Review Article

Ocular Blood Flow and its Determination and Relevance in Glaucoma

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Although intraocular pressure (IOP) is closely linked to the pathogenesis of primary open angle glaucoma (POAG) and reduction of IOP slows down the glaucoma damage, 12% of subjunctives with controlled IOP continue to have progressive visual field loss and about 30% of glaucoma patients never experience high IOP. Clinical existence of normotensive or low tension glaucoma confounds the traditional theory that elevated IOP is the only causative factor. Also various anti glaucoma drugs to lower IOP do not always prevent disease progress. Glaucoma may not be fully addressed by lowering IOP alone but also increasing the ocular perfusion dynamics by enhancing blood supply to the ocular tissues.

Multiple techniques should be used to measure all relevant vascular beds in glaucoma such as Carotids, Choroidal circulation, retinal circulation and optic nerve head.

We discuss usefulness of some techniques such as Color Doppler imaging, scanning laser ophthalmoscope (SLO) angiography, Heidelberg retinal flowmetry, Pulsatile ocular blood flow and Laser speckle tissue circulation analyzer to determine the ocular hemodynamics.

Raised intraocular pressure (IOP) is a major risk factor in the pathogenesis of glaucoma. All major clinical trials such as Ocular Hypertension Treatment Study (OHTH)[1], Early Manifest Glaucoma Trial (EMGT)[2] and Advance Glaucoma Intervention Study (AGIS)[3] showed that reduction of IOP slows down glaucoma damage. However these trials have also indicated that despite controlled IOP a number of glaucoma patients continued to have deterioration of their visual function.

There is about 20% - 30% of glaucoma patients who have never experienced IOP of more than 20mmHg but still show glaucomatous damage. Clinical existence of Normotensive (NTG) or Low Tension Glaucoma (LTG) also confounds the traditional theory that raised IOP is the only causative factor in the pathogenesis of glaucoma.

This determines that although raised IOP is the main risk factor for visual deterioration in glaucoma patients, there are also other risk factors contributing in the pathogenesis of glaucoma.

Over the years there has been great debate among the ophthalmic community about the mechanical or vascular effect, raised IOP can exert on the retinal axonal nerve fibers. Raised IOP can have mechanical effect and can also reduce the ocular blood flow (OBF). However is this alteration of blood flow a consequence of the glaucomatous disease or a primary vascular factor causing Glaucomatous Optic Neuropathy (GON).

The reduced ocular blood flow (OBF) in glaucoma can be a primary vascular dysfunction or secondary to elevated IOP resulting in ischemia of retinal axonal fibers leading to apoptosis defined as non-metabolic programmed cell death.

What ever argument is, it is important to measure ocular blood flow (OBF) in glaucoma patients to determine its relationship with the gradual visual loss.

Blood flow in glaucoma however does not depend upon one type of circulation but rather involves multiple circulations including retina, choroid and optic nerve head. So far there is not a single device or a technique, which can measure all three circulations. Therefore one has to employ multiple techniques to study these circulations.

Retinal circulation

It is supplied by central retinal artery, which is a first branch of ophthalmic artery. It is low level of flow and high level of 0_2 extraction system. It is characterized by blood retinal barrier, inner part of which is maintained by tight endothelial junctions. The system is auto-regulated by myogenic and metabolic mediators, such as partial pressure of oxygen (PCO_2) , partial pressure of carbon dioxide (PCO_2), angiotensin II and adenosine diphosphate.

Optic Nerve Head (ONH)

The anterior part of the optic nerve is divided into superficial nerve fiber layer, the pre-laminar region, the laminar region and the retro-laminar region. The superficial nerve fiber layer is supplied from arterioles arising from central retinal artery. The temporal nerve fiber layer may have an additional supply from cilio-retinal artery when ever present. The pre-laminar region is supplied by branches of the short posterior ciliary artery and via vessels originating from circle of Zinn and Haller. The laminar region is supplied either directly by short posterior ciliary artery or via arterial circle of Zinn and Haller. The retro-laminar part of the optic disc receives numerous perforating arterioles from pia mater and occasionally small branches from central retinal artery. The optic nerve head is the only part of central nervous system, which has no proper blood – brain barrier. There is evidence that there is some diffusion from surrounding choroid into optic nerve head. This makes optic nerve head circulation sensitive to chemical molecules like endothelin-1 and angiotensin II[4].

Choroidal Circulation

The choroid is supplied by posterior ciliary arteries and accounts for 85% of total blood flow in the eye. It is characterized by very high flow and low oxygen extraction[5].

The choricapillaris have fenestration therefore leaking smaller molecules like fluorescein into sub-retinal space. The choroidal circulation is poorly auto-regulated and therefore is dependent on perfusion pressure[6] but has rich autonomic innervation.

Perfusion Pressure

Ocular blood flow depends upon the perfusion pressure, which is the difference between the pressure in the arteries entering the eye and pressure in the veins leaving the eye. The pressure in the arteries entering the eye is equivalent to the mean arterial pressure measured in the brachial artery. Mean arterial pressure is defined as the diastolic pressure plus one third of the pulse pressure (difference between systolic and diastolic pressure). The pressure in the veins leaving the eye is equivalent to the intraocular pressure.

Blood flow is reduced if mean arterial pressure is reduced or IOP is increased.

Measurement of Ocular blood flow (OBF)

There is no single technique available which can accurately assess all the relevant vascular beds in glaucoma. However there are several non-invasive techniques available, which can provide reliable and accurate information. Some of these techniques are available in our country while some are not. However it is important to know the usefulness and limitation of all these techniques.

Color Doppler imaging (CDI)

This is an ultrasound technique, which combines B-scan imaging of the tissue with color representation of blood flow based on Doppler shift. It measures blood velocity in retrobulbar vessels such as ophthalmic artery, Central retinal artery and Posterior ciliary artery. These arteries are important specifically in glaucoma as they supply blood to the Choroid and Optic nerve head. CDI is a non invasive technique facilitating quantification of retobulbar blood velocities. It does require Pupil to be dilated and is not affected by media opacity[7-9].

Scanning Laser Ophthalmoscope Angiography (SLO)

SLO is a technique producing high resolution images of fundus. It uses different filters to perform fluorescein and Indo-cyanine green (ICG) angiography recorded on videotape at a rate of 30 images per second.

SLO angiography with fluorescein is analyzed using digital video analysis equipment. The amount of time for fluorescein dye to move from proximal to a distal location on a retinal vessel is measured by quantifying the brightness in two locations. The distance between these two locations is also measured to obtain mean dye flow velocity. One can also measures arterio-venous passage time (AVP) through the retina by measuring the time between first appearance of dye in a retinal artery and its corresponding vein.

SLO with ICG dye can image the choroidal circulation, which is not possible with fluorescein dye as it flows out of choroidal wall fenestration blocking the background view. ICG absorbs mid-infrared light and binds completely to plasma proteins and also because of larger molecule size stays inside choriocapillaries.

Reduced blood flow in retina, choroid and optic nerve head has been demonstrated in glaucoma patients using angiography[10].

Delayed filling and prolonged passage time has been also shown in retinal and choriodal circulation[11].

While the reduction of retinal circulation occurs in POAG, reduction of choroidal blood flow has been noticed in NTG[12].

On ICG, local filling defects, slow filling and increased leakage has been seen on Optic nerve head[13].

Heidelberg retinal flowmetery (HRF)

This is a scanning version of laser Doppler technology which analyses the Doppler shift in laser light and measures volumetric flow in capillary beds of choroid and optic nerve head[14].

It is non invasive technique requiring clear media and good fixation. It is highly sensitive to illumination changes and eye movements.

Some workers have shown that ocular blood flow in the ONH and retina of glaucoma patients is reduced[15].

Pulsatile Ocular Blood Flow (POBF)

The blood flow to the eye varies with the cardiac cycle. The choroidal volume and IOP are highest during systole and lowest during diastole. This pulsatile component of ocular blood flow is measured by recording the amplitude of IOP pulse wave causing changes in the ocular volume. The shortcoming of this technique is that it is influenced by scleral rigidity.

Reduced POBF has been observed in patient with POAG and NTG[16].

Laser Speckle Tissue Circulation Analyzer

This technique is developed in Japan and is based on the principle that a random speckle pattern in created when laser light is shown on retinal blood vessels. It measures blood flow indirectly by taking advantages of an optical effect.

This technique is mostly used to see the effect of Unoprostone and Timoptol on the ocular blood flow[17]

Ocular blood flow in Glaucoma

Various researchers have found reduced ocular perfusion in glaucoma patients with blood flow decreasing with increasing damage. There is reduction in blood flow involving optic nerve head, choroid and retina. Blood flow disturbances are more pronounced in Normal tension glaucoma than POAG[18]. It has also been shown that blood flow reduction is more marked in progressive than in non progressive eye[19].

Some reservations about these finding are that different workers have used different techniques measuring different aspects of ocular circulation. And this also involves different type of glaucoma at different stages of progression.

Topical medications influencing the ocular blood flow

Topical beta blockers

All topical beta blockers possess Ca++ channel blocking property. Betaxolol, a selective B 1 receptor blocker however exerts this property to its maximum. It has special Ca ++ channel blocking property for the voltage dependent Ca++ channels. By blocking the Ca++ channels, Betaxolol diminishes the Ca++ influx across the cell wall of smooth muscle cells and pericytes causing vasodilatation of the contracted vessels.

In several studies using Color Doppler imaging, increasing blood velocity and decreased resistance

index were found in retrobulbar and ocular vessels after the topical instillation of Betaxolol drops[20-22]. Some observer have not found similar improvement of ocular perfusion with the use of topical Betaxolol[23,24].

Carbonic Anhydrase Inhibitors (CAI)

It has long been know that systemic administration of Acetazolamide causes increase in the cerebral blood flow. A similar effect on the ocular circulation was found after short term topical and systemic application of Acetazolamide and Brinzolamide in in-vivo animal models[25,26].

In the human studies, using topical CAIs using scanning laser Ophthalmoscope with fluorescein and ICG, the retinal arterio-venous transit time was found to be decreased and the macular capillary transport velocity increased[23,27,28].

The mechanism of the accelerated retinal perfusion seen in humans after topical use of CAIs remains unclear but is though to be related to the release of CO_2 causing vasodilatory effect.

Unoprostone

It is a synthetic docosanoid showing low affinity for prostaglandin (PG) receptors but strong property of Ca++ channel blocking. This effect leads to decrease in intracellular Ca++ causing dose dependant vascular relaxation. By using Laser speckle tissue circulation analyzer Makimoto[29] found increase microcirculatory blood flow in human ocular fundus probably due to reduction in vascular resistance.

It has been shown that decrease in choroidal blood flow induced by intravenous Endothelin -1 was neutralized by topical instillation of Unoprostone as measured with laser Doppler flowmetery and laser interflowmetery[30].

However in one study[31], laser Doppler flowmetery failed to record any alteration in choroidal and ONH blood flow.

CONCLUSION

The raised IOP is no longer an integral part of glaucoma as a number of glaucoma patients have their IOP within the normal range (under21mmHg). Several well designed clinical trials have demonstrated the importance of IOP reduction in halting the progression of the glaucomatous damage. However these studies also confirm the involvement of other risk factors such a vascular dysregulation.

Effective management of glaucoma therefore requires management of mechanical (IOP) and vascular (OBF) forces simultaneously.

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