Autoregulation, a balancing act between supply and demand

Josef Flammer, MD; Maneli Mozaffarieh, MD

ABSTRACT • RÉSUMÉ

Regulation of blood flow is necessary to adapt to different conditions. Regulation of ocular blood flow (OBF) compensates for varying perfusion pressures (autoregulation), adapts to the retinal activity (neurovascular coupling), and keeps the back of the eye at constant temperature (thermoregulation). While all vessels are under the control of the vascular endothelial cells, the retinal vessels are additionally under the control of the neural and glial cells, and the choroidal vessels are influenced by the autonomic nervous system. The optic nerve head is additionally controlled by circulating hormones. If the regulation does not occur according to the needs of the tissue, it is referred to as vascular dysregulation. Such a dysregulation can be secondary in nature, as, for example, in multiple sclerosis, in which the high level of endothelin reduces OBF. Dysregulation, however, can also occur without any underlying disease and is characterized by an inborn tendency to respond differently to various stimuli, such as cold temperatures or mechanical or emotional stress. The constellation of these features is known as primary vascular dysregulation (PVD). Subjects with PVD have disturbed autoregulation leading to an unstable OBF. This instability, in turn, induces a repeated mild reperfusion injury. The resulting oxidative stress contributes to the pathogenesis of glaucomatous optic neuropathy.

La régulation du débit sanguin est nécessaire pour l'adaptation aux différentes conditions. Celle du débit sanguin oculaire (DSO) contrebalance les variations de pression de la perfusion (autorégulation), permet l'adaptation aux activités de la rétine (couplage neurovasculaire) et maintient l'arrière de l'œil à une température constante (thermorégulation). Si tous les vaisseaux demeurent sous le contrôle des cellules endothéliales vasculaires, les vaisseaux de la rétine sont aussi contrôlés par les cellules neurales et gliales, et les vaisseaux choroïdiens sont influencés par le système nerveux autonome. La papille optique est aussi contrôlée par les hormones en circulation. Si la régulation ne se fait pas selon les besoins des tissus, on parle alors de dysrégulation vasculaire. Une telle dysrégulation peut être naturellement secondaire comme, par exemple, dans la sclérose en plaques où le taux élevé d'endothéline réduit le DSO. La dysrégulation peut cependant survenir sans maladie sous-jacente et se caractérise par une tendance innée à répondre différemment à divers stimulus comme les températures froides ou le stress mécanique ou émotif. La constellation de ces traits est connue sous le vocable de dysrégulation vasculaire primaire (DVP). Les sujets atteints de DVP ont une autorégulation perturbée entraînant l'instabilité du DSO. À son tour, cette instabilité induit à répétition de légères blessures de reperfusion. Le stress oxydatif qui en résulte contribue à la pathogenèse de la neuropathie optique glaucomateuse.

Blood circulation serves to transport a large variety of molecules, including oxygen, cells such as leukocytes, and heat. Regulation of blood flow is necessary to adapt to the varying internal and external conditions. During exercise, for example, the oxygen demand of the muscles increases dramatically. When we move quickly from a warm to a cold environment, our circulation adapts to redistribute body temperature in order to avoid too much heat loss.

The overall blood flow is regulated by the cardiac output (Supplementary Fig. 1, available online), which is mainly controlled by the autonomic nervous system and circulating hormones. The distribution of this cardiac output (minute volume) to the different organs, or parts of organs, is regulated by the relative local resistance to flow.

Regulation of local resistance

All vessels are under the control of the vascular endothelial cells, which release vasoactive molecules. The most important molecules are nitric oxide, which induces vasodilation, and endothelin-1, which induces vasoconstriction. In addition, the vessels of the retina and the optic nerve head (ONH) are influenced by the activity of the neural and glial cells (so-called neurovascular coupling). Because of the blood–retina barrier, circulating hormones like

From the University Eye Clinic Basel, Basel, Switzerland

Presented in part at the International Ocular Blood Flow Symposium in Toronto, Ont., October 13, 2007

Originally received Dec. 13, 2007. Revised Mar. 10, 2008
Accepted for publication Mar. 13, 2008
Published online May 16, 2008

Correspondence to Josef Flammer, MD, University Eye Clinic Basel, Mittlere Str. 91, CH-4031 Basel, Switzerland; jflammer@uhbs.ch

This article has been peer-reviewed. Cet article a été évalué par les pairs.

Can J Ophthalmol 2008;43:317–21
doi:10.3129/i08-056

endothelin-1 or angiontensin II have no direct access to smooth-muscle cells and pericytes, and therefore have relatively little effect on retinal circulation. The situation is different in the choroid, which has fenestrated capillaries. Even larger molecules, such as hormones, escape the vessels and have direct access to smooth-muscle cells. These hormones in the choroid can also diffuse, to some extent, into the ONH (Fig. 1). For more information on this topic we refer to Flammer et al.[1]

Influence of circulating hormones

In a number of diseases, for example, multiple sclerosis,[2] endothelin is increased in the circulating blood. This leads to a reduction of choroidal blood flow and to some extent also to a reduction of ocular blood flow (OBF) in the ONH (Fig. 2). These diffusing molecules reach the vessels from the outside, thereby also influencing the blood–brain barrier, which in extreme situations is weakened to the extent of enabling even erythrocytes to escape from the vessels. This leads to the so-called "splinter hemorrhages" at the border of the ONH.[3]

Effect of reduced oxygen supply

Oxygen is crucial for the survival of tissues, but at the same time it is also potentially very toxic. Reactive oxidative species (ROS) damage cell structures.[4] ROS are mainly produced in the mitochondria. ROS production depends on the local oxygen tension and on the electrical potential of the mitochondria. The latter is a function of the proportion of reduced to oxidized redox carrier in the respiratory chain. If the oxygen supply is more or less constantly reduced (e.g., in the case of arteriosclerosis), the tissue can adapt to some extent to the change. If the oxygen supply is very low, however, tissue infarction may result. A reversible short drop of oxygen (Fig. 3) leads to a preconditioning.[5] In this way, the tissue can better tolerate subsequent drops of oxygen. The preconditioning is partially mediated by ROS. If the drop of oxygen is stronger, ROS production can exceed the organism's capacity to cope with free radicals (Supplementary Fig. 2, available online).[6] As a consequence, oxidative stress damages cellular structures. To some extent, these cellular structures can still be repaired (Supplementary Fig. 3, available online). If the induced damage, however, exceeds the repair capacity, structural damage will remain. After repeated insults, the structural damage accumulates, leading finally to a clinically detectable disease.

Vascular dysregulation

An insufficient oxygen supply to a certain tissue can be due to structural damage to the vessels (e.g., atherosclerosis or thrombosis) or to vascular dysregulation. Such a dysregulation can be local (e.g., due to a local dysfunction of the endothelial cells) or more or less systemic. The term "vascular dysregulation syndrome" in the context of glaucoma was first introduced by Flammer in 1994.[7] Later, a distinction was made between primary and secondary vascular dysregulation.[2] A systemic vascular dysregulation can be second-

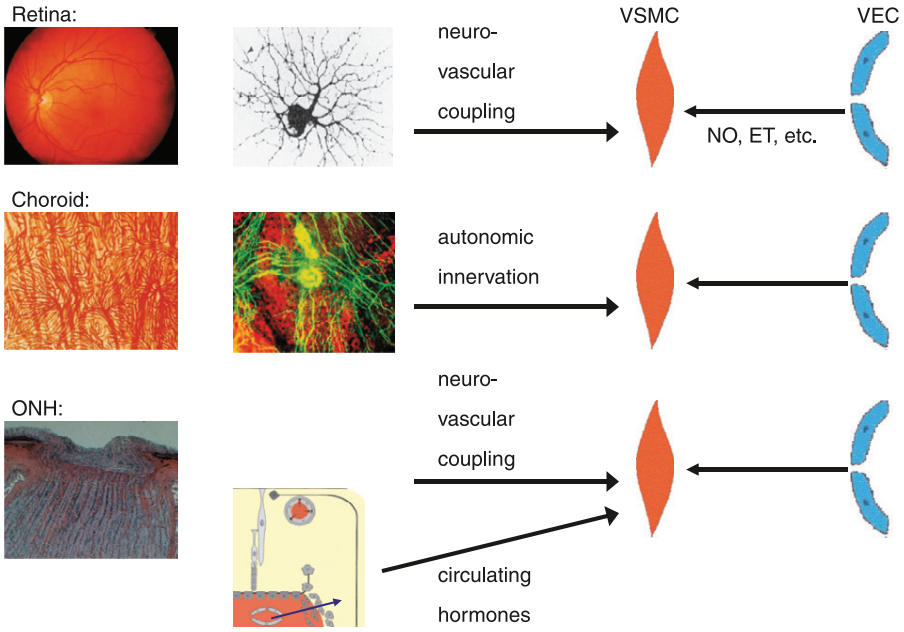

Fig. 1—Regulation of ocular blood flow (OBF): The regulation of OBF varies from one tissue to another. All vessels are under the control of the vascular endothelial cells (VECs). In addition, the vessels of the retina and optic nerve head (ONH) are influenced by neural and glial cells, whereas the vessels of the choroid are controlled by the autonomic nervous system. The vessels of the ONH are additionally influenced by circulating hormones. (VSMC, vascular smooth-muscle cell; NO, nitric oxide; ET, endothelin.)

ary, as, for example, in multiple sclerosis[2] and always occurs in the context of other diseases. The symptoms appear more or less simultaneously with the underlying disease and mitigate as the underlying disease is treated. Primary vascular dysregulation (PVD), however, occurs in otherwise healthy subjects, particularly (but not only) in young, slim females. Subjects with PVD have a compromised autoregulation[8] of ocular perfusion, explaining their increased risk of glaucoma, particularly normal-tension glaucoma.[9] For this reason, PVD will be discussed here in some more detail.

Primary vascular dysregulation

PVD syndrome is characterized by an inborn tendency to respond differently to a variety of stimuli, such as cold temperatures or emotional or mechanical stress. The symptoms might already be present in childhood but manifest clearly during puberty and improve as subjects get older, in particular during menopause. The syndrome is observed more often in females than in males, in slim than in obese people, in academics than in blue collar workers, and in Asians than in Caucasians. The leading symptom of PVD is cold extremities. People with PVD often state that they suffer from cold hands but, when measured, their feet are cold as well.[2] In addition, their feeling of thirst is reduced,[10] and although they normally drink enough this is not because they are thirsty but, rather, because they know that they have to drink. On average, people with PVD prefer drinking caffeine-containing beverages, and they smoke less than non-PVD subjects. They also have a prolonged sleep onset time.[11] This is due to the fact that there is a strong connection between foot temperature and sleep onset time. These subjects have colder feet, requiring longer to warm them up.

People with PVD also have an altered drug sensitivity. This is at least partially due to an altered gene expression of the ABC transport (ATP-binding cassette) proteins.[12] In general, these individuals require either a much lower dose of certain drugs (e.g., calcium channel blockers, beta blockers) or a higher dose of other classes of drugs (e.g., pain killers). People with PVD often have low blood pressure when they are young and particularly at night. Moreover, their endothelin level in circulating blood is increased, and the sensitivity to endothelin is blood pressure dependent (Fig. 4).[13]

PVD subjects more often show signs of splinter hemorrhages,[3] reversible diffuse visual field defects (best represented by the Bebie curve)[14] (Fig. 5), and activated astrocytes in their retina (Supplementary Fig. 4, available online).[15] In terms of circulation, their retinal vessels show a higher spatial irregularity[16] and are stiffer.[17] The vasodilation to flickering light is reduced (i.e., the neurovascular coupling is suppressed).[18] The OBF of patients with PVD is correlated with peripheral blood flow.[19,20] The circulation of their eye is paradoxically related to perfusion pressure, in other words, their autoregulation is disturbed (Supplementary Fig. 5, available online).[8] This disturbed autoregulation is the major link between PVD and glaucoma. A similar disturbance of autoregulation can be observed in glaucoma patients whose condition progresses despite a normal or normalized IOP.[21]

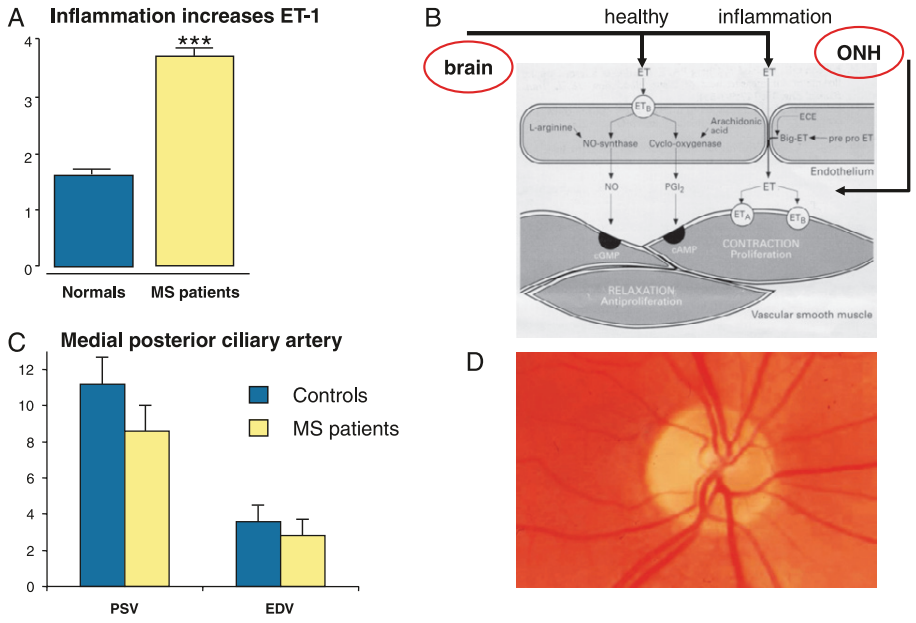

Fig. 2—The role of circulating hormones as demonstrated by the example of multiple sclerosis (MS): in MS the level of circulating endothelin is increased (A). A high level of endothelin has little influence on brain and retinal circulation as long as the blood–brain barrier is intact. In the choroid and optic nerve head (ONH), however, it reduces blood flow (B). This is the reason for a reduced blood flow in the retrobulbar vessels (C) and for the slight paleness observed in the ONH (D).

PVD patients have a higher risk of various eye diseases, including venous occlusions (in relatively young people without classical risk factors), arterial occlusions (again occurring at a relatively young age and without the classical risk factors) in the retina, the choroid, and the optic nerve head.[2] Of relevance in this context, however, is the increased risk of glaucoma.

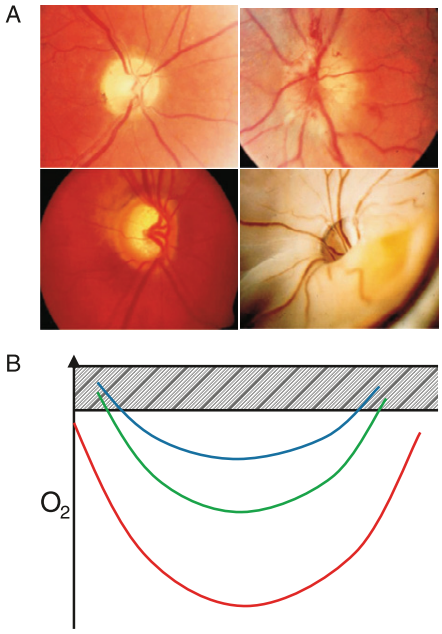

Fig. 3—The link between ocular blood flow (OBF) and optic nerve head (ONH) damage: (A) while a more or less constant reduction of OBF leads to pale ONH (e.g., multiple sclerosis) or in extreme situations to infarction (e.g., atherosclerosis) (top row), it is the instability of OBF that is related significantly to glaucomatous optic neuropathy (bottom row). (B) A reversible reduction of oxygen supply leads, depending on the level of oxygen concentration and the time of reduction, to preconditioning, reperfusion injury, or even to infarction. (Grey, normal range; blue, preconditioning; green, reperfusion injury; red, infarction.)

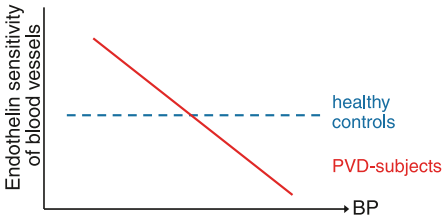

Fig. 4—Sensitivity to endothelin: while the endothelin sensitivity of blood vessels in subjects without primary vascular dysregulation (PVD) is independent of blood pressure (BP), the corresponding sensitivity in PVD subjects increases as blood pressure drops.[13] This explains, at least partially, a disturbed autoregulation in subjects with primary vascular dysregulation.

Autoregulation and glaucomatous optic neuropathy

Glaucomatous optic neuropathy (GON) is characterized by a loss of retinal ganglial cells and their axons together with major tissue remodelling leading to optic nerve excavation. A summary of our pathogenetic concept is presented in Supplementary Fig. 6 (available online). Crucial to it is the activation of glial cells,[22] especially of the astrocytes, which, in turn, alter the microenvironment not only in the ONH but also in the nerve and its surrounding sheets.

There is evidence that GON is related less to a constant blood flow reduction and more to an unstable OBF.[9] OBF is unstable if either IOP fluctuates at a high level or autoregulation is disturbed. Defective autoregulation of OBF in glaucoma patients has been postulated for decades.[23] The main cause of disturbed autoregulation is PVD syndrome.

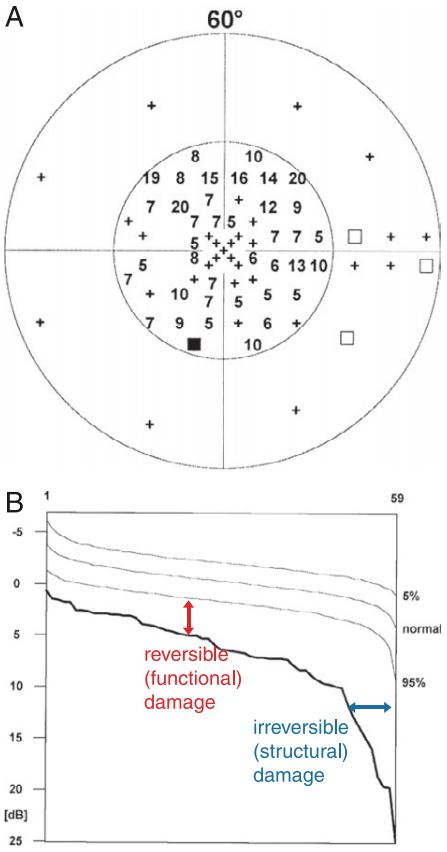

Fig. 5—Primary vascular dysregulation (PVD) and visual fields. Healthy subjects with PVD often have reversible diffuse types of visual field defects. Glaucoma patients with PVD, therefore, often have a combination of a local (irreversible) defect with a diffuse (reversible) defect, as demonstrated with the Octopus program G1 (A) and best illustrated by the Bebie curve (B).

The assumption that PVD plays a role explains why systemic hypotension in these subjects is a risk factor (because they cannot compensate with efficient autoregulation), why females more often suffer from normal-tension glaucoma than males (females suffer more often from PVD), why normal-tension glaucoma occurs more often in the Japanese than in Caucasians (Japanese suffer more often from PVD), but also why those with normal-tension glaucoma, and particularly why females more often have splinter hemorrhages (because PVD in itself is a risk factor for ONH hemorrhages). The involvement of reperfusion damage[1] explains why sleep apnea,[24] as well as shock-like states,[25] are risk factors to some extent.

The assumption of oxidative stress (partly due to repeated mild reperfusion) is supported by the following observations: glaucoma patients, particularly those with PVD, have increased DNA breaks, an upregulation of matrix metalloproteinases as well as the proteasome subunit 20S in their leukocytes, and an increased level of endothelin in their circulating blood.[26]

Conclusion

Oxidative stress due to unstable OBF contributes to GON.[1] OBF is unstable if either IOP fluctuates at a high level (or blood pressure at a low level) or if autoregulation is disturbed. We propose that the main cause of a disturbed autoregulation is the PVD syndrome.[8] The therapeutic consequences have been summarized elsewhere.[27]

Supplementary Figs. 1–6 for this paper can be found on the *CJO* Web site at http://pubs.nrc-cnrc.gc.ca/cjo/cjo.html. They are linked to this article in the online contents of the June 2008 issue.

References

1. Flammer J, Orgul S, Costa VP, et al. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res* 2002;21:359–93.
2. Flammer J, Pache M, Resink T. Vasospasm, its role in the pathogenesis of diseases with particular reference to the eye. *Prog Retin Eye Res* 2001;20:319–49.
3. Grieshaber MC, Flammer J. Does the blood-brain barrier play a role in glaucoma? *Surv Ophthalmol* 2007;52:S115–21.
4. Shibata N, Kobayashi M. The role for oxidative stress in neurodegenerative diseases [in Japanese]. *Brain Nerve* 2008;60:157–70.
5. Kamphuis W, Dijk F, Bergen AA. Ischemic preconditioning alters the pattern of gene expression changes in response to full retinal ischemia. *Mol Vis* 2007;13:1892–901.
6. Abramov AY, Scorziello A, Duchen MR. Three distinct mechanisms generate oxygen free radicals in neurons and contribute to cell death during anoxia and reoxygenation. *J Neurosci* 2007;27:1129–38.
7. Flammer J. The vascular concept of glaucoma. *Surv Ophthalmol* 1994;38:S3–S6.
8. Gherghel D, Orgul S, Dubler B, Lubeck P, Gugleta K, Flammer J. Is vascular regulation in the central retinal artery altered in persons with vasospasm? *Arch Ophthalmol* 1999;117:1359–62.
9. Flammer J, Haefliger IO, Orgul S, Resink T. Vascular dysregulation: a principal risk factor for glaucomatous damage? *J Glaucoma* 1999;8:212–9.
10. Teuchner B, Orgul S, Ulmer H, Haufschild T, Flammer J. Reduced thirst in patients with a vasospastic syndrome. *Acta Ophthalmol Scand* 2004;82:738–40.
11. Pache M, Krauchi K, Cajochen C, et al. Cold feet and prolonged sleep-onset latency in vasospastic syndrome. *Lancet* 2001;358:125–6.
12. Wunderlich K, Zimmerman C, Gutmann H, Teuchner B, Flammer J, Drewe J. Vasospastic persons exhibit differential expression of ABC-transport proteins. *Mol Vis* 2003;9:756–61.
13. Gass A, Flammer J, Linder L, Romerio SC, Gasser P, Haefeli WE. Inverse correlation between endothelin-1-induced peripheral microvascular vasoconstriction and blood pressure in glaucoma patients. *Graefes Arch Clin Exp Ophthalmol* 1997;235:634–8.
14. Bebie H, Flammer J, Bebie T. The cumulative defect curve: separation of local and diffuse components of visual field damage. *Graefes Arch Clin Exp Ophthalmol* 1989;227:9–12.
15. Grieshaber MC, Orgul S, Schoetzau A, Flammer J. Relationship between retinal glial cell activation in glaucoma and vascular dysregulation. *J Glaucoma* 2007;16:215–9.
16. Kochkorov A, Gugleta K, Zawinka C, Katamay R, Flammer J, Orgul S. Short-term retinal vessel diameter variability in relation to the history of cold extremities. *Invest Ophthalmol Vis Sci* 2006;47:4026–33.
17. Gugleta K, Kochkorov A, Katamay R, Zawinka C, Flammer J, Orgul S. On pulse-wave propagation in the ocular circulation. *Invest Ophthalmol Vis Sci* 2006;47:4019–25.
18. Gugleta K, Zawinka C, Rickenbacher I, et al. Analysis of retinal vasodilation after flicker light stimulation in relation to vasospastic propensity. *Invest Ophthalmol Vis Sci* 2006;47:4034–41.
19. Guthauser U, Flammer J, Mahler F. The relationship between digital and ocular vasospasm. *Graefes Arch Clin Exp Ophthalmol* 1988;226:224–6.
20. Hafez AS, Bizzarro R, Descovich D, Lesk MR. Correlation between finger blood flow and changes in optic nerve head blood flow following therapeutic intraocular pressure reduction. *J Glaucoma* 2005;14:448–54.
21. Gherghel D, Orgul S, Gugleta K, Gekkieva M, Flammer J. Relationship between ocular perfusion pressure and retrobulbar blood flow in patients with glaucoma with progressive damage. *Am J Ophthalmol* 2000;130:597–605.
22. Yuan L, Neufeld AH. Activated microglia in the human glaucomatous optic nerve head. *J Neurosci Res* 2001;64:523–32.
23. Ernest JT. Autoregulation of optic-disk oxygen tension. *Invest Ophthalmol* 1974;13:101–6.
24. Mojon DS, Hess CW, Goldblum D, et al. High prevalence of glaucoma in patients with sleep apnea syndrome. *Ophthalmology* 1999;106:1009–12.
25. Drance SM, Morgan RW, Sweeney VP. Shock-induced optic neuropathy: a cause of nonprogressive glaucoma. *N Engl J Med* 1973;288:392–5.
26. Flammer J, Mozaffarieh M. What is the present pathogenetic concept of glaucomatous optic neuropathy? *Surv Ophthalmol* 2007;52:S162–73.
27. Mozaffarieh M, Flammer J. Is there more to glaucoma treatment than lowering IOP? *Surv Ophthalmol* 2007;52:S174–9.

Key words: ocular blood flow, autoregulation, glaucomatous optic neuropathy, reperfusion injury, oxidative stress