Skeletal muscle blood flow and flow heterogeneity during dynamic and isometric exercise in humans

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Laaksonen, Marko S., Kari K. Kalliokoski, Heikki Kyröläinen, Jukka Kemppainen, Mika Teräs, Hannu Sipilä, Pirjo Nuutila, and Juhani Knutti. Skeletal muscle blood flow and flow heterogeneity during dynamic and isometric exercise in humans. Am J Physiol Heart Circ Physiol 284: H979–H986, 2003. First published November 21, 2002; 10.1152/ajpheart.00714.2002.—The effects of dynamic and intermittent isometric knee extension exercises on skeletal muscle blood flow and flow heterogeneity were studied in seven healthy endurance-trained men. Regional muscle blood flow was measured using positron emission tomography (PET) and an [15O]H2O tracer, and electromyographic (EMG) activity was recorded in the quadriceps femoris (QF) muscle during submaximal intermittent isometric and dynamic exercises. QF blood flow was 61% (P = 0.002) higher during dynamic exercise. Interestingly, flow heterogeneity was 13% (P = 0.024) lower during dynamic compared with intermittent isometric exercise. EMG activity was significantly higher (P < 0.001) during dynamic exercise, and the change in EMG activity from isometric to dynamic exercise was tightly related to the change in blood flow in the vastus lateralis muscle (r = 0.98, P < 0.001) but not in the rectus femoris muscle (r = −0.09, P = 0.942). In conclusion, dynamic exercise causes higher and less heterogeneous blood flow than intermittent isometric exercise at the same exercise intensity. These responses are, at least partly, related to the increased EMG activity.

DURING EXERCISE, blood flow is the most important factor affecting the oxygen supply and energy metabolism of muscle. In rhythmically contracting muscle, blood flow increases during the relaxation phase between contractions even at the low level of contraction intensity (25). In contrast, during the contraction period, blood flow will be limited or occluded due to an augmented intramuscular pressure (12, 29). It has been previously concluded that intramuscular pressure during static exercise is related to surface electromyographic (EMG) activity (29). It is also evident that dynamic exercise produces higher muscle blood flow compared with continuous isometric exercise in animals (19), probably due to more efficient muscle pump function (18). A more “dynamic” form of isometric exercise can be performed utilizing intermittent isometric contractions with resting periods. This exercise mode is, however, not a natural human way to move, whereas a stretch-shortening cycle of neuromuscular system is utilized daily.

It is not known whether perfusion responses differ between intermittent isometric and dynamic exercises. Skeletal muscle blood flow has been previously measured only during intermittent isometric exercise when using positron emission tomography (PET) (13–15, 21, 23). In general, it is difficult to use locomotory exercise with PET due to moving artifacts. This problem could be avoided by using isolated dynamic muscle actions and by fastening the exercising leg properly and limiting the range of motion to minimum. In the present study, the dynamic exercise mode was applied to PET to investigate 1) blood flow responses to dynamic and intermittent isometric exercise in humans, and 2) the perfusion heterogeneity during dynamic and intermittent isometric exercises.

MATERIALS AND METHODS

Subjects. Seven healthy endurance-trained men [25 ± 3 yrs, maximal oxygen uptake (V̇O2 max) 60.3 ± 4.1 ml·kg−1·min−1, body mass index 21.9 ± 1.2] volunteered for the study. Subjects had trained different endurance-type training (running, orienteering, and cross-country skiing) for several years on a regular basis (>5 times/wk and >60 min/session). All the subjects were fully informed of the purpose, nature, and potential risks of the study, and they gave their written informed consent to participate in this study. The Joint Commission on Ethics of the Turku University and Turku University Central Hospital approved the study protocol.

Study procedures. The subjects were instructed to avoid exercise and caffeinated beverages 24 h before the study. All subjects also fasted overnight for 10 h before the experiment. Before PET studies, the maximal isometric force (MVC) of knee extensors was measured bilaterally with a dynamome-
ter as described below. Thereafter, two catheters were inserted: one into an antecubital vein for saline infusion and injection of the tracer, and another in the opposite radial artery for blood sampling. The subjects were carefully fastened with two inelastic straps over the thighs to the imaging table with femoral regions of both legs in the field of view. This was done to avoid any movements in the femoral region during the experiment. The right leg was also adjusted to the dynamometer (I-KON, Chattanooga Group; Oxfordshire, UK) at a knee angle of 50°. In dynamic muscle actions, a dynamometer specially manufactured for this study was utilized. The left leg rested in an extended position, as previously described (13, 21). During the 20-min resting period before exercise, a transmission scan for the correction of photon attenuation was performed (Fig. 1). After that, two 15-min exercise periods were performed once with intermittent isometric and another with dynamic contractions in a randomized order with a 15-min resting period between the sets. Muscle blood flow was measured in the femoral region during the exercise 8 min after the commencement of exercise.

Measurement of skeletal muscle blood flow. Positron-emitting radiowater ([15O]H2O; half-life 2.05 min) was produced as previously described (33). An ECAT 931/08 tomograph (Siemens/CTI; Knoxville, TN) was used for two-dimensional (2-D) image acquisition. For the femoral muscle blood flow study, a 6-min dynamic scan with 6 × 5-s, 6 × 15-s, and 8 × 30-s frames was performed during exercise immediately after an intravenous injection of 1.4 ± 0.1 GBq (37 ± 4 mCi) [15O]H2O. The injection was given 8 min after the beginning of the exercise. Input function was obtained from arterial blood, which was continuously withdrawn at constant speed with a pump. Radioactivity concentration of blood was measured using a two-channel on-line detector system (Scanditronix; Uppsala, Sweden) cross calibrated with an automatic gamma counter (Wizard 1480 3", Wallac; Turku, Finland) and PET scanner (22). All data were corrected for dead time, decay, and measured photon attenuation. PET images were processed using the ordered subset expectation maximization and median root prior reconstruction algorithm with 150 iterations and a Bayesian coefficient of 0.3 (1). The delay between the input curve and the tissue curve was solved by fitting, and muscle blood flow was calculated by the autoradiographic method (28) voxel by voxel into flow images with a 250-s tissue integration time (22). Blood flow values in the quadriceps femoris (QF) muscle were also corrected by dividing measured blood flow with exercise load.

Regions of interest (ROIs) surrounding the extensors of the femoral muscles (QF muscles) and the individual muscle regions of the QF muscle group were drawn into four subsequent cross-sectional planes in both thighs as previously described (13). The muscle areas were defined as the vastus lateralis (VL), vastus intermedius (VI), vastus medialis (VM), and rectus femoris (RF). The average volume and mass of the QF ROI (182 ± 5 ml and 189 ± 2 g, respectively) were calculated by multiplying the amount of voxels in a ROI with the thickness of four adjacent planes (6.75 mm each) and further multiplying the volume by muscle density (1.04). Localization of the different muscle compartments of thigh muscles was done as previously presented (13). Spatial blood flow heterogeneity [relative dispersion (RD)] was determined as a SD divided by the mean blood flow value obtained from pooled voxel by voxel blood flow data from four planes (13, 24, 36).

Electromyography. EMG activity was recorded on-line (EISA 16-2; Freiburg, Germany) with surface electrodes (650437, Beckman miniature skin electrodes) from the VL and RF of the exercising leg. Electrodes with an interelectrode distance of 20 mm were placed longitudinally over the muscle bellies between the center of the innervation zone and the distal tendon of each muscle. In the VL, the electrode was ~5 cm distal to the end of scan area; in the RF, the electrode was within the scan area. Because of the quite large distance between the EMG electrode pairs, the cross-talk between muscles was assumed to have minimal influence on the recorded signals. The EMG signals were preamplified with a factor of 200, by an on-the-electrode mounted preamplifier (nonlinearity 0.03%), to minimize possible electrical noise. The EMG amplification factor was 500 (bandwidth from 10 Hz to 1 kHz per 3 dB), and it was synchronized and digitized with the force and knee angle records. For obtaining the quantity of EMG activity, the signals were full wave rectified and integrated.

**Fig. 1.** Study design. After the transmission scan (TR), the subject performed either isometric (ISO) or dynamic (DYN) exercise (EXE) for 15 min in a randomized order. During exercise, blood flow in the femoral region was measured using radiowater ([15O]H2O). Between bouts of exercise, there was a 15-min resting period. The illustration in the top right describes the exercise setting during positron emission tomographic (PET) scanning. Vastus lateralis (VL) and rectus femoris (RF) electromyographic (EMG) activity was measured using surface EMG electrodes. In addition, force production during exercise was measured using a force transducer, which was set anterior to the tibia above the malleolus medialis. The dotted line represents the situation during isometric exercise; the solid-lined leg corresponds to the range of motion during dynamic exercise. Both legs were tightly fastened to the imaging table with two straps (5 cm width each) over the thighs. The distance between the straps was 20–25 cm, and neither strap was in the scanning area.
and resting periods were performed continuously through the intermittent isometric exercise bout. The knee angle was set at 50° (Fig. 1). Dynamic exercise was performed in a continuous manner, and the subjects were freely allowed to choose their contraction frequency. The resistance of the dynamometer during the dynamic exercise was set to be equal to the individual isometric exercise level. The 15-min resting period between exercise sets was assumed to be sufficient to return the blood flow back to preexercise levels (8, 26, 35) and, furthermore, to ensure sufficient decay for the tracer. During exercise, produced tension in extension phase was measured with a force transducer, which was located anterior to the tibia above the malleolus medialis. Goniometry was placed on the medial side of the knee to electronically record the changes in the knee joint angle (Fig. 1). From these signals, the contraction and relaxation times were determined.

Other measurements and calculations. \( V_{\text{O}_2 \text{max}} \) was determined by treadmill running with direct respiratory measurements. The criteria used to establish the \( V_{\text{O}_2 \text{max}} \) was a plateau in the oxygen uptake despite an increase in intensity. The anthropometric thigh volume was measured once, 30 min before the PET experiment, according to the method of Saltin (30). The QF mass (\( QF_{\text{mass}} \)) was then calculated using the formula \( QF_{\text{mass}} = 0.307 \times V \times 0.333 \), where \( V \) is the thigh volume (11). The total QF blood flow was estimated by multiplying \( QF_{\text{mass}} \) with the average blood flow in the whole QF muscle region. The effect of exercise on the leg cross-sectional area was measured by performing extra 5-min transmission scans during both exercise modes for three subjects. The range of the difference in the cross-sectional area of the exercising leg between rest and exercise was 0.1–2.4% (isometric) and 0.9–1.5% (dynamic). During exercises, the cross-sectional area was similar between exercise modes (isometric 270 ± 69 and dynamic 268 ± 67 cm²). These differences are included in the error of the PET method.

Statistical methods. Statistical analyses were done using SAS/STAT statistical software (version 8.2, SAS Institute; Cary, NC). Normal distribution of parameters was tested using the Kolmogorov-Smirnov test. For the purpose of testing the differences of the average QF force production, EMG activity, blood flow, and flow heterogeneity values between different exercise modes, Student’s paired \( t \)-test was used. ANOVA for repeated measurements was performed to test the significance of differences between exercise modes and different muscle regions. After a significant \( F \)-test, pairwise differences were identified using the Tukey-Kramer post hoc procedure. A linear relationship between parameters was tested by the Pearson correlation coefficient (\( r \)). The significance level was set at \( P < 0.05 \). Data are presented as means ± SD.

RESULTS

Force and EMG activity. The \( QF_{\text{mass}} \) was 2.0 ± 0.2 kg (range 1.7–2.3 kg), and its produced MVC was 628 ± 102 N (range 524–838 N). In submaximal exercises (PET studies), the EMG activity varied between exercise modes (\( P < 0.001 \); Fig. 2). However, the force production was similar in both exercise modes (\( P = 0.126 \); Fig. 3A and Table 1). The contraction time during dynamic exercise, where the range of the knee angle was 55 ± 8° (range 44–67°), was shorter (\( P = 0.002 \)) than during isometric exercise (1.4 ± 0.3 and 2.0 s, respectively), but, in contrast, the relaxation times were similar in both exercise modes (dynamic 1.8 ± 0.5 s vs. isometric 2.0 s, \( P = 0.320 \)).

\( QF \) blood flow. \( QF \) perfusion in the resting leg was similar during both isometric and dynamic exercises (4.6 ± 2.7 and 3.8 ± 1.4 ml·100 g⁻¹·min⁻¹, \( P = 0.962 \), respectively). In the exercising \( QF \), perfusion was significantly higher than in the resting \( QF \) (\( P < 0.001 \)) in both exercise modes, and it was also significantly higher during dynamic than isometric exercise (dynamic 25.0 ± 3.9 ml·100 g⁻¹·min⁻¹ and isometric 14.1 ± 3.5 ml·100 g⁻¹·min⁻¹, \( P = 0.002 \), Fig. 3B). After \( QF \) blood flow values were corrected individually to similar workloads (produced average force during contraction), the \( QF \) blood flow was still 61 ± 41% (\( P = 0.003 \)) higher during dynamic exercise. Absolute whole \( QF \) blood flow, calculated by multiplying the \( QF \) flow with the estimated whole \( QF_{\text{mass}} \), was 87 ± 53% higher during dynamic than isometric exercise (500 ± 84 and 278 ± 53 ml/min, \( P = 0.002 \)). In all the different muscle parts of the \( QF \), blood flow values were significantly higher during dynamic than isometric exercise (\( P < 0.01 \); Fig. 4A). When comparing the changes in EMG activity and blood flow from isometric to dynamic exercise, subjects with a higher increase in EMG activity in the VL had also a higher increase in blood flow in the VL. In contrast, in the RF, the change in EMG activity was not related with the change in blood flow (Fig. 5). Examples of representative blood flow images during dynamic and isometric exercise are shown in Fig. 6.

Blood flow heterogeneity. Relative distributions of voxel by voxel blood flow values in the exercising \( QF \) during intermittent isometric and dynamic exercise are shown in Fig. 7. Blood flow in the whole \( QF \) was less heterogeneous (dynamic than isometric exercise (41 ± 8 and 48 ± 11%, \( P = 0.025 \); Fig. 3C and Table 2). Also, muscle region data demonstrated a tendency to reduced flow heterogeneity during dynamic exercise (\( P = 0.074 \)). In addition, there were differences in flow heterogeneity in different muscles (\( P < 0.001 \); Fig. 4B). The kurtosis and skewness values of the distributions in the whole \( QF \) were not different between exercise modes (dynamic vs. isometric: kurtos-
**DISCUSSION**

In the present study, the effects of dynamic and intermittent isometric exercises on skeletal muscle blood flow and flow heterogeneity were compared. Both exercise modes were performed with the same amount of force production, but blood flow in the whole QF and in its different muscle parts was higher during dynamic than isometric exercise. This was also the case after the whole QF blood flow was corrected individually to correspond the similar workloads. In addition, blood flow was less heterogeneous in the exercising QF during dynamic exercise. The present study also shows the possibility to measure skeletal muscle blood flow during dynamic exercise using PET.

Blood flow levels at rest and during isometric exercise in the present study agreed with previous studies using PET in humans (13, 17, 21), demonstrating that perfusion was approximately at the level of one-tenth PET and perfusion during dynamic exercise

### Table 1. Average force production during intermittent and dynamic exercise in each study subject

<table>
<thead>
<tr>
<th>Subject</th>
<th>Isometric (Force, N)</th>
<th>Dynamic (Force, N)</th>
<th>P value</th>
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<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>62</td>
<td>0.126</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
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<td></td>
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<td>3</td>
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</tr>
<tr>
<td>Means ± SD</td>
<td>63 ± 11</td>
<td>73 ± 17</td>
<td>0.126</td>
</tr>
</tbody>
</table>

The P value shows the difference between exercise modes.
of the estimated values during maximal exercise (2). In addition, in the present study, muscle perfusion values during intermittent isometric exercise were comparable with the values achieved during cycling at the exercise intensity of 24% of VO\(_2\)\(_{max}\) (10). However, significantly higher perfusion was detected during dynamic exercise. Ferguson et al. (6) have shown that higher contraction frequency (100 vs. 60 revolutions/min) during one-legged dynamic actions produces higher blood flow. We would like to note that in the studies of Ferguson et al. (5, 6), they reported the frequency as contractions performed in 60 s. Estimated from their studies, the average frequencies considering both contraction and relaxation times were ~33 and ~55 revolutions/min. In our study, contraction time was ~0.6 s shorter during dynamic than isometric exercise, and, therefore, the contraction frequency was only slightly higher during dynamic exercise (18 vs. 15 revolutions/min). However, because blood flow occurs mostly during the relaxation period between contractions, the difference in contraction frequencies between exercise modes in the present study is unlikely to explain the higher perfusion during dynamic action because the relaxation periods were similar between exercise modes (1.8 vs. 2.0 s). It has also been concluded that skeletal muscle blood flow during sustained exercise is determined by perfusion pressure, extravascular mechanical effects of muscle contraction, and the caliber of resistance vessels (20). However, the most important factor regulating blood flow during sustained exercise seems to be the metabolic rate of the muscle (9, 32). In the present study, average force production during both exercise modes was comparable, and, therefore, it was assumed that there was no difference in the metabolic rate between isometric and dynamic conditions (3). Furthermore, after QF blood flow values were corrected individually to equal workloads, QF blood flow was similarly higher during dynamic exercise. Thus one possible mechanism of higher blood flow during dynamic exercise might be the different mechanical effects of muscle contractions on the vasculature. Laughlin and Armstrong (19) have showed in animal studies that higher blood flow during dynamic exercise could be caused by the presence of
muscle fiber length changes during dynamic contraction (19), which may reflect more effective muscle pump function (18). In the present study, subjects performed continuous steady-state knee extension and flexion exercise when blood flow was measured during a 6-min scan. Consequently, we could only measure averaged extension and flexion flow. It has been previously reported that during low-level exercise (<30% MVC), an increase in exercise intensity had no effect on blood flow during the contraction period (12), whereas blood flow during the relaxation phase was closely related to intensity (12, 26).

It has been previously demonstrated that the increase in intramuscular pressure during static contraction is related to increased blood flow (26) and surface EMG activity at low-level exercise (29, 34). Unfortunately, we were not able to measure intramuscular pressure in the context of the present study, but it has been shown that intramuscular pressure can vary in different parts of activated muscle, which may affect blood flow distribution (31). In the present study, EMG activity in the VL and RF was higher during dynamic exercise, but the force production did not change markedly. Interestingly, a very significant positive relationship between the change in EMG activity and the change in blood flow was found in the VL but not in the RF. One reason for this might be the difference in the neuronal coding mechanism between these muscles during knee extension exercise (4, 16). We speculate that this might contribute to differences in recruitment patterns of the RF and VL muscles during dynamic and isometric exercises. Another explanation for the dissociation between EMG activity and blood flow could be the muscle length of the active QF muscle. During intermittent isometric exercise, the knee angle was set to 50° from the extended position, but during dynamic exercise the change in knee angle was ~55° from the extended position. This continuous change in angle probably activates the RF muscle more effectively than intermittent isometric exercise due to greater muscle fiber lengthening, whereas the VL is activated almost similarly during both exercise types. Furthermore, the anatomic differences between these two muscles (uniarticular vs. biarticular) might partly explain the observed findings. However, further studies may give more explanatory factors in this regard.

Blood flow heterogeneity values in individual muscle parts of the QF during isometric and dynamic exercise were slightly lower than in a previous study (13). Correspondingly, in the present study, perfusion heterogeneity appeared to be different in different muscle compartments. In addition, blood flow in the whole QF was less heterogeneous during dynamic than intermittent isometric exercise, which was supported by the finding of a tendency to lower heterogeneity during dynamic exercise in different muscle regions. The distribution of relative blood flow values (Fig. 7) was more concentrated near the mean value during dynamic than during isometric exercise, although the distributions seemed to be quite similar. Taken together, this suggests that blood flow is less heterogeneous during dynamic exercise, which is in accordance with previous finding of Ray et al. (27), who showed that increases in muscle blood flow during dynamic exercise are directed to newly recruited muscle areas causing decreased flow heterogeneity.

The use of PET allows direct assessment of regional blood flow in skeletal muscle. The blood flow method used in the present study has previously been compared with plethysmography (22), microspheres (7), and the steady-state PET method (28) with high accuracy to measure regional muscle blood flow in vivo. Previous exercise studies using PET have employed rhythmic, intermittent isometric contractions (13–15, 21). Naturally, during dynamic exercise, muscle fibers lengthen more than during isometric exercise, which might cause some moving artifacts on blood flow data. However, in the present study, both legs were very carefully fastened to the imaging table, and the exercising leg was also fastened to the dynamometer so that only the lower leg moved during exercise. The tightness of the straps was chosen so that the study subject could perform the exercise out of any uncomfortable sensations in the femoral regions and without any reduction in force production. This enabled us to prevent motion artifacts as much as possible during scanning in the thigh area. In addition, the effects of the exercise mode on the leg cross-sectional area were shown to be insignificant, although this was an indirect measurement of motion artifacts. However, the changes in muscle shape in superficial parts of the QF muscle during muscle actions might partly affect blood flow values, and, therefore, in the future, it is important to apply the gated scanning to PET when moving artifacts could be totally prevented. In any case, to our knowledge, this is the first study applying dynamic exercise during PET in humans. Even though there are some limitations in measuring muscle blood flow during dynamic exercise using PET at this stage, in the future this method may have many potential applications in studies investigating skeletal muscle blood flow and its regulation during exercise.

In conclusion, dynamic exercise causes higher and less heterogeneous blood flow in the exercising QF muscle compared with intermittent isometric exercise at the same exercise intensity. Higher blood flow might be due to more effective muscle pump function and, at
least partly, increased muscle fiber activation. In addition, less heterogeneous blood flow might be caused by more uniform recruitment of different muscle parts. Furthermore, we established that it is feasible to use the dynamic exercise mode in studies investigating the effects of low-level exercise on muscle metabolism.

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