeneously distributed between and within different muscles at rest and during submaximal exercise. Furthermore, both FFA uptake and perfusion distribute less heterogeneously within the muscles during submaximal exercise compared with rest. Against our hypothesis, mean perfusion and FFA uptake correlated reasonably well between different QF muscles, and the correlation was better than between perfusion and oxygen uptake. At the voxel level (small parts of muscles), correlation between perfusion and FFA uptake was only moderate during exercise.

Fig. 2. Skeletal muscle perfusion (A), oxygen uptake (B), and FFA uptake (C) at rest and during exercise between more (solid bars) and less active twins (open bars). Skeletal muscle oxygen uptake during exercise was higher in more than in less active twins \( (P = 0.05), \) RF, rectus femoris; VL, vastus lateralis; VM, vastus medialis; VI, vastus intermedius. Please notice the different scale in vertical axis between rest and exercise. *** \( P < 0.001, ** P < 0.01, \) and * \( P < 0.05 \) between muscles.

Fig. 3. Skeletal muscle perfusion (A) and FFA uptake (B) heterogeneity (relative dispersion) at rest and during exercise between more (solid bars) and less active twins (open bars). *** \( P < 0.001, ** P < 0.01, \) and * \( P < 0.05 \) between muscles.
and weak at rest. In addition, the results suggest that moderately increased physical activity and fitness do not have any significant influence on heterogeneity of FFA uptake or perfusion, or on the relationship between perfusion and FFA uptake.

Mean perfusion and FFA uptake were similar between the groups in both resting and exercising muscle, but muscle oxygen uptake was higher in the more than less active group in the exercising muscle. As both muscle perfusion and metabolic parameters are largely affected by several confounding factors (e.g., intensity, type of training, time of measurements, etc.), it is difficult to compare the results of the present study to previous studies. However, compared with other studies employing knee-extension exercise and measuring FFA uptake after 1 h of exercise (29, 58), the results are in good agreement. In the previous knee-extension exercise studies, leg FFA uptake has been similar at the same absolute (29) and relative (58) exercise intensities after endurance training. In contrast, during bicycle exercise, leg FFA uptake has been similar at the same absolute exercise intensity but increased at the same relative exercise intensity already after 5 min of exercise after the exercise training period (5). This discrepancy in the results between the studies may be due to more strenuous exercise mode (bicycle vs. one-legged, knee-extension exercise) with higher energy demands and larger changes in the internal milieu (increased plasma catecholamine and decreased insulin levels), which may increase the rate of lipolysis and affect muscle FFA uptake.

In the present study, exercise load during knee-extension exercise was set according to subjects’ QF mass to strain each gram of muscle by the same load in each subject, thus to have absolutely the same load in less active (“before training”) and more active (“after training”) subjects. As the between-groups differences in the load, muscle oxygen uptake, and whole body $\dot{V}O_2_{max}$ were at the same magnitude and same direction, it is reasonable to assume that the relative exercise intensity was also similar between the groups. Thus, according to cross-over concept by Brooks and Mercier (7), the results of no differences in FFA uptake in the present study are expected. Interestingly, oxygen uptake was higher in the more than less active...
group in the exercising muscles. Currently, we do not have any good explanations for this. Exercise training has been shown to improve mitochondrial oxidative capacity, increasing mitochondrial volume density, enzyme activities (16, 17), and coupling and regulatory properties (57, 60) of mitochondrial respiration in skeletal muscle. Thus increased muscle oxygen uptake during submaximal exercise in more active twins in the present study may be related to enhanced mitochondrial oxidative capacity. Increased oxygen uptake may also be related to increased use of intramuscular triglycerides as an energy source in the more active group, as it is known that more oxygen is needed to burn fats than other energy sources, and the use of FFAs from circulating blood tended to be lower in the more active group, although the difference was not statistically significant.

As endurance exercise training increases gluconeogenesis at rest and during exercise (6), it is also possible that the similar or unchanged FFA uptake in the present and two previous knee-extension exercise studies (29, 58) after 1 h of exercise is due to higher availability of glucose in trained subjects, enhancing the shunting of glucose to working muscles.

When critically comparing the results of this and previous studies, the main methodological advance in the present study is that, using radioactive tracers and PET skeletal muscle perfusion, oxygen uptake and FFA uptake were measured directly from the muscle tissue. Previously, these parameters have been measured mainly from arteriovenous differences across the whole leg (5, 29, 58), which means that confounding factors such as lipolysis on adipose tissue during exercise (52) could not be ruled out.

We cannot exclude the potential effects of small differences in physical activity and aerobic fitness on the results. The mean difference in \( V_{\text{O}2_{\text{max}}} \) between the brothers was 18%; that is, however, comparable to what has been achieved with 6 mo of training in some previous training studies (42, 48, 51, 55). Thus the difference cannot be considered totally negligible.

As in the previous human studies employing both isometric (22, 23, 25, 41) and dynamic (32) one-legged, knee-extension exercise, perfusion was considerably heterogeneous both between and within muscles. The novel finding in the present study is also that muscle FFA uptake distributes heterogeneously between and within muscles and quite similarly as perfusion. As with perfusion, FFA uptake was highest and least heterogeneous in the VI muscle during exercise. One reason for heterogeneous distribution of perfusion and FFA uptake between different muscles may be the different proportions of slow- and fast-twitch fibers in different muscles. As previously reviewed by Laughlin and colleagues (33), the fiber-type distribution between and within muscles is one of the main reasons for the level of perfusion in animal skeletal muscles. Early studies in human cadavers have shown that the proportion of slow-oxidative fibers is higher in the VI and VM muscles than in the two other QF muscles (11, 21), which fits well with our present and previous findings of higher perfusion and metabolism in these two muscles.

Muscle perfusion and FFA uptake distributed less heterogeneously within muscles during exercise than at rest in the present study. This agrees with the findings in previous studies regarding perfusion heterogeneity (25, 30, 32). Common explanations for lower perfusion heterogeneity during exercise have been enhanced capillary recruitment (38) and more uniform recruitment of different muscle parts (43). During the last decade, evidence has emerged that a key factor influencing perfusion distribution, at least in myocardium, is the heterogeneous metabolism within the tissue for which blood flow is matched (1, 13, 27, 59). Therefore, we also measured correlation and matching between perfusion, FFA uptake, and oxygen uptake in the present study.

It is assumed that blood flow correlates strongly with oxygen uptake, as oxygen is the most important substance needed in energy metabolism during exercise. This seems to be true at the whole body and limb level (3, 47), but, when individual muscles or tiny regions inside the muscle are considered, the correlation becomes weaker, and thereby also matching between blood flow and oxygen uptake poorer (23, 45). In the present study, only moderate correlation was found in perfusion and oxygen uptake between different muscles at rest and during submaximal exercise. The correlation was slightly lower than in a previous study of unrelated untrained and endurance-trained subjects (23), but the reason for that is unknown.

We found a relatively strong correlation between perfusion and FFA uptake between different muscles in the present study, and, against our hypothesis, it was even better than the correlation between perfusion and oxygen uptake. However, in line with the size dependency assumption discussed in the previous paragraph, the correlation was much weaker in smaller units, in the voxels of PET images. To the best of our knowledge, this is the first study reporting the association between local perfusion and FFA uptake in skeletal muscle, and thus no direct comparisons can be made. However, the correlation between local perfusion and glucose uptake within resting and exercising (electrical stimulation in animals and voluntary exercise in humans) skeletal muscle has been previously studied in both animals (19) and humans (41). The correlation coefficients for both resting (\( \sim 0.1 \)) and exercising
muscle (~0.5) in those studies were slightly lower as in the present study for FFA uptake and perfusion. Moderately increased physical activity and fitness did not induce significant changes in the heterogeneity of muscle perfusion and FFA uptake at rest or during exercise in the present study. We have previously shown that muscle perfusion distributes less heterogeneously in the QF muscles in endurance-trained than in unrelated untrained subjects (25). The results of the present study suggest that, when the effects of heredity are taken into account, increased physical activity would not cause changes in the heterogeneity of muscle perfusion and FFA uptake within and between muscles during exercise. However, we cannot exclude the effects of a smaller difference in fitness in the present than in our previous study.

Another explanation for different results between the studies may be related to fiber-type distribution within the muscles, as it seems that perfusion is least heterogeneous in the muscles containing most of type I muscle fibers. It is well known that endurance athletes usually inherently have predominance of type I muscle fibers in their muscles, or, in turn, athletes who have predominance of type I muscle fibers prefer endurance events. Thus it is reasonable to assume that the endurance athletes probably had a significantly larger proportion of type I muscle fibers than the untrained control subjects in our previous study in unrelated subjects (25). In the present study, the subjects had the same genetic background, and we observed that the heterogeneity of perfusion and metabolism were not different between the groups. As genotype is a stronger determinant of fiber-type distribution than training (49), it seems reasonable to believe that the basic reason for less heterogeneous perfusion in endurance-trained subjects is not the training per se but changes in fiber-type distribution, both training induced and inherited.

The smallest unit of the vascular system is a capillary. However, the capillaries are not the smallest functional units, since opening a single capillary cannot be controlled. Instead, the smallest physiologically controlled unit is the microvascular unit, which is a bunch of capillaries that originate from a single common terminal arteriole, covering an anatomically finite area at the level of one or few cubic millimeters (10, 34). In the present study, the voxel size, the smallest measured unit, and the unit from which the heterogeneity was measured, was 87 mm³. To conceptualize this in relation to vascular anatomy, it should be noted that this is several times larger than the size of a microvascular unit, and, therefore, the perfusion value of each voxel is an average of perfusion in several microvascular units. Thus the results of the present study do not necessarily reflect the heterogeneity in the microvascular units. However, based on the known inverse relation between the size of the measured unit (voxel) and the amount of heterogeneity (24), it can be concluded that the heterogeneity in all parameters would have been larger in microvascular units.

We used a one-legged, knee-extension exercise model in the present study. It is obvious that the heterogeneity of perfusion, FFA uptake, and oxygen uptake between the muscles may depend on the exercise model chosen. Based on early electromyography studies, it has been assumed that one-legged, knee-extension exercise causes quite even activation of at least the superficial QF muscles, with no or minor activation in other leg muscles (3). However, Richardson and coworkers (44), using T2-weighted MRI, more recently showed evidence that there is more variation in the activation of different QF muscles in knee-extensor exercise than during cycling at near maximal exercise intensity. Furthermore, roughly the same heterogeneity in perfusion and metabolism between the muscles as in the present study has been observed in previous PET studies during intermittent isometric knee-extension exercise (22), running (12), and cycling (unpublished observations). Thus it is reasonable to assume that the findings do not depend so much on the exercise model as speculated.

In conclusion, this study shows that long-term history of moderately increased physical activity tends to enhance skeletal muscle oxidative metabolism, but it does not have any significant influence on the FFA uptake or perfusion rates or their heterogeneity in muscle. Muscle FFA uptake and perfusion distributes heterogeneously between and within different muscles of QF muscle group at rest. Both FFA uptake heterogeneity and perfusion heterogeneity within the muscles decrease during submaximal knee-extension exercise compared with rest. Although mean perfusion and FFA uptake correlate reasonably well between different muscles, their association at the voxel level (87 mm³) is only moderate during exercise and weak at rest. Without the confounding effects of genetic factors, long-term history of moderately increased physical activity and aerobic fitness do not have any significant influence on the heterogeneity of FFA uptake or perfusion, or on the relationship between perfusion and FFA uptake. This, together with previous studies comparing unrelated endurance-trained and untrained subjects, suggests that the fundamental reason for less heterogeneous perfusion in endurance-trained subjects is not the training per se alone, but the combined effects of training and genetically determined factors, e.g., muscle fiber distribution.

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