of tissue of 20 μm will be necessary before we can assert with a high likelihood that worsening has taken place. However, this value is meaningless if we do not compare it with the total loss of thickness observed at the end stage of the disease. A loss of 20 μm in thickness is about 25% of the total thickness of the ganglion and nerve fibre layers in the perifoveal as well as peripapillary regions, and not far from 100% of the thickness at the periphery. This quick estimate is quite humbling, but it is encouraging that the

reproducibility is not necessarily dictated to us and could potentially be improved.

The above considerations emphasise that it is time to steer away from the "beauty contest" that has taken place between the various diagnostic technologies and approaches in the last two decades. The physiology, anatomy and pathology of the eye dictate that more than one tool is required to determine the presence of glaucoma and its severity, thus emphasising that the different measures complement one another.

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Correspondence to: R Zeimer, Wilmer Ophthalmological Institute, Johns Hopkins University, 600 N Wolfe Street, Woods 355, Baltimore, MD 21287, USA; rzeimer@jhmi.edu

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Blood flow in glaucoma

Blood flow in glaucoma

S Orgül

Glaucoma: a vascular dysregulation

I ncreased cupping of the optic nerve head, a result of progressive loss of the retinal nerve fibres and remodelling of the supporting connective tissue in and around the lamina cribrosa, characterises glaucomatous optic neuropathy. Although reducing intraocular pressure represents a relevant approach in the treatment of glaucoma, many details of the pathway leading to this clinical picture remain unclear, and various additional contributors to the damage, such as altered ocular blood flow, have also been postulated to play a part.¹ In this issue of the journal, Plange *et al*² present a study on the correlation of retinal blood flow with the size of the rim of the optic disc. Such a result is in line with recent histological findings showing a decrease in density of optic nerve capillary vessels in patients with primary open-angle glaucoma, whereas damage due to a secondary increase in intraocular pressure, such as in pseudoexfoliation, is devoid of such peculiarities.³ Further, the finding of hypoxia-inducible factor 1 α expression in the glia of the optic nerve head and the retina of glaucomatous donor eyes,⁴ as well as earlier studies suggesting that ocular blood flow is reduced in eyes before actual damage occurs, lend credence to the hypothesis of a pathophysiological role of ocular perfusion in glaucoma.^{5–7}

Although the haemodynamic theory of glaucomatous damage is nearly as old as the mechanical postulate, proponents of the haemodynamic theory have been less

successful in implementing their thoughts into daily practice, principally owing to methodological difficulties. Whenever blood flow is assessed clinically in the eye, the question of the real nature of the measured phenomenon is raised and the shortcomings are obvious. The methods currently used provide limited information on actual blood flow and usually concentrate on some aspects of perfusion, including vessel diameter, pulsatility and velocity of flow, or extrapolate on blood flow from its effect on light. Many studies also do not differentiate between a primary, actively damaging phenomenon and a secondary response to the neuronal atrophy.

The postulate of altered blood flow leading to glaucoma is not in contradiction with the finding that reducing intraocular pressure may be beneficial, considering that both intraocular pressure and ocular blood flow probably act in concert,⁸ and, consequently, patients with vascular dysregulation benefit from intraocular pressure reduction.^{9–10} However, most recent large treatment trials failed to show clearly the importance of vascular factors,^{11–15} many glaucomatologists today acknowledging only inheritance, family history, intraocular pressure level, cup–disc ratio, corneal thickness, disc diameter and axial length as risk factors.¹⁶ Admittedly, none of these trials were really designed to consider the effect of ocular blood flow. As a consequence, not only is the relevance of ocular blood flow in glaucoma unclear but also even the exact nature of the perturbation remains elusive.

Undoubtedly, enough blood is mandatory for proper function of the eye, and animal experiments suggest that moderately reduced perfusion may induce a loss of retinal nerve fibres, resembling glaucoma in some aspects.^{17–19} In some aspects, but not in all. Possibly, however, rather than quantitative aspects, qualitative characteristics may have to be considered.^{20–21} Prerequisites to healthy perfusion are proper quantities everywhere and at all times. Local and temporally limited disturbances of perfusion have been postulated as a potential source of trouble in patients with glaucoma.²² Such vascular dysregulation may, rather than leading to chronic hypoxaemia, provoke reperfusion damage, either cumulating after years in the local damage observed in glaucoma, or promoting damage induced by other mechanisms such as high or unduly variable intraocular pressure.

If the hypothesis of vascular dysregulation is to be considered, future studies raising the question of its relevance in glaucoma may be confronted, similarly patients with ocular hypertension without neuronal damage, by the fact that only some patients with vascular dysregulation develop disease.²² A history of frequent cold hands, even during warm weather, is a characteristic symptom of vasospastic syndrome.²² Other clinical features include low blood pressure,²² slower sleep onset,²³ decreased awareness of thirst coupled with low daily fluid intake²⁴ and low body mass index.²⁵ In general, individuals with vasospastic syndrome usually are otherwise healthy, and vasospasm does not need special treatment.²² A possible cause of vasospastic syndrome is vascular endotheliopathy.^{26–28} The vascular episodes can be provoked by many factors, such as exposure to cold, stress, emotions and nicotine, and possibly promote frequent daily episodes of hypoxia-reperfusion injury.²⁹

Mitochondria are the major site of oxygen consumption in mammals. The free energy released from the combustion

of substrates is converted to ATP. However, some of that energy is converted to heat owing to inefficiency in the coupling of ATP synthesis to oxygen consumption, a phenomenon known as mitochondrial proton leak. Mitochondrial proton leak or natural proton leak is a major contributor to basal metabolism, accounting for about 20–25% of the oxygen consumption of cells, tissues or a whole animal.^{30–33} Thus, for example, some of the higher metabolic rate of animals experimentally made hyperthyroid and of the lower metabolic rate of animals experimentally made hypothyroid is due to altered mitochondrial proton leak.^{34–37} The same mechanisms seem to account for the interspecies difference in mass-specific metabolic rates.^{38–39} The change in mitochondrial proton leak is probably mediated by uncoupling proteins.⁴⁰ The mitochondrial uncoupling protein 1 (UCP1) is normally found in the brown adipose tissue of mammals, where it causes thermogenesis. The UCP1 constitutes a pathway for the protons pumped by the respiratory chain to return to the mitochondrial matrix, bypassing the ATP-producing return pathway.⁴¹ Hence, activated UCP1 dramatically increases energy expenditure. This has attracted much attention for the control of body weight, and transgenic models overexpressing UCP1 or its close homologue UCP3 showed improved resistance to obesity.^{42–43} Of relevance for this discussion is another consequence of partial uncoupling, namely the lowering of mitochondrial membrane potential, thus reducing the mitochondrial production of superoxide radicals.⁴⁴ Recently, in a study using a perfused heart model and a transgenic model of mice in which a high expression level of UCP1 was obtained in the heart, UCP1 activity was shown to be low under normoxia but to be induced during ischaemia-reperfusion, and the presence of UCP1 was shown to protect against the damage induced by ischaemia-reperfusion, probably because it lowers mitochondrial hyperpolarisation during reperfusion.⁴⁵

Considering oxidative stress resulting from hypoxic/ischaemic episodes or on reperfusion of tissue in patients with vascular dysregulation, up regulation of mitochondrial uncoupling would protect against reperfusion damage. As soon as this compensatory mechanism fails, mitochondrial dysfunction may ensue and bring about neuronal functional variation, possibly resulting in long-term variability in visual field damage, and also be the source of a reduced aptitude to compensate for environmental stress such as increased intraocular pressure. In addition, enhanced oxidative stress

may result, leading to extensive tissue damage. An indication for reperfusion damage in patients with glaucoma particularly prone to vascular dysregulation can be inferred from the observation of enhanced intracellular repair mechanisms.⁴⁶ In such a context, mitochondrial protective treatment—for example, with Ginkgo—could be relevant.⁴⁷

As little as increased intraocular pressure, vascular dysregulation by itself probably does not provoke glaucoma, or only in extreme cases, and it is rather the failure of compensatory mechanisms, which determines the harm endured by the optic nerve. Consequently, as such a moment may occur when compensatory mechanisms are overwhelmed by the combined action of multiple risk factors, future therapeutic approaches need to consider the effect of all potential risk factors. In addition, a therapeutic approach to the damage to the vectors of compensatory mechanisms will need to be considered.

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Correspondence to: Dr S Orgül, University Eye Clinic Basle, Mittlere Strasse 91, PO Box, 4031 Basle, Switzerland; sorguel@uhbs.ch

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Minimally invasive strabismus surgery

Comparison of a new, minimally invasive strabismus surgery technique with the usual limbal approach for rectus muscle recession and plication

B J Kushner

A minimally invasive strabismus surgery procedure causes less inflammation postoperatively, but is harder, provides limited exposure and probably has a steep learning curve

There has been a trend in most surgical disciplines for performing procedures that are minimally invasive through increasingly smaller incisions. Dr Mojon is to be commended for his description of the minimally invasive strabismus surgery (MISS) technique described in this issue of the British Journal of Ophthalmology (see page 76). Descriptions of new strabismus surgical procedures are often published in an anecdotal manner, describing results in only several patients. It is refreshing to see a publication such as that of Dr Mojon¹ who tested this new procedure on 20 patients matched against a control group, with objective data comparing the two groups.

The main advantage of the MISS technique is that it causes somewhat less inflammation in the immediate postoperative period compared with the standard limbal approach. The main disadvantage is that the MISS technique is harder, provides more limited exposure and probably has a steep learning curve. Although Mojon¹ believes that a microscope is needed for this procedure, he also uses a microscope for surgery performed with the limbal approach.

Without debating the merits of using a microscope for all strabismus surgery, I would think that if surgeons are comfortable not using a microscope for standard strabismus surgery, they would not need it with the MISS technique.

Mojon's¹ study compares the MISS technique with the limbal approach, which I understand is widely used in Europe. I should add that all the advantages he found with the MISS technique would also be present with the fornix approach, which is widely used in the US and elsewhere. Although I personally do not routinely use the fornix approach, I believe it would be easier and provide better exposure than the MISS technique. For a surgeon who thinks that the limbal approach causes undue discomfort in the immediate postoperative period (I personally do not) the fornix approach is a reasonable alternative. Nevertheless the fornix approach may not be advisable in certain patients, specifically elderly people with thin conjunctiva. In these patients, MISS might be considered a preferable alternative to limbal surgery. However, these are the patients in whom one often wishes to use an adjustable suture technique. In such circumstances,

the limbal approach would still be necessary.

One advantage of the MISS technique over the limbal approach that was not emphasised by Mojon¹ relates to anterior segment ischaemia. Increasing evidence suggests that disruption of the perilimbal episcleral vessels, which occurs with a limbal incision, may predispose a patient to anterior segment ischaemia. Having recently experienced anterior segment ischaemia in a patient with Graves' orbitopathy, on whom I simultaneously recessed an adjacent inferior rectus muscle and medial rectus muscle (he had not undergone prior strabismus surgery), I am sensitive to this issue. The MISS technique may decrease the risk of anterior segment ischaemia in such patients. It may be a useful addition to our armamentarium in this setting, provided we are not planning to use an adjustable suture technique.

In summary, the MISS technique may have applications in some circumstances. It is not clear to me that its advantages outweigh the disadvantages for routine strabismus surgery. However, for the surgeon who does not wish to use the fornix approach and is concerned about postoperative discomfort with limbal surgery, it seems to be a viable alternative.

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Correspondence to: Dr B J Kushner, Department of Ophthalmology and Visual Sciences, University of Wisconsin Hospital and Clinics, Suite 206, 2870 University Avenue, Madison, WI 53705, USA; bkushner@facstaff.wisc.edu

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