Vascular Factors in Glaucoma

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INTRODUCTION

Primary open angle glaucoma (POAG) is a multifactorial optic neuropathy characterized by progressive retinal ganglion cell death and tissue remodeling of the optic nerve head (ONH). This is followed by visual-field defects corresponding to the damage of the neuroretinal rim (NRR). Prevalence of glaucoma is 0.7% in the 5th decade and it increases to 7.7% in subjects over 80 years of age.\(^1\)

Traditionally, diagnosis and treatment has been directed towards the control of increased intraocular pressure (IOP), which is the most important risk factor.

However, all patients with glaucomatous ONH damage do not have elevated IOP, and glaucomatous neuropathy may progress even at IOP in the low teens, called normal tension glaucoma (NTG). Some glaucoma patients continue to progress and subsequently develop irreversible loss of vision despite the medical lowering of IOP.

For instance, in the early manifest glaucoma trial (EMGT) the disease progression rate in the treatment group was 45% as compared to 62% in the control arm.\(^2\)

In the collaborative initial glaucoma treatment study (CIGTS) visual field progression occurred in ≥20% of participants during 8 years of follow-up.\(^3\) Specifically, increased incidence of visual field deterioration occurred with older age (increased risk of visual field (VF) loss by 40% every 10 years), race (nonwhites had a 50% increased risk relative to whites) and diabetes (59% increased risk relative to nondiabetic patients).\(^3\)

Likewise, 20% of NTG patients show continued visual field loss even after 5 years of IOP reduction treatment.\(^4\)

It is evident from these studies that the pathophysiological concept of glaucoma based only on IOP related damage is not complete. Glaucoma actually represents a spectrum where mechanical damage predominates at high IOP and vascular factors increasingly contribute to damage at lower IOP levels. However, both factors are inter-related as an increase in IOP decreases the blood flow to the optic nerve head and vice versa. Compromised ocular blood flow and deranged vascular autoregulation in the ONH is emerging as an important causative and contributing to glaucomatous optic neuropathy.\(^5\)-\(^9\)

BLOOD SUPPLY OF THE OPTIC NERVE HEAD

The optic nerve head consists of four distinct regions with a unique blood supply.\(^5\)-\(^13\) These regions, from anterior to posterior aspect, are as follows:

Surface Nerve Fiber Layer

This is the anterior most layer of the ONH. It contains the compact optic nerve fibers as they congregate from all over the retina and bend to run back. This part is essentially supplied by the retinal arterioles from the central retinal artery. However, in few cases the temporal part may be supplied by the posterior ciliary artery circulation from the underlying prelaminar region. When a cilioretinal artery is present, it
supplies the corresponding part of the surface nerve fiber layer.

**The Prelaminar Region**

This part consists of optic nerve fibers arranged in bundles, surrounded by glial tissue septa, which contain capillaries. This region is supplied mainly by centripetal branches from the peripapillary choroid in a sectoral manner. The peripapillary choriocapillaris and central retinal artery play no role in its blood supply.

**Lamina Cribrosa Region**

This forms a band of dense, compact connective tissue extending transversely across the entire width of the ONH. It is laminar in nature, with collagen bundles alternating with glial tissue. The lamina cribrosa region is supplied by centripetal branches arising directly from the short posterior ciliary arteries or from the intrascleral circle of Zinn and Haller in diameter, lie in the fibrous septa and form a dense capillary plexus which makes this part of the ONH a highly vascular structure.

**Retrolaminar Region**

This part of the optic nerve lies immediately behind the lamina cribrosa. It is enclosed by dura, arachnoid and pia. This region has centripetal and centrifugal vascular systems.

a. The centripetal system is the main and consistent vascular system, formed primarily by the recurrent pial branches from the peripapillary choroid and the Circle of Zinn and Haller (or the short posterior ciliary arteries), with additional pial branches from the central retinal artery.

b. A centrifugal system may be seen in some nerves and consists of a few inconstant branches from the central retinal artery.

In summary, the primary source of blood supply to the ONH is the posterior ciliary artery circulation via the peripapillary choroid and short posterior ciliary arteries (or the Circle of Zinn and Haller, when present).

**FACTORS INFLUENCING ONH CIRCULATION**

To understand the role of vascular insufficiency of the ONH in the pathogenesis of glaucoma, it is fundamental to understand the blood flow in the ONH in health and disease and the various factors that influence it. The blood flow depends upon three parameters: (1) vascular resistance (2) blood pressure, and (3) IOP. To calculate the ONH blood flow, the following formula is used:

\[
\text{Blood flow} = \frac{\text{Perfusion pressure}}{\text{Vascular resistance}}
\]

**Perfusion Pressure**

The perfusion pressure is essentially the difference between the mean arterial blood pressure (MABP) and the intraocular pressure (IOP):  
- MABP = Diastolic BP + 1/3 (Systolic BP - Diastolic BP)

Based on the above equation it is clear that a decrease in BP or an increase in IOP reduces perfusion pressure.

**Vascular Resistance**

The resistance of the vasculature depends upon the state and caliber of the vessels feeding the ONH circulation and rheological properties of the blood which is influenced by a large variety of hematologic disorders, particularly those causing increase in blood viscosity.

The state and caliber of the vessels feeding the ONH may be altered by many factors, including the following:

1. Autoregulation of blood flow is to maintain a relatively constant blood flow, capillary pressure and nutrient supply in spite of changes in perfusion pressure. Evidences show that blood flow in both the retina and ONH is autoregulated by neural, endothelial and myogenic mechanisms. The mediators of these mechanisms include oxygen, carbon dioxide, angiotensin – II, nitric oxide and endothelin-1. But various systemic and local factors can cause breakdown of this autoregulatory mechanism which are aging, arterial hypertension, diabetes mellitus, marked arterial hypotension from any cause, arteriosclerosis, atherosclerosis, hypercholesterolemia, vasospasm and probably regional vascular endothelial disorders.

2. Vascular endothelial vasoactive agents play an important role in modulating the local vascular tone. The vascular endothelial cells release various known endothelial vasoactive agents, which include prostanoids, nitric oxide, endothelins, angiotensins, oxygen free radicals, smooth muscle cell hyperpolarization, thromboxane A2 and other agents. Endothelial cells regulate vasomotor function not only by the vasoactive agents but can also function as mechanosensors. Pathophysiological changes in the vascular endothelial cell structure and/or function occur in most of
the major cardiovascular diseases, including atherosclerosis, diabetes mellitus, hypertension and ischemia.

3. Vascular changes in the arteries feeding the ONH circulation may be produced by vasospasm, arteriosclerosis, vasculitis, drug-induced vasoconstriction or dilatation, and a host of other systemic and cardiovascular factors.

**Arterial Blood Pressure**

It is clear from the above equation that arterial blood pressure is major factor which can affect the perfusion pressure in the ONH. Nocturnal arterial hypotension is an important risk factor for the development of ONH ischemic disorders. Therefore it is important to record the night time BP as the daytime recording gives no information about the BP during sleep. Noctural fall in BP coupled with an increase in IOP may be deleterious for the optic nerve. Over-treatment of systemic hypertension in a glaucoma patient can lead to low blood pressure and progression of optic neuropathy despite an adequately controlled IOP.

**Intraocular Pressure**

There is an inverse relationship between *IOP* and *perfusion pressure in the ONH*. Subjects those with a diastolic ocular perfusion pressure lower than 50 mm Hg had a 4 times greater risk of OAG than those with a perfusion pressure of 80 mm Hg. Lower systolic perfusion pressure more than doubled the relative risk (RR) and lower diastolic perfusion pressure (DPP) (< 55 mm Hg) more than tripled the RR of OAG.

In persons with normal BP and autoregulation, a much greater rise in IOP would be required before the ONH blood flow is compromised. By contrast, in persons with arterial hypotension, defective autoregulation or other vascular risk factors, even “normal” IOP may interfere with the ONH blood flow (e.g., in normal tension glaucoma). This mechanism is important in the pathogenesis of glaucomatous optic neuropathy, particularly in normal tension glaucoma.

Therefore a rise in IOP during sleep and concurrent development of nocturnal arterial hypotension may together constitute an important risk factor for ONH ischemia in vulnerable subjects and lead to progression of glaucoma.

**EVALUATION OF THE ONH CIRCULATION**

The measurement of ocular perfusion is must as low perfusion pressure has been implicated as an important risk factor in the various studies. The measurement of the ocular circulation is done by various imaging techniques such as color Doppler ultrasound imaging (CDI), transcranial Doppler, laser Doppler flowmetry, scanning laser Doppler flowmetry, magnetic resonance imaging, pulsatile ocular blood flow method, fluorescein fundus angiography, confocal scanning laser fluorescein angiography and retinal photography oximetry. These imaging techniques have their own limitations and none of them is currently accepted as a gold standard for measuring optic nerve head flow. Another important aspect is that one time measurements are not sufficient should be done throughout 24 hours so as to assess their variability and effect on perfusion in relation to the blood pressure.

Most of the recently advocated methods employ laser technology. All of them suffer from the fundamental flow that the laser beam in all of them is focused on the surface of the optic disk to measure the amount of blood flow in the ONH. The surface layer of the optic disk is supplied by the retinal circulation, whereas glaucomatous optic neuropathy is due vascular insufficiency in the deeper ONH circulation, supplied by the posterior ciliary artery circulation. Experimental study in monkeys have confirmed that laser Doppler flowmetry predominantly measures the blood flow in the superficial layers of the ONH supplied by the retinal circulation.

The same applies to Heidelberg retinal flowmetry (HRF), and to the laser speckle method. The other common error in blood flow measurements has been to equate blood velocity with the amount of blood flow in the ONH; blood velocity does not provide information about the quantity of blood flow unless we know the size of the lumen of the vessels (e.g. Use of color Doppler imaging). Therefore, none of the methods used so far provide scientifically valid information about the ONH blood flow and circulation.

**Ocular Blood Flow and Visual Field Defects in Normal Tension Glaucoma**

Recently, Logan et al measured tissue blood flow in a 10 pixel × 10 pixel box 200 μm from the disk margin in each quadrant, using the Heidelberg retina flowmeter (HRF, Heidelberg Engineering, Heidelberg, Germany). They reported that glaucomatous subjects had lower retinal hemodynamic values than control subjects in these areas. The retinal nerve fiber layer in the inferior sector of the retina and the tissue in the inferior sector of the ONH have been reported to have lower blood flow/unit nerve tissue volume than does the superior sector. This would mean
that the retinal ganglion cells and their axons in the inferior retina are more vulnerable to circulatory alterations than those in the superior retina. This corresponds with clinical findings that glaucomatous visual field defects are more commonly found in the superior visual field than in the inferior field.  

In addition, Yamazaki and Drance, using color Doppler imaging, reported that eyes with NTG and progressive visual field defects have significantly lower blood flow velocities and higher resistive indices in the short posterior ciliary and retinal arteries than eyes with relatively stable visual fields. These studies suggest that alterations in the circulation in glaucomatous eyes are associated with the glaucomatous visual field changes. However, only limited information is available on whether the retinal hemodynamics is altered in eyes with glaucomatous visual field changes.

Enrique Adan Sato et al determined the relationship between the blood flow parameters of the optic disk rim, measured with the Heidelberg retina flowmeter (HRF) and the glaucomatous visual field changes in 54 eyes of 54 patients with normal-tension glaucoma (NTG). Patients were selected whose visual field defects were confined to either the superior or inferior hemifield. Blood flow measurements were made in a 10° × 2.5° area of the superior and inferior neuroretinal rim within the optic disk. The mean blood flow (MBF) was calculated by the automatic full-field perfusion image analyzer program, and the ratio of the MBF in the superior to the inferior rim areas (the S/I ratio) was calculated from the same HRF image in order to minimize the variation in measurement conditions. They found out that the inferior rim blood flow was less than superior rim blood flow in patients with superior hemifield defect, and superior rim blood flow was reduced compared to inferior in patients with inferior hemifield defect. The mean S/I ratios of the MBF in the patients with superior hemifield defect was significantly higher than that in the patients with inferior hemifield defect and they concluded that the blood flow in the neuroretinal rim was found to correspond to the regional visual field defect in eyes with NTG. Reductions in flow were associated with reductions in function.

Clinical Significance of Ocular Perfusion Pressure in the Diagnosis and Management of Glaucoma

It has been reported that ocular perfusion pressure may affect an individual patient’s risk of developing and/or progression of glaucoma but currently there are multiple challenges to and limitations of accepting this concept.

Facts Favoring the Measurement of Ocular Perfusion Pressure in Glaucoma

1. Dysfunction of systemic vascular endothelium influence progression of OAG.
2. Glaucoma, especially normal-tension glaucoma, is significantly associated with the occurrence of episodic asymptomatic myocardial ischemias.
3. Importance of oxidative stress factors and mitochondrial function in OAG.
4. Increasing ocular circulation improves oxidative stress in retinal tissues.\(^{39-40}\)
5. OAG patients have abnormal autoregulatory response to changes in perfusion pressure.\(^{39-40}\)
6. Documented role of OPP in progression of glaucoma in population based studies.\(^{41,42}\)
7. Patients with NTG showed increased variability of nighttime blood pressure measurements.\(^{43}\)

**Facts Against the Measurement of Ocular Perfusion Pressure in Glaucoma**

1. Conflicting results of Beijing eye study which did not demonstrate the association of OAG with SBP, DBP or ocular perfusion pressure.\(^{44}\)
2. Brachial blood pressure unlikely to reflect true perfusion pressure at the optic nerve head.
3. Diurnal variation in IOP and BP
4. Lack of universally accepted position (sitting or standing) to measure BP
5. Influence of other variables on ocular perfusion pressure.\(^{45}\)

**Blood Pressure Lowering Medication and IOP**

The Thessaloniki Eye Study report involving 232 non-glaucoma subjects examined with the Heidelberg Retina Tomograph, showed that low diastolic PP, low diastolic BP and the use of BP-lowering agents were significantly associated with increased cupping and decreased rim area only in subjects with decreased diastolic BP (< 90 mm Hg) as a result of antihypertensive treatment.\(^{46}\) Similarly, in the Rotterdam Study low diastolic PP was associated with increased glaucoma prevalence only in subjects treated for hypertension.\(^{47}\) The type and duration of BP-lowering treatment may also contribute to glaucoma risk. In the European glaucoma prevention study the use of diuretics was an independent risk factor for OAG incidence (OR, 2.41; 95% CI, 1.12-5.19).\(^{48}\) The type of BP-lowering treatment may be an additional variable to consider when assessing PP.

**CONCLUSIONS**

Evidence from the literature may support an age independent positive association between BP and IOP. Understanding PP and its role in glaucoma could provide some insight into how these variables interfere, keeping in mind the apparent complexity of the interaction of PP with other potential risk factors for glaucoma. The role of PP in glaucoma pathogenesis thus warrants further research and cannot be currently considered in the assessment of an individual patient.\(^{49}\)

Following a review and interpretation of selected literature and the results of a 1-day group discussion involving glaucoma researchers and specialists with expertise in epidemiology, blood flow measurements, and cardiovascular physiology; Caprioli et al reported that accurate, reproducible, and clinically relevant measurements of blood flow within the optic nerve head and associated capillary beds are not fully achievable with current methodology.\(^{50}\)

Vascular factors may be important in a subgroup of patients with primary open-angle glaucoma, and particularly in patients with normal-tension glaucoma and evidence of vasospasm. Low ocular perfusion pressure and low blood pressure are associated with an increased risk of glaucoma in population-based studies. However, there is no evidence to support the value of increasing a patient’s blood pressure as therapy for glaucoma, and we lack crucial information about the microvascular beds in which perfusion is important in glaucoma, and the appropriate methods to evaluate their blood flow. There are also cardiovascular safety concerns associated with treatments designed to increase ocular perfusion pressure and blood flow by increasing blood pressure, especially in elderly patients.\(^{50}\)

Leske et al also concluded that current evidence supports the role of vascular factors as part of the multifactorial etiology of OAG. Since ocular perfusion pressure reflects the vascular status at the optic disk, it may be more relevant than systemic blood pressure alone. While the associations of OAG to perfusion pressure are strong, consistent and biologically plausible, they require careful interpretation. The evidence implicating a vascular etiology in OAG is mounting, but the clinical implications for patient management are still uncertain.\(^{51}\)

To conclude, recent population based studies have described the potential effects of low ocular perfusion pressure in the development and progression of OAG. Despite conflicting reports and the definite limitations on reliably measuring ocular perfusion pressure in patients with glaucoma, more work needs to be done in patients having documented low perfusion pressure and definite progression of glaucoma. It is prudent for the ophthalmologist to evaluate the blood pressure in all glaucoma patients, especially in normal pressure glaucoma, POAG patients with documented...
progression and those with coexisting systemic microvascular diseases. Patients on systemic anti-hypertensives with a low diastolic pressure or DPP < 50 mm Hg should be referred to the cardiologist for improving the perfusion of the optic nerve head.

REFERENCES

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“"I don’t know what your destiny will be, but one thing I do know; the only ones among you who will really be happy are those who have sought and found how to serve”

—Albert Schweitzer