The Literature

BY TOMAS M. GRIPPO, MD

CONTINUOUS INTRAOCULAR PRESSURE MONITORING WITH A WIRELESS OCULAR TELEMETRY SENSOR: INITIAL CLINICAL EXPERIENCE IN PATIENTS WITH OPEN ANGLE GLAUCOMA
Mansouri K, Shaarawy T*
British Journal of Ophthalmology, January 2011

How Close Are We to Continuous 24-hour IOP Measurement?

Elevated IOP is a leading risk factor for the development and progression of glaucoma and the only treatable one.1 The current clinical gold standard for measuring IOP is Goldman applanation tonometry (GAT). GAT’s major limitation is that it only provides a snapshot, usually taken during regular office hours, of the very dynamic parameter that is IOP. IOP varies throughout the night and day, is affected by body posture,2 and in many patients may be highest outside the usual office hours.3 Medications that reduce IOP also have a variable IOP-lowering effect throughout the 24-hour cycle.4-6 By measuring IOP only during office hours, the clinician may be left without valuable information when planning, prescribing, and adjusting glaucoma treatment. In the past several decades, many have searched for an implantable permanent device or a removable temporary one to monitor IOP continuously in humans.7

In this article, Mansouri and Shaarawy8 describe the first clinical experience with a novel technology for continuous IOP monitoring. In a small group of open-angle glaucoma patients, the investigators used the Sensimed Triggerfish (Sensimed AG, Lausanne, Switzerland), a soft contact lens with an embedded microelectromechanical system with wireless communication developed by Leonardi et al.9 The microfabricated strain gauge works by recording the change in curvature at the level of the corneoscleral junction. A change in curvature of about 3 µm corresponds to a change in IOP of about 1 mm Hg.9 This relationship is based on the assumption of a linear correlation but may differ depending on the level of pressure.

Fifteen patients who showed signs of glaucomatous progression despite controlled IOPs during their routine office visit underwent 24-hour monitoring with this device. Because the data obtained are provided in an arbitrary unit, GAT was performed before and after the sensor’s installation to obtain approximations. In almost 70% of the cases, the highest values were detected during nighttime hours, in agreement with data obtained from prior traditional sleep laboratory studies.10 Individual patterns, fluctuations, and peaks that occurred in between time points of low IOPs were also detected. Based on these findings, the authors adjust treatment for some patients.

For the first time, IOP data collected continuously for 24 hours without possible artifacts associated with nocturnal arousal could be observed.1 Although the device provides IOP information in arbitrary units and may be affected by corneal thickness and rigidity, it may provide an opportunity to better understand IOP fluctuations under physiologic and therapeutic conditions.

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COMBINING STRUCTURAL AND FUNCTIONAL MEASUREMENTS TO IMPROVE DETECTION OF GLAUCOMA PROGRESSION USING BAYESIAN HIERARCHICAL MODELS
Medeiros FA, Leite MT, Zangwill L, Weinreb RN*
Investigative Ophthalmology and Visual Science, June 2011

A New Methodology for Combining Longitudinal Information From Structural and Functional Tests to Improve the Detection of Glaucomatous Progression and Estimate the Rate of Change

Clinicians routinely compare structural and functional information to subjectively determine if glaucomatous progression has taken place. Previous studies have focused on describing how structural findings relate to functional findings or vice versa,11 but relatively little has been done to use this information together to objectively determine glaucomatous progression in a formal way.

In this study, Medeiros and colleagues propose a new methodology for combining longitudinal information from structural and functional tests to improve the detection of glaucomatous progression and estimate rates of change. As explained by the authors, this approach is based on joint modeling of longitudinal changes using Bayesian hierarchical models. Joint modeling enables a better characterization of the true underlying relationship between structural and functional tests. Information derived from one test is allowed to influence the inferences obtained from the other test. In other words, a change in the visual field that would otherwise be declared not statistically significant by an analysis of visual field data alone might be declared signifi-
cant after considering the structural changes occurring in the same eye.

This study included 257 participants who were observed for an average of 4.2 ±1.1 years. Included patients had glaucoma, were suspected of having glaucoma, or were healthy and annually with standard automated perimetry, optic disc stereophotographs, and scanning laser polarimetry with enhanced corneal compensation. The rates of change over time were measured using the visual field index (VFI) and average thickness of the retinal nerve fiber layer.

The current Humphrey visual field tests (Carl Zeiss Meditec, Inc., Dublin, CA) analyse the rate of VFI change over time using ordinary least squares (OLS) linear regression. In a comparison of the Bayesian method with the OLS method, the Bayesian method showed greater sensitivity and specificity. It also identified a significantly higher proportion of eyes with progression by Bayesian slopes of change for VFI or average retinal nerve fiber layer thickness average, resulting in a specificity of 100% (95% confidence interval: 88%-100%) for the combined method.

The authors concluded that the Bayesian hierarchical modeling approach for combining functional and structural tests performed significantly better than the conventional OLS method for the detection of glaucomatous progression, and they therefore suggested that this approach may provide better estimates of rates of change.

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YAG LASER PERIPHERAL IRIDOTOMY FOR THE PREVENTION OF PIGMENT DISPERSION GLAUCOMA: A PROSPECTIVE, RANDOMIZED, CONTROLLED TRIAL

Does Nd:YAG Laser Peripheral Iridotomy Significantly Reduce the Incidence of Conversion From Pigment Dispersion Syndrome With Ocular Hypertension to Pigmentary Glaucoma?

To date, the natural history of pigment dispersion syndrome has been characterized poorly. There has been scarce and conflicting information on the prevalence of the condition and the rate of conversion from pigment dispersion syndrome with ocular hypertension to pigmentary glaucoma.12 There is also conflicting evidence as to when to perform laser peripheral iridotomy (LPI) during the course of this condition and whether it is beneficial13-17.

To address the question of whether Nd:YAG LPI prevents progression from pigment dispersion syndrome with ocular hypertension to pigmentary glaucoma, Scott et al conducted this prospective, randomized, controlled 3-year trial of 116 patients with pigment dispersion syndrome and ocular hypertension. Of 116 patients, 57 were randomized to LPI and the remaining patients to observation. The primary outcome measure was the conversion to pigmentary glaucoma within 3 years, based on an analysis of full-threshold visual field using the Ocular Hypertension Treatment Study criteria. Surprising to some, of the 105 eyes that completed the study, eight eyes (15%) in the laser group and three eyes (6%) in the control group converted to glaucoma.

The authors acknowledged that there were a few sources of potential imprecision or bias in their study. Determining the main outcome as conversion based on the analysis of full-threshold visual fields might lack precision. They also suggested that, although iris concavity was one of the inclusion criteria, it was estimated subjectively and not measured by ultrasound biomicroscopy. The strength of this prospective study would have been improved if the authors had taken their analysis a step further and expanded on imaging of the anterior segment. They could have evaluated the anatomical and dynamic iris factors that might predispose individuals with pigment dispersion syndrome to progress to pigmentary glaucoma in spite of a patent LPI eliminating reverse pupillary block. An example of this would have been to evaluate the location of the insertion of the iris, as posterior iris insertion predisposes to the phenotypic expression of pigment dispersion syndrome and progresses to pigmentary glaucoma.18 As the authors acknowledged, the hypothesis assumes indozonular contact as an explanation for pigment dispersion.19 If there is no documented evidence of contact, it is possible that there may be more than one mechanism for pigment dispersion and, therefore, different degrees of response to LPI.

In summary, despite its limitations, the authors concluded that this study provided little evidence to support the use of Nd:YAG LPI in patients with pigment dispersion syndrome and established ocular hypertension during its 3-year period. The authors suggested that a possible explanation for their findings might be that the onset of ocular hypertension in pigment dispersion syndrome indicates a combination of pathologic changes that are irreversible20 and, hence, any intervention to decrease pigment release once ocular hypertension is established, such as an Nd:YAG LPI, might be ineffective. They acknowledged, however, that it is
possible that the treatment might be effective in patients without irreversible trabecular meshwork damage or in those with a documented increase in iridonzonal contact.

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Letters

GLAUCOMA SCREENINGS

The following reader-author exchange regards the article “Is Glaucoma Screening Worthwhile?” by Renata Picciani, MD; Richard K. Lee, MD, PhD; and Jeffrey D. Henderer, MD. The article appeared in our early spring 2011 edition.

A few years ago, there was a very interesting study from the United Kingdom titled “Inter-clinician variance in glaucoma diagnostic decisions” by Lisa Collins and Adrian R. Hill.1 In this study, 36 patients were selected, of whom 32 participants were referred from optometrists as glaucoma suspects and four participants were known normal. Each participant was examined in a 4-hour session by five experienced glaucoma specialists from different hospitals in the United Kingdom. There was a wide variance in the diagnostic decisions among these experienced glaucoma specialists. Another interesting finding from this study was that, the more diagnostic parameters (eg, IOP, cup-to-disc ratio) used by these glaucoma specialists to diagnose glaucoma, the greater the variance in their diagnostic decisions. In view of these findings, how would one expect a general ophthalmologist (like myself) to do any better?

In my opinion, the reason for wide discrepancies in diagnostic decisions is that we do not fully understand what is happening to the optic disc in glaucoma. We do not have any established parameter to diagnose preperimetric glaucoma (as this is the most vital point for screening). We used to have a parameter of raised IOP to make a glaucoma diagnosis, but the IOP parameter is becoming obsolete, as the incidence of normal-tension glaucoma (≤ 21 mm Hg) in studies has ranged from 3.6% to 61%, depending on the analyzed population.2 The cup-to-disc ratio parameter is also fading because of the great variance of the physiological cups among the general population. Additionally, the visual field parameter cannot pick up preperimetric glaucoma, since about 40% of the nerve fibers have to be destroyed before visual deficits are manifested,3 which would land us in the intermediate stage of glaucoma.

Although the newly discovered parameter for early glaucoma—thinning of the retinal nerve fiber layer (RNFL)—appears promising, it has its pitfalls. First, we do not know how much of the RNFL must be thinned prior to the diagnosis of glaucoma. Perhaps by that time, the pathological changes in the disc or field defects may start appearing as

well. Second, we cannot explain the cause of thinning of the RNFL occurring only in glaucomatous discs and not in other kinds of optic disc disease. It is difficult to utilize a parameter unless we understand the reason for doing it. Unless we find the true cause of thinning of the RNFL, we are left lost in a plethora of parameters and still have no true diagnostic yardstick for preperimetric glaucoma. Until that time, the screening projects may not be worthwhile.

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Dr. Henderer responds.

Dr. Hasnain brings up important points that are all too familiar to glaucoma specialists. Consensus is lacking with regard to what constitutes glaucomatous changes—at least very early changes. One would hope that the agreement between specialists would be much greater in the British study if the patients actually had glaucomatous disc and field damage (although I am unaware if visual field testing was part of the cited study). In the Ocular Hypertension Treatment Study (OHTS), about 170 patients converted from ocular hypertension to primary open-angle glaucoma by optic nerve head change, by visual field change, or by the combination of visual field change and optic nerve head change in roughly a 2:1:1 ratio. These results suggest that, in the earliest stage of glaucoma, both the field and disc need to be examined and there might be different mechanisms at work, as patients convert from ocular hypertension to disease. In short, our understanding of the pathophysiology of glaucoma is incomplete.

Currently, a diagnosis of glaucoma is typically based on assembling a set of information, such as characteristic optic nerve changes with corresponding field defects and risk factors for glaucoma such as IOP, family history, and central corneal thickness, for example. Glaucoma suspects, essentially by definition, do not have all those elements, but even if they do, it is possible to be misled. It is possible some patients who are treated will never progress, because they suffered a single insult that is no longer progressive, and it is possible that someone who may indeed develop glaucoma will go unrecognized and thus not be treated until his or her vision is affected.

Personally, I prefer to be honest with patients about the limits of my knowledge. I often explain to patients who are glaucoma suspects that I cannot tell if they have glaucoma but that, luckily, this disease is—depending on IOP and other risk factors like pigmented dispersion, pseudoexfoliation, central corneal thickness, and family history—often a slowly progressive optic neuropathy and I should be able to detect change in the nerve and field that would confirm the diagnosis before they develop visually significant changes that affect their quality of life.

So, what to do about screening? Ideally, we would screen for glaucoma with a cheek swab for DNA and ganglion cell counter that measures exactly how many retinal ganglion cells are present. The swab would reveal the genotype, which I could compare to a set of natural history studies to see if such patients develop glaucoma, and counting the ganglion cells—or the rate of apoptosis of those cells—would help me identify loss that exceeds age-matched controls. But, that ability is in the future.

The current state of affairs, as Dr. Hasnain mentions, is far from perfect. In fact, in my mind, it is so difficult to differentiate very early glaucoma from normal that it may be impractical to screen for this stage of disease. Rather, I believe, given our current abilities, it makes more sense to screen for disease that will affect patients within their lifetime. This may mean definitive moderate disease for many older patients and may mean advanced disease in the very elderly. The concept is to prevent too many false positives that consume resources and are one reason that screenings often are not cost-effective. In the young, however, who have many years ahead of them and in whom vision loss could be very problematic, erring on the side of being conservative by referring patients who are suspicious but not definitive for glaucoma at least provides for a baseline examination to use for future comparison. This includes screening patients with a family history of glaucoma, for example, to gauge the likelihood of developing glaucoma and screening patients at higher risk.

Screening is complicated in very early disease but not in moderate or advanced disease. But, as Dr. Hasnain points out, assessing glaucoma suspects in the office is often problematic. At this point, I would recommend that we not routinely seek to identify preperimetric or predisc-damage glaucoma on screening examinations. It just is not practical or perhaps even possible reliably with current technology in a community environment. The goal of glaucoma screening should be simplified to find people who are unaware of their disease and prevent them from losing more vision. That would be a substantial improvement over where we are now.

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