Central and peripheral contributors to skeletal muscle hyperemia: response to passive limb movement

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McDaniel J, Fjeldstad AS, Ives S, Hayman M, Kithas P, Richardson RS. Central and peripheral contributors to skeletal muscle hyperemia: response to passive limb movement. J Appl Physiol 108: 76–84, 2010. First published November 12, 2009; doi:10.1152/japplphysiol.00895.2009.—The central and peripheral contributions to exercise-induced hyperemia are not well understood. Thus, utilizing a reductionist approach, we determined the sequential peripheral and central responses to passive exercise in nine healthy men (33 ± 9 yr). Cardiac output, heart rate, stroke volume, mean arterial pressure, and femoral blood flow of the passively moved leg and stationary (control) leg were evaluated second by second during 3 min of passive knee extension with and without a thigh cuff that occluded leg blood flow. Without the thigh cuff, significant transient increases in cardiac output (1.0 ± 0.6 l/min, Δ15%), heart rate (7 ± 4 beats/min, Δ12%), stroke volume (7 ± 5 ml, Δ7%), passive leg blood flow (411 ± 146 ml/min, Δ151%), and control leg blood flow (125 ± 68 ml/min, Δ43%) and a transient decrease in mean arterial pressure (3 ± 3 mmHg, 4%) occurred shortly after the onset of limb movement. Although the rise and fall rates of these variables differed, they all returned to baseline values within 45 s; therefore, continued limb movement beyond 45 s does not maintain an increase in cardiac output or net blood flow. Similar changes in the central variables occurred when blood flow to the passively moving leg was occluded. These data confirm the role of peripheral factors and reveal an essential supportive role of cardiac output in the hyperemia at the onset of passive limb movement. This cardiac output response provides an important potential link between the physiology of active and passive exercise.

numerous factors contribute to the increase in blood flow to active skeletal muscle at the onset of exercise, ensuring the adequate supply of oxygen and removal of metabolic byproducts. The central and peripheral factors, which may include the skeletal-muscle pump (20, 24), mechanically induced vasodilation (6, 16, 29), mechanical distortion of arterioles (23), flow-mediated dilation (19, 22), and cardio-acceleration [increase in heart rate (HR)] resulting from muscle mechanoreceptor and chemoreceptor feedback (1, 2, 14), all have substantial support for their role in this hyperemic response. However, as a result of these numerous mechanisms, it is difficult to experimentally decouple them, allowing one to determine the magnitude of effect and temporal nature of any single mechanism.

Recently our group (31) and others (10, 28) have utilized a passive exercise protocol in combination with active exercise to partition the effects of metabolic and mechanical factors that result in the immediate and potentially long-term increase in blood flow. Wray et al. (31) reported that passive leg extension resulted in a cardio-acceleration and increased thigh blood flow to the moving leg within the first 5 s of movement and increased blood flow to the nonmoving (control) leg within 11 s of movement. Throughout this 3-min protocol cardio-acceleration was maintained, whereas blood flow to the moving leg returned to baseline values within 1 min. Therefore, it was concluded that the increased blood flow resulted from reduced vascular resistance, most likely a consequence of mechanical vessel deformation, as well as cardio-acceleration. During this investigation, however, stroke volume (SV) was not measured, and consequently cardiac output (CO) was assumed to remain constant. Gonzalez-Alonso et al. (10) measured leg blood flow and CO during passive and active leg extension and thigh compressions. Their results also revealed an increase in leg blood flow during passive limb movement and thigh compressions but no significant increase in CO. Furthermore, Ter Woerd et al. (28) reported no changes in leg blood flow or CO in control and spinal cord-injured patients during 20 min of passive leg exercise.

Therefore, in light of these studies, CO appears not to be associated with the increased hyperemia observed during passive exercise. We contend, however, that the absence of change in CO and/or leg blood flow reported in the latter two investigations might be attributable to inadequate time resolution to determine transient responses because the first measurements were reported several minutes after the start of passive exercise (10, 28). In fact, our previous paper (31) suggested that increased blood flow at the onset of passive exercise was transient, returning to baseline within 1 min; therefore, if CO does actually influence blood flow, it, too, may return to baseline values within 1 min. The observation of an increase in CO with passive movement would provide a valuable link between passive and active exercise, adding credence to the use of passive exercise as a valid model to study exercise-induced hyperemia without the parallel increase in metabolism that is associated with active exercise.

Consequently, it appears that further study of the central and peripheral factors that contribute to hyperemia at the onset of exercise is needed with a passive exercise protocol that includes greater time resolution, cardiac output measurements, and simultaneous blood flow quantification on the passively moved and control leg. Thus the primary aim of the present study was to determine the second by second kinetics of, and temporal relationship between, central and peripheral responses to passive limb movement to elucidate the mechanisms that influence hyperemia. Two hypotheses motivated this in-
vestigation: 1) CO is a major contributor to hyperemia at the onset of passive exercise and 2) increases in cardiac output and leg blood flow are transient, returning to baseline shortly after the onset of limb movement.

MATERIALS AND METHODS

Subjects and General Procedures

Nine healthy recreationally active men (33 ± 9 yr, 85 ± 17 kg, 180 ± 8 cm) participated in the present study. All protocols were approved by the Institutional Review Boards of the University of Utah and the Salt Lake City VA Medical Center, and written, informed consent was obtained by all subjects before their inclusion in the study. All studies were performed in a thermoneutral environment (22°C). Subjects reported to the laboratory in the fasted state and had not performed exercise within the past 24 h.

Passive Exercise Protocol

Subjects were required to lay supine for 20 min before the start of data collection and remained in this position throughout the entire protocol. The initial protocol consisted of a 30-s resting (baseline) followed by a 3-min bout of passive leg extension. One minute before the start of the passive exercise, a cuff placed distal to the knee on the passive leg was inflated to 250 mmHg, eliminating blood flow to the lower leg. The cuff, which remained inflated throughout the entire 3-min protocol, was necessary to eliminate fluctuations in blood flow to the lower leg as a consequence of changing gravitational and centrifugal forces as a consequence of the movement. Initial pilot work revealed minimal effect of either cuffing or not cuffing the control leg in the same manner, and, consequently, for subject comfort, a lower leg cuff on the control leg was not applied in these studies. Passive exercise was achieved by a member of the research team moving the subject’s lower leg through the range of motion defined by 90- and 180-degree knee joint angles at 1 Hz (throughout the protocol the control leg remained fully extended). Real-time feedback was provided by a position sensor to ensure a consistent range of motion and a metronome to maintain cadence. Before the start and throughout the protocol, subjects were encouraged to remain passive and resist any urge to assist with leg movement. To avoid a startle reflex and active resistance to the passive movement, subjects were made aware that passive movement would take place, but, to minimize the chance of an anticipatory response, they were not informed of exactly when this movement would initiate.

To further determine whether a causal relationship between central and peripheral factors existed, during an additional visit to the laboratory, 8 subjects repeated this protocol with complete occlusion of blood flow to the passive leg, eliminating hemodynamic changes in the leg. During this protocol, an upper thigh cuff (inguinal region) was inflated to 250 mmHg 3 min before passive movement and remained inflated throughout the 3 min of passive leg movement. The 3-min delay between cuff inflation and the start of passive movement allowed the temporary (30–45 s) rise in mean arterial pressure (MAP), resulting from the sudden occlusion of the upper thigh, to return to baseline.

Measurements

Femoral blood flow. Simultaneous measurements of femoral arterial blood velocity and vessel diameter were performed in the passive (moving) and control (stationary) legs distal to the inguinal ligament and proximal to the bifurcation with Logic 7 and Logic e ultrasound systems (General Electric Medical Systems, Milwaukee, WI). The Logic 7 and Logic e were equipped with a linear array transducers operating at an imaging frequency of 14 and 12 MHz, respectively. Vessel diameter was determined at a perpendicular angle along the central axis of the scanned area. Blood velocity was obtained using the same transducers with a Doppler frequency of 5 MHz. All blood velocity measurements were obtained with the probe appropriately positioned to maintain an insonation angle of 60° or less. The sample volume was maximized according to vessel size and was centered within the vessel on the basis of real-time ultrasound visualization. Arterial diameter was measured, and mean velocity values (angle-corrected, and intensity-weighted area under the curve) were then automatically calculated using commercially available software (Logic 7 and Logic e). Using arterial diameter and $V_{mean}$, blood flow in the femoral artery was calculated as $blood flow = V_{mean} \pi (vessel\ diameter)^2 \times 60$, where blood flow is in milliliters per minute.

Central variables. HR, SV, CO, and MAP were determined with a Finometer (Finapres Medical Systems, Amsterdam, The Netherlands). SV was calculated using the Modelflow method, which includes age, sex, height, and weight in its algorithm (Beatscope version 1.1; Finapres Medical Systems) (5), and has been shown to accurately track CO during a variety of experimental protocols including exercise (7, 8, 26, 27, 30). CO was then calculated as the product of HR and SV. Vascular conductance within each leg was calculated as leg blood flow/MAP.

Knee angle. During each protocol, knee joint angle of the passive leg was continuously recorded using a Vishay Spectroly 360-degree Smart Position Sensor (Vashay Intertechnology, Malvern, PA) mounted on a BREG X2 knee brace (BREG, Vista, CA) worn by each subject.

Data acquisition. Throughout each entire protocol, HR, SV, CO, MAP, ECG, and knee joint angle signals underwent A/D conversion and were simultaneously acquired (200 Hz) using commercially available data acquisition software (AcqKnowledge; Biopac Systems, Goleta, CA). In addition, this data acquisition software also acquired (10,000 Hz) the audio anterograde and retrograde signals from both Doppler ultrasound systems to serve as a qualitative indicator of blood velocity changes and to ensure accurate temporal alignment of blood velocity measurements obtained from these systems and the other signals collected (i.e., finometer and goniometer) (Fig. 1).

Data Analysis

The data acquisition software (AcqKnowledge, Biopac Systems) allowed second-by-second analyses of HR, SV, CO, MAP, and knee angle. The second-by-second anterograde and retrograde velocities were determined by the Doppler ultrasound systems (GE Logic 7 and Logic e). With the use of the anterograde and retrograde velocities and femoral artery diameters, anterograde, retrograde, and net blood flows were calculated for both the control and passive leg (as described above). Repeated-measures ANOVAs ($\alpha = 0.05$) utilizing simple contrasts were used to determine whether HR, SV, CO, MAP, retrograde flow, anterograde flow, and total flow for each second during the 3-min protocol differed from the 30-s baseline average. There were no post hoc statistical analyses performed on these data because these analyses (per second) were performed in an exploratory fashion (15), as our goal was ultimately to determine the beginning and end of a response (two comparisons). Paired $t$-tests ($\alpha = 0.05$) were used to determine whether the individual maximal relative changes in CO, HR, SV, MAP, and blood flow in the control leg differed because of blood flow occlusion to the passively moved leg. All data are presented as means ± SD.

RESULTS

Peripheral Response with Blood Flow to the Passive Leg

The peripheral responses are summarized in Table 1. As expected, baseline flows were similar for the passive leg (272.4 ± 55.1 ml/min) and control leg (290.5 ± 91.3 ml/min). At the onset of exercise, net blood flow in both the passive and
control legs transiently increased. Net blood flow in the passive leg became elevated 4 s after the start of exercise, reached a maximum value of 683.7 ± 171.6 ml/min (151% Δ) ~4 s later, and gradually returned to a level that was not different than baseline over the next 14 s (Figs. 2A, 3, and 4). This change in net blood flow was a consequence of a significant increase in both anterograde and retrograde blood flow. At the time net blood flow peaked, anterograde blood flow reached a maximum of 892 ml/min (115% Δ), while retrograde blood flow elevated by 46% to 208 ml/min. Net blood flow in the control leg demonstrated quite different kinetic characteristics, becoming elevated after 11 s, reaching a plateau (rather than a peak) of ~380 ml/min (43% Δ), and was intermittently elevated for the following 37 s (Figs. 2B, Table 1. Summary of the peripheral and central responses to passive exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Values</th>
<th>Max Value, min for MAP</th>
<th>% Change from Baseline</th>
<th>Time, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive leg blood flow, ml/min</td>
<td>272.4 ± 55.1</td>
<td>683.7 ± 171.6</td>
<td>151.0</td>
<td>8</td>
</tr>
<tr>
<td>Control leg blood flow, ml/min</td>
<td>290.5 ± 91.3</td>
<td>416.2 ± 244.4</td>
<td>43.3</td>
<td>11</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>6.6 ± 1.2</td>
<td>7.6 ± 1.1</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>61.1 ± 6.5</td>
<td>68.1 ± 7.4</td>
<td>11.7</td>
<td>12</td>
</tr>
<tr>
<td>SV, ml</td>
<td>109.5 ± 11.4</td>
<td>116.9 ± 10.9</td>
<td>6.8</td>
<td>21</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>85.9 ± 10.6</td>
<td>82.5 ± 11.1</td>
<td>-3.5</td>
<td>15</td>
</tr>
</tbody>
</table>

Applicable data are presented as means ± SD. For all variables, the maximum values were significantly different than baseline. The time column presents the time required for each variable to reach maximum value. CO, cardiac output; HR, heart rate; SV, stroke volume; MAP, mean arterial pressure.
3, and 4). Unlike the passive leg, net blood flow changes in the control leg resulted primarily from an increase in anterograde blood flow (Fig. 5, A and B), which, after reaching a maximum flow of $576.0 \pm 216.1$ ml/min (35% $\Delta$), returned to baseline values within 50 s following the onset of exercise. The retrograde blood flow in the control leg remained relatively unchanged from baseline (Fig. 5B). Hence, the change in net flow in the passively moving leg was greater and occurred predominately over 18 s, whereas the change in net blood flow in the control leg was not as great but remained intermittently elevated (1 out of every 5 data points) for a longer period of time. The difference between blood flow to the passive and control legs, which represents the hyperemic response attributable only to peripheral factors, became greater than baseline 5 s after the onset of limb movement and remained elevated for 18 s before returning to baseline values (Fig. 4B).

Central Response with Blood Flow to the Passive Leg

The central responses are summarized in Table 1. All changes in central variables were transient, becoming significantly elevated or reduced shortly after the onset of passive movement and returning to baseline within 45 s. CO became significantly greater than baseline (6.6 \pm 1.2 l/min) after 2 s of passive movement, steadily rose to a maximum of $7.6 \pm 1.1$ l/min (15% $\Delta$), and then decreased back to baseline, remaining significantly elevated for a total of 43 s (Figs. 2C, 3, and 4). SV became significantly elevated 11 s after the onset of passive exercise, peaked at $116.9 \pm 10.9$ ml (6.8% $\Delta$) by 21 s, and remained elevated for only 16 s (Figs. 2D and 3). HR also became significantly elevated within 3 s, increased from 61 \pm 7 to a maximum of $68 \pm 7$ beats/min (11.7% $\Delta$), and remained significantly elevated for 34 s (Figs. 2E and 3). These increases were accompanied by a significant decrease in MAP ($3.3 \pm 3.3$, $-3.5\%$) from 9–23 s following the onset of passive exercise (Figs. 2F and 3).

Vascular Conductance with Blood Flow to the Passive Leg

Baseline vascular conductance values were similar between the passive (3.2 \pm 0.7 ml · min$^{-1}$ · mmHg$^{-1}$) and control legs (3.3 \pm 1.0 ml · min$^{-1}$ · mmHg$^{-1}$). Vascular conductance in the passive leg revealed qualitatively similar results to blood flow, reaching a maximum value of $8.2 \pm 2.9$ ml · min$^{-1}$ · mmHg$^{-1}$ (159% $\Delta$) 8 s following the onset of limb movement and remaining significantly greater than baseline values for a total of 18 s. Meanwhile, vascular conductance in the control leg also displayed a similar pattern to that of blood flow, increasing to a plateau of $\sim4.6$ ml · min$^{-1}$ · mmHg$^{-1}$ (37% $\Delta$) 11 s after the onset of exercise and remaining significantly elevated for a total of 37 s. Hence, the analysis of both leg blood flow and leg vascular conductance revealed qualitatively similar results in both limbs.

Central and Peripheral Responses with No Blood Flow to the Passive Leg

Despite the absence of a hyperemic response in the passively moved leg because of blood flow occlusion, there remained significant increases in CO, HR, SV, and control leg blood flow at the onset of passive leg movement (Fig. 6). There was,
however, a slight but significant reduction in the CO and SV response and a trend for greater change in blood flow in the control leg when blood flow was occluded in the passively moved leg. During this trial, MAP displayed an immediate tendency to increase, rather than a significant decrease observed when the passive leg was not occluded. This dichotomy resulted in a significant difference between the relative changes from baseline between the two conditions (Fig. 6).

Fig. 3. The onset and duration of central and peripheral variables that responded to passive limb movement. The horizontal bars span from the first to last second in which that variable was statistically different from baseline (excluding random noise). Horizontal bars that are dark represent those variables that were not continuously elevated during that time. Arrows indicate whether the variables increased or decreased relative to baseline. The numbers located on the left-hand side and within each box indicate the time (s) and duration in which variables became and remained statistically different from baseline.

Fig. 4. Mean CO and femoral blood flow for the passive and control legs (A) and the mean difference between the passive and control leg blood flow (B) during the first 120 s of passive limb movement. Vertical lines represent the start of limb movement. Symbols above each graph indicate which points are statistically different than the 30-s baseline average. Error bars were omitted in A to enhance clarity.
DISCUSSION

With the use of second-by-second analysis of CO, SV, HR, MAP, and femoral blood flow, the kinetics of central and peripheral factors responsible for hyperemia at the onset of passive exercise were examined. There are three novel findings from this investigation: 1) on the basis of temporal analysis, a HR-driven increase in CO is an essential component of peripheral hyperemia at the onset of limb movement; 2) this increase in CO is independent of limb movement-induced peripheral hemodynamic changes; and 3) despite prolonged changes in both anterograde and retrograde blood flow throughout 3 min of limb movement, net femoral blood flow and CO are only transiently elevated during passive limb movement. These results not only help clarify which central and peripheral variables contribute to exercise-induced hyperemia but also, in contrast to previous reports, indicate that CO does, in fact, contribute to hyperemia at the onset of passive exercise.

Sequence of Events at the Onset of Passive Limb Movement

High temporal resolution and the simultaneous collection of multiple central and peripheral variables in this study allowed us to determine which factors were most likely responsible for hyperemia at the onset of passive limb movement (Fig. 3). The initial rapid response to limb movement was an increase in HR and CO observed within 2–3 s (Fig. 2), thus most likely a result of afferent signals from muscle and joint mechanoreceptors (1, 2, 11, 12, 14, 21). Limb hyperemia increased shortly thereafter (~4 s, Fig. 2), a consequence of both increased delivery of blood to the leg via augmented CO and increased vascular conductance in accordance with the hydraulic analogy of Ohm’s law (3) attributable to leg movement.

As already mentioned, following the onset of leg movement, there was an immediate HR increase with a concomitant rise in
CO (≈15%), a central response that elevated blood flow in both legs. In the control leg, blood flow increased significantly (≈43%) after 11 s attributable almost exclusively to this CO increase, whereas a more robust and immediate hyperemia (150% in ~4 s) was observed in the passively moved leg (Fig. 3), where both increased CO and limb movement acted in combination. Thus the elevated CO is preferentially accepted by the passive leg, where mechanically induced vasodilation occurs. In fact, when the upper thigh of the passive leg was occluded, blood flow in the control leg became significantly elevated within 3 s, rather than 11 s, a consequence of closing off the passive leg and redirecting blood flow to the control leg. The difference in blood flow between the control and passively moved legs highlights a defined role for both CO and rapid vasodilation, with the latter allowing approximately an additional onefold increase in hyperemia at the onset of leg movement (Fig. 4). However, the interaction between CO and vasodilation in the passive leg, as discussed above, confounds the exact quantification of the difference in blood flow between the two legs.

Because previous investigators have suggested that an increase in limb blood flow may lead to an increase in CO (10), it is important to note that here a significant increase in CO was observed at the onset of passive exercise even when an increase in leg blood flow in the passively moved leg was prevented via cuff occlusion (Fig. 6). Hence, these data indicate that an increase in leg blood flow is not obligatory for an increase in CO and thus do not support the contention that limb vasodilation is solely responsible for increased CO as previously implicated (10). The small but significant reduction in SV and CO, when blood flow was occluded in the passively moving leg, may have resulted from the absence of the muscle pump that usually assists with venous return to the heart, indicating that changes in limb hemodynamics support the rise in CO, albeit minimally under the conditions of the present study (Fig. 6).

Previous studies have either not measured CO (31) or reported that there was no increase in CO with passive exercise and, therefore, concluded that CO does not contribute to the hyperemia associated with limb movement (10, 28). We contend that the failure to see significant CO changes in these studies was attributable to inadequate time resolution in either the data acquisition or analysis. Indeed, the transient 15% increase in CO shortly after the onset of passive exercise could have easily been missed in the present study if CO measurements and analysis did not have high time resolution or did not occur within the first 45 s of the passive movement. Furthermore, in terms of absolute volume, the increase in CO was more than double that of the combined increase in blood flow to the passive and control leg. This difference can be explained by the likely parallel increase in blood flow to other vascular beds (e.g., arms, kidneys, etc.) as a result of the increased cardiac output and lack of exercise-induced sympathetic nerve activity with this passive model (32), which were not accounted for in this investigation. Similarly, during the passive leg occlusion trial, the trend for an increase in control leg blood flow was likely the result of the redirection of CO from the passively moved leg to other vascular beds that were not occluded.

During the period marked by elevated femoral blood flow, there was a small decrease in MAP by 3–4 mmHg (Figs. 2 and 3), which may be attributable to acute vasodilation in the passively moved leg. With all other things held constant, a decrease in pressure should act to reduce blood flow, but the concomitant influence of increased CO and the local decrease in peripheral resistance as a consequence of mechanically induced vessel dilation (6, 16) and/or flow mediated dilation resulting from increased shear stress (17–19, 22, 25) more than offset the decreased MAP, resulting in elevated blood flow and vascular conductance in the passively moved leg. In agreement with this concept, during the trial in which blood flow was occluded to the passive leg, there tended to be an immediate rise in MAP, likely attributable to the increase in CO and the absence of effective peripheral vasodilation in the passive leg. Along with the previously mentioned redirection of blood from the occluded leg, this rise in MAP helped explain the trend toward a greater increase in blood flow to the control leg during this trial (Fig. 6). However, the observation that blood flow in the control leg increased despite a decrease in MAP and no known mechanism for decreased resistance within that particular limb remains a conundrum.

**Transient Nature of the Hyperemic Response**

The response to limb movement described above is transient; therefore, this cascade of events must reverse. After ~25 s of limb movement, there is a secondary rise in retrograde blood flow in the passively moved leg (Fig. 5), an indication of vasoconstriction, which results in a reduced leg blood flow in the passively moved leg and promotes a long-term restoration of MAP to baseline values. This restoration of MAP will likely lead to baroreflex withdrawal and increased afterload, decreasing HR and SV (9), respectively, and ultimately resulting in the fall in CO to original baseline values. In addition, with passive exercise, there are neither descending motor command signals nor increased metabolism (10, 13) to yield metaboreceptor afferent signals typically associated with active exercise. It is likely that this lack of motor command and metaboreceptor afferent signals, in addition to an adaptation of the mechanoreceptors (4) resulting in decreased type III afferent feedback, facilitates the fall in CO back toward baseline values. Thus, at ~45 s after the onset of limb movement, CO returns to baseline values, shortly followed by the concomitant drop in control leg blood flow to baseline (Fig. 3A).

**Net, Anterograde, and Retrograde Femoral Blood Flow**

The fact that net femoral blood flow in the passive leg does increase and that this increase is only short lived is in contrast to previous reports that have indicated that femoral blood flow does not increase (28) or inferred that femoral blood flow remained elevated for up to 90 min of passive movement (13). Others have suggested femoral blood flow does increase but did not clearly document the actual time that the measurements were made in relation to the onset of movement (10). However, the present results are supported by our previous and less comprehensive study (no central variable measurements) (31) in which femoral blood flow was determined to be transient.

The kinetics of the net femoral blood flow in the passive leg is the result of the summed contribution of anterograde and retrograde blood flow. As previously mentioned, net blood flow in the passively moving leg became significantly elevated 4 s after movement began and remained elevated for ~18 s. This was a consequence of an increase in both anterograde and
retrograde blood flows, with the magnitude of change in anterograde flow being much greater than the magnitude of change in retrograde flow (Fig. 5A). It is likely that this initial rise in anterograde blood flow was attributable to the combination of increased CO and decreased vascular resistance within the muscle as a consequence of mechanically induced vasodilation (6, 16) and endothelial-mediated vasodilation resulting from shear stress (17–19, 22, 25) (Fig. 4B). The somewhat counterintuitive rise in retrograde blood flow, in the face of decreased vascular resistance, is possible if the increase in anterograde blood flow more than offsets the decrease in resistance. The subsequent fall in anterograde blood flow and continued rise in retrograde blood flow were likely attributable to falling CO and the onset of vasoconstriction associated with hyperperfusion of an essentially resting limb (31). Interestingly, after net blood flow returned to baseline, both anterograde and retrograde blood flow remained elevated, likely attributable to continued cyclic muscle length-dependent changes in vessel tortuosity that produced intermittent periods of decreasing and increasing vascular resistance, thus increasing the oscillatory nature of the blood flow. At this point, the increase in retrograde blood flow offset the increase in anterograde blood flow, resulting in the absence of long-term elevated net blood flow during passive limb movement.

**Experimental Considerations**

Variables analyzed in this investigation were collected utilizing multiple systems, with different signal-to-noise ratios that could influence the accuracy of the temporal relationships between variables. This concern does not, however, negate our main finding that the increase in CO occurs before the hyperemia, as the signal-to-noise ratio was greater for CO than it was for blood flow. Thus, if anything, it is more likely that the reported kinetics of CO, rather than blood flow, may be delayed relative to the true physiological response.

**Summary**

This study is the first to investigate CO, SV, HR, MAP, and femoral blood flow responses to passive exercise with second-by-second temporal resolution, a model that allows examination of the mechanisms responsible for movement-induced hyperemia without the parallel increase in metabolism associated with voluntary exercise. With this approach, it has been demonstrated that, in combination with peripheral vascular responses, a HR-driven increase in CO is not dependent on but is likely the primary initiator of movement-induced hyperemia. Furthermore, these cardiovascular responses to limb movement are transient in nature, as continued limb movement beyond 45 s does not sustain this response.

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**DISCLOSURES**

No conflicts of interest are declared by the author(s).

**REFERENCES**


