Relationship between muscle blood flow and oxygen uptake during exercise in endurance-trained and untrained men

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Kalliokoski, Kari K., Juhani Knuuti, and Pirjo Nuutila. Relationship between muscle blood flow and oxygen uptake during exercise in endurance-trained and untrained men. J Appl Physiol 98: 380–383, 2005. First published September 3, 2004; doi:10.1152/japplphysiol.01306.2003.—A recent study showed good correlation between regional blood flow (BF) and oxygen uptake (VO2) 30 min after exhaustive exercise. The question that remains open is whether there is similar good correlation between BF and VO2 also during exercise. We reanalyzed our previous data from a study in which BF and VO2 was measured in different quadriceps femoris muscles in seven healthy endurance-trained and seven healthy untrained men at rest and during low-intensity intermittent static knee-extension exercise (Kalliokoski KK, Oikonen V, Takala TO, Sipila H, Knuuti J, and Nuutila P. Am J Physiol Endocrinol Metab 280: E1015–E1021, 2001). When the mean values of each muscle were considered, there was good correlation between BF and VO2 during exercise in both groups (r2 = 0.82 in untrained and 0.97 in trained). However, when calculated individually, the correlations were poorer, and the mean correlation coefficient (r̄2) was significantly higher in the trained men (0.71 ± 0.07 vs. 0.40 ± 0.11, P = 0.03). These results suggest that there is large individual variation in matching BF to VO2 in human skeletal muscles during exercise, ranging from very poor to excellent. Furthermore, this matching seems to be better in the endurance-trained than in untrained men.

Blood flow (BF) is one of the most important factors regulating oxygen supply in skeletal muscle, especially during exercise. Already the early studies in humans have shown that in whole leg oxygen uptake (VO2) increases in parallel with increased exercise intensity and BF (2, 22). It is also well known from early animal studies (3, 16) and recent human studies (11, 12) that BF distributes unevenly among different muscles both at rest and during exercise. Whether VO2 also shows similar heterogeneity between different muscles has been mostly unknown until recently.

Using positron emission tomography (PET) as the study method, Mizuno and coworkers showed in humans that regional muscle VO2 along the proximal-distal axes of the quadriceps femoris (QF) muscle varies similarly as BF (17). Furthermore, BF and VO2 correlated well at 30 min after exhaustive exercise. The situation 30 min after exercise may not, however, reflect the situation during exercise; thus it is currently poorly known how well local BF and VO2 are matched during exercise, and this problem was recently emphasized (23). The only study that has previously explored the association between BF and VO2 during exercise obtained different results. Richardson and coworkers (21) showed, using magnetic resonance imaging (MRI) as the study method, that there is a large variation in matching muscle BF and VO2 during exercise. Thus definitely more studies are needed to clarify this issue.

In the present study, we tested the hypothesis that there is a good correlation in BF and VO2 in different muscles during exercise. We also hypothesized that training status might be associated with this relationship so that endurance-trained men might have better correlation than untrained men. To explore these hypotheses, we reanalyzed the data from a study in which BF and VO2 were measured in different QF muscles in endurance-trained and untrained men at rest and during exercise (14).

METHODS

Seven healthy male endurance-trained (age 26 ± 3 yr, body mass index 22.9 ± 2.6 kg/m², maximal VO2 67 ± 3 ml·kg⁻¹·min⁻¹) and seven healthy untrained men (age 24 ± 3 yr, body mass index 22.6 ± 2.6 kg/m², maximal VO2 46 ± 6 ml·kg⁻¹·min⁻¹) were studied (14). The endurance-trained subjects had trained several years on a regular basis at least 5 times and more than 7 h weekly. The untrained subjects exercised only occasionally and less than twice a week (0–2 h per week). Written, informed consent was obtained after the purpose, nature, and potential risks were explained to the subjects. The Joint Commission on Ethics of the Turku University and Turku University Central Hospital approved the study protocol.

The study was performed after the subjects had fasted overnight (>10 h). They were instructed to avoid exercise and caffeinated beverages 24 h before the studies. The subjects were positioned in supine position in the PET scanner with the femoral regions of both legs in the gantry. The right leg was fastened to a dynamometer (I-KON, Chattanooga Group, Oxfordshire, UK) at a knee angle of 50°, while the other leg rested in an extended position, as previously described (11, 14). Each study started with a 30-min resting period, during which a transmission scan for the correction of photon attenuation was performed. After that, a 60-min intermittent static exercise period was started. The exercise consisted of intermittent 2-s static contractions (10% of maximal isometric power) followed by 2 s of rest for a duration of 60 min (14). Muscle BF and muscle VO2 were measured independently of each other in the femoral region using PET and [15O]H2O and [15O]O2 as tracers. The methods have been described in details previously (14, 18, 19).

All PET image data were corrected for dead time, decay, and measured photon attenuation. PET images were processed using a two-dimensional-ordered subsets expectation maximization and median root prior reconstruction method (1).

Regions of interest surrounding the individual muscle regions of QF muscle group were drawn into four subsequent cross-sectional planes (each 6.75 mm thick) in the middle of both thighs as previously described (11, 14). The muscle areas were defined as rectus femoris, vastus lateralis, vastus intermedius, and vastus medialis. The muscle BF was calculated by the region of interest (ROI) method, where a region of interest was drawn for each muscle of interest. PET images were processed using the two-dimensional-ordered subsets expectation maximization method.

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vastus lateralis, vastus medialis, and vastus intermedius. Localization of the different muscle compartments of QF group was done on the basis of the individual transmission scans performed in all subjects.

Statistical analyses were done using SAS/STAT statistical analysis software release 8.2 (SAS Institute, Cary, NC). ANOVA for repeated measures was used for the analysis of statistical differences between the resting and exercising muscle and the groups. Pearson correlation coefficient was used in correlation analysis. All data are shown as means ± SE.

RESULTS

Figure 1 shows the relationship between muscle BF and \( V\dot{O}_2 \) in different muscles of QF muscle group when the mean values of BF and \( V\dot{O}_2 \) in each muscle were calculated. In the resting muscle, correlation of the group mean values was weaker in the trained than in the untrained men. In contrast, in the exercising muscle, this correlation was better in the trained men. The least squares fitting equations for the relationships between perfusion and \( V\dot{O}_2 \) during exercise were the following: [perfusion (ml·kg\(^{-1}\)·min\(^{-1}\)) = 5.70 \( \times \) \( V\dot{O}_2 \) (ml·kg\(^{-1}\)·min\(^{-1}\)) + 29.3] for the trained men and [perfusion (ml·kg\(^{-1}\)·min\(^{-1}\)) = 4.28 \( \times \) \( V\dot{O}_2 \) (ml·kg\(^{-1}\)·min\(^{-1}\)) + 82.2] for the untrained men. Although both mean correlations during exercise were reasonably good \((r > 0.9)\), there was a large variation between the subjects, and when \( r^2 \) was calculated individually it was significantly \((P = 0.03)\) higher in the exercising muscle in the trained \((0.71 ± 0.07)\) than in the untrained men \((0.40 ± 0.11)\) (Table 1). Interestingly, some of the untrained subjects had very poor correlation between BF and \( V\dot{O}_2 \) (UT3–UT5 in Table 1). On the other hand, some of the untrained subjects (UT2,

### Table 1. Individual correlation coefficients between muscle blood flow and oxygen uptake in the endurance-trained and untrained men at rest and during exercise and the exercise intensity

<table>
<thead>
<tr>
<th>Subject</th>
<th>Rest</th>
<th>Exercise</th>
<th>Intensity, N</th>
</tr>
</thead>
<tbody>
<tr>
<td>UT1</td>
<td>0.36</td>
<td>0.33</td>
<td>49</td>
</tr>
<tr>
<td>UT2</td>
<td>0.29</td>
<td>0.66</td>
<td>77</td>
</tr>
<tr>
<td>UT3</td>
<td>0.58</td>
<td>0.03</td>
<td>76</td>
</tr>
<tr>
<td>UT4</td>
<td>0.38</td>
<td>0.13</td>
<td>51</td>
</tr>
<tr>
<td>UT5</td>
<td>0.96</td>
<td>0.20</td>
<td>58</td>
</tr>
<tr>
<td>UT6</td>
<td>0.95</td>
<td>0.70</td>
<td>40</td>
</tr>
<tr>
<td>UT7</td>
<td>0.37</td>
<td>0.73</td>
<td>73</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>0.56 ± 0.11</td>
<td>0.40 ± 0.11</td>
<td>61 ± 15</td>
</tr>
</tbody>
</table>

ET, endurance trained; UT, untrained. *P < 0.05 between the groups during exercise.

### DISCUSSION

The findings in the present study supported our hypotheses only partly. Some individuals showed a good correlation between BF and \( V\dot{O}_2 \), whereas in others correlation was poor. However, the mean data for BF and \( V\dot{O}_2 \) are well correlated during exercise. Supporting the hypothesis, we found better correlation in the trained than in the untrained men.

Oxygen is the most important substance that muscles need during exercise and the supply of oxygen is dependent on BF. Thus they might be expected to correlate with each other quite well. When measuring BF and \( V\dot{O}_2 \) at the whole body level or across the whole leg during incremental exercise, this has been shown to be true \((2, 22)\). Whether the same is true inside the muscle has been unknown until lately because a lack of suitable method to study that question. However, recent advances in the application of the imaging methods have shed some light on this issue. Richardson and coworkers \((21)\) studied previously the association between muscle BF and oxygen metabolism during submaximal plantar flexion exercise using two different MRI methods. The results showed that
local BF and \( V_{\dot{O}_2} \) show considerable heterogeneity between the muscle regions, and what is even more interesting is that there is a large variation in matching local BF to \( V_{\dot{O}_2} \). The results in the present study using PET as the study method support these findings. We found that, although the mean data for BF and \( V_{\dot{O}_2} \) were well correlated during intermittent static knee-extension exercise, individual differences were large and that some subjects had very poor correlation. In addition, studies using near-infrared spectroscopy have shown that oxygen saturation, which reflects the balance between oxygen delivery and \( V_{\dot{O}_2} \), is heterogeneous within and between muscles (4, 6). This also shows that there is at least some mismatch between oxygen delivery and need. Taken together, these results suggest that local muscle BF and \( V_{\dot{O}_2} \) might not be so tightly related to each other as has been assumed.

In a recent PET study, Mizuno and coauthors (17) showed good correlation between BF and \( V_{\dot{O}_2} \) along the proximal-distal axes of the QF muscle both before and 30 min after exhausting one-legged cycling exercise. This study, however, has one principal problem because BF measured with radiolabeled water was also used for the calculation of \( V_{\dot{O}_2} \). The results in the present study using PET as the study method support these findings. We found that, although the mean data for BF and \( V_{\dot{O}_2} \) were well correlated during intermittent static knee-extension exercise, individual differences were large and that some subjects had very poor correlation. In addition, studies using near-infrared spectroscopy have shown that oxygen saturation, which reflects the balance between oxygen delivery and \( V_{\dot{O}_2} \), is heterogeneous within and between muscles (4, 6). This also shows that there is at least some mismatch between oxygen delivery and need. Taken together, these results suggest that local muscle BF and \( V_{\dot{O}_2} \) might not be so tightly related to each other as has been assumed.

Mismatch between ventilation and perfusion in the lungs is one of the main causes for inefficient pulmonary gas exchange in different lung diseases (9). The same step that occurs in the lungs when oxygen is released from the air to blood occurs in reversed mode in the muscle when oxygen is released from blood to the interstitial fluid in the periphery. Thus a corresponding supply-to-demand ratio for the muscle as the ventilation-to-perfusion ratio is in the lungs can be calculated from muscle \( V_{\dot{O}_2} \) and BF data. This is what Wagner did in the recent editorial (23) to the data obtained by Mizuno et al. (17) and what we also did to our data in the present paper. Data by Mizuno et al. (17) show considerably less heterogeneity in this ratio than we found in the present study. Conversely, this means that oxygen extraction fraction varies much more between the muscles than within the different regions of the same muscle. The reason for this is unknown but may be related to the different fiber type distribution in different muscles (7, 10) that may also cause differences in density of vascular routes in these muscles. These vascular adaptations may also partly explain why BF and \( V_{\dot{O}_2} \) were better matched in the trained subjects. This finding suggests that endurance training improves match between oxygen demand and supply in the skeletal muscle during mild submaximal exercise. This agrees with the early findings in myocardial tissue in humans (5).

The exercise intensity in the present study was quite low. It has been estimated that this type of exercise causes an increase in muscle BF that corresponds to the effects of whole body exercise at 20–25% of maximal \( V_{\dot{O}_2} \) (8, 14). Therefore, these
results cannot be directly extrapolated to higher exercise intensities. However, in the study by Richardson et al. (21), the exercise intensity was ~50–60% of maximal workload and still the clear mismatch was present. The perfect correlation between BF and V\textsubscript{O}\textsubscript{2} conversely means that there is no variation in oxygen extraction fraction between the muscle regions. Most probably that situation can be reached only at the very high exercise intensities when the oxygen extraction is near the maximal at 80–90% extraction level.

According to Whipp and Ward (24) the relationship between cardiac output (Q) and V\textsubscript{O}\textsubscript{2} at the whole body level is well described by the equation

\[ Q = k \cdot V\textsubscript{O}\textsubscript{2} + c \]

where the constants k and c both have values of ~5 when both Q and V\textsubscript{O}\textsubscript{2} are expressed as liters per minute. Because most of the increase in Q and V\textsubscript{O}\textsubscript{2} is due to the active muscles, it was not so surprising that we found roughly the same k also at the muscle level in the present study. The k values we obtained fit also well to the value of 5.3 calculated by Poole (20) from the previously published leg BF and V\textsubscript{O}\textsubscript{2} data (15). However, according to the present study, there seems to be at least a slight difference in this slope between the trained and untrained men at the muscle level.

In the present study, as also in the study by Mizuno et al. (17), BF and V\textsubscript{O}\textsubscript{2} were measured in the quite large muscle areas and not in the voxels of the PET images. The reason for this is that it is currently impossible to calculate V\textsubscript{O}\textsubscript{2} in the voxels of the PET images with reasonably good accuracy (13), although BF can be measured in the voxels with good accuracy (11). The same problems related to voxel size and signal-to-noise ratio are also present in the MRI method used by Richardson et al. (21). Thus there is a continuous need to develop the methods further so that muscle V\textsubscript{O}\textsubscript{2} can be calculated in smaller and smaller regions of muscle and all the way down to the level of microcirculation.

In conclusion, we have shown in the present study that there is large between-subject variation in correlation between BF and V\textsubscript{O}\textsubscript{2} in different quadriceps muscles during exercise. Furthermore, the correlation is better in endurance-trained than in untrained subjects.

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