The Vascular Concept of Glaucoma

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Abstract. The regulation of ocular perfusion is different for different parts of the eye. Observations on the retina can, therefore, not be extrapolated to the optic nerve head. Extraocular vessels, especially the short posterior ciliary arteries, might play a major role in regulation of ocular circulation, but additional regulation takes place in the eye itself. Dysregulation might be transient and, thus, not necessarily present and detectable at any one examination. Older patients with arteriosclerotic vessels may behave differently in this regard than do young, healthy animals. Not only the arterial but also the venous side of the circulation may be disturbed. Disk hemorrhages can not only be a sign of damage; they can also provoke ischemia. Besides hypoxia, diseased vessel walls might play a direct role in the pathogenesis of optic nerve head cupping. Finally, a relation between vascular dysregulation and aqueous-humor dynamics is conceivable. **(Surv Ophthalmol 38 [Suppl, May]:** S3–S6, 1994)

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There is evidence both from experimental studies and from clinical observations that increased intraocular pressure alters structural and neural elements of the optic nerve head. This, however, does not imply an identical pathomechanism in chronic primary open-angle glaucoma and in normal-tension glaucoma.

What Challenges the Pressure Theory?

Three of the many observations which can not be explained by a pure pressure theory are stated below.

1) In Japan, although the incidence of glaucomatous optic nerve head damage increases with age at about the same rate as it does in America or Europe, intraocular pressure (in contrast to the West) actually diminishes with advancing age.[37]

2) The average intraocular pressures of blacks and whites are about the same, yet the prevalence of glaucomatous damage is more than four times higher in blacks.[38]

3) Although men and women have about the same intraocular pressure, the prevalence of normal-tension glaucoma in females is double that in males.[28]

Besides an increased intraocular pressure, what separates glaucoma from normals? Many clinical and laboratory parameters have been described to be on the average different in chronic glaucoma patients compared to normals. The main factors are hemodynamic variables. Besides a few reports on rheological factors,[24] most investigations have dealt with vascular factors, such as *decreased* blood pressure,[18] ciliary perfusion pressure,[30] blood-cell velocity in the finger,[11] blood-cell velocity in the ophthalmic arteries,[33] intraocular pressure tolerance (pulse reactance curve),[42] and *increased* prevalence of cardial ischemia.[19] Hemodynamic alterations, therefore, may – independent from or in concert with intraocular pressure – damage the optic nerve head.[7]

How is Blood Flow Regulated in the Optic Nerve Head?

Let us for a moment concentrate on the regulation of the ocular circulation. The blood flow in every organ is a function of perfusion pressure and (inversely) of local resistance. Perfusion pressure in the eye equals local blood pressure minus intraocular pressure. Let us have a closer look at these variables. The resistance to flow (regulated by the size of the vessels) is not a con-

stant factor. It is, rather, dynamically regulated according to the need of the tissue. As the need of the optic nerve head might be more or less constant, the resistance is regulated to keep the flow constant, despite variations in perfusion pressure.[31] This phenomenon is termed autoregulation. Such regulation is not achieved by just one mechanism. It is, rather, the balanced result of many vasoconstrictive and vasodilatative mechanisms, occurring in different parts of the vessels, including the capillaries.

What Could be Wrong in the Local Regulation?

If, among many mechanisms, only one is disturbed (e.g., a depressed nitric oxide production in the endothelium cell layer[4]), this can, under normal conditions, be equilibrated by others. However, when the regulation is challenged, e.g., by a blood-pressure drop, the blood supply might be insufficient for a period of time. Instead of always being present, such disturbances might be transient, as is, for example, the depressed circulation in the brain at the beginning of migraine attack. However, even when the autoregulation is intact, the "target value" might vary. Let me again illustrate this with another biological example: Our body temperature is autoregulated. An infection shifts the "target value," and this shift is influenced by drugs, e.g., aspirin. Similarly, it is conceivable that patients with vasospastic disorders[13] may shift their "target value," and this might also be influenced by drugs.[21]

What Role Does the Blood Pressure Play?

Although patients with high intraocular pressure have an increased chance of systemic hypertension, those with progressive glaucomatous damage have an increased prevalence of systemic hypotension.[3,9,12,18]

Remaining to be clarified is to what extent low systemic blood pressure is a damaging factor in itself. The fact that patients with autonomic dysfunction, which causes very low blood pressure, e.g., the Shy-Drager Syndrome, very rarely develop glaucomatous damage (unpublished personal observation) indicates that regulatory mechanisms, leading to an increased local resistance, might be involved. This hypothesis is further supported by the following observations:

1) Patients with systemic hypotension are often vasospastic.[10]

2) Patients with carotid stenosis do not have related increased prevalence of glaucomatous damage.[29]

3) Drugs, such as angiotensin II, although increasing blood pressure, render the optic nerve head more sensitive to intraocular pressure increases.[39] On the other hand, calcium channel blockers, although they decrease blood pressure, increase ocular circulation, especially in the optic nerve head.[16]

All this indicates that local regulatory mechanisms might be even more important in glaucoma than is perfusion pressure.

Where Does Blood Flow Regulation Take Place?

Although all parts, including the capillaries might be involved, two regions seem to be of special relevance, the extraocular posterior ciliary arteries[14,15,25,26,43] and arterioles branching from arterial circles around the optic nerve head.[40] Pillunat[30] demonstrated that in normal-tension glaucoma patients the ciliary perfusion pressure is, in comparison to normals, more decreased than is the systemic blood pressure, measured on the arm. This can be explained by an increased resistance in the extraocular ciliary arteries. We found, indeed, very potent vasoconstricting mechanisms in these vessels in humans and in pigs.[14,15,25,26,43]

Nitric oxide and endothelin seem thereby to play a major role. Sugiyama et al.[40] demonstrated local vasoconstriction in the arterial branching from the arterial circle around the optic nerve head when stimulated by phenylephrine, an alpha-1-agonist. We emphasize that one should not extrapolate from retinal circulation to optic nerve head circulation. The group of Riva[16] showed, e.g., that nicardipine, a calcium-channel blocker, increases optic nerve head circulation, but not that of the retina.

What Role do the Veins Play?

In speaking about vascular disturbances, we normally concentrate on the arterial side, but primary or secondary dysregulation on the venous side is conceivable, as well.

Robert[32] demonstrated that after a sudden increase in intraocular pressure, the baseline brightness of the optic nerve head persisted only about 0.6 seconds in glaucoma patients, but about 2.4 seconds in normals. However, normals anesthetized with halothane,[31] which is known to dilate the veins, behaved like glaucoma patients in this regard.

A dysregulation in the veins could also explain splinter hemorrhages.[5]

Are Disk Hemorrhages Consequences or Causes of Optic Nerve Head Damage?

Small disk hemorrhages are often interpreted as a sign of a microinfarction.[6] On the other hand, functional damage normally develops only some days after the appearance of local hemorrhages.[36]

Let us briefly look at another part of the body. Subarachnoidal hemorrhages provoke cerebral vasospasms.[20] Their onset is known to be delayed for several days. Many vasoconstricting factors are present in the clot.[27] Among these factors, hemoglobin,[8] which binds nitric oxide (a very potent vasodilator) is of special importance. Hemorrhages, therefore, might not be the consequence but, rather, the cause of microinfarction.

What is the Role of the Vessel Wall?

Discussing vascular factors, we normally consider ischemia to be the villain. However, this might be only one side of the coin. Why do patients with nonarteritic anterior ischemic neuropathy develop a bland atrophy (optic atrophy without excavation), whereas patients with arteritic ischemia develop optic nerve head excavation?[35] The difference is the disappearance of the glial cells in the latter group, as in glaucoma patients.

Therefore, it is possible that a disease of the vessel wall might lead to a disappearance of glial cells which might then be followed by a loss of axons. This might also explain why in some instances optic nerve head excavation precedes visual field damage. The increased prevalence of immune-related diseases in normal-tension glaucoma observed by the group of Cartwright,[2] and the increased prevalence of anticardiolipine antibodies described by our group,[41] support the hypothesis that the vessel wall might be directly involved.

What is the Relationship Between Intraocular Pressure and Vascular Regulation?

Let me finally mention another interesting aspect. Schwartz[34] observed glaucoma-like disks with subsequently increased ocular pressure. How could this be explained? While we assume that increased intraocular pressure may interfere with vascular regulation, there are also indications that vascular dysregulations may be associated with changes in aqueous humor dynamics. Mäepea[23] has shown that the aqueous outflow system is similar to the blood vessels, and the group of Lepple[22] has demonstrated an effect of endothelin on the trabecular meshwork. It is, therefore, possible that in some instances the same underlying disorder might lead to vascular insufficiency and to increased intraocular pressure. Thus, it is conceivable that in a few patients one type of disorder might precede the other.

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