Effects of raised intraocular pressure on retinal, prelaminar, laminar, and retrolaminar optic nerve blood flow in monkeys

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Effects of increments in intraocular pressure on the blood flow in the retina and the distal part of the optic nerve were investigated in monkeys with the use of unlabeled microspheres. Moderate elevations in intraocular pressure which reduced the perfusion pressure (mean arterial blood pressure – intraocular pressure) to levels above 40 cm H₂O had only small effects in the retina and the prelaminar part of the optic nerve. In the laminar and retrolaminar parts, there was normal flow. At perfusion pressures less than 40 cm H₂O, retinal and prelaminar flow was proportional to the perfusion pressure. Retrolaminar flow tended to increase with decreasing perfusion pressure. At very high intraocular pressures which stopped blood flow in the retina and the prelaminar part of the optic nerve, there was a marked redistribution of the blood flow in the laminar region, the anterior portion being underperfused and the posterior overperfused. Close retrolaminar flow was increased; farther posteriorly flow was normal. After a period of ocular ischemia, there was marked reactive hyperemia in the retina and prelaminar and laminar parts of the optic nerve. No simple vascular explanation was found in monkeys for the degeneration of the optic nerve in glaucoma and the blockage of axoplasmic flow within the posterior part of lamina cribrosa in experimental ocular hypertension.

Key words: intraocular pressure, blood flow, retina, optic nerve, glaucoma

Anatomical studies indicate that in primates the blood supply to the distal part of the optic nerve is very complex. The capillary bed is continuous from the prelaminar part through the lamina to the retrolaminar part. The capillaries receive blood from recurrent branches from the retinal arterioles, from arterioles originating in the choroid, and from branches of intrascleral arterioles, pial arterioles, and the central retinal artery. There is some disagreement on the relative importance of the feeding vessels. Hayreh has repeatedly stressed the importance of choroidal and scleral branches from the short posterior ciliary arteries in the supply to the distal part of the optic nerve. Anderson, in a recent re-evaluation of the disc vasculature in man and owl monkeys, sought to de-emphasize the supply from the choroid. In their investigation of human eyes, Liebermann et al. confirmed the existence of a centripetal sup-
ply to the distal part of the optic nerve but stressed that there is also a longitudinal continuity of small vessels—not merely a capillary continuity—from the pia to the retina. This system anastomosed with the centripetal systems of blood vessels. These investigators found no retrolaminar distribution of arterioles originating in the choroid. A considerable variability in branches from the central retinal artery was reported by François and Fryczkowski.4

The pressure and flow conditions in the distal part of the optic nerve can be expected to be rather peculiar because of the difference in tissue pressure between the intracocular part and the part behind the lamina cribrosa. And a rise in intraocular pressure (IOP) above the normal level will have effects that are very hard to predict.

Several methods have been tried in attempts to elucidate the control of blood flow in the nerve head region. So far no method has proved ideal. After a previous study in which 15 μm radioactive microspheres were used to determine the blood flow in the different parts of the eye, it seemed likely that a modification of this approach could be used in determinations of regional blood flow in the optic nerve. With 15 μm spheres, the number recovered in the nerve head was so low that accurate determinations could not be done. Thus the average reduction in flow caused by a 28 cm H2O pressure rise was 30% with a 95% confidence interval from 5% to 55%. With smaller spheres, larger amounts can be injected without marked effects on the blood pressure and flow.

The purpose of the experiments reported here was to analyze by means of 8 to 10 μm microspheres the effects of pressure increments in the eye on the blood flow in the retina and the distal part of the optic nerve. Our hope was to find a straightforward explanation—e.g., one of those suggested by Alm and Bill,5 Gañer and Goldmann,6 or Hayreh7—for the nerve-damaging effect of high IOP in glaucoma. We also hoped to determine why axoplasmic flow is stopped in the lamina cribrosa at high IOPs in monkeys. No simple explanations were found.

Materials and methods

Two series of experiments were performed. In one series we determined the effect of raised IOP on the blood flow in the retina and the different parts of the optic nerve. In some of these experiments absolute flow values were determined, in others only relative. In the other series the pressure was maintained at a high level for 20 to 30 min in one eye and then lowered to normal levels just before the flow determination was made.

Series 1. The effect of raised IOP was studied in 41 young cynomolgus monkeys of both sexes weighing between 1.8 and 4.3 kg, in one vervet monkey, and in two old female baboons, 8 and 12 years of age and weighing 12 and 15 kg, respectively. Anesthesia was induced with sodium methohexital, 25 to 30 mg/kg b.w. intramuscularly, and maintained by intravenous injections of pentobarbital sodium. In all experiments one femoral artery was cannulated with a polyethylene catheter for blood pressure measurements, and in experiments aimed at quantitative flow determinations, the other femoral artery was cannulated for blood sampling. The animal was placed supine on a thermostatically controlled heating pad, and the body temperature was usually maintained between 37° and 38° C. The monkey was tracheotomized and artificially ventilated. Arterial blood samples were analyzed throughout the experiments for pH, PCO2 and PO2, and respiration was adjusted to result in normal levels. For injection of the microspheres, a thoracotomy was made, a steel cannula was connected to a polyethylene tubing, and a syringe was introduced into the left heart ventricle. Heparin was used to prevent coagulation.

The anterior chamber of either the left or right eye was cannulated with a needle gun and connected to a pressure transducer to measure the IOP. A second needle was connected to an external reservoir filled with mock aqueous humor. By varying the height of the reservoir, the desired IOP could be obtained. The pressure was raised by 30 cm H2O or more. In all experiments except two, the anterior chamber of the control eye was also cannulated, and the pressure was recorded. The microspheres were injected 20 to 30 min later. Black nonlabeled microspheres 8 to 10 μm in diameter suspended in saline and obtained from the 3M Co., St. Paul, Minn, were used at a concentration of 62.5 mg/ml. Prior to the injection, 1 drop of Tween 80 was added, and the spheres were disaggregated in a tissue homogenizer and diluted 1:1 with a 5% dextran solution (Macrodex;
Fig. 1A. Light micrograph of the distal part of the optic nerve in an eye with IOP higher than the systolic arterial blood pressure. There are no spheres in the prelaminar part of the nerve, P. In the laminar region, L, there was one sphere (arrow) close to the border against the retrolaminar part of the nerve. The laminar region was defined as that area where one could see a dense net of collagen fibers, some continuous or parallel with the sclera. In the retrolaminar region, RL, there were several spheres (arrow-heads at some).

Pharmacia Fine Chemicals, Uppsala, Sweden). Inspection under a microscope showed practically no aggregation or disruption of spheres. The number of spheres injected was 30 to 150 million in a volume of 1 to 2 ml. The injection took about 10 sec and was stopped immediately if the blood pressure increased by more than 10 cm H$_2$O. In experiments with quantitative flow determinations, the flow from one femoral artery was collected from the start of the injection and for 1 min thereafter. The monkey was then put to death by a rapid intracardial injection of saturated KCl solution. In five animals, the IOP was maintained at a high level for 5 to 7 hr before the flow determination. In this group, the perfusion pressure was about 40 cm H$_2$O throughout the experiments.

Both eyes, including 2 to 5 mm of the optic nerve, were carefully taken out. In order to keep the optic nerve straight in cases with long nerves, a thin thread was attached to the end of the nerve, and the eye was frozen at $-20^\circ$ C hanging by the thread. The two eyes were placed horizontally on a microtome stage and embedded in an aqueous gel of carboxymethylcellulose. The stage was then immersed into a mixture of solid carbon dioxide and hexane or acetone ($-78^\circ$ C). Sectioning was made in a refrigerator at $-15^\circ$ C essentially according to the Ullberg\textsuperscript{8} technique. An adhesive tape (No. 800, 3M Co.) was laid on the cut surface, and 60 $\mu$m sections were cut under the tape. In this way, a section supported by and adherent to the tape was obtained. All sections containing the lamina cribrosa (about 20 sections from each eye) were taken, and after being dried in a freezing room, the sections were numbered and the microspheres counted in a stereomicroscope at a magnification of 60 times. One drop of a mixture of Soluene (Packard) and isopropanol 1:1 was applied to the section, which was made quite transparent without displacement of the spheres. The regions inspected for spheres are shown schematically in Fig. 1.

The lamina cribrosa was difficult to clearly identify in many animals. Therefore 40 representative sections from experimental eyes where the IOP was higher than the systolic blood pressure were stained. And in two animals with perfusion pressures around 40 cm H$_2$O in the eye with high pressure, sections from both eyes were stained. One drop of 1% osmic acid was placed on the section in the region of the lamina cribrosa. After 1 min, the osmic acid was rinsed with water, and...
Fig. 1B. Blood flow was determined in those horizontal sections of the eye which included the distal part of the optic nerve. Regions investigated are shown with their flow values in mg/min/mm³.

The nerve head was stained with 1 drop van Gieson stain for 20 min. After being washed with water and alcohol, the sections were mounted on glass slides in Euparal (Flatters & Garnett Ltd., Manchester, England).

The blood flow in each region on the experimental side was expressed as a percentage of that on the control side by dividing the number of spheres on the experimental side with that on the control side and multiplying by 100. In 11 experiments, a quantitative measure of the blood flow in the control eye was determined by dividing the number of spheres per cubic millimeter of tissue by the number of spheres per microliter of blood in the reference sample. This sample had been collected over 1 min, and hence its concentration of spheres in number per microliter was numerically equal to the number of spheres per microliter of blood flow.

A Bürker chamber was used for sphere counting in blood samples. Approximate values for the volumes of the different regions were calculated from estimates of the area and the thickness of the sections. For estimations of the retrolaminar volumes, a millimeter paper was placed under representative sections, and the total volume was estimated by multiplying the mean area by the number and the thickness of the sections. The irregular form of the prelaminar area caused by the central retinal artery and the cupping made the volume calculation very uncertain in this region. It was even more difficult to determine the volume of the lamina cribrosa in this way. There was great individual variability in the thickness of the lamina cribrosa, and also the amount of collagen varied greatly. We therefore have used averages of observed values for the diameter and the thickness of the lamina. If the laminar part is a cylinder of 0.2 mm height with a diameter of 1.2 mm, an estimate of the volume of about 0.23 mm³ is given. The average area of the prelaminar part was two to three times that of the laminar part, and the volume was thus about 0.6 mm³. The volume of the retina samples investigated was about 1.4 mm³.

Series 2. In five experiments in cynomolgus monkeys, the eye pressure was maintained at a level higher than the systolic arterial blood pressure for 20 to 30 min, and the pressure was then lowered rapidly to the normal IOP. Thirty seconds later, the spheres were injected over a period of about 10 sec. Reference blood samples were collected as in the previous experiments, and after 1 min the monkey was put to death and the eyes processed as described above.

Results

During the experiments there were spontaneous fluctuations in mean arterial blood pressure (diastolic pressure plus one third of the difference between the systolic and diastolic pressures). The IOP was adjusted in such a way that the perfusion pressure defined as the mean arterial blood pressure minus the IOP was maintained at a reasonably constant level. At the time just be-
Fig. 2. Effects of raised IOP on the blood flow in the peripapillary retina. Individual values for flow in experimental eyes were expressed as percentages of those in the control eyes and plotted against the perfusion pressure (mean arterial pressure − IOP). Open circles represent eyes with IOP < 90 cm H₂O, solid squares IOP 90 to 119, solid circles IOP > 120 cm H₂O. Right pointing bars indicate 5 to 7 hr experiments, left pointing bars indicate baboons. Mean values (open squares) with their standard errors were calculated for perfusion pressures between 1 to 39 (n = 14), 40 to 79 (n = 13), 80 to 135 (n = 10). Triangle at origin indicates zero flow in seven experiments with the IOP higher than the systolic arterial pressure. The line connects the mean values.

Before the sphere injection, the mean arterial pressure ± S.E. was 138 ± 3 cm H₂O (n = 49). The IOP on the control side was 15 ± 0.7 cm H₂O (n = 33).

The accuracy of the microsphere method is dependent on the number of microspheres injected. To obtain as accurate figures as possible for the small regions of interest, we injected as many spheres as was possible without marked effects on the perfusion pressure. In almost all experiments, the injection of the spheres caused a rise in mean arterial pressure.

The average mean arterial pressure over the period of injection and the IOP over that period were used to calculate all perfusion pressures larger than zero. They thus tended to be a few centimeters of water higher than the pressure prevailing prior to the injection of the microspheres. Both the eye pressure and the blood pressure were measured with the heart level as the zero point. The true perfusion pressure is the pressure in the arteries entering the eye minus the pressure in the large veins at the point where they are about to leave the full influence of the IOP.

At that point, the venous pressure is practically equal to the IOP. And the perfusion pressure can thus be defined as the mean arterial blood pressure minus the IOP. The true perfusion pressure can be expected to be somewhat less than the perfusion pressures calculated in the experiments. This is due to the fact that the pressure in the small arteries entering the eye is less than that in the femoral artery. To produce true perfusion pressures of zero, the IOP has to be raised to a level equal to or surpassing the systolic arterial blood pressure. Under such conditions, both the artery and vein collapse, and the intraluminal pressures equal the IOP. To produce perfusion pressures of zero in some of the present experiments, the IOP was raised to a level 15 to 20 cm H₂O higher than the systolic arterial blood pressure.

The number of spheres in the different regions in the control eyes ranged from 87 to 810 in the retina, 37 to 381 in the prelaminar part of the optic nerve, 28 to 207 in the lamina, 78 to 844 in the first millimeter behind the lamina, 60 to 815 in the second millimeter, and 68 to 785 in the third millimeter.
behind the lamina. Fig. 1A shows a micro-
graph of the nerve head region, and Fig. 1B
shows average estimates of the blood flow in
the different parts in control eyes. In these
experiments, the left eye was used as a con-
trol in nine experiments, the right eye in
seven experiments. There were no statisti-
cally significant differences in blood flow be-
tween the left and right eyes and optic nerves
when used as controls.

It seemed possible that in experiments
with injection of large amounts of spheres,
the blood flow was reduced by the spheres
first arriving. If this were a serious problem,
there should be a negative correlation be-
tween flow in the eyes and the concentration
of spheres in the reference sample. No such
correlation was found. The number of spheres
injected thus did not seem to affect the flow
determinations.

Fig. 2 shows that in the retina there was a
tendency toward reduced blood flow at per-
fusion pressures between 40 and 80 cm H₂O
but that this reduction was very slight. At
pressures lower than 40 cm H₂O, the flow
was much more dependent on the perfusion
pressure. In the experiments in which the
eye pressure was increased to levels above
the systolic pressure, there was no flow in the
retina.

In the prelaminar part of the optic nerve
the conditions were very similar to those in

![Fig. 3. Blood flow in the prelaminar part of the optic nerve in the experimental eye plotted against the perfusion pressure. Symbols as in Fig. 2.](image)

![Fig. 4. Blood flow in the prelaminar part of the optic nerve in eyes with elevated IOP plotted against the flow in the peripapillary retina. Values were expressed as percentages of the values for the control eye. Symbols as in Fig. 2. The correlation coefficient was 0.80 which was significant at p < 0.01 level. The line is that of identity. Values at zero perfusion pressure (not shown) were zero in both regions and not included in the calculation of the correlation coefficient.](image)
Fig. 5. Blood flow in the laminar region of the optic nerve plotted against the perfusion pressure for blood flow through the eye. The values obtained in seven experiments with IOP higher than the systolic blood pressure are shown on the ordinate. Symbols as in Fig. 2.

results, but even at very low perfusion pressures, the average blood flow on the two sides seemed to be similar. In the experiments with zero perfusion pressure, the flow was 88% ± 18 (M ± S.E.) of that on the control side. These results indicate, of course, that the perfusion pressure plotted in the figure is not relevant for the lamina cribrosa. Part of the lamina seems to be outside the full influence of the IOP. In the sections stained with osmic acid and van Gieson stain, the localization of each sphere in the lamina was determined. All the 60 spheres recovered in the experiments with zero perfusion pressure were found in the posterior part, most of them near the posterior border, Fig. 1, A.

In representative stained sections from two eyes with perfusion pressure around 40 cm H$_2$O, a total of 43 spheres were recovered in the anterior half of lamina cribrosa, 77 in the posterior half. In the control eyes the corresponding figures were 38 and 45. At this pressure there was thus a tendency to redistribution of the blood flow, with the anterior portion receiving less blood than the posterior.

In the first millimeter behind the lamina, blood flow on the two sides was similar at perfusion pressures above 40 cm H$_2$O (Fig. 6). At lower pressures, the blood flow on the side with elevated pressure tended to be higher. At zero perfusion pressure in the eye, the first retrolaminar part had a flow of 163% ± 14 of the control eye (n = 7). The increase in flow was significant at the p < 0.01 level. In the second (Fig. 7) and third millimeter (not shown) of the optic nerve behind the lamina, the blood flow did not seem to be affected by increments in IOP.

The results of the experiments with 20 to 30 min of high IOP indicated that the retina and the prelaminar part of the optic nerve had rather efficient autoregulation over a wide range of perfusion pressures and that the overall flow in the lamina was little affected by the IOP. It seemed possible that a pressure elevation lasting 5 to 7 hr might have more marked effects than short-lasting elevations. But the results of five experiments performed with such periods of high IOP were not appreciably different from those with short periods, as shown in Figs. 2 to 7.

The increase in blood flow immediately behind the lamina cribrosa at very high IOPs was puzzling. It seemed possible that the overperfusion might be due to changes in vascular pressure conditions or to diffusion of vasodilating metabolites from the prelaminar part of the nerve. The experiments with flow determination at normal IOP but after a period of high pressure were performed to
elucidate this problem. Fig. 8 shows the result of five experiments. About 30 sec after the normalization of the eye pressure, the blood flow in the retina was much higher than on the control side, and this was true also for the prelaminar part and the lamina. Within the first retrolaminar part of the optic nerve, there was also a tendency to increased flow in three of five experiments. Further posteriorly the flow on the two sides was similar in most experiments.

Discussion

The precision in measurements of regional blood flow with the microsphere technique depends on the number of spheres recovered in the region, so that if x spheres are recovered, the standard deviation is \( \sqrt{x} \). The value of x required so that the 95% limits in repeated determinations are within 10% is 384.10 In many of the present experiments the recoveries were much less, which explains much of the variability in the results. More spheres could not be injected because increments in arterial blood pressure would invalidate the calculations of the perfusion pressure. The microsphere method thus is not ideal in determinations of the blood flow in the different parts of the optic nerve, but at present there is no better alternative.

The average values for absolute flow in the different regions in the control eyes may have considerable errors due to difficulties in determining the volumes of tissue of each region. There are no quite comparable data in the literature, but some comparisons can be made. Using 15 μm spheres and chloralose or pentobarbital anesthesia, Alm and Bill⁶ found a flow in the peripapillary part of the retina of...
Fig. 8. Blood flow in the experimental eye and the optic nerve in experiments with sudden reduction in IOP after a period with IOP higher than the systolic blood pressure. The flow values are expressed as percentages of those in the control eye. Each experimental eye has its own symbol.

0.18 mg/min/mm². In the region of the fovea, it was 0.28 mg/min/mm². With a 200 μm thickness of the retina, this corresponds to about 0.9 mg/min/mm³ in the peripapillary region. The present figure for a region of the retina including peripapillary and foveal areas was 1.1 ± 0.1 mg/min/mm³. Using a hydrogen-clearance method with the electrode close to lamina cribrosa, Ernest16 reported a blood flow in the optic disc of about 95 ml/min/100 gm. This result is in good agreement with the present figures, 1.2 ± 0.3 mg/min/mm³ in the prelaminar part and 2.0 ± 0.3 mg/min/mm³ in lamina. In the optic nerve 1 to 2 mm behind the surface of the nerve, the previous flow value obtained with microspheres5 was 1.5 mg/min/mg dry weight, which corresponds to a value of about 0.2 to 0.3 μl/min/mg wet weight. This value is less than the present figures, 0.59 and 0.50 mg/min/mm³ in the first and second millimeters of the nerve behind the lamina, respectively. Kollarits et al.,11 using ¹⁴C-antipyrine, reported a flow of 0.29 μl/min/mg in adult rhesus monkeys anesthetized with phencyclidine and nitrous oxide.

The error expected if the large amount of spheres injected had already altered seriously the flow conditions in the nerve and retina during the injection would be one of too low values. The comparisons made do not indicate marked early effects of the spheres.

Effects of increments in eye pressure. The results indicate that increments in IOP affect the blood flow and the blood vessels in the prelaminar, laminar, and close retrolaminar regions of the optic nerve but that from 1 mm behind the lamina, the flow is essentially independent of the eye pressure. The results confirm that retinal blood flow in autoregulated within a wide range of perfusion pressures.5,12 At about 40 cm H₂O perfusion pressure, it was about 20% to 30% less than at normal perfusion pressures, but further reductions in perfusion pressure caused marked reductions in flow. After a period of nonperfusion in the eye, there was marked reactive hyperemia, probably due to accumulation of metabolites during the period with nonperfusion. In the prelaminar part of the optic nerve, the conditions were very similar to those in the retina.

The normal mean flow in the laminar re-
gion, even at very high IOP, was deceptive. The stained preparations demonstrated that at zero perfusion pressure there was practically no flow in the anterior half of the lamina, since all spheres were recovered in the posterior half. It is known from experiments by Ernest and Potts\textsuperscript{13} that the pressure drop between the eye and the optic nerve occurs in the lamina cribrosa, but the exact localization of the main pressure drop within the lamina and the distribution of pressures within the lamina are not known. The present results suggest that the anterior half is under considerable influence of the eye pressure but that in the posterior half the tissue pressure is lower than the IOP.

Normal overall blood flow in the laminar region at zero perfusion pressure with redistribution of all the blood to the posterior part indicates that in the perfused region the blood flow was about twice the normal flow. Such overperfusion as well as the overperfusion in the first retrolaminar part, at very high IOPs, might be due to redistribution of the flow for mechanical reasons, or it might be due to vasodilation induced by diffusion of metabolites from the prelaminar part of the optic nerve and the anterior part of the laminar region. The reactive hyperemia seen within the lamina and in three out of five experiments also in the first retrolaminar part after normalization of the eye pressure supports the suspicion of metabolite accumulation. The variability in reactive hyperemia in the first retrolaminar part suggests that accumulation of metabolites in this region was mild compared to that in the lamina and the prelaminar parts.

**Blood flow and glaucoma.** In advanced chronic glaucoma there are marked degenerative changes in the optic nerve anterior to the lamina cribrosa as well as within the lamina, resulting in cupping of the optic disc. There may be changes also behind the lamina: the cavernous degeneration of Schnabel.

The direct cause of the degeneration of the nerve is not clear. Several mechanisms seem to be possible, and a combination of factors may very well contribute to a varying extent from one case to another. This point is well illustrated by the fact that glaucoma is usually caused by high IOPs but may develop even at normal eye pressures.\textsuperscript{7}

Goldmann was one of the early proponents of ischemia as the cause of optic nerve cupping in glaucoma, and in an elegant hypothesis Gafner and Goldmann\textsuperscript{6} offered a possible explanation for the vulnerability of the optic nerve head. According to their hypothesis, the pressure in the arteries supplying the optic nerve head is relatively low, and increments in eye pressure cause a diversion of blood from the optic nerve head to the extraocular tissues supplied by the same arteries. Accordingly, a moderate increment in eye pressure that affected retinal flow little might more or less stop the blood flow in the optic nerve head. The present results do not support this hypothesis. Optic nerve blood flow was not more pressure-sensitive than retinal flow.

Even if the shunt hypothesis of Gafner and Goldmann did not apply, it seemed possible that the optic nerve head had poor prerequisites for autoregulation of blood flow as compared to the retina. The hypothesis of Alm and Bill\textsuperscript{5} was based on the reports that the blood vessels supplying the optic nerve head were very small branches from the choroid.\textsuperscript{14} As a consequence, much of the vascular resistance could be expected to be outside the prelaminar tissue, which would make it difficult for metabolites accumulating in the tissue to influence the arterioles feeding the nerve head. Some support for this hypothesis was found in studies with 15 \(\mu\)m spheres,\textsuperscript{15} but as mentioned in the introduction, the low number of spheres which could be injected seriously limited the accuracy of the method.

Strong indications for efficient autoregulation of the blood flow in the prelaminar part of the optic nerve were subsequently reported by Ernest. Using a microelectrode for determinations of oxygen tension, he found that, after a sudden drop in blood pressure, there was only a transient reduction in oxygen tension in the prelaminar part of the optic nerve.\textsuperscript{15} And using a hydrogen clear-
ance method, he found that optic disc blood flow was autoregulated at perfusion pressures above 50 mm Hg or 68 cm H₂O. In these latter experiments the perfusion pressure was reduced by stepwise elevations of the IOP, the electrode was close to lamina cribrosa, and the central retinal artery was ligated.

The present results show that within a wide range of IOP autoregulation of the prelaminar part of the optic nerve is quite comparable to that in the retina. In both tissues, flow was very moderately reduced by increments in IOP until the perfusion pressure had been reduced to about 40 cm H₂O. Thus the "poor autoregulation" hypothesis does not apply. The experiments in old monkeys indicated that autoregulation was efficient even at relatively high age, and experiments performed after 5 to 7 hr of ocular hypertension indicated that autoregulatory vasodilatation did not fail even over such a period of time.

A vascular hypothesis has also been proposed to explain the formation of cavernous degeneration behind the lamina. According to Hayreh, retrolaminar degeneration of the optic nerve might be due to compression of choroidal arteries normally delivering blood to the retrolaminar optic nerve via pial vessels. This theory recently received support from studies in monkeys by Armaly and Araki. Two methods, the heated thermocouple method and determinations of the local oxygen tension, were used in these studies. The results indicated that increments in eye pressure affected the blood flow in the optic nerve head several millimeters behind the globe but that the reduction in flow was marked only at very high IOPs. The reduction in flow could be explained by assigning an important role to recurrent arterioles from the choroid supplying the distal part of the nerve. The experiments reported here gave entirely different results. The blood flow behind the lamina cribrosa changed very little for moderate changes in IOP. At very high IOPs it tended to increase just behind the lamina. Two or three millimeters behind the lamina there were no consistent changes in flow.

None of three rather attractive and straightforward vascular theories thus received support from the present experiments in monkeys. But one has to consider also the possibility of more discrete vascular effects. Figs. 2 and 3 show that even in the perfusion pressure region from 40 cm H₂O and upward, the flow in the experimental eye usually was somewhat lower than that in the control eye. The question arises whether the reduction in flow was homogeneous or if flow was reduced nonhomogeneously, some capillaries being seriously underperfused. A 25% reduction in flow in all capillaries can be expected to have very different effects from nonperfusion in 25% of the tissue. Another factor that has to be considered is that the flow to the tissue may be essentially normal or only slightly reduced. Still, in regions with capillary anastomoses connecting areas with high tissue pressure with low pressure regions within the lamina and behind the lamina, a rise in IOP will tend to increase flow through the anastomoses. This may affect capillary flow in the high pressure region, some capillaries being underperfused. Methods making possible an analysis of the metabolic state of small regions within the optic nerve head will have to be used to elucidate these questions.

Of course, nothing definite can be said from the present study about the conditions in human eyes. It is still possible that some ciliary branches reaching the optic nerve head have poor pressures and significant extracocular areas of distribution making the Gafner-Goldmann theory apply. In eyes with sclerotic arteries and arterioles or anterior ischemic optic neuropathy, autoregulatory mechanisms are likely to be exhausted even at normal eye pressures which will make increments in pressure reduce local blood flow in the retina and prelaminar part of the optic nerve. Finally, recurrent branches from the choroid may be more important in humans than in the monkeys investigated here. In the experiments of Armaly and Araki, rhesus monkey...
monkeys were used, which raises the possibility of species differences even within subhuman primates.

It is of some interest to compare the perfusion pressures normally prevailing in human eyes and those in monkeys. In erect man, the true perfusion pressure in the eye is about 75 cm H$_2$O.$^{19}$ In monkeys, the critical level where blood flow becomes very pressure-sensitive was around 40 cm H$_2$O. If the conditions in humans were similar, there would be a safety margin of about 35 cm H$_2$O or about 25 mm Hg before further increments in eye pressure result in marked reduction in overall blood flow in the retina and optic nerve head.

**Blood flow and axoplasmic transport.**

Several recent studies$^{20-23}$ have focused on the lamina cribrosa as a possible region where damage to the axons may start in glaucoma. Increments in eye pressure large enough to decrease the ocular perfusion pressure to about 40 cm H$_2$O cause marked changes in ultrastructure of the axons, with swelling, accumulation of vesicles, and mitochondria, and disruption of microtubules. Recent experiments by Minckler et al.$^{24}$ indicate that these changes start in the posterior part of the lamina cribrosa. In parallel with the disorganization of the axons, there is a block of anterograde as well as retrograde axoplasmic transport. Mild block of such transport has been observed even at ocular perfusion pressures of 80 to 120 H$_2$O, in experiments in which the IOP was elevated as little as 15 to 20 cm H$_2$O. In Minckler’s study,$^{24}$ nucleated chicken erythrocytes injected intravenously were recovered in the lamina cribrosa, indicating that blood flow was not stopped in the region with axonal injury, and it was concluded that the injury was a primary mechanical effect on the axons rather than secondary to vascular events.

In the present study, overall blood flow in the lamina as well as in the other parts of the distal nerve was not appreciably deranged at IOPs reported to produce marked effects on the axons. Sphere distributions in stained sections from two experiments with perfusion pressures around 40 cm H$_2$O indicated that the blood flow in the laminar region tended to become redistributed at IOPs affecting also prelaminar flow. But reduced blood flow in the anterior part and increased blood flow in the posterior part would hardly damage the posterior region.

The present experiments thus do not provide a simple “vascular” explanation for the development of optic nerve atrophy in glaucoma and block of axoplasmic flow in experiments with acutely elevated IOP. Discrete vascular effects as the cause for atrophy cannot be excluded, but reduced blood flow is unlikely to be involved in axoplasmic blockage.

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