Optic nerve circulation and ocular pressure

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Rapid, short-lasting elevation of ocular pressure level produces simultaneous reduction in blood-flow rate in the distal 6 mm. of the extraocular portion of the optic nerve of the rhesus monkey as monitored by the heated thermocouple technique. The magnitude of this reduction was very small until intraocular pressure (IOP) exceeded 50 mm. Hg following which markedly and progressively greater reduction in blood-flow rate occurred at higher IOP levels; maximum reduction was reached at IOP of 105 mm. Hg. The magnitude of reduction in blood-flow rate for each ocular pressure level was significantly greater when systemic arterial pressure was reduced. These effects were monitored 2 to 4 mm. behind the globe and became reduced at a more proximal location, disappearing at locations further than 6 mm. from the globe. The results suggested a reduction in nutrient blood flow to the optic nerve at the monitored site with elevation of IOP.

Experimental glaucoma in the owl monkey demonstrated the development of lesions similar to those of cavernous degeneration in the extraocular portion of the optic nerve. India ink injection technique demonstrated lack of filling of the vessels of this portion of the optic nerve at high ocular pressure levels. The reason for this finding was not clear. In view of the close similarity between the eye of the rhesus monkey and that of man, we chose to investigate the effect of ocular pressure level on blood-flow rate in the distal portion on the optic nerve using the heated thermocouple principle. The results to be presented in this communication demonstrated significant dependence of the circulation of the distal extraocular portion of the optic nerve on ocular pressure level such that progressive increase in ocular pressure level produces a progressive reduction in blood-flow rate in this region of the optic nerve.

Materials and method

The experimental animal used in this investigation was the adult rhesus monkey of either sex. Under pentobarbital anesthesia, tracheostomy was performed to maintain an open airway. An electrically heated pad was wrapped around the monkey to maintain body temperature. Femoral artery and vein were cannulated to monitor blood pressure and administer intravenous solutions and medications. A temperature bridge was inserted rectally to monitor body temperature. Lateral orbitotomy was performed and the lateral rectus was severed at its insertion and reflected away to expose the globe and the distal 1.5 cm. of the optic nerve. Using the operation microscope, the orbital fat was cleaned away from the optic nerve region to expose the optic nerve and its blood vessels as well as those com-
thermocouple
heating element
short ciliary
optic n-sag. ser.

Fig. 1. Block diagram of heated thermocouple flow meter experiment.

The short, posterior ciliary arteries could be seen on the upper aspect of the optic nerve forming two groups, medial and lateral, as they proceeded to penetrate the posterior pole. The heated thermocouple unit was placed into optic nerve substance 3 to 4 mm. behind the globe on the lateral aspect of the optic nerve away from the short posterior ciliary vessels. The other thermocouple junction was placed at a similar location, opposite the first, on the medial aspect of the optic nerve. The anterior chamber was then cannulated using a 20-gauge needle cannula connected to a reservoir containing Kreb's solution and a 25-gauge needle cannula connected to a pressure transducer to monitor ocular pressure level. Instrumentation and equipment were described previously and a block diagram of the preparation appears in Fig. 1.

The heating element consisted of a 2 mm. constantan wire 0.5 mm. in diameter connected by copper wire to a constant direct-current (DC) power supply. The heating current was kept constant unless otherwise specified (6 volts; 250 milliamperes). One junction of a chromel-constantan thermocouple was glued to the center of the heating element with its tip projecting half a millimeter beyond it. The combined unit was then glued to a stainless-steel stylus of a 25-gauge needle with its tip projecting 1 mm. beyond that of the thermocouple junction. This helped penetrate the substance of the optic nerve and stabilized the unit in position. Once the unit was placed, the thermocouple tip was 0.5 mm. deep into optic nerve substance just beneath the heating element which was snugly applied against the optic nerve surface. The second thermocouple junction was similarly mounted and placed also 0.5 mm. deep into optic nerve substance.

In order to validate the use of the heated thermocouple technique, we tested the assumption that the temperature of the unheated thermocouple junction represented the prevailing temperature at the site of the heating unit before the heating current was applied and that it was not modified during application of the heating current. The temperature difference between the two thermocouple junctions was continuously monitored. Furthermore, when the intensity of the heating current was varied in a controlled fashion, temperature difference varied also such
that temperature gradient \( \theta \) increased proportionately to the square of the intensity of the heating current over the entire range of temperature gradient encountered in the study (Fig. 2). This means that when everything else is kept constant, (i.e., blood pressure, body temperature, and ocular pressure level) heat conductivity at the selected site is constant. Consequently, when the heating current is constant, heat conductivity, \( K \), under a given condition may be expressed in arbitrary units as one over \( \theta \), where \( \theta \) is the resulting difference in temperature or temperature gradient. For the same constant heating current changes in \( K \) under different conditions would reflect changes in blood-flow rate and be directly proportional to these changes.\(^1\) There is evidence suggestive that this proportionality may not hold equally well for all flow-rate values and that this technique may underestimate high flow rates. For obvious reasons, direct calibration studies for this site were not feasible and were not undertaken. Instead, direct proportionality was assumed in the calculation of results.

Preliminary experiments revealed that rapid elevation of ocular pressure to a new level produces a rapid reduction in optic nerve temperature at the monitored site and a rapid increase in temperature gradient \( \theta \); these effects reach a constant value in 30 to 45 seconds which does not change appreciably in four to five minutes. Consequently, in developing the experimental protocol, each level of ocular pressure was maintained for one to two minutes in order to avoid the transient changes in \( \theta \) and better estimate the "steady-state" effect. Longer deviations of pressure increments were not pursued in this study in order to avoid secondary effects and concentrate on the primary effect of ocular pressure level on blood-flow rate at this site.

**Procedure.** Once the preparation of the experimental animal and equipment was completed and steady-state values for all measured variables were attained, the following experimental protocol was executed in three consecutive stages: in stage one, ocular pressure level was maintained at zero until steady-state \( \theta \) was attained. It was then rapidly raised by elevating the reservoir to reach a level higher than prevailing systolic arterial pressure and was maintained at that level for one to two minutes during which a new steady-state \( \theta \) was reached. Ocular pressure was then rapidly reduced back to zero and new steady-state \( \theta \) reached before the next stage was initiated.

The second stage consisted of progressive increments of ocular pressure level in steps of 10 to 15 mm Hg, until a level higher than systemic
arterial pressure was reached. At each increment, the level was maintained until steady-state was reached before the next increment in pressure was made. After reaching the highest level, a similar series of reduction in pressure, in steps of 10 to 15 mm Hg was executed until the level of zero was attained. Here again, each new level was maintained constant until a steady-state was reached before the next reduction in pressure was made.

Stage three consisted of maintaining ocular pressure level at zero, then rapidly injecting 100 mg pentobarbital intravenously to produce immediate circulatory arrest, and obtain a new steady-state. A typical experimental run is seen in Fig. 3.

Calculation of results. From stage three, one can calculate that portion of heat conductivity that reflects "normal" blood-flow rate, i.e., when ocular pressure level is zero and blood pressure changes from normal levels to zero. For example, when average blood pressure was 100 mm Hg, and ocular pressure was zero, was 1.40 C and C equals one over was 0.67. When circulation was completely arrested and ocular pressure level remained at zero, became 2.42 C and, consequently, became 0.41. The former represents half conductivity of the optic nerve with normal blood-flow rate and the latter represents heat conductivity of the optic nerve devoid of any blood flow. The difference will represent the contribution of blood-flow rate to heat conductivity.

From stage one, at the same average blood pressure value, was 1.50 C and C 0.67. When ocular pressure level was raised to 110 mm Hg, was 2.24 C and C became 0.45; the change in flow rate from zero to that prevailing at ocular pressure of 110 mm Hg is proportional to the change in corresponding C (0.15 to 0.41) or 0.37. To express this as a ratio of total blood-flow rate, one divides it by 0.25 (the C value that corresponds to total flow rate) and expresses it as a per cent, obtaining 15 per cent. This means that at an ocular pressure level of 110 mm Hg and an average blood pressure of 100 mm Hg, blood-flow rate at this site was reduced drastically to reach 15 per cent of its normal value. Using the same method, one can calculate for each level of ocular pressure the prevailing blood-flow rate as a per cent ratio of normal.

Results

Fig. 3 already demonstrates significant progressive increase in temperature gradient (reduction in heat conductivity) at progressively higher ocular pressure levels and shows the dependence of blood-flow rate in this region of the optic nerve on ocular pressure level. Of interest and significance in this regard is the stability of the effect in the ascending and descending limbs of ocular pressure change in stage two. Fig. 4 represents a typical set of data in a monkey with a prevailing arterial pressure of 140 80. Blood-flow rate at a given level of ocular pressure is the same irrespective of whether we use data of the ascending or of the descending limb of pressure change. There is progressive reduction of blood-flow rate as ocular pressure level is raised; the rate of this process is slow in the beginning and increases significantly as pressure levels exceed 50 mm Hg. It reaches a maximum value at an ocular pressure level of 125 mm Hg and is not reduced further at higher levels of IOP. This response was uniform in all experiments. The data obtained from the ascending limb of stage two in 15 monkeys are seen in Fig. 5. The average prevailing
Fig. 4. The effect of ocular pressure level on blood-flow rate in the optic nerve 4 mm. behind the globe. Ascending and descending phase. For explanation, see text.

Fig. 5. The effect of ocular pressure level on blood-flow rate 4 mm. behind the globe in 15 rhesus monkeys. For details, see text.

Fig. 6. The effect of ocular pressure level on blood-flow rate in the optic nerve 4 mm. behind the globe and its change with systemic arterial blood pressure. In (A) the arterial blood pressure was 130/80 mm. Hg; in (B) 100/65 mm. Hg.
blood pressure in these monkeys has a mean value of 103 mm. Hg and varied between 90 and 110 mm. Hg.

The effect of blood pressure level on heat conductivity and, consequently, on blood-flow rate is seen in Fig. 6. (A) was obtained in the initial phase of the experiment when prevailing blood pressure was 130/80. (B) Nembutal, in 2 mg. doses, was administered intravenously until blood pressure level was reduced to 100/65; at that time, stage two was repeated. The experimental animal was observed and allowed to recover the original blood pressure at which time stage three was performed. During the lower level of blood pressure, blood-flow rate was significantly reduced for all levels of ocular pressure. However, another important modification of the response can be seen; namely, a shift of the curve to the left. In (A) a great increase in the rate of reduction of blood-flow rate with rise in ocular pressure occurred at an ocular pressure level of 65 to 70 mm. Hg and maximum reduction in blood-flow rate occurred at an ocular pressure level of 105 mm. Hg or higher. In (B) on the other hand, the increase in rate of reduction in blood-flow rate occurred at an ocular pressure level of 45 to 50 mm. Hg and maximum reduction was reached at an ocular pressure level of 85 to 90 mm. Hg or higher.

The effect of location of the heating and referenced thermocouple on this response was investigated in six monkeys. The unit could not be placed closer than 1.5 to 2 mm. from the globe into the optic nerve without damage to neighboring vascular structures. Posteriorly, it could be placed reliably as far back as 12 to 15 mm. from the globe. The effect of ocular pressure remained unchanged when the unit was located between 1.5 and 4 mm. from the globe. There was marked reduction in effect beyond that location and complete disappearance of the effect when placed 7 mm. or more behind the globe.

The effect of raising ocular pressure level in the fellow eye was also investigated. No consistent discernible effect on heat conductivity could be elicited when ocular pressure level in the experimental eye was kept constant while IOP in the fellow eye was raised above systolic blood pressure.

Comments and interpretations

The results clearly demonstrate that rapid, short-lasting elevation of ocular pressure level produces rapid reduction of blood-flow rate in the extraocular portion of the optic nerve; this effect extends over the distal 5 to 6 mm. of the optic nerve and disappears rather suddenly in more proximal locations. Typically, the magnitude of this effect is uniformly small as ocular pressure level is raised between 0 and 40 mm. Hg. It increases markedly thereafter showing marked individual variability which was related to the systemic arterial pressure level such that a lower systemic arterial pressure was associated with a greater reduction at these levels. At an ocular pressure level of 60 to 70 mm. Hg, blood-flow rate was reduced to 50 per cent of its normal value at this region. Reduction in flow rate reaches maximum value at ocular pressure level of 105 mm. Hg and is not modified further by increases in ocular pressure level remaining at approximately 15 per cent of its normal value.

The marked effect of arterial blood pressure is equally obvious. Blood-flow rate is reduced at all levels of ocular pressure when the arterial blood pressure is reduced. Equally important is the finding that under these conditions the point at which the rate of reduction increases markedly and the point at which maximum reduction in flow rate is reached, occur at remarkably lower ocular pressure levels.

Before elaborating further on the mechanism and significance of this effect, one must elucidate the nature of the measured variable. Where in the vascular tree is flow rate reduced? In the arteries, arterioles, capillaries, venules, or veins? Heat conductivity is not specific in this regard and is sensitive to flow in all these portions
of the vascular bed. This region of the optic nerve has the short ciliary arteries coursing on the surface of the optic nerve giving small branches to the pia and optic nerve surface before they reach their intrascleral destination. Additionally, the center of the optic nerve contains the central retinal artery and vein; in the substance of the optic nerve, there is its nutrient vascular bed at the capillary and small vessel level. Which of these compartments is affected by raised ocular pressure level in the manner reflected by heat conductivity measurement in this study? We have shown that choroidal blood-flow rate is affected linearly by an increased ocular pressure level. Since this is derived primarily from the short posterior ciliary arteries, a similar reduction may be expected to occur in the extraocular portion of these vessels in the immediate vicinity of the globe. Since they have some contribution to neighboring extraocular structures, including the optic nerve and its sheaths, one does not expect blood-flow rate in these arteries to cease even when the intraocular circulation is completely collapsed; in fact, one may expect a slight increase in flow rate in these extraocular branches as the major distal recipient bed of the choroid becomes collapsed since the venous portion is not under the influence of ocular pressure, i.e., central retinal vein and orbital veins. However, in fact, one does not see the expected linear reduction in flow rate in this region nor does the reduction rate become less at higher ocular pressure levels; furthermore, when heat conductivity is monitored 7 to 10 mm. behind the globe where the central retinal vein is still within the optic nerve argues against flow in this vessel being the main determinant of the response. In the specimens collected in this study, the central retinal artery and vein were seen to penetrate the optic nerve 8 to 17 mm. behind the globe.

There now remains the nutrient flow in the optic nerve substance; this flow is derived from direct branches of short ciliary arteries in this region to the pia and optic nerve. These, however, are not in the domain of ocular pressure influence and, if a change were to occur, it would have been in the direction of augmented rather than reduced flow. The same holds true for branches arising from the central retinal artery. There are, in addition, recurrent branches of the short ciliary arteries, after they have penetrated the sclera, that supply this region of the optic nerve. These would be under the influence of ocular pressure and the extent of their reach posteriorly may, understandably, be limited at a certain distance from the globe. The effect of ocular pressure on these arterial branches would be small until it successfully overcomes the intravascular pressure and produces significant narrowing of the lumen leading to marked reduction in flow.
rate. The expected effect on flow rate would be in general agreement with these results and would explain the interaction between ocular pressure and systemic arterial pressure in this regard.

From the above, it seems warranted to conclude that nutrient flow to the optic nerve in this region is the one most likely reflected in the results. Attempts to more definitively exclude other components of the vascular bed and specifically distinguish nutrient flow as the affected component were made and the results will be reported in a separate publication.

The significance of the above effect is obvious for angle closure glaucoma where ocular pressures attain high enough level to markedly reduce flow rate to this portion of the optic nerve sufficient to interfere with the viability of optic nerve fibers in this region. Of interest is the critical importance of systemic arterial pressure in this regard. A reduced level of arterial pressure will greatly augment the efficiency of this effect and reduce the level of ocular pressure which is necessary to embarrass this circulation. However, it does not necessarily follow that this effect is not relevant for open-angle glaucoma where pressure levels are usually lower and lasting for longer periods of time. For, although reduction of total flow with moderate ocular pressure elevation is small, the distribution of this reduction may not be uniform such that certain small areas may suffer considerably greater reduction sufficient to embarrass function and viability of the optic nerve fibers in this region. Furthermore, while in general we describe the behavior of ocular pressure level in open-angle glaucoma as one of slow, progressive elevation occurring over years of time, another important feature is the marked diurnal fluctuations in ocular pressure levels that at times reach magnitudes similar to those encountered in angle-closure glaucoma. Typically, open-angle glaucoma in the young (20 to 40 years of age) is associated with such wide fluctuation during which ocular pressure level reaches a magnitude sufficient to produce corneal edema and its symptoms. In the older age group, similar high levels were encountered where ocular pressure was carefully and frequently monitored. The relative role of these two types of pressure elevation in the production and progression of visual function loss in open-angle glaucoma is not yet defined nor is their mechanism or site of action clearly understood or necessarily identical. Thus, the findings of this study may be relevant to open-angle glaucoma as well.

So far it has been assumed that these effects of short lasting elevation of ocular pressure on flow rate are not appreciably different from those of more prolonged elevation. It is conceivable that this assumption may not be entirely correct and that consecutive secondary changes may occur with prolonged elevation to aggravate or reduce the magnitude of the reported effects.

REFERENCES