Effects of Oxygen and Carbon Dioxide on Human Retinal Circulation

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Purpose. Carbogen, a gas mixture of 95% O₂ and 5% CO₂, is given to patients with retinal artery obstruction in an attempt to improve retinal oxygenation. The purpose of this study was to compare the effects of carbogen and 100% O₂ breathing on retinal blood flow.

Methods. On two separate occasions, 12 normal, healthy volunteers breathed air and then either 100% O₂ or carbogen while laser Doppler velocimetry measurements and monochromatic fundus photographs were taken. Retinal vessel diameter, maximum velocity of red blood cells, and volumetric blood flow rate were determined in a main temporal vein.

Results. Both 100% O₂ and carbogen caused significant average reductions in vessel diameter (14.1% and 10.6%, respectively), maximum red blood cell velocity (42.1% and 27.3%, respectively), and blood flow (56.4% and 42.2%, respectively). The average vasoconstriction of the large retinal veins caused by carbogen was not significantly smaller than that caused by 100% O₂. The average reductions in maximum red blood cell velocity and blood flow caused by carbogen were significantly smaller than those caused by 100% O₂ (P < .001 and P < .01, respectively).

Conclusions. In normal subjects, inhalation of carbogen leads to less reduction in blood flow than inhalation of 100% O₂, presumably by reducing the vasoconstriction of small arterioles induced by elevated oxygen levels. Investig Ophthalm Vis Sci 1993;34:2866-2870.

Central retinal artery occlusion is a medical emergency treated by ocular massage, reduction of intraocular pressure (IOP), and inhalation therapy with gases containing high oxygen concentrations. Carbogen, a gas mixture of 95% O₂ and 5% CO₂, is one of the gases that has been recommended for administration 10 minutes every hour during the day and every 4 hours at night.¹⁻³

Inhalation therapy is provided with the hope that hyperoxic blood from the choroid circulation may supply the ischemic inner retina and that additional oxygen may be delivered through a partially perfused retinal circulation. Flower and Patz⁴ reported that hyperbaric oxygen was necessary to improve the oxygenation of the inner retina in cats and miniature pigs with occluded retinal circulation. One hundred percent O₂ breathing returned the electroretinographically recorded b-wave (a measure of functional integrity of the Müller cells in the inner retinal layers) to only 45% of normal amplitude. More recent studies, however, have suggested that normobaric 100% oxygen breathing can provide some oxygen to the inner retina in cats and miniature pigs with occluded retinal circulation.

In normal subjects, inhalation of 100% O₂ for 5 minutes causes a 12% and 15% decrease in the diameter of the large retinal arteries and veins, respectively, and also results in a decrease in retinal blood flow of approximately 64%.⁵ Because the delivery and removal of metabolites and gases to the retina is proportional to blood flow, this large decrease in blood flow caused by 100% O₂ could perhaps have deleterious effects.

Carbon dioxide has been found to diminish the vasoconstrictive effect of high O₂ concentrations.⁶ Carbogen is therefore used in the treatment of central retinal artery occlusion in the hope that it will cause a smaller decrease in vessel diameter and blood flow than 100% O₂.
In a study of the effects of carbogen and 100% O₂ breathing for 5 minutes, Deutsch et al.¹⁰ found no significant differences between the constriction of the main retinal arteries or veins of normal subjects produced by these two gases. More recently, however, Sponsel et al.,¹¹ using the blue field entoptic simulation technique, found that macular capillary leukocyte velocity was significantly higher during carbogen breathing than during 100% O₂ breathing in normal volunteers. In the current study, we determined the effects of carbogen and 100% O₂ breathing not only on retinal venous diameter (D), but also on centerline maximum erythrocyte velocity (V_max), and volumetric blood flow rate (Q) using bidirectional laser Doppler velocimetry (BLDV) and monochromatic fundus photography.

MATERIALS AND METHODS

Twelve normal, nonsmoking volunteers aged 19–33 years (mean age, 27 ± 5 years) took part in this study. All subjects had normal results on eye examination and no history of ocular disease. None of the subjects were taking medication at the time of the study. The protocol used in this study was approved by our institutional human experimentation committee. Tenets of the Declaration of Helsinki were followed. Informed consent was obtained from all subjects after the nature of the procedure had been explained.

After pupillary dilatation with tropicamide 1%, Polaroid color fundus photographs and monochromatic fundus photographs were then taken using a Zeiss fundus camera and Polaroid Polacolor 2 (Polaroid, Cambridge, Massachusetts) and Kodak Plus-X pan (Eastman Kodak, Rochester, New York) films.

Baseline BLDV measurements of V_max were taken in a temporal retinal vein of one eye of each subject, first during air breathing, and then between 3½ to 5½ minutes of either 100% O₂ or carbogen breathing. Gases were administered at 1 atm through a mouthpiece while a clamp was applied to the nose. Measurements were obtained in the sitting position. One hundred percent O₂ or carbogen was given randomly without the subjects' knowledge of the type of gas. In 10 subjects, more than 24 hours passed between the administration of carbogen and 100% O₂; in the other two subjects, they were administered only 1 hour apart.

After the BLDV recordings and while subjects were still breathing a given gas, fundus photographs were taken. Immediately after breathing 100% O₂ or carbogen, heart rate and brachial artery systolic and diastolic blood pressure were determined using a Datascopes ACCUTORR 1A noninvasive blood pressure monitor (Datascopes Corporation, Paramus, NJ). Topical proparacaine HCL 0.5% was applied to each eye, and IOP was determined by Goldmann applanation tonometry. Measurements of blood pressure, IOP, and heart rate are summarized in Table 1.

Projected photographic negatives were used to measure the diameter of the vein at the location of the BLDV recordings. D was determined by averaging the measurements from six photographs. The method for determining V_max has been described previously.¹² Retinal volumetric blood flow (Q) was calculated from the equation:

\[ Q = \frac{V_{\text{mean}} \cdot \pi D^2}{4} \]

where \( V_{\text{mean}} \) represents the mean velocity of whole blood. We have assumed that \( V_{\text{mean}} = CV_{\text{max}} \), with C being a constant equal to \( 1/6 \).¹³

Measurements of D were performed by one experienced observer, and V_max determinations were performed by another experienced observer. Each was masked as to the type of gas breathed.

Mean brachial artery blood pressure (BP_m) was determined using the relation \( BP_m = \frac{1}{3}(BP_s + BP_d) \), where \( BP_s \) and \( BP_d \) are the brachial artery systolic and diastolic pressures, respectively. Perfusion pressure (PP) was calculated from the relation PP = \( 2/3BP_m - IOP \).

Linear regression, correlation analysis, and two-tailed paired Student's t-tests were used in a statistical evaluation of the data. Values with a P value smaller than 0.05 were considered to be statistically significant.

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TABLE 1. Averages and SD of Heart Rate (HR), Systolic Blood Pressure (BP_s), Diastolic Blood Pressure (BP_d), Mean Blood Pressure (BP_m), Average Intraocular Pressure (IOP), and Perfusion Pressure (PP) Immediately After 100% Oxygen (O₂) and Carbogen (CO₂) Breathing
RESULTS

Table 2 summarizes the values of D, V_{max} and Q during air breathing and during 100% O_2 or carbogen breathing. Figure 1 shows the percentage decreases in D, V_{max}, and Q during O_2 or carbogen breathing, whereas Table 2 shows the absolute values of these parameters. Breathing O_2 caused significant average reductions of 14.1 ± 4.9% SD (22.3 ± 8.75 μm) in D, 42.1 ± 12.6% (0.75 ± 0.27 cm/sec) in V_{max}, and 56.4 ± 13.7% (7.22 ± 2.97 μl/min) in Q (paired t-test, P < .001 in all cases). Carbogen breathing also caused significant reductions of 10.6 ± 5.4% (14.0 ± 7.6 μm) in D, 27.3 ± 12.6% (0.73 ± 0.27 cm/sec) in V_{max}, and 56.4 ± 13.7% (7.22 ± 2.97 μl/min) in Q (P < .001 in all cases).

Carbogen breathing produced significantly smaller average percentage decreases in V_{max} and Q than O_2 breathing (P < .001 and P < .01, respectively). Although carbogen breathing caused a smaller average decrease in D than O_2 breathing, this difference did not reach statistical significance.

A significant correlation was observed between the percentage decrease in D and the percentage decrease in Q during O_2 breathing (correlation coefficient, r = 0.77, P < .001, Fig. 2), whereas this correlation was not significant for carbogen inhalation (r = 0.33, P > 0.1).

Average baseline values for D, V_{max}, and Q before 100% O_2 breathing were not significantly different than the average baseline values before carbogen breathing. No significant differences in average IOP, BP_a, BP_r, PP, or heart rate were observed between measurements obtained immediately after the inhalation of 100% oxygen and carbogen. No significant correlations were observed between D, V_{max}, or Q and both blood pressure or perfusion pressure.

DISCUSSION

The results of this study show that both carbogen and 100% O_2 breathing produce significant decreases in D, V_{max} and Q in normal adults. Moreover, the reductions in V_{max} and Q during carbogen breathing are significantly smaller than those observed during 100% O_2 breathing.

![FIGURE 1. Comparison of the percentage decrease from baseline in venous diameter (D), maximum velocity of red blood cells (V_{max}), and volumetric blood flow rate (Q) during 100% O_2 breathing and carbogen breathing for each of the 12 subjects. Average percentage decreases in V_{max} and Q were significantly smaller during carbogen breathing than during 100% O_2 breathing (two-tailed paired Student’s t-test, P < .05).](image-url)
Effects of O₂ and CO₂ on Human Retinal Circulation

Oxygen Carbogen

10 15 20 decrease in 0 5 10 is 20 % decrease in D

FIGURE 2. Percentage decrease in volumetric blood flow rate (Q) versus percentage decrease in main temporal vein diameter (D) during 100% O₂ (A) and carbogen breathing (B). There is a significant correlation during O₂ breathing (r = 0.77, P < 0.01; Q = 25.8 + 2.18D) and no significant correlation during carbogen breathing (r = 0.33, P > 0.10).

We observed no significant difference between the vasoconstriction produced by 100% O₂ or carbogen, a finding similar to the results of Deutsch et al showing a very similar vasoconstrictive effect produced by both gases.

Our results show that the difference in Q reduction produced by 100% O₂ and carbogen is mainly the result of a difference in V max changes and less the result of a difference in the changes in D measured in the main vessels. Perhaps 5% CO₂ counteracts the vasoconstriction caused by high O₂ tensions at the level of small arterioles not measured in this study. Such an effect could explain the difference in V max changes observed between the two gases. Because no significant differences in BP, PP, or heart rate were detected between measurements obtained immediately after 100% O₂ and carbogen breathing, the different effects of these two gases are probably not caused by differences in their systemic effects.

The significant correlation detected between the decrease in diameter of the large vessels measured and the decrease in flow during 100% O₂ breathing, and the lack of a significant correlation during carbogen breathing (Fig. 2), support the hypothesis that CO₂ may affect Q by adjusting the caliber of the smaller retinal arterioles.

The average baseline values for D, V max, and Q in our study are similar to those previously reported. The average decrease in Q of 56% produced by 100% O₂ inhalation is also within the range of that observed by Riva et al using BLDV. The 14% decrease in D during 100% O₂ breathing is also close to values obtained by fundus photography.

Using the blue field simulation technique, which assesses macular circulation, Sponsel et al reported decreases of 20% in leukocyte velocity with 100% O₂ breathing and an increase of 26% in leukocyte velocity during carbogen breathing. These results also suggest that retinal blood flow during carbogen breathing is greater than it is during oxygen breathing.

In conclusion, the present study demonstrates that in the normal retina, the decreases in V max and Q produced by carbogen breathing are significantly smaller than those caused by 100% O₂ breathing. These results suggest that carbogen is associated with a better perfusion of the inner retina than 100% O₂. Whether this provides a better oxygenation of the inner retina can only be ascertained by studies looking at the effects of these two gases on the PO₂ of the inner retina.

Care should be exercised when extrapolating these results, obtained in normal subjects, to what may happen in the retina of older individuals with vascular occlusion. Further studies are needed to elucidate whether carbogen may indeed provide better perfusion or better oxygenation of the inner retina, or both, than 100% O₂ in patients with retinal artery occlusion.

Key Words
laser Doppler velocimetry, carbogen, oxygen, volumetric blood flow rate, human retina

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References
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