PII: S1350-9462(97)00006-2

Optic Nerve Blood-Flow Abnormalities in Glaucoma

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Progress in Retinal and Eye Research Vol. 17, No. 2, pp. 267 to 289, 1998

Printed in Great Britain
1350-9462/98/$19.00 + 0.00

Abstract—Glaucoma can be defined as an optic nerve disease with typical morphological and functional changes. There are many risk factors associated with this neuropathy. The best known factor is an increased intraocular pressure. There are, however, many other risk factors. Among them, vascular factors play a major role. Although such vascular factors have been postulated more than hundred years ago, it is only recently that the physiology and pathophysiology of the optic nerve head circulation is, to some extent, understood. New instruments have been developed to measure ocular blood flow including blood flow in the optic nerve head. Although most of the studies indicate that circulation is changed in glaucoma patients, there is little association between glaucoma and arteriosclerosis. The main cause for the circulation disturbance in glaucoma seems rather to be a vascular dysregulation leading to local vasospasm and to systemic hypotension.

1. INTRODUCTION

Primary open-angle glaucoma (POAG) is an insidiously progressing multifactorial disease of unknown origin. Clinically, it is characterized mainly by optic disc excavation, visual-field loss (Fig. 1), and, often, increased intraocular pressure (IOP). Already at the time of von Graefe, optic disc excavation and visual-field loss were not unvariably linked to increased IOP (von Graefe, 1857). Although there are a large number of publications describing the clinical manifestations of glaucoma, the exact pathomechanism of glaucomatous damage is still not clear. Experimental, clinical, and epidemiological studies indicate that many factors (so called risk factors) might be involved. There is no doubt that increased IOP is the best known and most extensively studied risk factor with major therapeutic consequences. However, evidence from studies on normal-tension glaucoma and ocular hypertension suggest that elevation of IOP is neither necessary nor sufficient to produce glaucomatous optic neuropathy. These observations imply that there might also be variables other than increased IOP involved in the pathogenesis of glaucoma. Among such other variables discussed in the literature, vascular risk factors are the most extensively studied (Drance et al., 1973), but before discussing them some basic anatomical and functional aspects of the optic nerve head circulation should be described.

2. ANATOMY

2.1. *Embryological Aspects*

The embryological development of the vascularization of the anterior optic nerve has been summarized in Table 1. The vascularization of the optic nerve begins in the eighth gestational week (Sturrock, 1975). By that time, the formation of the optic grooves, of the optic vesicles, and of the optic cups have successively taken place (Barishak, 1992). Toward the end of the fourth week, blood vessels which will be connecting to the dorsal ophthalmic artery during the fifth gestational week, cover the external surface of the optic cup. Closure of the embryonic fissure occurs during the sixth week, and branches from the dorsal ophthalmic artery and the ventral ophthalmic artery form the precursors of the temporal and nasal posterior ciliary arteries, respectively. During the eighth gestational week, capillaries develop on the optic nerve, along with the differentiation of the pial cells. A very large increase in vascularity of the optic nerve occurs between the eighth and eighteenth week, most of which occurs from the twelfth week onwards. By the end of the third month of gestation, small branches of the

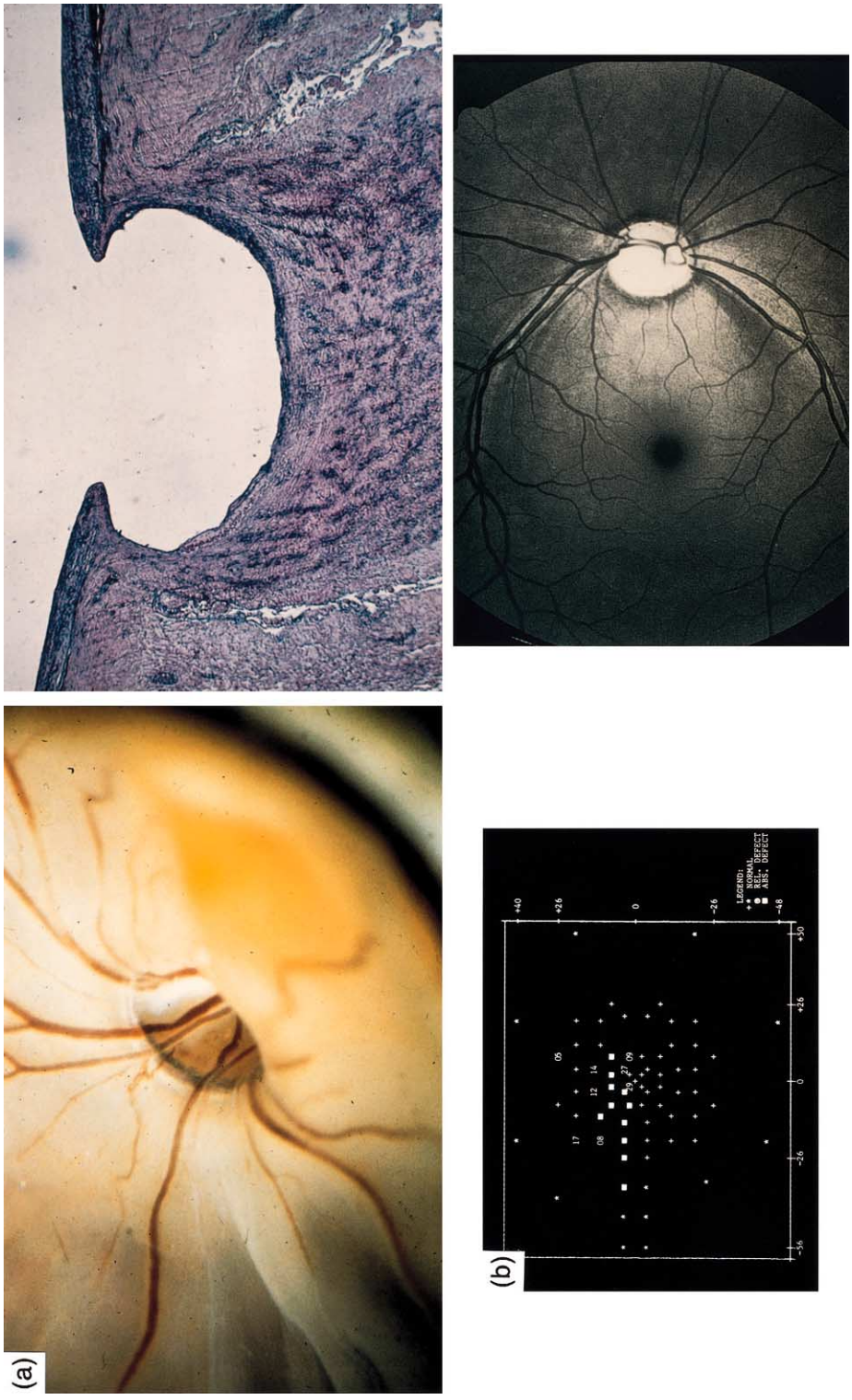

Fig. 1. (a) Glaucomatous optic nerve head (ONH) atrophy with deep excavation (photo taken of a cadaver eye) together with a histopathological picture of the ONH of a glaucoma patient. (b) Retinal nerve fiber layer photography taken with a red-free filter together with a corresponding visual field defect measured with the Octopus Program G1. (Flammer, 1996, with permission of Karger)

Table 1. *Embryonic Development of the Anterior Optic Nerve Vasculature*

Third week	appearance of the optic groove
Fourth week	appearance of the optic vesicle appearance of the optic cup and of the embryonic fissure appearance of blood vessels covering the neural tube
Fifth week	development of the hyaloid vasculature connection of the dorsal ophthalmic artery with vessels around the cup
Sixth week	closure of the embryonic fissure formation of the temporal and nasal posterior ciliary arteries
Eighth week	development of capillaries on the optic nerve
Third month	increase in vascularity of the optic nerve begin of development of the arterial circle of Haller and Zinn
Fourth month	vascularization of the precursor of the lamina cribrosa
Fifth month	achievement of the vascularization of the meningeal layers of the optic nerve
Sixth month	anastomosis of components of the arterial circle of Haller and Zinn

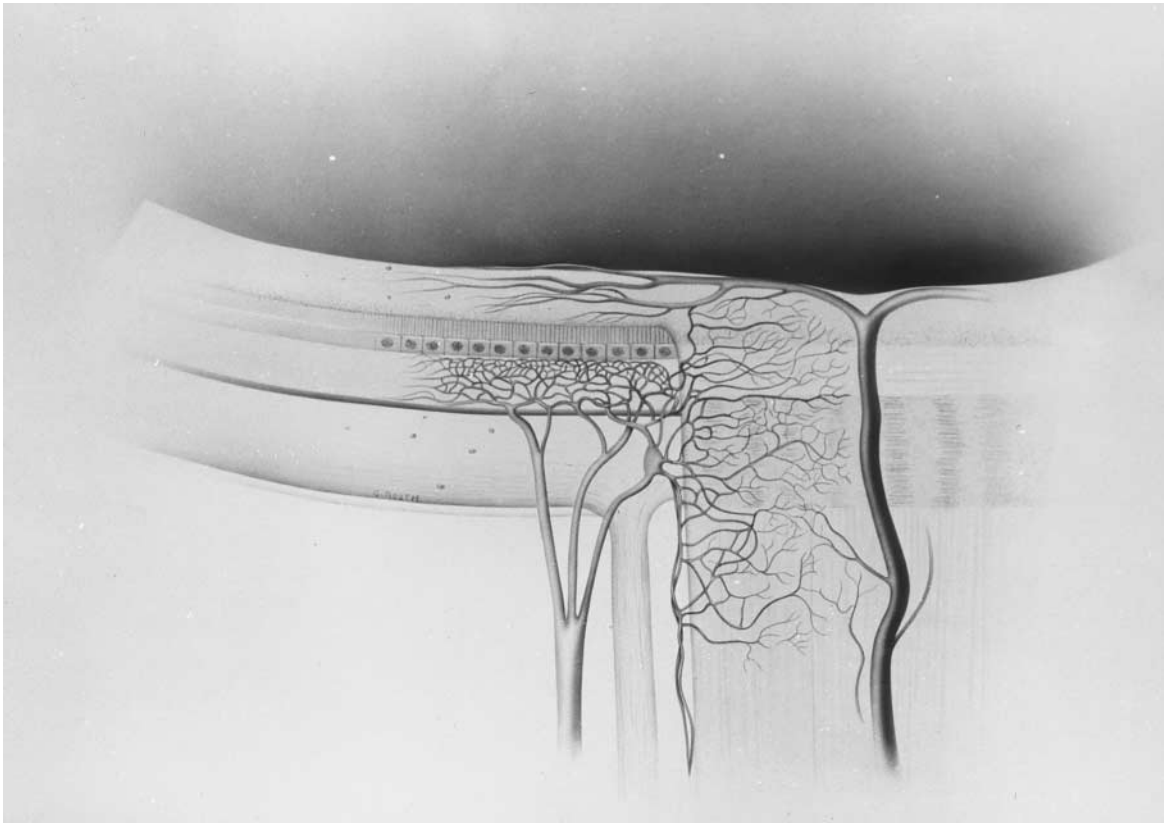

Fig. 2. Anatomy of the optic nerve head blood supply. The major arterial input is derived from the short posterior ciliary arteries. (Cioffi and Van Buskirk, 1996 with permission of Mosby Publisher)

short posterior ciliary arteries form the precursor of the arterial circle of Haller and Zinn. The vascularization of the lamina scleralis (future lamina cribrosa) develops during the fourth month, when vascularized scleral connective tissue penetrates into the glial septa. During the fifth month, the vascularization of the meningeal layers of the anterior optic nerve is achieved. During the sixth month, components of the arterial circle of Haller and Zinn have anastomosed, and the vascularization of the anterior optic nerve is completed (Ozanics and Jakobiec, 1982).

2.2. *Anatomy of the Adult Anterior Optic Nerve Vasculature*

The arterial supply of the adult optic nerve (Fig. 2) is derived entirely from branches of the ophthalmic artery (Orgül and Cioffi, 1996). The latter is the first branch of the internal carotid artery which is approximately 5 mm in diameter at the point where the ophthalmic branch occurs. The ophthalmic artery itself is approximately 0.5 mm in diameter and branches off from the carotid at an angle of 90°. The ocular branches of the ophthalmic artery are the central retinal artery and one to five posterior ciliary trunks, which usually divide into multiple branches, forming separate groups of main posterior ciliary arteries. The most common of the posterior ciliary trunks are the medial and lateral posterior ciliary trunks. The main posterior ciliary arteries divide further into several short posterior ciliary arteries, just before or after piercing the sclera (Hayreh, 1962). Often, the medial and lateral paraoptic short posterior ciliary arteries anastomose and form an elliptical circle around the optic nerve within the sclera approximately 100–300 μm posterior to the suprachoroidal space, i.e. the arterial circle of Haller and Zinn (Olver et al., 1994). This usually intrascleral (but occasionally extrascleral) arterial network has been suggested to be incomplete in most instances. The anterior portion of the optic nerve may be divided into four regions: (a) the superficial nerve fiber layer; (b) the prelaminar region; (c) the laminar area region; and (d) the retrolaminar region.

The vascular pattern of the superficial nerve fiber layer is one of a network of both vessels from the prelaminar region and branches from the central retinal artery and main retinal arteries. Additionally, the temporal nerve fiber layer may have an arterial contribution from a cilioretinal artery. No choroidal or choriocapillaris contribution is observed in this region. Vessels derived from the vascular bed of the retinal arteries tend to be arterioles and precapillaries, while vessels derived from the prelaminar region tend to be precapillaries and capillaries.

Immediately posterior to the nerve fiber layer is the prelaminar region, which is adjacent to the peripapillary choroid. This region receives arterial supply via direct branches of the short posterior ciliary arteries and via vessels originating from the arterial circle of Haller and Zinn. Some authors have also suggested the presence of a choroidal arterial blood supply to the prelaminar anterior optic nerve, while other investigators argued in favor of ciliary branches (except for occasional small arterioles) coursing simply through the choroid (Onda et al., 1995). The angioarchitecture in the prelaminar region is characterized by a diffuse network of a few arterioles and largely predominating precapillaries and capillaries (Lieberman et al., 1976). These vessels are arranged around and within the nerve fiber bundles and within the astrocytic septae.

The lamina cribrosa is supplied by transversely entering vessels. The short posterior ciliary arteries, either directly or via the arterial circle of Haller and Zinn, provide the principal arterial input to this portion of the nerve. The peripapillary choroid may contribute occasional small arterioles. The vessels entering the posterior portion of the lamina cribrosa tend to be larger (arterioles) than those entering the anterior portion (precapillaries and capillaries).

Most of the blood supply to the retrolaminar portion of the optic nerve occurs through numerous vessels perforating from the pia mater. The intraseptal vessels of the retrolaminar optic nerve are primarily large precapillaries and capillaries, derived from arteries and arterioles emanating from the pial sheath. These pial vessels obtain their supply either directly from the ophthalmic artery or indirectly from recurrent branches from the

posterior ciliary arteries. The central retinal artery contributes to the blood supply of the retrolaminar optic nerve by occasional small branches within the nerve, but not to a significant extent.

Remarkably, in view of the abundant arterial supplies from many source vessels, the venous drainage of the anterior optic nerve occurs almost exclusively via a single vein, the central retinal vein (Cioffi and Van Buskirk, 1996). In the nerve fiber layer, blood is drained by small veins that converge and empty, ultimately, into the central retinal vein. In the prelaminar, laminar, and retrolaminar regions, venous drainage also occurs via the central retinal vein or centripetal tributaries to the central retinal vein. Occasionally, small venules connecting the optic nerve and the peripapillary choroid can be identified, mainly within the prelaminar region. In the peripheral aspects of the laminar and retrolaminar regions, some optic nerve venous drainage may also be via pial veins. These pial veins ultimately drain into the central retinal vein prior to exiting the optic nerve.

Within the anterior optic nerve, arterial capillary and venous channels resemble, ultrastructurally, those of the central nervous system. They are not fenestrated and have tight junctions. They do not leak fluorescein or other tracers. Therefore, this microvascular bed forms a blood–nerve barrier.

3. PHYSIOLOGY OF BLOOD-FLOW REGULATION IN THE ANTERIOR OPTIC NERVE

The perfusion of an organ or part of an organ depends on (a) perfusion pressure; (b) vascular resistance; and (c) local blood viscosity. In the present context we will mainly discuss the vascular resistance to flow. This local resistance is physiologically regulated by changing the local diameter of the vessels. Hagen–Poiseuille's law predicts that the resistance varies inversely with the fourth power of the lumen diameter. This law is theoretically only applicable to rigid tubes and to laminar flow. Intravascular measurements in mesenterial arterioles and venules of cats (Lipowsky et al., 1978), however, demonstrated that, indeed, the vascular blood flow *in vivo* also varies approximately with the fourth power of the vessel radius. The vascular tone is permanently regulated by a number of regulatory systems and factors, such as circulating hormones, as well as metabolic, myogenic and neurogenic factors. The endothelial cell layer acts as an important mediator for the response to these factors (Haefliger et al., 1994). The different systems are strongly interrelated. For the sake of simplicity, however, we will describe them step by step.

As an extension of the central nervous system, the optic nerve has several characteristics in common with other parts of the brain, including the autoregulation of blood flow. As relatively little is known of optic nerve head blood-flow regulation, some aspects of the retinal and choroidal circulation which might be related to optic nerve head circulation will be discussed, as well. In general, autoregulation keeps local perfusion constant or adapted to the local metabolic needs and, thus, within certain limits, largely independent of the local perfusion pressure. This is accomplished in two principal ways: (a) by metabolic; and (b) by myogenic mechanisms (Johnson, 1986). In tissues with metabolic autoregulation, the arterioles adjust their resistance to maintain the concentration of some critical metabolites in the tissue at a constant level. In tissues with myogenic autoregulation, presumed pacemaker cells in the arterioles sense the transmural pressure difference and induce an adjustment of arteriolar tone by cell to cell propagation of signals through the smooth muscle cells. In ocular tissues (including the optic nerve head) both types of mechanisms seem to be involved (Bill, 1985).

3.1. *Metabolic Autoregulation*

The concentrations of O_2, CO_2, K^+, H^+, and adenosine, as well as the intercellular osmolarity influence the vascular tone (Orgül et al., 1995b). The autoregulatory response to decreased blood flow seems to be mediated by oxygen-dependent mechanisms (Kontos et al., 1978; Sullivan and Johnson, 1981).

Whereas hyperoxia and hypocapnia decrease anterior optic nerve blood flow by arteriolar constrictions, hypoxia and hypercapnia increase optic

nerve head (ONH) blood flow. Overall, the terminal arterioles are more sensitive to reduction in tissue oxygen than are the larger arterioles.

Current evidence suggests that an endothelium-dependent, indometacin-sensitive mechanism is a key element in hypoxia-induced vasodilatation (Busse et al., 1983, 1984). Therefore, some prostaglandins are the most probable mediators. In retinal hypoxia-induced vasodilation, adenosine has also been shown to be involved. Nitric oxide is another vasodilator. Its role in the autoregulatory response to decreased blood flow seems to be minor (Thompson et al., 1996). The hemodynamic response to hyperoxia in the retinal circulation has recently been demonstrated to be mediated by endothelin (Takagi et al., 1996).

3.2. *Myogenic Autoregulation*

As local blood pressure and, hence, the transmural tension are increased, arterioles respond actively with constriction (Johnson, 1986). Myogenic regulation has been demonstrated in various organs, including the optic nerve. The exact mechanism of the myogenic regulation is still under investigation. It is known, however, that the extracellular calcium concentration plays a role and that calcium antagonists inhibit its response. The myogenic contraction is, at least partly, mediated by endothelial factors (Davies and Tripathi, 1993).

3.3. *Neurogenic Control of Vessels*

The autonomic nervous system supplies a network of vasomotor nerve fibers (Kurihara and Yazaki, 1995). The nerve fibers form a plexus in the adventitia of the resistance vessel walls and send extensions to form varicosities on the outer surface of the media. Neurotransmitters are released from the varicosities towards the smooth muscle cells. The nerve fibers consist of three kinds of fibers: (a) adrenergic; (b) cholinergic; and (c) non-adrenergic/non-cholinergic (nitric oxide) (Nilsson, 1996; Toda et al., 1996). Norepinephrine produces vasoconstriction by stimulating α-receptors, and acetylcholine evokes vasodilatation by stimulating M_3-receptors. In addition to these classical neurotransmitters, several substances are released in the nerve terminals (Table 2).

The eye has a rich supply of autonomic nerves within the uvea, the posterior ciliary arteries, and the extraocular portion of the central retinal artery (Alm, 1977; Flügel-Koch et al., 1994a,b). Vessels in the retina and the prelaminar portion of the optic nerve, however, have no neural innervation. Consequently, stimulation of the sympathetic nerve system might influence retinal and optic nerve head perfusion indirectly, at most. Nevertheless, α- and β-adrenergic receptors have been demonstrated in the retinal vessels.

Table 2. *Neurohumoral Substances Affecting Vascular Tone*

	Vasoconstrictors	Vasodilators
Peptides	Angiotensin II	Natriuretic peptides
	Vasopressin	Kinins
	Endothelins	Substance P
	Neuropeptide Y	Calcitonin gene-related peptide
		Vasoactive intestinal peptide
		Glucagon
Nonpeptides	Catecholamine (α_1)	Catecholamine (β_1)
	Serotonin	Histamine
	Thromboxane A_2	Adenosine
	Leukotrienes	Prostacyclin
	Endogenous digitalis-like substance	Endothelium-derived relaxing factor/nitric oxide

3.4. *Humoral Control of Blood Flow*

Physiologically, the circulating blood contains a number of vasoactive hormones (Kurihara and Yazaki, 1995). They might act partially through mediation of the endothelial cells (see below) and partially directly on the smooth muscle cells and pericytes of the vessels. In the optic nerve head, the smooth muscle cells and pericytes do not have direct contact with circulating blood due to a potent blood–nerve barrier. Furthermore, a scleral flange at least partially prevents a free diffusion of substances from the choroid into the optic nerve head. The following hormones might be of relevance.

Renin is a proteolytic enzyme secreted by cells of the juxtaglomerular apparatus, but also in the eye. It acts on a plasma globulin (angiotensinogen) by splicing off a decapeptide (angiotensin-I). Angiotensin-I has no appreciable activity but is activated by a second proteolytic enzyme, the angiotensin-converting enzyme (ACE), to form the highly active octapeptide, angiotensin-II (Peach, 1979). Angiotensin-II constricts ocular vessels by activating A-1 receptors (Meyer et al., 1995). The ACE is located in the membrane of the endothelial cells. *In vivo* experiments reveal a decrease in ONH perfusion under angiotensin-II infusion (Jossi and Anderson, 1983).

Plasma epinephrine is predominantly released from the adrenal medulla and plasma norepinephrine is mostly a result of spillover into the systemic circulation from noradrenergic nerve endings. Both constrict vessels by stimulation of α-receptors (see neurogenic regulation) and, in certain vascular beds, dilate vessels by β_2-receptor stimulation. Circulating catecholamines constrict choroidal vessels. Whether they have a direct effect on the optic nerve head remains to be clarified (Yu et al., 1994).

Vasopressin is a small peptide synthesized in the supraoptic and paraventricular nuclei in the hypothalamus and is secreted from the nerve endings projecting into the posterior pituitary gland. Vasopressin induces vasoconstriction through V_{1A}-receptors in vascular smooth muscle cells. Its role in ONH circulation is not known.

Natriuretic peptides: The atrial natriuretic peptide (ANP) is produced in the cardiocytes of the atria in response to myocardial stretch induced by volume expansion. The brain natriuretic peptide (BNP) is predominantly produced in the ventricular myocardial cells, whereas the C-type natriuretic peptide CNP is produced by the vascular and endothelial cells in response to several stimuli, such as cytokines. Natriuretic peptides cause natriuresis and have a vasodilator effect (Table 2). They can be considered as a counterpart of the renin–angiotensin system. Their role in ONH circulation is also not yet known.

3.5. *Endothelial Vasoactive Factors*

Within the cardiovascular system, the endothelium lies in a strategic anatomical position between blood components and smooth muscle cells and pericytes. It regulates permeability and exerts metabolic functions by activating and influencing the coagulation, platelet function, and fibrinolysis. In addition, vasoactive substances are released (Lüscher et al., 1990). In the present context, we confine ourselves to the latter aspect.

The endothelial cells release vasoactive substances both spontaneously and after local stimulation. Such a stimulation can be chemical, e.g. circulating hormones, or physical, e.g. shear stress or wall tension. The locally released mediators can be classified into vasodilators (EDRFs = endothelial-derived relaxing factors) and vasocon-

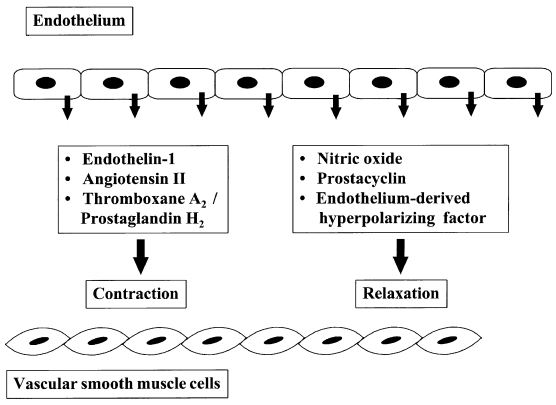

Fig. 3. Schematic representation of the endothelium-derived constricting and relaxing factors

strictors (EDCFs = endothelial-derived constricting factors) (Fig. 3).

In isolated porcine and human ophthalmic and ciliary arteries and in the perfused porcine eye, inhibition of nitric oxide formation causes a marked vasoconstriction, demonstrating that there is a basal formation of nitric oxide which leads to an active dilation of the vasculature (Yao et al., 1991). In the human and porcine ophthalmic arteries, acetylcholine, bradykinin, and histamine evoke additional endothelium-dependent relaxations also mediated by nitric oxide (Haefliger et al., 1992).

The most important constricting factor is endothelin-1 (ET-1). Endothelin is a 21-residue peptide (Lüscher et al., 1992). There are three distinct endothelin genes that encode distinguished sequences (ET-1, ET-2, ET-3). These three isoforms are diversely and unevenly distributed in the body. Endothelin-1 is rapidly synthesized in the endothelial cells in response to hypoxia, ischemia, or shear stress, and its plasma half-life is about 5 min. The functional half-life of ET-1, however, is much longer due to a strong binding to its receptor. Endothelins act through binding to two classes of transmembrane receptors: ET_A and ET_B. ET_A receptors are mainly found on vascular smooth muscle cells and pericytes and mediate the vasoconstrictor action of endothelin. In isolated ophthalmic arteries, ET-1 evokes potent contractions. The smaller the vessel, the higher the sensitivity to endothelin (Haefliger et al., 1993). ET-1 decreases blood flow to anterior optic nerve, when applied locally (Orgül et al., 1996), or injected into the vitreous body (Nishimura et al., 1996). In the perfused porcine eye, ET-1 increases ocular blood flow at very low dosages and reduces it at higher doses (Meyer et al., 1993). This dual action of ET-1 is due to the activation of ET_B at lower concentrations, and to the activation of ET_A receptors at higher concentrations (Flammer, 1997).

4. BLOOD-FLOW QUANTIFICATION IN HUMANS

Many different methods to quantify intraocular and extraocular blood flow have been developed in the last two decades. Their major limitations are that most of them basically measure blood-flow velocity and are not able to fully quantify flow. Measurements of the optic nerve perfusion is especially difficult because of the small volume of the tissue being studied, and the fine caliber of the vessels which, in addition, are mostly not directly visible.

4.1. *Angiography*

Fluorescein angiography allows us to visualize retinal vessels with high definition and is, therefore, the "gold standard" for the diagnosis of diseases of the retinal vasculature. For optic nerve blood-flow measurements, however, this method has some limitations: it provides information only on the most superficial vasculature of the optic nerve, and blood flow in the deeper layers of the optic nerve can only be analyzed qualitatively by evaluating the density of the diffused staining (Schwartz, 1994). The standard technique that is used to determine fluorescein angiographic abnormalities of the anterior optic nerve requires the injection of 5 cc of 10% sodium fluorescein intravenously, followed by standard photographs or video throughout the fluorescein cycle, that is, the filling of the arteries and veins by fluorescein and the subsequent drainage of fluorescein from the retinal veins. A lack of filling in the arterial phase is defined as "fluorescein defects". These are absolute defects if the lack of filling persists throughout the fluorescein cycle, or relative defects, if some filling occurs in a later phase (Spaeth, 1977). With the use of computerized image analysis and densitometry, fluorescein dye curves were produced for various parts of the ocular circulation, including the superficial anterior optic nerve. Various parameters, such as peak time (time to reach maximal intensity of fluorescein minus first appearance time) as well as ascending slope of the fluorescein dye curve, can be measured to estimate the time required for the dye to pass through the blood vessels of the anterior optic nerve (Lambrou, 1995). The temporal resolution of the scanning laser ophthalmoscope (50 frames/sec) has been applied to investigate

retinal blood velocities from digital video fluorescein angiograms.

4.2. *Blood-Flow Measurement Based on the Doppler Effect*

The Doppler effect summarizes changes of wavelength reflected by moving particles. This can be applied to acoustic waves, as well as to electromagnetic waves, such as light (Bebie, 1996). In ophthalmology, acoustic waves are used for flow measurements in extraocular (not directly visible) vessels (Sergott et al., 1994), whereas light waves (laser) are used for the quantification of intraocular blood flow (visibly accessible tissue) (Riva et al., 1982).

4.2.1. *Color Doppler imaging*

Color Doppler imaging (CDI) is a very useful and established method, in general medicine and in ophthalmology (Lieb et al., 1991). It allows the measurement of blood-flow velocity in defined vessels, but does not provide a real quantification of blood flow. We will describe this method only very briefly.

The color Doppler imaging is based on three types of echographic signals: (a) a conventional B-mode ultrasound provides a two-dimensional cross-section through the tissue; (b) a color-coded Doppler signal is superimposed, allowing the visualization of blood flow and its direction; and (c) a pulsed Doppler gives information on flow parameters in selected parts of this cross-section. The flow parameters are: peak-systolic velocity (PSV), end-diastolic velocity (EDV), and the calculated parameter resistivity index (RI = (PSV – EDV)/PSV). CDI allows a measurement of the blood velocity in the ophthalmic artery, the central retinal artery, and the posterior ciliary arteries (Kaiser et al., 1996b,c). The short-term reproducibility is quite good (Senn et al., 1997). However, there is a marked physiological long-term fluctuation, and the results are

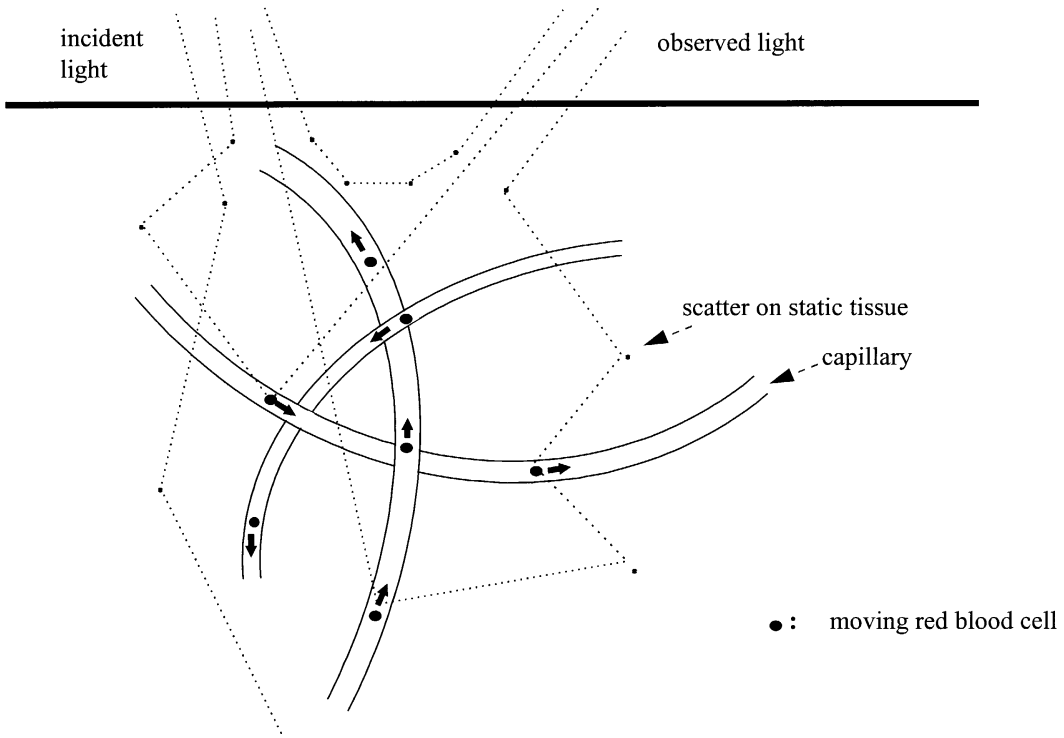

Fig. 4. Schematic view of the light scattering model underlying tissue flowmetry

strongly dependent on the technician's experience. Furthermore, the results depend on certain variables, including smoking (Kaiser et al., 1997a).

4.2.2. *Laser Doppler flowmetry*

The laser Doppler flowmetry (LDF) is an important step forward in the ONH blood-flow measurement. It allows a more or less continuous quantification of some flow parameters over a limited period of time. The major disadvantage is the fact that the measurement is limited to a small part of the ONH and that we do not know exactly the tissue volume included in the measurement. Whereas the method ascertains time changes, it is still very limited for comparison between individuals (Petrig and Riva, 1996).

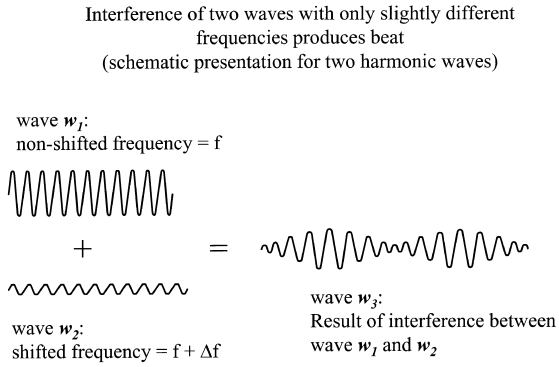

Fig. 5. Schematic representation of the interference between the shifted and non-shifted light leading to beat

The method in brief: a continuous laser light is projected on the ONH. The reflected and backward scattered light is then analyzed (Fig. 4). Whereas the vast majority of the light is backscat-

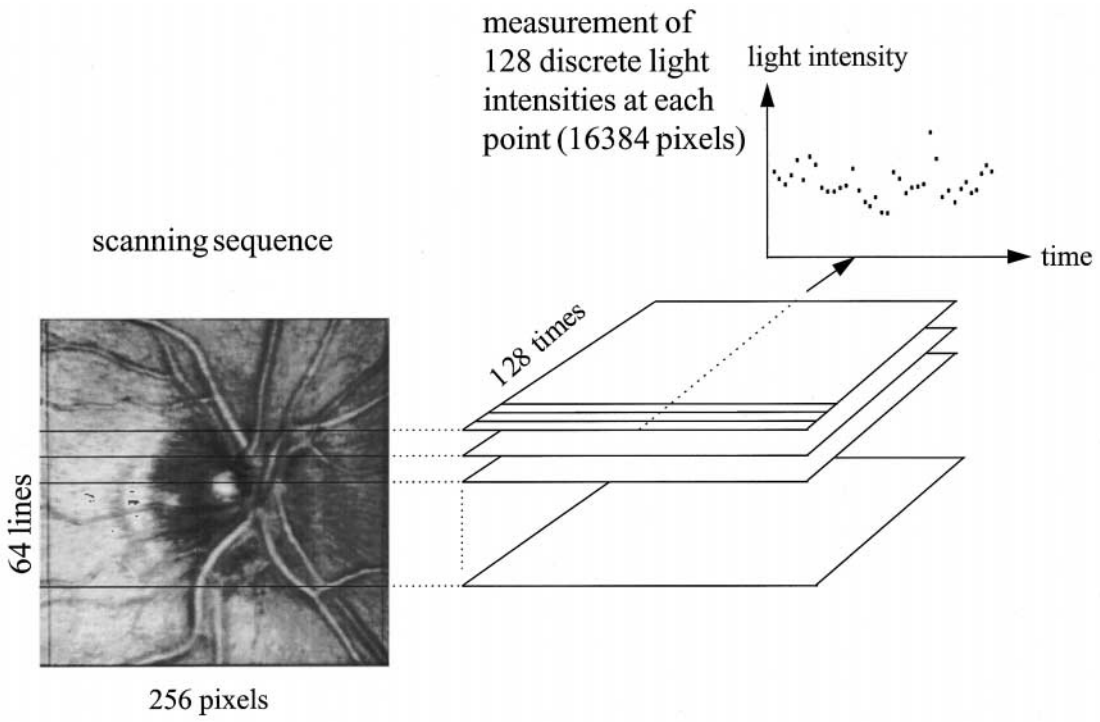

Fig. 6. Sequential scanning of 64 horizontal lines. Each line is scanned 128 times. This repeated scanning process results in different information of brightness for each test location. This variation of brightness is further evaluated by means of a Fourier analysis

tered without shift of the wavelength, a small portion of the light is shifted in frequency in proportion to the velocity of the moving particles. The non-shifted and the shifted light interfere, resulting in a variation in light intensity (Fig. 5). This variation in intensity can be further processed by Fourier analysis, providing a so-called power spectrum. The method was mainly applied in experimental animal studies and is now being introduced for application in humans.

4.2.3. *Scanning laser Doppler flowmetry*

A new application of laser Doppler flowmetry principle has been achieved in a device which combines the laser Doppler flowmeter principle with a scanning laser system (Michelson and Schmauss, 1995). This device is commercially available and is called ''Heidelberg Retina Flowmeter (HRF)''. This device generates a two-dimensional map showing the microvascular perfusion of the tissue to be studied. The area of interest is examined line by line (64 horizontal lines of 256 points) which is scanned sequentially a total of 128 times. This process takes approximately 2 sec (Fig. 6). The resolution of the measurements, however, is limited by this scanning frequency. Blood flow-related parameters, ''volume'', ''flow'', and ''velocity'', can be quantified in any location of the perfusion map, placing a square of variable size in the area of interest. In contrast to the LDF, the HRF has primarily been directly applied on humans.

Further methods to quantify ocular blood flow and ONH blood flow, such as magnetic resonance imaging (Prünte et al., 1995), laser speckle flowmetry (Tamaki et al., 1994), or the Langham pulsatile ocular blood flow measuring system (Langham et al., 1989) are presently under evaluation.

5. GLAUCOMATOUS OPTIC NEUROPATHY

After having described some aspects of anatomy and physiology of ONH blood flow and the currently available methods to quantify it, we will now summarize what is known about ONH blood flow in glaucoma. Before we do this, let us consider some general aspects of glaucoma and of the pathophysiology of the glaucomatous damage.

5.1. *What is Glaucoma?*

Phenomenologically, glaucoma is a syndrome of progressive optic neuropathy, characterized by ONH excavation with consecutive defects in retinal sensitivity with visual-field damage and other psychophysical alterations (Van Buskirk and Cioffi, 1992). Although the clinical picture of glaucoma is well described, the exact mechanism leading to this specific type of damage is not yet clear. Most theories concerning the pathogenesis can be grouped into one of two broad categories: (a) mechanical; and (b) vasogenic mechanisms (Flammer, 1985). There is no doubt that increased IOP can lead to glaucomatous damage. Because IOP is easy to assess, glaucoma has been defined by some ophthalmologists as a disorder of aqueous humor dynamics. Because not all glaucoma patients suffer from increased IOP, the term, ''low- or normal-tension glaucoma'', was introduced. Not to violate the pressure concept, an increased sensitivity to IOP was postulated in normal-tension glaucoma. As a consequence, only IOP-lowering treatment was accepted for glaucoma.

There is evidence both from experimental studies and from clinical observations that increased IOP alters structural and neural elements of the ONH. However, two basic questions still remain: (a) does the increased IOP primarily impair the blood perfusion of the ONH or does it primarily produce mechanical damage to the glial cells or the neurons? (b) Are other factors besides the IOP involved in the pathogenesis of the defect, and, if so, can they be influenced?

5.2. *What Challenges the Pressure Theory?*

There are many observations which can hardly be explained by pure pressure theory. Let us list a few examples:

1. As many as 1/6 of the patients with glaucomatous damage do not have increased IOP even with repeated testing (Sommer et al., 1991).
2. Ocular hypertension is 10-times more common than glaucomatous neuropathy (Bengtsson, 1981).
3. Although men and women have approximately the same IOP, the incidence of normal-tension glaucoma in females is about twice that of males (Orgül et al., 1995a).
4. The average IOPs of blacks and whites are about the same; yet, the incidence of glaucomatous damage is higher in blacks (Tielsch et al., 1991).
5. In Japan, although the incidence of glaucomatous ONH damage increases with age at about the same rate as it does in America or Europe, the IOP (in contrast to the West) truly diminishes with advancing age (Shiose et al., 1991).
6. The presence and the progression of glaucomatous damage is extremely weakly related to the level of IOP (Weber et al., 1993).
7. Although timolol produces more pressure reduction than does betaxolol, betaxolol-treated patients seem to have a better visual-field prognosis than do those treated with timolol (Messmer et al., 1991).
8. The occurrence and progression of glaucomatous damage is significantly related to other risk factors, such as systemic hypotension and vasospastic diathesis (Flammer et al., 1992).

5.3. *Combined Mechanical and Vascular Concept*

Over 10 years ago, a concept which combines mechanical and vascular aspects was proposed (Flammer, 1985). This concept was based on the phenomenology of the psychophysical and morphological aspects of the glaucomatous damage. Glaucomatous visual-field damage can be diffuse (this does not mean totally homogeneous), local, or both (Flammer et al., 1985). The best and most convenient method available to separate these two components is the so-called "Bebie-curve", a cumulative defect distribution curve representation of visual-field defects (Bebie et al., 1989). The diffuse component is not specific, as it can also be due to cataract and narrow pupil. Nevertheless, there is no doubt that glaucoma can also produce diffuse nerve fiber loss (with corresponding concentric ONH excavation), leading to a diffuse visual-field damage. The diffuse component of the visual-field damage is related to IOP (Flammer et al., 1982) (or, rather, to IOP peaks), whereas the localized component of the defect is only very weakly related to IOP (Niesel and Flammer, 1980). Patients with a diffuse component of damage tend to have changes in color vision (Flammer and Drance, 1984) and contrast sensitivity (Zulauf and Flammer, 1993), whereas patients with purely localized visual-field defects often have normal color vision. This might also explain why patients with so-called ocular hypertension (increased IOP without scotomas in the visual field) often have color vision changes. Patients with predominantly localized ONH or field defects tend to be older and, on average, have less IOP elevation (Glowazki and Flammer, 1987).

5.4. *Is Normal-Tension Glaucoma a Separate Entity?*

If we consider all open-angle glaucoma patients, we realize that there is no clear-cut separation between glaucoma patients with an IOP in the statistically normal range and glaucoma patients with increased IOP. Instead, we are dealing with a continuum. Current evidence suggests that there are only minor differences in optic nerve damage between patients with and those without elevated IOP (Jonas et al., 1995). Therefore, it is difficult or even impossible to separate normal-tension from high-tension glaucoma patients. Even if possible, such a separation is of little clinical help. However, for research purposes a grouping into normal-tension and high-tension glaucomas might sometimes be helpful for the following reasons: general experience shows that the lower the IOP at which damage occurs or progresses, the higher the chance to find other risk factors. Therefore, when for scientific purposes we are searching for other factors involved in the pathogenesis, it is especially productive to analyze so-

called normal-tension glaucoma patients. However, it is obvious that a factor involved in the group of normal-tension glaucomas can also be involved in the high-tension glaucomas, although the probability of such involvement in an individual case might be lower (Flammer, 1996).

5.5. *Differential Diagnosis of Normal-Tension Glaucoma*

Do other diseases mimic normal-tension glaucoma? The answer to this question depends on the terminology. If we define glaucomatous damage phenomenologically, summarizing all the diseases leading to ONH excavation, we can reformulate the question as follows: which risk factors, or rather, which diseases can lead to such a clinical picture with ONH excavation called glaucomatous optic neuropathy? This implies for the clinician that, in a first step, the phenomenological diagnosis of a pathological excavation and of its progression is made, and in a second step risk factors leading to such an excavation are evaluated. Indeed, rare diseases, such as giant cell arteritis (Orgül et al., 1994), ONH hemorrhages (Orgül and Flammer, 1994b), tumors or empty sella (Rouhianen and Teräsvirta, 1989), and even trauma to the optic nerve, can also lead to an ONH excavation, either by themselves or in concert with other risk factors.

Should we separate high-tension glaucoma from normal-tension glaucoma? In addition to the fact described above that we are dealing with a continuum, any separation according to a defined IOP is totally arbitrary. In an individual case, it is possible that IOP was high in earlier stages of the disease process and normal at the time a patient is examined (such a normalization of IOP can e.g., occur in the pigment dispersion syndrome), or that IOP peaks are present but not yet detected. However, this is also true for other risk factors; e.g., blood pressure drops at night may not yet have been detected or vasospasms might have been overlooked, or present before menopause, but no longer present when the patient is seen by the doctor. In some patients, spasms might only occur under emotional stress and not be present during a clinical evaluation, etc. Furthermore, damage might develop in patients having several risk factors simultaneously, such as increased IOP and vasospasm (Schulzer et al., 1990).

6. VASCULAR RISK FACTORS

6.1. *What Points Towards Vascular Risk Factors?*

In scientific research evaluating potential risk factors, an incidence study in a larger population is an ideal approach. Practically, however, most of the studies are done by comparing the frequency of a corresponding factor in a glaucoma population and in a non-glaucoma population. For the reasons described above, previous comparisons of this nature have especially been conducted between normal-tension glaucomas and controls. A number of different factors, including rheologic and vascular factors have been described (Hamard et al., 1994). Most of them are still controversial. Risk factors might be causal, e.g., low blood pressure or non-causal, such as microvascular changes in the brain. Although non-causal factors may not be directly involved in the pathogenesis of a glaucomatous defect, they point towards a basic underlying disease.

In the following, we will confine ourselves to vascular risk factors (Flammer, 1994). Among them very frequent, most probably causal, as well as potentially treatable factors, are systemic hypotension and vasospastic diathesis.

6.2. *The Role of Blood Pressure*

IOP correlates very weakly positively with the level of systemic blood pressure (Tielsch et al., 1995). This means that patients with high IOP have an increased risk of systemic hypertension, and vice versa. Glaucoma patients with progressive glaucomatous damage, as well as normal-tension glaucoma patients, however, have a clearly increased prevalence of systemic *hypotension* (Hayreh et al., 1994b; Kaiser et al., 1993b). Whereas systemic hypotension is a major risk factor, systemic hypertension is a minor risk factor for glaucomatous damage. In younger patients,

systemic hypertension may even protect against damage, whereas older hypertensive patients have a slightly increased risk (Tielsch et al., 1995). The latter fact might be due to the development of arteriosclerosis. The association between glaucomatous damage and low blood pressure has been described by a number of authors (Bechetoille and Bresson-Dumont, 1994; Demailly et al., 1984; Drance et al., 1973; Freyler and Menapace, 1988; Gramer and Leydhecker, 1985). Therefore, there is little doubt that low blood pressure is an essential risk factor, similar to an increased IOP. Therefore, as we have to search for IOP peaks, we have also to search for blood pressure dips. Consequently, 24-h monitoring of blood pressure provides a much better estimation of the real blood pressure than does a single measurement during a consultation.

It remains to be clarified to what extent low blood pressure or low perfusion pressure is a damaging factor in itself. The fact that patients with autonomic dysfunction causing a very low blood pressure (e.g., the Shy–Drager syndrome) or with orthostasis due to autonomic diabetic neuropathy very rarely develop glaucomatous damage indicates that counter-regulatory mechanisms leading to an increased local resistance might be additionally involved (Flammer, 1994). This hypothesis is further supported by the following observations:

1. Patients with systemic hypotension are often vasospastic (Gasser, 1991).
2. Patients with carotid stenosis (leading to a low perfusion pressure) do not have a relevantly increased incidence of glaucomatous damage (Pillunat and Stodtmeister, 1988).
3. Drugs, such as angiotensin-II, although increasing blood pressure and perfusion pressure, make the ONH even more sensitive to IOP increase (Jossi and Anderson, 1983) and, on the other hand, calcium-channel blockers can increase ONH perfusion even when they decrease blood pressure (Harino et al., 1992). The results of animal studies correspond to the clinical observation that calcium-channel blockers can improve the visual fields of some patients, even if the blood pressure is decreased (Flammer and Guthauser, 1987).

These observations indicate that local regulatory mechanisms might be even more important than perfusion pressure.

6.3. *Local Resistance to Flow*

When considering increased local resistance, the first factor which comes to mind is arteriosclerosis. Although experimental studies indicate that arteriosclerosis might increase the sensitivity to IOP (Hayreh et al., 1994a) and, although some arteriosclerotic patients do have a sclerotic type of glaucoma (Geijssen, 1991), there is very little evidence in the literature that arteriosclerosis is a major risk factor for glaucomatous damage. Indeed, we often see patients with extensive glaucomatous damage having neither signs of arteriosclerosis nor typical risk factors for arteriosclerosis, such as smoking or hyperlipidemia. Even diabetes, although mentioned in most textbooks as a risk factor, seems not to increase the sensitivity to IOP (Lepidi et al., 1997). Moreover, patients with extensive arteriosclerosis and myocardial infarction or cerebral vascular diseases seem not to have an increased risk of glaucoma. Nevertheless, increased local resistance is important. This resistance, however, may be more often due to a functional vascular dysregulation rather than to structural changes.

6.4. *Vascular Dysregulation*

As described above, the ONH blood flow is at least to some extent autoregulated, similar to that of the retina. A dysfunction of the local regulatory system may lead to hyperperfusion, e.g., in the retina in early stages of diabetes, or to hypoperfusion, as has been shown in the retina during attacks of vasospasms (Baksi, 1984). Vasospasms or angiospasms are normally defined as inappropriate vasoconstrictions without recognizable anatomical causes. However, autoregulation also implies the capacity of an organ to regulate its blood supply in accordance with its functional and metabolic needs. For example, it is known that functional tasks, such as speech, listening, or arm work, cause a local increase in cerebral blood

flow, coupled with increases in local metabolism. During attacks of migraine with aura, these activities are not accompanied by a normal cerebral blood-flow increase (Lauritzen et al., 1983). Therefore, the vasospastic diathesis might not only be expressed by a local vasoconstriction, but possibly also by a lack of appropriate vasodilatation (Flammer, 1996). Normally, ONH blood flow increases after flickering light provocation (Riva et al., 1996). It is conceivable that such an adaptation might be insufficient in patients with vasospastic diathesis.

Dysregulation can be temporary and more or less localized to a few organs or even only to a part of an organ. The clinical symptoms depend on the location of the spasms (Miller et al., 1981). For example, the symptoms in the Raynaud syndrome are mostly localized in the fingers.

6.4.1. *The vasospastic syndrome*

According to our new definition, vasospasms are reversible constrictions or insufficient dilatations of otherwise healthy or arteriosclerotic vessels. Although such spasms normally lead to reversible functional damage, they can sometimes provoke structural ischemic lesions. Neither the etiology nor the pathophysiology of the vasospastic syndrome is fully understood. There is ample evidence that the local hormone ET-1 might play an important role (Lüscher, 1991). The clinical pictures vary. Typical manifestations include variant angina, Raynaud's syndrome, migraine, and systemic hypotension (Mahler et al., 1989). Women are more often affected than men, young individuals more often than elderly. The vasospastic syndrome can disappear after menopause. The vascular crisis can be provoked by many factors, such as emotions, nicotine, and exposure to cold. Before the diagnosis of vasospastic diathesis is made in an individual patient, endocrine, hematological and neurological disorders, as well as vascular diseases need to be excluded (Gasser, 1991).

The most accurate method to verify vasospasms is the direct observation of capillaries in the nailfold skin (capillary microscopy), viewed under indirect illumination once the skin has been made transparent by the application of a drop of oil (Mahler et al., 1989).

6.4.2. *Ocular vasospastic syndrome*

Vasospasms in the retinal vessels in association with unstable primary angina and with migraine have been reported (Baksi, 1984). Such retinal spasms are rare. Spasms, however, may occur more often in the ciliary or choroidal vessels (Gasser et al., 1986) or even directly in the ONH. Under clinical conditions the ONH vessels are not visually accessible, and, therefore, such spasms might be missed. Originally, the involvement of the eye in the vasospastic syndrome was hypothetical, based on studies on visual fields and peripheral circulation (Guthauser et al., 1988). The term "presumed ocular vasospastic syndrome", was introduced (Flammer et al., 1992). In a number of patients with unexplained visual-field defects, peripheral spasms were observed. Such visual-field defects worsened in some of these patients after cold provocation and often improved after calcium-channel blocker treatment. The fact that the observed visual-field defects were not homonymous, implied the involvement of a prechiasmal lesion. The ONH of patients with the presumed ocular vasospastic syndrome is mostly normal (especially in children and young adults) (Kaiser et al., 1993a), sometimes pale, and, rarely, especially in older patients, excavated. The correlation of the optic nerve head appearance with age in the vasospastic patients suggests that these vasospasms might, indeed, be a risk factor for glaucomatous damage. In addition, such spasms may also increase the risk for other ophthalmic diseases, such as anterior ischemic optic neuropathy (Kaiser et al., 1996a), venous thrombosis in young individuals (Messerli and Flammer, 1996) or central serous chorioretinopathy (Prünte and Flammer, 1996).

6.4.3. *Vasospasms and glaucoma*

After having observed patients with vasospasms showing an increased prevalence of glaucoma (Flammer et al., 1987), we could show an

increased prevalence of vasospasms in patients with glaucoma, especially in those without increased IOP (Gasser and Flammer, 1991). These clinical observations have been confirmed by other authors (Drance et al., 1988). A relationship between headache and normal-tension glaucoma has also been described (Phelps and Corbett, 1985), although, the relationship between glaucoma and headache still remains controversial (Klein et al., 1993; Orgül and Flammer, 1994a). The observation that CO_2 can improve visual fields in some patients (Pillunat et al., 1994) points again to the probable involvement of vascular dysregulation in glaucomatous damage.

How angiospasms might lead to glaucomatous damage is still not well understood. The majority of patients with vasospastic diathesis do not develop glaucoma. Possibly, if only one blood flow regulating mechanism is perturbed, under basal conditions this can be equilibrated by others (Flammer, 1996). However, if this equilibrium is further challenged, e.g., by a blood pressure drop or by IOP increase, the system may decompensate, and the blood supply might be insufficient for a period of time. There is a further way in which angiospasms might induce glaucomatous damage. In a way similar to that in which infections shift the "target value" of body temperature, patients with vasospastic disorders might temporarily shift the "target value" of blood-flow autoregulatory mechanisms, potentially inducing tissue ischemia. This might explain a presumed insufficient autoregulation of ONH blood flow (Ulrich et al., 1988), as has been repeatedly suggested in the last 20 years (Anderson, 1996; Ernest, 1976).

6.5. *Findings in Blood-Flow Measurements*

Recent technical developments have made possible a quantification of blood flow, at least of blood-flow velocity in different tissues. The outcome of all these studies has shown that blood-flow velocities are, on average, slower in glaucoma patients than in normals. However, there is a large overlap of these two populations. In studies which compared flow parameters between high-tension and normal-tension glaucomas, normal-tension glaucoma patients tend to have lower blood-flow velocity than do those with high-tension glaucoma. Whatever method used, the intraocular blood-flow velocities have been found to be decreased in the retina (Grunwald et al., 1982; Wolf et al., 1993) as well as in the ONH (Michelson et al., 1996), but even more so in the choroid (Prünte and Flammer, 1989). Interestingly, not only the intraocular blood-flow parameters are altered, but also those of the retro-ocular vessels (Kaiser et al., 1997b). The example of the outcome of color Doppler imaging measurements is presented in Fig. 7.

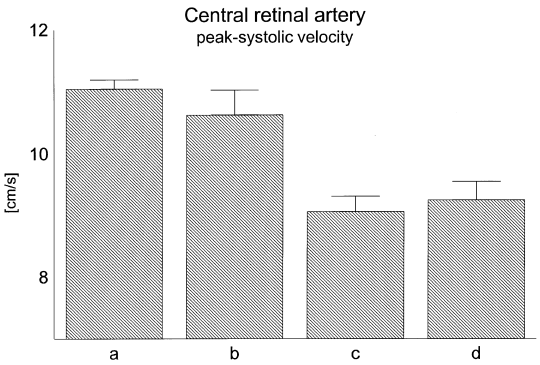

Fig. 7. Color Doppler imaging: retinal mean peak-systolic blood flow velocities in controls (a); primary open-angle glaucoma patients with ocular hypertension (b); patients with progressive primary open-angle glaucoma despite IOP within the normal range (c); and normal-tension glaucomas (d) (Kaiser *et al.*, 1996b)

Even in the systemic circulation, the blood-flow velocities seem to be decreased (Nasemann et al., 1994), especially in the capillaries (Gasser and Flammer, 1991), as described before. This indicates that the altered perfusion in the glaucomatous eyes might not, at least not exclusively, be secondary to the glaucomatous damage.

There are a number of additional observations pointing towards an underlying vascular disease, such as changes of the conjunctival vessels (Orgül and Flammer, 1995), gliosis-like retinal alterations (Graf et al., 1993), preservation of the nerve fibers around retinal vessels (Chihara and Honda, 1992), the impaired prognosis of discs with ciliary retinal vessels (Shihab et al., 1985), peripapillary vasoconstriction (Rader et al., 1994), brain ische-

mia detected by MRI (Ong et al., 1995; Stroman et al., 1995), impaired hearing in some glaucoma patients (Susanna and Basseto, 1992), and silent myocardial ischemia (Waldmann et al., 1996).

6.6. *Inter-Relationship Between Vascular Factors and IOP*

We have listed a number of vascular changes occurring in glaucoma, especially in normal-tension glaucoma. Are these factors independent of IOP? There are a number of possible relationships. Glaucoma is a multifactorial disease. Therefore, it is conceivable that the existence of one risk factor alone, such as increased IOP or vasospasms, only rarely leads to damage unless it is very pronounced. However, the concurrence of two or more risk factors, such as slightly increased IOP together with low blood pressure and vasospasms, might much more often lead to damage. In a glaucoma clinic, mostly those patients with damage get attention. This is a selection more according to damage than to risk factors. This could explain why, in a glaucoma population, risk factors very often are present simultaneously, although in the total population such factors might be independent. Furthermore, it is conceivable that an underlying disorder leading to vascular dysregulation might also influence the IOP (Wiederholt et al., 1994). The regulation of outflow channels for the aqueous humor, the ciliary muscle, and the trabecular meshwork has some similarity to that of blood vessels. Finally, not only can the arteries and capillaries be dysregulated but also the veins (Flammer, 1994). This might contribute to a number of changes, including disk hemorrhages, which probably are not a consequence of ischemia but, rather, a cause thereof (Orgül and Flammer, 1994b).

7. CONCLUSION

The phenomenology of glaucomatous damage is well known. The pathogenesis of this damage, however, is poorly understood. From clinical, as well as experimental studies, it is known that, etiologically, several factors must be involved. Besides increased IOP, vascular risk factors are especially important (Fig. 8). However, arteriosclerosis and its risk factors are of minor importance. Systemic hypertension, dyslipidemia, and diabetes are weak risk factors, if at all.

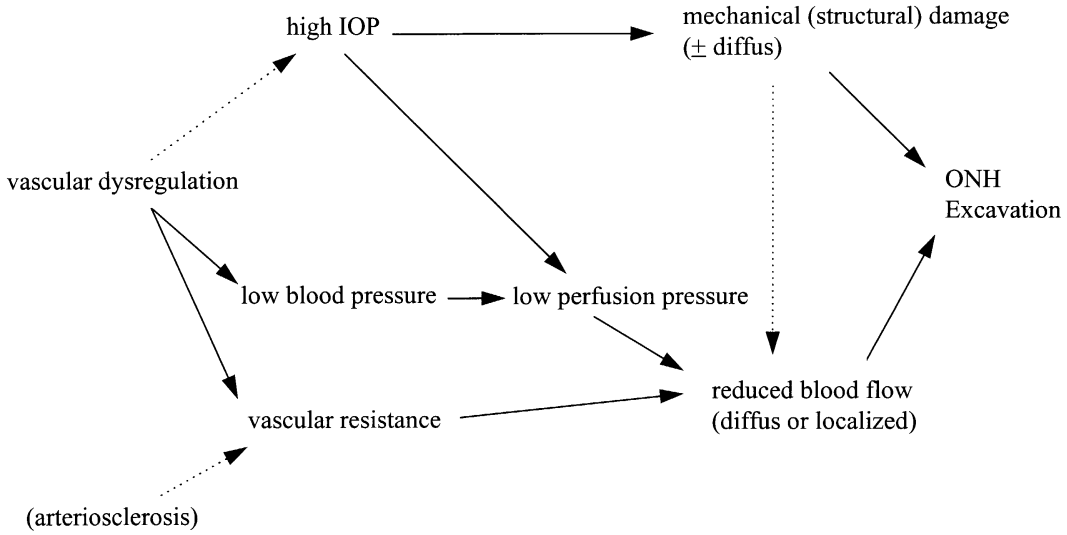

Fig. 8. Hypothetical concept for the pathogenesis of glaucomatous damage of the optic nerve head

Nonetheless, even if it occurs often in young individuals (especially in females), vascular dysregulation seems to be a major risk factor. Such dysregulation may lead to systemic hypotension and to local vasospasms, but also to a disturbed autoregulation of blood flow in the optic nerve head, choroid, and other ocular tissues. The influence of vasoactive drugs, such as calcium-channel blockers (Gaspar et al., 1994; Gasser and Flammer, 1990), gives interesting insights into the pathogenesis of glaucoma, especially into the role of vascular risk factors. Certainly, their usefulness for long-term treatment needs to be studied in more detail (Flammer, 1993).

8. FUTURE DIRECTIONS

We are convinced that the available instruments to quantify ocular blood flow will improve in the next few years. This, in turn, will allow us to study, in more detail, the physiology and pathophysiology of ocular blood flow and, specifically, of optic nerve head blood flow. This will also allow us to evaluate, more accurately, the influence of drugs.

It remains to be clarified how far the vascular disturbances are indeed primary, and to what extent they might be secondary. Furthermore, we need to establish how far these circulation disturbances are causal or just an epiphenomenon. Besides treating the known risk factors, such as increased IOP or decreased circulation, it could also be that methods will be available to protect the ganglion cells and the axons from damaging factors. All this might, hopefully, lead to a better understanding of the disease and to a more efficient prevention or even treatment of the damage.

Acknowledgements—The authors thank Dr Phillip Hendrickson for help with the editing of this manuscript.

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