Nature is teaching us to be humble in our quest to measure structure and function in glaucoma

R Zeimer

Relationship between structure and function with regard to glaucoma

The study by Kanadani *et al*¹ to elucidate the relationship between structure and function, especially with regard to glaucoma, is timely. Their paper is particularly interesting in that it provides information on not one but two measures of function: the visual field and the multifocal visual evoked potential technique. The investigators report that macular thicknesses (measured by optical computerized tomography) were in agreement with the 10-2 Humphrey visual field and multifocal visual evoked potential technique to the same degree as the two functional tests. Local agreement was present as well; inferior and superior sectors showed abnormal macular thickness in 78% and 65% of the points.

These results, obtained at the macula, give a message similar to that of other structural measures such as peripapillary nerve fibre layer thickness and morphometry of the optic nerve head. The message seems to be that though there is good overall agreement between structure and function, it is not sufficient to yield a test that provides an unequivocal measure of damage in a given patient. Gone are the days when we hoped that a unique quantitative objective measure would be found and would replace subjective tests prone to noise and artefacts and demanding expert interpretation.

Does this mean that we should give up on our effort to perform quantitative and objective tests in glaucoma? I opine that the answer is "no", but clearly we are forced to delve more deeply into the subject and accept the fact that valuable information will be gleaned only if we approach the subject with more sophistication.

This optimistic view is based on the fact that, under certain circumstances, one can obtain a tight association between structural damage and functional loss. For example, Harwerth and Quigley (*Arch Ophthalmol* 2006;124:853-9) have shown that the density of ganglion cells (measured by histology) corresponds well with function assessed by standard clinical perimetry, but they have also shown that

to achieve this close correlation, it is necessary to take into account some important factors such as topographical location and logarithmic behaviour.

The relationship between structure and function needs to be examined locally. This relationship can be studied in the macula, in the peripapillary region and at the optic nerve head.

My group has suggested that the macula is an interesting location to assess glaucoma damage because the variation in anatomy among normal subjects is low, it contains the cell bodies of half of the total ganglion cells, and loss of function in the central field of vision is bound to have an effect on quality of life. In the macula, the density of ganglion cells varies with eccentricity from the fovea. Thus, we can expect that function is affected by loss of ganglion cells in a different manner at the perifoveal region, where ganglion cells abound, than at the periphery, where ganglion cells are sparse. The potential clinical implication is that, for a given severity (percentage) of ganglion cell loss at the periphery, the dB loss shown by perimetry will be different from that at the central macula.

The peripapillary region is another valuable location. Measurements in this region provide information on the number of axons converging towards the optic nerve head and is therefore global in essence. The temporal-superior and temporal-inferior sectors harbour the axons from the peripheral ganglion cells. The low density of ganglion cells in this region may yield a relationship between structure and function that is specific to the periphery. Moreover, the peripapillary region is less likely to be affected by comorbidity than the macula.

Finally, the optic disc also needs to be considered. Although it suffers from a large variability among individuals, it has the potential of being sensitive to local pathology at the level of the lamina cribrosa. Moreover, the changes in topography at the optic nerve head are dramatic and, under expert examination, may show

morphological cues that are unique. Clinically, examination of stereophotographs of the disc is still the 'gold standard' for trials, and many clinicians have found that quantitative measures of optic nerve head parameters are valuable in making a therapeutic decision.

The other important factor that we need to take into consideration when assessing the relationship between structure and function is the logarithmic nature of functional indices. In the same manner that the response of the retina to light is not linear, the loss in stimulus sensitivity is not proportional to the number of ganglion cells, but rather exhibits a logarithmic behaviour. This implies that a dramatic loss of half the ganglion cells would lead only to a $10 \log_{10} 0.5 = 3$ dB reduction in sensitivity. On the other hand, when only $\frac{1}{4}$ of the tissue remains, a reduction of 3 dB would correspond to a change of only $\frac{1}{4}$ the normal value, namely from $\frac{1}{4}$ to $\frac{1}{16}$ the initial tissue thickness. This example illustrates the fact that function, assessed by stimulus intensity, is inherently insensitive to the initial loss of ganglion cells. Thus, structural measurements have the potential to be sensitive in detecting initial damage, whereas perimetry is sensitive in detecting progression at a later stage.

Location on the fundus and logarithmic behaviour are not the only limitations to devising diagnostic tests for glaucoma. When attempting to detect the transition from health to disease, the variation among the healthy population has a central role. No matter how sensitive and reproducible our method is, we have to contend with the fact that only a deviation equal to twice the standard deviation of the values in healthy individuals will let us consider, with 97.5% confidence, that the deviation is not attributed to chance. This is a constraint that we cannot change. For example, various studies agree that the variability of neural tissue thickness is about 15 μm at both the macula and the peripapillary region. Thus, a loss of at least 30 μm needs to occur before we can assert that glaucomatous damage has taken place. However, the total amount of tissue that can be lost to glaucomatous damage is only about 80 μm . Thus, it is inherent that we cannot expect to diagnose the onset of glaucoma until 38% (30/80) of the tissue has been lost.

When attempting to detect progression, the reproducibility of the instrument is a key factor. To gain 97.5% confidence that glaucomatous worsening has occurred, the change needs to be equal to twice the reproducibility of the instrument. For example, if we measure the thickness of the ganglion cells and that of the nerve fibre layer with a method that has a reproducibility of 10 μm (considered excellent for local measurements), a loss

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

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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