Hyperbaric hyperoxia reduces exercising forearm blood flow in humans

Darren P. Casey,1 Michael J. Joyner,1 Paul L. Claus,2 and Timothy B. Curry1

1Department of Anesthesiology and 2Division of Preventative, Occupational, and Aerospace Medicine, Mayo Clinic, Rochester, Minnesota

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Casey DP, Joyner MJ, Claus PL, Curry TB. Hyperbaric hyperoxia reduces exercising forearm blood flow in humans. Am J Physiol Heart Circ Physiol 300: H1892–H1897, 2011. First published March 18, 2011; doi:10.1152/ajpheart.00165.2011.—Hypoxia during exercise augments blood flow in active muscles to maintain the delivery of O2 at normoxic levels. However, the impact of hyperoxia on skeletal muscle blood flow during exercise is not completely understood. Therefore, we tested the hypothesis that the hyperemic response to forearm exercise during hyperbaric hyperoxia would be blunted compared with exercise during normoxia. Seven subjects (6 men/1 woman; 25 ± 1 yr) performed forearm exercise (20% of maximum) under normoxic and hyperoxic conditions. Forearm blood flow (FBF; in ml/min) was measured using Doppler ultrasound. Forearm vascular conductance (FVC; in ml·min−1·100 mmHg−1) was calculated from FBF and blood pressure (in mmHg; brachial arterial catheter). Studies were performed in a hyperbaric chamber with the subjects supine at 1 atmospheres absolute (ATA) (sea level) while breathing normoxic gas [21% O2, 1 ATA; inspired PO2 (PiO2) = 150 mmHg] and at 2.82 ATA while breathing hyperoxic normoxia (7.4% O2, 2.82 ATA, PiO2 ≈ 150 mmHg) and hyperoxic (100% O2, 2.82 ATA, PiO2 ≈ 2,100 mmHg) gas. Resting FBF and FVC were less during hyperbaric hyperoxia compared with hyperbaric normoxia (P < 0.05). The change in FBF and FVC (Δ from rest) during exercise under normoxia (204 ± 29 ml/min and 229 ± 37 ml·min−1·100 mmHg−1, respectively) and hyperbaric normoxia (203 ± 28 ml/min and 217 ± 35 ml·min−1·100 mmHg−1, respectively) did not differ (P = 0.66–0.99). However, the ΔFBF (166 ± 21 ml/min) and ΔFVC (163 ± 23 ml·min−1·100 mmHg−1) during hyperbaric hyperoxia were substantially attenuated compared with other conditions (P < 0.01). Our data suggest that exercise hyperemia in skeletal muscle is highly dependent on oxygen availability during hyperoxia.

DURING DYNAMIC EXERCISE there is an increased metabolic demand that is matched closely by increases in skeletal muscle blood flow and O2 delivery. In conditions in which O2 availability is compromised, such as hypoxia, there is local vasodilation and an increased blood flow that ensures delivery of O2 to respiring tissues under metabolic stress. The combination of the two conditions (hypoxia and exercise) elicits a greater vasodilator response and thus an augmented blood flow response (3, 5, 6, 24, 25, 34, 35). The augmented hypoxic exercise hyperemia is proportional to the hypoxia-induced fall in arterial O2 content, thus preserving muscle O2 delivery and ensuring it is matched to demand.

Conversely, under hyperoxic conditions muscle blood flow at rest in humans is reduced (2, 13, 22, 37). Moreover, there is some evidence that suggests that muscle blood flow is reduced during and after hyperoxic exercise compared with normoxic conditions (11, 22, 31). Reich and colleagues (22) demonstrated that postexercise calf blood flow is reduced at hyperbaric pressures while breathing 100% O2. However, these findings are limited by the delay (~30 s) in blood flow measurements following contractions and the uncertain effects of increased atmospheric pressure per se. Measurements made during exercise (i.e., thermo- and dye-dilution techniques) have demonstrated that leg blood flow is reduced during leg kicking and cycle exercise when comparing normobaric hyperoxia [fraction of inspired O2 (FIO2) = 100% O2] with normobaric normoxia, without any difference in O2 consumption and delivery between the two conditions (11, 31). However, these studies only examined the leg blood flow response to small increases (< 10%) in arterial O2 content. Therefore, the aim of the current study was to investigate the blood flow response in the exercising forearm to larger increases in estimated arterial and venous O2 content via hyperbaric hyperoxia. We hypothesized that there will be a reduction in exercise blood flow that mirrors the estimated increase in O2 content.

METHODS

Subjects. A total of eight young healthy subjects (7 men and 1 woman) volunteered to participate in the study. Subjects completed written, informed consent and were nonobese (body mass index < 28 kg/m2), nonsmokers, and not taking any medications. A detailed history and physical exam directed toward hyperbaric O2 therapy risks was performed by a board-certified Undersea and Hyperbaric Medicine Physician (P. L. Claus) before each subject’s study day. Additionally, chest X-rays and a 12-lead electrocardiogram were performed as part of the standard screening procedures for exposure to hyperbaric oxygenation. Studies were performed after an overnight fast, and the subjects refrained from exercise and caffeine for at least 24 h before the study. The female subject was studied during the early follicular phase of the menstrual cycle. All study protocols were approved by the Institutional Review Board and were performed according to the Declaration of Helsinki.

Forearm exercise. Subjects performed rhythmic forearm exercise with a handgrip device by the right arm at 20% of each subject’s maximal voluntary contraction (mean, 44 ± 3 kg; and range, 25–57 kg), determined at the beginning of each experiment. The weight was lifted 4 to 5 cm over a pulley at a duty cycle of 1 s contraction and 2 s relaxation (20 contractions/min) using a metronome to ensure correct timing. The average weight used for forearm exercise was 8.8 ± 0.7 kg.

Arterial catheterization. A 20-gauge, 5-cm catheter (model RA-04020, Arrow International, Reading, PA) was placed in the brachial artery of the exercising arm under aseptic conditions after local anesthesia (2% lidocaine) for measurement of arterial pressure and was continuously flushed (3 ml/h) with heparinized saline.

Heart rate and systemic blood pressure. Heart rate (HR) was recorded via continuous three-lead ECG. A pressure transducer connected to the arterial catheter measured beat-to-beat blood pressure (Cardiocap/5, Datex-Ohmeda, Louisville, CO). Beat-to-beat stroke volume was calculated from the brachial arterial pulse pressure wave by model flow analysis. Model flow computes an aortic waveform based on nonlinear pressure-volume, pressure-compliance, and pres-
sure-characteristic impedance equations, incorporating age, sex, height, and body mass (32). Cardiac output was calculated as the average stroke volume multiplied by the HR.

**Forearm blood flow.** Brachial artery mean blood velocity was determined with a 4-MHz pulsed-Doppler probe (model 500 V, Multigon, Mt. Vernon, NY) proximal to the catheter insertion site. A linear 15-MHz Doppler ultrasound probe (M-Turbo, Sonosite, Bothell, WA) was placed immediately proximal to the velocity probe to measure brachial artery diameter. Brachial artery blood velocity was measured throughout each condition with a probe insonation angle of 60°. Brachial artery diameter measurements were obtained at end diastole between contractions during steady-state conditions. Forearm blood flow (FBF) was calculated as the product of mean blood velocity (in cm/s) and brachial artery cross-sectional area (in cm²) and expressed as milliliters per minute (ml/min).

**Experimental protocol.** A schematic diagram of the general experimental design is illustrated in Fig. 1. Each trial included a Po2 normalization period (5 min), followed by a resting baseline condition (2 min), and then by rhythmic forearm exercise (4 min) at 20% maximal voluntary contraction. All studies were performed in a hyperbaric chamber at ~1,000 ft above sea level with the subjects supine and consisted of three separate exercise trials. Ambient temperature in the hyperbaric chamber during the study trials was maintained at approximately thermoneutral with a climate control system.

**Trial 1** was performed at 1 atmospheres absolute (ATA) (unpressurized chamber) while breathing normoxic gas (air) (21% O2; inspired Po2 (Pio2) ≈ 150 mmHg). The hyperbaric chamber was then pressurized to 2.82 ATA over 5–10 min. **Trial 2** was performed at 2.82 ATA while breathing hyperbaric normoxic gas (7.4% O2; Pio2 ≈ 150 mmHg). **Trial 3** was performed at 2.82 ATA while breathing hyperoxic gas (100% O2; Pio2 ≈ 2,100 mmHg). Breathing 7.4% O2 at 2.82 ATA is equivalent to breathing air at 1 ATA and served as a pressure control trial to confirm that any changes in blood flow are independent of pressure changes. The 100% O2 at 2.82 ATA served as the hyperoxic trial and was used to study the blood flow response during markedly increased levels of arterial and venous O2 content. Inspired gas (air, 7.4% O2, and 100% O2) was supplied at ambient pressure via a tight-fitting, nonrebreathing, silicone oronasal mask connected to a demand regulator. The fit of the mask was adjusted by tightening the mask until no air leaks were apparent to the subject during inhalation against a closed valve. The total time of the hyperbaric exposure was limited to 49 min to prevent the need for decompression for study personnel who breathed air throughout the hyperbaric exposure. Each trial consisted of a Po2 normalization period (5 min), rest (2 min), and exercise (4 min). fsw, feet of sea water.

**Statistical difference was set a priori at P < 0.05.**

Estimated arterial O2 content (CaO2) was calculated under each condition as:

\[
CaO_2(\text{ml/dl}) = \left[\text{hemoglobin (g/dl)}\right] \times 1.36(\text{ml O}_2/\text{g of hemoglobin}) \times SaO_2(%) \times 100 + 0.003(\text{ml/dl}) \times PaO_2(\text{mmHg})
\]

where \(SaO_2\) is arterial saturation, \(PaO_2\) is the partial pressure of arterial O2, 1.36 is the O2 capacity of hemoglobin, and 0.003 is the solubility of O2 in plasma. A hemoglobin value of 14 g/dl was used across trials and is based on average values observed in young male subjects from our previous studies (4–6). \(PaO_2\) values were derived from the Alveolar Air Equation:

\[
PAO_2(\text{mmHg}) = FIO_2 \times (Pa - P_{H_2O}) - PaCO_2 \times \left[FiO_2 + (1 - FiO_2)/0.8\right]
\]

where \(Pa\) is the barometric pressure, \(P_{H_2O}\) is the water vapor pressure in the airways (47 mmHg), \(PaCO_2\) is the partial pressure of arterial CO2 (estimated to be 40 mmHg), and 0.8 represents the assumed respiratory quotient. The average \(Pa\) on the study days was 733 ± 1 mmHg (range, 729–737), and this was used in the calculations of \(PaCO_2\) for the

**Fig. 1.** Detailed hyperbaric exposure timeline. Hyperbaric exposure is shown in atmospheres absolute pressure (ATA) units. **Trial 1** (normoxia) was performed at 1 ATA while breathing normoxic gas (air; 21% O2). **Trials 2 and 3** took place at 2.82 ATA while breathing 7.4% and 100% O2, respectively. Breathing 7.4% O2 at a depth of 2.8 ATA is the equivalent to breathing room air at sea level and served as a "pressure control" trial. Breathing 100% O2 at a depth of 2.82 ATA served as the hyperoxic trial. Each trial consisted of a Po2 normalization period (5 min), rest (2 min), and exercise (4 min).
Cardiac output, l/min 5.8

Mean arterial pressure, mmHg 86

(P2) produced a greater increase in MAP compared with hyperbaric normoxia (7.4 and 21% O2) compared with 1 ATA (Table 1. Resting HR was slightly lower at 2.82 ATA (for both mass index, 24 kg/m2). Seven (6 men and 1 woman) of the eight subjects completed the study protocol. One subject did not complete the protocol because of ear pain associated with the pressurization of the chamber. Those subjects completing the study were 25 ± 1 yr of age, 180 ± 4 cm in height, and 78 ± 4 kg in weight (body mass index, 24 ± 1 kg/m2).

**Systemic hemodynamic responses.** The group data for systemic hemodynamic responses to combined forearm exercise and pressurization with each inspired O2 level are presented in Table 1. Resting HR was slightly lower at 2.82 ATA (both 7.4 and 21% O2) compared with 1 ATA (P < 0.05). However, the change in HR from rest to exercise did not differ between trials (P = 0.20). Pressurization of the chamber to 2.82 ATA resulted in higher MAP at rest and during exercise. Hyperoxia (2.82 ATA at 100% O2) produced a greater increase in MAP during exercise compared with both the normoxia (1 ATA at 21% O2; P < 0.01) and hyperbaric normoxia (2.82 ATA at 7.4% O2; P < 0.05) trials. Cardiac output at rest (P = 0.75) and during exercise (P = 0.87) was not different between trials.

**FBF and conductance.** Presented in Table 2 are group data (means ± SE) forearm hemodynamics at rest and during exercise under each condition. FBF and FVC at rest and during exercise did not differ between normoxic (1 ATA at 21% O2) and hyperbaric normoxic (2.82 ATA at 7.4% O2) conditions. Hyperoxia (2.82 ATA at 100% O2) reduced resting FBF and FVC compared with hyperbaric normoxia (P < 0.05). Of particular interest to the current study, hyperoxic exercise caused a substantial reduction in FBF and FVC compared with the normoxic and hyperbaric normoxic exercise conditions (P < 0.01). The changes (Δ) in FBF and FVC (relative to resting values) were also reduced during hyperoxic exercise (Fig. 2, A and B).

**Estimated arterial O2 content.** The estimated PaO2 during the hyperbaric hyperoxia trial (1,773 mmHg) is substantially greater than during normobaric normoxia and hyperbaric normoxia trials (85 and 89 mmHg, respectively). The PaO2 during hyperbaric hyperoxia would result in a ~25–30% increase in the estimated CaO2 compared with the other trials (24.4 vs. 18.9 ml O2/100 ml).

**DISCUSSION**

In the present study, we determined the impact of hyperbaric oxygenation on the blood flow and vasodilator response to rhythmic forearm exercise in young healthy adults. Our primary goal was to examine whether FBF and conductance would decrease in response to hyperoxic exercise to a similar magnitude to the increases previously observed during hypoxic exercise. The major observation in this study is that large increases in estimated systemic O2 content resulted in a substantial reduction in exercising FBF despite significantly higher perfusion pressures. Interestingly, the blunted ΔFVC during hyperoxic exercise (~25% lower) mirrored the estimated increase in arterial O2 content (~25–30%) in the present study. These findings parallel our previous findings in which hypoxia-mediated increases in ΔFVC during exercise mirrors the fall in O2 content (5, 6).

Previous attempts at examining the effect of hyperoxic O2 on exercising blood flow have been limited to measuring postexercise flows (via plethysmography). Along these lines, postexercise calf blood flow following foot ergometry under hyperoxic conditions (3 ATA at 100% O2) was shown to be significantly reduced (22). Studies that have examined blood flow responses to acute hyperoxia during dynamic exercise have been limited to small increases in PaO2 using 100% O2 under normobaric conditions. Kajser (16) originally reported that arterial-venous O2 difference in the arm increased during hyperoxic exercise, thus suggesting a decreased muscle blood flow. However, FBF was not directly measured. Direct measurements of flow indicate that there is an ~8–10% reduction in leg blood flow in response to a ~10% increase in arterial O2 content during hyperoxic (FIO2 = 100% O2) exercise (9, 11, 31). As noted earlier, these findings are limited to small increases in O2 content. Therefore, our data are the first evidence to demonstrate that hyperbaric oxygenation decreases blood flow and vasodilation in active muscle groups during exercise.

**Table 2. Forearm hemodynamics at rest and with exercise during normoxia, hyperbaric normoxia, and hyperoxia**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rest (21% O2)</th>
<th>Exercise (21% O2)</th>
<th>Rest (7.4% O2)</th>
<th>Exercise (7.4% O2)</th>
<th>Rest (100% O2)</th>
<th>Exercise (100% O2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm blood flow, ml/min</td>
<td>50 ± 12</td>
<td>254 ± 38</td>
<td>57 ± 12</td>
<td>261 ± 37</td>
<td>48 ± 10†</td>
<td>214 ± 30*</td>
</tr>
<tr>
<td>Forearm vascular conductance, ml·min⁻¹·100 mmHg⁻¹</td>
<td>60 ± 16</td>
<td>288 ± 51</td>
<td>66 ± 17</td>
<td>284 ± 49</td>
<td>53 ± 12†</td>
<td>217 ± 34*</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.01 vs. other exercise values; †P < 0.05 vs. 2.82 ATA at 7.4% O2.
vasoconstrictor action of O2 on the arterial and arteriolar wall. Resistance under hyperoxic exercise conditions may be a direct contracting forearm (12). Finally, the increase in vascular sympatholysis and therefore enhanced vasoconstriction in the elevated levels of O2 (21). Along the same lines, an increase in has been observed in porcine coronary arteries exposed to constriction via a reduction in basal nitric oxide (NO) production (36). Additionally, vasoconstriction via prostaglandin-mediated vasodilation following isometric exercise is reduced during hyperoxia (14). However, hyperoxia does not appear to enhance the magnitude of change in sympathetic nerve activity to nonactive skeletal muscle during dynamic exercise (26). Therefore, it is unclear whether a greater amount of sympathetic vasoconstrictor activity contributed to the reduced FBF and vasodilation during hyperbaric exercise. Furthermore, we cannot rule out the possibility that increased O2 levels may have attenuated functional sympatholysis and therefore enhanced vasoconstriction in the contracting forearm (12). Finally, the increase in vascular resistance under hyperoxic exercise conditions may be a direct vasoconstrictor action of O2 on the arterial and arteriolar wall. Along these lines, some evidence suggests that the vascular response (i.e., constriction) to hyperoxia in the hindlimbs of dogs is not mediated by the autonomic nervous system but rather direct action of high arterial O2 tension (1).

A decreased release or responsiveness to local vasodilators within the contracting muscle under hyperoxic conditions could also promote a shift in the vasoconstrictor/vasodilator balance and consequently alter vascular tone. In this context, prostaglandin-mediated vasodilation following isometric exercise is reduced during hyperoxia (36). Additionally, vasoconstriction via a reduction in basal nitric oxide (NO) production has been observed in porcine coronary arteries exposed to elevated levels of O2 (21). Along the same lines, an increase in free radical production (i.e., superoxide anions) during hyperbaric oxygenation causes vasoconstriction in the cerebral circulation of rats via inactivation of NO (39). However, recent evidence suggests that NO metabolites are unaffected in humans during normobaric hyperoxic exercise (9).

Potential mechanisms for reduced blood flow during hyperoxic exercise. A greater increase in MAP without a change in cardiac output and a reduction in FVC indicates that vascular resistance was increased during hyperoxic exercise (relative to the other trials). Hyperoxia reduces muscle sympathetic nerve activity at rest (14, 26, 37); however, the impact of hyperoxia during exercise is less clear. During isometric forearm exercise hyperoxia enhances metaboreflex sensitivity, which results in a greater sympathetic and blood pressure reactivity (14). However, hyperoxia does not appear to enhance the magnitude of change in sympathetic nerve activity to nonactive skeletal muscle during dynamic exercise (26). Therefore, it is unclear whether a greater amount of sympathetic vasoconstrictor activity contributed to the reduced FBF and vasodilation during hyperoxic exercise. Furthermore, we cannot rule out the possibility that increased O2 levels may have attenuated functional sympatholysis and therefore enhanced vasoconstriction in the contracting forearm (12). Finally, the increase in vascular resistance under hyperoxic exercise conditions may be a direct vasoconstrictor action of O2 on the arterial and arteriolar wall. Along these lines, some evidence suggests that the vascular response (i.e., constriction) to hyperoxia in the hindlimbs of dogs is not mediated by the autonomic nervous system but rather direct action of high arterial O2 tension (1).

Accumulating evidence suggests that erythrocytes have the ability not only to sense changes in O2 but also to modulate vascular tone (via release of ATP and/or NO), thus leading to appropriate changes in blood flow and matching O2 delivery with metabolic need (10). Under conditions of hemoglobin desaturation and mechanical deformation, ATP is released from erythrocytes and is thought to contribute to the augmented blood flow during hypoxic exercise (15, 27, 28). Therefore, an attenuated release of ATP in response to large increases in O2 may have blunted the blood flow response to exercise via these or related mechanisms.

Experimental considerations. There are four potential limitations to our study that should be mentioned. First, in the present study, despite our efforts, we were unable to directly measure arterial and venous blood gases because of maximal Po2 limits (999 mmHg) of our commercially available arterial blood gas analyzers. Additionally, the blood gas analyzers are not able to be used in the hyperbaric chamber and blood samples obtained under pressure are subject to supersaturation and bubbling of O2 upon decompression for analysis, which can result in significant reading errors (7). Therefore, our estimated increase (~25–30%) in arterial O2 content during hyperoxia is based on calculated values of arterial Po2 as described in METHODS. The estimated O2 tensions from the current study are similar to those previously reported using direct measurements of PacO2 (i.e., micro-O2 electrode or arterial blood sample) in subjects exposed to hyperbaric O2 (8, 19, 29, 30). Additionally, we were not able to determine whether O2 consumption in the active forearm was different between trials. However, previous studies have demonstrated that O2 consumption of an active limb is not different between normoxic and hyperoxic conditions (23, 31).

Second, the present study could not differentiate between changes in muscle and skin circulation. Along these lines, normobaric hyperoxia causes cutaneous vasoconstriction under resting normothermic conditions (38). However, the blood flow measured by Doppler techniques during normobaric forearm exercise is largely influenced by the active muscles rather than...
changes in skin circulation (18). Therefore, it is likely that the reduction in flow during hyperbaric hyperoxic exercise in the present study mainly reflects changes in skeletal muscle blood flow.

Third, the calculated cardiac output values in the present study did not differ between trials at rest or during exercise. These findings are in contrast to previous reports that suggest resting cardiac output is reduced during hyperbaric hyperoxia (17, 20, 30, 33). This discrepancy may be explained by the stroke volume being derived from the beat-to-beat brachial arterial pulse pressure wave using model flow analysis in the current study, whereas other studies have relied on thermal and indicator dilution methods. Along these lines, estimating cardiac output from pulse contour analysis may not be sensitive enough to detect changes and/or may not be accurate under the experimental conditions of the current protocol.

Finally, the trial order (normoxia vs. hyperoxia) used in the present study was not randomized. The effects of hyperbaric hyperoxia on the recovery of skeletal muscle blood flow following exercise (i.e., time to return to resting baseline values) are unknown. The time limits on the hyperoxic exposure to ensure safety prevented us for allowing for long (>10 min) recovery periods. Therefore, to minimize the effect of hyperoxia on subsequent trials, we performed the hyperbaric hyperoxic trial last in all studies. It is important to note that the blood flow and vasodilator responses during normoxic and hypoxic forearm exercise are highly reproducible across multiple trials and therefore the effect of not randomizing the interventions should have been minimal (4).

Conclusions. This study demonstrates that hyperbaric oxygenation reduces FBF and vasodilation during rhythmic exercise in humans compared with normoxic and hyperbaric normoxic control conditions but that estimated O2 delivery remains constant. Taken together with our previous work, our data suggest that exercise hyperemia in skeletal muscle is highly dependent on O2 availability during hyperoxia as well as hypoxia.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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HYPEROXIA AND EXERCISING MUSCLE BLOOD FLOW


