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Volume 16-2
2015

The journal of the World Glaucoma Association

Abstracts and Review of Glaucoma Literature

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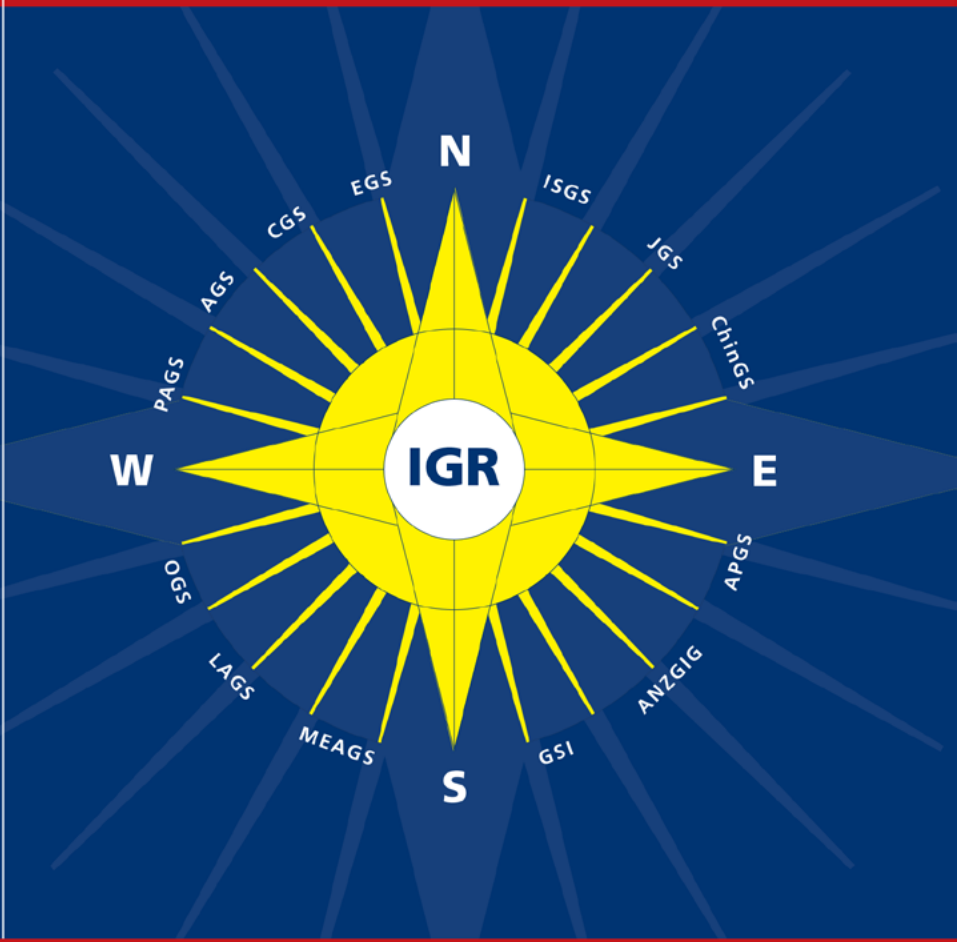

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WGA Executive Office, c/o Jan van Goyenkade 11, 1075 HP Amsterdam, The Netherlands
Tel: +31 20 679 3411 E-mail: IGR@worldglaucoma.org

Published by Kugler Publications, P.O. Box 20538, 1001 NM Amsterdam, The Netherlands, on behalf of the World Glaucoma Association.

Cover design: Cees van Rutten, The Hague, The Netherlands
Typesetting: 3bergen, www.3bergen.com

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From the WGA Executive Office

Our first online-only issue was a success and we are happy with this result. The statistics show that the E-pub and E-pdf versions have been downloaded by over 4,000 users and the total number of hits at the IGR website is over 90,000 since its release in December.

Did you notice the next occasion of World Glaucoma Week (March 8-14, 2015)? More information on inspiring awareness events of your colleagues around the world is available via www.wgweek.net. Also, do take a look at the world map of WGW-2015 events planned so far, which is changing every hour. On page 12 the members of the WGW Committee provide you with their personal opinions why WGW is so important.

Within the next 3 months, the 6th World Glaucoma Congress will be held in Hong Kong from June 6-9, 2015. Via the WGA website, a preview of the extensive program is available. Please refer to page 8 of this issue, to find all details on the program reported by the WGC-2015 Program Planning Committee.

Please enjoy this IGR and let me know your thoughts regarding our efforts in this and all WGA initiatives. You can reach me at (Fechtner@worldglaucoma.com). You can also contact our WGA Executive Office (info@worldglaucoma.org) if you need any information or have questions on IGR or WGA related matters. I look forward to hearing from you.

Professor Dr. Robert D. Fechtner, Executive Vice President

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6th World Glaucoma Congress 2015

There are several reasons for you to come to Hong Kong, and the program is an important one. The program planning committee has worked hard during the last two years to offer you the best possible glaucoma meeting at the 6th World Glaucoma Congress.

The program includes topics from all the different areas of glaucoma research and practice: basic science, clinical science, surgery and translational science. With six plenary sessions, 16 symposia and more than 60 courses, there is plenty to learn and interchange. Earlier in the process, proposals for symposia and courses were received and evaluated. This allowed the participation of bright new colleagues willing to contribute with their ideas and experiences. The program, therefore, is nurtured from people with different backgrounds and from all over the world. The committee worked hard with the 600 abstracts submitted as posters. The best abstracts will be selected for brief presentations.

New this year, the Presidential Symposium: Glaucoma Innovation and Opportunities, is presenting the state of the art in glaucoma during the inaugural ceremony in the very first day of the Congress. From genetics, translational glaucoma or epidemiology to grand rounds, the film festival or hot debates in surgery, the list of topics covers all aspects of our subspecialty. The congress has around 300 faculties that will travel to Hong Kong from all over the world to share their knowledge. Among them are the worldwide known colleagues that have become the opinion leaders, but also new young professionals that are showing competence and knowledge as well as originality in publications and scientific meetings.

The program chairs were helped by the program committee members, suggestions from members of the Board of Governors, other colleagues, the MCI team, the WGA office and the leadership of Robert Fechtner and Jeffrey Liebmann. Thank you all for helping us to put together an outstanding program.

Come to the World Glaucoma Congress to learn, discuss, see old friends and make new ones. Grow your network and take home new ideas applicable in your practice and savour the food for thought that will accompany you on your way back.

See you in Hong Kong!

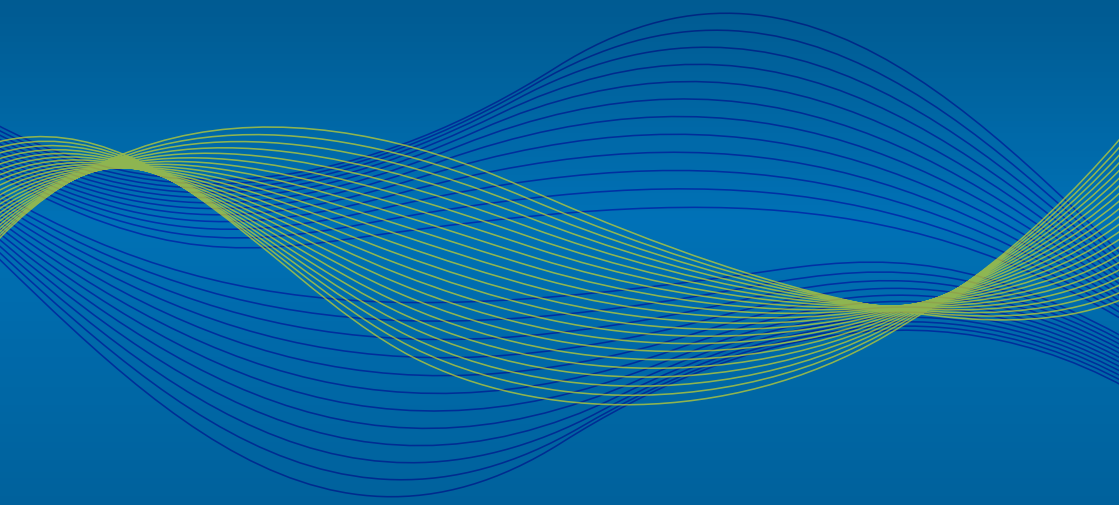
Program Planning Committee Co-Chairs,

Tin Aung

Jonathan Crowston

Fabian Lerner

Tarek Shaarawy



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Biotechnology advances 2014; 32: 971-983

The pathophysiology and treatment of glaucoma: a review

Weinreb RN, Aung T, Medeiros FA
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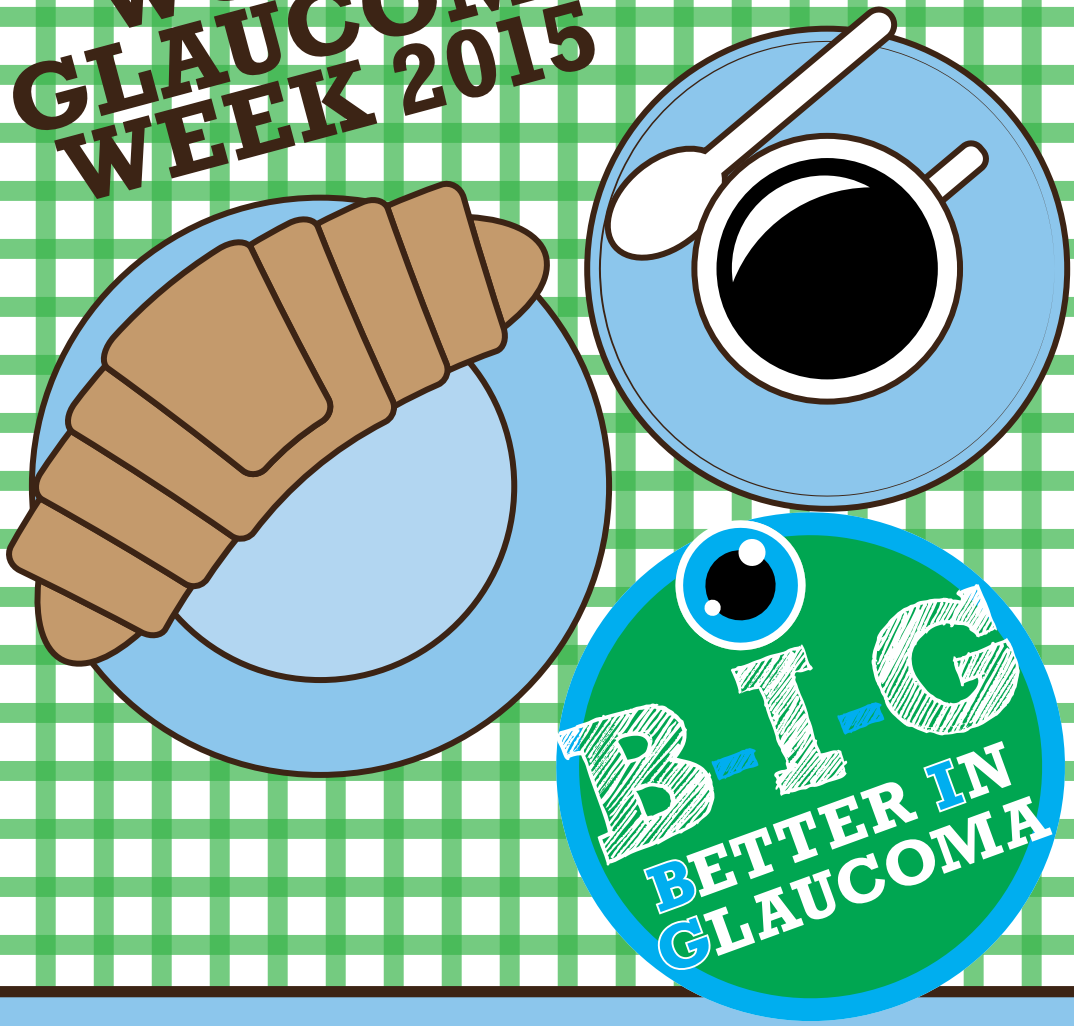

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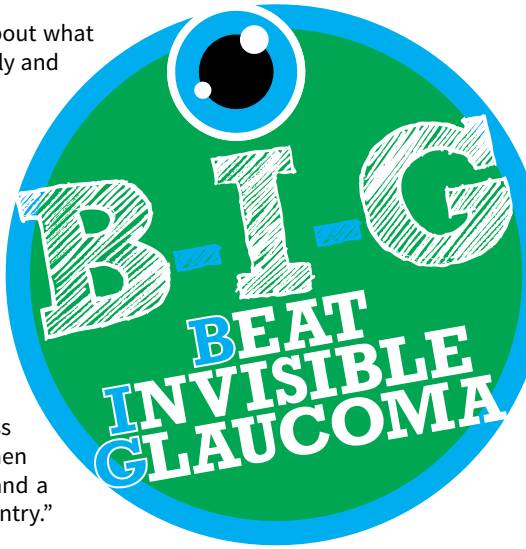
World Glaucoma Week 2015

World Glaucoma Week Committee members about what World Glaucoma Week means to them personally and why is it so important.



Harrison Abutiate
Ghana

"Thank God we have another opportunity to save some eyes of friends and family, from being stolen by glaucoma 'HINTA ANIFRAYE', the silent thief of sight. Our focus for free public eye screening and glaucoma awareness creation is on our market women who are regarded as mothers and a great economic block in the country."

Jillia Bird
Antigua

"Late diagnosis of open-angle glaucoma ruined the quality of my mother's life and by extension mine…not to mention the 5.9 million others worldwide estimated by 2020."

"WORLD GLAUCOMA WEEK successfully raises awareness of the Silent Thief of Sight in a B-I-G way, and helps to improve Early Detection and Treatment rates. Plus, raising awareness is FUN!"

María Alejandra Carrasco
Argentina

"What I enjoy most of the World Glaucoma Week is working together with ophthalmologists, patient associations, media and health authorities with the same objective: to diagnose the early glaucoma, preserve vision and quality of life of the population."

Ivan Goldberg
Australia

”It is the ‘sneak thief of sight’: glaucoma causes progressive visual loss; that loss is irreversible; it does not provoke symptoms till advanced; the afflicted person has no warning that slowly, steadily an undiagnosed condition is stealing away their vision. Early diagnosis and effective treatment are essential to minimize disability, which is tragic for the individual, for the family and for the community.“

“World Glaucoma Week coordinates activities around the world to increase awareness of the need for regular optic nerve checks to enable that earlier diagnosis. This applies especially to family members, who have a tenfold increased risk. World Glaucoma Week is an exciting, global initiative composed of hundreds of separate events with a common theme: be aware, get your eyes checked!”

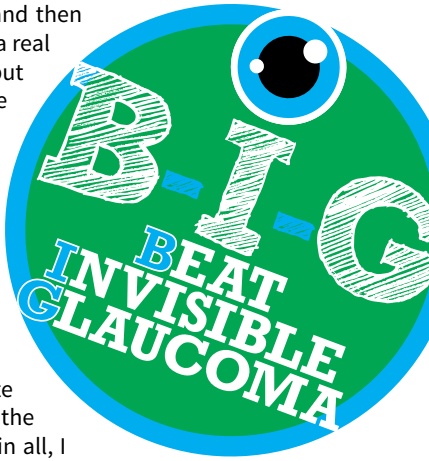
Visit www.wgweek.net to view the World Glaucoma Week 2015 activities map!

Geoff Pollard
Australia

”World Glaucoma Week is the opportunity to remind the community of the dangers of un-detected glaucoma, which remains a major cause of low vision and blindness worldwide. This is even more important for the direct (close) relatives of people already diagnosed with glaucoma as the incidence of glaucoma in that family group is up to ten times higher than the general community. Hosting a B.I.G Breakfast is an ideal way for a person to ensure their family knows to have regular optic nerve checks as part of a comprehensive eye test.”

Robert Ritch
United States of America

"When Ivan Goldberg and George Lambrou started the first World Glaucoma Day years ago, little did we know how it would grow into World Glaucoma Week and be celebrated worldwide. The first Glaucoma Day was a rather heady experience and took a lot of work to get off the ground. Making up the logo and then putting it into 50 different alphabets was a real job. Many countries participated actively, but the one that stands out is Antigua where Jillia Bird screened half the population of the island, held Glaucoma Day parades, TV and radio shows on glaucoma and even had a set of stamps issued by the government of Antigua. It was truly a remarkable job and Jillia now, having steadily moved up, is President of the World Glaucoma Patient Association. Another person who got strongly involved from the beginning was Harry Abutiate in Ghana, who is now Vice President of the World Glaucoma Patient Association. All in all, I remember it as a truly rewarding experience to have been able to pull off attracting so many people and so many countries in a relatively short period of time.



World Glaucoma Week grew partly out of the fact that different religions have holidays on different days of the week, and to have one day as a World Glaucoma Day at an inopportune time, led us to expand the events into World Glaucoma Week, affording the opportunity for greater expansion and more leeway for extended programs. All in all, it has done a great deal to increase glaucoma awareness."

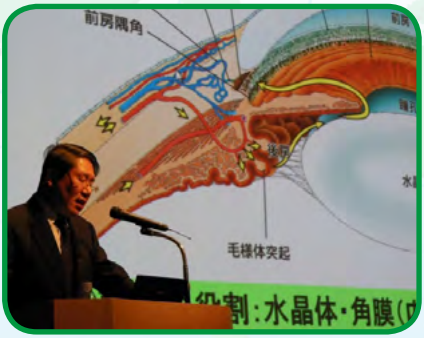
Tarek Shaarawy
Switzerland

"World Glaucoma Week has so far saved so many people, we remain determined to saving more and more"

Tetsuya Yamamoto
Japan

"The World Glaucoma Week is important because the prevalence of glaucoma is 5% in people aged over 40 years in Japan and most of the patients DO NOT know that they have suffered from it. I, very personally, remember that we conducted a large population study for glaucoma some 15 years ago in Tajimi City, and we were involved in it eagerly. Tajimi citizens are well motivated to screen eye diseases especially glaucoma since then. This is why WGA events have been most actively held in Tajimi since 2008. Dr Aiko Iwase, very enthusiastic lady doctor manages virtually all of the Tajimi events (Figs. 1 and 2). Glaucoma patients are very well managed in the city through her WGW activities and cares."

"Looking all over Japan, Japan Glaucoma Society and Glaucoma Friend Network, our glaucoma patients association, host several WGA events in Tokyo and Osaka every year (Figs. 3 and 4). Moreover, we plan to have a new event named 'Green Light-up' in five cities this year, which symbolizes glaucoma. We hope that the new strategy calls more attention from citizens."



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If you were unable to attend **WGC-2013** and you would be interested in registering for the virtual meeting, please visit the WGA website (**www.worldglaucoma.org**) for all details and a sneak preview of some of the symposiums.

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Glaucoma Opinion

Visual field testing in early glaucoma

C. Gustavo De Moraes
Edward S. Harkness Eye Institute
Columbia University Medical Center

There is a growing body of evidence that early **glaucomatous damage involves the macula**. The macula is often defined, but not always, as the retinal region within ± 8 degrees from the foveal center, although other authors employ other definitions. This area corresponds to about 2% of the retinal area, contains approximately 30% of the retinal ganglion cells (RGCs), and is represented by over 50% of primary visual cortex.[1,2] Loss of the macula and thus central vision significantly affects patients' health-related quality of life (HRQoL).[3-5] There is compelling evidence that glaucoma affects the macula and that macula damage can occur early in the disease process.[6]

> 24-2 SAP misses 16% of central field defects detected with 10-2 SAP and/or OCT

However, glaucomatous damage to the macula is often missed in clinical practice. Some of the reasons are: 1. traditional glaucoma knowledge supports that glaucoma is fundamentally a peripheral disease; 2. inherent limitations of conventional clinical tests to detect damage to the macula; and 3. the paucity of large, prospective studies that describe the nature of glaucomatous damage to the macula. We have shown that macular damage is prevalent among patients with early glaucoma if one employs the appropriate tools to assess it, namely 10-2 standard automated perimetry (SAP) and high-resolution optical coherence tomography (OCT). This information comes from a prospective database in which all patients with or suspected glaucoma have undergone 10-2 and 24-2 testing in an unbiased fashion.[6]

There is currently no gold standard to define progressive loss of visual function due to glaucoma, although the 24-2 SAP has been used for that purpose. However, 24-2 SAP misses 16% of central field defects detected with 10-2 SAP and/or OCT.[7] The primary reason for the poor performance is it does not sample the part of the central region most vulnerable to glaucoma. This can be seen in Figure 1 where the points of the 24-2 test pattern are superimposed on a pseudo-color map of the average RGC layer thickness loss in the macular region of an eye with early glaucomatous damage.[6]

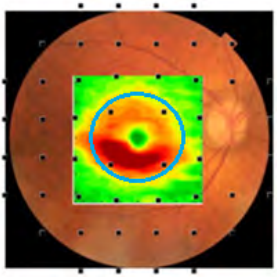

Fig. 1. The average loss of macular retinal ganglion cells + plexiform layer (RGC+) thickness of patients with early glaucomatous damage is shown in pseudo-color (hot colors meaning thicker). The RGC+ is superimposed on a fundus photo and 24-2 SAP grid. The visual field test points are morphed to account for the displacement between photoreceptors and RGCs. Note that only four of 54 locations are testing the macula (± 8°, blue circle) region and these are poorly sampling the region with the most RGC damage.[6]

Moreover, in some patients structural damage as measured with the fdOCT can be detected earlier than functional damage as measured with SAP.[8] Thus, the guidelines of first Consensus Meeting of the World Glaucoma Association stated that an accurate evaluation of glaucoma progression requires a combination of both structural and functional tests.[9]

Using a retrospective 10-2 longitudinal database,[10-12] we described the pattern of progression with this test, as an analogy to the studies using 30-2 fields performed over 20 years ago.[13] As shown in Figure 2, eyes with superior hemifield defects have an arcuate pattern approximately 3° to 5° above fixation, which is deeper in eyes with more advanced disease. As severity increases, the scotoma then elongates toward the physiologic blind spot and spreads toward the nasal periphery, sparing the area corresponding to the papillomacular bundle. For inferior hemifield defects, a similar pattern was seen, although it was slightly farther from fixation.[14]

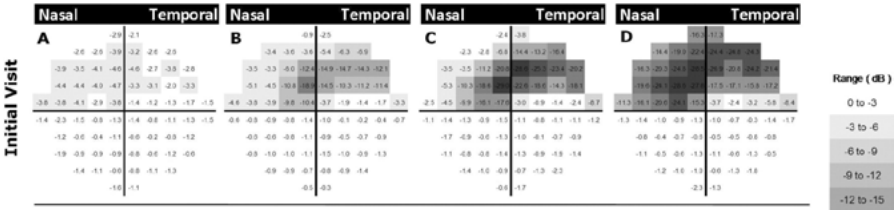

Fig. 2. Schematic view of the average pattern deviation maps of superior initial parafoveal scotomas of 80 eyes (all flipped to represent right eyes) in a cross-sectional analysis. 10-2 visual field results were divided into subgroups based on the severity of glaucoma using their pattern standard deviation (PSD). Cross-sectional data were used to create an average pattern deviation map that was generated by averaging pattern deviation map values of 10-2 visual field point-by-point within each subgroup (A, B, C, and D). The grayscale is shown on the right. Superior defects are present (A) in the earliest stage as a diffuse arcuate, (B) later in the disease process a deeper defect above the fixation point is seen. (C and D) The defect later appears larger and closer to the physiologic blind spot and the nasal periphery, sparing the area corresponding to the papillomacular bundle.

In another study, Hood *et al*.[14] tested an anatomical model of local glaucomatous damage to the macula with high density perimetric visual field data; the portion of the model associated with the upper visual field (inferior retina) is shown in Figure 3. The model accurately predicted a 'vulnerable macular region' and a 'less vulnerable macular region'. Note that there is a good correspondence between these vulnerability regions and the pattern of visual field damage described in Figure 2.

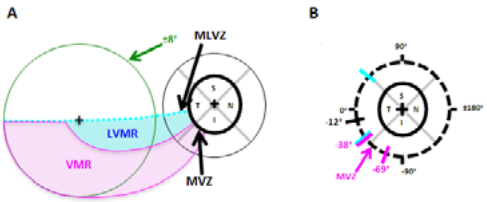

Fig. 3. According to the Hood model, there is a 'vulnerable macular region' (VMR, magenta) and a 'less vulnerable macular region' (LVMR, cyan). A. The portion of the model associated with the upper visual field (inferior retina) is shown; it contains a LVMR (cyan) and a VMR (magenta). B. The regions of the disc associated with the VMR and LVMR are indicated by the magenta and cyan diagonal lines, respectively.

> 10-2 tests rates of progression were up to two times faster than the corresponding 24-2 tests performed in the same eyes in the same follow-up period."

Additionally, we investigated whether 10-2 visual field tests detected more progression than the conventional 24-2 testing.[12] When comparing rates of progression of the 24-2 visual field index with the 10-2 central field index, 10-2 tests rates of progression were up to two times faster than the corresponding 24-2 tests performed in the same eyes in the same follow-up period. Figure 4 presents data from one such patient whose Humphrey visual field index revealed non-significant rates of progression (-0.2%/yr), whereas the 10-2 revealed catastrophic progression (−3.4%/yr).[12] If followed only with the 24-2, most clinicians would assume this eye would not become blind within the patient's life and would thus not modify treatment. However, a more detailed analysis with 10-2 fields shows this eye would become blind over ten times faster and thus enhanced treatment is advised.

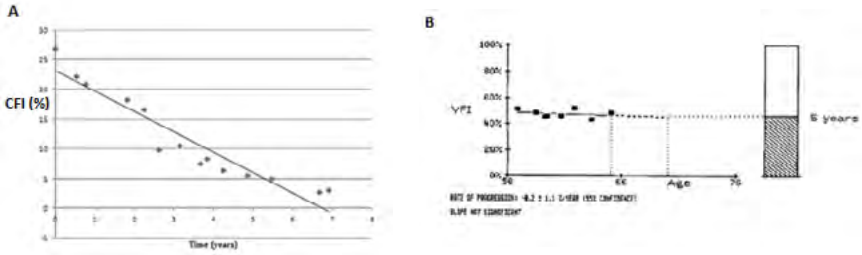

Fig. 4. A. The 10-2 central field index (CFI) of a patient over a seven-year period. B. The 24-2 visual filed index (VFI) from the Glaucoma Progression Analysis printout (GPA, Carl Zeiss Meditec, Inc., Dublin, CA) for the same data. Note that the slope measured with 24-2 fields did not reach statistical significance, although the CFI revealed a slope of -3.4%/yr at $P < 0.001$.

> Additionally, in some patients macular RGC loss measured with OCT can precede macular RNFL loss and may be missed with 24-2 SAP.

Additionally, in some patients macular RGC loss measured with OCT can precede macular RNFL loss and may be missed with 24-2 SAP. Figure 5 A and B depicts the macular retinal nerve fiber layer (mRNFL, left) and macular retinal ganglion cells + plexiform layer (mRGC+,

right) of a patient followed between 8/2008 and 2/2011. Note that there was a substantial drop-out in mRGC+ thickness in only one year (between 3/2009 [blue line] and 4/2010 [yellow]), which was not seen when measuring mRNFL thickness. Further, the 24-2 SAP tests in the period did not reveal any significant change (Figure 5D), although the 10-2 tests revealed expansion of a superior arcuate defect (Figure 5C).

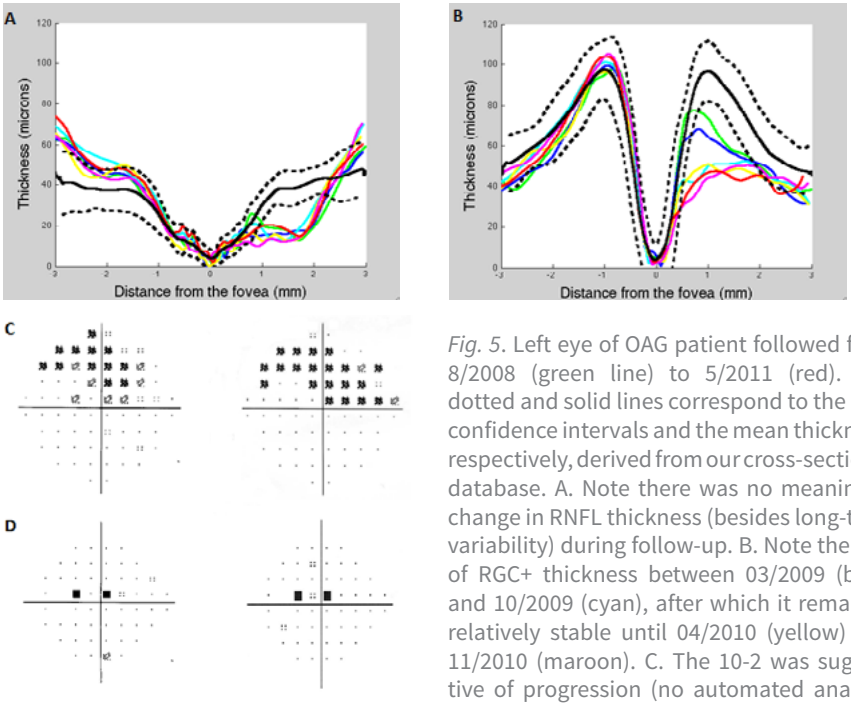

Fig. 5. Left eye of OAG patient followed from 8/2008 (green line) to 5/2011 (red). The dotted and solid lines correspond to the 95% confidence intervals and the mean thickness, respectively, derived from our cross-sectional database. A. Note there was no meaningful change in RNFL thickness (besides long-term variability) during follow-up. B. Note the loss of RGC+ thickness between 03/2009 (blue) and 10/2009 (cyan), after which it remained relatively stable until 04/2010 (yellow) and 11/2010 (maroon). C. The 10-2 was suggestive of progression (no automated analysis software available yet). D. The 24-2 did not reveal any significant change.

In summary, **clinicians should be encouraged to perform 10-2 visual field tests in patients with early glaucoma, and not only in severe cases with scotomata close to fixation**. In particular, eyes with clinical signs of glaucomatous optic neuropathy with normal 24-2 SAP or those with OCT findings suggestive of macular damage may benefit from 10-2 testing. If damage is then confirmed, these eyes should be followed with a combination of 24-2 and 10-2 tests to monitor progression.

Acknowledgement

I wish to thank Dr. Donald C. Hood, PhD, Columbia University.

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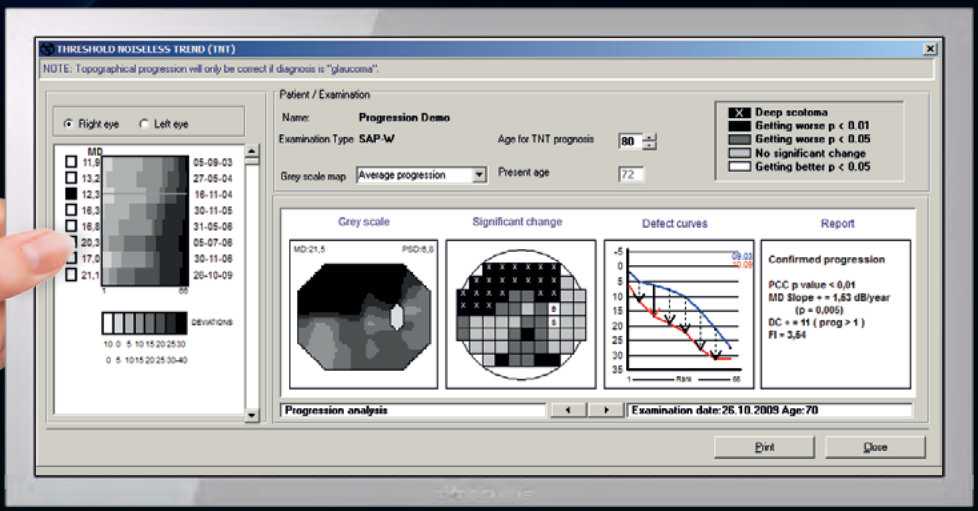

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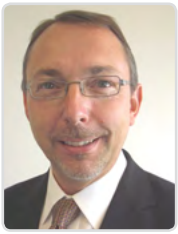
Meeting Highlights

Top-Five of the Optometric Glaucoma Society Meeting

Denver, Colorado, USA, November 10-12, 2014


Murray Fingeret, John Flanagan, Tony Realini

• Future clinical trial design can be shortened by using structure and function in combined hierarchical models in order to:

- compare the power of rate-based analyses with conventional survival analysis, using data acquired to optimize the measurement of rates;
- evaluate the (potential) gain to be derived from adding structure to function measurements;
- provide data on rate (velocity) of progression to power future trials and identify the shortest feasible trial duration.

(Ted-Garway Heath, London, UK)

• Progression can occur at all levels of intraocular pressure (IOP), which has motivated us to find additional susceptibility factors. It is intriguing to ask whether IOP's weak association with progression is attributable to other factors, or whether we are falling short in our approach to measuring IOP. (Ted-Garway Heath, London, UK)

• The relationship between IOP fluctuation and glaucoma progression remains inconclusive. An analysis of the data from the Advanced Glaucoma Intervention Study was among the first to demonstrate that patients with greater IOP variability were more likely to have progressive visual field changes over time. Other studies, such as the Early Manifest Glaucoma Trial, have failed to confirm this. Peak IOP, however, has been shown to be associated with disease progression. (Steve Mansberger, Portland, OR, USA)

• Our observation of early preferential loss of inferior macular ganglion cells led us to examine the relationship between structural and functional loss in glaucoma. To compare OCT of the macula to visual fields, we utilize a 10-2 testing pattern. With 24-2, only four of the test locations fall within the macula; with 10-2 testing, most of its points fall within the same region. We found that a 10-2 field often showed small paracentral defects attributable to early macular ganglion cell loss. (Donald Hood, New York, NY, USA)

• Non-adherence is a significant problem in glaucoma. Studies have demonstrated that patients who do not adhere to their treatment regimen are more likely to progress than those who do. In one study, the risk of progression was nearly twofold higher among non-adherent patients. (Steve Mansberger, Portland, OR, USA)

Top-Four of the Scientific Meeting of the Australian and New Zealand Glaucoma Interest Group

Brisbane, Queensland, Australia, February 6-7, 2015

Anne Brooks

• Intraocular pressure – Complexities and clinical relevance

IOP is a dynamic parameter that undergoes constant variation, along with a circadian rhythm in which IOP is higher at night than during the day. A major cause of IOP variation is changes in head and body positions, which result in IOP elevation with neck flexion or extension, or any recumbent position. Aqueous humor dynamics studies have indicated that positional changes in IOP are likely due to changes in episcleral venous pressure. In contrast, the circadian rhythm of IOP appears to be largely due to a nocturnal reduction in aqueous humor production rate, outflow facility, and uveoscleral flow rate. Although the clinical significance of IOP variations remains to be fully elucidated, appropriate selection of therapy can help to minimize fluctuations. (Arthur Sit, Rochester, MN, USA)

• Twenty years of remote and indigenous health

Over a period of 17 years, the Cape York Eye Health Project has provided 18,841 Optometrical Consultations, 9848 spectacles, 7530 Diabetic consultations, 4010 Ophthalmic consultations and 1,196 surgeries, mostly cataract, to a remote population of 17,000 people spread across a landmass the size of the state of Victoria. The most significant obstruction to the project has been the Federal State three-year political cycle, the one year public servant turnover cycle, and the six- to 12-month staff turnover in remote clinics. The other significant problem is that that 'medical' health delivery systems are only the tip of the health iceberg. Health care involves a seamless journey from conception to a healthy and stimulating childhood, to an advanced education, a job and home ownership. This is a journey that is denied in its entirety to up to a million Australians, including a sizeable part of the Indigenous population. A breakdown in this journey particularly at the level of conception to the age of five years can result in poor health outcomes, poor job outlooks, poverty and in many cases jail. Comprehensive health care, and attendant educational capacity, starts at conception. (Mark Loane, Brisbane, Australia)

• Single cell electrophysiology following acute intraocular pressure elevation in mice

Following an acute IOP injury in mice, retinal ganglion cells show impaired ability to generate action potentials measured using whole cell patch clamp. This impaired excitability recovered at a later stage and was associated with an increase in ganglion cell membrane resistance suggesting morphological change over time.

Slower recovery of excitability was observed in older animals, which correlates with previous data using the electroretinogram to measure ganglion cell function. (Eamonn Fahy, Melbourne, Australia)

• Use of trypan blue dye in diagnosis of hypotony

Bill Morgan presented an novel technique using trypan blue as an aqueous humor tracer dye to visualize the preferential flow pattern of aqueous following its injection into the anterior chamber. In cases of hypotony where the diagnosis is unclear it is most useful in highlighting preferential flow into cyclodialyisis clefts and can be seen to reflux back from the cleft during aspiration aiding the demarcation of such clefts. It is useful also in detecting occult bleb leak, over drainage and excess lymphatic flow from blebs. (Bill Morgan, Perth, Australia)

Top-Five of the Latin American Glaucoma Society (SLAG) Meeting

Bogotá, Colombia, November 21-22, 2014

Sebastião Cronemberger

• The assessment of retinal nerve fiber layer (RNFL) thickness and the stereometric parameters of the optic nerve head (ONH) are indispensable to establish the differential diagnosis between megalopapilla (pseudo glaucoma) and glaucoma. Two patients (mother, 31 years old and her daughter, three years old, who had had unnecessary antiglaucomatous treatment for two years) had the diagnosis of megalopapillae (the optic discs areas were equal to or larger than 3.37 mm^2 in both patients by confocal scanning laser ophthalmoscopy (CSLO, HRTII). The complete ophthalmic examination, including the diurnal curve of IOP with the IOP measurement at 6:00 a.m. with Perkins tonometer with the patients in a supine position in bed and in darkness and before they had stood up, central corneal thickness measurement and the peripapillary RNFL thickness measurement using the spectral domain optical coherence tomograghy (Spectralis HRA + OCT) were normal. The mother's standard automated perimetry was also normal. (Sebastião Cronemberger, Brazil)

• Unlike classic trabeculectomy, the trabeculectomy with suprachoroidal derivation has the advantage of using two different drainage pathways to lower the IOP, the anterior chamber to subconjunctival space fistula and the uveoescleral drainage through the suprachoroidal space. This novel procedure achieved a statistically significant reduction of the intraocular pressure after 24 months of follow-up. It is an effective and safe surgical technique. (Rodolfo A. Perez Grossmann, Perú)

• Laser iridotomy (guidelines)
When? 1. Acute primary angle closure; 2. Contralateral eye; 3. Potential occludable angle (very narrow angle in at least two quadrants or 180° with less than 20°, Shaffer I-II); 4. Pigment dispersion syndrome: only in patients < 40 years old presenting a posterior iris convexity by UBM.
How? Location: nasal or temporal superior quadrant to avoid prismatic effects and ghost images; Technique: one to five shots of 5-15 mJ. No repetition of shots in the same place. If a partial opening is seen, we must reduce the strength before the second shot; Complications: slight hemorrhage (up to 71.2% of patients); posterior synechiae (9.6%); iritis (6.4%); IOP increase (9.8%); cataract (16.7%) (LOCS III). (John Jairo Aristizabal, Colombia)

• Ten normal volunteers were examined with the GDx in a two-day protocol under eight testing conditions (1% pilocarpine, 10% phenylephrine, 1% tropicamide, or no drops, with room lights on or off). The twelve GDx's parameters were compared under the eight testing conditions, using two ways ANOVA for repeated measurements and Tukey HSD post hoc test. Ten of the twelve parameters were statistically significantly different ($P < 0.05$) when measured under the three medication or no medication conditions, controlling for the ambient light status. There were no significant differences when measured with the light on or off, controlling for use of drops. Nerve fiber layer measurements with the GDx were influenced by drugs affecting pupillary diameter, but not by the status of room light or ciliary muscle tone. (Augusto Paranhos, Brazil)

• An Atlas of Glaucoma (Apple Story) was launched and the SLAG members discussed and approved the first Latin-American Consensus on primary angle-closure glaucoma.

Top-Six of the Russian Glaucoma Society Annual Meeting

Moscow, Russia, December 5-6, 2014

Eugeny Egorov

The Congress, as was planned, brought together more than 1200 participants from Russia, the Commonwealth of Independent States (CIS) and other countries (incl. Austria, Bulgaria, Finland, Germany, Italy, Canada, etc). The Congress had 29 interesting sections and more than 120 reports.

• Morphological changes in visual centers seen in Alzheimer disease and glaucoma are indicative of transsynaptic extension of pathological process to central nervous system structures in both conditions. (Valery Erichev, Moscow, Russia)

• Yuri Astakhov discussed the clinical implications of risk factors and particularly the contribution of correct evaluation of objective findings, targeted selection of patients for advanced glaucoma examination, adequate choice of medications and timely referral for surgical treatment. (Yuri Astakhov, Saint-Petersburg, Russia)

• Blood flow deficiency in retrobulbar vessels plays more important role at the beginning of glaucoma development. (Nataly Kurysheva, Moscow, Russia)

• Dmitry Sychev reported the mechanisms of tolerance impairment in the course of IOP-lowering therapy and particularly quantitative and qualitative changes in biotargets and effector systems of conjunctiva and sclera cells. (Dmitry Sychev, Moscow, Russia)

• When using BB + PG fixed combination it is less expensive to achieve 'target' IOP-level and the number of patients achieving the recommended IOP-level is higher compared to the other fixed combinations of glaucoma medications. (Alex Kuroyedov and the Scientific Vanguard Group, Russia, Belarus, Kazakhstan, Uzbekistan)

• Under current conditions, the problem of patient's active involvement in the course treatment is becoming a problem of crucial importance. A patient should be taught of rules and standards of prophylactic medical examination, technique of eye drops and other medications administration, IOP-level and visual field self-control tests. (Olga Kiseleva, Moscow, Russia)

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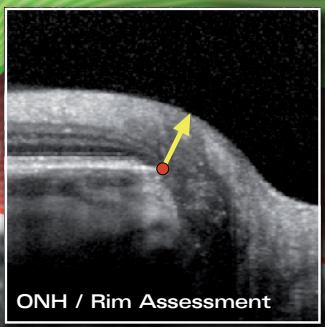

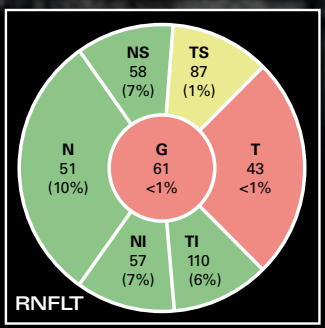

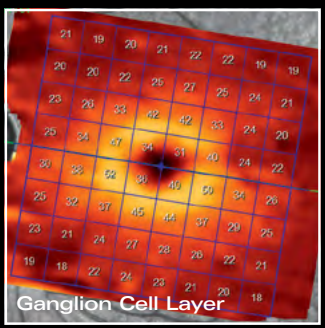

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Editor's Selection

With the multitude and variety of publications it seems almost impossible for the ophthalmologist to intelligently read all the relevant subspecialty literature. Even the dedicated glaucomatologist may have difficulty to absorb 1200+ yearly publications concerning his/her favorite subject. A solution to this confusing situation may be a critical selection and review of the world literature.

Robert N. Weinreb, Chief Editor

Anatomical structures

Laminar alterations and disc hemorrhage

Comment by Atsuya Miki, Osaka, Japan

56961 Recent structural alteration of the peripheral lamina cribrosa near the location of disc hemorrhage in glaucoma, Lee EJ, Kim TW, Kim M, Girard MJ, Mari JM, Weinreb RN, Investigative Ophthalmology and Visual Science 2014; 55: 2805-2815

Disc hemorrhage has long been associated with both development and progression of glaucoma.[1] Nevertheless, the exact mechanism for disc hemorrhage in glaucoma is yet to be determined. In this study, Lee and colleagues proposed a possible association between disc hemorrhage and the lamina cribrosa deformation in glaucomatous eyes using enhanced depth imaging optical coherence tomography (EDI OCT). Previously, one cross-sectional study suggested a relationship between disc hemorrhage and lamina cribrosa deformation.[2] The authors of the current study conducted a prospective study to further clarify this potential relationship.

In 45 eyes with glaucoma, EDI OCT images taken before and after the occurrence of disc hemorrhage were compared to see whether there is any structural alteration of the lamina

cribrosa. Structural alteration in this study was defined as either an outward deformation or a radial disruption of the lamina cribrosa exceeding the limit of test-retest variability. Forty out of 45 eyes with disc hemorrhage (88.9%) showed structural alteration, whereas only 11.1 % (4/36) of control eyes (glaucomatous eyes without disc hemorrhage for at least one year) did so. In addition, the largest structural alteration occurred in areas near the disc hemorrhage location in all eyes in the disc hemorrhage group. These results support the notion that **disc hemorrhage and structural alteration of the lamina cribrosa occur concurrently or within a very short interval** in the process of glaucomatous optic nerve damage.

This study suggests that disc hemorrhage is not only a risk factor for glaucoma but is directly involved in the pathophysiology of glaucomatous optic neuropathy. Despite several limitations the authors mentioned in the discussion, the findings of the current study is a significant step forward for the better understanding of the pathogenesis of glaucomatous optic neuropathy, as well as for the better risk profiling of glaucoma.

> Disc hemorrhage is not only a risk factor for glaucoma but is directly involved in the pathophysiology of glaucomatous optic neuropathy

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Disc characteristics and RNFL defects

Comment by Harsha Rao, Hyderabad, India

57392 Optic disc characteristics in patients with glaucoma and combined superior and inferior retinal nerve fiber layer defects, Choi JA, Park HY, Shin HY, Park CK, JAMA ophthalmology 2014; 132: 1068-1075

Optic disc phenotype has long been a topic of interest in glaucoma management. There have been previous studies evaluating the relationship between optic disc phenotypes and glaucoma. In a recent cross-sectional study, Choi et al. compared the optic disc characteristics of glaucomatous eyes with initial single hemisphere involvement to glaucomatous eyes with initial bi-hemisphere involvement. They found that **greater disc ovality**

on fundus photographs (defined as the ratio between the longest and shortest optic disc diameters) and larger horizontal tilt angle on optical coherence tomograph scans were significantly associated with bi-hemisphere involvement in early glaucoma. The authors discussed that the degree of optic disc tilt seemed to be an indicator of altered biomechanics of the posterior peripapillary sclera in eyes with glaucoma. They also hypothesized that eyes with glaucoma and increased optic disc tilt may be associated with the relatively symmetrical shearing forces across the superior and inferior sides of the lamina cribrosa compared with eyes with other disc phenotypes. This is an interesting new finding which has potential clinical implications. However, the relationship between optic disc phenotype and the severity of glaucoma may not be that simple. Although disc ovality was statistically significantly associated with bi-hemisphere damage, the strength of association was quite poor. The coefficient of determination of the univariate associations between bi-hemisphere damage and either the disc ovality score or the horizontal tilt angle was around 4%. The same result for the multivariate model was not provided by the authors. Nevertheless, the current study definitely provides a starting point for exploring the mechanical theory of glaucomatous damage further. Recent optical coherence tomography techniques have also opened up avenues to better evaluate the optic disc phenotype and with greater objectivity. Longitudinal studies evaluating optic disc characteristics in suspect eyes developing glaucoma and established glaucoma eyes that progress would be able to provide more robust evidence for the importance of optic disc phenotype in glaucoma.

Basic Science

Trabecular structure and pilocarpine effects

Comment by Michael Fautsch, Rochester, MN, USA

57211 The structure of the trabecular meshwork, its connections to the ciliary muscle, and the effect of pilocarpine on outflow facility in mice, Overby DR, Bertrand J, Schicht M, Paulsen F, Stamer WD, Lütjen-Drecoll E, Investigative Ophthalmology and Visual Science 2014; 55: 3727-3736

One of the challenges in glaucoma research is the inability to generate animal models that represent the disease. This is in part due to the differences in outflow pathways between primate and non-primate animals. Mice, like humans, have a continuous Schlemm's canal, a lamellated trabecular meshwork and they do not exhibit washout. In this interesting study by Overby and colleagues, they describe the three-dimensional structure of the ciliary muscle in mice and found significant similarities with primate eyes. For example, the investigators found an intricate elastin fiber network that connects the inner wall of Schlemm's canal to the cornea anteriorly, the ciliary body internally and the choroid and ciliary muscle posteriorly. Additionally, the authors identified tendons extending from the ciliary muscle to the juxtacanalicular region, inner wall of Schlemm's canal and ciliary body, populating the extensive elastin network, similar to primate eyes. The authors also showed that the ciliary body and trabecular meshwork are innervated by VAChT-containing nerve fibers, and that addition of pilocarpine can influence outflow facility in perfused eyes.

> One of the challenges in glaucoma research is the inability to generate animal models that represent the disease

Together, **these findings show significant similarity to primate eyes suggesting that ciliary muscle tendon integration into the elastin network within the trabecular meshwork may provide a mechanism for active regulation of outflow by contraction and relaxation of the ciliary muscle**. This would presumably affect outflow facility by maintaining patency of the Schlemm's canal by modulating tension on the inner wall and juxtacanalicular tissue, similar to what has been proposed for primates. This is an excellent paper that further validates mice as an animal model that can be used to understand the role of aqueous humor dynamics and IOP in normal and glaucoma-like models of the disease. Future studies examining aged mouse models will be important to determine whether they show thickening and extracellular matrix changes seen in human aged normal and glaucoma eyes.

Translaminar pressure gradient

Comment by Rand Allingham, Durham, NC, USA

57047 Optic neuropathy induced by experimentally reduced cerebrospinal fluid pressure in monkeys, Yang D, Fu J, Hou R, Liu K, Jonas JB, Wang H, Chen W, Li Z, Sang J, Zhang Z, Liu S, Cao Y, Xie X, Ren R, Lu Q, Weinreb RN, Wang N, Investigative Ophthalmology and Visual Science 2014; 55: 3067-3073

Damage to retinal nerve fibers at the lamina cribrosa is pathognomonic for glaucoma. While it has been clear for over a century that IOP plays an important role in glaucomatous optic neuropathy (GON), numerous population-based studies have found that normal IOP is present in a high percentage of glaucoma cases. More recently, there has been a growing interest in how the translaminar pressure difference, produced by IOP and cerebrospinal fluid pressure (CSFp), may be related to GON. Several retrospective and prospective clinical studies support the role of reduced CSFp in POAG. Notably lacking have been chronic animal models to investigate this hypothesis. In the first of its kind, Yang and co-workers have studied the effect of *chronically* reduced CSFp in an experimental monkey model. A lumbar-peritoneal CSF shunt was placed in eight animals, was opened in four and remained closed in the control group. CSFp was reduced from 7.4 mmHg to 1.6 mmHg in the experimental group and was unchanged in the control group. Animals were examined regularly for a year. Reduced CSFp was associated with bilateral, progressive reduction in retinal nerve fiber layer thickness (RNFL) in two of four study animals, a disc hemorrhage in a third animal, and no changes in a fourth. Monkeys that demonstrated reduced RNFL also had reduced optic nerve rim area and increased optic nerve cupping. However, deformation of the lamina cribrosa was not observed. Control animals demonstrated no changes.

> Several retrospective and prospective clinical studies support the role of reduced CSFp in POAG. Notably lacking have been chronic animal models to investigate this hypothesis

This study suggests that **chronically reduced CSFp produces RNFL thinning and optic nerve changes that are similar to those seen in GON**. Longer-term observation and histological studies are needed to clarify the nature of this optic neuropathy and its relationship with glaucoma. The implications of this research, if confirmed, represents a major step forward in our understanding of the disease we call glaucoma.

Measuring scleral stiffness non-invasively

Comment by Crawford Downs, Birmingham, AL , USA

57212 Noninvasive measurement of scleral stiffness and tangent modulus in porcine eyes, Leung LK, Ko MW, Ye C, Lam DC, Leung CK, Investigative Ophthalmology and Visual Science 2014; 55: 3721-3726

Scleral biomechanics likely plays an important role in the development and progression of glaucoma and myopia, but the contribution of scleral material properties (stiffness) to these diseases is not well understood. Experimental and numerical studies indicate that the peripapillary sclera is influential in determining ONH biomechanics because it defines the mechanical boundary condition for the contained ONH at the scleral canal, and scleral elongation is a central pathologic feature in myopia development. Leung and colleagues describe a method to measure scleral tangent modulus using a five-mm-diameter flat indenter in intact eyes. They tested this method in 15 porcine eyes *ex vivo*, and calculated scleral stiffness and tangent modulus as a function of IOP. **Both scleral stiffness and tangent modulus were positively correlated with IOP**, which matches previous results from inflation studies of both human and non-human primate scleral shells. The methodology used relies on several key assumptions for calculation of the reported parameters. First, the reaction of the intact eye to perturbation, in this case indention, involves stretching of the entire ocular coat including the cornea and ONH. Ocular rigidity is a well-known metric of this phenomenon. So, the change in IOP resulting from scleral indentation is confounded by the reactions of the cornea and ONH, which was not taken into account. Also, initial IOP was controlled with a needle into the anterior chamber during the indention experiments, and therefore some reflux into the needle would be expected with a one-mm-depth indention that occurred over three seconds, confounding the IOP response measurement. Finally, the calculations of scleral wall stress, and hence tangent modulus, were based upon Laplace's Law, which is only valid for perfectly spherical pressure vessels of uniform thickness and homogeneous material properties – none of these strictly apply to the eye. Hence, while indention may yet prove to be a plausible method to measure scleral biomechanics *in vivo*, additional validation is needed.

A susceptibility gene in zebrafish and men

Comment by Calvin Pang, Hong Kong, P.R. China

57288 Discovery and functional annotation of SIX6 variants in primary open-angle glaucoma, Carnes MU, Liu YP, Allingham RR, Whigham BT, Havens S, Garrett ME, Qiao C, Katsanis N, Wiggs JL, Pasquale LR, Ashley-Koch A, Oh EC, Hauser MA, PLoS Genetics 2014; 10: e1004372

This is a paper on an important study that involves sequence characterization, functional analysis in zebrafish, and clinical investigation of patients carrying specific sequence variants. First, the **identification of a common variant, Asn141His (rs33912345), in the *SIX6* gene and its association with primary open-angle glaucoma (POAG, $p = 4.2 \times 10^{-10}$) was reported**. In another study by Iglesias *et al*.,[1] rs33912345 was also associated with POAG ($p = 6.09 \times 10^{-3}$). This variant is in linkage disequilibrium with another *SIX6* variant rs10483727, which was associated with POAG in a genome-wide association study by Wiggs *et al*.[2] These findings together give evidence for *SIX6* as a susceptibility gene of POAG.

Carnes *et al*. also demonstrated that the *SIX6* variants have functional impacts on SIX6 expression and protein function. Particularly, **an approximately threefold reduction in optic nerve volume was found upon depletion of the *six6a* ortholog in Zebrafish**, indicating the involvement of SIX6 in the development of the optic nerve. SIX6 thus may have biological implications in glaucoma.

In clinical investigations of 30 POAG patients, Carnes *et al*. found that the rs33912345 risk allele (C) was correlated with thinner retinal nerve fiber layers (RNFL). Interpretation of this, however, should be cautious, as the authors did not address the severities of glaucoma in the patients. It is possible that patients carrying the C allele might have more advanced glaucoma than those with the non-risk allele (A). Glaucoma staging and severity should be taken into account. Nevertheless, in a recent study by Cheng *et al*.,[4] the C allele was associated with thinner RNFL in nonglaucomatous eyes, in line with the findings of this paper, which gives important information on the association of *SIX6* variants with the progression of RNFL loss in glaucoma.

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Autoregulation of ONH blood flow

Comment by Alon Harris, Indianapolis, IN, USA

57185 Longitudinal alterations in the dynamic autoregulation of optic nerve head blood flow revealed in experimental glaucoma, Wang L, Cull G, Burgoyne CF, Thompson S, Fortune B, Investigative Ophthalmology and Visual Science 2014; 55: 3509-3516

A complete understanding of the complex physiology of vascular regulation in ocular tissues remains enigmatic in glaucomatous optic neuropathy due to imaging specific modalities, location of measure, and various other methodological considerations. In an effort to advance our understanding of the dynamic nature of blood flow autoregulation during fluctuating perfusion pressure Wang and colleagues present a novel dynamic autoregulation (dAR) analysis to explore the hypothesis that the optic nerve head (ONH) blood flow autoregulation is disrupted during early stages of experimental glaucoma (EG) in non-human primates. The authors' work builds upon their previous finding that ONH blood flow is mildly increased during an early stage of EG and thereafter declines progressively in close correlation with the loss of retinal nerve fiber layer thickness. In the current investigation, the authors' dAR modeling focuses on the time course of the ONH blood flow response within the first 60 seconds after the IOP challenge, whereas their previous methodology (static autoregulation) was limited to a measurement window of after a three-minute or greater period of stabilization.

> The authors' works depict a complex pattern of hemodynamic changes within the ONH after chronic IOP elevation

The authors found **IOP predominates within the first few seconds, causing a steep blood flow decrease at a constant rate of decline; and after the initiation of autoregulation, equivalence was gradually reached at a given time point**. The authors' works depict a complex pattern of hemodynamic changes within the ONH after chronic IOP elevation suggesting a biphasic, stage-dependent response and impaired dynamic autoregulation in EG. The authors should be congratulated, as their work is thoughtfully

planned and very specific to a time course of autoregulation assessment not previously investigated. The authors' novel findings shed light on the complex and truly dynamic physiology of vascular response to fluctuating perfusion pressure and contributing ischemic insult to the ONH in glaucoma.

One limitation of this investigation is that perfusion pressure may affect ONH blood flow differently if manipulations are induced by IOP variation compared to blood pressure fluctuations. Another factor to consider is the use of a single blood flow imaging technique (laser speckle imaging), which limits applicability of these results to the ONH without corresponding measures in the retina. Overall, these data provide an outstanding contribution to the field and the novel findings advance our understanding of vascular contributions to glaucomatous pathophysiology.

Neuroprotection

Comment by Adriana DiPolo, Montreal, Quebec, Canada

57402 Neuroprotective effects of C3 exoenzyme in excitotoxic retinopathy, Wang Y, Wang Y, Yang Q, Guo L, Yin Y, Fan N, Zhou X, Cai SP, Kaufman PL, Liu X, Experimental Eye Research 2014; 125: 128-134

The C3 exoenzyme is a toxin produced by the bacterium *Clostridium botulinum* that selectively inhibits a subfamily of the Rho GTPases (RhoA, RhoB and RhoC). These Rho proteins regulate multiple processes including actin dynamics and cell motility in response to extracellular signals. Inactivation with C3 was previously shown to stimulate retinal ganglion cell survival and axon regeneration after optic nerve crush.[1,2]

Wang et al. investigated the effect of intravitreal administration of C3 on N-methyl-D-aspartate (NMDA)-induced retinal damage in adult Sprague-Dawley rats. Their data convincingly show that **C3 attenuated thinning of the inner plexiform layer and apoptotic cell loss in the ganglion cell layer**. However, **the neuroprotective effect of C3 was transient and did not reach significant values at 72 hours after administration**.

The results are interesting and support a beneficial role of C3, however, the findings presented could be extended in a number of ways. First, the quantification of cells in the ganglion cell layer was carried out using cresyl violet, which does not distinguish ganglion cells from displaced amacrine cells.

> C3 might exert a combination of neuroprotective and pressure lowering effects that might be highly beneficial in the context of glaucoma

Given that both cell types are susceptible to NMDA damage, the extent of C3-mediated neuroprotection specifically on ganglion cells remains to be determined. Second, the NMDA model is acute and leads to extensive retinal damage. It will be of future interest to evaluate the efficacy of C3 in glaucoma models. Lastly, although the survival effect of C3 is likely to occur via Rho inhibition, its precise mechanism of action is unknown. Future studies are needed to identify effectors downstream of Rho that promote neuronal survival.

Interestingly, it is now recognized that RhoA and its target Rho kinase (ROCK) regulate cytoskeleton dynamics in trabecular meshwork cells hence controlling aqueous humor outflow.[3] (Pattabiraman and Rao, 2010). Furthermore, C3 was shown to increase outflow facility in organ cultures of monkey anterior segments (Liu et al., 2005). This raises the intriguing possibility that C3 might exert a combination of neuroprotective and pressure lowering effects that might be highly beneficial in the context of glaucoma.

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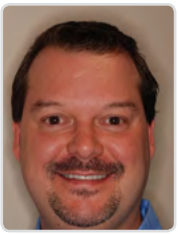
Clinical Examination Methods

IOP fluctuation



Comment by Tony Realini, Morgantown, West Virginia, USA

57023 Circadian intraocular pressure patterns in healthy subjects, primary open angle and normal tension glaucoma patients with a contact lens sensor, Agnifili L, Mastropasqua R, Frezzotti P, Fasanella V, Motolese I, Pedrotti E, Iorio AD, Mattei PA, Motolese E, Mastropasqua L, Acta Ophthalmologica 2014; 0:

Agnifili and colleagues from Italy have conducted an interesting prospective study in which healthy subjects, normal-tension glaucoma patients, and primary open-angle (high-tension) glaucoma patients (one eye from ten individuals in each group) underwent continuous 24-hour intraocular pressure (IOP) monitoring using the Triggerfish contact lens-based device. The Triggerfish device does not directly measure IOP but rather infers it based on changes in corneal curvature; the device's output is not measured in pressure units but in millivolt equivalents. The outcome of interest was the 24-hour IOP pattern of each group. Such studies have been completed previously, albeit using intermittent (every one to three hours) IOP assessments via more familiar tonometers (Goldmann, pneumotonometer, etc.); a few 24-hour studies have also been conducted with the Triggerfish, but these have not directly compared outcomes in different patient groups. This study's results support that the device's output does reflect IOP qualitatively: as is known from prior studies, the **current study demonstrated nocturnal IOP peaks in all three groups**. Interestingly, both the height and the breadth of the nocturnal peak was greatest in the POAG group, followed by the NTG group, and finally by the normal group.

> It is important to identify the specific IOP behaviors that increase the risk of progression

Taken on their own, **these data reveal potential differences in circadian IOP variability both between the glaucomatous and normal states**, and smaller (and insignificant given the sample size) differences between POAG and NTG. In a broader context, this study – like others before it – offer a preview of the potential clinical application of this and other continuous IOP monitoring devices. Certainly there will not be a need to know the circadian behavior of every one of our glaucoma patients – for instance, it would have little relevance in a patient with stable structural and functional parameters. In a progressing patient – particularly one whose daytime office-based IOP seems adequately controlled – characterization of nocturnal IOP could reveal uncontrolled IOP elevations that might warrant more intensive nighttime therapy to suppress. Much more work is necessary,

however, to more fully characterize circadian IOP using this and other devices. For, as this study demonstrates, even normal subjects exhibit nocturnal IOP elevations. Given this, what is the clinical relevance of a nocturnal IOP rise in a progressing glaucoma patient? Continuous circadian IOP monitoring addresses the problem we face of a low sampling rate for IOP assessment. What remains, however, is to identify the specific IOP behaviors that increase the risk of progression.

Visual Field progression

Comment by Murray Fingeret, Brooklyn, NY, USA

57477 Evaluation of Octopus Polar Trend Analysis for detection of glaucomatous progression, Holló G, Naghizadeh F, European Journal of Ophthalmology 2014; 24: 862-868

The detection of visual field progression is an important part of the management of individuals with glaucoma. To improve the recognition of field progression, the manufacturers continue to modify their displays to alert clinicians when change is developing. The Octopus Polar Trend Analysis (PTA) (Haag-Streit AG, Koeniz-Berne, Switzerland) is part of the software analysis package for the Octopus perimeter. PTA provides a visual display of points getting worse (or better), using the spatial relationship between the test location and retinal nerve fiber layer (RNFL) angle to the optic disc as its method of display. Quantified data are not provided as this display is meant to alert the clinician the change and the need to evaluate other parts of the progression software package. PTA is based upon linear pointwise linear regression analysis, which is an analytic tool also used in other progression tools. In this study by Hollo and Naghizadeh, the ability of PTA to detect change in 52 individuals with glaucoma followed over a 5 year period was investigated. Subjects were divided between progressors and non-progressors. OCT RNFL and Ganglion Cell complex (GCC) linear regression analysis was also performed over time. Only up to 50% of the group showing change with PTA also showed progression upon OCT analysis. This finding has been seen before and is always surprising as there are differing ways that progression develops. The correlation between structural and functional tests often is not strong. For the progression group in this study, change was identified earlier with PTA. **This study confirmed that the PTA display was able to recognize change** and importantly, provided an alert to clinicians that they need to be concerned that the condition was not stable and their patients require further assessment.

Macular perimetric defects

Comment by Shaban Demirel, Portland, OR, USA

57448 A Test of a model of glaucomatous damage of the macula with high-density perimetry: implications for the locations of visual field test points, Hood DC, Nguyen M, Ehrlich AC, Raza AS, Sliesoraityte I, De Moraes CG, Ritch R, Schiefer U, Translational Vision Science & Technology 2014; 3: 5

Recently, there has been increased interest regarding when macular visual function is compromised in glaucoma that has resulted in reevaluation of the dogma that glaucoma is a disease of the peripheral visual field until quite late in its course. In this article, Hood *et al*. test a model of glaucomatous macular (central 8° radius) visual field damage. Their proposition is that the macular representation of the visual field is comprised of a less vulnerable macular region (LVMR), predominantly in the inferior visual field but also including a small part of the cecocentral superior visual field, and a vulnerable macular region (VMR) within the superior visual field. This uneven vulnerability of the central visual field is due to the relative vertical offset of the fovea and optic nerve head (ONH) in the retina and the fact that axons from retinal ganglion cells (RGCs) responsible for the superior macular visual field (in the inferior retina) enter the ONH predominantly in its relatively more susceptible inferior quadrant. Axons from RGCs that are responsible for the LVMR in the inferior macular visual field (in the superior retina) enter the ONH predominantly in its relatively less susceptible temporal quadrant.

In addition, the authors set out to determine if individualizing visual field assessment for each eye, based on its relative positioning of fovea and ONH, improved performance over an analysis that treated all eyes the same. Finally, Hood et al. examined the impact of adding two additional test locations to the commonly used 24-2 visual field pattern on the ability to detect visual field abnormalities in 31 eyes selected because they had scotoma affecting the superior macular region.

Results were fairly decisive. In eyes that were selected because they displayed localized damage to the superior macula visual field, damaged locations were significantly more likely to be in the VMR. Between 35 and 77% of visual field locations in the VMR were damaged, depending on the criterion used, compared to between three and 35% of LVMR locations being damaged when using the same criteria. However, **there seemed to be little benefit (*i.e.*, increasing the number of VMR locations showing damage while decreasing the number of LVMR locations showing damage) when visual field analysis was individualized, except perhaps in eyes that displayed the most extreme anatomy.**

Perhaps the result that had the most immediate clinical applicability was the finding that **adding two locations to the 24-2 visual field pattern greatly increased the number of VMR region abnormalities that were detected.** The authors suggest that this kind of hybrid test pattern could put us on a path to detecting macular visual field defects without the need to perform both a 24-2 and a 10-2 test. However, the search for best placement of additional test locations was not exhaustive, as only locations that were part of the 10-2 pattern were considered. Therefore, the optimal placement for additional test locations in a hybrid visual field test remains to be determined. Still, the prospect of extracting almost as much information from a hybrid visual field pattern as from the 24-2 and 10-2 tests in combination should be exciting to patients, technicians and physicians alike.

Translaminar pressure gradient

Comment by Tae-Woo Kim, Bundang-gu, Seongnam, Korea

57451 Estimated trans-lamina cribrosa pressure difference versus intraocular pressure as biomarker for open-angle glaucoma. The Beijing Eye Study 2011, Jonas JB, Wang NL, Wang YX, You QS, Xie XB, Yang DY, Xu L, Acta Ophthalmologica 2014; 0:

Jonas et al. examined whether an estimated trans-lamina cribrosa pressure difference (TLCPD), which was based on the body mass index, diastolic blood pressure and age, correlated with markers for glaucoma better than intraocular pressure (IOP). They found that open-angle glaucoma (OAG) was associated with higher TLCPD but not with IOP. In addition, retinal nerve fiber layer thickness was associated with lower TLCPD but not with IOP. Taken together, **TLCPD as compared with IOP was better associated with the presence of open angle glaucoma and with the amount of glaucomatous optic nerve damage.** The results of this study are in line with the previous studies and support that low orbital cerebrospinal fluid pressure may play a role in the pathogenesis of glaucomatous optic neuropathy. Stronger association of TLCPD than IOP was not observed with angle closure glaucoma, which is generally considered to be derived from pure IOP elevation.

Primary open-angle glaucoma is a multifactorial disease, in which various parameters are considered to be involved. Although elevated IOP is a well-known risk factor for primary OAG, it is frequent to see patients with IOP within the statistically normal range. It is not uncommon to see large backward bowing of the lamina cribrosa in those patients as is in patients with high tension glaucoma.[1] One may hypothesize that lower orbital cerebrospinal fluid pressure may be related with this phenomenon by facilitating the posterior displacement of the lamina cribrosa by the IOP-induced mechanical stress. Although the individual variation of true orbital CSF pressure is currently unknown as it is not currently

measurable, one may consider the possibility that the IOP-induced mechanical stress may still play a significant role in the optic nerve damage even in eyes with low IOP. Low CSF pressure may be one factor that makes this scenario possible.

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Comment by Sung Chul Park, New York, NY, USA

57451 Estimated trans-lamina cribrosa pressure difference versus intraocular pressure as biomarker for open-angle glaucoma. The Beijing Eye Study 2011, Jonas JB, Wang NL, Wang YX, You QS, Xie XB, Yang DY, Xu L

Cerebrospinal fluid (CSF) has been implicated in the pathogenesis of primary open-angle glaucoma (POAG). Low CSF pressure[1-3] and stagnated CSF around the optic nerve head[4,5] have been demonstrated in eyes with POAG. Theoretically, lower CSF pressure may result in greater trans-lamina cribrosa pressure difference (TLCPD) and consequently greater stress and strain in the lamina cribrosa, contributing to development and progression of glaucomatous optic neuropathy.

Jonas *et al.* investigated the association between TLCPD and presence/severity of OAG and angle-closure glaucoma (ACG), by calculating the CSF pressure using an equation derived from a previous study. They found that the **presence/severity of OAG was more strongly associated with TLCPD than with intraocular pressure (IOP), whereas the presence/severity of ACG was associated only with IOP.** As acknowledged by the authors, this study is limited by the use of calculated CSF pressure, not directly measured one.

> The thickness, density and rigidity of the lamina cribrosa and surrounding sclera will influence the physical/biological changes in the lamina cribrosa associated with TLCPD

Additionally, because both eyes of subjects were included in the analysis, it is possible that the data from one eye were included in the glaucoma group and the data from the fellow eye were included in the non-glaucoma group, while the body-mass-index and blood pressure data of the subject were used in both glaucoma and non-glaucoma groups.

Despite these limitations, the authors' findings are informative and warrants more elaborate investigations on the role of CSF pressure in the glaucoma pathophysiology.

Various noninvasive methods to measure the CSF pressure have been suggested including untrasound time of the flight techniques, transcranial Doppler ultrasonography, and tympanic membrane displacement, but more reliable and reproducible method to measure the CSF pressure is needed considering that CSF pressure measured by lumbar puncture may be different from the CSF pressure around the optic nerve head. Investigators should also consider that similar TLCPD does not necessarily mean similar stress and strain in the lamina cribrosa. For example, an eye with TLCPD of 10 mmHg may have IOP of 15 mmHg and CSF pressure of 5 mmHg, or IOP of 30 mmHg and CSF pressure of 20 mmHg. Additionally, the thickness, density and rigidity of the lamina cribrosa and surrounding sclera will influence the physical/biological changes in the lamina cribrosa associated with TLCPD.

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Aqueous dynamics assessment by MRI

Comment by Carol Toris, Cleveland, OH, USA

57078 In vivo assessment of aqueous humor dynamics upon chronic ocular hypertension and hypotensive drug treatment using gadolinium-enhanced MRI, Ho LC, Conner IP, Do CW, Kim SG, Wu EX, Wollstein G, Schuman JS, Chan KC, Investigative Ophthalmology and Visual Science 2014; 55: 3747-3757

Clinical studies of aqueous humor dynamics are key to understanding the normal physiology of the eye, pathological changes in diseases that affect IOP and mechanisms by which glaucoma treatments work. When it comes to uveoscleral outflow, the problem has always been finding methods that are accurate, reproducible, sensitive to small changes and of course, noninvasive. Ho and a strong team of seven other investigators describe a new *in vivo* method to assess aqueous humor dynamics in rats that one day may be applicable to spatiotemporal studies of aqueous humor dynamics in humans.

Gadolinium (Gd) -enhanced MRI enabled examination of fluid movement through the eye under several experimental conditions that changed IOP. Altered aqueous humor dynamics and ocular tissue permeability changes were monitored over time in a noninvasive manner. The rats were divided into four groups, one group with microbead injections into the anterior chamber to obstruct the trabecular meshwork and increase fluid resistance, and three groups treated with either, timolol, latanoprost or brimonidine, drugs that lower IOP by different mechanisms. Detailed statistical tests were undertaken of the MRI images of the anterior chamber and vitreous cavity that included initial rate of Gd signal increase, peak GD signal enhancement, time to peak, and area under the curve in the Gd signal time courses. The microbead injections increased IOP, and the MRI images showed reduced Gd clearance from the anterior chamber suggesting slowed drainage. The three glaucoma drugs lowered IOP and showed increased Gd clearance from the anterior chamber suggestive of improved drainage (latanoprost) or slowed production (timolol) or possibly both (brimonidine). Additionally, brimonidine affected the Gd signal of untreated fellow eyes indicating systemic effects from topical dosing.

A future study of chronic glaucoma that masks the treatment groups and measures flow rates in microliters per minute will be a gigantic step towards a new, long-awaited research tool for clinical study of aqueous humor dynamics.

Detecting glaucoma

Comment by Steve Mansberger, Portland, OR, USA

56995 Glaucomatous optic neuropathy evaluation project: factors associated with underestimation of glaucoma likelihood, O'Neill EC, Gurria LU, Pandav SS, Kong YX, Brennan JF, Xie J, Coote MA, Crowston JG, JAMA ophthalmology 2014; 132: 560-566

This study evaluated the detection of glaucoma using 42 non-stereoscopic optic disc photographs and estimated the optic disc characteristics that influence detection. The 197 participants used an online website to grade the photographs for features of glaucoma including disc size, shape, tilt, peripapillary atrophy, vertical cup-to-disc ratio, cup shape, cup depth, retinal nerve fiber layer defects, and presence of disc hemorrhage. They used a four-point scale from unlikely (score 1) to certain (score 4) to estimate the probability of glaucoma.

The authors used the grades from 37 glaucoma specialists as the reference standard and defined misclassification when the participant's score differed by > one point. A participant score higher than the reference score was overestimation of glaucoma, and a lower score was underestimation. **Ophthalmology trainees and comprehensive ophthalmologists**

misclassified optic discs at a rate of 35% and 33%, respectively with similar rates of underestimation (~23%) and overestimation (~10%) of glaucoma. Features associated with misclassification included detection of nerve fiber loss, disc hemorrhage, rim loss (or thinning), and vertical cup-to-disc ratio. Large discs were associated with an overestimation of glaucoma likelihood.

Eye care providers need better case finding of glaucoma

The study limitations are clearly outlined in the manuscript. The study results may be different from the true clinical situation because participants did not have access to stereoscopic photographs. Also, the study did not externally validate the results to a dilated eye exam in a medical clinic, which is most likely the true clinical situation for case finding of glaucoma. It is not clear how the participants would be able to estimate the size of the optic discs considering this feature was most common with overestimation of glaucoma.

This study provides important information regarding the features of glaucoma that result in misclassification. Evaluation of the optic disc remains a key part of the ophthalmic examination, and for case finding of glaucoma. Several population-based studies suggest that approximately 40% of patients with glaucoma were unaware they had glaucoma despite a recent eye exam. Overall, this suggests that eye care providers need better case finding of glaucoma and the manuscript suggest targets of teaching for trainees and clinicians.

Comment by Remo Susanna Jr., Sao Paulo, Brazil

56995 Glaucomatous optic neuropathy evaluation project: factors associated with underestimation of glaucoma likelihood, O'Neill EC, Gurria LU, Pandav SS, Kong YX, Brennan JF, Xie J, Coote MA, Crowston JG, JAMA ophthalmology 2014; 132: 560-566

In this Internet-based study with multinational participation, a series of 42 monoscopic optic disc photographs of healthy and glaucomatous eyes were presented to clinicians using the GONE Project Program Ophthalmology. Participants were ophthalmic clinicians, glaucoma subspecialists, comprehensive ophthalmologists, and ophthalmology trainees from 22 countries who self-registered for the Glaucomatous Optic Neuropathy Evaluation.

Trainees and comprehensive ophthalmologists underestimated glaucoma likelihood in a mean (SD) of 22.1% (1.6%) and 23.8% (1.8%) of discs, respectively. Ophthalmology trainees and comprehensive ophthalmologists overestimated glaucoma likelihood in a mean (SD) of 13.0% (1.2%) and 8.9% (1.3%) of discs, respectively based on optic discs graded by glaucoma subspecialists.

Underestimation of vertical cup-disc ratio and failure to identify retinal nerve fiber layer loss, disc hemorrhage, or rim loss were most likely to lead to underestimation of glaucoma.

Overestimation of glaucoma likelihood was associated with overestimation of retinal nerve fiber layer loss, rim loss, vertical cup-disc ratio, disc hemorrhage, and incorrect assessment of disc tilt and was more likely in large discs.

There are several limitations of this study, some of them pointed out by authors include the use of monoscopic disc images, and differences in the skill of the expert group (invited) and participants (self-selected) of different countries.

The ability to detect the disease may be influenced by time of experience, continuous medical education, conditions of work, and other factors. Because of that, the current findings of this study cannot be generalized to all general ophthalmologists. Also the participants are from different countries with different expertise on diagnosing glaucoma. Depending on the quality of the medical education in each country and the other parameters cited above, the results could be influenced in one-way or another. It would be nice if the authors have presented this information.

Also the interobserver agreement in glaucoma likelihood (κ, 0.63; 95% CI, 0.60-0.67) for the glaucoma subspecialists reflects that there is still a substantial disagreement between them.

Despite of that, the results of this study are in agreement with two previous studies[1,2] with different methodology and provides important targeted teaching tools for medical education modules, focusing on specific aspects of disc examination.

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Medical Treatment

Long-lasting drug delivery

Comment by Tina Wong, Singapore

57479 28-day intraocular pressure reduction with a single dose of brimonidine tartrate-loaded microspheres, Fedorchak MV, Conner IP, Medina CA, Wingard JB, Schuman JS, Little SR, Experimental Eye Research 2014; 125: 210-216

This study describes the use of microspheres as a drug delivery carrier for controlled drug delivery of anti-glaucoma drug, brimonidine tartrate, by a single subconjunctival injection. **Both *in-vitro* and *in-vivo* studies were conducted as a proof of principle and showed extended IOP reduction in normotensive rabbits over a 28-day period.**

In order for a drug delivery system to really indicate clinical promise, a few critical questions on the delivery system must be addressed.

Calculation of the entrapment efficiency as well as efforts to remove un-entrapped drug from the microspheres would provide additional information on the characteristics of the microsphere delivery platform as well as to distinguish the localization of the drug, *i.e.*, whether the drug is loaded in the core or on the periphery of the microspheres for more accurate characterization.

Supporting studies on the mechanism of release are essential to determine the fate of the particles under *in vivo* conditions

Initial two-day-released amounts are not reported here, and therefore it is plausible to consider that the drug may not be distributed homogenously in the microspheres, therefore lending to an initial burst effect in the first few days. As a consequence, this could have an effect on the total extended release period of the microsphere system and its ability to provide steady consistent IOP lowering *in vivo*. Interestingly, the release rate per day hovers around the maximum allowable brimonidine concentration which would appear that the system is quite efficient at loading brimonidine. However, modifications into PLGA microspheres to reach a release rate in between the minimum and maximum allowable concentrations would be more ideal.

It is hard to confirm by visual inspection alone that particle degradation occurs by day 35. Supporting studies on the mechanism of release are essential to determine the fate of the particles under *in vivo* conditions. Although the formulation appears to demonstrate some positive effects in animals, it is clear that more mechanistic work is required in the understanding of the system and to establish the actual release *in vivo* and longer term effect of a single-dose application.

Surgical treatment

Prophylactic Iridotomy in Angle-Closure suspects

Comment by Tin Aung and Mani Baskaran, Singapore

56868 Association between baseline iris thickness and prophylactic laser peripheral iridotomy outcomes in primary angle-closure suspects, Lee RY, Kasuga T, Cui QN, Porco TC, Huang G, He M, Lin SC, Ophthalmology 2014; 121: 1194-1202

In this paper, Lee *et al*.[1] evaluated the association of iris thickness (IT at 750 microns and 2000 microns) using anterior segment optical coherence tomography (ASOCT) before laser peripheral iridotomy (LPI) with angle widening (as assessed by trabecular iris-space area -TISA at 500 and 750 microns from the scleral spur) after laser peripheral iridotomy (LPI). The study was conducted on 52 hospital-based primary angle closure suspect (PACS) patients of Caucasian and Chinese ethnicity. They found that a **thinner iris was predictive of wider angle width after LPI**, after adjusting for age, gender and pupil diameter. These findings may have implications in predicting which angle closure patients will respond well to LPI.

This study used a simple model and did not consider the influence of lens factors such as the lens vault, or intraocular pressure, which are important components of the anterior chamber milieu that determines angle width and the pressure difference between the anterior and posterior chambers.[2] The sample size was small and of mixed ethnicity. Iris thickness is a dynamic factor, however, only static measures were collected in the study.

An earlier study in a larger sample of Chinese subjects found contradictory findings,[2] namely a thicker iris (as measured by iris thickness at 2000 microns) was associated with greater change in angle width, after adjusting for other factors such as lens vault, anterior chamber width, axial length and intraocular pressure.

> Further work is suggested using the three-dimensional scans available with swept source anterior segment OCT

Factors related to how the images were obtained may have influenced the difference in findings. The posterior limit of the iris is generally imaged poorly with ASOCT, and the iris measurements can be prone to errors due to poor delineation of the posterior pigmented layer. The extent of angle widening after LPI may differ between light and dark conditions, and according to the position of iris insertion.[3]

Further work is suggested using the three-dimensional scans available with swept source anterior segment OCT, which by utilizing iris and angle data over 360°, may be more accurate and have lower variability compared to ASOCT.

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Comment by Robert Feldman, Houston, TX, USA

56868 Association between baseline iris thickness and prophylactic laser peripheral iridotomy outcomes in primary angle-closure suspects, Lee RY, Kasuga T, Cui QN, Porco TC, Huang G, He M, Lin SC, Ophthalmology 2014; 121: 1194-1202

Anterior segment optical coherence tomography (ASOCT) is becoming an increasingly valuable tool with which to evaluate the anterior segment. ASOCT provides high resolution images of the anterior segment from which quantitative information about the angle can be derived. While gonioscopy is still an invaluable examination tool, ASOCT offers new opportunities to evaluate how anatomy is related to anterior segment disease.

The spectrum of primary angle closure (PAC) disease (including primary angle closure suspects [PACS], PAC, and primary angle closure glaucoma [PACG]) is precipitated by changes in anterior segment anatomy.

> Further study into the dynamics of the iris with treatment is important to unlocking the mechanism of this disease and in monitoring continued efficacy of treatment.

Iris anatomy and configuration is an important facet of the disease process and severity, and thicker irides have been suggested to be associated with angle closure. However, characterization of and the role the iris plays in the disease mechanism has not yet fully been elucidated.

The goal of Lee *et al.*'s study was to determine if there was an association between baseline iris parameters and a change in the iris anatomy after laser peripheral iridotomy (LPI). ASOCT images were obtained from 52 White and Chinese PACS patients before and after LPI. Iris thickness, curvature, and trabecular-iris space area (TISA) at 500 µm (TISA500) and 750 µm (TISA750) from the scleral spur were evaluated.

They found that lower baseline iris thickness was associated with a decrease in iris curvature and an increase in TISA after LPI, meaning thinner irides were more likely to exhibit a greater flattening and opening of the angle with LPI.

While the results of this study are important and a crucial start to examining the role of the iris in angle closure, there are limitations. **Data was only analyzed with images from the nasal quadrant**, which limits extrapolation of this data to the entire angle circumference. This was due to limitations of the ASOCT technology employed in this study (1 meridian was imaged). Newer technology, such as with Tomey's CASIA SS-1000 (Nagoya, Japan) can now image 128 meridians (256 angles, or every 1.4 degrees) and provide three dimensional reconstruction, which can provide information about the entire peripheral angle. However, this study does demonstrate the anatomic efficacy of LPI and presents a possible factor for quantitating efficacy.

Further study into the dynamics of the iris with treatment is important to unlocking the mechanism of this disease and in monitoring continued efficacy of treatment.

Side effects from iridotomy-on-the-side

Comment by Stefano Gandolfi, Parma, Italy

56864 Dysphotopsia after temporal versus superior laser peripheral iridotomy: a prospective randomized paired eye trial, Vera V, Naqi A, Belovay GW, Varma DK, Ahmed II, American Journal of Ophthalmology 2014; 157: 929-935

The authors have addressed the issue of newly-onset visual disturbances after an uneventful laser peripheral iridotomy (LPI) in eyes with angle closure. Traditionally, most of the available guidelines and textbooks suggest to place the LPI in an iris area fully covered by the upper eyelid, thereby reducing the possibility of symptoms induced by the straylight entering freely into the eye through the iridotomy. Recently, several reports, showing patients complaining of symptoms in spite of a fully covered LPI, have raised new doubts on where to place the LPI in order to avoid dysphotopsias.

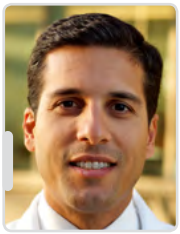
Vera et al. enrolled, then, 208 patients, with bilateral angle closure, and placed LPI temporally in one eye and superiorly in the other. **Dysphotopsia proved more common in eyes with superior LPI (10.7%) than in eyes with temporal LPI (2.4%)**. This striking difference

is highly significant. In fact, the study is properly sized to support the conclusions, and the scientific reasoning is consistent with the outcomes: interestingly, the authors' data support the hypothesis that a 'base-up' prism-like effect, induced by the tear meniscus, is the responsible for the onset of dysphotopsia when LPI is placed superiorly.

> Recently, several reports, showing patients complaining of symptoms in spite of a fully covered LPI, have raised new doubts on where to place the LPI in order to avoid dysphotopsias

Vera *et al*.'s conclusions push the scientific community to re-consider the preferred pattern of LPI placement in eyes with angle closure. Gathering comparable data in different anatomical phenotypes (for example in eye with pigment dispersion syndrome and a deep anterior chamber) could prove useful and informative.

Selective Laser Trabeculoplasty



Comment by Kaweh Mansouri, Geneva, Switzerland

57327 Predictors of success in selective laser trabeculoplasty for Chinese open-angle glaucoma, Lee JW, Liu CC, Chan JC, Lai JS, Journal of Glaucoma 2014; 23: 321-325

Selective laser trabeculoplasty (SLT) is controversially discussed as first-line therapy in glaucoma patients. Its use has experienced numerous ups and downs, depending on geography, reimbursement rates, and other factors. With the introduction of alternative technologies (*e.g*., pattern scanning laser and micropulse trabeculoplasty) laser therapy is attracting increasing interest.

> The effect of SLT on NTG has not been widely studied.

Despite its widespread use, important issues such as an understanding of the exact mechanisms by which SLT works, as well as predictors of success remain largely unknown.

Lee *et al*. investigated the determinants of succes after SLT in a Chinese population from Hong Kong. Patients received bilateral 360° SLT in the same session. This study is of interest for several reasons. First, little data is available on SLT efficacy in Chinese populations. Second, nearly half of patients had normal tension (NTG) glaucoma.

The effect of SLT on NTG has not been widely studied. **The authors reported a success rate of 53%** (*e.g*., IOP-lowering of ≥ 20 mmHg after one month), **with a mean IOP-lowering of 19.8%**. **In successful eyes, IOP lowering was 32%, demonstrating SLT's usefulness in**

NTG eyes. This level of IOP reduction could label SLT a 'laser prostaglandin' under two caveats: It works in roughly one out of two eyes and with diminishing results over time.

Being able to better predict which eyes would respond might increase clinician's acceptability of SLT. This study shows that higher baseline IOP, thinner RNFL thickness, and use of topical cardbonic anhydrase inhibitors are associated with SLT success. This latter result is perplexing and the authors theorize that its is not so much the use of CAIs but rather the absence of prostaglandin eyedrops, in line with the presumed pro-inflammatory effects of SLT. This finding needs confirmation. A recent study did not find higher success in eyes without anti-inflammatory therapy after SLT.[1] Limitations of the study are the short follow-up and absence of appropriate statistical analysis to account for the inclusion of both eyes of the same patients.[2]

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Aqueous drainage devices

Comment by Brian Francis, CA USA

57092 Three-year Treatment Outcomes in the Ahmed Baerveldt Comparison Study, Barton K, Feuer WJ, Budenz DL, Schiffman J, Costa VP, Godfrey DG, Buys YM, Ophthalmology 2014; 121: 1547-1557.e1

This study discusses the three-year results of a randomized trial (Ahmed Baerveldt Comparison Study) of the treatment of glaucoma with the two most commonly used aqueous tube shunts: the Ahmed Glaucoma Valve FP-7 (AGV) and Baerveldt Glaucoma Implant 350 (BGI). The authors defined failure as IOP > 21 mmHg or not reduced by 20% from baseline, IOP < 5 mmHg, reoperation for glaucoma or removal of implant, or loss of light perception vision, and found that the **success rates were similar between the two groups**. **However, the AGV group required more medications and resulted in a greater risk of reoperation for glaucoma**. **The BGI group experienced more serious postoperative complications** (associated with a two-line decrease in Snellen acuity or need for further surgical intervention to treat the complication) than the AGV group.

The study groups were comprised of patients meeting the criteria for 'refractory glaucoma' for which aqueous tube shunt surgery was recommended. These criteria included: failed

trabeculectomy or history of other intraocular surgery, diagnosis of secondary glaucoma known to have a high failure rate with trabeculectomy (such as neovascular, uveitic, or ICE syndrome). The randomization scheme was appropriately rigorous and included stratification based on diagnosis. Neither the investigator nor the patient was masked to the treatment arm. The retention of patients was excellent at one year (132/143 AGV, 116/133 BGI) and good at three years (106, 100).

> If a patient has moderate glaucoma and is more tolerant of using glaucoma medications, they may be more appropriate for an Ahmed valve

The primary outcome measure was failure to control IOP, and as noted this was similar between the groups. The authors have a detailed subanalysis that helps to elucidate the more subtle differences between AGV and BGI groups. Thus, as clinicians, we can tailor surgical treatment based on patient needs.

For example, if a patient has moderate glaucoma and is more tolerant of using glaucoma medications, they may be more appropriate for an Ahmed valve. However, if a patient has lower IOP requirements and is less tolerant of glaucoma medications, a Baerveldt implant may be more beneficial.

A similar randomized trial, the Ahmed versus Baerveldt (AVB) Study, has similar findings, albeit with a lower failure rate for BGI than AGV reaching statistical significance. While the current study found more complications in the BGI group, the AVB Study reported no significant difference, but with a higher surgical reintervention rate in the BGI group.

In conclusion, with the increase in aqueous tube shunt implantations, it is important to delineate the differences in performance between implants. This allows more informed decision-making on the part of the patient and surgeon. The ABC Study is a key step in this direction.

Comment by Steven Gedde, Miami, FL, USA

57192 Effect of early treatment with aqueous suppressants on ahmed glaucoma valve implantation outcomes, Pakravan M, Rad SS, Yazdani S, Ghahari E, Yaseri M, Ophthalmology 2014; 121: 1693-1698

Pakravan and colleagues conducted a randomized clinical trial to evaluate the effect of early treatment with aqueous suppressants on the outcomes of Ahmed glaucoma valve (AGV) implantation. Patients undergoing AGV surgery were randomized to receive timolol-dorzolamide fixed-combination drops twice daily when the intraocular pressure (IOP) exceeded ten mmHg, or conventional medical therapy. A stepwise regimen of glaucoma

medications was used in both study groups to maintain IOP at a target level of 15 mmHg or less. Mean IOP was lower in the group with early aqueous suppressant treatment at 54 weeks (14.0 mmHg vs 16.8 mmHg, p = 0.012), despite a similar mean number of glaucoma medications (1.8 vs 1.6, p = 0.184). **The success rate (6 mmHg < IOP < 15 mmHg and ≥ 30% reduction from baseline) was higher in the group receiving early medical treatment at one year (63.2% vs 33.3%, p = 0.008).** The frequency of a hypertensive phase (IOP > 21 mmHg in first three months postoperatively) was reduced in the early treatment group (20.4% vs 66.0%, p < 0.001), but no significant difference was observed in the rate of choroidal effusions or other complications between study groups.

> Early treatment with aqueous suppressants after AGV implantation may beneficially influence surgical outcomes by reducing the level of inflammatory mediators delivered to the plate and/or decreasing the hydrostatic pressure in the bleb with less compression of the capsule

The capsule surrounding the end plate of a glaucoma drainage implant offers the major resistance to aqueous outflow through the device. An early exposure of the plate to aqueous humor rich in inflammatory mediators could contribute to the development of a thicker capsule. A higher hydrostatic pressure within the bleb cavity may also compress and compact the capsule, resulting in decreased permeability. Early treatment with aqueous suppressants after AGV implantation may beneficially influence surgical outcomes by reducing the level of inflammatory mediators delivered to the plate and/or decreasing the hydrostatic pressure in the bleb with less compression of the capsule.

Subjects enrolled in the study were relatively young (mean age 44 years), and only 2.1% had primary open-angle glaucoma. This is not a typical population undergoing glaucoma surgery and could affect the generalizability of findings. The target pressure of 15 mmHg in the study may have been more aggressive than needed and resulted in overtreatment in some patients. Subdividing subjects into qualified and complete successes is less meaningful, given the different criteria for use of medical therapy between study groups. The AGV is a valved implant, and study results may not be applicable to non-valved implants that delay aqueous humor delivery to the end plate. Despite these limitations, the authors are to be congratulated for adding important information to the medical literature regarding glaucoma drainage implants.

Drug-delivery implant

Comment by Malik Kahook, Denver, CO, USA

57435 Evaluation of an injectable thermosensitive hydrogel as drug delivery implant for ocular glaucoma surgery, Xi L, Wang T, Zhao F, Zheng Q, Li X, Luo J, Liu J, Quan D, Ge J, PLoS ONE 2014; 9: e100632

Long-term drug delivery using polymeric depot reservoirs for the treatment of various ophthalmic diseases has been extensively studied. In this report, Xi and colleagues investigate the use of a thermosensitive hydrogel for controlled release of mitomycin C (MMC) both *in vitro* and *in vivo*. The effects of MMC (both with and without gel) *in vitro* and *in vivo* were predictable with cytotoxicity and prolonged survival of blebs in treated rabbits. **The duration of bleb survival in both MMC and Gel+MMC were similar and in line with previous publications.** The initial burst release of MMC from the hydrogel was significant (> 50%/24 hr) revealing that further work will be needed to enhance the delivery profile and to potentially expand this system as a platform technology.

> A major hurdle is proving an advantage of a long-term depot over current methods of drug delivery that would justify a change in practice

Creating long-term drug delivery systems for ophthalmic applications is difficult and this study illustrates some of the obstacles that are present when attempting to translate findings from *in vitro* to *in vivo*. One specific hurdle is scaling up production of product in a way that is feasible economically. The authors state the 'simple preparation [of the gel] can avoid the denaturation of bioactive proteins and peptides that results at extreme conditions (*e.g.*, heating, organic solvent, etc.)'. Realistically, the same simple preparation methods used in small scale studies will not be feasible when attempting to increase batch manufacturing while adhering to good manufacturing practice (GMP) standards that are required by regulatory agencies.

Another major hurdle is proving an advantage of a long-term depot over current methods of drug delivery that would justify a change in practice. While this report illustrates a novel method for delivering MMC to the subconjunctival space in a rabbit model of glaucoma filtration surgery, the benefits over traditional MMC delivery methods are not clear. Further work by the authors may tease out specific advantages to their polymer system.

Comment by Tina Wong, Singapore

57435 Evaluation of an injectable thermosensitive hydrogel as drug delivery implant for ocular glaucoma surgery, Xi L, Wang T, Zhao F, Zheng Q, Li X, Luo J, Liu J, Quan D, Ge J, PLoS ONE 2014; 9: e100632

Hydrogel is a thermally-reversible gel that gels at body temperature. The F127 hydrogel is well-known and made from a PEG-PPG-PEG polymer and in this study the authors have 'extended' the PEG tails on either side to construct a hydrophobic biodegradable 'oligomer'. By making this extension, they seem to have developed a gel that can sustain release of MMC for several days, after an initial burst effect. There is no sustained release from the unmodified F127 gel. The authors' explanation is that the hydrophobic moiety achieves sustained release by 'holding on' to the MMC molecules.

The animal data report a prolonged survival of the bleb with an associated reduction in scar tissue formation as indicated by amount of collagen and myofibroblast population. Further studies will help determine the longer term safety of the gel *in vivo*. The idea of using the TMC-PEG-PPG-PEGTMC copolymer is an interesting concept, but since it is a 'new' material, it will need to undergo safety testing as required of any new material.

Therapeutic outcomes

Visual Field Improvement

Comment by Kouros Nouri-Mahdavi, Los Angeles, CA, USA

57034 Visual field improvement in the collaborative initial glaucoma treatment study, Musch DC, Gillespie BW, Palmberg PF, Spaeth G, Niziol LM, Lichter PR, American Journal of Ophthalmology 2014; 158: 96-104.e2

Visual field improvement as an (or the) outcome measure for treatment of glaucoma was originally suggested by Dr. George Spaeth and although some of us are firm believers, solid proof has been scant. Musch and colleagues tested the hypothesis that clinically significant visual field improvement happens after significant reduction of the intraocular pressure (IOP) in glaucoma patients in the CIGTS database. A minimum improvement in MD of three dB was required before a given eye was considered improving. Similar criteria were used to detect visual field deterioration (*i.e.*, a loss of ≥ three DB). **A similar proportion of eyes demonstrated improvement or progression through five years of follow-up, after which worsening of the visual field was slightly more common.**

> There was also a dose-response relationship between better IOP control and likelihood of VF improvement

The investigators went to great length to rule out potential confounding issues such as a regression to the mean effect. Interestingly, visual field improvement was associated with IOP measures demonstrating better control during follow-up such as lower mean or minimum IOP. The latter is a very interesting finding as previously, worsening of glaucoma has been linked to higher peak IOP in some studies.

There was also a dose-response relationship between better IOP control and likelihood of VF improvement. This begs the question whether achieving IOPs lower than estimated target pressures could actually lead to better outcomes barring hypotony and potential side effects of such treatment.

One caveat is that although worsening cataract was predictive of visual field deterioration, it is not clear how much of the persistent VF improvement could have been due to cataract extraction. The authors do mention that a visit prior to CE was predictive of worsening VFs. By nature, the stringent guidelines of the study protocol with regard to enrollment and baseline VF measurements reduce the risks that improvements seen were purely caused by noise or learning effect. Based on changes in the VFs between the two baseline fields, the investigators determined that about 4% of repeat tests would demonstrate a gain or

loss that met their criteria for change. An interesting finding was the more **remarkable improvement in eyes with more advanced glaucoma (average of -10 dB) that underwent surgery compared to eyes treated medically**.

Overall, the results present solid evidence for and confirm our collective experience that visual field improvement after IOP reduction is a real phenomenon in glaucoma. As yet unpublished results from our research team have shown improvement in regional rates of change consistent with the results of this study. It may be finally time to think out of the box and expect more than disease stability in our glaucoma patients.

Comment by Chris Johnson, Iowa City, IA , USA

57294 A Control experiment for studies that show improved visual sensitivity with intraocular pressure lowering in glaucoma, Anderson AJ, Stainer MJ, Ophthalmology 2014; 121: 2028-2032

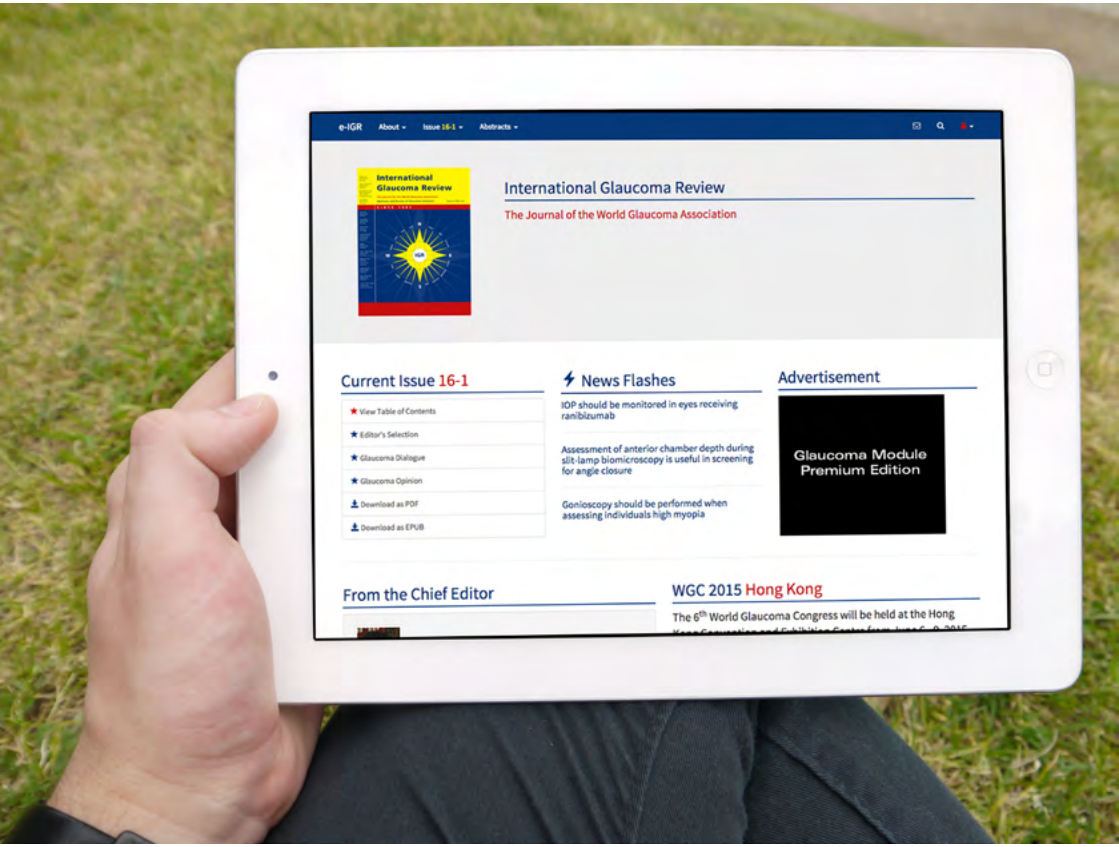
Anderson and Stainer address a fundamental question in glaucoma – is the improvement in contrast sensitivity (perimetric increment threshold sensitivity) in glaucoma due to a general relationship between intraocular pressure (IOP) and visual sensitivity that is not directly related to glaucoma, or is the improvement in visual sensitivity for treated glaucoma (lowering of IOP) due to a reversible dysfunction that has been produced by high IOP? To address this question, the authors evaluated the IOP and visual field results from the Ocular Hypertension Treatment Study (OHTS). The OHTS data set is particularly valuable because it includes a large sample size (more than 1,300 patients) that was then followed for a long time interval with meticulous quality control and assessment procedures. Approximately half (692) of the participants in OHTS received treatment to lower IOP and about half (618) were watched carefully with no treatment administered. Additionally, the untreated group was offered treatment after five years of follow-up.

> Improvements in visual sensitivity in glaucoma after treatment is due to a reversal of a glaucoma-induced dysfunction of retinal ganglion cells produced by chronic elevated IOP.

Using a careful and thorough analysis of the relationship between IOP changes in the treated and untreated groups and visual field sensitivity for widespread (mean deviation or MD) and localized (pattern standard deviation or PSD) perimetric variation, the authors found **that there was no significant difference in MD or PSD for the treated participants in comparison to the untreated participants**. There was also no change in MD

or PSD for the untreated patients who received treatment at a later date. **These findings suggest that there is no relationship between IOP and visual field sensitivity that is unrelated to glaucoma** and suggests that improvements in visual sensitivity in glaucoma after treatment is due to a reversal of a glaucoma-induced dysfunction of retinal ganglion cells produced by chronic elevated IOP.

This is a finding of high importance in terms of the current treatment regimens for glaucoma and the quality of life experienced by the patient. Also, it demonstrates the value of retrospective analysis of results from well-controlled multicenter clinical trials as well as the importance of framing meaningful and significant clinical management questions that additionally provide insights on the mechanisms underlying the glaucomatous disease process.



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- ★ Optic neuropathy induced by experimentally reduced cerebrospinal fluid
- ★ Factors associated with underestimation of glaucoma likelihood
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Published by the World Glaucoma Association in collaboration with
Kugler Publications, Amsterdam, The Netherlands