OCULAR BLOOD FLOW AND GLAUCOMA

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Primary open angle glaucoma **(OAG)** is a multi-factorial 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.

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, the so 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. .

In the collaborative initial glaucoma treatment study **(CIGTS)** substantial visual field loss occurred in 10-13.5% of participants during 5 years of follow-up. Specifically, increased incidence of visual field deterioration occurred with older age (increased risk of VF loss by 40% every 10 years), race (nonwhites had a 50% increased risk relative to whites) and diabetes (59% increased risk relative to non-diabetic patients). Likewise, 20% of normal tension glaucoma (NTG) patients show continued visual field loss even after 5 years of IOP reduction treatment.

Therefore these facts doubt the pathophysiological concept of glaucoma based only on IOP, and compel us to contemplate to find other associated factors causing damage and subsequent progression of the disease.

Compromised ocular blood flow and deranged vascular autoregulation in the ONH is emerging as the most important factors in the various studies throughout the world. Mounting evidence suggests that glaucoma patients have reduced blood flow to the retina, choroid and optic nerve. Still it is not yet known whether the vascular component is consequent to increased IOP or the two risk factors are independently acting to affect the ONH damage in the long run. Some of the vascular risk factors which may be related to OAG pathogenesis include: aging, systemic blood pressure, nocturnal hypotension, ocular perfusion pressure, migraine, disk hemorrhage, diabetes and directly assessed reductions of ocular blood flow.

Pathophysiology of Various Factors that Influence the 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.

To calculate the ONH blood flow, the following formula is used:

$$\text{Blood Flow} = \frac{\text{Perfusion pressure}}{\text{Vascular Resistance}}$$

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Perfusion pressure- When we deduct IOP from mean arterial blood pressure (MABP) then we get perfusion pressure.

- **Perfusion Pressure = MABP - IOP**
- **MABP = Diastolic BP + 1/3 (Systolic BP - Diastolic BP)**

Based on the above equation we can say that decrease in BP or increase in IOP reduces perfusion pressure.

The blood flow depends upon three parameters: (1) vascular resistance, (2) BP, and (3) IOP.

Vascular Resistance: It 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 increased blood viscosity.

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.

Intraocular pressure: There is an inverse relationship between IOP and perfusion pressure in the ONH. 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. A rise of IOP during sleep and concurrent development of nocturnal arterial hypotension may together constitute an important hidden risk factor for ONH ischemia in vulnerable subjects.

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 OBF imaging techniques which are relatively complicated. These are transcranial Doppler, laser Doppler flowmetry, scanning laser Doppler flowmetry, magnetic resonance imaging, pulsatile ocular blood flow method (Figure 1), color Doppler ultrasound imaging (CDI) (Figure 2), fluorescein fundus angiography, confocal scanning laser fluorescein angiography, retinal photography oximetry and temperature measurement. These imaging techniques reveal the information which is not always valid scientifically and these methods have there own limitations. Another important aspect is that the measurements should be done throughout 24 hours so as to assess there variability.

We will describe two important techniques with which we are exposed to:

Pulsatile ocular blood flow:

This is the technique measured with Pneumotonometer (Figure 1) in which pulsatile waveform is created with each heart beat. Seventy percent of the total blood flow is measured by pneumotonometer. It is a well known fact that central retinal artery circulation accounts only 10% of the total ocular blood flow and rest of the circulation is formed by the posterior ciliary artery. Eighty five percent of the total ocular blood flow is made up of the ciliary circulation[24,25] and it is the main supply of the optic nerve head and therefore POBF has got importance in the glaucomatous damage. It utilizes the pressure-volume relationship as described by Langham and Toney, and Silver et al is relevant in investigating blood flow in choroidal circulation.

Color Doppler Imaging (CDI):

It detects changes in the frequency of sound reflected from flowing blood, allowing estimation of flow velocity. A simultaneous B-mode imaging and pulse wave Doppler facility is achieved with the help of high frequency probes of 7.5-10 mHz frequency. Colour doppler is applied on the B-scan image to identify the desired vessel which is next interrogated by placing a sample volume curser angled approx 60 to the flow, and a waveform is obtained. The vessels imaged are Ophthalmic artery (figure 3), Central retinal artery (figure 4), Short and long posterior ciliary arteries (figure 5).

Effect of Systemic Medications on Ocular Blood Flow

It has been found that certain drugs can affect OBF. These drugs are following:

1. **Antihypertensive medications:** It has been found that centrally acting calcium channel blockers nimodipine and lomerizine increase ocular blood flow whereas the peripherally acting like nifedipine do not cause. Other studies also suggest that angiotensin converting enzymes may lead to increase in the blood flow along with the decreasing IOP; although no study is done in the glaucoma patients.
2. **Estrogens:** It was found in Rotterdam eye study that the females on Hormone replacement therapy and post menopausal are at lesser risk of developing glaucoma. [32] These are also known to be neuroprotective.
3. **Nitric oxide:** It is a mediator of vasodilatory response to Bradykinin, histamine, acetylecholine, substance P, and insulin. Nitric oxide synthase reduces the choroidal and optic nerve head blood flow besides causing decrease in the choroidal blood flow while going into dark from light.
4. **Ginko biloba extract:** It has been showed as a neuroprotective for retinal ganglion cells in experimental studies. It has also been found to increase normal artery blood flow in normal subjects.

Topical Medications Affecting Ocular Blood Flow

Many existing medications are able to interact with vasculature, altering ocular blood flow, therefore, it is essential that current and future medications for glaucoma be evaluated for their effect on ocular circulation.

1. Effect of dorzolamide on augmentation of OBF in the ONH: Dorzolamide, a topical carbonic anhydrase inhibitor (CAI), was one of the first topical CAIs labeled by the FDA for the treatment of glaucoma. It decreases IOP by about 18% through a block of the carbonic anhydrase enzyme at the level of the ciliary body. In POAG patients timolol does not seem to alter the ocular hemodynamics, whereas dorzolamide increases the retinal microcirculation and ocular blood flow (OBF). Increased OBF with dorzolamide is possibly caused by a direct vasodilator effect of dorzolamide and not secondary to a decrease in IOP. The pre-systolic velocity of CRA in glaucomatous eyes and the end –diastolic velocity of the ophthalmic and central retinal artery significantly increases with dorzolamide. The minimal velocity of the central retinal vein showed significantly higher values after the instillation of dorzolamide.

2. Effect of Latanoprost: A study showed that Latanoprost increases ocular blood flow besides decreasing IOP in normal subjects.

3. Beta blockers (Timolol and Betaxolol) in various studies have found not to later the ocular blood flow. The long-term treatment with ophthalmic betaxolol improves ocular hemodynamics by lowering the resistivity index of the ophthalmic artery and results in an improvement in the visual fields of patients with

NTG. In view of this positive effect on blood flow and visual function, betaxolol is recommended in the management of patients with NTG.

4. Brimonidine does not alters the ocular hemodynamics.

5. Rho kinase Inhibitors: These are newer addition to medical management of glaucoma which increase the blood flow by relaxation of smooth muscles. These are still under trial phase.

References

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