
REGIONAL RETINAL BLOOD FLOW AND VASCULAR AUTOREGULATION

S. M. B. RASSAM, V. PATEL, H. C. CHEN AND E. M. KOHNER

London

SUMMARY

The temporal retina is larger than the nasal retina and contains the metabolically active fovea. The variation in the distribution of blood between the temporal and nasal retinal circulations was investigated in 15 healthy volunteers, and the autoregulatory capacity of the temporal and nasal circulations was quantitated using 60% oxygen in the inspired air. Retinal blood flow was determined from red cell velocity using laser Doppler velocimetry and retinal vessel diameter from retinal photographs using a digital image analysis system. Volume flow was lower in the nasal than the temporal circulation by 52.49% ($p<0.001$). This is a consequence of both significantly smaller vessels (20.4%, $p<0.001$) and slower blood velocity in the nasal circulation (24.64%, $p=0.003$) compared with the temporal vessels. After breathing 60% oxygen for 10 minutes, there was significant vasoconstriction (temporal, $10.42\pm 1.24\%$, $p<0.001$; nasal, $7.66\pm 1.48\%$, $p<0.001$), slower red cell velocity (temporal, $27.10\pm 3.92\%$, $p<0.001$; nasal, $27.36\pm 5.51\%$, $p<0.001$) and a significant reduction in the volumetric flow rate (temporal, $41.16\pm 3.64\%$, $p<0.001$; nasal, $37.99\pm 5.07\%$, $p<0.001$). The reduction in the haemodynamic parameters was comparable in the temporal and nasal circulations, indicating similar autoregulatory capacity. Retinal vascular conductance was calculated from volume flow and retinal perfusion pressure. It was 53% larger in the temporal than the nasal circulations. This provides an index of the metabolic needs of the different regions of the retina.

The retinal vessels are the main source of oxygen delivery to the inner retina.¹ Previous studies have shown retinal blood flow to be higher in the temporal than nasal retinae.^{2,3} This was explained by the facts that the temporal retina is both larger than the nasal retina and contains the metabolically active macula.^{4,5}

From: The Diabetic Retinopathy Unit, R.P.M.S., Hammer-smith Hospital, London, UK.

Correspondence to: Professor E. M. Kohner, The Diabetic Retinopathy Unit, Department of Medicine, R.P.M.S., Hammer-smith Hospital, Du Cane Road, London W12 0NN, UK.

Oxygen has always been known to be a vital element in the metabolism of tissues. Because the retina has a high metabolic activity and requires more oxygen per gram of tissue than any other tissue in the body,⁶ the concentration of oxygen needs to be maintained at relatively stable levels. Cusick and associates⁷ first reported in 1940 that retinal vessels constrict at high oxygen tensions, signifying autoregulation. Oxygen-induced autoregulation caused controversy since the definition of autoregulation did not include changes other than that of perfusion pressure,⁸ until Guyton *et al.*⁹ expanded the definition to include local metabolites including oxygen. The lack of functional sympathetic innervation to the human retinal vessels makes metabolic autoregulation essential.¹⁰ Evidence for this comes from the work of Dollery *et al.*¹¹ who found that vasoconstriction of the retinal vessels in response to oxygen was unaffected by stellate block or thoracic sympathectomy. Also, Alm and Bill,¹² in their excellent work, found that pre-retinal oxygen tension was maintained constant in cats despite a reduction in perfusion pressure of the eye from 130 mmHg to 50 mmHg. They concluded that oxygen tension is a fundamental stimulus and therefore maintained over a relatively wide range of perfusion pressures.¹²

No distinction has yet been made between the regulatory mechanisms of the temporal retina and the nasal retina; in view of the high metabolic activity of the macula supplied by the temporal vasculature, the autoregulatory response may selectively control flow to the macula more than to the rest of the retina.¹³ To test this hypothesis, retinal haemodynamic measurements were performed on both the temporal and nasal circulations before and after breathing oxygen.

METHODOLOGY

Study Subjects

Fifteen healthy volunteers were recruited, age range 20–60 years (mean \pm SD, 38.53 \pm 10.34 years). All

subjects had a normal physical examination, visual acuity of 6/12 or better, normal ocular examination and normal intraocular pressures. Informed consent was obtained from the study subjects after a full detailed explanation of the protocol. Approval from the local ethics committee was granted in accordance with the principles laid down by the Declaration of Helsinki.

Systemic pO₂ and pCO₂ Changes

To study the normal metabolic autoregulation of the retinal circulation to oxygen, local oxygen tension in the retinal tissue was increased using 60% oxygen in the inspired air. This level of oxygen was chosen since it is within the autoregulatory range of the retina.¹⁴ The 60% oxygen in the inspired air was achieved using an MCO-1 disposable oxygen mask (Henleys Medical Supplies, Herts, UK). Working on the Venturi principle this mask delivers a relatively accurate percentage of oxygen in the inspired air by controlling the rate of flow of air mixed with the oxygen.

A separate study was performed on 7 of the subjects to determine the systemic changes in the partial pressure of oxygen (pO₂) and carbon dioxide (pCO₂) during the inhalation of 60% oxygen, and also to quantitate the time it takes for these changes to stabilise. The subjects were connected to a transcutaneous pO₂ and pCO₂ TC100 monitor (Radiometer, Copenhagen) and were allowed to breathe 60% oxygen through an MCO-1 disposable oxygen mask. Baseline and final pO₂ and pCO₂ levels were noted and the time it took to achieve the equilibrium.

The average time taken for stabilisation of arterial pO₂ was less than 10 minutes (see below). Therefore, it was decided from the outset of the study to use 60% oxygen in the inspired air for 10 minutes, allowing for this equilibrium, before any retinal haemodynamic measurements were performed.

Study Design

Pupillary dilatation was achieved with tropicamide 1% (Minims, Smith & Nephew, Romford, UK), after which the subjects were allowed to rest for a period of 30 minutes. Blood pressure, pulse and intraocular pressure measurements were taken and retinal haemodynamic studies were performed. These included laser Doppler velocimetry and monochromatic retinal photography (see below). The subjects were then made to breathe 60% oxygen for 10 minutes prior to repeating laser Doppler velocimetry and retinal photography.

Blood Velocity Measurement

Retinal blood flow was determined from red cell velocity using bidirectional laser Doppler velocime-

try (Oculix, Philadelphia, USA).¹⁵ This technique utilises the shift in frequency produced when a monochromatic laser beam from a helium-neon laser (632.8 nm, irradiance 80 mW/cm²) is reflected from moving red blood cells in the retinal vessels. This shift in frequency is directly proportional to the red cell velocity. The frequency-shifted light is collected by a pair of photoreceptors and stored on the hard disc of a minicomputer (Masscomp, Mass., USA); the collected data were analysed later in a randomised masked fashion. Since flow of blood in a vessel is parabolic,¹⁶ only the maximally shifted frequency was used, representing the maximal centreline red cell velocity (V_{\max}).

Vessel Diameter Measurement

Vessel diameter (D) was determined from monochromatic fundus photographs. The photographs were taken with a 30° Zeiss fundus camera (Carl Zeiss, Oberkochen, Germany) linked to an electrocardiographic monitor through a time-delay device. This device triggered the shutter of the camera at a predetermined point from the electrocardiographic R-wave, and thus allowed all the fundus photographs to be taken in mid-diastole. This technique eliminates the effect of pulsatility on the variation in vessel diameter measurements.¹⁷ The film used was Kodak Technical Pan film (Kodak, Rochester, NY, USA) and the photographs were taken through a red-free 570 nm interference filter to enhance the resolution of the vasculature.¹⁸ The fundus photographs were projected through a video camera, digitised by an image analysis computer (Context Vision, Linköping, Sweden) and projected on a 512×512 pixel monitor. From the images, retinal vessel diameters were determined using the well-documented method of the half-height of the transmittance profiles.¹⁹ Vessel diameter measurements were corrected for the magnification of the camera and the ocular refraction using tables adopted from the work of Bengtsson and Krakau.²⁰ Three photographs were taken at each time point during the study and the three vessel diameter measurements from each of the three photographs were averaged.

Site of Blood Flow Measurement

Blood flow in the superior and inferior temporal veins is similar, as shown by Feke *et al.*³ and Riva *et al.*² using the laser Doppler technique. Therefore, either the superior or the inferior temporal veins were chosen to measure retinal blood flow, within one disc diameter from the disc edge before any bifurcation. Venous flow was chosen rather than arterial flow because of the limitations of the instrumentation.³ Flow in retinal veins has been shown to be similar to that of the corresponding

Table I. Basic clinical parameters of the study subjects (mean \pm SD)

Age (years)	38.53 \pm 10.34
Pulse (beats/min)	73.14 \pm 13.53
Systolic blood pressure (mmHg)	122.9 \pm 10.50
Diastolic blood pressure (mmHg)	80.30 \pm 6.80
Mean arterial blood pressure (mmHg)	95.32 \pm 7.47
Intra-ocular pressure (mmHg)	15.73 \pm 2.52
Perfusion pressure (mmHg)	47.81 \pm 5.46

retinal arteries, adhering to the theory of conservation, since the retinal circulation lacks lymphatic flow.^{2,3}

A Polaroid fundus photograph was obtained to mark the exact position of the velocity measurement on the vein. This later provided a reference point for the site of vessel diameter determination.

Volumetric Flow Rate

The volumetric flow rate (Q) was calculated by multiplying the mean red cell velocity (V_{mean}) by the cross-sectional area (A) of the vessel ($Q = V_{\text{mean}} \cdot A$). To determine the mean red cell velocity, the maximal centreline red cell velocity (V_{max}) was divided by a factor of 1.6 according to the work of Baker and Wayland¹⁶ and Damon and Duling,²¹ since blood does not flow like a perfect Newtonian fluid. The cross-sectional area of the vessel was determined from vessel diameter (D). The formula to calculate the flow therefore becomes:

$$Q = \frac{V_{\text{max}}}{1.6} \cdot \frac{\pi \cdot D^2}{4}$$

Retinal Perfusion Pressure

Blood pressure was determined using a Takeda automated digital blood pressure meter (A&D Engineering, Calif., USA) calibrated with a random zero mercury sphygmomanometer (Hawksley & Sons, UK). Intraocular pressure was measured with Goldmann applanation tonometry. Mean arterial blood pressure (MAP) was calculated by adding the diastolic blood pressure (BP_D) to one-third the difference between the systolic (BP_S) and diastolic blood pressures ($MAP = 1/3[BP_S - BP_D] + BP_D$). Perfusion pressure (PP) was determined by subtracting the intraocular pressure (IOP) from two-thirds the mean arterial blood pressure ($PP = 2/3MAP - IOP$).¹³

Retinal Vascular Conductance

From the values of retinal volume flow and ocular

Table III. Results of transcutaneous measurements of systemic partial pressure of oxygen (pO_2) and systemic partial pressure of carbon dioxide (pCO_2) before and after breathing 60% oxygen for 10 minutes

	pO_2	pCO_2
Baseline (mmHg)		
Mean \pm SD	7.70 \pm 2.36	5.10 \pm 0.76
Range	4.00 to 11.60	N/A
Maximal level (mmHg)		
Mean \pm SD	25.70 \pm 7.05	5.00 \pm 0.69
Range	16.20 to 35.00	N/A
Time taken (minutes)	7.86 \pm 1.03	N/A

perfusion pressures determined, conductance ($\mu\text{l}/\text{min}/\text{mmHg}$) of the retinal vessels was calculated. This is retinal blood flow per unit of perfusion pressure and is calculated by dividing retinal volume blood flow by the perfusion pressure.²²

STATISTICAL ANALYSIS

Results are expressed as mean \pm SEM except where otherwise stated. One-way analysis of variance (ANOVA) was used initially to determine whether significant differences existed. If significant differences were found Student's t -test was applied (Oxstat II, Microsoft, 1985). Retinal haemodynamics between the temporal and nasal circulations were compared using an unpaired Student's t -test. Changes in retinal haemodynamics after breathing oxygen were compared with baseline data using a paired Student's t -test. Results were considered to be statistically significant when $p \leq 0.05$.

RESULTS

The basic clinical parameters of the study subjects are summarised in Table I. Haemodynamic data for temporal and nasal vessels are summarised in Table II.

Systemic pO_2 and pCO_2 Changes

The rise in pO_2 was 233.8% on average while the pCO_2 did not show any significant change during oxygen breathing. The average time taken for stabilisation of arterial pO_2 was 7.86 minutes (Table III).

Haemodynamic Parameters Before Oxygen

It is apparent that the nasal vessels are significantly smaller than the temporal vessels by 20.4% ($p < 0.001$). The velocity of red cells is slower in the nasal vessels by 24.64% relative to their velocity in the temporal vessels ($p = 0.003$). The volumetric flow

Table II. Haemodynamic parameters before and after breathing oxygen (mean \pm SEM)

	Temporal		Nasal	
	Pre- O_2	Post- O_2	Pre- O_2	Post- O_2
Vessel diameter (μm)	158.63 \pm 5.37	142.15 \pm 5.30	126.27 \pm 4.93	116.60 \pm 5.05
Red cell velocity (cm/s)	2.07 \pm 0.11	1.51 \pm 0.12	1.56 \pm 0.11	1.16 \pm 0.12
Blood flow ($\mu\text{l}/\text{min}$)	15.47 \pm 1.24	9.00 \pm 0.84	7.35 \pm 0.66	4.70 \pm 0.63
Conductance ($\mu\text{l}/\text{min}/\text{mmHg}$)	0.331 \pm 0.031	0.193 \pm 0.021	0.156 \pm 0.014	0.009 \pm 0.013

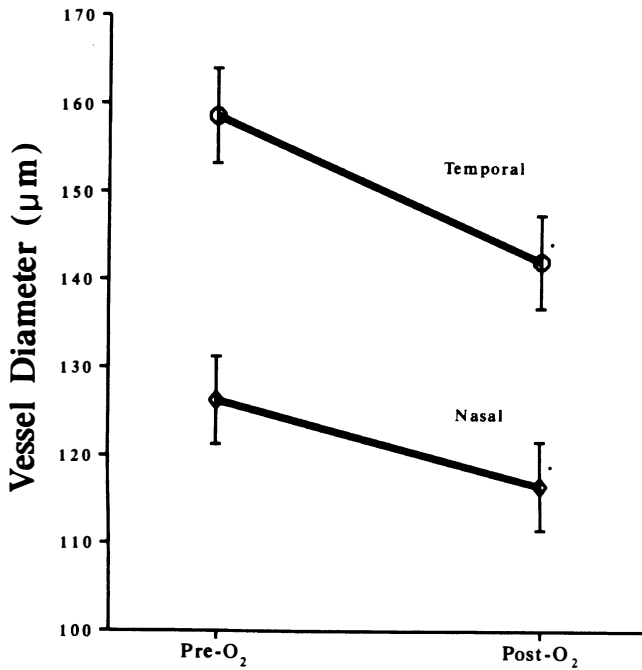


Fig. 1. Retinal vessel diameters before and after breathing oxygen. Results are expressed as mean \pm SEM. * $p < 0.001$ in comparison with pre-oxygen data.

rate is lower in the nasal than the temporal circulations by 52.49% ($p < 0.001$). Conductance value of the nasal circulation is significantly smaller ($p < 0.001$) and almost half that of the temporal circulation (52.87%).

Haemodynamic Parameters after Oxygen

There was significant vasoconstriction in the temporal circulation by $10.42 \pm 1.24\%$ ($p < 0.001$) and in

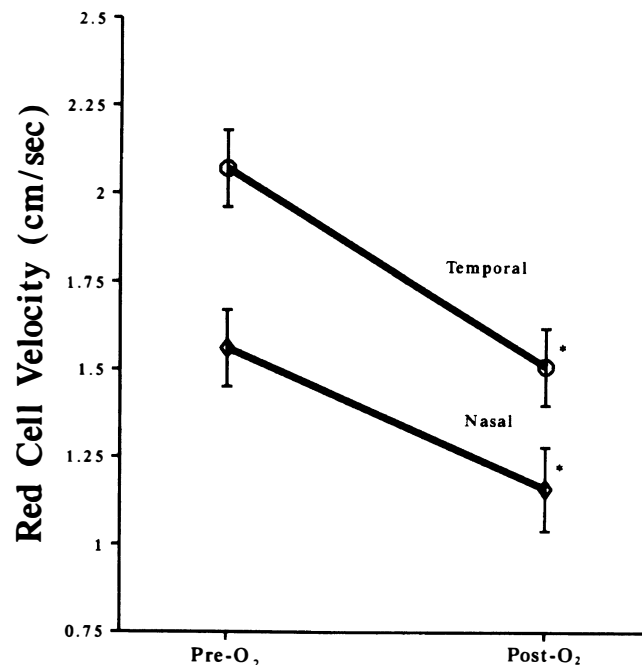


Fig. 2. Retinal blood flow before and after breathing oxygen. Results are expressed as mean \pm SEM. * $p < 0.001$ in comparison with pre-oxygen data.

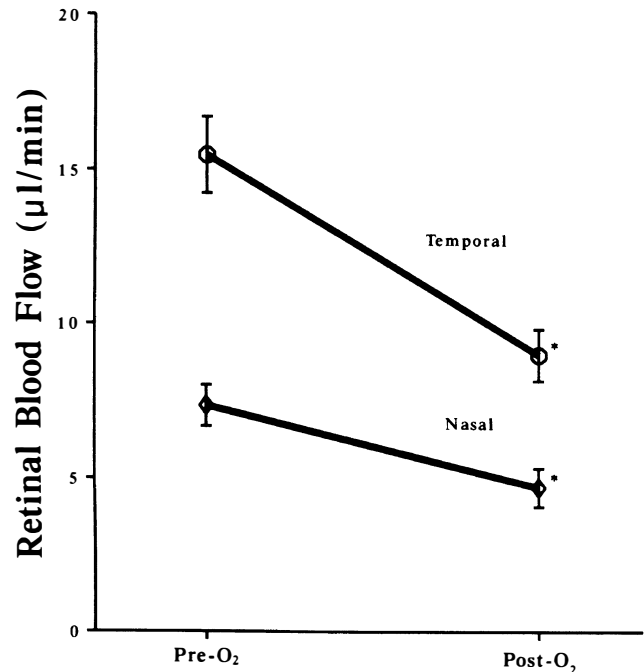


Fig. 3. Retinal blood flow before and after breathing oxygen. Results are expressed as mean \pm SEM. * $p < 0.001$ in comparison with pre-oxygen data.

the nasal circulation by $7.66 \pm 1.48\%$ ($p < 0.001$) after breathing 60% oxygen for 10 minutes (Fig. 1). No significant difference was found in the amount of vasoconstriction between the temporal and nasal circulations. A comparable and significant reduction in red cell velocity in the temporal ($27.10 \pm 3.92\%$) and nasal ($27.36 \pm 5.51\%$) circulations ($p < 0.001$) was seen (Fig. 2). The reduction in retinal blood flow was significant ($p < 0.001$) and comparable in both the temporal ($41.16 \pm 3.64\%$) and nasal ($37.99 \pm 5.07\%$) circulations (Fig. 3). A significant and comparable reduction in the conductance values of both the temporal ($41.16 \pm 3.64\%$) and nasal ($37.99 \pm 3.64\%$) circulations was seen after breathing 60% oxygen ($p < 0.001$) in comparison with baseline (Fig. 4).

No change in the systolic and diastolic blood pressures was noted during oxygen breathing.

DISCUSSION

This study quantitates retinal blood flow and vascular metabolic autoregulation to 60% oxygen. It also delineates the difference between the temporal and nasal circulations.

Breathing 60% oxygen using an MCO-1 mask produced a significant rise in systemic pO_2 without any change in the pCO_2 . This is important since, theoretically, the hyperoxia produced may induce respiratory depression leading to a concurrent hypercapnia.²³ Carbon dioxide is known to have a more potent effect on retinal autoregulatory mechanisms than oxygen.²⁴ Therefore this technique allowed the study of the effect of hyperoxia alone without the influence of carbon dioxide.

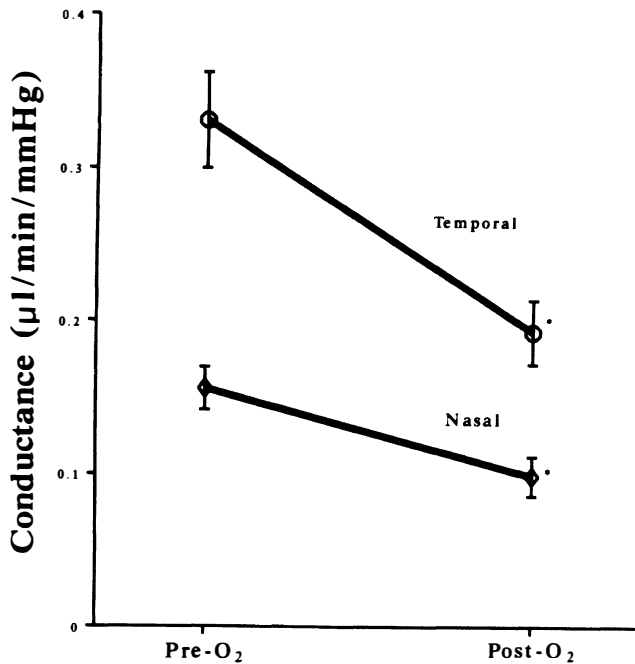


Fig. 4. Retinal vascular conductance before and after breathing oxygen. Results are expressed as mean \pm SEM. * $p < 0.001$ in comparison with pre-oxygen data.

In this study, blood velocity was faster in the temporal circulation by 24.64%. This is comparable to the difference of 27% documented by Oberhoff *et al.*²⁵ in 1965, using fluorescein transit time. The difference in the volumetric flow rate found in our study (52.49%) is not far off that recorded by Riva *et al.*² in 1986, who found 45% higher flow in the temporal than the nasal veins, measured by laser Doppler velocimetry and projection micrometry in 12 healthy volunteers. Riva *et al.* found that this difference in flow correlates significantly with the difference in temporal and nasal vascular cross-sectional area. On the other hand Feke *et al.*³ in 1989, using a similar technique in 10 healthy volunteers, found 65% higher flow in the temporal than the nasal retina. Using labelled microspheres, Alm and Bill⁴ in 1973 showed that the macular blood flow was 4 times larger than the flow in the intermediate and peripheral retina. Therefore, the higher flow rate in the temporal circulation may be explained by the fact that the temporal retina has 20–25% more tissue than the nasal retina.^{4,5}

The conductance of a circulation is used as a measure of its ability to allow blood flow through at a given perfusion pressure, thus providing an index of the metabolic needs of the retina independent of changes in perfusion pressure. To our knowledge, no study has looked at this index in the retina previously. In this study, conductance of the temporal circulation was 52.87% larger than that of the nasal circulation. This indicates that at a given perfusion pressure, flow in the temporal retina is twice as large as that in the nasal retina. However,

the temporal retina is only 20–25% larger than the nasal retina.^{4,5} This means that a gram of tissue in the temporal retina is supplied by more blood than a gram of tissue in the nasal retina. This may reflect the high metabolic need of the macula.

Breathing 60% oxygen in this study produced an average rise in the transcutaneous oxygen tension of 233% after the 10 minutes. The significant vasoconstriction produced can be interpreted in terms of the explanation given by Dollery *et al.*²⁶ They proposed that during hyperoxia, the retina obtains practically all its oxygen from the choroidal circulation. The retinal vasculature becomes redundant as a supply of oxygen with resultant vasoconstriction. Riva *et al.*²⁷ challenged this viewpoint by demonstrating a higher pre-retinal pO₂ tension in comparison with the pO₂ in an area of retina adjacent to the choroid. Also the rise in pO₂ in the periarterial area of the retinal vessels preceded the decrease in retinal blood flow, indicating an autoregulatory response of the retinal circulation to hyperoxia.

Most of the literature on retinal haemodynamics is concerned with the temporal circulation. Therefore, for the purpose of comparing the autoregulatory changes in our study with other studies in the literature, the temporal circulation is referred to in this section. A reduction in blood velocity of 27.05% and a decrease in vessel diameter of 10.39% in our study are in close agreement with the findings of the only other study that used 60% oxygen in the inspired air by Fallon *et al.*²⁸ He found a 36% decrease in macular blood velocity and a 10% decrease in temporal retinal vein diameter in response to breathing 60% oxygen using the blue field entoptic phenomenon and fundus photographs. Previous workers have shown that oxygen levels in the inspired air up to 80% lie within the autoregulatory range of the retinal circulation.¹⁴ Levels of more than 80% oxygen causes a profound rise in vitreal oxygen tension signalling an override of the autoregulatory mechanisms of the retinal circulation. Hickam and Frayser²⁹ demonstrated alteration of retinal metabolism when oxygen in the inspired air rose above 60%. For these reasons, 60% oxygen in the inspired air was chosen rather than 100%. Nevertheless, Hickam *et al.*, using the mean circulation time of fluorescein in normal volunteers, found 14.9% narrowing in the retinal veins,³⁰ a reduction in the velocity of fluorescein by 27%³¹ and a decrease in retinal blood flow by approximately 57% after breathing 100% oxygen.³² This is not surprisingly higher than the decrease in retinal blood flow in our study (41.82%). Riva *et al.*³³ found a 64% reduction in retinal blood flow, 53% decrease in velocity and 12% decrease in vessel diameter using laser Doppler velocimetry after breathing 100% oxygen. Similarly, Grunwald *et al.*³⁴ found a 61% decrease in retinal

blood flow in response to 100% oxygen. All these studies are comparable to each other, but give higher values than our study, as expected from the higher percentage of oxygen in the inspired air.

No other study has looked at retinal vascular autoregulation in different regions of the retina. Because of the higher metabolic activity of the macula, autoregulation to changes in local metabolites is expected to be more strictly controlled in the temporal than the nasal circulations. However, in this study there was no significant difference in the volumetric flow rate after breathing oxygen between the temporal (41.82%) and nasal (36.05%) circulations. This may be explained by the fact that the extra oxygen demands of the metabolically active macula have already been met by the higher flow in the temporal retina, as discussed above. The increased oxygenation with hyperoxia will, therefore, have the same effect on all parts of the retinal circulation.

In conclusion, the distribution of blood to different parts of the retina seems to be finely tuned according to functional tasks and metabolic needs. The autoregulatory mechanisms then seem to oversee this delicate balance and make the necessary adjustments to blood flow to the retina as a whole in response to any change in its environment.

Key words: Laser Doppler velocimetry, Retinal blood flow, Retinal vascular autoregulation.

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