For years, the question as to whether blood flow plays a role in the pathogenesis of glaucomatous damage has been controversial. The large number of publications on this topic illustrates this, and a review is warranted. Herein we discuss the questions asked most often.

Can We Measure Ocular Blood Flow?
Indeed, it is challenging to measure ocular blood flow (OBF)—several methods are used, but there is no gold standard as yet. Nevertheless, OBF can be measured, and different instruments are already in daily use, both for clinical and research purposes. Although these different techniques quantify blood flow or blood-flow velocity in different vessels using different methods, the outcomes are often well correlated (see Table 1).

Is Ocular Blood Flow Altered in Glaucoma?
Even if we acknowledge the limitations of the different technologies used to measure OBF, the results in the literature are unambiguous. This reduction is more pronounced in normal-tension than in high-tension glaucoma and more distinct in cases with progressing damage as compared to those with stable disease. Besides a secondary component caused by atrophy, there is an important primary component of OBF reduction, which also has a predictive value. The fact that hypoxia-related factors are upregulated in eyes of glaucoma patients indicates oxygen depletion. It is, however, not constant hypoxia, but rather the fluctuation of oxygen supply that leads to tissue damage, likely because of oxidative stress. Low perfusion pressure and disturbed autoregulation are important causes of insufficient and fluctuating oxygen supply, and both systemic hypotension and disturbed autoregulation are often consequences of the primary vascular dysregulation syndrome. The observed splinter hemorrhages in these patients are a consequence of a local breakdown of the blood–brain or blood–retinal barrier. The often associated vein occlusions can be a consequence of a local vein dysregulation.

Is Reduced Ocular Blood Flow of Predictive Value?
Several independent studies demonstrated convincingly that a reduced OBF is, indeed, a risk factor for further progression. In other words, a reduced OBF has an effect similar to that of an increased IOP (Figure 1). Is Ocular Blood Flow Reduction a Cause or a Consequence of Glaucomatous Damage?
It is obvious that blood flow is reduced in atrophic tissues. Therefore, there is a secondary component caused by atrophy. Interestingly, however, there are also many indications of a primary component. First of all, blood flow reduction can be observed in other parts of the body as well, such as in the nailfold capillaries, which obviously cannot be a consequence of glaucomatous damage. In addition, reduction of OBF often precedes further glaucomatous damage, which indicates that there must be an important primary component.

Do We See Signs of Hypoxia in Glaucoma Patients?
Both in the retina and in the optic nerve head of glaucoma patients, the hypoxia inducible factor 1α (HIF) is increased. HIF is produced constantly by all types of cells. Under normoxic conditions, HIF is oxidized, and then marked by ubiquitin and degraded by proteasomes. If, however, oxygen concentration is low, degradation is decreased and the concentration of HIF increases. HIF acts as a transcription factor...
and leads to an upregulation of a number of proteins, such as erythropoietin, vascular endothelial growth factor (VEGF), endothelin, and the von Willebrand factor. Correspondingly, all these factors have been described as increased in glaucoma patients.

**Is Hypoxia Sufficient to Induce Glaucomatous Optic Neuropathy?**

A slight but constant reduction of oxygen supplied to an organ like the eye interestingly does not lead to major damage. Most tissues have a certain capacity to adapt to hypoxia. In patients with multiple sclerosis (MS) endothelin plasma concentration, for example, is increased markedly and therefore OBF is decreased. Although a few of these patients get some degree of optic nerve head atrophy, they do not excavate more often than in subjects without MS, a fact that is also true for a number of other diseases, such as polyarthritis. Contrary to the findings in conditions with constant oxygen reduction, unstable, fluctuating OBF is likely to cause glaucomatous damage. Indeed, variation of OBF correlates with progression of glaucomatous damage.

**Why is Ocular Blood Flow Unstable in Glaucoma Patients?**

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. Reduced autoregulation occurs particularly in patients who suffer from primary vascular dysregulation (PVD) syndrome.

**What is the Role of Blood Pressure?**

Although low blood pressure has been described as a risk factor for glaucomatous damage and its progression for decades, the majority of ophthalmologists still neglected the role of systemic arterial hypotension. Not only have recent studies re-emphasized the important contributory role of low blood pressure, but also they have shown that a fluctuation of blood pressure is even more relevant. Finally, the best predictor for glaucomatous damage progression is the fluctuation of perfusion pressure.

**Can we Measure Ocular Perfusion Pressure?**

Traditionally, ocular perfusion pressure (OPP) is calculated as the difference between systemic blood pressure (measured in the upper arm) and the retinal venous pressure (assumed to be equal to IOP). Beside the fact that systemic blood pressure is only a relatively weak estimate for retinal arterial pressure, retinal venous pressure is definitively not necessarily equal to IOP. Although this simplification might be acceptable for the majority of healthy people, it is not applicable for glaucomatous patients. Therefore, to quantify OPP, we should measure blood pressure (arterial and venous pressure) directly in the eye. This can be done with the help of an ophthalmodynamometer.

**What are the Signs and Symptoms of a Primary Vascular Dysregulation?**

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. All these symptoms tend to decline with age.
How is Ocular Blood Flow in Primary Vascular Dysregulation Subjects?

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, despite their anatomically normal appearance. However, 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.
Why Does Unstable Ocular Blood Flow Lead to Glaucomatous Optic Neuropathy?

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.14

Can the Activation of the Astrocytes be Visualized Clinically?

Activated astrocytes not only change their gene expression, but also their morphology. They lose their regular pattern and subsequently increase light scattering. This contributes to the blur that glaucoma patients often experience. The backscatter of light also leads to glinting spots in the retina observed by ophthalmologists (see Figure 2).15

What is the Link between Ocular Blood Flow and Splinter Hemorrhages?

Traditionally, splinter hemorrhages were considered to be a consequence of either microinfarction or small vessel rupture. However, we suggested that these hemorrhages are rather a consequence of a local breakdown of the blood–retinal or blood–brain barrier.16 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 (Figure 3).

The molecules mentioned above interfere with the barrier function and can be increased by diffusion from the circulating blood via fenestrated capillaries of the choroid into the optic nerve head and the adjacent retina or they can be produced—at least to some extent—locally in the retina. The latter is more relevant for retinal hemorrhages in diabetes than for optic nerve head hemorrhages in glaucoma patients. In other words, vascular dysregulation not only leads to an inappropriate vascular tone, but eventually also to a barrier dysfunction. It is therefore not surprising that the chance of damage progression is higher in areas where hemorrhages occur and that these hemorrhages occur more often in females and in NTG patients. Although hemorrhages occur more often in NTG patients, their frequency is reduced if oxygen supply is improved by reducing IOP.

What is the Relationship between Retinal Vein Occlusion and Glaucoma?

Retinal vein occlusions are found more often in glaucoma patients. Furthermore, both glaucomatous damage and vein occlusion occur more often in subjects with PVD. We suggested that the vein occlusion is not caused primarily by thrombus formation, but rather by a local dysregulation of the vein, either in the lamina cribrosa or at the arteriovenous crossing.17 This dysregulation again is likely a consequence of a local increase of vasoactive molecules, such as endothelin, either diffusing from the circulating blood or produced in the neural tissue of the retina (Figure 4). This, in turn, occurs particularly in hypoxic tissue. Therefore, a primary arterial dysfunction may lead to secondary venous dysfunction.

In summary, unstable oxygen supply caused by IOP or blood pressure fluctuations or disturbed autoregulation leads to increased oxidative stress, a main contributor to glaucomatous damage (Figure 5).18