Do vasoregulatory mechanisms in exercising human muscle compensate for changes in arterial perfusion pressure?

Kathryn L. Walker, Natasha R. Saunders, Dennis Jensen, Jennifer L. Kuk, Suzi-Lai Wong, Kyra E. Pyke, Erin M. Dwyer, and Michael E. Tschakovsky

Human Vascular Control Laboratory, School of Kinesiology and Health Studies and Department of Physiology, Queen’s University, Kingston, Ontario, Canada

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Walker KL, Saunders NR, Jensen D, Kuk JL, Wong SL, Pyke KE, Dwyer EM, Tschakovsky ME. Do vasoregulatory mechanisms in exercising human muscle compensate for changes in arterial perfusion pressure? Am J Physiol Heart Circ Physiol 293: H2928–H2936, 2007. First published August 17, 2007; doi:10.1152/ajpheart.00576.2007.—We tested the hypothesis that vasoregulatory mechanisms completely counteract the effects of sudden changes in arterial perfusion pressure on exercising muscle blood flow. Twelve healthy young subjects (7 female, 5 male) lay supine and performed rhythmic isometric handgrip contractions (2 s contraction/2 s relaxation 30% maximal voluntary contraction). Forearm blood flow (FBF; echo and Doppler ultrasound), mean arterial blood pressure (arterial tonometry), and heart rate (ECG) were measured. Moving the arm between above the heart (AH) and below the heart (BH) level during contraction in steady-state exercise achieved sudden ~30 mmHg changes in forearm arterial perfusion pressure (FAPP). We analyzed cardiac cycles during relaxation (FBFrelax). In an AH-to-BH transition, FBFrelax increased immediately, in excess of the increase in FAPP (~69% vs. ~41%). This was accounted for by pressure-related distension of forearm resistance vasculature [forearm vascular conductance (FVCrelax) increased by ~19%]. FVCrelax was restored by the second relaxation. Continued slow decreases in FVCrelax stabilized by 2 min without restoring FBFrelax. In a BH-to-AH transition, FBFrelax decreased immediately, in excess of the decrease in FAPP (~37% vs. ~29%). FVCrelax decreased by ~14%, suggesting pressure-related passive recoil of resistance vessels. The pattern of FVCrelax was similar to that in the AH-to-BH transition, and FBFrelax was not restored. These data support rapid myogenic regulation of vascular conductance in exercising human muscle but incomplete flow restoration via slower-acting mechanisms. Local arterial perfusion pressure is an important determinant of steady-state blood flow in the exercising human forearm.

vasodilation; vasoconstriction; muscle blood flow; myogenic; metabolism

MUSCLE BLOOD FLOW IN EXERCISE is a function of local muscle perfusion pressure and vascular conductance. With the onset of exercise, there is a need for increased oxygen delivery to meet the metabolic demand of the muscle. In submaximal small-muscle-mass exercise, where arterial oxygen content does not change, muscle blood flow determines oxygen delivery and steady-state muscle blood flow is linearly related to exercise intensity (21, 22). This is commonly described as a matching of muscle blood flow to metabolic demand and is thought to be accomplished via a combined effect of a number of vasodila-
tory mechanisms [for review, see Clifford and Hellsten (4)] and a potential contribution of the muscle pump, depending on exercise intensity and mode (17, 25, 34).

Manipulations of arterial oxygen content have previously been shown to result in compensatory adjustments in exercising human muscle blood flow to maintain oxygen delivery for a given exercise intensity (7). In contrast, the response of vasoregulatory mechanisms to altered perfusion pressure-induced changes in oxygen delivery may be less effective (31, 36, 37). Wright et al. have demonstrated that force output of electrically stimulated contracting human hand muscle is sensitive to changes in perfusion pressure evoked either by altering hand position relative to heart level (36) or via metaboreflex-induced elevation in systemic arterial blood pressure (37). Similar alterations in electrically stimulated canine muscle force output when oxygen delivery is systematically altered (9) would suggest that in the experiments of Wright et al., exercising muscle blood flow was altered with perfusion pressure and vasoregulatory mechanisms did not fully compensate. Unfortunately, muscle blood flow measurements were not possible in those studies.

In a previous investigation, we demonstrated that forearm exercising muscle blood flow changes in proportion to lower-limb metaboreflex-induced elevations in systemic arterial pressure (31). This occurred both when the elevated arterial pressure was established before the onset of forearm exercise or progressively during steady-state exercise and suggests that arterial perfusion pressure is an important determinant of exercising muscle blood flow. However, that experiment was designed to examine interactions of local vasodilator and sympathetic vasoconstrictor influences, which prevented examination of perfusion pressure effects per se.

With this as a background, we tested the hypothesis that vasoregulatory mechanisms completely counteract the effects of sudden changes in arterial perfusion pressure on exercising muscle blood flow. To do this, we rapidly altered forearm arterial perfusion pressure (FAPP) during continuous forearm exercise by changing arm position between above and below heart level. The results are the first to demonstrate the existence of an initial rapid and slower secondary vasoregulatory response to altered perfusion pressure in exercising human skeletal muscle. However, these responses do not fully compensate for changes in arterial perfusion pressure.
METHODS

Subjects

Twelve healthy, young Queen’s University students (7 males, 5 females) volunteered for this study. After receiving a complete verbal and written description of the experimental protocol and potential risks, each subject provided signed consent to the testing procedures. The study was approved by the Health Sciences Human Research Ethics Board at Queen’s University, which operates under the terms of the Declaration of Helsinki.

Experimental Design

Forearm exercise. Forearm exercise consisted of rhythmic isometric handgrip squeezing (2 s contraction/2 s relaxation duty cycle) at 30% of maximal voluntary contraction (MVC). This represents a “moderate” intensity of exercise (i.e., subjects are able to perform this exercise for prolonged period without any difficulty or changes in steady-state hemodynamics). On arrival in the laboratory, subjects lay supine and were instrumented for measurement of hemodynamic responses. They were then asked to perform three MVCs separated by an adequate recovery time, and the largest was chosen to represent MVC. During the exercise trials, one channel of the data-acquisition display on the data-collection computer showed the handgrip force output relative to the desired target level of 30% MVC. This feedback combined with a signal beep was used by the subjects to maintain consistent handgrip force output and timing. The exercise was performed continuously throughout manipulations in arm position relative to heart level (see Fig. 1).

Manipulation of forearm arterial perfusion pressure. Figure 1 illustrates the use of changes in arm position relative to heart level (mid-forearm ∼21 cm above vs. ∼21 cm below heart level, as in Ref. 25) to achieve alterations in local FAPP. Briefly, the arm was supported on a hinged arm rest attached to a pulley system, which allowed an experimenter to raise or lower the arm during the 2-s period of an isometric handgrip contraction. Contraction severely limited arterial inflow (see Fig. 2) and has been demonstrated to result in maximal forearm venous emptying (25). We therefore reasoned that on relaxation the local forearm vasculature would suddenly be exposed to a new pressure environment dependent on the change in hydrostatic column. The arm positions in this experimental setup created a difference of −30 mmHg in the local FAPP between arm positions, as demonstrated previously (25).

Experimental protocol. Figure 1 illustrates the two experimental protocols, performed in sequence (the order was counterbalanced across subjects). Briefly, subjects lay supine with their arm positioned either above or below heart level. Following 1 min of resting baseline, the rhythmic, isometric handgrip exercise began. After 5 min, arm position was changed during a 2-s contraction period. Careful attention was paid by the subjects to maintain contraction intensity and duration at all times. Transitions in arm position were performed every 4 min during a 2-s contraction period (see Figs. 1 and 2). Following the cessation of the first protocol, a 20-min rest period occurred before the onset of the second protocol.

Data Acquisition and Analysis

Measurement of hemodynamic responses. Subjects were instrumented for beat-by-beat measurements as follows. Heart rate was obtained via standard CMs placement of ECG electrodes. Mean arterial blood pressure was measured on the contralateral arm supported at heart level via arterial tonometry (Colin 7000; Trudel Medical, London, ON, Canada). FAPP was then determined by adding or subtracting the pressure equivalent in millimeters of mercury of the measured hydrostatic column (mid-forearm to heart level), associated with arm-above- or arm-below-heart positions, from the blood pressure measured continuously at heart level. Brachial artery
springs, CO) at 200 Hz. Data-acquisition system (Chart 4.0; ADInstruments, Colorado performed continuously and were collected on a personal computer between arm-above and arm-below positions. These measures were probe, and the quality of the Doppler signal were unaltered configuration of the arm, the position of the Doppler ultrasound blood flow during forearm exercise, and it was ensured that the has extensive experience with the measurement of brachial artery before another attempt to move the arm was made. Our laboratory original position and was allowed to reestablish a steady state arm-position transition, the arm was immediately returned to the positions. In cases where the signal was compromised during an artery lumen. With this setup, a clear Doppler signal could be the right elbow. The angle of the transducer crystal relative to the skin surface was 45°. The ultrasound gate was set to insonate the entire ultrasonography (Vingmed System 5; GE Medical Systems). Briefly, a 4-MHz flat probe was fixed to the skin velocimetry (Multigon 500B Transcranial Doppler; Multigon Indus- mean blood flow velocity (MBV) was measured with pulsed Doppler velocimetry (Multigon 500B Transcranial Doppler; Multigon Industries, Yonkers, NY). Briefly, a 4-MHz flat probe was fixed to the skin over the brachial artery just proximal to the antecubital fossa region of the right elbow. The angle of the transducer crystal relative to the skin surface was 45°. The ultrasound gate was set to insonate the entire artery lumen. With this setup, a clear Doppler signal could be achieved at rest, during exercise, and in the transition between arm positions. In cases where the signal was compromised during an arm-position transition, the arm was immediately returned to the original position and was allowed to reestablish a steady state before another attempt to move the arm was made. Our laboratory has extensive experience with the measurement of brachial artery blood flow during forearm exercise, and it was ensured that the configuration of the arm, the position of the Doppler ultrasound probe, and the quality of the Doppler signal were unaltered between arm-above and arm-below positions. These measures were performed continuously and were collected on a personal computer data-acquisition system (Chart 4.0; ADInstruments, Colorado Springs, CO) at 200 Hz.

Brachial artery diameter measurements were performed immediately proximal to the site of the MBV measurements by using echo ultrasonography (Vingmed System 5; GE Medical Systems). Briefly, a 10-MHz linear probe was positioned over the brachial artery and a clear image of the vessel was obtained immediately before the last 30 s of each arm position to provide a diameter estimate for calculation of the steady-state forearm blood flow (FBF) during the relaxation phase (FBFrelax). It was not possible to obtain diameter measurements immediately following arm transition at the same time as velocity measurements, so diameter measures were again made following the first 10 contractions to confirm that diameter had not changed. It has been previously demonstrated (32) that these arm-position changes do not result in a change in brachial artery diameter. Diameter estimates were made from the average of three manual caliper placements on frozen-screen images of the artery during diastole. All measurements were made by the same operator in a given experiment.

The experiments were performed in a cool environment (room temperature, 18–20°C). To ensure minimal resting FBF to the skin, the forearm and hand were cooled with the temporary application of an ice pack (33) when necessary, before the onset of experiments. The ice pack was removed at least 5 min before the onset of any exercise, and FBF was confirmed to remain minimal during this time.

Assessment of vasoregulation. To understand how local FAPP affected the steady-state hemodynamic response, the following quantifications were performed. Steady-state exercising FBF was calculated by using the average MBV over an eight-duty-cycle section (~32 s) immediately before arm repositioning as FBF = MBV × 60 s × min⁻¹ × π × (brachial artery diameter/2)², where FBF is in milliliters per minute, MBV is in centimeters per second, and brachial artery diameter is in centimeters. The flow through the muscle when it is contracting is a function of the pressure gradient, the vascular conductance, and the mechanical effects of muscle contraction. These mechanical effects can clearly impede flow during contraction and might enhance flow during relaxation (the muscle-pump effect). The contribution of resistance-vessel caliber vs. muscle mechanical effects cannot be isolated when averaging blood flow across duty cycles. Therefore, because vascular conductance refers specifically to the state of dilation of resistance vessels, researchers have variously referred to flow/pressure calculations for contracting skeletal muscle as “apparent” (6, 14, 15, 24) or “virtual” (29, 30) conductance. Virtual forearm vascular conductance (FVCvirt) was calculated as FVCvirt = (FBF/FAPP) × 100, where FVCvirt is in milliliters per minute per 100 mmHg. Flow per 100 mmHg was used so that FVCvirt is quantitatively similar to the units for FBF.

To quantify vasoregulatory dynamics (vasodilation and vasoconstriction) in response to the change in FAPP, we examined the equivalent of a cardiac cycle in the relaxation phase between contractions that was unaffected by either muscle relaxation or contraction (see Fig. 2). FBFrelax and FAPP during the relaxation phase were used to calculate relaxed forearm vascular conductance (FVCrelax). We do not term this a virtual conductance because 1) we account for the local change in arterial blood pressure with altered arm position, 2) the cardiac cycle chosen is unaffected by potential immediate muscle relaxation-induced negative venous pressure or contraction-induced impedance, and 3) maintenance of the same contraction intensity.
across transitions in arm position means that there are no changes in the mechanical effects of contraction. Therefore, $FV_{C_{\text{relax}}}$ represents the contribution of resistance-vessel caliber to muscle blood flow independent of muscle mechanical effects and allows detection and quantification of potential immediate rapid, and delayed slower, vasoregulation.

The arterial pressure at the level of the exercising arm was used to calculate $FV_{C_{\text{relax}}}$ based on a rationale outlined previously (25). Briefly, with contractions the venous volume is continuously emptied. Thus, immediately on release of contraction, the effective local pressure gradient across the vascular bed has negligible venous pressure and can therefore be estimated by the local arterial pressure. In support of this rationale is the observation of immediate increases and decreases in FBF with increases and decreases in forearm position-induced FAPP.

There were two transitions from arm above to arm below in protocol 1 and two transitions from arm below to arm above in protocol 2. These respective pairs of transitions were assessed independently and were observed not to differ. Therefore, they were averaged together within each subject to provide a single representative response per subject for statistical analysis of the dynamic change when FAPP was altered.

**Statistical Analysis**

Assessment of the hemodynamic response to a change in arm position was evaluated with one-way repeated-measures ANOVA (SigmaStat 3.0; SPSS, Chicago, IL) across time within each of the arm-position transitions (above to below, below to above). The Holm-Sidak multiple pair-wise comparison procedure was used for post hoc identification of specific differences across time.

Comparison of the main effects of arm position and trial on steady-state hemodynamics [e.g., for arm-above-heart level across the two protocols (protocol 1: initial adjustment to steady-state exercise, return to arm-above-heart level; protocol 2: adjustment of arm position following adaptation to steady state in arm-below-heart level, second adjustment of arm position to arm above-heart-level)] were performed with two-way repeated-measures ANOVA (SigmaStat 3.0). Differences were further evaluated via the Holm-Sidak pair-wise multiple-comparison procedure. Significance in all instances was set at $P < 0.05$. Data are presented as means $\pm$ SE.

**RESULTS**

**Resting Forearm Hemodynamics**

At rest, FBF ($FBF_{\text{rest}}$) was $\sim 33\%$ higher in the arm-above-heart position ($63.7 \pm 8.5$ vs. $48.0 \pm 7.5$ ml/min, $P < 0.05$), whereas mean arterial pressure at heart level was also slightly (-5%) but significantly higher ($86.9 \pm 2.2$ vs. $82.5 \pm 2.7$ mmHg, $P < 0.05$).

**Maintenance of Exercise Intensity**

Figure 3 illustrates the exercise intensity for the five contractions immediately preceding and the five contractions immediately following a change in arm position. The exercise intensity across contractions was well maintained in the below-to-above heart level transition. There was a slight but statistically significant ($P < 0.05$) reduction in contraction intensity for the second and fifth contractions following transition from above to below heart level.

**Hemodynamic Adjustments to Changes in Arm Position**

Above to below heart level. Figure 4 presents the $FBF_{\text{relax}}$, FAPP, and $FV_{C_{\text{relax}}}$ during relaxation between contractions (see Fig. 2A) in response to the transition in arm position from above to below heart level. An immediate, substantial increase in $FBF_{\text{relax}}$ was observed on lowering of the arm ($P < 0.001$). This was out of proportion to the change in FAPP, such that the calculated $FV_{C_{\text{relax}}}$ also demonstrated an immediate increase ($P < 0.001$). Following the increase in local hydrostatic pressure contribution to FAPP with change in arm position, FAPP remained steady for the duration of the 4-min period of arm below heart.

By the second relaxation following arm lowering, $FBF_{\text{relax}}$ had dropped significantly from the level observed during the first relaxation ($P < 0.001$) but was still substantially elevated compared with steady-state arm-above before arm lowering ($P < 0.001$). $FV_{C_{\text{relax}}}$ by the second relaxation had returned to match that in the arm-above position before lowering of the arm ($P = 0.576$). Thereafter, both $FBF_{\text{relax}}$ and $FV_{C_{\text{relax}}}$ remained stable through to 39 s of exercise following arm lowering.

Measurements taken at 2 and 4 min following lowering of the arm demonstrated a further reduction in $FBF_{\text{relax}}$ from that at 39 s ($P = 0.019$ and $P = 0.045$, respectively). However, this level of $FBF_{\text{relax}}$ was still substantially elevated compared with steady-state arm-above-heart level before arm lowering. $FV_{C_{\text{relax}}}$ was also significantly reduced at 2 and 4 min after arm lowering vs. at 39 s ($P = 0.013$ and $P = 0.018$, respectively), and this level was also significantly below that in arm-above steady state immediately before arm lowering ($P = 0.010$ and $P = 0.014$, respectively).

Below to above heart level. Figure 5 presents the $FBF_{\text{relax}}$, FAPP, and $FV_{C_{\text{relax}}}$ between contractions (see Fig. 2B) in response to transition in arm position from below to above heart level. An immediate, substantial decrease in $FBF_{\text{relax}}$ was...
observed on raising of the arm \((P < 0.001)\). This was out of proportion to the change in FAPP, such that the calculated \(FVC_{\text{relax}}\) also demonstrated an immediate decrease \((P < 0.001)\). Following the decrease in local hydrostatic pressure contribution to FAPP with change in arm position, FAPP remained steady for the duration of the 4-min period of arm above heart.

By the third relaxation following arm raising, \(FBF_{\text{relax}}\) had returned to match that in the arm-below position before raising of the arm \((P = 0.892)\). Thereafter, no statistically significant changes in \(FVC_{\text{relax}}\) occurred through to 39 s after arm raising. However, at 2 min following arm raising, \(FVC_{\text{relax}}\) was elevated compared with steady-state arm below immediately before arm raising \((P = 0.001)\). At 4 min, \(FBF_{\text{relax}}\) was no longer statistically significantly different from steady-state arm-below-heart level immediately before arm raising \((P = 0.08)\).

**Steady-State Hemodynamics**

Figure 6 presents the steady-state hemodynamics in arm-above vs. arm-below positions. For FBF, there was a main effect for arm position \((P < 0.001)\) but no main effect of trial \((P = 0.215)\) or interaction of arm position with trial. This indicates a consistency in steady-state FBF within arm positions during repeated manipulations in arm position.

There was a main effect of arm position \((P < 0.001)\) on FAPP. However, there was no main effect of trial \((P = 0.545)\) or interaction between arm position and trial \((P = 0.947)\) for FAPP, indicating a consistency in systemic arterial pressure during repeated manipulations in arm position.

\(FVC_{\text{virt}}\) calculated by using the local FAPP also demonstrated a main effect for arm position \((P = 0.045)\) but no main...
effect of trial ($P = 0.899$) and no interaction between arm position and trial ($P = 0.755$). This indicates a consistency in FVC$_{\text{virt}}$ within arm positions during repeated manipulations in arm position. This is consistent with greater dilation under reduced perfusion-pressure conditions when the arm is above vs. below heart level.

**DISCUSSION**

The major novel findings of this study are as follows. First, immediate changes in FBF$_{\text{relax}}$ following a change in arm position during steady-state exercise exceeded changes in FAPP, consistent with an immediate transmural pressure-distension effect on resistance vessel caliber (FVC$_{\text{relax}}$) in exercising human skeletal muscle. A rapid restoration of FVC$_{\text{relax}}$ but not FBF$_{\text{relax}}$ occurred within seconds of this altered distension, consistent with a rapid myogenic vasoregulatory compensation that is able to restore FVC$_{\text{relax}}$ but not FBF. Second, a slower change in FVC$_{\text{relax}}$ occurred with maintained altered FAPP. However, substantial differences in steady-state FBF$_{\text{relax}}$ and FBF between arm positions remained. This effect was independent of whether steady state was achieved in a transition from rest to exercise or with transitions in arm position during steady-state exercise. These latter findings demonstrate that vasoregulatory mechanisms do not completely compensate for arterial perfusion pressure-induced changes in exercising muscle blood flow. Therefore, local arterial perfusion pressure is an important determinant of the steady-state muscle blood flow achieved at a given exercise intensity.

**Immediate Changes in Resistance Vessel Caliber with Altered FAPP: Evidence for a Mechanical Distension Effect**

Repositioning of the forearm between above- and below-heart levels during exercise changes both the pressure gradient for FBF and the transmural pressure within the forearm resistance vasculature. The repositioning of the forearm during the 30% MVC contraction phase was critical to isolating immediate effects of perfusion pressure on the forearm vasculature. A 30% MVC contraction empties venous volume regardless of arm position (25). This meant that from the relaxation phase immediately before vs. immediately after changing arm position, there would be no difference in venous pressure and the only change to the local pressure gradient for flow would be on the arterial side. Therefore, changes in FBF would have to reflect changes in arterial perfusion pressure and/or resistance vessel caliber (i.e., vascular conductance).

Examination of a single cardiac cycle during this relaxation phase allowed us to partition the contribution of perfusion pressure and vascular conductance to the change in FBF$_{\text{relax}}$. Examination of a single cardiac cycle during this relaxation phase allowed us to partition the contribution of perfusion pressure and vascular conductance to the change in FBF$_{\text{relax}}$. We have used this approach previously to understand the dynamic response of vasoregulatory mechanisms in isolation of mechanical muscle-pump effects (23, 25). This analysis revealed an immediate change in calculated FVC$_{\text{relax}}$ on contraction release that was in the same direction as the change in transmural pressure.

There are three possible explanations for this observation. First, it could be an active vasodilation. However, there was no change in contraction intensity or altered flow:metabolism imbalance during the 2-s contraction when arm position was changed compared with other contractions. Therefore, we believe this calculated change in FVC$_{\text{relax}}$ cannot be explained by active vasodilation. Second, it could be argued that much of the flow during relaxation did not cross the microcirculation and that the difference in flow through the brachial artery simply represented altered forearm arterial capacitance. However, any forearm arterial-volume reduction occurred with the contraction initiated in the previous arm position, so there could not have been differences in arterial capacitance between the relaxation immediately preceding vs. following the contraction during arm transition. A further argument against an arterial capacitance effect due to transmural pressure is that it would be maintained in the new arm position. Instead, we observed restoration of FVC$_{\text{relax}}$ within the next 1–2 relaxation phases. Therefore, we believe our data clearly demonstrate an immediate, transmural pressure-induced change in resistance-vessel distension with altered arm position, effectively altering forearm vascular conductance. Such a mechanical disten-
sion effect has been observed previously in isolated vessel preparations (3, 5).

**Evidence for Myogenic Vasoregulation in Exercising Muscle Vasculature**

A rapid (within a few seconds) myogenic response to altered vessel distension has been observed in isolated vessels (3, 5, 18) and in resting human skin and muscle vascular beds (12, 16). However, no previous studies have investigated the existence and nature of myogenic vascular control during continuous exercise in humans. We observed a rapid response to the immediate changes in resistance-vessel distension with altered arm position. This response restored FVCrelax within one relaxation when the arm was lowered or within two relaxations when the arm was raised. Because there was no change in contraction intensity, and only a very brief period of flow:metabolism mismatch during the previous relaxation, it is unlikely that this change in FVCrelax is due to metabolic (4) or muscle-activation vasoregulatory mechanisms (35). Instead, we interpret it to reflect a functional myogenic reflex response in the vascular bed of exercising human muscle. Because no further changes were observed up to at least 39 s following arm-position change, this myogenic response appears fully expressed in exercising human skeletal muscle in the initial few seconds.

Additionally, it must be remembered that during rhythmic muscle contractions, the resistance vessels are subjected to intermittent changes in interstitial pressure that are typically well above arterial pressure (11, 27). In this context, the observation of myogenic responsiveness in exercise means that resistance-vessel smooth muscle is able to sense and respond to altered transmural pressure that is evident only between contractions.

Previously, we observed that gradual elevation of systemic blood pressure during forearm exercise via calf ischemic exercise results in an increase in FBF proportional to the change in pressure (31) with no change in FVC. The current results suggest that these previous observations of maintained FVC while FAPP increased likely reflected a counteractive myogenic vasoconstriction to maintain resistance-vessel caliber.

**Matching of Muscle Blood Flow to Contractile Work**

Once the initial myogenic constriction had restored FVCrelax, FBFrelax remained elevated or reduced in proportion to the change in forearm arterial perfusion pressure until at least 39 s. By 120 s, FVCrelax had changed some more, indicating a further-delayed, slow vasoregulatory response. However, this only partially restored FBF, so that steady-state FBF in the arm-below position was ~33% higher than in the arm-above position (Fig. 6). This was the case whether exercise began in the arm-below or the arm-above position or whether the transition during exercise was from above to below vs. below to above.

We confirmed that the contraction intensity, duration, and duty cycle were the same in both arm positions (Fig. 3). Additionally, there was no change in forearm orientation between arm positions, so there was no change in mechanical advantage. Thus exercise intensity in terms of contractile work performed was maintained across arm positions. Therefore, these data demonstrate a dissociation between exercising muscle blood flow and exercise intensity due to alterations in arterial perfusion pressure.

Although forearm muscle oxygen consumption was not measured in this study, we believe this study also suggests that arterial perfusion pressure can alter blood flow:metabolism matching in this exercise model. We acknowledge that without measurements of forearm oxygen consumption, we cannot be certain that oxygen cost of forearm exercise was identical between arm positions. However, given that contractile work was not different between arm positions, a potential difference in oxygen cost would require that metabolic efficiency is acutely affected by arm position. Furthermore, the magnitude of this difference would have to equal that of the blood flow difference if blood flow:metabolism matching was maintained between arm positions. Therefore, to conclude that arterial perfusion pressure altered blood flow:metabolism matching requires only the assumption that a difference in metabolic efficiency between arm positions, should it even be possible, was less than the 33% difference in blood flow.

In this context, it has been shown that the oxygen cost per unit contractile work can be altered by changes in duty cycle (8) and 2) slowly increase out of proportion to the contractile work if the work rate is above the so-called lactate threshold (19, 20). However, at constant duty-cycle work rates below the lactate threshold, oxygen consumption reaches a steady-state level that does not change with time (1), i.e., there is no change in metabolic efficiency. The work rate chosen for this study was one that allowed the subjects to comfortably continue with exercise for the duration of the experiment (~20–30 min). It was not possible to conclusively demonstrate that this work rate was below the lactate threshold. However, even if it was above threshold, this effect would have occurred for both arm positions, and if blood flow:metabolism matching was occurring in response to such a change in metabolic efficiency, we would have observed a progressive increase in the steady-state blood flow with repeated arm transitions. This was not the case (see Fig. 6).

Additionally, Hughson et al. (10) measured forearm oxygen consumption during forearm exercise above vs. below heart level at two different work rates. In both cases the increase in oxygen consumption from rest to steady state was not statistically significant between arm positions. Closer examination of their Table 1 data indicate that these non-statistically significant increases in oxygen consumption were 16% less in the arm-below vs. arm-above position. This is in the opposite direction to the blood flow differences between arm positions in the present study and argues against the contention that a 33% higher blood flow when the arm is exercising below heart level in our study can be explained by a 33% higher oxygen consumption. Taking all of these points into consideration, we interpret the present study as demonstrating that blood flow:metabolism matching in exercising muscle can be altered by changes in arterial perfusion pressure. Indeed, evidence that blood flow:metabolism matching can be disrupted under certain exercise conditions has been found previously (for review see Ref. 13).

With sudden changes in steady-state exercising FBF, imbalance between metabolite production and washout from the interstitial space would be predicted by the metabolic hypothesis of exercise hyperemia to trigger metabolic vasoregulation...
(28). The results of this study lead us to speculate that this type of vasoregulatory control may not be adequate to deal with the effect of altered perfusion pressure. To our knowledge, no studies have looked at the change in interstitial vasodilator metabolites in response to altered exercising muscle blood flow during steady-state exercise. This would appear to be a critical test of metabolic vasoregulation in exercising muscle.

**Strengths and Limitations**

This study was able to detect the existence and temporal and magnitude characteristics of immediate rapid, and delayed slower, vasoregulatory mechanisms in vivo. However, this in vivo model can only discuss the resistance vasculature response as a whole, and it remains to be investigated via appropriate in situ preparations where in the resistance vasculature these responses occur.

Furthermore, the use of relaxation-specific measures of FBF and FAPP allowed us to uncover the dynamic response of the resistance vasculature, independent of mechanical muscle-con traction effects, and to reveal mechanical distension effects of altered perfusion pressure. We believe that this approach directly isolates rapid changes in resistance-vasculature caliber because it assesses flow at the time when veins have been emptied, and therefore venous resistance due to changes in distension cannot be involved. However, estimates of FAPP used a single measurement of the hydrostatic column. It is therefore acknowledged that, given the angle of the forearm, there was a distribution in FAPP around this mean estimate, and the actual FAPP perturbation and response at specific sites in the forearm vasculature varied around this mean. Furthermore, it is clear that the strength of the myogenic response varies along the length of the vascular tree (for review see Ref. 26), so the results here represent the integrated response of potentially different local responses across the entire forearm vascular bed.

Finally, measurements of brachial artery blood flow include muscle, skin, and nonnutritive blood flow. This is an unavoidable condition in vivo studies in humans and needs to be considered as a source of potential error in estimation of muscle blood flow changes. However, the following analysis identifies that the magnitude of this error would be quite small.

Resting blood flow in the forearm under the conditions we established in our laboratory (cool environment, cooled arm and hand) are typically in the 15- to 30-ml/min range. If the forearm and hand are not cooled, we often observe oscillations in FBF that are likely due to the rhythmic opening and closing of temperature-sensitive arteriovenous anastomoses in acral skin (2). Our experience is that these can result in up to fourfold increases in FBF, indicating that the capacity for skin blood flow is substantial. It is essential to eliminate these anastomosis-induced oscillations, and this is easily accomplished by skin cooling. We observed a steady, low resting FBF before initiating our exercise and in return to rest between our exercise trials. This confirms that these oscillations were eliminated.

It is not possible to identify how much of this low resting FBF is specific to the skin. The total forearm volume typical for young, healthy subjects in our study is 700–1,200 ml. Even if we use an extremely generous estimate that 50% of this is skin, this would translate to 15 ml/min. In exercise, we observed FBF during relaxation in the order of 400–700 ml/min depending on arm position and timing of position change. Thus 15 ml/min represents ~2–3% of the total flow. Given that total FBF changes by ~75% in the immediate transition from above to below heart (see Fig. 4), this would be at most ~12 ml/min for the skin. Therefore, we conclude that if prior cooling of the forearm and hand is employed, skin blood flow would not appear to affect our identification of vasoregulatory responses specific to the muscle.

**Conclusions**

In summary, this study is the first to demonstrate functional, rapid-acting myogenic vasoregulation in exercising human skeletal muscle. This mechanism reverses changes in resistance-vessel distension with altered perfusion pressure but does not restore exercising muscle blood flow. Additional, slower-acting mechanisms responsible for matching blood flow to exercise intensity effect only minor and incomplete adjustments in blood flow, such that steady-state exercising muscle blood flow is substantially dependent on forearm perfusion pressure.

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**REFERENCES**

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VASOREGULATION WITH ALTERED PERFUSION PRESSURE


