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Vascular Dysregulation: A Principal Risk Factor for Glaucomatous Damage?

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Both intraocular pressure (IOP) and vascular factors appear to play an important role in the pathogenesis of glaucomatous optic neuropathy (GON). Arteriosclerosis and its risk factors are of minor importance, whereas vasospastic syndrome clearly is associated with GON. A vascular endotheliopathy seems to be involved in the diathetic hyperresponsiveness to stimuli, such as coldness or emotional stress. This in turn leads to a compromised autoregulation, and thereby renders the eye more sensitive to IOP or to a decrease in blood pressure. A variation in ocular perfusion may lead to an increase in free oxygen radicals. This may finally lead to apoptosis.

Key Words: Autoregulation—Apoptosis—Free oxygen radicals—Glaucomatous damage—Glaucomatous neuropathy—Reperfusion damage—Vascular dysregulation—Vasospasm.

Several lines of evidence suggest that tissue ischemia participates in the pathogenesis of glaucomatous optic neuropathy (GON).[1] A number of methods of measuring ocular[2] and optic nerve[3] blood flow velocity have been recently developed. Although each method carries its own limitations,[4] their application in patients with glaucoma has invariably indicated a disturbed circulation in a proportion of these patients.[5]

On average, patients with glaucoma, especially those with normal-tension glaucoma and patients with high-tension glaucoma whose disease progresses despite normalized intraocular pressure (IOP), have a slower blood flow velocity in the retina,[6] in the choroid,[7–9] and in the optic nerve head.[10] Blood flow also is reduced in retrobulbar vessels,[11] in large vessels such as the carotids,[12] and especially in the acral capillaries[13] and precapillaries.[14] Patients with glaucoma also frequently have small ischemic lesions in other organs, such as the brain,[15] the ear,[16] and the heart.[17] Therefore, at least one component of this vascular disturbance in glaucoma must be primary.[5]

This review deals with some physiologic, pathophysiologic, and pharmacologic aspects of ocular circulation in glaucoma.

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How Much Blood Flows Through an Organ?

Blood circulation in the body is under control of many mutually interdependent regulatory systems, such as the autonomic nervous system, circulating hormones, and myogenic and metabolic autoregulation. Although some regulatory mediators act directly on the vascular smooth muscle or capillary mural cells, the vascular endothelial cell layer is the major mediator for local control of vascular resistance.[18] Total body blood perfusion is equal to cardiac output, and is mainly under the control of the autonomic nervous system and circulating hormones. The distribution of the total cardiac output between the different organs of the body is regulated by the local control of vascular resistance.

To highlight the role of cardiac output, blood pressure, and local vascular resistance in the blood supply to a given organ, we can formulate a few simplified and theoretical situations. Assume the following possible conditions for any given patient:

1) Cardiac output decreases while vascular resistance throughout the body remains constant. The conse-

quence is a decrease in blood pressure and a linear decrease in perfusion in all organs.

2) Local vascular resistance decreases in all organs by an equivalent percentage while cardiac output remains unchanged. The outcome here is a decrease in blood pressure without any alteration in perfusion of the individual organs.
3) A drug selectively reduces vascular resistance in only one or a few organs, without affecting either the vascular resistance in other organs or the cardiac output. In this situation blood pressure decreases only slightly, perfusion in the affected organs increases, but perfusion in the rest of the body decreases slightly.

The conclusion that can be drawn from these different sets of conditions and consequences is that the blood supply of a given organ depends not merely on blood pressure, but rather on the cardiac output and vascular resistance of a given organ in relation to the mean vascular resistance of the rest of the body. Perfusion of a given tissue depends on the relationship between perfusion pressure and local resistance to flow. Accordingly, an assessment of the hemodynamic influence of a drug should not be based primarily on its influence on blood pressure, but rather on a knowledge of its influence on both cardiac output and especially on the vascular resistance of a given organ in relation to the overall change in vascular resistance in the body.

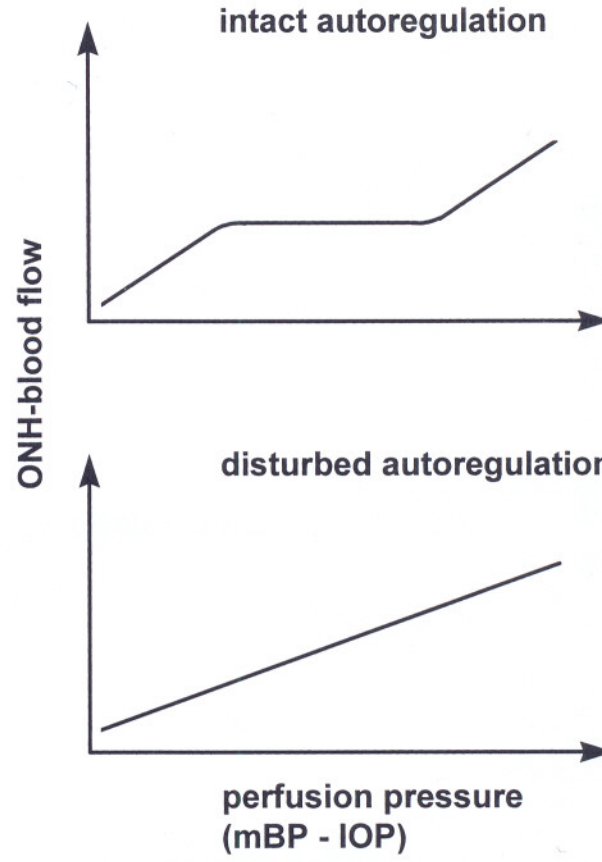

FIG. 1. Within a certain range, an intact autoregulation is capable of maintaining constant blood flow despite some variations in perfusion pressure. ONH, optic nerve head; mBP, mean blood pressure; IOP, intraocular pressure.

Regulation of Ocular Perfusion

In addition to the above-mentioned physiologic and pharmacologic principles, some specific aspects of ocular perfusion (described in detail elsewhere[19]) must be considered. First, choroidal and retinal circulation are anatomically separate and behave quite differently under physiologic and pathophysiologic conditions.

Second, the optic nerve head (ONH) circulation displays characteristics common to other circulation systems, such as: 1) the brain circulation (e.g., the blood–brain barrier and some autoregulation);[20] 2) the retinal circulation (e.g., the lack of autonomic innervation of the vessels and the blood drainage through the central retinal vein); and 3) the choroidal circulation (e.g., the arterial supply by the ciliary vessels[21,22] and some diffusion of vasoactive hormones such as angiotensin II or endothelin-1 from the choroid into the ONH, bypassing the blood–brain barrier[19,23]).

Third, perfusion pressure, defined as the difference between arterial and venous pressure, depends on IOP. The venous pressure in the orbit is approximately 8 mmHg (depending on body position). To remain distended, the pressure in the lumen of the vein must exceed that of the surrounding tissue. In the eye, venous pressure must be marginally higher than IOP.

What Could Cause Reduced Ocular Perfusion in Glaucoma?

If blood flow in the retina and ONH is well regulated,[24–28] how might these tissues become ischemic? Theoretically, there are two possibilities: either the capacity of the regulatory mechanisms (autoregulation) is exceeded, or the regulatory mechanisms are defective[29] (Fig. 1).

The former condition occurs when IOP is markedly increased or blood pressure markedly decreased. However, damage occurs in the vast majority of patients with glaucoma despite only a mild decrease in or even normal perfusion pressure. Therefore, it is reasonable to assume that autoregulation itself is defective,[30,31] which would

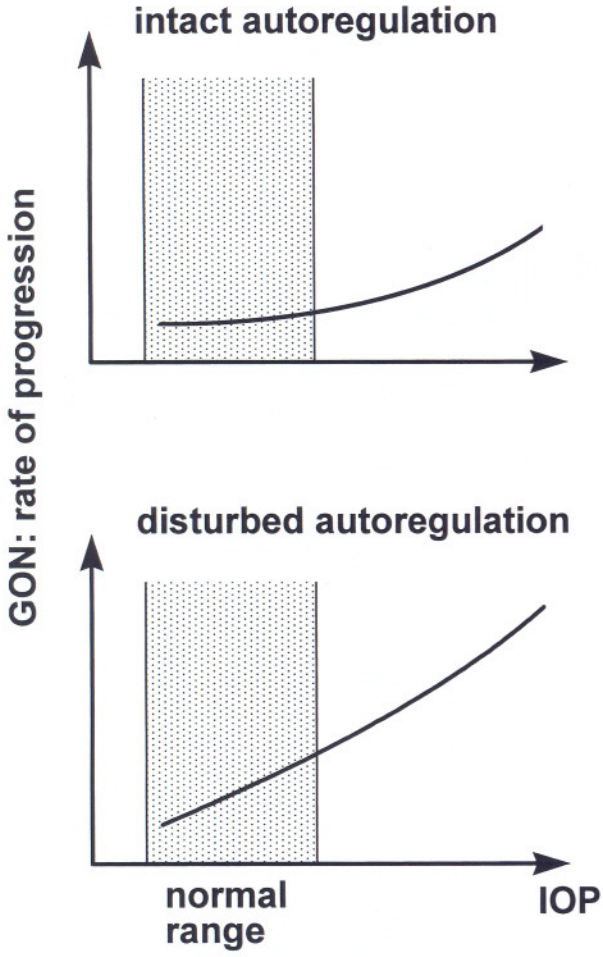

FIG. 2. If vascular and hemodynamic conditions are normal, only higher levels of intraocular pressure (IOP) may lead to glaucomatous optic neuropathy (GON) and its progression. If, however, the optic nerve head lacks autoregulation, IOP within the normal range may already be damaging.

explain why IOP plays some role even in normal-pressure glaucoma[32–35] (Fig. 2). Defective autoregulation implies an inadequate response to a challenge, such as a decrease in perfusion pressure or an increase in local metabolic need. Theoretically, deficient responses to such challenge might be due to a number of underlying conditions, such as anatomic variance of the optic nerve vasculature,[21] arteriosclerosis, or vasospastic diathesis.[36,37] It should be noted, however, that vasospasm can occur in both diseased vessels and anatomically normal vessels.

What is the Relationship Between Arteriosclerosis and Glaucomatous Damage?

Arteriosclerosis occurs in the ocular circulation relatively frequently.[38] Quantification of arteriosclerosis *in vivo,* however, is difficult, and an unequivocal appraisal of the relationship between arteriosclerosis and glaucomatous damage still has not been completed. Experimental studies indicate that arteriosclerosis might increase sensitivity to IOP,[39] and that some patients with arteriosclerosis do have a sclerotic type of glaucoma.[40]

However, there is scant evidence in the literature to support the theory that arteriosclerosis is indeed a major risk factor for glaucomatous damage (Table 1). Neither risk factors for arteriosclerosis nor arteriosclerotic alterations in the carotid vessels could be demonstrated to be clearly related to the prevalence of GON.[41–43] Levels of fibrinogen, an indicator for arteriosclerosis, are not higher in patients with glaucoma than in control subjects.[44] Risk factors for arteriosclerosis, such as hyperlipidemia[45] or smoking,[46,47] are risk factors for cataract, ocular arterial occlusions, venous occlusions, and age-related maculopathy. Although smoking seems to be related to increased IOP,[42,48,49] its association with GON or an increased sensitivity to IOP has not yet been demonstrated. Hypercholesterolemia does influence vasoreactivity,[50,51] but its relationship to glaucomatous damage in humans has not yet been established.[44,52] Increased body mass index also is a risk factor for arteriosclerosis, but patients with glaucoma tend to have a normal[53] or even low[54] body mass index. In older textbooks diabetes has been described as a major risk factor for glaucoma, but it now seems to be a minor risk factor for GON,[55] and it is not yet clear whether patients with diabetes are more sensitive to increases in IOP.[56,57]

Increased blood pressure, another risk factor for arteriosclerosis, slightly increases the risk of GON in elderly patients, but may even be protective in younger individuals.[58] Systemic hypotension, however, has long been described as a major risk factor for GON.[59–63] Tolerance to elevated IOP has been reported to be decreased in patients with systemic hypotension,[64–67] and some authors have reported lower blood pressure in patients with nor-

TABLE 1. *Risk profile for arteriosclerosis and glaucomatous optic neuropathy GON)*

Risk factors	Arteriosclerosis	GON
Fibrinogen increase	++	∅
Hypercholesterolemia	+++	∅
Smoking	+++	∅
Diabetes	+++	+
Systemic hypertension	++	(+)
Systemic hypotension	∅	+++
Body mass index		
high	+	∅
low	∅	(+)
Sex		
male	+	∅
female	∅	++

mal-tension glaucoma than in those with high-tension glaucoma.[68–71] Although arteriosclerosis tends to develop earlier and more extensively in men than in women,[72] women have normal-pressure glaucoma more often than men[73] and exhibit more extensive glaucomatous damage than men despite similar IOP.[74]

Taken together, these observations cannot exclude the possibility of involvement of arteriosclerosis in the development of GON. However, it is obvious that arteriosclerosis does not underlie the disturbed autoregulation and decreased ocular perfusion in the majority of patients with glaucoma. Other causes of GON, such as a primary vascular dysregulation, therefore must exist.

What is the Role of Vasospastic Syndrome?

Vasospastic syndrome[36] is characterized by a constitutional increased vascular response to stimuli such as cold temperatures or emotional stress.[37] The nature of this disorder is not yet understood on a molecular level. It mainly involves the arterioles of the peripheral circulation in predisposed patients, but it also can occur in other vascular beds such as the coronary arteries.[75]

We have described ocular involvement in some patients with these vasospastic (mostly nonglaucomatous) symptoms, and introduced the term "presumed ocular vasospastic syndrome."[76–80] We further demonstrated presumed ocular vasospastic syndrome to be a risk factor for anterior ischemic optic neuropathy,[81] retinal venous occlusion,[82] central serous chorioretinopathy,[83] and especially for glaucoma.[13,84,85] Indeed, close to half of the patients who exhibit GON despite normal IOP, and many patients who exhibit glaucomatous damage at only slightly elevated IOP, may have a vasospastic diathesis.[5] The risk profile for GON is quite different from that of some other eye diseases (Table 2).

The well described association between systemic hypotension and GON also should be considered within the context of a vascular dysregulation. In patients with vasospastic diathesis there is an increased prevalence of systemic hypotension. In patients with glaucoma, the

TABLE 2. *Currently known associations between eye diseases and arteriosclerosis and vascular dysregulation*

	Arteriosclerosis	Vascular dysregulation
Cataract	+++	∅
SMD	+++	∅
Retinal arteriolar occlusion	+++	+
Retinal venous occlusion	++	+
Serous chorioretinopathy	∅	++
Glaucomatous optic neuropathy	(+)	+++

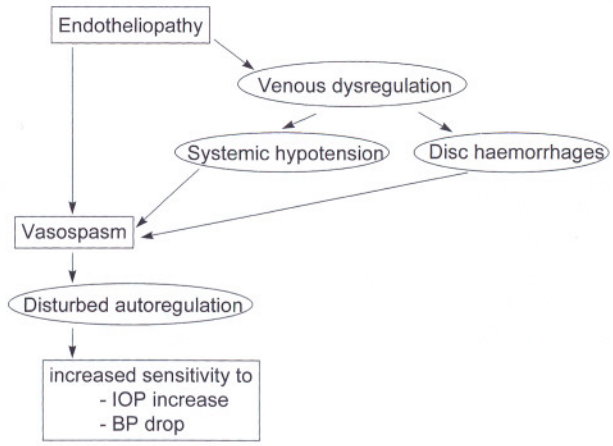

FIG. 3. Endothelial dysfunction may lead to increased sensitivity of the eye to increases in intraocular pressure (IOP) or decreases in blood pressure.

sensitivity to endothelin, the plasma concentration of which is higher in patients with glaucoma than in control subjects,[86,87] is inversely related to blood pressure.[88] This indicates that decreases in blood pressure not only result in decreased perfusion pressure but also, in predisposed patients, can result in increased local vascular resistance.[5] This in turn might explain why some patients with very low blood pressure but no vasospastic diathesis do not exhibit GON, whereas patients with vasospastic diathesis but only mild systemic hypotension do.[1]

Although we do not understand the basic underlying disorder in patients with vasospastic diathesis, there are some indications that it could be due at least in part to a vascular endotheliopathy[19] (Fig. 3). Patients with normal-pressure glaucoma exhibit impaired production of cyclic guanine monophosphate (cGMP)[89] and a de-

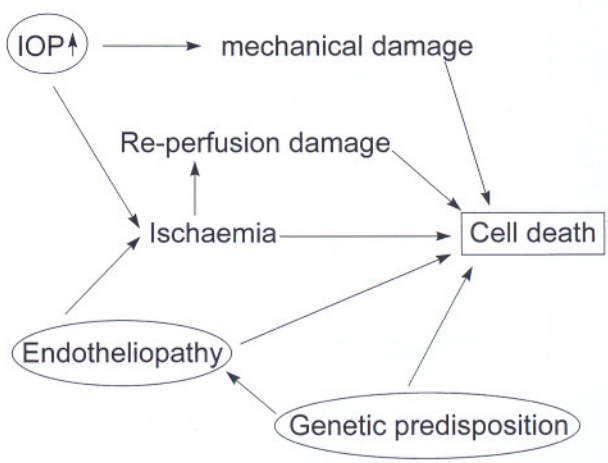

FIG. 4. Possible mechanisms whereby intraocular pressure and endotheliopathy may lead to cell death in glaucoma.

creased response to the endothelium-dependent vasodilator acetylcholine.[90]

A final important issue concerns the reason why a vasospastic disorder is more harmful than arteriosclerosis to the ONH. There are several possible explanations. First, increased vascular resistance due to arteriosclerosis in larger and mid-sized vessels may be compensated for by reduced resistance in small arterioles and capillaries.[20] Second, perfusion may vary more dramatically in patients with vasospastic disorders and lead to reperfusion damage[91] (Fig. 4). Finally, the underlying endotheliopathy may have additional effects, such as a disturbance of the interaction between endothelial cells and astrocytes.[19]

Therapeutic Approaches

Theoretically, there are several strategies for the prevention of GON: IOP reduction; blood pressure increase; treatment of vascular dysregulation; and protection of neural and glial cells from ischemic lesions or reperfusion damage. Whereas reduction of IOP is clinically routine, the other approaches are still under investigation (Fig. 5).

The benefit of an increase in blood pressure might depend on how it is achieved. Blood pressure can be stabilized in some patients by an increase of physical activity and increased intake of salt and water.[85] If this is insufficient, patients can be treated with a low dosage of fludrocortisone.[92,93] Results from controlled studies have yet to be obtained. Vascular dysregulation can be influenced by a low dose of calcium channel blockers.[94,95] High dosages of calcium channel blockers, as are used to treat systemic hypertension, can have severe side effects.[96,97] These side effects, however, are observed mostly in patients with arteriosclerosis and particularly in patients with diabetes,[98,99] and are dose dependent.[100] Clinical experience[5] and experimental studies[101] have shown that very low dosages of calcium channel blockers, such as 5 mg nifedipine, can prevent vasospasm, especially an endothelin-1-induced spasm.[101–104] These low dosages have no or only very little influence on blood pressure. Because the typical patient with vasospasm and glaucoma is relatively young and has neither arteriosclerosis or diabetes, low doses of a calcium channel blocker is an appropriate therapy for selected cases with severe vasospasm.

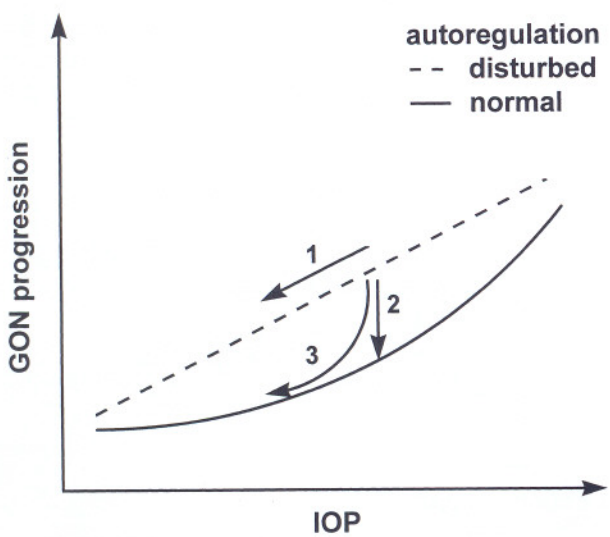

FIG. 5. Theoretically, three approaches should be considered for treatment of patients with glaucoma who have defective autoregulation: 1) reduction of intraocular pressure (IOP); 2) normalization of autoregulation; and 3) a combination of 1 and 2. GON, glaucomatous optic neuropathy.

Observations that nifedipine and other calcium channel blockers improved visual fields in patients (most of them without glaucoma) provided important indirect evidence for the involvement of the eye in vasospastic syndrome in some patients.[78,105] However, whether patients with glaucoma benefit from long-term treatment with calcium channel blockers remains an open question.[106] Clinical experience indicates that the only patients who benefit from such long-term treatment are those with well established vasospasm[95,107] in whom extensive systemic hypotension has been excluded or treated.

Magnesium also is capable of resolving endothelin-1-induced spasm,[108] but its usefulness in patients with glaucoma has not yet been proven.[109] Endothelin blockers will soon become available for clinical use, and theoretically, we can expect some benefit from these drugs. Dipyridamol also increases ocular perfusion both *in vitro*[110] and *in vivo*,[111] but again, it is not known whether patients with glaucoma benefit from this treatment. For treatment of severe spasm in children, a low dosage of propranolol, a beta blocker with some calcium antagonistic effects, has been proposed.[112] Collectively, the drugs currently available for the therapy of GON are not optimal, and the search for safe and more effective treatments should continue.

Conclusion

Phenomenologically, GON is well characterized. Its pathogenesis, however, is still poorly understood. Both IOP and vascular factors appear to play an important role. Surprisingly, arteriosclerosis and its risk factors are of minor importance, whereas the so-called vasospastic syndrome is clearly associated with GON. A vascular

endotheliopathy seems to be involved in this diathetic hyperresponsiveness to stimuli such as coldness or emotional stress. This in turn could lead to compromised autoregulation, and thereby render the eye more sensitive to an increase in IOP or a decrease in blood pressure. It is uncertain whether damage to the ONH and ganglion cells is a consequence of ischemia, reperfusion injury, or disturbed communication between endothelial and glial cells.

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