Ocular Blood Flow in Glaucoma

An Essay

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Summary

Glaucoma is one of the leading causes of irreversible blindness in the World. It accounts for 13.5% of the global causes of blindness. Glaucoma is increasingly recognized as a condition for which not only elevated intraocular pressure, but also non pressure dependent risk factors are responsible. An underlying vascular etiology has been proposed in the development of glaucomatous optic neuropathy.

Glaucoma can be divided into five main subgroups; congenital glaucoma, primary open angle glaucoma, primary closed angle glaucoma, secondary open angle glaucoma (pigmentary glaucoma, exfoliation syndrome, lens related glaucoma , post-traumatic glaucoma, ghost cell glaucoma and angle recession glaucoma), secondary closed angle glaucoma (e.g. Neovascular glaucoma).

A number of conditions such as congenital glaucoma, angle closure glaucoma, or secondary glaucomas clearly show that increased intraocular pressure is sufficient to cause glaucomatous optic neuropathy. Conversely, the existence of normal tension glaucoma on one hand and patients with ocular hypertension on the other, indicate that other factors might also be involved in the pathogenesis of glaucomatous optic neuropathy, either damaging the nerve directly by poor blood

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List of Abbreviations

ATP	= Adenosine Triphosphate.
AVP	=Arteriovenous Passage.
BBB	= Blood Brain Barrier.
BP	=Blood Pressure.
CDI	=Color Doppler Imaging.
CLBF	= Canon Laser Blood Flowmetry.
CNS	=Central Nervous System.
DNA	=Deoxy Ribonucleic Acid.
EDV	= End Diastolic Velocity.
EDVFs	= Endothelial Derived Vasoactive Factors.
ES	= Exfoliation syndrome.
ET	= Endothelin.
ETC	= Electron Transport Chain.
GON	= Glaucomatous Optic Neuropathy.
HRF	= Heidelberg Retinal Flowmeter.
HTG	= High Tension Glaucoma.
ICG	= Indocyanine Green Angiography.
IOP	=Intraocular Pressure.

ITC	=Iridotrabecular Contact.
LDF	=Laser Doppler Flowmetry.
LDV	=Laser Doppler Velocimeter.
MMPs	=Matrix Metalloproteinases.
NO	=Nitric Oxide.
NOS	=Nitric Oxide synthase.
NTG	= Normal Tension Glaucoma.
O2--	=Superoxide.
OAG	=Open Angle glaucoma.
ONH	=Optic Nerve Head.
OBF	=Ocular Blood Flow.
PAC	=Primary Angle Closure.
PACS	=Primary Angle Closure Suspect.
PAS	=Peripheral Anterior Synechia.
PDS	=Pigment Dispersion Syndrome.
PEX	=Pseudoexfoliation Syndrome.
PG	=Pigmentary Glaucoma.
POAG	=Primary Open Angle Glaucoma.
POBF	= Pulsatile Ocular Blood Flow.
PP	=Perfusion Pressure.

PSV	= Peak Systolic Velocity.
PVD	=Primary Vascular Dysregulation.
TM	=Trabecular Meshwork.
ROS	=Reactive Oxygen Species.
RGCs	=Retinal Ganglion Cells.
RI	=Reperfusion Injury.
RNS	=Reactive Nitrogen Species.
RVA	=Retinal Vessel Analyzers.
SLO	= Scanning Laser ophthalmoscopic Angiography.
SVD	=secondary vascular dysregulation.

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Introduction

Glaucoma is one of the leading causes of irreversible blindness in the World. It accounts for 13.5% of the global causes of blindness. It is characterized by progressive visual field loss and distinctive excavation of the optic nerve head ***(Grieshaber and Flammer, 2005).*** The most recent World Health Organization alert estimated that more than 100 million people are glaucoma suspects, over 20 million suffer from glaucoma and over 5 million people are blind as a result of the disease ***(Januleviciene et al., 2008).***

Glaucomatous optic neuropathy is the most common optic neuropathy, which is distinguished by progressive loss of retinal ganglion cells including their axons, and by tissue remodeling of the optic nerve head ***(Battaglia et al., 2004).*** Tissue remodeling involving both the optic nerve head and the retina. This leads clinically to a visible cupping of the disc and measurable thinning of the nerve fiber layer of the retina. The glaucomatous patients experience progressive visual field damage along with a decrease in contrast and color sensitivity ***(Mozaffrieh et al., 2008).***

Glaucoma is increasingly recognized as a condition for which not only elevated intraocular pressure, but also non pressure dependent risk factors are responsible. An underlying

vascular etiology has been proposed in the development of glaucomatous optic neuropathy. Evidence of a vascular failure leading to circulatory alterations of the optic nerve head, the retina, the choroid, or the retrobulbar vessels has been found in both primary open-angle glaucoma and normal tension glaucoma. However, the exact nature of such a vascular failure is not clear. Various vasogenic pathomechanisms such as, atherosclerosis, small vessel disease, vasospasm, autoregulatory dysfunction, or other factors have all been considered to contribute to the nerve fiber layer loss in glaucomatous optic neuropathy ***(Delaney et al., 2006).***

Reduction in ocular blood flow has been shown in both cross-sectional and prospective glaucoma studies. Vasospasm, in all its forms, has been consistently described in patients with glaucoma, particularly in normal tension glaucoma, in which migraine is an independent risk factor for field progression. In addition, systemic vascular endothelial dysfunction has been documented in normal tension glaucoma. Vascular dysfunction is an important factor in the pathogenesis of glaucoma. In the clinical context, a simple question about a history of cold hands/feet or migraine should alert the clinician to the possible role of vasospasm in individual patients with glaucoma ***(Delaney et al., 2006).***

The regulation of retinal blood flow is very similar to the regulation of blood flow in the brain, with the exception that retinal vessels have no autonomic innervation and therefore its regulation depends even more on the activity of endothelial cells. These cells release a number of factors, the so-called endothelium derived vasoactive factors, which on one hand regulate the size of the vessels by influencing vascular smooth muscle cells locally, and on the other hand, via intraluminal release of these factors influencing platelet aggregation and the size of the vessels globally. In addition, both the neural and glial cells, also influences the size of the vessels. This is known as neurovascular coupling ***(Mozaffarieh et al., 2008a).***

Unfortunately, various and numerous techniques appraising different aspects of the ocular circulation were used, hampering a clear understanding of the role of blood flow in glaucoma. A number of conditions such as congenital glaucoma, angle closure glaucoma, or secondary glaucomas clearly show that increased intraocular pressure is sufficient to cause glaucomatous optic neuropathy. Conversely, the existence of normal tension glaucoma on one hand and patients with ocular hypertension (increased intraocular pressure without recognizable damage) on the other, indicate that other factors might also be involved in the pathogenesis of glaucomatous optic neuropathy, either damaging the nerve

directly or rendering it more sensitive to intraocular pressure. However, the interpretation of the available data is difficult. Blood flow reduction may, at least partly, be due to secondary adaptation to a reduced demand. Furthermore, blood flow alterations have been described in various parts of the ocular circulation and it remains unclear. Circulatory disorders in parts of the eye other than the anterior optic nerve may encroach on axonal survival. Finally, the influence of additional factors such as sex, plasma levels of endothelin- 1, systemic blood pressure, and vasospasm remains to be clarified ***(Emre et al., 2004).***

Recent studies revealed that there is a higher incidence of open-angle glaucoma in men than in premenopausal women. The difference between the sexes is less pronounced after menopause. This leads to the supposition that a relationship exists between glaucoma and ovarian function loss, as estrogens are known to enhance blood flow in many tissues ***(Battaglia et al., 2004).***

Technology provides the capability to perform a more complete assessment of retinal vascular autoregulation. The relationship of dysfunctional vascular autoregulation, or dysregulation, to the pathogenesis of glaucoma has a rich history dating back more than 80 years. Quantitative studies began 50 years ago when the relationship between changes in retinal arterial diameter and changes in intraocular pressure in