Dynamic response characteristics of local muscle blood flow regulatory mechanisms in human forearm exercise

Natasha R. Saunders, Kyra E. Pyke, and Michael E. Tschakovsky

School of Physical and Health Education and Department of Physiology, Queen’s University, Kingston, Ontario, Canada

Submitted 5 October 2004; accepted in final form 24 November 2004

Saunders, Natasha R., Kyra E. Pyke, and Michael E. Tschakovsky. Dynamic response characteristics of local muscle blood flow regulatory mechanisms in human forearm exercise. J Appl Physiol 98: 1286–1296, 2005. First published December 3, 2004; doi:10.1152/japplphysiol.01118.2004.—We sought to understand the nature of control mechanisms involved in the adaptation of exercising muscle hyperemia. Seven subjects performed rhythmic forearm exercise under two exercise conditions: small step 1 (step increase from rest to 40% peak forearm vascular conductance [FVC], in ml·min⁻¹·100 mmHg⁻¹) for 5 min followed by small step 2 (further increase to 80% peak FVC for 5 min), and large step (step increase from rest to 80% peak FVC for 5 min). FVC data were fit with a two-component exponential as appropriate. For the rapid phase I response, FVC dynamic response characteristics (time delay, time constant) were not affected by the magnitude of the work intensity increase when the transition began from rest, but were slower in the 40–80% transition. Rest-80% gain was greater than either rest-40% or 40–80% transitions but represented the same proportion of the phase I + phase II gain across all transitions (57 vs. 56 vs. 57%, respectively, P = 0.975). For the slower phase II response, dynamic response characteristics were not affected by the magnitude of the work intensity increase when the transition began from rest. The time constant was not altered when the transition began from exercise vs. rest. We conclude that 1) dynamic response characteristics of exercise hyperemia control mechanisms are not affected by the magnitude of work rate increase when forearm exercise is initiated from rest, 2) phase I but not phase II dynamic response characteristics are sensitive to baseline exercise intensity, and 3) the mechanisms contributing to phase I result in the same relative response magnitude, regardless of the size of the step increase in exercise intensity or the baseline from which it is initiated.

The factors that regulate adjustments in muscle blood flow to meet changes in exercising muscle metabolic demand have been studied extensively. Commonly, approaches to understanding vasoregulatory control of exercise hyperemia have focused on the contributions of various putative vasodilators to the magnitude of the steady-state response (8, 27, 29). There has also been some effort to examine contributors to vasoregulatory control during the adaptation of blood flow to steady state (30, 35). However, these approaches have also examined effects only in terms of magnitude.

The application of system control principles from engineering offers a unique approach to understanding the nature of the control systems governing physiological responses to exercise (16). While this approach has been used extensively to model gas-exchange kinetics and understand underlying control sys-

Received for publication September 4, 2004. Published online with DOI 10.1152/japplphysiol.01118.2004.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
between step increases of different magnitudes, starting from rest, and between step increases initiated from rest baseline vs. exercise baseline. Therefore, we tested the hypothesis that the adaptation of exercising muscle blood flow to step changes in work rate does not demonstrate dynamic linearity.

**METHODS**

**Subjects**

Seven healthy young subjects (3 female, 4 male) volunteered for this study. The mean age of the subjects was 24.4 ± 0.9 yr, height was 174.1 ± 2.6 cm, and weight was 78.7 ± 5.1 kg. After receiving a complete verbal and written description of the experimental protocol and potential risks, each subject provided signed consent to the testing procedures on a form approved by the Health Sciences Human Research Ethics Board at Queen’s University.

Subjects completed one visit for a peak vascular conductance assessment protocol and two visits to measure blood flow dynamics on 3 separate days, each separated by at least 72 h. Subjects were instructed to abstain from alcohol and caffeine ingestion and exercise for 12 h before the study. Each of the three testing sessions occurred at the same time of day for a given subject in a temperature-controlled room (20°C).

**Experimental Design**

**Subject monitoring.** Subjects assumed a supine posture with their left arm extended laterally at heart level for 20 min before beginning any dynamic handgrip exercise. Handgrip exercises involved raising and lowering a weight through a vertical distance of 5 cm by squeezing a handgripping device connected to a pulley system. Exercise took place at a contraction rate of 1:2-s work-rest schedule with concentric and eccentric contractions each contributing to ~50% of the work phase and with a metronome providing the timing.

Throughout each trial, heart rate (ECG), mean arterial blood pressure (MAP; arterial tonometry; Colin 7000, Trudell Medical, London, ON), and brachial artery mean blood velocity (MBV; pulsed Doppler velocimetry, Multigon 500B, Transcranial Doppler, Multigon Industries, Yonkers, NY) were collected continuously on a computer-based system at 200 Hz. Brachial artery MBV was measured from the spectra of a pulsed Doppler ultrasound signal. A flat probe with an operating frequency of 4 MHz was fixed to the skin over the brachial artery in the antecubital fossa region of the right elbow. The angle of the transducer crystal relative to the skin was 45°. The ultrasound gate was set to insonate the total width of the artery lumen. With this setup, a clear Doppler signal was maintained both at rest and during the handgrip exercise. The brachial artery was imaged continuously using two-dimensional B-mode ultrasound imaging with a linear 10-MHz probe (Vingmed System 5 GE Medical Systems) sited over the brachial artery immediately proximal to the pulsed Doppler probe. Brachial artery images were stored on videotape for offline analysis of diameters.

**Peak Vascular Conductance Assessment Protocol**

To assess peak forearm vascular conductance (FVC) and to determine the weight to be used for the step exercise tests, subjects completed a forearm exercise test with a progressive increase in work rate (Fig. 1A). The test involved recording 1 min of baseline MBV, arterial diameter, and MAP, followed by measurement of these variables after onset of contractions using the handgripping device with the pulley system. Weight was continuously added to the pulley system at a rate of ~1.33 kg/min, and subjects continued to exercise until they could no longer squeeze the handgripping device across the 5 cm and coordinate contractions with the metronome.

We identified the 40 and 80% peak FVC workloads from the ramp test protocol (see Fig. 2) to be the workloads used in our assessment of dynamic response characteristics of local muscle blood flow regulatory mechanisms. These workloads were chosen to 1) achieve an adequate step increase response magnitude so that the dynamic characteristics of the blood flow response could be easily quantified, and 2) avoid workloads at which the subjects would accumulate fatigue over the repeated trials (i.e., ones where the perceived effort of work increased across subsequent trials due to accumulation of fatigue). Pilot work in our laboratory indicated that 80% peak FVC was a good estimate of a work rate, which allowed us to maximize our cumulative, equal step increases from rest to exercise and exercise to exercise while maintaining consistency of response across repeated trials for all transition types.

**Blood Flow Dynamics Protocol**

Subjects completed three trials of both step exercise tests (parts A and B) (Fig. 1B) on each of the two visits subsequent to the peak conductance assessment visit (therefore, six trials in total). The order of part A vs. B was counterbalanced across subjects. In each exercise trial for part A, data were collected for 1 min of rest, followed by a

![Fig. 1. Schematic representation of experimental protocol. A: peak vascular conductance assessment test. Subjects exercised at a progressively increasing exercise intensity until forearm exhaustion. B: step exercise tests. Subjects rested for 1 min followed by step increases to 40% (part A1) and 80% (part A2) peak forearm vascular conductance (FVC). Following a 15-min rest period, subjects were measured for 1 min of rest followed by a single step to 80% (part B) FVC. Order of A1 and A2 vs. B was counterbalanced across subjects. See text for further details.](http://fiji.physiology.org/Downloaded from 10.220.33.2 on October 15, 2017)
step increase in workload, resulting in 40% peak FVC for 5 min, followed again by a further increase in workload, resulting in 80% peak FVC for 5 min. For part B, data were collected for 1 min of rest, followed by a step increase in workload, resulting in 80% peak FVC for 5 min. Each trial was separated by at least 15 min of rest to allow blood flow to return to baseline.

Data Analysis

MBV and MAP were analyzed offline, and each trial within parts A and B was averaged over 3-s (duty cycle duration) time bins. All six trials across the 2 days were then averaged together to provide a single, mean response per subject. For the peak conductance test, the trial was averaged over 15-s time bins (5 duty cycles). Brachial artery diameter was measured manually from the videotaped two-dimensional B-mode ultrasound images. On-screen calipers were placed on a clear section of the vessel wall at three points on a frozen screen image of the brachial artery during diastole and then averaged to generate the vessel diameter for that time interval. Diameter measurements for the progressive exercise test were taken every 30 s. For the step tests, diameter measurements were taken every 30 s during rest; at 0, 5, 10, 20, 40, and 60 s after each exercise transition; and every 30 s for the remaining 4 min posttransition. All diameter measures were made by the same operator. A line of best fit for these data was then generated by using an exponential model, which resulted in even distribution of residuals along the length of the model fit. These criteria resulted in the use of first-, second-, or third-order exponential models, depending on the diameter response profile observed. This approach minimizes the effect of random diameter measurement error on blood flow.

Forearm blood flow (FBF) was calculated as:

\[ \text{FBF} = \text{MBV} \cdot 60 \text{ s} \cdot \text{min}^{-1} \cdot \pi \cdot (\text{brachial artery diameter/2})^2 \]

where the FBF is in ml/min, the MBV is in cm/s, and the brachial artery diameter is in cm.

FVC was calculated as:

\[ \text{FVC} = (\text{FBF/MAP}) \cdot 100 \]

where FVC is in ml·min⁻¹·100 mmHg⁻¹. Flow per 100 mmHg was used so that FVC was quantitatively similar to the units for FBF. FVC across contraction-relaxation cycles represents the combined effect of muscle contraction-induced mechanical impedance and enhancement of blood flow and vascular conductance. It is, therefore, recognized as a “virtual” conductance (17), and this is what is meant by FVC.

Peak FVC. Peak FVC was defined as the FVC achieved at the plateau of the exercise response in the progressive exercise test. Forty and eighty percent peak FVC were calculated as:

40% Peak FVC = (Peak FVC – Resting FVC) × 0.4 + Resting FVC

and

80% Peak FVC = (Peak FVC – Resting – FVC) × 0.8 + Resting FVC

Thus these FVC levels represented 40 and 80% of the increase in FVC from rest to peak. The weight lifted at the time that 40 and 80% FVC were achieved was used as the weights for the step changes in exercise intensity examined in this study (see Fig. 2).

Kinetic analysis. The time course changes in FVC were analyzed by fitting an exponential curve to the average results of the trials for each subject in each step condition using a least squares procedure. Briefly, for the rest-40% peak FVC step (part A1), a two-component exponential model was fit to the data. For the rest-80% and 40–80% peak FVC steps (parts A2 and B), a three-component model was fit to the data. This model had a baseline component (G0), three (parts A2 and B) amplitude terms (G1, G2, and G3), three time constants (τ1, τ2, and τ3), and three time delays (TD1, TD2, and TD3) (Fig. 3).

\[ Y(t) = G_0 + G_1 [1 - e^{-t/TD_1}] \cdot \mu_1 + G_2 [1 - e^{-t/TD_2}] \cdot \mu_2 + G_3 [1 - e^{-t/TD_3}] \cdot \mu_3 \]

where

\[ \mu_1 = 0 \text{ for } t < TD_1 \text{ and } \mu_1 = 1 \text{ for } t \geq TD_1 \]

\[ \mu_2 = 0 \text{ for } t < TD_2 \text{ and } \mu_2 = 1 \text{ for } t \geq TD_2 \]

\[ \mu_3 = 0 \text{ for } t < TD_3 \text{ and } \mu_3 = 1 \text{ for } t \geq TD_3 \]

where \( Y(t) \) is the time-dependent variation in FVC.

The time delay for the three-component exponential was not fixed to that of the second component for the following reasons. In visual examination of these and other data from our laboratory [blood flow dynamic responses in forearm and leg exercise in lung disease patients and healthy controls (unpublished observations)], it was clearly observed that there is not a smooth exponential increase from the onset of phase II as, would be evident if both the second and third component combined to explain the response from that point. Rather, we clearly observe a flattening of the phase II response and then an additional delayed steepening, representing the onset of a phase III. Attempts to fit these data with a phase III time delay fixed to that of phase II result in a worsening of the residual profile along the length of the fit (i.e., the same effect on fit as would be observed if one were using a single exponential to fit the clear biphasic response observed in moderate exercise). This approach was further supported by the fact that fitting of a third component with an independent time delay

\[ J \text{ Appl Physiol} \cdot \text{VOL} 98 \cdot \text{APRIL} 2005 \cdot \text{www.jap.org} \]
resulted in the identification that this time delay differed significantly between the rest-80% and 40–80% transitions.

Statistical Analysis

The effects of exercise transition (rest-40% peak FVC vs. rest-80% peak FVC vs. 40–80% peak FVC) on the kinetic-fitting parameters for FVC were analyzed by a repeated-measures one-way ANOVA, except for $G_3$, $\tau_3$, and TD, which were analyzed by using paired t-tests, as there were only two transitions demonstrating a third component. The level of significance was set at $P < 0.05$, and significant differences for ANOVA were further assessed with Tukey’s post hoc tests. Data are presented as means ± SE.

RESULTS

Figure 2 shows a representative tracing of FBF, MAP, and FVC for one subject during the peak conductance assessment test. Typical of the response across all subjects, FBF increased linearly until the subject reached the maximum weight (~20 kg for this subject) attainable while still performing the contraction correctly. MAP remained stable over the exercise bout until ~12 kg, upon which it began to rise. Also at this point, FVC began to plateau, and thus peak FVC for this subject was ~470 ml·min$^{-1}$·mmHg$^{-1}$. For this subject, the weight lifted at 40 and 80% peak conductance was 6 and 12 kg, respectively.

The average MAP responses across subjects for parts A and B are depicted in Fig. 4. MAP appears to have risen slightly (~3 mmHg) at the onset of rest-to-40% peak FVC exercise followed by a further increase in MAP (~6.5 mmHg above rest for both A2 and B) following the onset of 80% peak FVC exercise. There was no difference in MAP at the end of parts A and B.

As anticipated, resting baseline FVC did not differ between step trials ($A_1$ and $B$, $G_0 = 58.9 ± 8.3$ and $58.7 ± 11.1$ ml·min$^{-1}$·mmHg$^{-1}$, respectively, $P = 1.0$) (see Fig. 5A). End-exercise values ($A_2$ and $B$) also did not differ between step trials [total gain ($A_1 + A_2$) = 376.0 ± 119.2 ml·min$^{-1}$·mmHg$^{-1}$ vs. $B = 407.1 ± 152.8$ ml·min$^{-1}$·mmHg$^{-1}$, $P = 0.299$] (Fig. 5A). The magnitude of total gain in FVC for $A_1$ and $A_2$ was not different, indicating the relative magnitude of increase in targeted FVC was successfully achieved ($A_1$, 170.2 ± 17.26 ml·min$^{-1}$·mmHg$^{-1}$ vs. $A_2$, 205.8 ± 31.1 ml·min$^{-1}$·mmHg$^{-1}$, $P = 0.591$) (Fig. 5B).

Dynamic response of FVC. Figure 5A presents the mean FVC adaptation for all seven subjects. Figure 5B represents the exponential best fit of these data for each of the transitions. They have been time aligned in this figure to aid comparison of dynamic response parameters, as indicated in
and, therefore, data are based on delayed (3.9 ± 0.5 s, 40 – 80% peak FVC), the time to onset was significantly when the transition was initiated from an exercise baseline exercise transitions.

The contribution of the first-phase response (G1) to the total contribution of the first two phases (G1 + G2) was not different among all three transitions and accounted for over one-half of the observed response magnitude (rest-40% peak FVC, 56.5 ± 5.5% vs. 40–80% peak FVC, 57.6 ± 4.7% vs. rest-80% peak FVC, 56.7 ± 3.0%, P = 0.970) (Fig. 8).

Gain of the FVC Response

Rapid phase I response. For the same step increase in exercise intensity, the gain (G1) was not altered by baseline exercise condition from which the increase was initiated (rest-40% peak FVC, 96.6 ± 17.1 ml·min⁻¹·mmHg⁻¹ vs. 40–80% peak FVC, 97.8 ± 14.2 ml·min⁻¹·mmHg⁻¹, P = 0.994). It was ∼1.81-fold higher in the rest-80% peak FVC transition (175.6 ± 22.7 ml·min⁻¹·mmHg⁻¹, P = 0.001).

Slower phase II response. For the same step increase in exercise intensity, the gain (G2) was not altered by baseline exercise condition from which the increase was initiated (rest-40% peak FVC, 68.7 ± 7.0 ml·min⁻¹·mmHg⁻¹ vs. 40–80% peak FVC, 71.5 ± 11.5 ml·min⁻¹·mmHg⁻¹, P = 0.974). It was ∼1.87-fold higher in the rest-80% peak FVC transition (129.5 ± 10.0 ml·min⁻¹·mmHg⁻¹, P = 0.001).

Very slow phase III response. The difference in the average gain (G3) between transitions did not reach statistical significance (40–80% peak FVC, 42.6 ± 15.8% vs. rest-80% peak FVC, 114.7 ± 43.6, P = 0.105). Again, there was considerable variability between subjects in the response across the two transitions, and it is likely that lack of statistical significance represents a type II error.
DISCUSSION

This study provides the first rigorous application of an empirical model and system analysis techniques to the responses of muscle blood flow at the onset of small muscle mass exercise. The novel findings of this study are as follows. First, adaptations from rest to 40% peak FVC were second order, whereas adaptations to 80% were third order for six of seven subjects, regardless of baseline exercise condition. Second, dynamic response characteristics (time delay, time constant) of the rapid first adaptation phase were not affected by the magnitude of the work intensity increase when the transition began from rest, but were delayed and slower, respectively, in the exercise-to-exercise transition. Third, dynamic response characteristics of phase II were not affected by the magnitude of the work intensity increase when the transition was initiated from rest, but the time delay was significantly longer when the transition was initiated from exercise. In contrast to the rapid phase I response, the time constant of adaptation was not altered when the transition began from exercise vs. rest. Finally, the magnitude of the rapid phase I adaptation represented the same proportion of the combined phase I and phase II magnitude across all exercise transitions.

These data demonstrate that 1) dynamic response characteristics of local blood flow regulatory control mechanisms involved in the initial rapid phase I and slower phase II response are not altered by the magnitude of the exercise step when exercise is initiated from rest (dynamic linearity when exercise initiated from rest), 2) dynamic nonlinearity is evident in the rapid phase I but not slower phase II response when comparing rest-to-exercise vs. exercise-to-exercise transitions, 3) the mechanism(s) responsible for the rapid phase I response appears to be activated to the same relative degree, regardless of

Fig. 6. Individual FVC adaptations during forearm exercise transitions for part A (open circles) and part B (solid circles). Exponential functions (solid lines) that yielded lowest mean squared error are also shown. Note: absolute FVC at 40 and 80% peak FVC work rates differ across subjects in accordance with differences in peak FVC achieved.
the magnitude of the exercise intensity increase or whether increases in exercise intensity are initiated from rest or exercise.

**Investigating Dynamic Response Characteristics of Blood Flow Regulation**

Dynamic responses of blood flow control systems can be characterized by parameters quantifying the time delay (the delay between the onset of a given stimulus and the onset of the response) and the time constant (the rate at which the response increases, i.e., “slope,” which specifically reflects dynamic linearity). The number of independent sets of control systems can be determined by the number of distinct phases of a response. To date, a number of studies have provided dynamic blood flow response profiles (19, 35, 37, 38, 40, 41). However, the goal of these studies was not to quantify the dynamic response characteristics of the blood flow response and examine these characteristics across a range of step increases in work rate. There has only been one attempt to characterize the dynamic response characteristics of blood flow adaptation to exercise across different work rates (28). However, a number of critical limitations in that study preclude a clear understanding of blood flow regulatory dynamics. These include 1) transitions initiated from a nonphysiological baseline of passive kicking exercise, 2) data averaged at 10-s intervals, and 3) a lack of transitions of equal magnitude starting from both rest and exercise baselines.

Fig. 7. Average values (±SE) of calculated parameters of the FVC on-kinetics in 3 exercise transitions: A1, rest to 40% peak FVC; A2, 40 to 80% peak FVC; B, rest to 80% peak FVC. G1, G2, and G3: magnitude of increase in FVC of first phase of response from rest to the first plateau, second phase of response from the first plateau to the second plateau, and third phase of response from the second plateau, respectively; TD1, TD2, and TD3: time from onset of exercise to onset of first, second, and third phase of response, respectively; τ1, τ2, and τ3: time to reach 63% of G1 from onset of first phase, G2 from onset of second phase, and G3 from onset of third phase, respectively. *Significantly different from transitions indicated in figures, P < 0.05.
It has been proposed by both groups that muscle contraction-response in the human forearm reported by our laboratory (42) and the contraction intensity-dependent rapid vasodilatory response of isolated dog muscle is due to vasodilation. Hamann et al. (10) that all of the hyperemia following a single contraction was initiated from rest or from an exercise steady state. exercise intensity increase, regardless of whether that in-nism(s) is activated in proportion to the magnitude of the phase I component of the response and that this mechanism(s) dominates the rapid increase was initiated from a baseline of rest or exercise (see Fig. 7). However, with initiation from exercise, both the time delay and the time constant were slower. This appears to contrast with a recent study by Saunders and Tschakovsky (31), which examined rest-to-exercise and exercise-to-exercise transitions similar to A1 and A2 in the present study. In that study, the FVC was assessed from the blood flow during relaxation phases of exercise to avoid mechanical impedance to blood flow with contractions and demonstrated identical adaptation onset and rate of increase between the two transitions. This discrepancy may be explained as follows. Substantial retrograde arterial flow is consistently observed on contraction (31, 42, 44). It may be that the initial effect of increased contraction intensity on the averaged flow over a duty cycle is greater in the exercise-exercise transition, thus accounting for the slower phase I “virtual” FVC response in the 40 – 80% peak FVC transition in the present study. Unfortunately, an interaction between the timing of the contraction and the cardiac cycle prevents a reliable quantification of this effect.

Rapid phase I response: dynamic linearity and feed-forward control? Currently, it is thought that both the muscle pump and rapid vasodilatory mechanisms contribute to the initial rapid increase in blood flow at the onset of a change in exercise intensity [for review, see Tschakovsky and Sheriff (43)]. However, the relative role of these mechanisms may depend on the nature of the exercise performed. Previous work from our laboratory has demonstrated that emptying of forearm veins in the dynamic forearm exercise model employed in this study is maximized at low-contraction intensities (31, 42). Thus, in the present study, any muscle pump contribution would be expected to be maximized in the rest-to-40% peak FVC transition.

If the muscle pump were active in the rest-to-exercise transitions in this forearm exercise model, we would expect a combined vasodilatory and muscle pump contribution to the rapid phase I rest-to-40% peak FVC transition. In contrast, the rapid phase I rest-to-80% peak FVC transition would have an increased vasodilatory contribution, but no increase in the muscle pump contribution. Finally, there would only be a vasodilatory contribution to the rapid phase I 40-to-80% peak FVC transition (31). Thus we would have expected to see the greatest relative rapid phase I magnitude in the rest-to-40% peak FVC transition. However, the phase I response magnitude was proportional to the size of the exercise intensity increase, regardless of whether the increase was initiated from a baseline of rest or exercise (see Fig. 8). This observation indicates that, in this exercise model, vasodilatory mechanism(s) dominates the rapid phase I component of the response and that this mechanism(s) is activated in proportion to the magnitude of exercise intensity increase, regardless of whether that increase is initiated from rest or from an exercise steady state.

These data are consistent with the recent demonstration by Hamann et al. (10) that all of the hyperemia following a single 1-s contraction of isolated dog muscle is due to vasodilation and the contraction intensity-dependent rapid vasodilatory response in the human forearm reported by our laboratory (42). It has been proposed by both groups that muscle contraction-induced mechanical distortion of resistance vessels may initiate rapid relaxation of resistance vessel smooth muscle. This may represent the “feed-forward” component of vasodilatory blood flow control to exercising muscle, in that it is initiated with the onset of contractions, not an accumulation of error signal. This would be similar in effect to the feed-forward neurohumoral control of respiration at exercise onset (5), which initiates a rapid but incomplete response, requiring additional slower feedback control adjustment to steady state. In this schema, the exercise intensity is a function of the contraction intensity (force production), which is proportionally dependent on the number of muscle fibers recruited and, therefore, the degree to which mechanical forces (1) can distort resistance vessels.

This feed-forward control system demonstrates dynamic linearity (same time constant) across the range of exercise intensity increases initiated from a baseline of rest in this study. When exercise was initiated from rest, the magnitude of the exercise intensity increase did not affect either the time delay or the time constant of the response (see Fig. 7). However, with initiation from exercise, both the time delay and the time constant were slower. This appears to contrast with a recent study by Saunders and Tschakovsky (31), which examined rest-to-exercise and exercise-to-exercise transitions similar to A1 and A2 in the present study. In that study, the FVC was assessed from the blood flow during relaxation phases of exercise to avoid mechanical impedance to blood flow with contractions and demonstrated identical adaptation onset and rate of increase between the two transitions. This discrepancy may be explained as follows. Substantial retrograde arterial flow is consistently observed on contraction (31, 42, 44). It may be that the initial effect of increased contraction intensity on the averaged flow over a duty cycle is greater in the exercise-exercise transition, thus accounting for the slower phase I “virtual” FVC response in the 40 – 80% peak FVC transition in the present study. Unfortunately, an interaction between the timing of the contraction and the cardiac cycle prevents a reliable quantification of this effect.

Slower phase II response: dynamic linearity and feedback control? Unlike the phase I response, the phase II time constant was not slowed in the transition initiated from an exercise baseline. However, its onset was delayed. This indicates that either the onset of production of vasodilatory factors responsible for this phase was delayed, or they did not accumulate as rapidly to a threshold level that could initiate changes in vascular conductance, or both. Such a delay might occur if the initial increase in blood flow during phase I was greater, delaying changes in factors associated with a balance between O2 demand and supply, such as red blood cell deoxygenation-induced vasodilation (9). However, given that the phase I response provided the same relative increase as in the rest-to-exercise transitions, it appears that such an explanation is unlikely. Alternatively, the higher baseline blood flow at 40% peak FVC compared with rest may have had a “washout” effect, thereby slowing the rate of accumulation of vasodilatory factors to a threshold level that could initiate the increase in FVC.

It must be recognized that observations of similar time constants across different ranges and magnitudes of step increases in response do not conclusively demonstrate that the same mechanisms are involved. Rather, it simply reflects that the combination of mechanisms involved results in the same
adaptation characteristics. Thus dynamic linearity observed for phase II should not be taken to indicate that the mechanisms responsible are identical, only that their response characteristics result in the same functional adaptation.

As suggested by Hughson (13), the phase II response is consistent with a control system that is relying on feedback error signals communicating mismatch between metabolic rate and blood flow. This “mismatch” is the basis for the classic metabolic hypothesis of blood flow control (7) in which by-products of muscle metabolism accumulate as a result of imbalance between production and washout. The present study has identified a consistency in the rate of adaptation of FVC due to this “feedback” part of the blood flow response across exercise transitions. This indicates a consistent “speed of response” capability of this set of vasoregulatory mechanisms. Response speed in this case would be dependent on either vasodilator accumulation rates, or activation and effect of signaling pathways for smooth muscle relaxation (18), or both.

Adenosine has been identified as one potential candidate for this type of metabolic feedback control, demonstrating increases in interstitial concentration with increasing work intensity (27). Another type of mechanism sensitive to mismatch between metabolic rate and blood flow could be the red blood cell (9). There is approximately a $\pm 10$-s delay after the onset of forearm exercise before $O_2$ content of venous blood draining forearm muscle begins to decrease (14). In addition, recent application of near-infrared spectroscopy to examine muscle oxygenation adjustments with the onset of leg exercise (6, 34) indicates time delay in muscle deoxygenation of between 6 and 12 s and a time constant of change of between 5 and 12 s. Finally, intracellular $O_2$ in isolated frog muscle also does not drop immediately at the onset of contractions (11).

These observations suggest that greater release of ATP from red blood cells (9) may be initiated within 6–12 s of a change in exercise intensity. An additional delay in accumulation to adequate levels would likely be required. These values appear consistent with a delayed contribution of red blood cell deoxygenation-induced vasodilation that fits with the 21- to 27-s time delay for the onset of the slower phase II vascular conductance adaptation in this study.

A critical gap in our current understanding of the changing vasoregulatory environment in the muscle is a lack of information on the time course of interstitial accumulation of vasodilatory factors. The present study suggests a consistency across exercise transitions for the phase II set of mechanisms. Our observations of marked differences between the phase I and phase II vasoregulatory response speed also indicate fundamental differences in the way in which these different sets of mechanisms may evoke vasodilation in resistance vessels.

A “very slow” phase III component of vasoregulation. In the present study, we have identified that exercise transitions into the exercise intensity domain requiring 80% of the peak FVC response result in a third-order response, regardless of whether that transition was initiated from rest or moderate exercise. This delayed, very slow phase III response is similar to the established “slow component” $O_2$ uptake kinetic response observed in “heavy” exercise (23–25). Whether this slow component represents completion of adaptation to demand for oxygen delivery established by the initial increase in exercise intensity, or whether it represents vasoregulatory adjustments that are due to delayed recruitment of additional, less metabolically efficient type II muscle fibers as some motor units fatigue (4, 26) is unclear. However, Koga et al. (15) recently demonstrated a very slow phase III component of the muscle blood flow response to leg kicking exercise that they suggested may be associated with the slow component of the observed $O_2$ uptake kinetic response.

This study was not designed to assess muscle metabolic responses; therefore, it remains to be determined whether this vasodilatory response coincides with the slow-component oxidative metabolic response observed in heavy exercise (23–25). The onset of the very slow phase III response was significantly delayed in the 40–80% vs. rest-80% peak FVC transition. This suggests that the onset of signals or conditions in the muscle initiating the phase III response to the same exercise intensity is dependent on the baseline exercise intensity from which the exercise intensity increase is initiated.

Further interpretation of this very slow phase III response in the present study is hampered by the substantial variability across subjects (see Fig. 6). The time constant and the gain averaged across subjects were not statistically significant, despite being $\sim 160\%$ ($P = 0.16$) and $\sim 170\%$ ($P = 0.10$) greater, respectively, in the rest-80% vs. 40–80% peak FVC transition. However, this likely represents a type II error. Thus we submit that blood flow regulation in the third response phase likely does not demonstrate dynamic linearity, and that the magnitude of this response to a given absolute exercise intensity is sensitive to the baseline condition from which exercise is initiated.

Advantages and Limitations

The application of multiple repeats and comparison of rest-to-exercise and exercise-to-exercise transitions allowed us to quantify parameters describing the adaptive response with adequate precision and investigate blood flow regulation from a control theory perspective. However, it is acknowledged that the conclusions regarding the dynamics of vasoregulatory control must be confined to the mode of exercise (rhythmic, dynamic small muscle mass exercise, not limited by central adaptations), and the range of exercise steps examined. For this reason, it remains to be determined whether the control system characteristics observed in this study extend to step increases in exercise intensity below the rest-to-40% peak FVC examined in this study. Furthermore, it was not possible to examine the effect of contraction impedance of blood flow on the time delay and time constant of the response. Both of these limitations need to be addressed in future studies.

Conclusions

This study sought to examine the dynamic response characteristics of exercising muscle blood flow control mechanisms. We conclude that blood flow control systems are characterized as second order with moderate exercise and as third order when exercise intensity increases to 80%
peak FVC requirements. The rapid phase I response in this exercise model is dominated by a vasodilatory mechanism(s) that is activated in proportion to the size of the exercise intensity step and may represent a vasodilatory “feed-forward” control. This control system also demonstrates dynamic linearity when exercise steps are initiated from rest. The slower phase II response onset is also sensitive to the baseline exercise intensity from which the exercise step was initiated. Furthermore, the time constant of this phase is consistent across a range of exercise steps, indicating dynamic linearity of this control system. Finally, the very slow phase III response onset appears to be sensitive to the baseline exercise intensity from which the exercise step was initiated.

ACKNOWLEDGMENTS

The authors thank the study participants for their time and effort.

GRANTS

This project was supported by a Natural Sciences and Engineering Research Council of Canada (NSERC) operating grant and Canada Foundation for Innovation and Ontario Innovation Trust New Opportunities Infrastructure grants to M. E. Tsakaras, N. R. Saunders was supported by an NSERC PGs A Award. K. E. Pyke was supported by an Ontario Graduate Scholarship Award.

REFERENCES

37. Shoemaker JK, Naylor HL, Poizg ZI, and Hughson RL. Failure of prostaglandins to modulate the time course of blood flow during


