Role of adenosine in regulating the heterogeneity of skeletal muscle blood flow during exercise in humans

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1Turku PET Centre, Departments of 2Clinical Physiology and Nuclear Medicine, 3Medicine, and 4Anesthesia and Intensive Care, University of Turku, Turku, Finland; 5IM Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, St. Petersburg, Russian Federation; 6Institute of Sports Medicine, Bispebjerg Hospital, Copenhagen, Denmark; 7Department of Exercise Science, Concordia University, Montreal, Canada; and 8Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

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Heinonen I, Nesterov SV, Kemppainen J, Nuutila P, Knuuti J, Laitio R, Kjaer M, Boushel R, Kalliokoski KK. Role of adenosine in regulating the heterogeneity of skeletal muscle blood flow during exercise in humans. J Appl Physiol 103: 2042–2048, 2007. First published September 20, 2007; doi:10.1152/japplphysiol.00567.2007.—Evidence from both animal and human studies suggests that adenosine plays a role in the regulation of exercise hyperemia in skeletal muscle. We tested whether adenosine also plays a role in the regulation of blood flow (BF) distribution and heterogeneity among and within quadriceps femoris (QF) muscles during exercise, measured using positron emission tomography. In six healthy young women, BF was measured at rest and then during three incremental low and moderate intermittent isometric one-legged knee-extension exercise intensities without and with theophylline (P < 0.001). Adenosine receptor blockade did not have any effect on mean bulk BF or BF heterogeneity within and among muscles from the mean values of the four QF compartments. Mean BF in the whole QF and its four parts increased, and heterogeneity decreased with workload both without and with theophylline (P < 0.001). Adenosine receptor blockade did not have any effect on mean bulk BF or BF heterogeneity among the QF muscles, yet blockade increased within-muscle BF heterogeneity in all four QF muscles (P = 0.03). Taken together, these results show that BF becomes less heterogeneous with increasing exercise intensity in the QF muscle group. Adenosine seems to play a role in muscle BF heterogeneity even in the absence of changes in bulk BF at low and moderate one-leg intermittent isometric exercise intensities.

posterior emission tomography; perfusion distribution; quadriceps; theophylline

SKELETAL MUSCLE BLOOD FLOW increases linearly with incremental power output and metabolic demand due to regulatory signals that elicit a close coupling between blood flow and muscle oxygen consumption (1, 31). Apart from the bulk blood flow level, blood flow distribution and its heterogeneity within and among muscles also plays an important role in matching nutrient and oxygen delivery to the local needs of the tissue (18).

Blood flow heterogeneity has been associated with the efficiency of oxygen and nutrient delivery and, ultimately, tissue oxygenation and is therefore a functionally essential parameter (10, 27). Anatomical structure of the vascular tree is one important determinant of skeletal muscle blood flow distribution, but also physiological factors play a role since, for instance, exercise affects blood flow distribution and its heterogeneity (12, 17, 20). It is, however, not well known how local blood flow is distributed within human muscle with increases in exercise intensity or the mechanisms regulating flow heterogeneity. The regulation of muscle blood flow is believed to be mainly the result of the interplay between neural vasconstrictor activity and locally released vasoactive substances, with the latter considered being more important after the first few contractions (4, 7). Many substances have been proposed to contribute to local vasodilation in exercising muscle, but despite numerous studies the precise mechanisms regulating skeletal muscle blood flow remain poorly understood (15, 35).

Adenosine, which mediates its effects via four different G protein-linked receptors (A1, A2A, A2B, and A3), is believed to be an important regulator of skeletal muscle blood flow, especially during exercise when blood flow and metabolism are mismatched. Interstitial adenosine concentration, measured by the microdialysis technique, increases in the exercising human muscle at a rate associated with the intensity of muscle contraction and the magnitude of muscle blood flow (5, 6, 13, 21, 22), although some concerns have been raised that tissue injury would also be involved (34). However, the studies attempting to resolve the question of whether adenosine regulates local vasodilation in skeletal muscle during muscular contractions are controversial. Several animal (25, 29, 30, 39) and human (24, 32) studies, but not all (14, 19), show that adenosine is involved in the regulation of muscle blood flow during exercise. Furthermore, it has been speculated that local metabolic vasodilator agents, such as adenosine, may have more impact on flow heterogeneity than on global blood flow (3, 8, 35).

With this background, we sought to test 1) how blood flow distribution and its heterogeneity changes with increasing exercise intensity within and among quadriceps femoris (QF) muscles and 2) what role adenosine plays in the regulation of muscle blood flow distribution and its heterogeneity. We utilized the one-legged intermittent isometric knee-extension exercise model that is the most suitable for positron emission tomography (PET) studies, while the muscle pumping pattern of dynamic exercise can be mimicked. The role of adenosine was investigated by nonselective adenosine receptor blockade with intravenous infusion of theophylline in the same protocol.
that has previously been shown to be effective in blocking adenosine receptors and induce a significant reduction in limb blood flow during exercise (38). We hypothesized that if the primarily role of adenosine is to decrease skeletal muscle blood flow heterogeneity as suggested previously (9), blood flow heterogeneity would be increased during exercise under the theophylline treatment.

METHODS

Subjects. Seven healthy, nonobese, and nonsmoking women were recruited into this study. However, arterial catheterization failed in one subject, and thus blood flow quantification was possible only in six subjects (age 24.0 ± 2.6 yr, height 171.5 ± 2.3 cm, weight 62.1 ± 4.6 kg, body mass index 21.0 ± 1.1 kg/m², maximal oxygen uptake 2.4 ± 0.2 l/min). The purpose, nature, and potential risks were explained to the subjects before they gave their written, informed consent to participate. The possibility of pregnancy was excluded by a pregnancy test before participation. The subjects were not taking any medication other than possible oral contraceptives. Subjects were studied in the early follicular phase of their menstrual cycle to minimize any confounding effects of reproductive hormones on the control of blood flow (26). Subjects also fasted overnight, and they avoided caffeine-containing beverages such as coffee, tea, and cola drinks for at least 48 h before the experiments. Exhaustive exercise was also avoided 24 h before the study. The study was performed according to the Declaration of Helsinki and was approved by the Ethical Committee of the Hospital District of South-Western Finland.

Study design. The study design is shown in Fig. 1. The experiment day started with a MRI study to obtain anatomical references from the femoral region. Thereafter, the PET studies were conducted to measure muscle blood flow. Before the PET experiments, the antecubital vein was cannulated for tracer and theophylline administration. For blood sampling, a radial artery cannula was placed under local anesthesia in the contralateral arm. Subjects were then moved to the PET scanner, and similar blood flow measurements as those without theophylline were performed at three exercise intensities. ECG and heart rate were continuously monitored during the PET measurements, and blood pressure was measured continuously with an automatic apparatus (Omron M5-1, Omron Healthcare, Europe Hoofddorp, The Netherlands). Maximal oxygen uptake was determined within 3 wk from the PET measurements using an electrically braked cycle ergometer (Ergoline 800 S, Biot, Germany) with direct respiratory measurements (Medikro 202; Medikro, Kuopio, Finland) using an incremental protocol with 2-min ramps at 25 W starting from 50 W.

Measurements of blood flow. Positron-emitting tracer (15O-H2O) was produced as previously described in detail (38). The ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN) was used in three-dimensional mode for image acquisition. This PET scanner provides an axial field of view of 15.5 cm and produces 63 transaxial slices with a slice thickness of 2.4 mm. Photon attenuation was corrected by 5-min transmission scans performed both at the beginning of the first and second PET study. All data were corrected for dead time, decay, and measured photon attenuation, and the images were reconstructed into a 256 × 256 matrix. Thus the voxel size in the present study was 2.6 × 2.6 × 2.4 mm and blood flow was measured in voxels of 16 mm³. For the measurement of blood flow, on average 455 ± 34 MBq of 15O-H2O was injected intravenously, and after 20 s, dynamic scanning began for 240 s (48 × 5-s frames) for measurements at rest and for 140 s (28 × 5 s) for measurements during exercise. During exercise, the tracer infusion was started after 5 min of exercise. Arterial blood was continuously withdrawn during the PET scans with a pump to determine the blood time-activity curve. The radioactivity concentration in arterial blood was measured using a two-channel online detector system (Scanditronix, Uppsala, Sweden) that was cross-calibrated with an automatic gamma counter (Wizard 1480 3′′, Wallac, Turku, Finland) and the PET scanner. The delay- and dispersion-corrected arterial radioactivity was used as an input function. The autoradiographic method and one-compartment model with 200-s (rest measurements) and 90-s (exercise measurements) integration times were applied to calculate blood flow voxel by voxel in the parametric blood flow images (20, 36). The method has been previously compared against plethysmography (28) and the steady-state PET method (36) in humans and against the microsphere method in dogs (11) with high accuracy in measuring regional muscle blood flow in vivo.

Regions of interest and calculation of blood flow heterogeneity. Regions of interest surrounding the QF and its four different compartments were drawn into four subsequent cross-sectional planes in the upper part of the thigh region. The localization of different muscle regions was based on the individual magnetic resonance images. The muscle areas were defined as muscle vastus intermedius (VI), muscle rectus femoris (RF), muscle vastus medialis (VM), and muscle vastus lateralis (VL). Blood flow values of each voxel (16-mm³ piece of muscle) from the defined ROIs were extracted from parametric blood flow images. The obtained values from the four planes were pooled, and the mean and SD of the voxel values were calculated for the

Exercise at three different workloads (50, 100, and 150 N), and each load lasted 10 min with 5-min breaks in between. At all three intensities, blood flow was measured after 5 min of exercise. Instructions about maintaining the exercise intensity and rest and exercise periods were provided to the subject by light-emitting diode lights and also cued by specific sounds from the dynamometer. After the first section of the study, the subjects were removed from the PET scanner, and a 90-min rest period followed.

Theophylline was then infused into the antecubital vein and continued for 30 min. The infused dose was 6.9 mg/kg body wt (total dose 422 ± 34 mg, range 382–480 mg), which has been previously shown to decrease muscle blood flow during exercise and thus effectively block adenosine receptors (32). After the cessation of theophylline infusion, the subjects were allowed to rest for another 30 min. Thereafter, the subjects were positioned back into the PET scanner, and similar blood flow measurements as those without theophylline were performed at three exercise intensities. ECG and heart rate were continuously monitored during the PET measurements, and blood pressure was measured continuously with an automatic apparatus (Omron M5-1, Omron Healthcare, Europe Hoofddorf, The Netherlands). Maximal oxygen uptake was determined within 3 wk from the PET measurements using an electrically braked cycle ergometer (Ergoline 800 S, Biot, Germany) with direct respiratory measurements (Medikro 202; Medikro, Kuopio, Finland) using an incremental protocol with 2-min ramps at 25 W starting from 50 W.

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![Fig. 1. Study design. Before the PET studies, magnetic resonance imaging (MRI) for femoral region was performed. PET measurements were started after transmission scan at rest, and blood flow was measured (arrows) first at baseline. Thereafter, blood flow was measured during one-legged intermittent isometric exercise with increasing workloads (50, 100, and 150 N, respectively) with 15-min resting periods between the bouts of exercise. The same exercise protocol and blood flow measurements were repeated after 90 min of rest and theophylline infusion.](http://jap.physiology.org/10.1152/jappl.00065.2007)
whole QF and separately for each four muscles. As an index of blood flow heterogeneity (relative dispersion) within the muscles, coefficient of variation (CV) of the voxel values of all five regions (QF, VL, RF, VM, and VL) were calculated separately as $CV = SD/mean \times 100\%$. Heterogeneity among the QF muscles was calculated as above but, instead of from voxel values, from the four mean blood flow values.

**Statistical analysis.** Statistical analyses were performed using SAS/STAT statistical software (version 8.2, SAS institute, Cary, NC). The effects of exercise and theophylline on mean and $CV$ of blood flow in the whole QF was tested using two-way ANOVA for repeated measurements (exercise intensity and theophylline as factors). The effects of exercise and theophylline on mean and $CV$ of blood flow in the four muscles of the QF was tested using three-way ANOVA for repeated measurements (exercise intensity, theophylline, and muscle as factors). If a significant main effect(s) was found, pairwise differences were identified using the Tukey-Kramer post hoc procedure. The significance level was set at $P \leq 0.05$. Results are given as means ± SD.

**RESULTS**

**Blood pressure, heart rate, and rate pressure product.** At baseline, heart rate was $68 \pm 10$ beats/min, systolic blood pressure $121 \pm 11$ mmHg, diastolic blood pressure $80 \pm 12$ mmHg, mean arterial blood pressure $94 \pm 10$ mmHg, and rate pressure product (RPP) $6,385 \pm 1,500$ mmHg·beats$^{-1}$·min$^{-1}$. During exercise, all of these parameters increased with increasing exercise intensity (Table 1). Adenosine receptor blockade with theophylline had no significant effect on any of these parameters at rest (heart rate $72 \pm 20$ beats/min, systolic blood pressure $123 \pm 15$ mmHg, diastolic blood pressure $79 \pm 13$ mmHg, mean arterial blood pressure $93 \pm 13$ mmHg, and RPP $6,935 \pm 3,064$ mmHg·beats$^{-1}$·min$^{-1}$; $P$ value in all was not significant) or during exercise (Table 1).

**Blood flow and flow heterogeneity within and among QF muscles.** At baseline, mean blood flow in the whole QF was $4.4 \pm 1.8$ ml·100 g$^{-1}$·min$^{-1}$ (Fig. 2A). Mean blood flow at rest was at the same level in VI ($5.3 \pm 2.1$ ml·100 g$^{-1}$·min$^{-1}$), VM ($4.3 \pm 1.2$ ml·100 g$^{-1}$·min$^{-1}$) and VL ($4.2 \pm 2.0$ ml·100 g$^{-1}$·min$^{-1}$). In RF ($3.5 \pm 1.6$ ml·100 g$^{-1}$·min$^{-1}$; $P = 0.02$), blood flow was significantly lower than in VI but not compared with the other two muscles.

Mean blood flow in the whole QF (Fig. 2A) and its four compartments (Fig. 3B) increased with workload similarly both without and with theophylline. Adenosine receptor blockade with theophylline did not have any significant effect on mean bulk blood flow in the whole QF ($P = 0.5$) or its compartments ($P = 0.2$).

![Fig. 2. Mean blood flow (A) and flow heterogeneity (B) in the whole quadriceps femoris (QF) muscle group at rest and during exercise without (shaded bars) and with theophylline (open bars). Blood flow heterogeneity in QF at rest (B) did not differ statistically from the values during exercise ($P = 0.06$), and theophylline did not affect mean blood flow or its heterogeneity at the level of whole QF. **$P < 0.001$ compared with preceding exercise intensity. ***$P < 0.001$ compared with rest (A) and exercise 1 and 2 (B).**](http://jap.physiology.org/content/jap/103/6/2044/F2)

However, there were differences in blood flow increases between the four muscles with respect to the specific intensities of exercise (Fig. 3A). In VI, blood flow increased significantly both from the lowest to modest ($P < 0.001$) and from the modest to the highest ($P < 0.001$) exercise intensity. On the other hand, in RF, blood flow increased significantly only from the lowest to modest ($P < 0.01$) but not from modest to the highest ($P = 1.0$) exercise intensity. In contrast to this, in VM and VL, blood flow did not increase significantly from the lowest to modest ($P = 0.73$ and $P = 0.08$, respectively) but increased significantly from modest to the highest ($P < 0.001$ in both) exercise intensity. In all muscles, blood flow increased

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**Table 1. Heart rate, blood pressure, and related calculations during exercise**

<table>
<thead>
<tr>
<th></th>
<th>Without Theophylline</th>
<th>With Theophylline</th>
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<tbody>
<tr>
<td></td>
<td>EXE 1</td>
<td>EXE 2</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>75±12</td>
<td>81±12*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>94±6</td>
<td>95±7</td>
</tr>
<tr>
<td>BPs, mmHg</td>
<td>121±8</td>
<td>123±12</td>
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<tr>
<td>BPD, mmHg</td>
<td>81±5</td>
<td>81±6</td>
</tr>
<tr>
<td>RPP, mmHg·beats$^{-1}$·min$^{-1}$</td>
<td>7,163±1,522</td>
<td>7,744±1,794*</td>
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</tbody>
</table>

Values are means ± SD. EXE, exercise protocol; HR, heart rate; MAP, mean arterial pressure; BPs, systolic blood pressure; BPD, diastolic blood pressure; RPP, rate pressure product. *$P < 0.05$ compared with previous exercise intensity. †$P < 0.05$ compared with EXE 1. ‡$P < 0.01$ compared with EXE 1 and EXE 2.
significantly from the lowest to the highest exercise intensity ($P < 0.001$).

At baseline, blood flow heterogeneity within (across) the whole QF was $50 \pm 11\%$ (Fig. 2B). At the individual muscle level, there were no differences in blood flow heterogeneity between the four QF muscles at rest, except between VI and VM (CV in VI $36 \pm 7\%$ and in VM $54 \pm 15\%; P = 0.02$) (CV in RF $41 \pm 11\%$ and in VL $45 \pm 15\%$). In control exercise across all intensities, blood flow heterogeneity within the whole QF decreased (Fig. 2B), but out of the four individual parts of QF, within-muscle heterogeneity decreased only in the VL (Fig. 3B). This differentiation of responses was due to a dominant effect in VL. During exercise with adenosine receptor blockade blood flow heterogeneity was unchanged from control exercise in the whole QF ($P = 0.35$; Fig. 2B), but in the four individual parts of QF, heterogeneity increased slightly but significantly ($P = 0.03$; Fig. 3B). Most of the increase in within-muscle heterogeneity seemed to be confined to the lowest exercise intensity ($P = 0.08$).

Acute low-intensity exercise increased between-muscle region heterogeneity compared with rest ($P = 0.05$; Fig. 4). However, mean blood flow heterogeneity among the four muscles decreased (blood flow became more uniform among the four muscles) with increasing (higher) exercise intensity (Fig. 4). This was mainly due to a larger increase in mean blood flow in VL (124% from lowest to highest exercise intensity) than in the other three muscles (VI 55%, $P = 0.02$; RF 66%, $P = 0.06$; VM 58%, $P = 0.03$). Theophylline did not affect blood flow heterogeneity among the four QF muscles when exercise intensity was increased ($P = 0.8$).

**DISCUSSION**

Recent human studies have shown that acute exercise affects skeletal muscle blood flow heterogeneity, but the potential mechanisms behind this have remained poorly understood. We tested the role of adenosine in this regulation by measuring muscle blood flow heterogeneity during nonselective blockade...
already engaged in exercise (33), and this is the most likely reason for decreased blood flow heterogeneity observed in VL only, as well as for decreased variability among the QF muscles. Due to the more uniformly distributed mean blood flows between the four QF muscles at baseline, blood flow was less heterogeneous at rest than during the two lowest exercise intensities, but this difference disappeared when exercise intensity was increased further. Thus it seems that blood flow within a large muscle group becomes more uniform with increasing exercise intensity when more muscle fibers are activated to produce more force and flow is directed also to the newly activated, more superficial muscle fibers. Taken together, acute exercise with increasing exercise intensities indeed affects skeletal muscle blood flow and its heterogeneity within the human muscle, but it has not been known whether specific vasoregulatory substances such as adenosine are involved in this phenomenon, and this was also tested in the present study.

The effects of adenosine receptor blockade on muscle blood flow and its heterogeneity during exercise. Several animal studies have shown that adenosine contributes to vasodilation during muscular contractions in skeletal muscle (25, 29, 30, 39), although there are also some exceptions (14, 19). In humans, unspecific adenosine receptor blockade with theophylline has also been shown to reduce femoral blood flow ~20% during a single exercise bout employing a similar model, measured by ultrasound Doppler at an exercise intensity corresponding to ~48% of peak power output, suggesting thereby that adenosine plays an important role in the regulation of the mean (limb) level of muscle blood flow (32). This reduced blood flow is compensated for by increasing oxygen extraction to meet the similar metabolic demands of muscle without and with adenosine receptor blockade (32). Contrary to our hypothesis, adenosine receptor blockade with theophylline did not influence mean bulk blood flow either in QF or in its different compartments in the present study. This may be due to the low and moderate exercise intensities used in the present study compared with that of Rådegran and Calbet (32), since it is generally thought that the contribution of adenosine to exercise hyperemia increases when blood flow and metabolism are mismatched, as is the case during strenuous exercise. In fact, favoring this assumption, Martin and colleagues (24) recently showed that unspecific adenosine receptor blockade diminished blood flow (~15%) only at the highest workload during forearm exercise. Another difference between our study and previous human studies is the blood flow method. Although ultrasound imaging of blood flow in a large feed artery of the forearm (24) or thigh (32) has been used in the previous studies, we employed PET imaging of muscle tissue, enabling direct measurement of regional inter- and intramuscular perfusion. Furthermore, previous human studies have been performed during dynamic exercise, whereas intermittent isometric mode of exercise was used in the present study to minimize the possible artifacts of moving objects in imaging. It can also be questioned whether adenosine receptors were effectively blocked with the intravenously infused unspecific adenosine receptor blocker theophylline. However, the same methods as in the study of Rådegran and Calbet (32) regarding blockade was used in the present study, and in their study a reduction in blood flow during blockade was observed. Thus it is assumed that we were able to block adenosine receptors to same extent.

Blood flow heterogeneity with the increasing exercise intensity. An important aspect in the present study is the effect of increases in exercise intensity on blood flow and its heterogeneity in the whole QF and its compartments and on the distribution of blood flow between the muscles. It was shown in the present study that blood flow heterogeneity in the whole QF decreases with increasing workload. This can be mainly explained by the decreased variability in mean blood flow values of the individual muscles of QF with the increasing exercise intensity that was further mainly explained by a larger increase in blood flow in VL than in the other muscles (toward the values observed in the three other muscles). This could reflect that VL was also proportionally activated the most in this exercise model when exercise intensity was increased. Interestingly, VL was also the only individual muscle of QF in which heterogeneity was significantly decreased from the lowest to the highest exercise intensity. It has previously been shown that, when exercise intensity is increased, blood flow is directed to newly recruited muscle fibers rather than to fibers
Accordingly, the differences in blood flow distribution we observed between conditions must have been due to adenosine receptor blockade. This pattern seemed, however, to be confined only to the lowest exercise intensity.

The role of vasoactive substances in the regulation of local blood flow in skeletal muscle and blood flow heterogeneity and how they are linked to the signals of the metabolic status and demands of muscle have been poorly understood. Emerging evidence, including our present and previous studies (16), suggests that vasoactive compounds regulate both bulk limb flow and also local microvascular blood flow in skeletal muscle and can thereby function to match local delivery of oxygen to metabolic demand. It has been speculated already years ago that local metabolic vasodilator agents, such as adenosine, may have more impact on blood flow heterogeneity rather than global flow (3, 8, 35), but the direct evidence for that has been lacking. The results of the present study support the view that adenosine serves mainly to decrease the heterogeneity of intramuscular flow distribution (in this exercise model), as suggested previously (9). In the present study, within-muscle blood flow heterogeneity was increased locally in QF muscles during adenosine receptor blockade despite no changes in mean blood flow in four QF muscles. This may imply that theophylline, by inhibition of phosphodiesterase enzymes, had an effect of increasing flow locally within some regions of different muscles and, by blocking the action of adenosine, decreasing flow in other regions. Additionally, adenosine receptor blockade did not influence the distribution of blood flow between the four QF muscles, which also supports the locality of the effects of adenosine.

As mentioned, theophylline had the largest effect on blood flow heterogeneity during the lowest workload in four muscles of QF, and the effect seemed to diminish when the exercise intensity was increased. Combining this finding to previous findings (24, 32) of the largest influence of adenosine on bulk blood flow at the highest intensities in humans, it can be concluded that adenosine may be more important in matching local muscle blood flow than the mean level of flow at lower exercise intensities, whereas at higher intensities adenosine also affects bulk blood flow. Furthermore, despite its effects on blood flow heterogeneity locally in the muscles of QF during low exercise intensity, our study supports the view proposed by Martin et al. (23) that adenosine may not be obligatory for exercise hyperemia, at least during low exercise intensities, which reflects the redundancy of blood flow regulation. This means that other regulators may compensate in the absence of locally acting adenosine, although it is believed that the influence of adenosine on exercise hyperemia increases with increasing exercise intensity. Yet it cannot be excluded that theophylline itself affected the modestly increased local heterogeneity in the present study since it has been observed that theophylline itself can induce slight vasodilation at baseline and during low exercise intensities (32, 37) by producing an increase in intracellular cyclic AMP due to the nonselective inhibition of phosphodiesterase enzymes (2). Moreover, the possibility exists that the activation patterns of working muscles were altered to some extent at the lowest exercise intensity without and with theophylline treatment, which could have also affected heterogeneity. However, this seems not to be the case since theophylline did not change mean blood flows among QF muscles in any exercise intensity. Finally, one possible limitation in our study is the lack of time-control experiments without theophylline. Therefore, it is unknown whether the relatively long experiment day itself would have affected the results.

In conclusion, there are two novel findings in the present study. First, this study demonstrates that skeletal muscle blood flow heterogeneity decreases with increasing exercise intensity due to newly activated muscle mass and decreased mean blood flow variability between muscles engaged in exercise. Second, adenosine receptor blockade with theophylline increases local skeletal muscle blood flow heterogeneity modestly and does not reduce bulk blood flow during exercise, which suggests that adenosine plays only a minor role in the control of muscle blood flow during low and moderate exercise intensities. Thus our findings suggest that adenosine may play a more important role in local microvascular vasodilation and flow heterogeneity, and thus potentially coordinating localized flow to muscle metabolic demands in an intensity-dependent manner rather than altering mean bulk blood flow in contracting skeletal muscle in humans.

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