THE ROLE OF OCULAR BLOOD FLOW IN THE PATHOGENESIS OF GLAUCOMA

Yulia Primitasari, Evelyn Komaratih

Ophthalmology Departement Universitas Airlangga, Surabaya
+6281234523930, yulia.spm@gmail.com

Abstract. Glaucoma is currently the second leading cause of blindness worldwide and the prevalence is expected to increase. Despite lowering of IOP, vascular risk factors, genetics, and other systemic conditions could progress the glaucoma damage. Ocular blood flow has emerged as an increasingly prevalent glaucoma risk factor in large population-based trials. Abnormal perfusion and the subsequent ischemia of the ONH play a major role in the glaucomatous damage. OBF is unstable if IOP fluctuates on a high enough or blood pressure on a low enough level to exceed temporarily the autoregulation capacity. IOP fluctuation is also related to both an increase in scotomas and an increase in diffuse visual fields damage. OBF is unstable if autoregulation itself is disturbed. In glaucoma the response of retinal and optic nerve head blood flow to flicker stimulation is reduced. Primary vascular dysregulation appears to be associated with abnormal retinal neurovascular coupling, because vasospastic subjects show a reduced response to flicker stimulation.

Keywords: ocular blood flow, glaucoma

Introduction

Glaucoma is currently the second leading cause of blindness worldwide and the prevalence is expected to increase. As the world population ages, it is expected to rise to 79.6 million by 2020. Despite its prevalence, much remains to be determined about this chronic progressive optic neuropathy. It has been over 100 years since intraocular pressure (IOP) was first included in the disease description of an optic neuropathy that resulted in blindness\(^1\). Other glaucoma risk factors that may be responsible for disease progression despite lowering of IOP include vascular risk factors, genetics, and other systemic conditions. Ocular blood flow has emerged as an increasingly prevalent glaucoma risk factor in large population-based trials. In the Rotterdam eye study, patients with an ocular perfusion pressure lower than 50 mmHg had a four times greater risk of developing open angle glaucoma (OAG) than those with a perfusion pressure of 80 mmHg. The Egna-Neumarkt study found positive correlations between systemic blood pressure and both the diagnosis of OAG and elevated IOP. It is currently unclear whether ischemia is secondary to increased IOP through faulty autoregulation of ocular blood flow or if a primary vascular component promotes damage to the optic nerve and retinal ganglion cells in certain OAG patients. Recent studies have also suggested that perfusion instability, rather than a progressive decline in ocular blood flow, may contribute to OAG\(^2\).

It is well established that the main risk factor for glaucoma is elevated intraocular pressure (IOP) and reducing IOP is effective in slowing down the progression of the disease, but some patients still progress despite adequately controlled IOP. Several studies implicated vascular risk factors in the pathogenesis of glaucoma, blood pressure (BP) and ocular perfusion pressure (OPP) being the most studied. This vascular hypothesis is based on the premise that abnormal perfusion and the subsequent ischemia of the ONH play a major role in the glaucomatous damage\(^3\). The OPP is the difference between arterial and venous BP. In the eye the venous pressure almost
equals IOP. As such the OPP can be estimated as the difference between the arterial pressure and IOP. The relationship between BP and glaucoma is complex and controversial. On the one hand some studies indicate that systemic hypertension is a risk factor for glaucoma but the other studies indicate that low systemic BP is a risk factor for development and progression of glaucoma.

Over the years, many clinical studies have detected ocular blood flow (OBF) deficits in OAG patients. Blood flow parameters in OAG patients have been shown to be reduced in the retrobulbar, retina, optic nerve head (ONH) and choroidal circulations. These vascular deficits may be one of the first manifestations of glaucoma. The vast majority of studies reveal a reduced OBF in glaucoma patients. In contrast, OBF is normal or even above normal in patients with ocular hypertension. Importantly, OBF is more reduced in normal-tension glaucoma (NTG) patients than in high-tension glaucoma patients. In other words, the lower the intraocular pressure (IOP) at which damage occurs, the higher the probability of finding reduced OBF. Furthermore, OBF is significantly more reduced in glaucoma patients with progressing disease than in patients with no progression. Several independent studies demonstrated that a reduced OBF is a risk factor for further progression. In other words, a reduced OBF has an effect similar to that of an increased IOP. OBF is unstable if IOP fluctuates on a high enough or blood pressure on a low enough level to exceed temporarily the autoregulation capacity. Indeed, IOP fluctuation is related to both an increase in scotomas and an increase in diffuse visual fields damage. OBF, however, is also unstable if autoregulation itself is disturbed. Autoregulation is the ability of a vascular bed to maintain its BF despite changes in perfusion pressure. Reduced autoregulation occurs particularly in patients who suffer from primary vascular dysregulation (PVD) syndrome. This term was introduced by Flammer describing otherwise healthy subjects that show abnormal regulation in response to temperature changes and mechanical or emotional stress. The basis for this dysregulation is not clear, but may be related to vascular endothelial dysfunction. Several observations indicate that endothelial dysfunction is associated with glaucoma. It has been proposed that disturbances in OBF in OAG are partly related to systemic vascular dysregulation. Dysfunction of the innermost layer of the blood vessels, the endothelium, is thought to play a role in this vascular dysregulation. Vascular tone and blood flow are partially regulated by the endothelium through the release of vasoactive substances such as nitric oxide and endothelin-1. In addition, both endothelin and nitric oxide (NO) are key regulators of ONH and choroidal BF at baseline and during isometric exercise. In the ONH there is evidence that glial cells play a role in autoregulatory processes. This may be related to loss of autoregulation in glaucoma, because astrocytes are considered to play a key role in tissue remodeling of the ONH. In the ONH astrocytes are involved in autoregulation during an increase in IOP.

Unfortunately, there are no pathognomonic symptoms or signs for the diagnosis of PVD. PVD tends to occur more often in females, in people with low body-mass index, and in subjects with high physical and mental activity. The leading symptoms are cold hands and feet and relatively low blood pressure, particularly at night. Interestingly, with a closer look, other signs, such as episodes of silent myocardial ischemia, altered beat-to-beat variation in electrocardiography, alteration in electroencephalography, altered gene expression in the lymphocytes, increased endothelin plasma levels, and others, can be found. When specifically asked for, these patients often indicate that they have a reduced feeling of thirst, altered drug sensitivity, increased smell sensitivity, and altered sleep behavior with a delayed sleep-onset time, in particular when they feel cold.
Pulse waves in retinal vessels propagate faster in subjects with PVD than in non-PVD subjects, which indicates that the rigidity of their retinal vessels is higher, in these patients spatial irregularity of retinal vessels is increased, neurovascular coupling is decreased, and autoregulation of OBF is disturbed. The dysfunction of the autoregulation likely depicts the causal relationship between PVD and glaucomatous damage. Unstable OBF leads to unstable oxygen supply, which in turn triggers oxidative stress. An increased concentration of superoxide anions in an area where the production of nitric oxide (NO) is increased augments the production of the very damaging molecule peroxynitrite. Indeed, the production of NO is increased in astrocytes of these patients, activated either by mechanical stress or by endothelin. Unlike superoxide, NO diffuses easily into other cells and therefore also from astrocytes into neurons and their axons.

The regulation of retinal blood flow is very similar to the regulation of blood flow in the brain, with the exception that retinal blood flow has no autonomic innervation and therefore its regulation depends even more on the activity of endothelial cells. This regulation by the endothelial cells is crucial to the cell’s ability to adapt to changes in perfusion pressure, which is known as autoregulation. Neural and glial cells also influence the size of the retinal vessels – this is known as neurovascular coupling. The regulation of blood flow in the choroid is different from that of blood flow in the retina. The choroidal vessels are extensively autonomically innervated, and the capillaries are fenestrated. In addition to providing oxygen and other molecules to the retina, the choroid regulates the temperature of the back of the eye and most likely contributes to the fine tuning of accommodation by regulation of volume. Blood flow in the optic nerve head is regulated in a similar way to that in the retina with the important exception that no efficient blood–brain barrier (BBB) exists in the optic nerve head. Consequently circulating molecules such as vasoactive hormones, enzymes, or even drugs, have direct access to the smooth muscle cells and pericytes of the vessels in the optic nerve head.

In glaucoma the response of retinal and ONH BF to flicker stimulation is reduced. Primary vascular dysregulation appears to be associated with abnormal retinal neurovascular coupling, because vasospastic subjects show a reduced response to flicker stimulation. In keeping with this idea endothelial dysfunction may be also related to the altered responses seen in glaucoma. The level of IOP, however, does not appear to be directly related to the reduced hyperemic response, because short-term elevation does not influence flicker-induced vasodilatation. Astrocytes play a key role in mediating the vasodilator response associated with neural activity. Activated astrocytes in glaucoma are also potential sources of impaired vasodilator response to flicker stimulation, although this hypothesis remains unproven.

Splinter hemorrhages were considered to be a consequence of either microinfarction or small vessel rupture. However, it is suggested that these hemorrhages are rather a consequence of a local breakdown of the blood–retinal or blood–brain barrier. If this barrier is malfunctioning, not only on the level of endothelial cells (because of increased concentrations of VEGF and endothelin), but simultaneously on the level of the basal membrane (because of increased concentration of metalloproteinase-9 [MMP-9]), then occasionally erythrocytes will escape from the vessels, which thus explains the clinical picture of hemorrhage.

Conclusion
Glaucoma is a comprehensive term for a heterogeneous disease comprising multiple etiologies. Alterations in ocular blood flow have become increasingly implicated in glaucoma disease pathology. Patients suffering from vascular impairment, and therefore, faulty regulation of blood flow may be unable to compensate for physiologic fluctuations in IOP and blood pressure to maintain ocular perfusion pressures. This may result in chronic, intermittent
ischemic and reperfusion damage to the ONH, which contributes to glaucomatous optic neuropathy. Continuing research is needed to investigate the relationship between vascular dysregulation in glaucoma patients and nonclinical outcomes such as visual function and optic nerve changes are necessary.

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