Albrecht von Graefes Arch. Klin. Ophthalmol.
213, 283–290 (1980)

Graefes Archiv
für klinische und experimentelle
Ophthalmologie

Ocular Hypertension in Primary Glaucoma: A New Hypothesis

G. Cristini[1], A. Consolani[2], and F. Lazzari[3]

[1] Ia Clinica Oculistica, Facoltà di Medicina e Chirurgia, Università di Bologna, Italia
[2] Ia Clinica Oculistica, Ospedale S. Orsola, Bologna, Italia
[3] Istituto di Idraulica, Facoltà di Ingegneria, Università di Bologna, Italia

Abstract. Some considerations of the vascular events occurring in the uvea during the course of glaucoma are reported and a mathematical model is adopted to clarify the interdependence between intraocular pressure, rate of blood flow, blood pressure gradient, and the number of unobstructed capillary vessels in the uveal membrane. By means of this mathematical model the physiopathological vascular cause of the rise in intraocular pressure is confirmed (also independently of an obstacle to aqueous outflow), and the clinical implications in relation to visual sensory impairment are emphasized.

Zusammenfassung. Es werden die vaskulären Vorgänge in der Aderhaut bei Glaukom besprochen und ein mathematisches Modell wiedergegeben, welches gestattet, den Zusammenhang zwischen dem Augeninnendruck, der Blutströmung, dem Blutdruckgefälle in den Uveagefäßen und der Zahl der in der Aderhaut befindlichen offenen Haargefäße zu klären. Dieses mathematische Modell bestätigt, unabhängig von einer Behinderung des Kammerwasserabflusses, die physiopathologische vaskuläre Ursache für den Anstieg des Augeninnendruckes. Es wird die klinische Bedeutung dieser Hypothese bezüglich der sensoriellen Sehherabsetzung hervorgehoben.

Introduction

In the field of ophthalmology it is probably true that primary glaucoma is the disease which has given rise to the largest number of theories, especially as regards ocular hypertension. "The danger, of course, in studying so vast a problem is that in trying to unravel its intricacies we tend to become so specialized, each in our particular pursuit, that a broad and comprehensive view of the whole becomes increasingly difficult. Vascular events monopolize the attention of this investigator, the angle of the anterior chamber of that other" (Duke-Elder, 1949).

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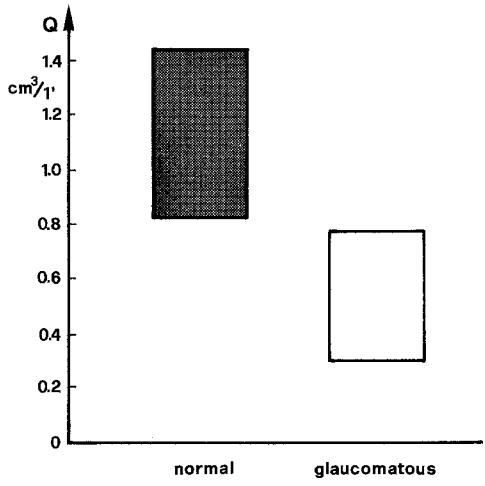

Fig. 1. Blood flow rate measured in glaucomatous eyes as compared with normal eyes in patients of the same age (from Cristini et al., 1975c)

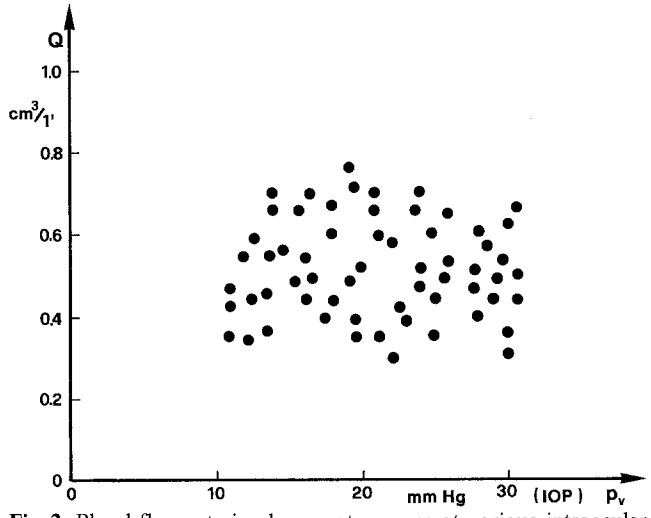

Fig. 2. Blood flow rate in glaucomatous eyes at various intraocular pressure levels (from Cristini et al., 1975c)

The importance of changes in the chamber angle is the subject of a vast literature. Contributions have been made by many eminent ophthalmologists, especially Goldmann (1955), who exerted great influence on later ophthalmological thinking. The same cannot be said, however, for evaluations of vascular events occurring in the whole uvea. This seems strange when we consider the essential importance which ophthalmologists grant to vascular nervous changes in connection with visual sensory impairment. Also, experimental, pathological, and clinical studies have drawn attention to the significant pathological aspects of uveal circulation in ocular hypertension. Research done by Dieter (1925) and Fritz (1950) drew attention to the rise in lateral pressure in the uveal

capillaries in glaucoma, and Thomassen (1947, 1949) observed that variations in intraocular pressure (IOP) follow parallel changes in episcleral venous pressure.

At the pathological level, Elschnig (1928) pointed out that the choroid, in glaucomatous patients, was thinner than normal owing to an evident obliteration of the capillary network. These findings were subsequently confirmed by Cristini (1950, 1951) and by François and Neetens (1964) and were thought to be one of the causes of the IOP increase (Cristini, 1950), or at least associated with an obstacle to aqueous outflow (Urrets and Zavalia, 1952). A reduced vascularity of the choroidal bed was also suggested by angiographic studies (Hayreh, 1969, 1978) and bio-hemo-photometric uveal research (Cristini and Fiorenzi, 1961; Cristini and Forlani, 1961; Cristini et al., 1962).

In recent years rheography has allowed deeper investigations into the qualitative aspects of uveal circulation and the calculation of ocular blood flow (Cristini et al., 1975a, b, c), confirming the preliminary observations of Van Beuningen and Fischer, 1957) with another method.

It has been possible to ascertain that blood flow in glaucoma is always reduced, often to half of its value, and that it remains reduced even if IOP values are not increased. In Figs. 1 and 2 the values found in normal and in glaucomatous eyes are shown with rate of blood flow expressed in $cm^3/1'$.

Purpose of the Research

A mathematical model was employed to explain the reduction in blood flow rate due to partial loss of the vascular bed after capillary obliteration, as observed pathologically in the choroid of most glaucomatous eyes. This could constitute an essential hemodynamic factor in the rise in IOP. This model clearly shows the interdependence between IOP rate of blood flow, blood pressure gradient, and the number of vessels involved in the circulatory network. To make things simpler, blood was compared with water under the same physical conditions (Newtonian rheological characteristics were hypothesized). It was assumed that the blood vessels involved with flow would have equal length and calibre (constant in normal conditions), and that the respective inflow and outflow pressures would be equal for all ducts. It was also assumed that, when limited to the calculation of blood flow rate, the influence of warping in the blood vessels would be negligible. The assumption was also made that a rise in the ductal pressure gradient would produce a rise in IOP owing to ductal enlargement, and a subsequent increase in uveal tissue volume, which would be constricted within the semirigid structure of the corneoscleral shell while the normal rate of aqueous flow would remain unchanged (Fig. 3).

Mathematical Model

In accordance with Poiseuille's formula (1846) (where n is the number of capillaries involved with flow, l is the length, and ω is the area of cross-section

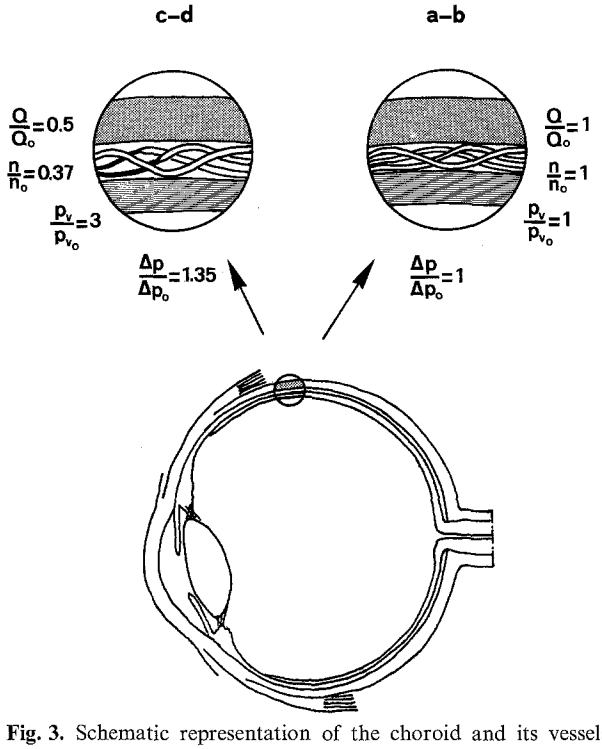

Fig. 3. Schematic representation of the choroid and its vessels in normal conditions (**a** and **b**) and in glaucomatous eyes (**c** and **d**). In the latter, the vascular network is reduced due to vessel occlusion, but the thickness of the choroidal membrane is increased owing to the increased pressure gradient in the open vessels

of each, $\Delta p = p_e - p_u$ is the pressure difference between inflow and outflow sections, η is the coefficient of viscosity, and k is a constant) the volumetric rate of flow (Q) will be:

$$Q = k n \Delta p \omega^2 / \eta l \tag{1}$$

or, since $\omega^2/\eta l$ is constant for the assumed hypothesis [named c, the following constant],

$$[c = k\omega^2/\eta l], \tag{2}$$

it results in

$$Q = c n \Delta p. \tag{3}$$

The rate of blood flow is directly proportional to the product $n\Delta p$; or, where n is equal, to the pressure difference Δp; or, where Δp is equal to the number (n) of the capillaries involved with flow. On the other hand, where rate of blood flow (Q) is equal, n and Δp are inversely proportional.

It should be observed finally that in capillary pressure there is a linear decrease from inflow to outflow sections. If normal values are 0, there will be:

$$Q_0 = c n_0 \Delta p_0. \tag{4}$$

If (3) is divided by (4), the result is:

$$Q/Q_0 = n \Delta p / n_0 \Delta p_0. \tag{5}$$

If it is assumed that Q/Q_0 is a parameter in an orthogonal Cartesian system of reference, with n/n_0 in the abscissa and $\Delta p/\Delta p_0$ in the ordinate, the relation (5) is graphically transformed into a series of curves (Fig. 4), each of which is related to a certain constant value of the parameter Q/Q_0.

When another Cartesian system of reference is related to the former, which has the axis $\Delta p/\Delta p_0$ in common, the variable p_v/p_{v_0} is expressed on the other axis, where p_v is IOP.

It results, under normal conditions in:

$$Q = Q_0, \quad n = n_0, \quad \Delta p = \Delta_{p_0}, \quad p_v = p_{v_0}, \tag{6}$$

and all variables, including parameter Q/Q_0, assume the unitary value:

$$Q/Q_0 = 1, \quad n/n_0 = 1, \; \Delta p/\Delta p_0 = 1, \quad p_v/p_{v_0} = 1. \tag{7}$$

In Fig. 4 this circumstance is represented by points A and B.

If part of the blood vessels become obstructed in pathological conditions, the pressure difference Δp, previously distributed along the whole blood duct, is now concentrated in the segment above and below the occlusion (if complete). Above the occlusion the pressure is higher than in conditions of previous flow, and the blood vessels and choroid become dilated, resulting in increased IOP owing to the rigidity of the corneoscleral shell.

The nearer the occlusion of the duct is to its exit from the uvea, the more pronounced its dilating effect will be on the choroid, with a consequent rise in IOP (p_v). This rise is favoured by an increase in the hydrodynamic pressure difference (Δp) which, even if outflow pressure (p_u) remains constant, will always produce an increase in inflow pressure (p_e). An increase in Δp is indispensable to maintain the rate of blood flow because of the reduction in number of capillaries.

If (in pathological conditions) $\Delta p/\Delta p_0$ has a value of about 1.35, p_v almost trebles ($p_v/p_{v_0} = 3$), as can be seen in point C of Figure 4 (see also Figs. 3c and 3d). In the first approximation, the graphic relation that connects $\Delta p/\Delta p_0$ to p_v/p_{v_0} can be identified in the line B-C. In the same pathological conditions, the rate of blood flow (Q) is reduced to half and the parameter Q/Q_0 will therefore be 0.5. This, associated with $\Delta p/\Delta p_0 = 1.35$, allows point D to be determined: The value 0.37 for n/n_0 corresponds to this point, which means that the number (n) of unobstructed blood vessels is reduced to approximately 37% of the number (n_0) open under normal conditions of flow.

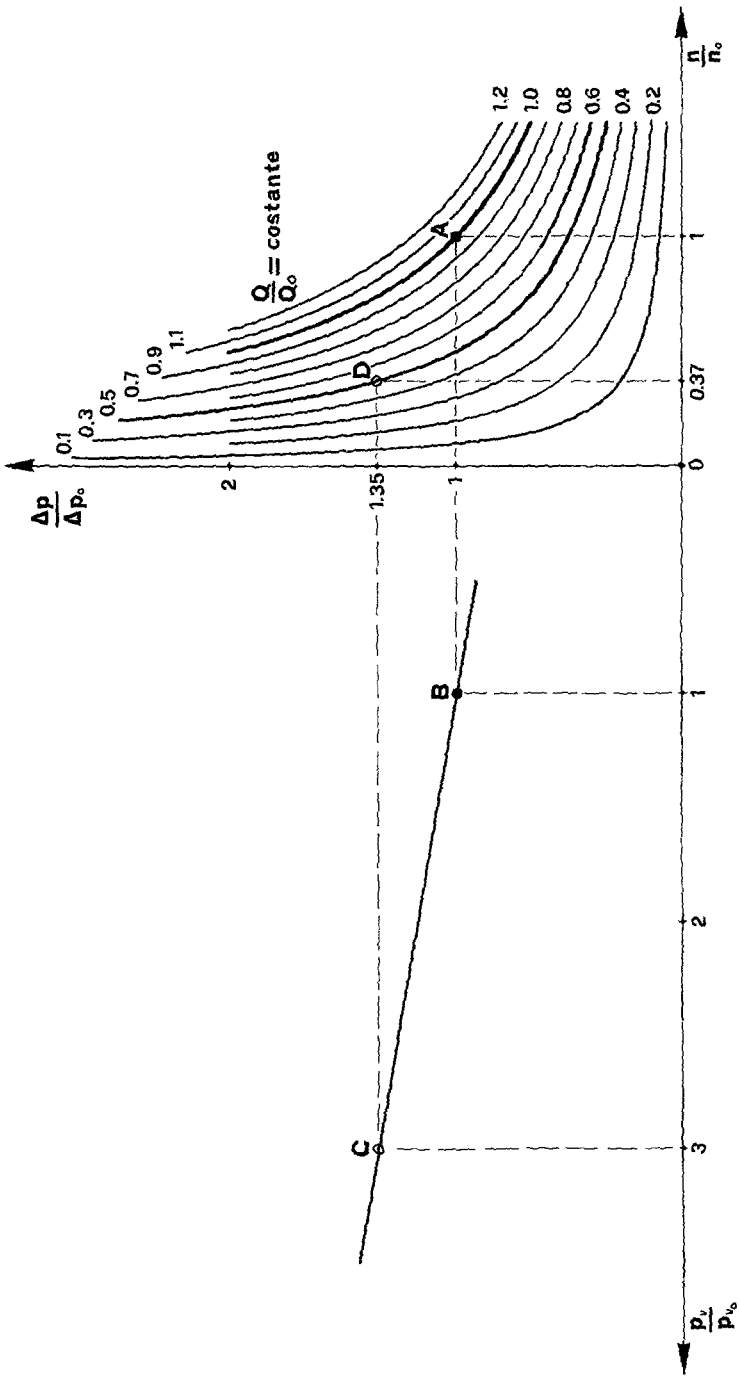

Fig. 4. This figure shows Cartesian diagrams connecting the variable $\Delta p/\Delta p_0$ to the variable n/n_0 with parameter Q/Q_0 and to the variable p_v/p_{v_0}. A and B refer to normal conditions, and C and D to glaucomatous eyes. The curves were drawn by a plotter operated by a table computer

Considerations

The double Cartesian diagram (Fig. 4) with its obvious limitations, allows some insight into the physiopathological uveal events which may occur in the eye. While some of these events, for example IOP (p_v) and rate of blood flow (Q), can be measured, others, like $\Delta p/l$ (blood pressure gradient in the afferent uveal vessels, l being the length of the vessel, and Δp the pressure at its extremities) and n (number of capillaries in the uveal network), can only be estimated.

The physiopathological events and the interdependence can be summarized as follows: (1) A reduction in the rate of blood flow without a concomitant increase in IOP (p_v) suggests that the blood pressure gradient ($\Delta p/l$) remains unvaried while the number (n) of uveal capillaries involved with flow is reduced; (2) a reduction in the rate of blood flow (Q) with a concomitant increase in IOP (p_v) suggests that the blood pressure gradient ($\Delta p/l$) is increased and the number (n) of uveal capillaries involved with flow is reduced; and (3) an unchanged rate of blood flow (Q) accompanied by a rise in IOP (p_v) indicates that the pressure gradient of the uveal vessels ($\Delta p/l$) is increased and the number (n) of uveal capillaries involved with flow is reduced.

It is considered that any one of these hemodynamic events can occur in glaucomatous eyes according to the various pathological conditions of the patient's vascular network. It follows that in the choroid of the glaucomatous eye, due to the decrease in the number of vessels, the rate of blood flow (Q) is lower than normal, notwithstanding the increase in the pressure gradient ($\Delta p/l$).

In the glaucomatous eye, an abnormal hemodynamic rate is present, which in vivo causes the volume of the choroid to increase though the rate of blood flow is lower than normal, as confirmed by rheographic findings (Cristini et al., 1975b, c). Conversely, the post mortem choroid is thinner as shown by pathological findings.

If this pathogenetic hypothesis for ocular hypertension is valid, ocular hypertension would assume a more limited pathological significance in the development of optic atrophy than previously believed because the rise in IOP (p_v) follows the increase in the pressure gradient $\Delta p/l$ of the afferent uveal vessels including the vessels of H–Z circle, and the blood supply of the nervous parenchyma would thus be increased. On the one hand, if ocular hypertension can damage the optic nerve mechanically, on the other hand, it is a hemodynamic advantage as it causes a greater blood supply which under particular conditions could compensate for the previous damage. It is likely that in cases of terminal glaucoma 'sine tensione' this active hemodynamic event does not occur apart from other events which fall outside the scope of this paper.

Conclusions

This mathematical model draws attention to vascular events in the uvea during the course of primary glaucoma, but does not disprove the hypothesis of an obstacle to aqueous outflow in ocular hypertension. It is suggested, however,

that the symptoms of both nervous tissue and uveal tissue impairment may have a common vascular pathological denominator, and this cannot be neglected in evaluations of provocative tests and the mechanism of action of various drugs.

References

Cristini, G.: The rationale of ocular hypertension in glaucoma. Acta XVI Concilium Ophthalmologicum, Britannia, 865 (1950)

Cristini, G.: Common pathological basis of the nervous ocular symptoms in chronic glaucoma. Br. J. Ophthalmol. **35**, 11 (1951)

Cristini, G., Fiorenzi, G.: Uveale Bio-Hämo-Fotometrie (Eine neue Messmethode der Uveadurchblutung am Lebenden). Klin. Monatsbl. Augenheilk. **138**, 216 (1961)

Cristini, G., Forlani, D.: Die Bio-Hämo-Fotometrische Messung der uvealen „Blutdicke" des normalen Menschenauges. Klin. Monatsbl. Augenheilk. **139**, 520 (1961)

Cristini, G., Forlani, D., Scardovi, C.: Choroidal circulation in glaucoma. Bio-Hemo-Photometry in chronic open angle glaucoma. Br. J. Ophthalmol. **46**, 99 (1962)

Cristini, G., Meduri, R., Giovannini, A.: A new method for determining the blood quantity in the eye in a unit of time. Albrecht von Graefes Arch. Klin. Ophthalmol. **197**, 1 (1975a)

Cristini, G., Meduri, R., Giovannini, A.: Bulbar rheographic semeiology. Ann. di Ottalm. Clin. Ocul. **101**, 319 (1975b)

Cristini, G., Meduri, R., Giovannini, A.: Bulbar-rheo-oculographic and fluxometric indexes in simple chronic glaucoma. Ann. di Ottalm. Clin. Ocul. **101**, 335 (1975c)

Dieter, W.: Über den Zusammenhang zwischen osmotischem Druck, Blutdruck, insbesondere Kapillardruck, und Augendruck nach neuen experimentellen und klinischen Untersuchungen. Arch. Augenheilk. **96**, 179 (1925)

Duke-Elder, S.: The physiology of the intraocular fluids and its clinical significance. Am. J. Ophthalmol. **32**, 1638 (1949)

Elschnig, A.: Glaukom. In: Henke Lubarsch Handbuch der speziellen pathologischen Anatomie und Histologie. Berlin: Springer 1928

François, J., Neetens, A.: Vascularity of the eye and the optic nerve in glaucoma. Arch. Ophthalmol. **71**, 219 (1964)

Fritz, A.: A preliminary note on the development of occasional transient (ca. 1 min) hypertensive crises in the uveal capillaries in glaucoma. Bull. Soc. Belg. Ophthalmol. **95**, 392 (1950)

Fritz, A.: Preliminary note on the inhibitory action of adrenaline procaine and the hypotensive action of retro-ocular tetra-ethyl-ammonium chloride infiltrations in the transient hypertensive crises affecting the uveal capillaries in glaucoma. Bull. Soc. Belg. Ophthalmol. **95**, 396 (1950)

Goldman, H.: Clinical aspects of the outflow of the aqueous humor. In: Glaucoma. A symposium. Oxford: Blackwell 1955

Hayreh, S.: Blood supply of the optic nerve head and its rôle in optic atrophy glaucoma and oedema of the optic nerve. Br. J. Ophthalmol. **53**, 721 (1969)

Hayreh, S.: Glaucoma. Conceptions of a disease: Pathogenesis of optic nerve damage and visual field defects. Stuttgart: Thieme 1978

Poiseuille, J.: Sur le mouvement des liquides dans les tubes capillaires. Memoire presenté par divers savants étrangers à l'Académie des Sciences, Paris (1846)

Thomassen, T.L.: The venous tension in eyes suffering from simple glaucoma. Acta Ophthalmol. **25**, 221 (1947)

Thomassen, T.L.: The safety-valve of the eye. Acta Ophthalmol. **27**, 413 (1949)

Urrets, A., Zavalia, H.: Note sur la pathogénie du glaucome. Ann. Ocul. **185**, 701 (1952)

Van Beuningen, E.G.A., Fischer, F.W.: Die arterielle Minutenvolumenbestimmung und ihre klinische Bedeutung. Ber. Dtsch. Ophthalmol. Ges. **61**, 218 (1957)

Received February 2, 1980