Immediate exercise hyperemia in humans is contraction intensity dependent: evidence for rapid vasodilation


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Tschakovsky, M. E., A. M. Rogers, K. E. Pyke, N. R. Saunders, N. Glenn, S. J. Lee, T. Weissgerber, and E. M. Dwyer. Immediate exercise hyperemia in humans is contraction intensity dependent: evidence for rapid vasodilation. J Appl Physiol 96: 639–644, 2004. First published October 24, 2003; 10.1152/japplphysiol.00769.2003.—We tested the hypothesis that rapid vasodilation proportional to contraction intensity contributes to the immediate (first cardiac cycle after initial contraction) exercise hyperemia. Ten healthy subjects performed single 1-s isometric forearm contractions at 5, 10, 15, 20, 30, 50, and 70% maximal voluntary contraction intensity (MVC) in arm above heart (AH) and below heart (BH) positions. Forearm blood flow (FBF; brachial artery mean blood velocity, Doppler ultrasound), mean arterial pressure (arterial tonometry), and heart rate (electrocardiogram) were measured beat by beat. Venous emptying (measured with a forearm strain gauge) was already maximized at 5% MVC, indicating that increases in contraction intensity did not further empty the forearm veins. Immediate increases in FBF were linearly proportional to contraction intensity from 5 to 70% MVC in AH (slope = 4.4 ± 0.5%ΔFBF/%MVC). In BH, the immediate increase in FBF demonstrated a curvilinear relationship with increasing contraction intensity and was greater than AH at 15, 20, 30, and 50% MVC (P < 0.05). Peak changes in FBF were greater in BH vs. AH from 10 to 50% MVC, even when venous refilling was complete (P < 0.05). These data support the existence of a rapid-acting vasodilatory mechanism(s) at the onset of human forearm exercise.

In a rest-to-exercise transition, muscle blood flow typically increases in a biphasic manner to a steady-state level proportional to muscle metabolic demand (7, 12, 17). A striking characteristic of this adaptation is the immediate and substantial increase in muscle blood flow after release of the first contraction of exercise (11–13, 18, 21). Because blood flow through a muscle vascular bed is thought to be proportional to the arteriovenous pressure difference across that bed and the vascular conductance of that bed, a number of studies have been conducted to determine whether the muscle pump, vasodilation, or both play an immediate role in the hyperemia at the onset of exercise (9, 11, 12, 21, 23). Considerable evidence for a muscle pump contribution exists, but whether the muscle pump is the exclusive contributor or whether a rapid vasodilatory mechanism(s) exists remains controversial.

Studies that support an exclusive muscle pump effect have examined the onset of mild or moderate locomotion in dogs or rats walking on a treadmill. These studies demonstrate that the magnitude of the initial rapid adjustment in blood flow is related to speed (contraction frequency) not grade (contraction intensity) (11, 12). More invasive studies have used video microscopy in situ to directly measure the time course of vessel diameter responses to muscle stimulation or direct application of known vasodilators to microvessels (3, 8, 23). These studies suggest that the onset of vasodilation exhibits a 4- to 6-s delay from the time muscle contraction or vasodilator application begins. Taken together, these studies argue that metabolic vasodilatory mechanisms are too slow to account for the immediate increase in blood flow at exercise onset and that the muscle pump is the sole contributor.

In contrast, early work in the 1960s from Corcondilas et al. (1) demonstrated a contraction-intensity dependence of the forearm muscle blood flow response to single 0.3-s contractions. This is consistent with rapid vasodilation, but because of the poor time resolution of strain gauge plethysmography flow measurement, assessment of the change in magnitude of muscle blood flow as a function of time was again limited. More recently, Doppler blood flow measures in both human and animal single contraction models have revealed an immediate increase in muscle blood flow following a single 1-s contraction that finally reached a peak by the fourth to sixth cardiac cycle (4, 9, 21). This flow pattern is inconsistent with an exclusive muscle pump effect in the first few seconds of exercise. However, a limitation of these studies is that they could only infer that the second cardiac cycle after contraction provided evidence for vasodilation (4, 21).

Given the continued controversy in this area and the limitations of previous experiments, we employed Doppler ultrasound and arterial tonometry to obtain noninvasive, beat-by-beat measures of forearm blood flow (FBF) and arterial blood pressure after single 1-s contractions across a range of forearm contraction intensities in arm above and below heart positions. We tested the hypothesis that rapid vasodilation contributes to the increase in exercising muscle blood flow observed in the first cardiac cycle after release of a brief contraction. We reasoned that, because muscle pump effectiveness already appears maximized with mild contractions in animal locomotion (10, 12, 14), an exclusive muscle pump effect would be supported by a similar magnitude in the immediate hyperemia across a range of forearm isometric contraction intensities. In contrast, a proportional relationship between the magnitude of immediate hyperemia and contraction intensity would demonstrate that vasodilation proportional to muscle activation must...
be occurring. Our results are consistent with the existence of a rapid vasodilation proportional to muscle activation at the onset of human forearm exercise.

**METHODS**

**General Methods**

**Subjects.** Ten healthy subjects (3 men and 7 women; age 24.5 ± 1.6 yr) participated in this study and gave written consent on a form approved by the Queen’s University Health Sciences Research Ethics Board after receiving full written and verbal details of the experimental protocol and any potential risks involved. Seven of the 10 subjects completed arm above and arm below protocols on separate days, and one of these subjects completed only arm above trials.

**Subject monitoring.** Subjects arrived at the laboratory in a rested state at least 2 h after eating. They assumed a supine position with their right arm supported such that the mid forearm was ~20 cm above or below heart level, which results in an ~30 mmHg difference in local forearm pressure. Heart rate (HR) was monitored with an electrocardiogram standard CM5 lead placement. Mean arterial pressure (MAP) was measured at heart level by arterial tonometry on the resting arm (Colin 7000, Trudell Medical Instruments).

**Forearm venous volume.** Strain gauge plethysmography (EC-6 plethysmograph, D. E. Hokanson) was used to measure changes in forearm volume as a surrogate for venous volume after single contractions. Briefly, a mercury-in-Silastic rubber strain gauge was positioned around the forearm at the point of largest circumference. Before the onset of a contraction, the strain gauge was balanced to nullify any change in forearm volume as a surrogate for venous volume after single contractions. Briefly, a mercury-in-Silastic rubber strain gauge was positioned around the forearm at the point of largest circumference. Before the onset of a contraction, the strain gauge was balanced to nullify any change in forearm volume as a surrogate for venous volume after single contractions. Briefly, a mercury-in-Silastic rubber strain gauge was positioned around the forearm at the point of largest circumference.

**Detecting differences in venous emptying between conditions with strain gauge measurements requires consideration of 1) the resolution of strain gauge measurements and 2) whether differences in forearm volume immediately after release of contraction, which are undetectable with this resolution, would represent physiologically significant differences in venous pressure between contraction intensities. In this context, strain gauge measurements can detect the pulsatile changes in forearm volume occurring with each cardiac cycle in an unoccluded forearm (~0.03 ml/100 ml). The volumes measured immediately postcontraction represent the low end of the venous pressure-volume relationship. Therefore, it is unlikely that the limits of strain gauge forearm volume measurement resolution contribute to a physiologically relevant error in interpreting observed forearm volume changes to indicate similar postcontraction venous pressure environments across contraction intensities.

**MBF.** Brachial artery mean blood velocity (MBV) was measured with a 4-MHz pulsed Doppler probe (model 500V TCD, Multigon Industries, Mt. Vernon, NY) securely fixed to the skin over the brachial artery above the antecubital fossa. With this placement, probe insolation angle relative to the skin is ~45°, and the brachial artery is approximately parallel to the skin surface. During pilot studies, arterial cross-sectional area (10-MHz linear echo Doppler ultrasound probe operating in B mode, Vingmed System Five, GE Medical) was measured in each arm position to confirm that arterial diameter was not different between arm positions and did not change in response to brief elevations in arterial inflow after single contractions across the range of intensities used in this study. This means that measured changes in MBV are directly proportional to changes in FBF. Thus percent change (Δ) FBF is reported in the figures, and calculated forearm vascular conductance (FVC) is a function of MBV and MAP in this study.

**Forearm contractions.** We investigated the beat-by-beat forearm hemodynamic (FBF, FVC) response to single 1-s isometric forearm contractions at 5, 10, 15, 20, 30, 50, and 70% maximal voluntary contraction (MVC) strength. Subjects performed three MVC attempts before the start of the experiments. The peak MVC achieved was used to determine submaximal %MVC targets. Isometric handgrip force feedback for the subjects was displayed continuously on a computer data acquisition system (Powerlab, ADInstruments). Subjects achieved the target force and duration for each trial by displacing the force readout line to the desired level in time with a 1-s signal light. Force profiles generally demonstrated a progressive increase to the target force over the first 0.5 s.

**Specific Experimental Protocol**

Each subject performed three trials at each %MVC in both arm above heart and arm below heart positions. These trials were averaged together to yield a single response profile per subject, and these average values for each subject were used in the statistical analysis. The order (ascending contraction intensity vs. descending contraction intensity) was counterbalanced across subjects. Briefly, after 10 s of measurements at rest, the subjects were prompted to perform a single forearm contraction in time with the signal light, and data were continuously recorded. A 2-min rest period separated each trial, during which brachial artery MBV, MAP, and HR returned to baseline well before the onset of each new trial.

**Data Acquisition and Analysis**

MBV, MAP, and ECG were collected at 200 Hz with a data acquisition system (Powerlab, ADInstruments) on a dedicated computer. Baseline values for MBV, MAP, and HR were quantified as the average over the 10-s rest period before contraction. The immediate exercise hemodynamic response was derived from the first cardiac cycle after release of contraction that was unaffected by contraction (see Fig. 1). The onset of this cardiac cycle occurred on average 0.7 ± 0.06 s after contraction release.

**Statistical Analysis**

The effect of arm position and contraction intensity on MAP, HR, %change in MBV, and %change in FVC was analyzed via two-way repeated-measures ANOVA. Post hoc analysis was performed by using Tukey’s test for pairwise comparisons. In addition, linear regression of %change in MBV and FVC vs. contraction intensity was performed for arm above heart level data, and a quadratic regression was fit to the arm below heart level data. Significance was set at P < 0.05. Data are presented as means ± SE. All statistical tests were
performed with a commercial statistical package (SigmaStat 2.03, SPSS).

RESULTS

Forearm Venous Emptying

Figure 2 illustrates the immediate reduction in forearm volume in the arm below heart condition after the release of a brief contraction across the range of contraction intensities investigated in this study. Results are qualitatively similar for arm above heart, with little or no change in forearm volume evident in that position. From these data, it is clear that venous emptying is maximized at low contraction intensities. Therefore, muscle pump effectiveness in terms of venous emptying does not appear to be contraction intensity dependent in this exercise model.

MAP and HR Responses

There were no changes in HR or MAP from rest to post-contraction. Mean group values for HR were in the mid to upper 50 beats/min range. Mean group values for MAP were in the mid to upper 80 mmHg range.

FBF and FVC

Figure 3 illustrates the beat-by-beat %ΔFBF after forearm isometric handgrip contractions across a range of contraction intensities in both arm positions. The progressive, beat-by-beat increase in FBF, peaking by approximately the third to fourth cardiac cycle, is evident for all contraction intensities. Figure 6 illustrates the peak %ΔFVC occurring in the fourth cardiac cycle in arm above vs. arm below heart level conditions. Peak %ΔFVC was greater in the below vs. above heart level condition at 10, 15, 20, 30, and 50% (P < 0.05).

Of primary interest in this study was the FBF response in the first cardiac cycle after contraction release. This is plotted vs. contraction intensity in Fig. 4A for both arm positions and demonstrates the linear increase of immediate exercise hyperemia in proportion to contraction intensity in the arm above heart condition. In contrast, the arm below heart condition demonstrates a curvilinear relationship, such that the slope of the relationship is initially greater than arm above heart level but becomes less than arm above heart level at higher contraction intensities. The absence of a difference between arm positions at low contraction intensities when venous emptying is already maximized may indicate a lack of muscle pump effectiveness in this isometric forearm contraction model.

Calculated FVC using heart level MAP is similar to FBF (Fig. 4B). However, when FVC is recalculated by estimating the pressure gradient across the forearm by assuming venous pressure to be zero (muscle contraction-induced emptying of venous volume) and accounting for the hydrostatic contribution to arterial pressure at the forearm, it is clear that FVC changes are not different between arm positions across all contraction intensities (see Fig. 5). This is consistent with muscle activation, and subsequently vasodilation, being similar between arm positions.

DISCUSSION

This study was designed to test the hypothesis that rapid vasodilation contributes to the immediate increase in exercising muscle blood flow after release of a single brief contraction. The key novel findings of this study are 1) immediate exercise hyperemia is linearly related to muscle contraction intensity in the human forearm contracting above heart level and 2) the greater magnitude of immediate exercise hyperemia with the arm in the dependent position can be explained by the effect of a similar change in vascular conductance under
greater local arterial driving pressure. These new data provide strong evidence for the existence of a rapid-acting vasodilatory mechanism(s) in human skeletal muscle, the net effect of which is 1) proportional to muscle activation and 2) influenced by local arterial driving pressure.

Rationale

A difficulty in attempting to determine the separate contributions of the muscle pump vs. vasodilatory mechanisms at the onset of exercise lies in the fact that both may be initiated. Thus changes in blood flow in a given rest-to-exercise transition might be due to either one or both of these mechanisms. In the present study, we attempted to minimize the potential contribution of the muscle pump by utilizing the arm above heart position to minimize initial forearm venous volume (6, 15), isometric contractions to minimize muscle relaxation-induced active venous opening (5), and to examine the pattern of immediate exercise hyperemia across a range of contraction intensities since contraction intensity does not appear to enhance muscle pump function (10–12, 14). Under these conditions, we reasoned that, if the muscle pump were the sole contributor to the immediate increase in blood flow after the first contraction of exercise, we would not see any, or at most a slight, contraction intensity-dependent hyperemia across a range of contraction intensities. Conversely, if a rapid vasodilatory mechanism(s) contributes to immediate exercise hyperemia, the immediate increase in blood flow would be proportional to contraction intensity.

Evidence for Rapid Vasodilation

We observed that the magnitude of the immediate increase in blood flow after the release of a single contraction was proportional to contraction intensity. The observation in our experimental model that forearm venous emptying is already maximal at very low contraction intensities (see Fig. 2) sup-

Fig. 4. A: %ΔFBF from baseline for the first cardiac cycle after release of contraction plotted against a range of contraction intensities (%MVC). Best-fit linear regression for arm above heart level condition: %ΔFBF = 3.4(%MVC) + 10.6, r² = 0.99. Best-fit quadratic regression for %ΔFBF = −22.2 + 9.2(%MVC) − 0.06(%MVC)². B: %ΔFVC (calculated by using heart level blood pressure for both arm positions) from baseline for the first cardiac cycle after release of contraction, plotted against range of contraction intensities. Best-fit linear regression for arm above heart level condition: %ΔFVC = 3.6(%MVC) + 4.1, r² = 0.99. Best-fit quadratic regression for arm below heart level condition: %ΔFVC = −22.2 + 8.9(%MVC) − 0.06(%MVC)². ○, Arm above heart level condition (n = 10); ◊, arm below heart level condition (n = 9). * Significantly different from arm above heart level (P < 0.05).

Fig. 5. %ΔFVC (calculated by using local forearm level arterial blood pressure within each arm position, and assuming venous pressure of −0 mmHg) from baseline for the first cardiac cycle after release of contraction, plotted against range of contraction intensities (%MVC). Best-fit linear regression for arm above heart level condition: %ΔFVC = 3.6(%MVC) − 0.4, r² = 0.99. Best-fit quadratic regression for arm below heart level condition: %ΔFVC = −34.3 + 6.4(%MVC) − 0.04(%MVC)². ●, Arm above heart level condition (n = 10); ◊, arm below heart level condition (n = 9).

Fig. 6. Peak %ΔFVC (calculated by using heart level blood pressure for both arm positions) from baseline for the fourth cardiac cycle after release of contraction (see Fig. 3), plotted against a range of contraction intensities. Best-fit linear regression for arm above heart level condition: %ΔFVC = 6.6(%MVC) − 10.4, r² = 0.99. Best-fit quadratic regression for arm below heart level condition: %ΔFVC = −8.9 + 17.5(%MVC) − 0.15(%MVC)². ●, Arm above heart level condition (n = 10); ◊, arm below heart level condition (n = 9). *Significantly different from arm above heart level (P < 0.05).
ports the interpretation that an increase in muscle pump effectiveness cannot explain the substantial proportional increase in immediate exercise hyperemia with increasing contraction intensity. Thus we believe the results of this study have clearly identified a contribution of vasodilation to immediate exercise hyperemia. More specifically, these data indicate a contraction intensity-dependent vasodilation, with at most a minor contraction intensity-dependent muscle pump effect in the isometric forearm contraction model in this study.

**Arm Position Effect: Elevated Early Exercise Hyperemia in a Dependent Limb**

We observed a fundamental difference in the contraction-intensity dependence of the immediate %ΔFBF and FVC response between arm positions. Although these relationships were linear for the arm above heart position, they were curvilinear in the arm below heart (dependent) position, with a steeper slope across the low to middle contraction intensities (see Figs. 4–6). Importantly, these arm position differences extended to the peak %ΔFBF and FVC responses (see Fig. 6).

We interpret these data to indicate that greater immediate exercise hyperemia in a dependent limb can result from the interaction of a given change in vascular conductance with a greater local arteriovenous pressure gradient after contraction-induced venous emptying (i.e., removal of hydrostatic column in the veins but not arteries). However, we also observed that the peak %ΔFBF and FVC responses at a given contraction intensity were substantially greater in the below vs. above heart position at a time when arterial inflow would have already restored below heart forearm venous volume (Fig. 6). This latter observation is not entirely consistent with greater arterial inflow in the dependent position being a function of the arteriovenous pressure gradient and warrants further investigation.

**Dependency of Rapid Vasodilation on Experimental Model**

Recently, innovative studies from Sheriff’s lab (10, 11, 14) have indicated that, in rodent treadmill locomotion exercise, vasodilation is substantially (~5 s) delayed in rest-to-exercise and exercise-to-exercise transitions and that immediate blood flow increases match changes in stride frequency but not intensity. These data suggest an exclusive muscle pumping effect. This is consistent with the study conducted by Wunsch et al. (23) involving direct application of vasodilators to isolated rodent arterioles, in which the onset of vasodilation occurred after ~5 s. However, in the human forearm, exercise hyperemia demonstrates a biphasic adaptation in which the immediate increase in FBF reaches a plateau by ~5 s of exercise, and this plateau is maintained until a further elevation in FBF begins at ~15–20 s of exercise (16). Such a dynamic profile is inconsistent with a delay of ~5 s in the onset of vasodilation.

Our data demonstrating an immediate contribution of vasodilation are consistent with the dynamics of the blood flow response observed in forearm exercise (16) and with the response of muscle blood flow to a single contraction in both dogs (9) and humans (21). Whether the basis of differences in our observations vs. the recent data from Sheriff’s lab (10, 11, 14) are species dependent or muscle activation dependent is not clear. It has been proposed that muscle activation in the 1-s forearm contraction model is the equivalent of accumulated muscle activation in the rodent or dog over a period of 5 s of treadmill locomotion (11). However, both magnitude and duration must be considered when differences in vasodilatory delay are assessed between the present study and mild treadmill locomotion in rats (10, 11, 14). Species size and gait differences, as well as exercise modality, have the potential for influencing muscle activation magnitude and duration. For example, activities such as stair climbing, rowing, or downhill skiing can involve contractions of intensity and duration similar to the forearm contractions in this study.

**Potential Mechanisms**

Van Teefelen and Segal (22) have demonstrated that vasodilation increases in proportion to the tension developed by a given number of active motor units and in proportion to the number of active motor units at a given tension. This is consistent with the spatial distribution of microvascular units relative to motor unit fibers (2). In the present study employing voluntary contractions, increases in both motor unit recruitment and tension per motor unit likely contributed to the contraction intensity-dependent vasodilatory response.

Mechanisms that account for rapid vasodilation remain elusive. Recently, Sheriff and Hakeman (11) demonstrated that blockade of nitric oxide affects early exercise hyperemia but only after ~4 s of treadmill locomotion in dogs. Wunsch et al. (23) assessed the onset of vasodilation induced by K+, acetylcholine, adenosine, and nitric oxide and found that a delay of ~5 s existed between the time of direct application of these substances to isolated rat arterioles and the onset of vasodilation. Venous emptying-mediated vasodilation also has an onset that is delayed by ~5 s from the onset of venous emptying (20). Thus the above known vasodilatory mechanisms do not appear to be able to explain the rapid vasodilation observed in this study. One intriguing possibility that remains unexplored is that of a mechanical distortion effect on resistance vessels due to muscle contraction. Interstitial pressure, indicating the compressive force of muscle contraction, increases in proportion to muscle contraction intensity (19). Whether this can induce proportional, rapid alterations in smooth muscle vascular tone remains to be determined.

In summary, we evaluated the immediate exercise hyperemia after a single contraction under experimental conditions where everything possible was done to minimize the muscle pump effect (arm above heart level, isometric contraction, range of contraction intensities). Under these conditions, we observed that the magnitude of the immediate (first cardiac cycle after release of a brief contraction) exercise hyperemia was proportional to contraction intensity. These data provide compelling evidence for the existence of a rapid-acting vasodilatory mechanism(s) in human forearm exercise. The nature of this mechanism(s) remains to be determined.

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**REFERENCES**


