· Review ·

Alteration in ocular blood flow and its effect on the progression of glaucoma

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眼血流的变化对青光眼病情进展的影响

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摘要
青光眼是由多种因素引起的神经退行性疾病,眼压过高会损害视神经而导致永久性视力丧失。虽然青光眼的基本病理生理机制尚未确定,但眼组织如视神经,视网膜,脉络膜以及虹膜的血流改变是青光眼发病的重要危险因素。由于不同因素所引发的视神经损害的有限认知,测量方法和治疗方面缺乏,人们对青光眼的理解存在障碍。尽管研究人员在不断地积累证据,力证眼血流的变化在青光眼发病机制中起着重要的作用,但大部分情况下,对于眼血流的变化和青光眼的患病风险之间的关系,他们都持有多样甚至矛盾的结论。本文中,我们回顾了青光眼的不同方面以及眼血流在疾病发展中的影响。
关键词:眼血流;青光眼;疾病进展

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Abstract
• Glaucoma is a multifactorial neurodegenerative disease that can result in permanent vision loss by damaging optic nerves due to higher pressure in the eye. Although most of the fundamental pathophysiological mechanisms involved in glaucoma are undetermined but alteration in ocular blood flow (OBF) in tissues such as optic nerve, retina, choroid and iris is an important risk factor for glaucoma. Various factors such as limited knowledge of the factors causing optic nerve damage, confusion in the measurement assays and lack of therapies, make hindrances in the understanding of glaucoma. Researchers are continuously accumulating evidence to suggest that alterations in OBF play important role in the pathogenesis of glaucoma but most of the times they have diverse and contradictory conclusions regarding changes in the OBF and risk of glaucoma. In this article we have reviewed different aspects of glaucoma and the effect of OBF in the disease progression
• KEYWORDS: ocular blood flow; glaucoma; disease progression
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INTRODUCTION

Glaucoma is a term describing a group of ocular disorders that usually cause optic nerve damage[1]. Commonly glaucoma has no clear warning signs, it develops gradually and the change in vision is detected at an advanced stage. In recent years, the definition of glaucoma has extended to include genetic, vascular, anatomical and other systemic causes[2-3]. After cataracts, glaucoma is the second-leading cause of blindness in the world[4]. Several types of glaucoma have been reported including primary open-angle glaucoma (OAG), angle-closure glaucoma, normal tension glaucoma, pigmentary glaucoma, trauma-related glaucoma, acute glaucoma, childhood glaucoma and exfoliation syndrome. OAG and closed-angle glaucoma are the two main types of glaucoma[5-6]. There is a significant correlation between impaired vascular function and glaucoma progression;

however, the mechanisms by which vascular impairments may translate to glaucoma progression are still unclear[7].

Several clinical studies involving glaucoma patients have shown reduced ocular blood flow (OBF) in the retinal[8], retrobulbar[9], optic nerve head (ONH)[10] and choroidal[11] circulations. Various studies have reported worsened OBF in patients with primary OAG and ocular hypertension. It has also been suggested that patients with progressed glaucoma have worse ocular hemodynamics than non - progressed patients[12-13]. However, these studies did not succeed to confirm the pathogenic relationship of glaucoma with poor ocular hemodynamics. In this article we have reviewed the potential role of OBF in the progression of glaucoma.

GLAUCOMA

In 2010, there were 60.5 million people with OAG in the world, and this number is presumed to increase to 79.6 million by 2020[14-15]. Glaucoma has been classified into various types but the most clinically useful classification of the glaucoma is formulated by Barkan[16] which divides glaucoma into open-angle and angle-closure. Upon further subdivision it produces either primary or secondary glaucoma (Figure 1). Open-angle chronic glaucoma develops gradually with no pain and symptoms at the initial stages. Angle-closure glaucoma however is characterized by redness and pain with a sudden spike in intraocular pressure[17].

ANATOMY, PHYSIOLOGY AND BLOOD SUPPLY TO THE EYE

The ophthalmic artery (OA) is the first major branch of the internal carotid artery that supplies blood to the eye. The arterial input to the eye is provided by several branches from the ophthalmic artery, which is derived from the internal carotid artery. These branches include the short and long posterior ciliary arteries, the central retinal artery, and the anterior ciliary arteries[18-19]. The blood flow to the retina is supplied by retinal and choroidal circulation systems. These systems are structurally and functionally different and are derived from the OA. Blood supply to the inner retinal layers and a small part of the optic nerve is provided by the retinal circulation while the outer retinal layers and most parts of the anterior optic nerve are supplied by the choroidal vasculature[19]. Ocular circulation has a complex mechanism because of the necessity to supply different ocular structures with nutrients without interfering with the visual pathway. The OBF is highly regulated in order to adapt to changing metabolic needs during changing visual function, to compensate for varying perfusion pressures and finally to keep the temperature at the back of the eye constant[19].

ROLE OF OCULAR BLOOD FLOW AND GLAUCOMA

Process of ocular circulation involves the supply of nutrients to the ocular structures avoiding the intrusion of visual pathway. Maintenance of temperature constancy at back of the eye along adjustment of variation in visual function, metabolic needs as well as perfusion pressures is brought about by proper regulation of OBF (PMID: 12150988). In current practice, OBF seems to be an important factor involved in glaucoma

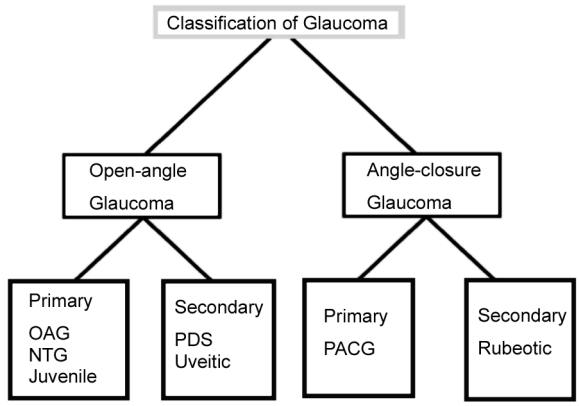

Figure 1 Classification of glaucoma Illustration of primary and secondary types of open-angle and angle-closure glaucoma. Both OAG and ACG are further subdivided into primary and secondary glaucoma. NGT and Juvenile come under OAG as primary glaucoma while pigment dispersion syndrome as secondary. Similarly rubeotic and uveitic are grouped under secondary ACG.

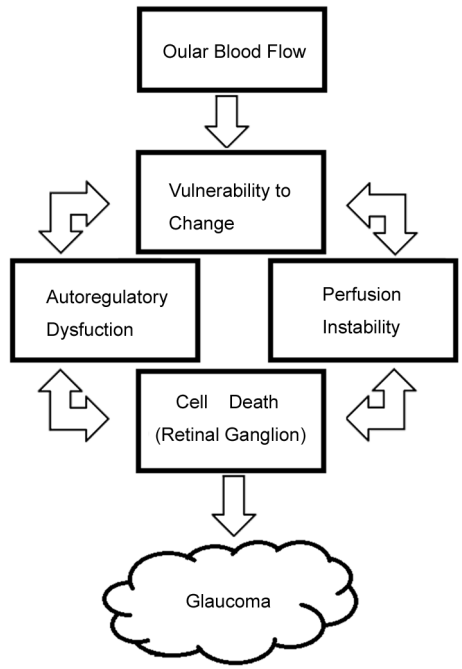

Figure 2 Ocularblood flow and glaucoma pathogenesis Illustration of reduced ocular blood flow in the pathogenesis of glaucoma and associated apoptosis.

pathogenesis (Figure 2). A large number of studies have examined the relationship between blood flow of the eye and glaucoma. OBF in various tissues (*e.g.* retina, iris, optic nerve and choroid) was found to be reduced in glaucoma patients[20]. Many clinical studies have been carried out to clarify the association of ocular blood flow and the progression of glaucoma, using different assessment techniques; however these studies have yielded partially[21]. In a study, an association between end diastolic blood velocity in the ophthalmic artery and the central retinal artery and ocular perfusion pressure was found in patients with progressive glaucoma, but not in patients with non-progressive glaucoma[22]. Such abnormal association between mean arterial pressure (MAP) and ocular blood flow parameters has

been reported in another study, indicating abnormal blood flow autoregulation in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT). During changes in posture, patients with glaucoma exhibit an abnormal response in blood velocities in the central retinal artery[23-24].

Unstable oxygen supply is reported to contribute to GON. Actually, unstable oxygen tension ultimately leads to local oxidative stress with many harmful consequences like activation of the glial cells, alteration of their morphology and expression of gene. As a result of these effects the level of nitric oxide as well as the metalloproteinases increases locally. The nitric oxide diffuses out to the neuronal axons in surrounding and fuses with the superoxide anion to produce peroxynitrite which can damage the cells. The metalloproteinases lead tissue remodelling by digesting extracellular matrix. Development of GON is brought about as a result of axon damage and tissue remodeling by nitric oxide and metalloproteinases respectively.

For decades, glaucoma was believed as nothing more than a disease associated with elevated intraocular pressure (IOP). In recent years we have come to understand that in addition to higher levels of IOP, genetic, vascular, brain and immune related factors also play role in the pathogenesis of glaucoma. A number of conditions such as angle-closure glaucoma and congenital glaucoma clearly show that increased intraocular pressure (IOP) is sufficient to lead to glaucomatous optic neuropathy (GON). Large-scale studies have validated that lowering IOP is a beneficial treatment but also that a portion of patients show progression of the disease despite low IOP[25-26]. In spite of the better understanding of several other potential risk factors, IOP pressure reduction is still the only proven treatment for the management of open-angle glaucoma (OAG)[27]. Mechanical theory states that an elevated pressure results in to elongation, stretching and ultimately collapse of the laminar beams and their posterior displacement. The axons of the retinal ganglion cells get damaged either directly by increased pressure or indirectly by the deformation of tissues. Vascular theory depicts that increased IOP may also disturb blood supply and eventually leads to tissue ischemia and finally cell death[28].

Advanced Glaucoma Intervention Study (AGIS) has reported the effect of IOP reduction after surgical intervention on the progression of visual field (VF) deficits. Reducing IOP to less than 18 mmHg, 14.4% of patients still had VF deterioration after 7y. However, Early Manifest Glaucoma Trial (EMT) has shown that treatment was helpful in slowing the progression, with 45% of the treatment group as compared with 62% of the control[26,29-32]. The Ocular Hypertension Treatment Study (OHTS) recruited 1836 patients with ocular hypertension. Patients were divided into two groups and had been followed-up for more than 6y. In one group, a 20% initial IOP decrease was achieved, while the other group was left untreated as a control group. Glaucoma development was 4.40% in the group with 20% reduction from the initial IOP, while 9.50% was observed in the control group without IOP reduction. This study showed a significant delay in the progression of glaucoma by IOP reduction, demonstrating that a target IOP reduction up to 20% of the initial value, leads to a lower rate of glaucoma progression[33-34].

Studies have revealed reduced blood flow in the choroid, retina and optic nerve head (ONH) in glaucoma patients[33-35]. Reduction of retinal blood flow usually occurs in both high-tension glaucoma (HTG) and normal-tension glaucoma (NTG) while reduction in choroidal blood flow occurs only in normal-tension glaucoma (NTG)[36]. Reduced pulsatile ocular blood flow (OBF) has also been observed in patients with primary open-angle glaucoma and normal-tension glaucoma[37-38], where reduction in OBF was more prominent in patients with visual field loss[39]. Studies have shown that breathing carbon dioxide, improved the visual field, demonstrating that the short term reversibility of visual field defects was due to improved ocular blood circulation[40]. Some studies indicate that glaucoma patients have relatively narrow arteries, particularly at the ONH border[28,41], however the exact size of the retinal vessels in diseased and control subjects is not yet determined. Heidelberg retina flowmeter (HRF) analysis suggests that OBF in the retina and ONH is reduced in glaucoma patients[33]. Though these studies were not validated by few other reports in which the same HRF method was employed[42-43].

Risk factors that may be responsible for the progression of glaucoma despite lowering OBF include vascular risk factors, genetics, and other systemic conditions[44-47]. Other vascular diseases, such as diabetes, a disease with many vascular complications[48-49] have conflicting reports about a potential role in the pathology of OAG[50], although significant correlation with diabetes has been determined by some studies[51-52]. Microvascular diseases, including systemic hypertension, peripheral vascular disease, and possibly diabetes mellitus, are associated with glaucomatous optic neuropathy[53-54]. However population-based studies, such as the Baltimore eye survey, the Barbados eye study, and the Rotterdam study failed to support an association between diabetes and OBF in glaucoma. It is also possible that diabetes and hypercholesterolemia do not directly influence ocular vascular regulation in a capacity that contributes to OAG[40]. Abnormalities in the circulation of blood to the anterior optic nerve have been cited by many investigators as potential causative factors in the development of glaucomatous optic neuropathy[40,55]. Research suggests that glaucoma patients have abnormalities in blood rheology with increased blood viscosity and reduced erythrocyte deformability[55-58]. These studies are still controversial, as the validity of the various hemodynamic measurement techniques remains under investigation.

ABNORMAL OBF AND IOP

The pathogenesis of optic nerve damage in glaucoma patients is multifactorial and attributed to a combination of mechanical and vascular factors, with intraocular pressure (IOP) playing a major role. The fluctuation of IOP with the heart rate is the ocular pulse amplitude (OPA) and the volume of the pulsatile blood that flows through the eye is directly related to the OPA[59-60]. The effect of IOP on abnormal OBF has been

investigated by a number of methods and it suggested that IOP affects both ocular blood flow[61-63]. Although the role of IOP in the progression of glaucoma is not clear, however much of our understanding relies upon the association of high IOP with that of abnormal OBF. There are many theories which can be grouped into two categories, mechanical (axonal) and ischemic (vascular) mechanisms. The mechanical mechanism suggests that increased IOP causes injuries to ganglion cells axons and their soma. According to the vascular mechanism, consequence of lamina cribrosa distortion induced by IOP elevation is the compression of blood vessels at the ONH, which in turn reduces the OPP, and producing regional hypoxia. Both mechanisms are not likely to be mutually exclusive. Many researchers support a combined vascular and mechanical theory in abnormal OBF and in the progression of glaucoma[64-70].

CONCLUSION

To summarize such studies regarding glaucoma is however difficult because alterations of the OBF and the risk of developing or worsening of glaucoma have diverse and contradictory conclusions. Decreased OBF is reportedly associated with glaucoma, but there is no evidence based procedure to support the increase in blood pressure as a therapy for glaucoma. Cardiovascular safety concerns also arise if we choose to increase the OBF by increasing blood pressure in glaucoma patients.

FUTURE PROSPECTS

Glaucoma will continue to be a sight threatening disease, unless we understand the core information and procedures associated with OBF in glaucoma. Future research must focuses on novel drugs with new action mechanism that can lower intraocular pressure (IOP) in glaucoma. Future research should also consider how to improve abnormal ocular blood flow in glaucoma patients. Stem cells can also play a key role if we increase our focus over the potential of intraocular delivery of neurotrophic factors through stem cells.

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