Effects of supplemental oxygen on forearm vasodilation in humans

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Crawford, Paul, Peter A. Good, Eric Gutierrez, Joshua H. Feinberg, John P. Boehmer, David H. Silber, and Lawrence I. Sinoway. Effects of supplemental oxygen on forearm vasodilation in humans. *J. Appl. Physiol.* 82(5): 1601–1606, 1997.—Supplemental O_2 reduces cardiac output and raises systemic vascular resistance in congestive heart failure. In this study, 100% O_2 was given to normal subjects and peak forearm flow was measured. In *experiment 1*, 100% O_2 reduced blood flow and increased resistance after 10 min of forearm ischemia (flow 56.7 ± 7.9 vs. 47.8 ± 6.7 ml·min^{-1}·100 ml^{-1}; $P < 0.02$; vascular resistance 1.7 ± 0.2 vs. 2.4 ± 0.4 mmHg·min·100 ml·ml^{-1}; $P < 0.03$). In *experiment 2*, lower body negative pressure (LBNP; −30 mmHg) and venous congestion (VC) simulated the high sympathetic tone and edema of congestive heart failure. Postischemic forearm flow and resistance were measured under four conditions: room air breathing (RA); LBNP+RA; RA+LBNP+VC; and 100% O_2+LBNP+VC. LBNP and VC did not lower peak flow. However, O_2 raised minimal resistance (2.3 ± 0.4 RA; 2.8 ± 0.5 O_2+LBNP+VC, $P < 0.04$). When O_2 alone (*experiment 1*) was compared with O_2+LBNP+VC (*experiment 2*), no effect of LBNP+VC on peak flow or minimum resistance was noted, although the return rate of flow and resistance toward baseline was increased. O_2 reduces peak forearm flow even in the presence of LBNP and VC.

vascular resistance; lower body negative pressure; venous congestion

PREVIOUS WORK in normal subjects suggests that supplemental O_2 increases peripheral vascular resistance (4, 6). This response, in part, seems to be due to a reduction in cardiac output, which in turn is due to a reduction in heart rate and stroke volume (4, 6). This effect is not due to an increase in sympathetic drive because prior reports suggest that supplemental O_2 lowers or does not change muscle sympathetic nerve activity in humans (8, 20). These findings may be pathophysiologically important; a recent report indicated that supplemental O_2 lowered cardiac output and raised peripheral vascular resistance and pulmonary capillary wedge pressure in patients with end-stage heart failure (7).

In addition to potential cardiac effects of O_2, preliminary observations in humans with left ventricular-assist devices suggest that, even when cardiac output remains fixed, vascular resistance rises (7). This suggests that hyperoxia may act as a peripheral vasoconstrictor. However, there has been very little prior work in humans directly examining the effects of supplemental O_2 on peripheral vascular function. O_2 can inactivate nitric oxide (19) and also interfere with prostaglandin-mediated vasodilator mechanisms (24); both systems may be operative in mediating peripheral dilator function in humans (2, 3, 5, 12).

In the present study, we had two goals. First, we wanted to examine the effects of supplemental O_2 on the peak forearm reactive hyperemic blood flow (RHBF) response in normal humans. The forearm RHBF response is independent of changes in cardiac output (27) and is therefore a specific index of peripheral vascular function. Accordingly, any effect of O_2 on the RHBF response would provide support for the concept that O_2 has direct effects on the peripheral vasculature.

Second, we wished to examine whether acute limb congestion and heightened sympathetic tone would modify the vascular effects of O_2 on the peripheral circulation. Peripheral edema and heightened sympathetic tone are commonly seen in subjects with heart failure who receive supplemental O_2.

METHODS

We performed 2 groups of experiments in 15 healthy adults. All subjects were studied in our human investigation laboratory. Informed consent was obtained from each subject before he or she was studied.

In *experiment 1* [$n = 8$ (7 men and 1 woman); mean age 26 ± 3 yr], we measured forearm blood flow and vascular resistance (FVR) after 10 min of forearm circulatory arrest in subjects breathing room air (RA) and after breathing 100% supplemental O_2 delivered for 15 min; supplemental O_2 was begun 5 min before forearm circulatory arrest was begun. On the basis of results of *experiment 1*, we performed *experiment 2* ($n = 7$ men; mean age 27 ± 3 yr). In this study, we measured the peak forearm flow parameters under four study conditions: *1*) breathing RA; *2*) breathing RA during the application of lower body negative pressure (LBNP) at −30 mmHg (RA+LBNP); *3*) breathing RA during LBNP and after acutely venous congesting (VC) the forearm (RA+LBNP+VC); and *4*) during LBNP with associated forearm VC as the subjects breathed 100% O_2 (O_2+LBNP+VC).

Experiment 1

Effect of 100% O_2 administration on forearm dilator capacity. Mercury-in-Silastic strain-gauge plethysmography with the venous occlusion technique was used to measure forearm blood flow (9, 26). The technique, as used in our laboratory, has been described in detail previously (21, 23). Briefly, the strain gauge was externally calibrated to a tension of 10 g before being placed on the forearm. The forearm was supinated and elevated, and the gauge was ~10 cm above the heart and the olecranon process. Before any flow measurements were performed, the hand circulation was occluded for at least 1 min (11). To familiarize the subjects with the technique and to exclude any potentially artificially low values, a 1-min arterial occlusion was done (18). This also enabled us to adjust the occluding cuff and strain gauge to

eliminate any potential cuff artifact. After recovery from this stimulus, the wrist cuff was reinflated, baseline limb flows were recorded (2 min), and then the upper arm cuff was inflated to 250 mmHg. RHBFs were measured on the release of 10 min of arterial occlusion. Blood flows were measured at 5 and 15 s, and then every 15 s for 3 min. The highest measurement was considered the peak reactive hyperemic flow, and it occurred at either 5 or 15 s after the release of forearm circulatory arrest. The flow response measured over the 3-min period after the release of circulatory arrest will be referred to as the "total flow response." With the strain-gauge method, the units of flow are ml·min^{-1}·100 ml^{-1} of tissue. Arterial blood pressures were measured on the opposite arm by an automated cuff (model 1846SX, Dinamap, Tampa, FL). FVR (mmHg·ml^{-1}·min·100 ml tissue) was calculated by dividing the mean arterial pressures (MAP) by the forearm flow.

Experiment 2

Effect of LBNP, VC, and 100% O_2 on forearm dilator capacity. Postischemic flow measurements were performed under four experimental conditions in each subject. Ten- to fifteen-min rest periods were allowed between each trial. The RA intervention was always performed first and was identical to the control portion in *experiment 1*. The LBNP trial was always performed as the second intervention. This paradigm was included to examine the effects of isolated heightened sympathetic activity on limb flow. LBNP of −30 mmHg was used because it is a relatively potent sympathoexcitatory stimulant that disengages both low- and high-pressure baroreceptors (13). LBNP was begun during the sixth minute of forearm circulatory arrest and was continued until the 3 min of postischemic forearm flow measurements were completed. During the RA+LBNP+VC portion of the study, forearm VC was initiated 5 min before forearm circulatory arrest was initiated. VC was achieved by inflating the upper arm cuff to 90 mmHg. VC increases forearm volume by ~5% (14). In the final portion of this study, supplemental O_2 was added to LBNP+VC. O_2 (100%) was delivered by non-rebreathing face mask beginning 5 min before forearm circulatory arrest was initiated and was continued for the 3 min of postischemic forearm flow measurements.

Statistics

In *experiment 1*, a repeated-measures analysis of variance was used to examine the effects of O_2. The two main effects examined were the presence or absence of O_2 (2 levels of the variable) and flow (or resistance) at each time point after the release of circulatory arrest (13 levels of the variable). If a significant interaction was present (O_2 × time), then pairwise comparisons were performed by examining the simple effects. The effect of O_2 on peak flow (and minimum resistance) was determined by using a paired *t*-test.

In *experiment 2*, the various interventions were compared by using repeated-measures analysis of variance testing for two main effects: the specific interventions (RA vs. RA+LBNP vs. RA+LBNP+VC vs. O_2+LBNP+VC; 4 levels) and the flow (or resistance) during the 3 min of measurement (13 levels). Comparisons of the four interventions at a given time point were performed by examining the simple effects. A one-way analysis of variance was used to compare peak responses, and, when a significant *F*-value was observed, Tukey's test was used to determine differences between mean values. All data are expressed as means ± SE. A $P < 0.05$ was considered statistically significant.

Table 1. *Effects of 100% O_2 hemodynamic variables measured during resting conditions*

	Control	100% O_2
HR, beats/min	57.9 ± 2.6	50.6 ± 2.1*
MAP, mmHg	80.0 ± 2.8	89.1 ± 3.6*
Forearm blood flow, ml·min^{-1}·100 ml^{-1} of tissue	4.0 ± 0.5	3.4 ± 0.7
Forearm vascular resistance, mmHg·min·100 ml of tissue·ml^{-1}	22.9 ± 3.4	36.1 ± 6.6*

Values are means ± SE; $n = 8$ for all observations. HR, heart rate; MAP, mean arterial blood pressure. Resting values were obtained before reactive hyperemic responses in *experiment 1* were examined. *Significantly different, control vs. O_2 value, $P < 0.05$ (paired *t*-test).

RESULTS

Experiment 1

Effects of O_2 on resting values. The effects of O_2 on MAP, heart rate, resting forearm flow, and FVR are shown in Table 1. O_2 (100%) increased MAP and vascular resistance, whereas resting heart rate fell and resting forearm flow was unchanged.

Effects of O_2 on responses to forearm circulatory arrest. Peak forearm flow was lower and minimum vascular resistance was greater in the presence of O_2 (Fig. 1, *A* and *B*). The effects of O_2 were sustained throughout the 3 min of data collection (Fig. 2, *A* and *B*). If the effects of O_2 were analyzed by using vascular conductance (flow divided by MAP), we would have observed a similar effect; O_2 lowered conductance (O_2 main effect $P < 0.001$; statistical interaction $P < 0.001$). Simple effects for conductance showed a statistical lowering of conductance at each of the 13 time points evaluated.

If resting flow were subtracted from postischemic values, we would have still observed an O_2 effect (main effect $P < 0.004$; interaction $P < 0.001$; simple effects showing statistical differences at each time point). The heart rate and blood pressure data for this experiment are shown in Table 2.

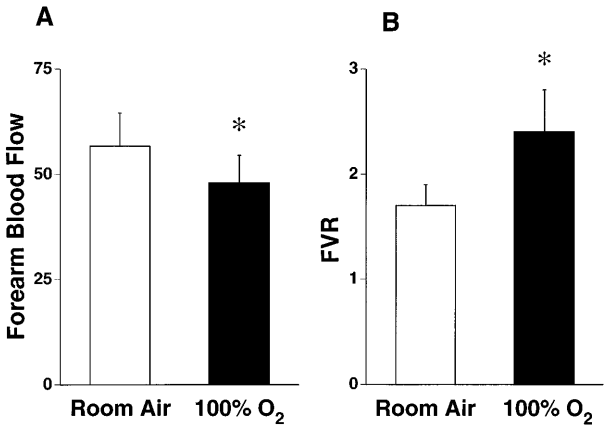

Fig. 1. Peak forearm blood flow (*A*) and minimal forearm vascular resistance (FVR; *B*) after 10 min of forearm ischemia with and without supplemental O_2 supplied with non-rebreathing mask. Flow is expressed as ml·min^{-1}·100 ml^{-1}, and resistance is expressed as mmHg·ml^{-1}·min·100 ml. *$P < 0.05$.

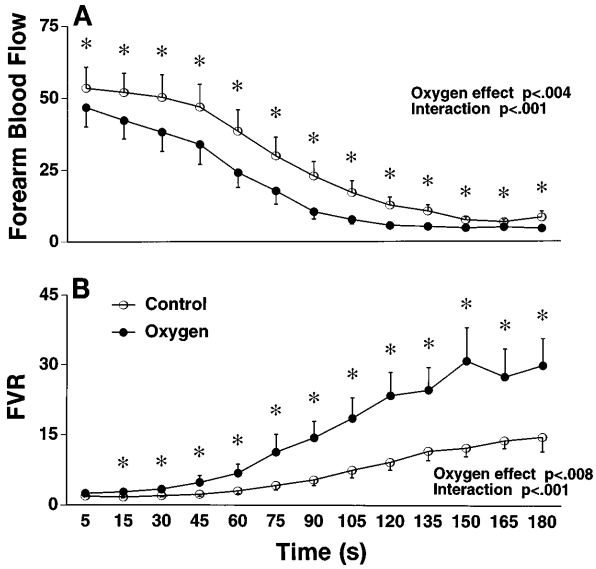

Fig. 2. Forearm blood flow (*A*) and FVR (*B*) responses measured for 3 min after release of a 10-min forearm circulatory arrest. Pointwise comparisons were made by using simple effects method. Units for flow and resistance are defined as in Fig. 1. *$P < 0.05$.

Experiment 2

Compared with RA alone, RA+LBNP and RA+LBNP+VC did not alter the minimal vascular resistance. However, the minimum FVR response during O_2+LBNP+VC was different from that seen during RA alone (Fig. 3). The peak flow was not different during the four interventions.

When data were analyzed over the entire 3 min of collection, an intervention simple effect was noted at most time points (Fig. 4, *A* and *B*). Analysis of the curves (Fig. 4) suggests that the various interventions had a graded effect on flow and resistance. If conductance values were analyzed, we would have noted similar effects (intervention main effect $P < 0.001$; interaction $P < 0.001$). The heart rate and blood pressure data for *experiment 2* are shown in Table 3. It is interesting to note that an intervention main effect was present for both heart rate and MAP. Analysis of this mean data suggests that O_2 raised MAP and lowered heart rate even in the presence of LBNP and VC.

Table 2. *HR and blood pressure values during RHBF of experiment 1*

	MAP, mmHg		HR, beats/min	
Time, s	Control	O_2	Control	O_2
5	85.4 ± 4.1	94.6 ± 3.9	57.3 ± 1.6	53.1 ± 1.9
15	77.9 ± 3.8	93.9 ± 3.9*	58.8 ± 1.6	55.0 ± 2.0
30	79.3 ± 3.4	95.3 ± 4.4*	58.3 ± 1.7	55.8 ± 2.4
45	81.0 ± 3.9	97.3 ± 4.4*	57.5 ± 1.6	53.9 ± 2.0
60	80.6 ± 3.1	96.6 ± 4.5*	58.3 ± 2.0	51.4 ± 2.3
75	80.4 ± 4.0	95.5 ± 4.5*	58.0 ± 2.2	51.9 ± 2.4
90	81.8 ± 3.3	92.6 ± 3.7*	58.8 ± 2.2	52.6 ± 2.6
105	78.5 ± 3.4	94.8 ± 3.8*	57.0 ± 2.5	52.5 ± 2.0
120	79.4 ± 3.1	95.8 ± 4.2*	56.8 ± 2.7	51.8 ± 1.8
135	81.4 ± 3.1	94.8 ± 4.1*	57.3 ± 2.9	51.5 ± 2.1
150	81.5 ± 3.1	95.9 ± 4.0*	57.5 ± 2.4	53.8 ± 2.8
165	82.8 ± 3.8	95.9 ± 4.2*	56.6 ± 2.2	51.4 ± 2.1
180	80.4 ± 3.1	95.3 ± 3.2*	55.3 ± 1.6	52.5 ± 2.3
I effect		$P < 0.001$		$P < 0.002$
T effect		NS		$P < 0.016$
I × *T*		$P < 0.026$		NS

Values are means ± SE; $n = 8$. RHBF, reactive hyperemic blood flow. I, O_2 intervention; *T*, time effect; I × *T*, interaction effect; bottom 3 lines of data, interaction effect; NS, not significant. *Difference in MAP between control and O_2 at a given time point, $P < 0.05$.

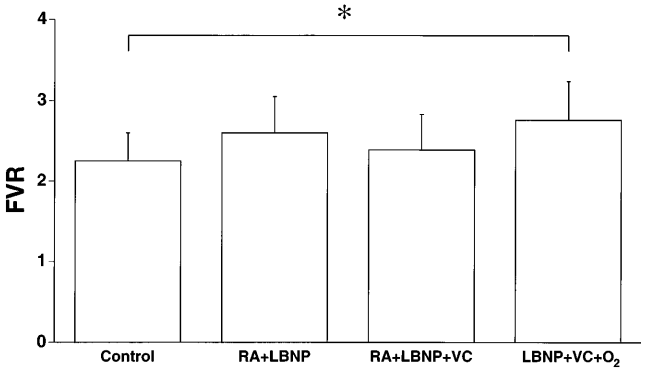

Fig. 3. Comparison of minimal vascular resistance (expressed as $mmHg \cdot ml^{-1} \cdot min \cdot 100$ ml) under 4 study conditions in *experiment 2* ($n = 7$). RA, room air; LBNP, lower body negative pressure; VC, venous congestion. *$P < 0.05$, Tukey's test.

Comparison of Experiments 1 and 2

In an effort to examine the influence of limb congestion and heightened sympathetic tone on the vascular effects of O_2 effect, we compared the O_2 trial during *experiment 1* to O_2+LBNP+VC in *experiment 2*. LBNP+VC did not lower peak flow or raise minimal vascular resistance. However, LBNP+VC did reduce flow and raise resistance during later stages of the 3-min postischemic data collection periods (Fig. 5).

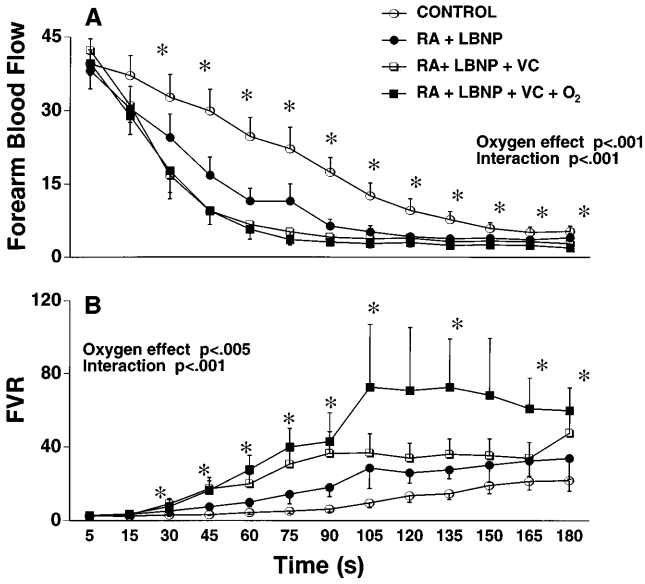

Fig. 4. Comparison of forearm blood flow (*A*) and FVR (*B*) responses to 4 paradigms in *experiment 2*. *Intervention simple effect at a given time point. Units for flow and resistance are defined as in Fig. 1.

Table 3. *HR and blood pressure values during RHBF of experiment 2*

Time, s	MAP, mmHg				HR, beats/min			
	Control	+LBNP	LBNP + VC	LBNP + VC + O_2	Control	+LBNP	LBNP + VC	LBNP + VC + O_2
5	87.3 ± 3.3	88.1 ± 3.2	89.7 ± 3.8	95.7 ± 6.2	59.3 ± 4.4	71.0 ± 4.0	69.4 ± 4.1	66.6 ± 3.2
15	81.4 ± 2.4	82.3 ± 4.5	89.3 ± 3.3	92.4 ± 4.5	60.0 ± 4.0	72.0 ± 3.9	71.7 ± 3.5	65.3 ± 1.7
30	82.1 ± 3.3	86.3 ± 3.3	87.4 ± 3.5	92.7 ± 5.3	59.1 ± 3.9	72.0 ± 4.1	71.0 ± 3.5	62.6 ± 2.5
45	82.4 ± 2.5	87.4 ± 2.8	89.9 ± 4.0	93.7 ± 4.9	59.3 ± 4.1	71.3 ± 3.6	70.4 ± 3.6	62.0 ± 2.4
60	85.1 ± 4.4	84.3 ± 3.3	87.3 ± 3.4	94.1 ± 4.6	56.7 ± 3.5	70.1 ± 3.1	68.0 ± 3.5	59.1 ± 2.3
75	81.9 ± 3.1	86.0 ± 3.8	88.9 ± 3.7	92.9 ± 5.1	57.0 ± 3.4	70.4 ± 3.9	68.4 ± 3.6	59.0 ± 3.0
90	83.1 ± 3.9	83.4 ± 4.0	88.4 ± 3.5	92.9 ± 4.6	59.3 ± 4.6	70.1 ± 3.6	69.0 ± 4.1	59.3 ± 1.8
105	83.0 ± 3.0	85.7 ± 2.7	88.6 ± 3.7	92.3 ± 4.5	57.3 ± 3.8	69.4 ± 3.2	65.3 ± 2.8	60.7 ± 3.2
120	83.7 ± 3.3	86.4 ± 2.8	89.4 ± 3.2	93.3 ± 4.6	59.4 ± 4.6	67.9 ± 2.6	66.6 ± 4.0	60.0 ± 3.4
135	82.0 ± 3.1	84.7 ± 2.9	88.4 ± 3.2	92.6 ± 3.5	59.4 ± 4.9	69.6 ± 3.7	68.7 ± 4.0	62.0 ± 2.9
150	83.6 ± 3.2	86.1 ± 2.8	87.4 ± 4.0	90.4 ± 4.3	57.0 ± 4.0	69.6 ± 3.5	69.0 ± 3.9	61.0 ± 2.5
165	82.0 ± 2.5	85.0 ± 2.5	87.1 ± 3.8	89.6 ± 4.1	57.4 ± 3.6	72.1 ± 3.4	69.3 ± 3.4	60.4 ± 2.6
180	83.3 ± 2.7	87.3 ± 3.2	87.9 ± 2.9	92.1 ± 3.8	56.7 ± 2.9	69.9 ± 4.0	68.6 ± 3.3	59.9 ± 2.3
I effect				$P < 0.006$				$P < 0.001$
T effect				$P < 0.027$				$P < 0.005$
I × *T*				NS				NS

Values are means ± SE; $n = 7$. LBNP, lower body negative pressure; VC, venous congestion.

DISCUSSION

A prior study demonstrated that supplemental O_2 lowers cardiac output and raises left ventricular filling pressures in nonhypoxic congestive heart failure patients (7). In this prior report, we were unable to determine whether O_2 had a direct effect on peripheral blood vessel dilator capacity.

In the present study, O_2 caused a rise in MAP, a fall in heart rate, and an increase in FVR. We would surmise that O_2 had a direct effect on vascular resistance, thereby raising MAP and evoking a baroreflex-mediated fall in heart rate. These observations are consistent with prior reports demonstrating that O_2 evokes a direct peripheral vasoconstrictor effect (1). Bredle et al. (1) used a perfused hindlimb technique in a canine model to examine the effects of O_2 on the peripheral circulation. Hyperoxia caused a rise in limb vascular resistance and a fall in limb O_2 consumption, suggesting that O_2 vasoconstricts and redistributes blood flow within the canine hindlimb.

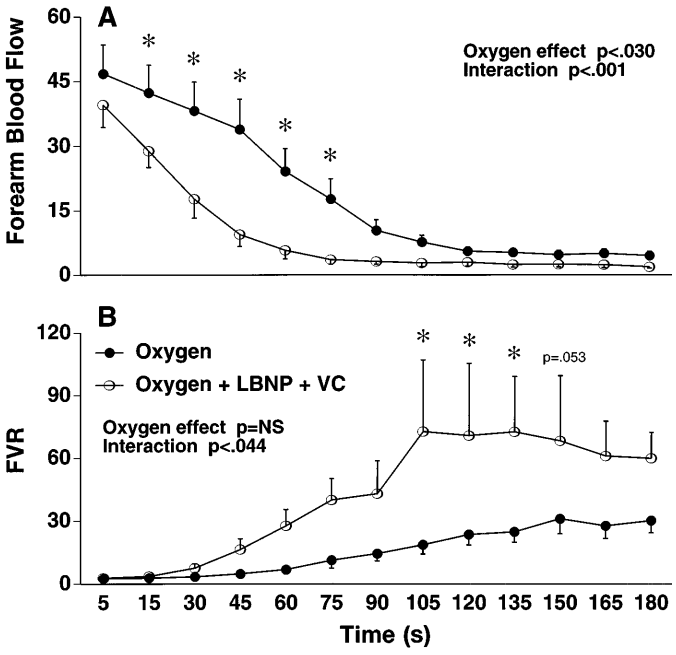

Fig. 5. Comparison of effects of O_2 with and without LBNP and VC. NS, not significant. Units for flow and resistance are defined as in Fig. 1. *$P < 0.05$.

In the present study, we found that supplemental O_2 reduced vasodilator responses after 10 min of forearm ischemia. In *experiment 2*, LBNP and limb congestion had no effect on peak flow or minimal resistance. When supplemental O_2 was added, minimal resistance rose and the rate of return of O_2 toward baseline was increased. Comparison of the data from *experiments 1* and *2* suggests that limb congestion and LBNP accelerate the rate of return of peak flow toward baseline. These results suggest that supplemental O_2 has a very potent effect on the peripheral circulation that is capable of partially opposing powerful dilator influences within the ischemic forearm that are independent of any potential central cardiac effects. These effects of O_2 are not obscured in the presence of heightened sympathetic tone and limb congestion.

Potential Mechanisms For Our Findings

It is unlikely that 100% O_2 increased sympathetic tone and reduced peak forearm flow. Prior data suggest that if supplemental O_2 has any effect on sympathetic discharge, it acts to reduce it (8, 20). Nitric oxide, a free radical generated in endothelium from L-arginine by nitric oxide synthase, is an important vasorelaxant (15). This substance has been found to be important in mediating vasodilatory responses seen during exercise (5, 17). However, its role in mediating postischemic flow is less clear. Recent work by Tagawa et al. (25) suggests that it has a modest effect on total flow and no effect on peak flow. It is interesting to note that nitric oxide is destroyed by O_2, hemoglobin, and other free radicals. Studies by Obara et al. (16) suggest that prolonged exposures of rabbits to 100% O_2 reduced both endothelial-dependent and -independent pulmonary arterial dilator responses. Of note, these effects were prevented

by pretreatment with superoxide dismutase, a free radical scavenger.

Recently it has been suggested that nitric oxide is delivered to the tissues via oxygenated hemoglobin. It is intriguing to speculate that hyperoxygenated blood decreases O_2 extraction by the tissue (1) and in the process diminishes nitric oxide delivery, thereby reducing tissue vasodilation (10). Clearly, more work will be necessary to test this intriguing hypothesis.

Prior work using a neonatal umbilical arterial model demonstrated that O_2 reduced prostacyclin formation by 30% (24), and prostacyclin is an important vasodilating prostaglandin (24). These prior findings are relevant to the present report because vasodilating prostaglandins, as opposed to nitric oxide, are thought to play an important role in determining the magnitude of both the peak and total reactive hyperemic responses to forearm ischemia (2, 3, 12).

Results of *experiment 2*, and comparison of *experiments 1* and *2*, suggest that heightened sympathetic tone and limb congestion do not act in concert with 100% O_2 to reduce peak flow or to increase minimal resistance. However, these factors do appear to accentuate the effect of O_2 on the total postischemic flow response. Mechanistic interpretation of these data will require further study. Parenthetically, the lack of effect of limb congestion and LBNP on peak flow and minimal resistance is consistent with prior observations (21, 22).

Limitations

First, our findings do not in themselves provide evidence that this peripheral vascular effect of O_2 is physiologically detrimental to normal subjects or individuals with heart failure. Future studies examining exercise will be necessary to address this. It should be emphasized that prior work in canine models suggests that hyperoxia not only lowers limb flow but may also cause a maldistribution of blood flow and a concomitant paradoxical reduction in O_2 extraction (1). In *experiment 2*, we used acute alterations in limb volume and sympathetic tone to mimic chronic peripheral responses seen in heart failure. It will be important to examine the effects of O_2 on forearm flow responses directly in subjects with decompensated congestive heart failure.

In conclusion, this study demonstrates that O_2 decreases the magnitude of the limb vasodilator response to forearm ischemia. These effects of O_2 are still noted when sympathetic nervous system activity and forearm interstitial volume are acutely increased.

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REFERENCES

1. **Bredle, D. L., W. E. Bradley, C. K. Chapler, and S. M. Cain.** Muscle perfusion and oxygenation during local hyperoxia. *J. Appl. Physiol.* 65: 2057–2062, 1988.
2. **Carlsson, I., I. Sollevi, and Å. Wennmalm.** The role of myogenic relaxation, adenosine and prostaglandins in human forearm reactive hyperemia. *J. Physiol. (Lond.)* 389: 147–161, 1987.
3. **Carlsson, I., and Å. Wennmalm.** Effect of different prostaglandin synthesis inhibitors on post-occlusive blood flow in human forearms. *Prostaglandins* 26: 241–251, 1983.
4. **Daly, W. J., and S. Bondurant.** Effects of oxygen breathing on the heart rate, blood pressure and cardiac index of normal men—resting, with reactive hyperemia, and after atropine. *J. Clin. Invest.* 41: 126–132, 1962.
5. **Dyke, C. K., D. N. Proctor, N. M. Dietz, and M. J. Joyner.** Role of nitric oxide in exercise hyperemia during prolonged rhythmic handgripping in humans. *J. Physiol. (Lond.)* 488: 259–265, 1995.
6. **Eggers, G. W. N., H. W. Paley, J. J. Leonard, and J. V. Warren.** Hemodynamic responses to oxygen breathing in man. *J. Appl. Physiol.* 17: 75–79, 1962.
7. **Haque, W. A., J. Boehmer, B. S. Clemson, U. A. Leuenberger, D. H. Silber, and L. I. Sinoway.** The hemodynamic effects of supplemental oxygen administration in congestive heart failure. *J. Am. Coll. Cardiol.* 27: 353–357, 1996.
8. **Hardy, J. C., K. Gray, S. Whisler, and U. Leuenberger.** Sympathetic and blood pressure responses to voluntary apnea are augmented by hypoxemia. *J. Appl. Physiol.* 77: 2360–2365, 1994.
9. **Holling, H. E., C. Boland, and E. Russ.** Investigation of arterial obstruction using a mercury-in-rubber strain gauge. *Am. Heart J.* 62: 194–205, 1961.
10. **Jia, L., C. Bonaventura, J. Bonaventura, and J. S. Stamler.** *S*-nitrosohaemoglobin: a dynamic activity of blood involved in vascular control. *Nature* 380: 221–226, 1996.
11. **Kerslake, D. M.** The effect of the application of an arterial occlusion cuff to the wrist on the blood flow in the human forearm. *J. Physiol. (Lond.)* 108: 451–457, 1949.
12. **Kilbom, Å., and Å. Wennmalm.** Endogenous prostaglandins as local regulators of blood flow in man: effect of indomethacin on reactive and functional hyperemia. *J. Physiol. (Lond.)* 257: 109–121, 1976.
13. **Mark, A. L., and G. Mancia.** Cardiopulmonary baroreflexes in humans. In: *Handbook of Physiology. The Cardiovascular System. Peripheral Circulation and Organ Blood Flow.* Bethesda, MD: Am. Physiol Soc., 1983, sect. 2, vol. III, pt. 2, chapt. 21, p. 795–814.
14. **McClain, J., C. Hardy, B. Enders, M. Smith, and L. Sinoway.** Limb congestion and sympathoexcitation during exercise: implications for congestive heart failure. *J. Clin. Invest.* 92: 2353–2359, 1993.
15. **Moncada, S., and A. Higgs.** The L-arginine-nitric oxide pathway. *N. Engl. J. Med.* 329: 2002–2012, 1993.
16. **Obara, H., Y. Hoshino, M. Mori, K. Mikawa, and S. Iwai.** Endothelium-dependent relaxation in isolated pulmonary arteries from rabbits exposed to hyperoxia. *Crit. Care Med.* 17: 780–785, 1989.
17. **O'Leary, D. S., R. C. Dunlap, and K. W. Glover.** Role of endothelium-derived relaxing factor in hindlimb reactive and active hyperemia in conscious dogs. *Am. J. Physiol.* 266 (*Regulatory Integrative Comp. Physiol.* 35): R1213–R1219, 1994.
18. **Patterson, G. C., and R. F. Whelan.** Reactive hyperemia in the human forearm. *Clin. Sci. (Lond.)* 14: 197–211, 1955.
19. **Rubanyi, G. M., and P. M. Vanhoutte.** Superoxide anions and hyperoxia inactivate endothelium-derived relaxing factor. *Am. J. Physiol.* 250 (*Heart Circ. Physiol.* 19): H822–H827, 1986.
20. **Seals, D. R., D. G. Johnson, and R. F. Fregosi.** Hyperoxia lowers sympathetic activity at rest but not during exercise in humans. *Am. J. Physiol.* 260 (*Cell Physiol.* 29): C873–C878, 1991.

21. **Sinoway, L., and S. Prophet.** Skeletal muscle metaboreceptor stimulation opposes peak metabolic vasodilation in humans. *Circ. Res*. 66: 1576–1584, 1990.
22. **Sinoway, L. I., J. S. Wilson, R. Zelis, J. Shenberger, D. P. McLaughlin, D. L. Morris, and F. P. Day.** Sympathetic tone affects human limb vascular resistance during a maximal metabolic stimulus. *Am. J. Physiol.* 255 (*Heart Circ. Physiol.* 24): H937–H946, 1988.
23. **Sinoway, L. I., K. J. Wroblewski, S. A. Prophet, S. M. Ettinger, K. S. Gray, S. K. Whisler, G. Miller, and R. L. Moore.** Glycogen depletion-induced lactate reductions attenuate reflex responses in exercising humans. *Am. J. Physiol.* 263 (*Heart Circ. Physiol.* 32): H1499–H1505, 1992.
24. **Stuart, M. J., B. N. Yamaja Setty, R. W. Walenga, J. E. Graeber, and C. Ganley.** Effects of hyperoxia and hypoxia on vascular prostacyclin formation in vitro. *Pediatrics* 74: 548–553, 1984.
25. **Tagawa, T., T. Imaizumi, T. Endo, M. Shiramoto, Y. Harasawa, and A. Takeshita.** Role of nitric oxide in reactive hyperemia in human forearm vessels. *Circulation* 90: 2285–2290, 1994.
26. **Whitney, R. J.** The measurement of volume changes in human limbs. *J. Physiol. (Lond.)* 121: 1–27, 1953.
27. **Zelis, R.** Comparison of the reflex reactivity of skin and muscle veins in the human forearm. *J. Clin. Invest.* 48: 1870–1877, 1969.