Effect of raised intraocular pressure on the retinal and choroidal circulation

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The effect of acutely elevated intraocular pressure upon the retinal and choroidal circulation was studied in young farm pigs. Still and cine fluorescence angiograms were used to document the circulatory status. Increased ocular pressure slowed filling in both retinal and choroidal vessels. The choriocapillaris fills as small patches which eventually coalesce, the initial filled areas resembling patchy choroiditis or the pattern of drusen. Increased intraocular pressure slows the forward velocity of fluorescein in retinal vessels, but the no-flow point depends on the combination of intraocular and systemic arterial pressure. There was no evidence of selective perfusion of "preferential channels" even at high intraocular pressure. The radial peripapillary capillaries were seen to derive primarily from intraretinal arterioles. Embarrassment of flow in the radial capillaries at high intraocular pressure was seen in some studies, but this was not a constant feature. It was also noted that the blood supply of the optic disc in the pig appears distinct from that of the surrounding retina, and in several experiments the disc was noted to fluoresce before any retinal vessels filled.

According to François and Neetens, François and Neetens, Lagrange and Beavieux were the first to consider local disturbances of the vascular supply induced by elevated intraocular pressure primarily responsible for the anatomical and functional lesions of the posterior segment of the eye in glaucoma. Since then numerous authors have declared themselves in favor of a vascular etiology for the posterior pole changes seen in states of increased ocular pressure, and Harrington has reviewed the subject.

Histopathological studies of the posterior pole vessels in humans with glaucoma have been made by Cristini and more recently by François and Neetens. The former noted a reduction of the capillary network at the lamina cribrosa and the peripapillary choroidal vascular network. Two of the three eyes studied by François and Neetens had absolute glaucoma and marked uveal vascular lesions. In one eye with moderate, well-controlled intraocular hypertension the uveal vessels appeared normal and the vascular changes were confined to the retina and optic nerve. In this instance the number of capillaries was reduced at the disc, mainly on the temporal side.

In a study of acute glaucoma induced in owl monkeys, the effect of raised ocular...
pressure on the ocular vascular system was studied by means of India ink or neoprene injections. Gross and histological examinations revealed significantly less filling of retinal, choroidal, and optic nerve capillaries in glaucomatous eyes. The posterior pole of the eye and temporal portion of the optic nerve were especially susceptible to change. In cats, moderate elevations in ocular pressure led to reduced filling of posterior pole capillaries of the retina as evidenced by reduced India inking. Selective involvement of the radial peripapillary capillaries was seen in one instance.

Fluorescence angiographic studies of the optic nerve head circulation in patients with glaucoma have recently been described by Hayreh and Walker. They noted a reduction in fluorescence of the optic disc in glaucoma patients with both significant changes at the optic disc and visual-field defects.

Recent advances in techniques and instrumentation of retinal fluorescence angiography allow one to study intact microcirculation including the capillaries. The present work is concerned with retinal and choroidal vascular changes in experimentally induced, acute elevations of intraocular pressure in the intact eye.

**Methods**

Five series of studies were made with young, white farm pigs weighing 18 to 25 kilograms. Anesthesia was induced with thiopental sodium and maintained, after tracheal intubation, with 1 per cent flurane and a 2:1 mixture of nitrous oxide and oxygen. The position of the eye was controlled with stay sutures in the tendons of the recti, and a ring of four micromanipulators. The animal’s blood pressure was recorded with a C.E.C. strain gauge transducer, attached to a P.E. 60 catheter which led from the femoral artery into the aorta, and a Devices M.4 recorder. The frequency and depth of respiration were also monitored in one animal.

The pig’s head was positioned so that a minimum of pull on the tendon sutures was necessary to bring the disc area into the center of the camera field. The ocular pressure was raised by applying an 8 mm. diameter plastic suction cup to the eye just posterior to the limbus, and a Devices M.4 recorder. The cup was attached to an electric vacuum pump, and negative pressures ranging from 80 to 350 mm. Hg were produced. Intraocular tension was measured before, during, and immediately after each suction experiment. Photographs were taken before, during, and after suction. Recovery time of at least 10 to 15 minutes was allowed between experimental runs.

Intraocular tension was measured in the pigs with a calibrated Schiotz tonometer with its various weights. In two studies the pressure in the anterior chamber was recorded with a Statham P.23G transducer via a short needle, to calibrate the Schiotz tonometer. The Schiotz tonometer readings were generally higher than the pressures recorded via the anterior chamber needle.

Fluorescein was injected via a catheter which was placed in an ear artery and threaded down into the carotid artery, obviating manipulation of the carotid artery and surrounding structures of the neck.

Fluorescence photographs were taken with a vertically mounted Zeiss fundus camera. The exciting filter was a Baird Atomic interference type B.S12 and the barrier filter a Zeiss type 213030. Thirty-five millimeter pictures were taken every 0.6 second with motorized Nikon F.36 cameras and 16 mm. cine with a Bolex R.16. Kodak Tri-X film was used with regular development.

**Results**

**Effects of limbal suction on the pig eye.** Normal intraocular pressure of the pig was 20 mm. Hg (Schiotz) or below. Within a few seconds after applying the limbal suction cup to the eye, the intraocular pressure rose and then remained at a constant elevated level for several minutes. There was a direct relationship between the degree of suction and the increase of intraocular pressure (see also Mikuni and Yoneyama, 1960). After several minutes of constant suction the intraocular pressure slowly began to drop. Suction was never applied for more than 5 minutes at a time. No corneal haze or optical distortion was noted even with pressures as high as 70 mm. Hg (Schiotz). After removing the suction cup the intraocular pressure fell below the presuction value. No deleterious effects on the conjunctiva or sclera, other than temporary hyperemia and slight grooving at the site of suction, were noted.

**Systemic effects of altering intraocular pressure.** No significant alterations in pulse rate, blood pressure, or respiration were noted when the intraocular pressure was...
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Vascular alterations at the posterior pole of the eye.

Choroid. In control photographs, both cine and still, the choroidal blush is the first evidence of fluorescein entering the posterior segment of the eye. This is true in the pig, cat, monkey, and man. The filling of the choriocapillaris is rapid but nonuniform, and a geographical pattern of filling is seen at normal intraocular pressures. Increasing the intraocular pressure causes the choroidal circulation to slow, and reveals more clearly the manner in which the choriocapillaris is supplied. For example, in one instance where the intraocular pressure was elevated to 36 mm. Hg (Schiötz), choroidal capillary filling was markedly delayed. Dots of fluorescein were seen in the choroid above the disc 3 seconds after the dye injection, within the next 3 seconds these dots enlarged and coalesced (Fig. 1, A to D). This would indicate that the choriocapillaris fills as small independent segments rather than as a continuum over the entire surface, and this agrees with evidence gathered during ballotini injection studies. Note that the segmental filling of the choriocapillaris resembles a pattern of patchy choroiditis or multiple drusen.

Retina and optic disc. Alterations in the circulation to both the retina and optic disc were demonstrated in pig eyes as the intraocular pressure was raised.

Fig. 1. Pig 172. Choroidal filling at an intraocular pressure of 36 mm. Hg and systemic arterial mean pressure of 67 mm. Hg. A series of pictures taken at 3.0, 3.7, 4.2, and 5.5 seconds after injection of fluorescein into the carotid artery shows choroidal fluorescence appearing as a series of islands which later coalesce. Note the regression of fluorescein in a retinal arteriole in C compared to B.
**Vessel caliber.** Sinuous pulsation of the retinal arterioles became more prominent as the intraocular pressure was increased. At moderately increased values of intraocular (less than 40 mm. Hg) there was no detectable change in vessel caliber between systole and diastole, but near the no-flow point small caliber changes in arterioles occurred in time with the pulse wave.

The caliber of nine arterioles and nine venules was measured at a normal pressure (12 and 20 mm. Hg) and increased intraocular pressure (40 and 44 mm. Hg) in two animals (Table I). The diameter of the veins increased by an average of 1.4 per cent and that of the arterioles decreased by an average of 3.4 per cent. Neither change was statistically significant.

**Blood flow velocity.** Increased intraocular pressure slowed filling and emptying of the retinal vessels in all phases. The change was clearly seen as a prolongation of the transit time of dye through the retinal circulation, but a more accurate quantitative estimate was made by measuring the movement of the dye front on cine films taken at 32 frames per second.

| Table I. Changes in caliber (µ) of arterioles and veins with elevated intraocular pressure |
|---------------------------------|---------------------------------|
| **Arterioles**                  | **Veins**                       |
| Control | Poc 40 mm. Hg | Control | Poc 40 mm. Hg |
| 125     | 117            | 82      | 80             |
| 45      | 44             | 67      | 57             |
| 53      | 54             | 45      | 45             |
| 123     | 124            | 106     | 214            |
| 43      | 41             | 46      | 48             |
| 57      | 48             | 53      | 47             |
| 53      | 47             | 41      | 41             |
| 29      | 31             |         |                |

As the intraocular pressure increased, the flow slowed and became more obviously pulsatile. At levels of intraocular pressure approaching the no-flow point there was a substantial backflow in the retinal arterioles in diastole (Fig. 2). It is of interest that there was no measurable diameter change of the retinal arterioles between systole and diastole on cine studies which showed considerable backflow in diastole. As the intraocular pressure increased the mean forward velocity of flow slowed but the no-flow point was reached at widely differing values of intraocular pressure in different animals (Table II). This appeared to be related to the level of mean systemic arterial pressure in the animal (Fig. 3). A comparison of data in 2 animals, one with a mean arterial pressure of 88 mm. Hg and the other of 150 mm. Hg showed that the mean forward velocity of flow in the retinal arterioles was approaching zero in the first instance at an intraocular pressure of 50 mm. Hg, and in the second of 80 mm. Hg (Fig. 3).

**Capillary perfusion.** Increased intraocular pressure slowed capillary filling and exaggerated time differences between filling of different parts of the capillary bed. Almost all capillaries appeared to be perfused even when flow was slowed to less
than 10 per cent of control values. There was no evidence of selective perfusion of “preferential channels” (Fig. 4).

Radial peripapillary capillaries of the pig were seen to derive primarily, if not exclusively, from intraretinal arterioles and not from those of the disc (Fig. 5). A few radial peripapillary capillaries were continuous with the disc and their arteriolar supply could not be ascertained. In several instances dye was slower to empty from some radial peripapillary capillaries than other retinal capillaries, suggesting possible selective embarrassment to flow in situations of increased intraocular pressure, but this was not apparent in all studies.

No gross damage to capillaries or other retinal vessels was apparent after several trials of elevated pressure, nor was vascular leakage of fluorescein noted at any time during the experiment.

**Vascular supply of the optic disc.** The blood supply of the optic disc in the pig appears to be distinct from that of the surrounding retina except for some slight overflow of disc capillaries into parts of the peripapillary retina. The disc fluoresced in some experiments with elevated intraocular pressure before any retinal vessels filled. It was not possible to visualize the individual vessels which supplied the nerve head.

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Fig. 2. Pig 173. Movement of the dye front in millimeters from a reference point on the optic disc in a retinal arteriole 160 μ diameter at two levels of intraocular pressure, 27 mm. Hg (x – x) and 50 mm. Hg (O – O). Flow is pulsatile at both levels of intraocular pressure but the mean forward flow is much lower and the backflow in diastole much greater at the higher level of intraocular pressure.

Fig. 3. Pigs 173 and 174. Plot of percentage change (from control) in mean velocity of flow in the axial stream of two large arterioles as intraocular pressure is increased. In Pig 173, with a systemic arterial mean pressure of 88 mm. Hg blood flow ceased at an intraocular pressure just above 50 mm. Hg, while Pig 174, with a systemic arterial mean pressure of 150 mm. Hg, maintained retinal flow of an intraocular pressure above 80 mm. Hg.

Fig. 4. Pig 172. Capillary filling at intraocular pressure of 36 mm. Hg. Filling is almost complete apart from a small area of capillaries near the disc that filled later. (White line = 1 mm.)
Fig. 5. Pig 172. Filling and emptying of the retinal capillaries at an intraocular pressure of 36 mm. Hg. As the capillaries begin to fill 10.1 seconds after injection (A), radial capillaries are seen to be supplied by intraretinal arteriolar branches (arrow) and not from the disc. As the capillaries empty (B) some dye is slow to leave certain of the radial capillaries (arrows).

cently demonstrated that the disc in humans is fed by two separate vascular networks, that the segment in front of the lamina cribrosa is derived from the central retinal artery, and that the portion behind the lamina, responsible for the initial deep disc glow, is in phase with the choroidal circulation.

Discussion

Evidence exists which suggests that there is impairment of retinal and optic nerve head circulation in glaucoma. Most of this is based on clinical impression, or post-mortem study of chronically involved eyes. The work of Hayreh and Walker is an initial attempt to study the circulatory changes in the optic nerve head by fluorescence photography in humans affected by chronic glaucoma. Their work reveals that in the later stages of glaucoma, with disc cupping and field loss, there is obviously less vascularity of the nerve head than in normal individuals. The technique used did not allow any accurate assessment of retinal capillary circulation, We have examined the effects of altered intraocular pressure upon the posterior pole circulation of the normal pig eye. Our interest was to ascertain the role of the radial peripapillary capillaries in glaucoma.

We chose to study the pig eye because it is similar in size and fundus color to that of man, and it has radial peripapillary capillaries. It is important to point out that our results relate to acute elevations of intraocular pressure in the young, anesthetized pig and not to a human afflicted with chronic glaucoma. The pig lacks a central retinal artery and its retinal vascular supply differs somewhat from that of man and other primates.

Our work shows that it is possible to use a limbal suction cup for elevating intraocular pressure in the pig and that in this animal transient marked elevations in ocular tension do not noticeably alter corneal clarity or other optical properties of the eye. It was possible to obtain high definition fluorescein angiograms, both still and
increased intraocular pressure reduces blood flow through both the retinal and choroidal vessels. Quantitative estimates of change in retinal arteriolar flow were made by measuring the velocity of the dye front in the axial stream. At high velocities of the order of 100 mm. per second, the errors are large because only two or three frames are obtained while the dye front is moving across the field of view. This error is much reduced at lower velocities of flow.

Retinal arteriolar flow is pulsatile, and the pulsation is much increased at higher values of intraocular pressure. It is of interest that the retinal vessels showed little visible change apart from a sinuous pulsatile movement at high values of intraocular pressure when the mean forward velocity was less than 10 per cent of normal. The value of intraocular pressure at which retinal blood flow ceased appeared to be closely related to the systemic arterial pressure of the animal. Thus, it appears that the transmural pressure in the arteriole (mean arteriolar pressure-intraocular pressure) is probably the main determinant of retinal blood flow under the circumstance of these experiments. The use of general anesthesia conceivably may have diminished vascular autoregulatory responses.

The level of the systemic arterial pressure and the intraocular pressure probably play an important role in the pathogenesis of the posterior pole lesions of human glaucoma. For example, it is well known that diminishing the blood pressure in some hypertensive patients with glaucoma will lead to progressive loss of field. Our results regarding the effect of elevated intraocular pressure on the radial peripapillary capillaries are inconclusive. Some of the radial peripapillary capillaries emptied more slowly than other capillaries, but no level of intraocular pressure which permitted retinal flow caused obliteration of the radial peripapillary capillary pattern. It was also of interest that even high levels of intraocular pressure that approached the no-flow point did not seem to alter the general capillary pattern or lead to preferential flow through some capillaries.

The dichotomy between the optic nerve head and retinal circulation was clearly demonstrated in the pig, and this seems also to be true for man and monkey. It is difficult to imagine how the selective field defects of glaucoma in humans can be due solely to vascular alterations in the nerve behind the lamina cribrosa. No doubt further anatomical work on the blood supply to the optic disc in man and animals will be required.

At present we are extending our studies to include glaucoma patients. Until we complete this study we can not speculate upon the relationship of our present findings to human glaucoma.

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REFERENCES


