Oxygen supply to the retina from the retinal and choroidal circulations at normal and increased arterial oxygen tensions

C. T. Dollery, C. J. Bulpitt, and Eva M. Kohner

During oxygen breathing small retinal vessels constrict severely and retinal blood flow drops to less than half the value on air. This paper contains a quantitative explanation of why this occurs based on published figures for the arteriovenous oxygen difference and blood flow in the retinal and choroidal circulations. The choroid has a high blood flow and a low arteriovenous oxygen difference. Once the arterial oxygen tension, p_aO_2, rises to about 270 mm. Hg, the intake of the oxygen extraction from the choroidal blood can be met from dissolved oxygen. When p_aO_2 rises above this level the oxygen tension in the choroidal tissue and venous blood rises in step with it because the capacity of reduced hemoglobin to buffer changes in oxygen pressure is lost. At a p_aO_2 of 400 mm. Hg, 97 per cent of the retina between the choriocapillaris and the deep retinal capillaries is supplied with oxygen from the choroid compared with 60 per cent on air. At higher values of p_aO_2 there is a delivery of oxygen from the choroid to the deep retinal capillaries and under hyperbaric oxygen almost the whole thickness of retina could be supplied with oxygen from the choroid alone.

Key words: Retinal vessels, oxygen consumption, retinal blood flow, choroidal blood flow, oxygen tension, hyperbaric oxygenation, mathematical analysis, vasoconstriction, retrolental fibroplasia.

The retinal blood vessels are more sensitive to changes in arterial oxygen tension than those of other circulations. When a normal subject changes from breathing air to oxygen at 1 atmosphere pressure the oxygen saturation of the hemoglobin in retinal venous blood rises from 55 to 82 per cent, whereas the flow drops to 57 per cent of that observed during air breathing. Because of the rise in retinal venous oxygen saturation the fall in oxygen uptake is even greater and the uptake during oxygen breathing is only 44 per cent of that observed during air breathing.[7] The retinal vessels also show large changes in their caliber when the arterial oxygen tension is varied. In normal subjects the small arterioles are narrowed by an average of 30.2 per cent when breathing oxy-

From the Department of Medicine, Royal Postgraduate Medical School, Ducane Road, London, W.12, England.

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gen at 1 atmosphere. As their resistance is inversely proportional to the fourth power of the radius this suggests a very large increase in vascular resistance during oxygen breathing.[3]

Most circulations adjust their vascular resistance when the arterial oxygen tension is changed, but only enough to keep the supply of oxygen roughly constant. As the hemoglobin is very nearly fully saturated during air breathing in an individual with normal lungs the increase in oxygen delivery during oxygen breathing is accounted for solely by dissolved oxygen. Available oxygen is increased by only about 6 per cent.

The explanation for this apparent sensitivity of the retinal vessels to oxygen may lie in the dual blood supply to the retina (Fig. 1). The retinal capillaries supply the anterior part of the retina and the choroidal circulation supplies the more posterior or deep part, particularly the rods and cones. The choroid is an extremely vascular tissue, consisting of large-diameter capillaries, and recent measurements show that it has an extremely high blood flow and a very low arteriovenous oxygen difference. Because of the low arteriovenous difference in the choroidal bed, during oxygen breathing the choroidal venous blood will become fully saturated. The oxygen tension in the choroidal venous blood can then rise to a high level and the proportion of the retina supplied with oxygen by the choroidal circulation may be greatly increased.

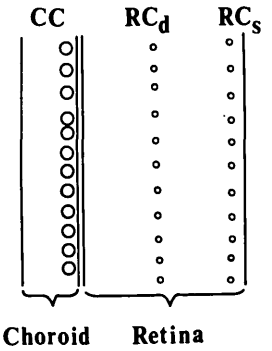

Fig. 1. Cross-sectional diagram of the retinal blood supply. The choroid consists of close-packed large-diameter capillaries, *CC*. The retinal capillaries form two layers, RC_s and RC_d, in most parts of the retina. The deep capillaries, RC_d, lie about 100μ from the choroid and the retinal veins drain from this layer.

Assumptions

To calculate the proportion of the retina supplied by the retinal and choroidal circulations under different circumstances it is necessary to make a number of assumptions. The first of these is a figure for the retinal and choroidal blood flow. We have taken the figures of Friedman, Kopald, and Smith,[6] who used an inert gas washout technique in anesthetized animals. They found the choroidal blood flow to be 1,200 ml. per 100 Gm. of tissue per minute and the retinal blood flow to be 166 ml. per 100 Gm. of tissue per minute. The second assumption involves the saturation of the retinal venous and choroidal venous blood. This has been measured in man in the retinal circulation by Hickam and Frayser.[7] These authors found that the retinal venous saturation was 55 per cent during air breathing and 82 per cent during oxygen breathing at 1 atmosphere. At pH 7.4 these saturations are equivalent to pO_2 values of 28.5 and 48 mm. The arteriovenous difference across the uveal tract of the dog eye has been measured by Elgin.[5] Elgin found an arterial oxygen tension of 85 mm. during air breathing and a uveal venous tension of 69 mm. During oxygen breathing the average arterial oxygen tension was 419 mm. and the average uveal venous tension 252 mm. As the arterial oxygen tension in anesthetized animals does not rise as high as it does in a normal man breathing oxygen, these figures must be adjusted. We have assumed a figure of 600 mm. Hg for the arterial oxygen tension in man during oxygen breathing at 1 atmosphere. We have also assumed that the arteriovenous oxygen tension difference in the human choroid would be the same as in the dog uveal circulation, namely, 167 mm. This

gives a figure for choroidal oxygen tension during oxygen breathing at 1 atmosphere of 433 mm. Hg. It is also necessary to make assumptions about the thickness of the retina. The retina varies from approximately 300μ thick near the optic disc to less than 150μ at the periphery. Furthermore, the retinal capillaries do not run on the surface of the retina but penetrate into it, forming a deep layer from which the retinal veins drain. We have assumed that that part of the retina which is supplied by both the retinal and choroidal circulations lies between this deep layer of capillaries and the choriocapillaris and is 100μ thick. We have taken the diffusion constant to be 1.7×10^{-5} ml. of oxygen per minute per square centimeter of retina at 37° C. in a concentration gradient of 1 atmosphere per centimeter.[8]

It is first necessary to calculate the oxygen consumption per 100 Gm. of retina per minute. Assuming a choroidal blood flow of 1,200 ml. per 100 Gm. of tissue per minute and an A-V difference of 0.5 ml. of oxygen per 100 ml. of blood, the oxygen uptake is 6 ml. per 100 Gm. of tissue per minute. The corresponding calculation for the retinal circulation gives a figure of 13 ml. per 100 Gm. per minute. It is difficult to know how much overlap there is between the retinal and choroidal tissue pools whose blood flow is measured by the inert gas washout method. We have assumed that they are separate and have therefore taken an average value of 9.5 ml. of oxygen per 100 Gm. per minute to represent the oxygen uptake.

Oxygen diffusion in the retina

The rate of diffusion across a square centimeter of retina parallel to the surface is $\frac{Ddp}{dx}$, where D is the diffusion constant and $\frac{dp}{dx}$ is the rate of change of oxygen pressure with depth. The rate of accumulation of oxygen at a point x cm. from the surface will be $D\frac{d^2p}{dx^2}$, and under steady state conditions this must equal the oxygen consumption at that point M ml. of O_2 per cubic centimeter of tissue.[8]

$$M = D\frac{d^2p}{dx^2}. \qquad (1)$$

The solution of this equation is:

$$p = \frac{Mx^2}{2D} + Bx + p_o, \qquad (2)$$

where p_o is the oxygen pressure constantly maintained at the surface and B is a constant of integration. When $x = 0$, $p = p_o$.

In a tissue consuming oxygen the value of p will fall as the distance from the blood supply increases and a point will be reached either where $p = 0$ or, in the case of the retina which is supplied from both sides, where the pressures from the choroidal and the retinal circulations balance. At this point diffusion of oxygen must stop and the concentration gradient $\frac{dp}{dx}$ becomes zero. If x_b cm. is the distance from the choroidal surface where the pressures balance then:

$$\frac{dp}{dx} = 0 = \frac{Mx_b}{D} + B; \qquad (3)$$

$$\therefore \quad B = -\frac{Mx_b}{D}$$

and, by substitution of Equation 2,

$$p = \frac{Mx^2}{2D} - \frac{Mxx_b}{D} + p_o.$$

At the point where the pressures balance $x = x_b$ and the equation simplifies to:

$$p = \frac{Mx_b^2}{2D} - \frac{Mx_b^2}{D} + p_o,$$

or

$$p = p_o - \frac{Mx_b^2}{2D}. \qquad (4)$$

If the oxygen pressure constantly maintained at the choroidal surface is p_c and at the retinal surface it is p_r, the point of

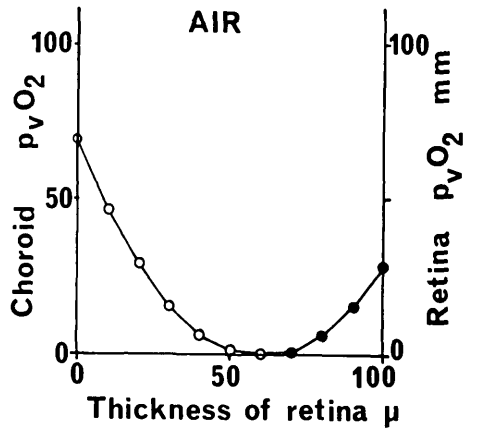

Fig. 2. Open circles show the oxygen tension at different depths from the choroidal capillaries; closed circles, from the retinal. Approximately 60 per cent of the retina lying between the choroid and the deep retinal capillaries is supplied from the choroid during air breathing.

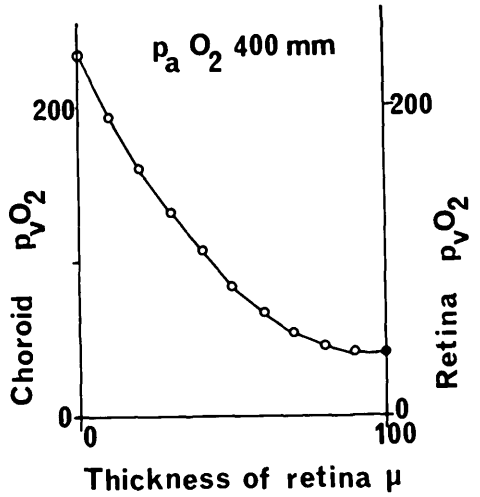

Fig. 3. Oxygen tension at different depths in the retina lying between the choroid and the deep retinal capillaries when the arterial oxygen tension, p_aO_2, is 400 mm. Hg. This value of p_aO_2 would be found when breathing approximately 70 per cent oxygen at N.T.P. Under these conditions 97 per cent of the retina between the choroid and the deep retinal capillaries is supplied from the choroid.

balance, x_b cm. from the choroidal surface, can be calculated. If the thickness of retina between the choroid and the deep retinal capillaries is 0.01 cm., the distance between the point of balance and the deep retinal capillaries will be $0.01 - x_b$. Thus:

$$p_c - \frac{Mx_b^2}{2D} = p_r - \frac{M(0.01 - x_b)^2}{2D}.$$

This equation simplifies to:

$$x_b = \frac{2D}{0.02M}(p_c - p_r) + 0.005. \qquad (5)$$

As all the other values have been measured, this equation can be solved at different values of p_c and p_r, which are given in Figs. 2 and 3. During air breathing 40 per cent of the retina between the two circulations is supplied by the retinal vessels (Fig. 2); if the arterial oxygen tension, p_aO_2, is increased to 400 mm. Hg, 97 per cent of the thickness of the retina between the two circulations can be supplied from the choroid (Fig. 3). At higher pressures there is a net delivery of oxygen from the choroid to the deep retinal capillaries.

Oxygen diffusion from the choroid alone

If the retinal vessels are interrupted, the tissue oxygen tension will fall as distance from the choroid increases and a point will be reached where $p = 0$. At this point diffusion of oxygen must stop and the concentration gradient $\frac{dp}{dx}$ becomes zero.

If x_a is the distance from the choroid where $p = 0$, then, from Equation 2,

$$p = 0 = \frac{Mx^2}{2D} + Bx_a + p_o.$$

When the oxygen pressure gradient $\frac{dp}{dx} = 0$, the constant of integration, B, can be calculated from Equation 3:

$$\frac{dp}{dx} = \frac{Mx_a}{D} + B,$$

so when $\frac{dp}{dx} = 0$

$$B = -\frac{Mx_a}{D},$$

substituting this value of B in Equation 2

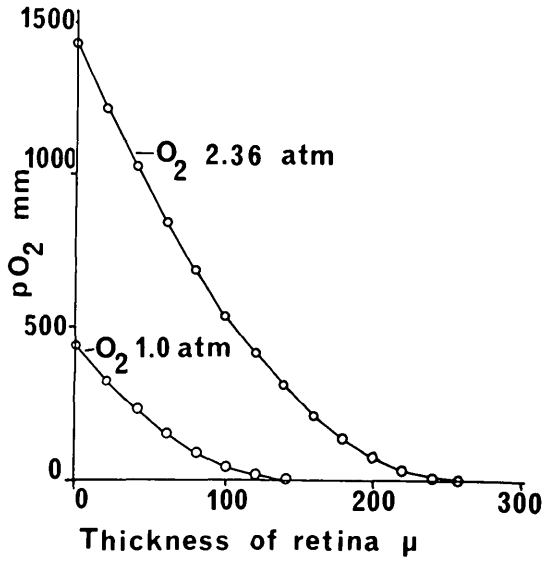

Fig. 4. Oxygen tension, pO_2, at different depths in the retina while breathing oxygen and with the retinal vessels occluded. During oxygen breathing at N.T.P. the choroid could supply about 140μ of the retina with oxygen. If the inspired oxygen pressure is raised to 2.36 atmospheres the choroid can supply the retina to a depth of 260μ, which is the whole thickness in most parts.

when $x = x_a$ gives the value of x_a which is the greatest depth to which oxygen can penetrate in a tissue supplied from one surface.

$$x_a = \sqrt{\frac{2Dp_o}{M}}. \qquad (6)$$

During oxygen breathing at 1 atmosphere this distance is 143μ from the choroidal surface and at 2.36 atmospheres, with an assumed choroidal venous oxygen pressure, p_vO_2, of 1,430 mm. Hg the distance is 260μ. Thus, at this high oxygen pressure, the oxygen supply from the choroid can supply the whole thickness of the retina. Hickam and Frayser[7] observed that the oxygen saturation in the retinal veins rose to about 94 per cent during oxygen breathing at 2.36 atmospheres.

The oxygen tension at different points in the thickness of the retina can be calculated by substituting for B in Equation 2. Since

$$B = -\frac{Mx_a}{D}$$

and

$$x_a = \sqrt{\frac{2Dp_o}{M}},$$

$$B = -\sqrt{\frac{2Mp_o}{D}};$$

from Equation 2:

$$p = \frac{Mx^2}{2D} - x\sqrt{\frac{2Mp_o}{D}} + p_o. \qquad (7)$$

Calculated pressures at different depths in the retina during oxygen breathing at N.T.P. and at 2.36 atmospheres are shown in Fig. 4.

Discussion

These calculations suggest that under conditions of air breathing the choroid supplies oxygen to about 60 per cent of the retinal tissues lying between the choriocapillaris and the deep retinal capillaries. If the oxygen concentration in the inspired gas is increased to about 70 per cent the proportion of the retina supplied with oxygen from the choroid rises to 97 per cent. It is not surprising that the oxygen uptake from the retinal circulation appears to fall.

To calculate the proportional change in oxygen uptake from the retinal vessels during the change from air to oxygen breathing it is necessary to make an assumption about the amount of oxygen supplied to the retina which lies between the superficial and deep retinal capillaries. In much of the retina, although not at the macula, this tissue is as thick as the tissues lying between the deep retinal capillaries and the choroidal vessels. If it is assumed that this retinal tissue receives an amount of oxygen equivalent to that supplied to the deep retinal tissues from the retinal capillaries during air breathing, it is possible to calculate the proportional change in oxygen uptake. The oxygen up-

take from the retinal vessels while breathing 70 per cent oxygen with an arterial pO_2 of about 400 mm. would fall to about 50 per cent of that observed during air breathing and on 100 per cent oxygen to less than 50 per cent. This figure agrees well with the value measured by Hickam and Frayser,[7] but too much should not be made of this agreement because the assumptions have been chosen with their measurements in mind.

Most of the assumptions on which these calculations are based seem reasonable. Experimental verification may be difficult because of the inaccessibility of the choroidal vessels. The assumption most likely to be incorrect is the one concerning the uniformity of oxygen uptake through the retinal tissue. However, nonuniformity may alter the point at which the oxygen supplied by the two circulations balances but not the principle underlying the calculations.

The effect depends upon the high flow and low arteriovenous oxygen difference in the choroidal circulation. The power of unsaturated hemoglobin to buffer changes in oxygen pressure is lost as soon as the venous hemoglobin saturation becomes complete. Increasing the proportion of oxygen in the inspired air to about 40 per cent allows the whole of the oxygen extraction by the choroid to be met from dissolved oxygen and beyond this point the choroidal pO_2 will mount rapidly.

The calculations suggest that the whole of the oxygen supply of the retina could be met from the choroid under conditions of increased oxygen pressure. In practice oxygen therapy has not proved of much value in retinal arteriolar obstruction but it may be the diffusion of other molecules such as glucose through the retina which is the limiting factor. It is not practical to increase the concentration gradient of these substances to the same extent as can be achieved with oxygen.

The severe and apparently disproportionate vasoconstriction observed in the retinal circulation may after all be an autoregulatory response to a raised tissue pO_2. It is not clear why the choroidal vessels do not autoregulate, but their large caliber and high flow suggest that they may have another function besides oxygenation of the retina. This function may be cooling the retinal pigment epithelium, which is the main site of energy absorption in the eye.

The potential ability of the choroid to oxygenate the whole thickness of the retina has interesting implications for understanding the physiological problem of retrolental fibroplasia. If premature human infants or kittens are exposed to high oxygen concentrations in the inspired gas, severe vasoconstriction occurs in retinal vessels.[1] It is interesting to note that Ashton and Cook[2] showed that retinal vasoconstriction did not occur in kittens exposed to oxygen if the retina was detached. Furthermore, detachment of the retina after vasoconstriction had occurred reversed it. The retina of a 7-month-old human fetus is about 175 μ thick, a little thinner than that of the adult, and the vasoconstriction is most severe at the periphery where the retina is thinner. In 80 per cent oxygen at N.T.P. the choroid could supply retinal tissue about 135 μ thick, which would suffice for all except the area close to the posterior pole. However, the involvement of the periphery is probably not due only to the thinness of the retina; the peripheral vessels are also the most immature. Complete closure on exposure to oxygen appears to be a reaction confined to immature vessels. The vasoconstriction observed during oxygen breathing is greater in young adults than in old ones.[10] In premature infants it appears that the increase in vasomotor tone is sufficient to close the vessels completely. The vessels partly reopen when the infant is placed in air but if the exposure has been for more than a few hours irreversible changes take place with vascular proliferation and fibrosis.

We are not the first to suggest that oxy-

gen from the choroidal circulation might be responsible for vasospasm in the retinal circulation, but this is the first time that a quantitative physiological explanation has been proposed.[4]

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