ORIGINAL ARTICLE

The effect of acute exercise with increasing workloads on inactive muscle blood flow and its heterogeneity in humans

Ilkka Heinonen · Dirk J. Duncker · Juhani Knuuti · Kari K. Kalliokoski

Abstract The distribution of blood flow between active and inactive skeletal muscles has been sparsely studied in humans. Here we investigated non-exercising leg blood flow in six healthy young women during intermittent isometric one leg knee extension exercise with increasing workloads. Positron emission tomography was used to measure blood flow in hamstring muscles of the exercising leg, and whole thigh muscles as well as its knee extensor and hamstring compartment of the resting leg. Mean blood flow to the hamstrings of the exercising leg (5.8 ± 2.6 ml/100 g/min during the highest exercise workload) and whole thigh muscle of the resting leg (7.1 ± 3.8 ml/100 g/min) did not change significantly from rest (4.0 ± 0.7 and 4.7 ± 1.9 ml/100 g/min, respectively) to exercise, but flow heterogeneity increased substantially at increasing workloads. Importantly, during the highest exercise workload, mean blood flow in the knee extensors of the resting leg decreased (5.5 ± 3.0 ml/100 g/min at rest and 3.4 ± 2.0 ml/100 g/min during exercise, $p < 0.01$) while flow heterogeneity increased ($28 \pm 8\%$ at rest and $83 \pm 26\%$ during exercise, $p < 0.05$). Conversely, in hamstring muscles of the resting leg blood flow increased from 3.9 ± 1.0 ml/100 g/min at rest to 11.5 ± 6.8 ml/100 g/min during exercise ($p < 0.05$) while flow heterogeneity increased from 30 ± 7 to $58 \pm 19\%$ ($p < 0.05$). In conclusion, while mean whole thigh muscle blood flow of the resting leg remains at resting level during one leg exercise of the contralateral leg, redistribution of blood flow between muscle parts occurs within the thigh. Based on previous studies, nervous constraints most probably act to cause this blood flow distribution.

Keywords Blood flow · Inactive muscles · Exercise · Humans

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Introduction

Due to the finite amount of circulating blood volume and pumping capacity of heart, a proper distribution of blood flow between different organs is of utmost importance during vigorous exercise when energy demand of many locomotor muscles increases substantially (Laughlin et al. 1996, 2011). Regional vasodilation within the active skeletal muscle is mostly mediated by metabolic vasodilation, which results in nearly 90% of available cardiac output being delivered to the exercising muscles during maximal exercise (Laughlin et al. 1996, 2011). Many animal studies indicate that regional distribution of cardiac output is also regulated by systemic vasoconstriction of non-exercising muscles, but due to the methodological constraints, this has

remained sparsely studied in humans. Largely undefined are also the possible changes in inactive muscle blood flow heterogeneity in response to exercise (Heinonen et al. 2010a, b, 2011). Blood flow heterogeneity is a, functionally, essential parameter as it has been associated with efficacy of oxygen and nutrient delivery and, ultimately, tissue oxygenation (Duling and Damon 1987). The heterogeneity of skeletal muscle blood flow in humans decreases from rest to exercise, and with increasing exercise intensities if only exercise intensity is high enough (Heinonen et al. 2007). Conversely, heterogeneity of blood flow within inactive muscle groups of the exercising leg usually increases during exercise (Heinonen et al. 2010a, b, 2011). It is, however, largely unknown how human muscle blood flow behaves in the contralateral non-exercising leg and its different muscle groups while the ipsilateral leg is exercising, and how increasing exercise workloads affect this behavior.

In the present study, we therefore measured mean blood flow and blood flow heterogeneity by positron emission tomography in non-exercising m. quadriceps femoris and posterior hamstring muscles during one-leg intermittent isometric knee-extension exercise with increasing exercise workloads. The results indicate that while mean whole thigh muscle blood flow of the resting leg remains similar to the resting values, marked redistribution of blood flow between and within inactive muscle groups occurs within the thigh.

Methods

Subjects

Six healthy, non-obese, and non-smoking women were recruited in this study (age 24.0 ± 2.6 years, height 171.5 ± 2.3 cm, weight 62.1 ± 4.6 kg, BMI 21.0 ± 1.1 kg/m^2, $V\mathrm{O}_{2\max}$ 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. 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 prior to 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.

The same subjects served as subjects in our previous study where exercising muscle blood flow central hemodynamics (blood pressure and heart rate responses) were studied and reported (Heinonen et al. 2007).

Study design

The experiment day started with a magnetic resonance imaging (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 administration. For blood sampling for blood flow calculations, a radial artery cannula was placed under local anesthesia in the contralateral arm. Subjects were then moved to the PET scanner with the femoral region in the gantry and the left leg was fastened to a dynamometer (Diter Petkin, Oy Diter-Elektroniikka Ab, Turku, Finland) at a knee angle of 40°. After a transmission scan, basal blood flow was measured while the subject was lying at rest. Thereafter, the subject was allowed to briefly familiarize with the one-legged intermittent isometric knee-extension exercise model. The exercise model consisted of 1-s isometric contractions of the knee extensors followed by 2-s pause interval. The subject performed 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 workloads, blood flow was measured after 5 min of exercise. Instructions about maintaining the exercise workload, and rest and exercise periods were provided to the subject by LED lights and also cued by specific sounds from the dynamometer. ECG and heart rate was continuously monitored during the PET measurements and blood pressure was measured continuously with an automatic apparatus (Omron, M5-1, Omron Healthcare, Europe B.V. Hoofddorf, The Netherlands).

Measurements of blood flow

Positron-emitting tracer (^{15}O-H$_2$O) was produced as previously described in detail (Sipilä et al. 2001). The ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN, USA) was used in 3D 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 16 mm^3. During exercise, blood flow was measured after 5 min of exercise onset. Arterial blood was continuously withdrawn during the PET scans with a pump to determine the blood time-activity curve. The radioactiv-

ity 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-sec (rest measurements) and 90-sec (exercise measurements) integration times were applied to calculate blood flow voxel by voxel into parametric blood flow images (Heinonen et al. 2007; Ruotsalainen et al. 1997). Radio-water (^{15}O-H_2O) is widely used for the measurement of blood flow in many tissues in the human body including brain, myocardium, liver, kidney, and skeletal muscle. The method has been validated against microsphere method in skeletal muscle in dogs (Fischman et al. 2002).

Regions of interest and calculation of blood flow heterogeneity

Regions of interest (ROIs) surrounding the posterior hamstring muscles of the working leg and resting leg, whole thigh musculature of the resting leg, and knee extensors, thus m. quadriceps femoris (QF) of the resting leg were drawn into seven subsequent cross-sectional planes of parametric blood flow image. The localization of different muscle regions was based on the individual MRI images. Blood flow values of each voxel (16-mm^3 piece of muscle) from the defined ROIs were extracted from parametric blood flow images. The obtained values from the seven planes were pooled and the mean and SD of the voxel values were calculated. As an index of blood flow heterogeneity (relative dispersion) within the muscles, coefficient of variation (CV) of the voxel values of all muscle regions was calculated separately as CV = SD/mean × 100%.

Statistical analysis

Statistical analyses were performed using SAS/STAT statistical software (version 9.2, SAS institute Inc., Cary, NC, USA). The effects of exercise and its intensities on mean blood flow and its heterogeneity were tested using one-way ANOVA for repeated measurements (exercise intensity as a factor). If a significant main effect(s) was found, pair wise differences were identified using the Tukey–Kramer post hoc procedure. The significance level was set at $P < 0.05$. Results are reported as means ± SD.

Results

Responses of heart rate and blood pressure of exercise workloads are shown in Table 1. There was a modest

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

|	REST	EXE1	EXE2	EXE3
HR (bpm)	68 ± 10	75 ± 12	81 ± 12	90 ± 15*
MAP (mmHg)	94 ± 10	94 ± 6	95 ± 7	97 ± 3
SAP (mmHg)	121 ± 11	121 ± 8	123 ± 12	126 ± 12
DAP (mmHg)	80 ± 12	81 ± 5	81 ± 6	82 ± 7

HR heart rate, *MAP* mean arterial pressure, *SAP* systolic blood pressure, *DAP* diastolic blood pressure

* $p < 0.05$ compared to REST

increase in heart rate due to local knee-extension exercise, but no significant changes in blood pressure. As previously published (Heinonen et al. 2007), incremental exercise resulted in increases in skeletal muscle blood flow in the active quadriceps muscle from 4.4 ± 1.8 ml/min/100 g to 37.6 ± 6.1 ml/min/100 g (highest exercise intensity), while blood flow heterogeneity was minimally affected (50 ± 11% at rest and 48 ± 3% at the highest level of exercise). During this exercise protocol, as shown here, mean blood flow in the inactive posterior hamstring muscles of the exercising leg did not change significantly ($p = 0.1$) from rest to exercise (Fig. 1a), however, blood flow heterogeneity markedly increased (Fig. 1b). Similarly, whole thigh muscle blood flow in the non-exercising contralateral leg remained similar to resting levels during one leg knee extension exercise ($p = 0.47$, Fig. 2a), but blood flow heterogeneity increased (Fig. 2b). However, in the inactive m. quadriceps femoris of the contralateral non-exercising leg mean blood flow slightly decreased, while flow heterogeneity significantly increased, from rest to the highest exercise workload (Fig. 3a, b). Conversely, in the posterior hamstring muscles of the resting contralateral leg mean blood flow slightly increased during the highest exercise workload compared to rest (Fig. 4a), while flow heterogeneity also increased (Fig. 4b).

Discussion

The present study shows that whole thigh muscle blood flow in the contralateral non-exercising leg during one leg knee extension exercise remains similar to pre-exercise resting levels. Novel finding is that a small increase in posterior hamstring muscle blood flow during the highest exercise workload was accompanied by a simultaneous decrease in blood flow to m. quadriceps femoris in the same resting leg. In addition, in both these muscle groups, as well as in the inactive posterior hamstring muscles of the exercising leg, blood flow heterogeneity increased from rest to exercise and increased progressively with each exercise
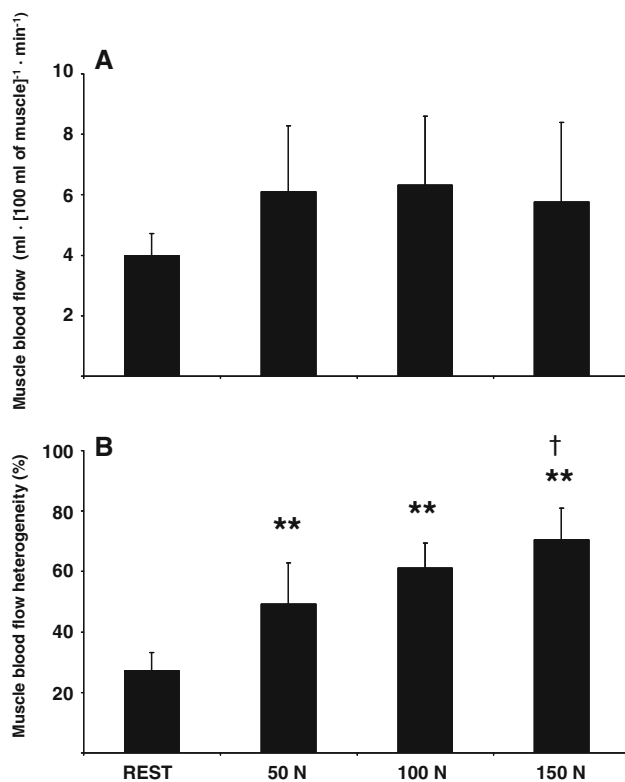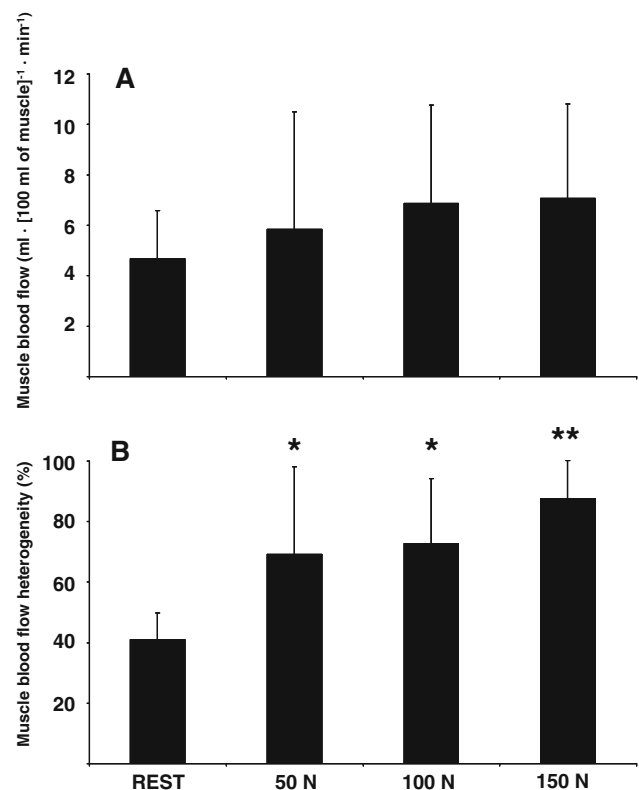
Fig. 1 Mean blood flow (**a**) and blood flow heterogeneity (**b**) in inactive posterior hamstring muscles of the exercising leg. **$p \leq 0.01$ compared to rest, †$p < 0.05$ compared to 50 N. Despite unchanged mean blood flow, flow heterogeneity increased from rest to exercise in posterior muscles

Fig. 2 Mean blood flow (**a**) and blood flow heterogeneity (**b**) of the whole thigh muscles in resting contralateral leg. *$p < 0.05$, **$p < 0.01$ compared to rest. Whole thigh mean blood flow was unchanged, but heterogeneity increased from rest to exercise

level. The implications of these findings will be discussed in depth.

Whole thigh and posterior hamstring muscle blood flow

We have previously reported that working muscle blood flow increased (~tenfold) along increases with exercise workload in this specific intermittent isometric knee-extension exercise model, while its blood flow heterogeneity decreased (by ~13%) from the lowest to the highest exercise workload (Heinonen et al. 2007). Now we report novel findings regarding the mean blood flow levels and blood flow distribution in the non-exercising contralateral leg while the ipsilateral leg is performing intermittent isometric knee extensor exercise at increasing exercise workload.

We have previously observed that inactive muscle blood flow in the working limb remains close to resting levels during dynamic knee-extension exercise, but flow heterogeneity increases substantially (Heinonen et al. 2010a, b, 2011). This phenomenon was suggested to reflect neuronal constraints of the sympathetic branch to blunt flow increments in the areas other than working muscles (Heinonen et al. 2010b). The present study extends those findings by showing that blood flow heterogeneity is further enhanced

when exercise workload is increased. Another interesting finding in the present study is that the simultaneous decrease of blood flow in the non-exercising m. quadriceps femoris compensated for the slight increase in posterior hamstring muscle blood flow, so that whole thigh muscle blood flow was minimally affected.
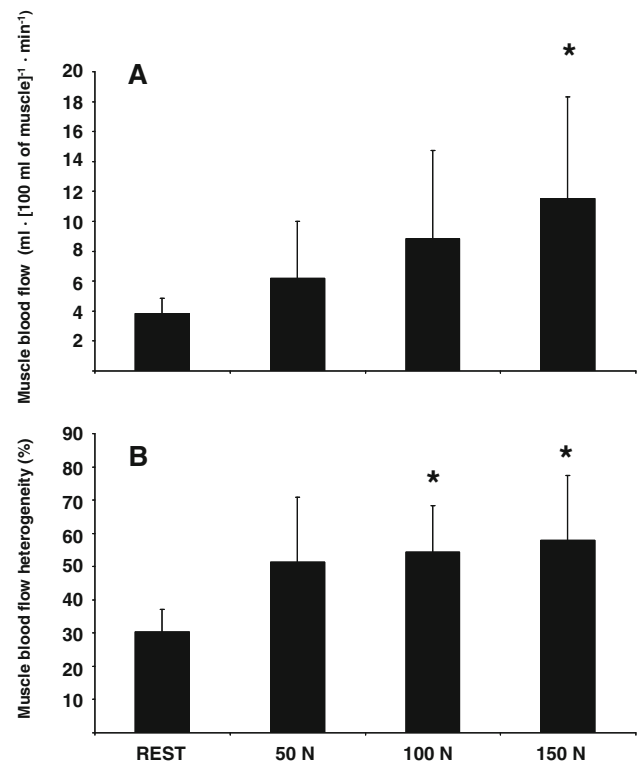
The increase in posterior hamstring muscle blood flow was rather unexpected as subjects were encouraged to contract only their knee extensors and let all other body parts remain in a resting state. These findings suggest that despite this encouragement involuntary activation of posterior hamstring muscles of the contralateral non-exercising leg may inadvertently have occurred in an attempt to stabilize body posture and maximize force production of the working knee extensors, thereby causing a small increase in posterior muscle blood flow. Since blood flow to the knee extensors of the non-exercising leg decreased (and similarly, by 30–40%, in all four heads of QF, data not shown), whole thigh blood flow remained unchanged from rest. These findings are in agreement with the observations on leg blood flow (Mortensen et al. 2009), and forearm blood flow (Bevegard and Shepherd 1966). The decrease in flow is also sometimes seen as decreased oxygen saturation values in the 'resting' leg (Freyschuss and Strandell 1968),
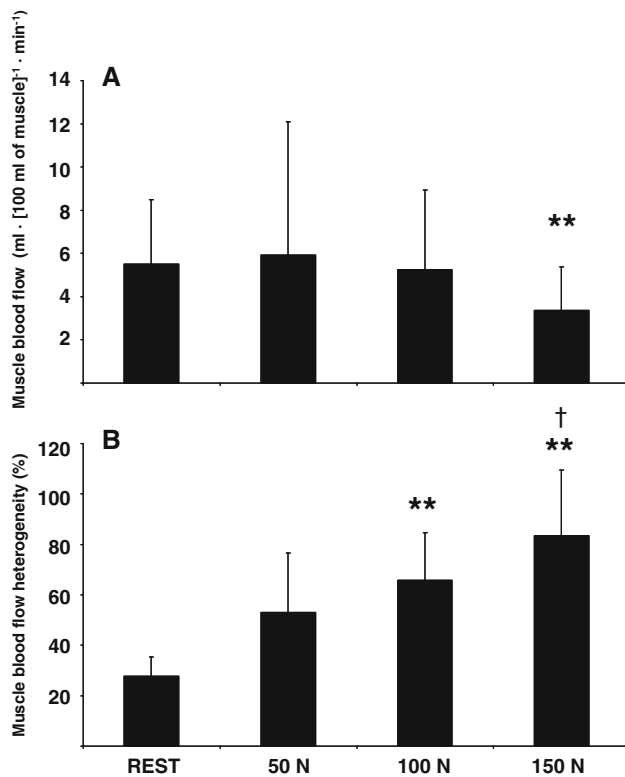
Fig. 3 Mean blood flow (**a**) and blood flow heterogeneity (**b**) in inactive m. quadriceps femoris muscle of the resting contralateral leg. ******$p < 0.01$ compared to rest, †$p < 0.05$ compared to 50 N. Mean blood flow decreased and flow heterogeneity increased during the highest exercise intensity compared to rest

Fig. 4 Mean blood flow (**a**) and blood flow heterogeneity (**b**) in inactive posterior hamstring muscles of the resting contralateral leg. *$p < 0.05$ compared to rest. Both mean blood flow and flow heterogeneity increased from rest to exercise

which could indicate either increased oxygen consumption or increase in vascular resistance of the limb. However, this increase in vascular resistance of the limb can be regarded as an acute effect of blood flow distribution since it has recently been shown by Padilla et al. (2011) that during prolonged exercise (~60 min), conduit (brachial) artery blood flow increases due to the thermal influences.

Our results fit well with the studies that in the early 1990s aimed at elucidating the controversy whether isometric contraction of the forearm evokes vasoconstriction or vasodilation in the muscles of the contralateral arm. In a study in which EMG activity of the resting arm was recorded, decrease in forearm vascular resistance indicating vasodilation was noted, which was associated with a substantial increase in EMG (Cotzias and Marshall 1993). Importantly, however, when subjects were allowed to see their EMG activity and try to control their resting arm as relaxed as possible, vascular resistance increased in that arm, indicating vasoconstriction (Cotzias and Marshall 1993). Thus, isometric contraction of the forearm evokes primarily vasoconstriction in the muscles of the contralateral forearm, but this response may be overcome by muscle vasodilation occurring secondary to unintended muscle contraction that we also observed in resting posterior mus-

cles, or as part of the alerting response to acute stress (Cotzias and Marshall 1993). Moreover, these responses of isometric forearm contraction appear to be a function of time, as in a study by Jacobsen et al. (1994), vascular resistance in the contralateral resting arm first decreased transiently at the onset of exercise, followed by a return to baseline at the end of exercise. This finding is also suggestive of neurogenic vasodilator mechanisms contributing to flow increase in the early phase of exercise (Sanders et al. 1989), though straightforward neurogenic vasodilation in humans still remains debatable (Joyner and Halliwill 2000; Joyner and Dietz 2003). However, Jacobsen et al. (1994) also importantly showed that in the leg vasculature, in the absence of an increase in EMG activity vascular resistance remains unchanged during the first minute of sustained handgrip exercise, but increases to exceed the baseline by the end of exercise (Jacobsen et al. 1994). Although our exercise model was isometric but intermittent in nature that was also fairly demanding and sustained steady state for 10 min (blood flow measurements during the last 5 min), also the results of Jacobsen et al. are well in accordance with our findings in the present study.

It is also important to note that despite increased mean blood flow in these posterior hamstring muscles found in

the present study, flow heterogeneity also increased. This means that in some parts of the muscle flow was indeed enhanced, but not uniformly, and in some areas flow was actually unchanged or even reduced. Fairly similar observations were also made from the posterior muscles of the exercising leg, with the difference that mean blood flow remained similar to the resting baseline. We interpret also these findings to represent nervous constraints of the sympathetic activation to blunt flow increments in non-exercising muscles and muscle parts, the effect that is likely the most readily seen in resting contralateral knee extensors.

Blood flow in non-working knee extensors

Although vascular resistance was not consistently elevated in resting QF muscle from rest to exercise and further with increasing exercise workload, it is likely that reduced blood flow and increased blood flow heterogeneity stems from the nervous constraints to distribute blood flow to active muscles, despite the fact that for instance heart rate increased only modestly in response to exercise, which is typical for many studies applying short duration isometric (though sustainable) contractions of limited muscle groups (Hansen et al. 1994). In this respect it is interesting, as also highlighted by Thomas (2010), that Moore et al. (2010) recently introduced a novel concept suggesting that there can be constitutive α-adrenergic activity that is below the threshold to cause vasoconstriction, but importantly appears to be able to reduce conductive vasodilation in inactive muscles during exercise. Alternatively, or complementarily with SNA effect, changes in vasomotion that are generally regarded to be non-neural and non-humoral but inherent to vascular wall smooth muscle cells (Pradhan and Chakravarthy 2011; Haddock and Hill 2005), could have also contributed to the response. However, either of these possibilities could not have been directly answered in the present study, but warrant further investigations, such as direct recordings of MSNA, which we did not have access to in the present study. Moreover, the phenomenon could also be directly elucidated in resting humans by direct intra-arterial infusion of noradrenaline that should increase muscle blood flow heterogeneity, or drug such as phentolamine that should cause more uniform blood flow by releasing the tonic resting constriction.

Although responses of SNA to different organs likely vary, it is generally considered that SNA activation is triggered similarly to all muscular vascular beds in response to exercise. Supporting this idea, Hellsten's group recently reported that release of noradrenaline (NA), as measured directly by microdialysis from muscle interstitial space, increases essentially similarly in working and non-working knee extensor muscles during one leg exercise (Mortensen et al. 2009), though NA blood spillover has been reported to be higher in exercising compared to resting leg (Savard et al. 1987, 1989). Taken together, these findings suggest that the release of NA could indeed be greater in exercising muscle, but compensated for by an increased washout resulting in similar interstitial concentrations. Nevertheless, after the release local sympatholytic factors then modulate the action of NA in the working muscle, while such actions are not present in non-working QF and NA elicits vasoconstriction. In this respect our study extends these findings importantly since we here document that blood flow in non-working knee extensors, likely due to these direct local actions of NA, decreases and heterogeneity increases during the highest exercise workload.

The findings discussed above can also be extended to the working knee extensors, where flow heterogeneity usually tends to decrease with increasing exercise workload, but does not decrease below resting levels (Heinonen et al. 2007). If the exercise intensity is low, it may even increase from rest (Kalliokoski et al. 2000; Heinonen et al. 2007). Although distribution of muscle blood flow is affected by the heterogeneity of muscle fibers recruitment, the spatial distribution of motor units (and their fibers) as well as the heterogeneity of their metabolic demands, one could also think that the most uniform blood flow would be the best possible for the exchange of oxygen and other nutrients in every condition of exercise. However, now that we observed that flow heterogeneity was increased in non-working knee extensors, and others have shown MSNA effects being uniformly transferable to all muscular vascular beds, there is likely also similar inherent inclination to increase flow heterogeneity in working muscle seen in respective resting muscle. This results in net outcome that is increased or unchanged flow heterogeneity from rest to exercise, while in the absence of this influence exercising blood flow heterogeneity would likely be much more uniform and lower compared to rest. It is our reasoning that the primary purpose of this response is to direct the flow to only those muscle parts and fibres that are truly engaged in exercise. It is thus collectively highly prominent that increased sympathetic nervous activity triggered with higher force production indeed plays a role to improve the distribution of muscle perfusion during exercise, both between muscles, as well as within exercising muscle.

In conclusion, we report in the present study that there is redistribution of blood flow between major muscle groups within the thigh of the resting leg during high intensity one leg knee extensor exercise. Whole thigh muscle blood flow does not change from rest despite blood flow increases in posterior hamstring muscles since blood flow is reduced in knee extensors. Decreased mean blood flow and increased flow heterogeneity in non-exercising knee extensors during the highest exercise workload suggest that nervous constraints of blood flow likely maximize blood flow

distribution for effective oxygen diffusion and exercise performance.

References

Bevegard BS, Shepherd JT (1966) Reaction in man of resistance and capacity vessels in forearm and hand to leg exercise. J Appl Physiol 21:123–132

Cotzias C, Marshall JM (1993) Vascular and electromyographic responses evoked in forearm muscle by isometric contraction of the contralateral forearm. Clin Auton Res 3:21–30

Duling BR, Damon DH (1987) An examination of the measurement of flow heterogeneity in striated muscle. Circ Res 60:1–13

Fischman AJ, Hsu H, Carter EA, Yu YM, Tompkins RG, Guerrero JL, Young VR, Alpert NM (2002) Regional measurement of canine skeletal muscle blood flow by positron emission tomography with H2(15)O. J Appl Physiol 92:1709–1716

Freyschuss U, Strandell T (1968) Circulatory adaptation to one- and two-leg exercise in supine position. J Appl Physiol 25:511–515

Haddock RE, Hill CE (2005) Rhythmicity in arterial smooth muscle. J Physiol 566:645–656

Hansen J, Thomas GD, Jacobsen TN, Victor RG (1994) Muscle metaboreflex triggers parallel sympathetic activation in exercising and resting human skeletal muscle. Am J Physiol 266:H2508–H2514

Heinonen I, Nesterov SV, Kemppainen J, Nuutila P, Knuuti J, Laitio R, Kjaer M, Boushel R, Kalliokoski KK (2007) Role of adenosine in regulating the heterogeneity of skeletal muscle blood flow during exercise in humans. J Appl Physiol 103:2042–2048

Heinonen I, Kemppainen J, Kaskinoro K, Peltonen JE, Borra R, Lindroos MM, Oikonen V, Nuutila P, Knuuti J, Hellsten Y, Boushel R, Kalliokoski KK (2010a) Comparison of exogenous adenosine and voluntary exercise on human skeletal muscle perfusion and perfusion heterogeneity. J Appl Physiol 108:378–386

Heinonen IH, Kemppainen J, Kaskinoro K, Peltonen JE, Borra R, Lindroos M, Oikonen V, Nuutila P, Knuuti J, Boushel R, Kalliokoski KK (2010b) Regulation of human skeletal muscle perfusion and its heterogeneity during exercise in moderate hypoxia. Am J Physiol Regul Integr Comp Physiol 299:R72–R79

Heinonen I, Saltin B, Kemppainen J, Sipila HT, Oikonen V, Nuutila P, Knuuti J, Kalliokoski K, Hellsten Y (2011) Skeletal muscle blood flow and oxygen uptake at rest and during exercise in humans: a pet study with nitric oxide and cyclooxygenase inhibition. Am J Physiol Heart Circ Physiol 300:H1510–H1517

Jacobsen TN, Hansen J, Nielsen HV, Wildschiodtz G, Kassis E, Larsen B, Amtorp O (1994) Skeletal muscle vascular responses in human limbs to isometric handgrip. Eur J Appl Physiol Occup Physiol 69:147–153

Joyner MJ, Dietz NM (2003) Sympathetic vasodilation in human muscle. Acta Physiol Scand 177:329–336

Joyner MJ, Halliwill JR (2000) Sympathetic vasodilatation in human limbs. J Physiol 526(Pt 3):471–480

Kalliokoski KK, Kemppainen J, Larmola K, Takala TO, Peltoniemi P, Oksanen A, Ruotsalainen U, Cobelli C, Knuuti J, Nuutila P (2000) Muscle blood flow and flow heterogeneity during exercise studied with positron emission tomography in humans. Eur J Appl Physiol 83:395–401

Laughlin MH, Korthuis RJ, Duncker DJ, Bache RJ (1996) Control of blood flow to cardiac and skeletal muscle during exercise. In: Rowell LB, Shepherd JT (eds) Handbook of Physiology. A Critical, comprehensive presentation of physiological knowledge and concepts. section 12: exercise: regulation and integration of multiple systems, American Physiological Society, New York, pp 705–769

Laughlin MH, Davis, Secher NH, van Lieshout JJ, Arce A, Simmons GH, Bender SH, Padilla J: Bache RJ, Merkus D, Duncker DJ (2011) Peripheral circulation. In: Baldwin, Wagner, Eddington (eds) Comprehensive physiology; handbook of physiology, American Physiological Society, Wiley & sons, Inc

Moore AW, Bearden SE, Segal SS (2010) Regional activation of rapid onset vasodilatation in mouse skeletal muscle: regulation through adrenoreceptors. J Physiol 588:3321–3331

Mortensen SP, Gonzalez-Alonso J, Nielsen JJ, Saltin B, Hellsten Y (2009) Muscle interstitial ATP and norepinephrine concentrations in the human leg during exercise and ATP infusion. J Appl Physiol 107:1757–1762

Padilla J, Simmons GH, Vianna LC, Davis MJ, Laughlin MH, Fadel PJ (2011) Brachial artery vasodilation during prolonged lower-limb exercise: role of shear rate. Exp Physiol 96(10):1019–1027

Pradhan RK, Chakravarthy VS (2011) Informational dynamics of vasomotion in microvascular networks: a review. Acta Physiol (Oxf) 201:193–218

Ruotsalainen U, Raitakari M, Nuutila P, Oikonen V, Sipila H, Teras M, Knuuti MJ, Bloomfield PM, Iida H (1997) Quantitative blood flow measurement of skeletal muscle using oxygen-15- water and PET. J Nucl Med 38:314–319

Sanders JS, Mark AL, Ferguson DW (1989) Evidence for cholinergically mediated vasodilation at the beginning of isometric exercise in humans. Circulation 79:815–824

Savard G, Strange S, Kiens B, Richter EA, Christensen NJ, Saltin B (1987) Noradrenaline spillover during exercise in active versus resting skeletal muscle in man. Acta Physiol Scand 131:507–515

Savard GK, Richter EA, Strange S, Kiens B, Christensen NJ, Saltin B (1989) Norepinephrine spillover from skeletal muscle during exercise in humans: role of muscle mass. Am J Physiol 257:H1812–H1818

Sipilä HT, Clark JC, Peltola O, Teräs M (2001) An automatic [15O]-H2O production system for heart and brain studies. J Label Comp Radiopharm 44:S1066–S1068

Thomas GD (2010) Ready, set, flow! But how does the flow know where to go? J Physiol 588:3633–3634