Volume 16-3
2015

International Glaucoma Review

The journal of the World Glaucoma Association

Abstracts and Review of Glaucoma Literature

www.e-IGR.com

SINCE 1984

ISSN 1566-1040

American Glaucoma Society

Asian Pacific Glaucoma Society

Australian and New Zealand Glaucoma Interest Group

Canadian Glaucoma Society

Chinese Glaucoma Society

European Glaucoma Society

Glaucoma Society of India

International Society for Glaucoma Surgery

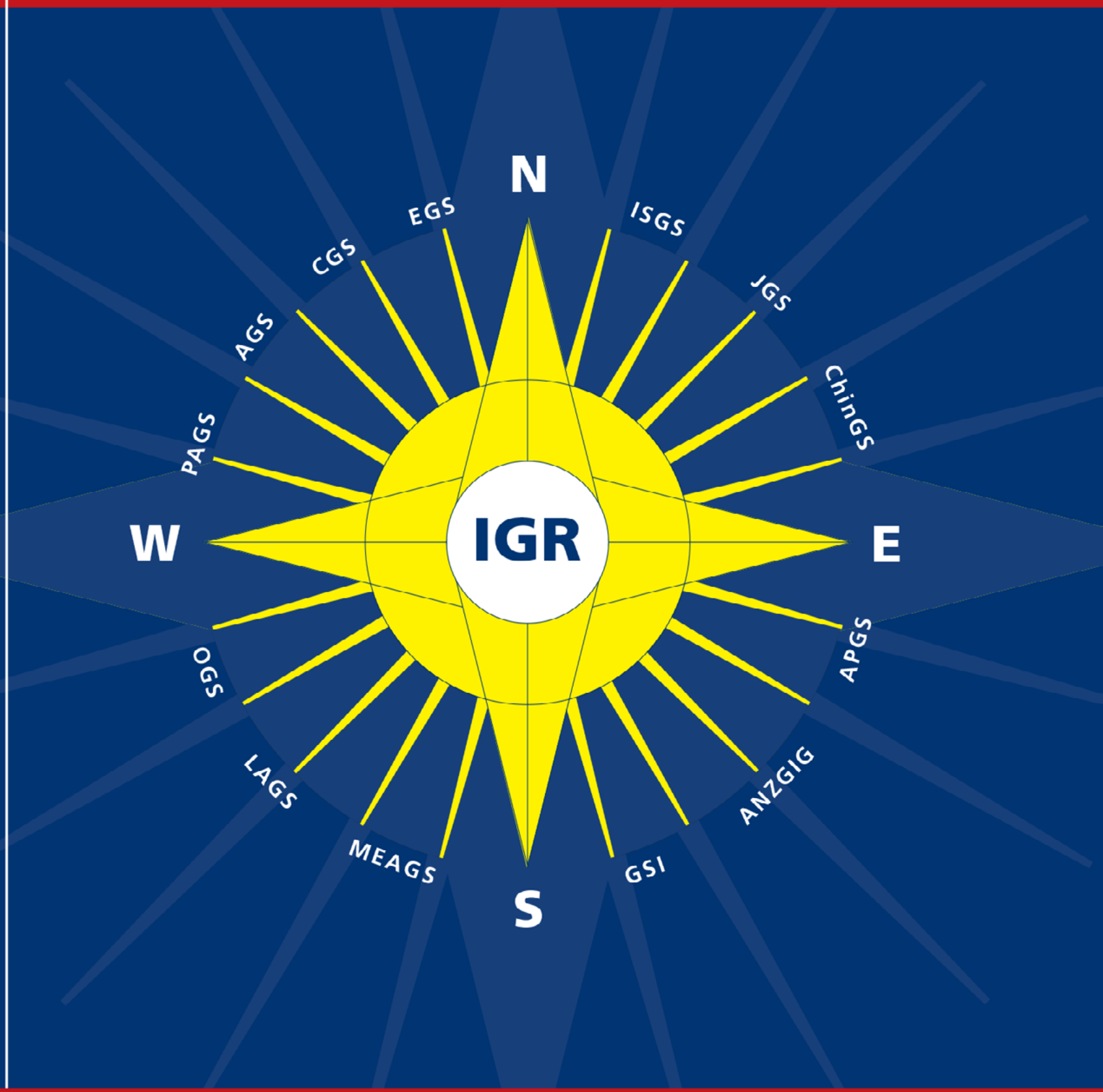
Japan Glaucoma Society

Latin American Glaucoma Society

Middle East African Glaucoma Society

Optometric Glaucoma Society

Pan American Glaucoma Society



6TH WORLD GLAUCOMA CONGRESS ISSUE

SPECTRALIS®

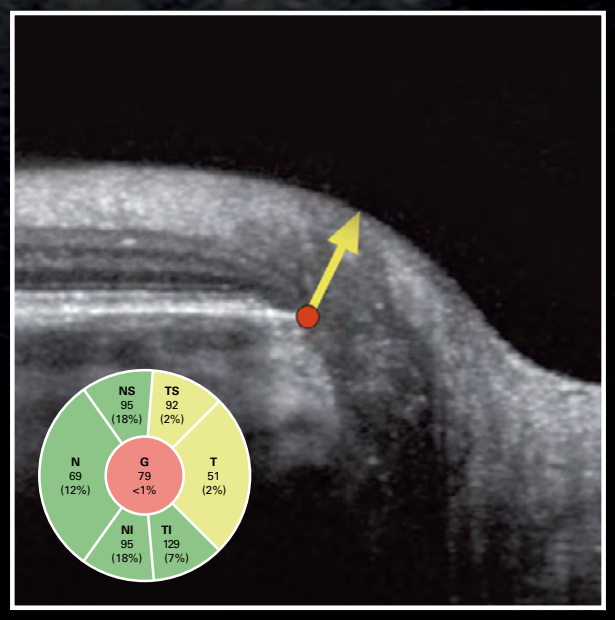
Glaucoma Module Premium Edition

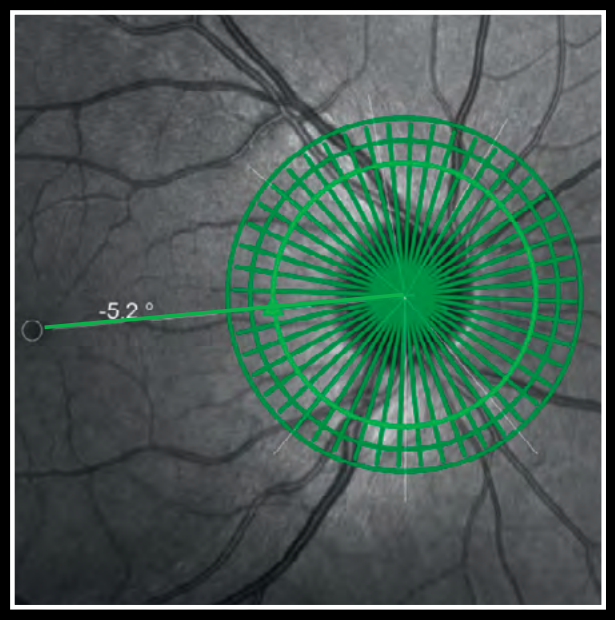
WGC: Monday, June 8, 17:45-18:45 · Room S223

Satellite Symposium:

Optic Nerve Head Analysis using the Minimum Rim Width Parameter

Claude F. **Burgoyne**: „The fundamentals of minimum rim width analysis“
Murray **Fingeret**: „Minimum rim width analysis in daily clinical practice“
Tae-Woo **Kim:** „Applying BMO-MRW strategy in diagnosing preperimetric“





The **SPECTRALIS®** system is an ophthalmic imaging platform with an upgradable, modular design. This platform allows clinicians to configure each SPECTRALIS to the specific diagnostic workflow in the practice or clinic. Options include: OCT, multiple laser fundus imaging modalities, widefield and ultra-widefield modules, and scanning laser angiography.

The **Glaucoma Module Premium Edition** provides a comprehensive analysis of the optic nerve head, retinal nerve fiber layer, and ganglion cell layer by precisely matching unique scan patterns to the fine anatomic structures relevant in glaucoma diagnostics.

www.HeidelbergEngineeering.com

HEIDELBERG ENGINEERING

ISSN 1566-1040

INTERNATIONAL GLAUCOMA REVIEW

A Quarterly Journal
Volume 16 no. 3

Kugler Publications, Amsterdam, The Netherlands

Information on the member Glaucoma Societies of the WGA can be found in the WGA Global Directory of Glaucoma Societies at www.worldglaucoma.org

Registration

Access to IGR Online is complimentary for all members of glaucoma societies affiliated to the WGA. However, you are required to register before you can access the abstracts and make use of other features of the IGR website.
Your pass word and user name (your e-mail address) have been provided by e-mail. However, if you lost your password you can retrieve it by using the “forgot pass word” function here: http://www.e-igr.com/Member

Alternatively, you may register in three easy steps:

1. Keep your IGR ID at hand. Your IGR ID is included in all IGR e-mail correspondence.
2. Go to the registration form at: http://www.e-igr.com/register and provide us with the requested information. You have to choose your own username and password. A few moments after having filled out the registration form, you will receive an e-mail at the address you indicated.
3. Follow the easy steps described in that e-mail to activate your registration.

Now start to use all the features offered by IGR Online.
Please take note of the terms of use and privacy policy of IGR Online. Your membership is personal and cannot be shared. Interested colleagues are advised to join one of the participating societies.

Should you have any questions, please contact us at info@e-igr.com

ISSN 1566-1040

Contact Information

All correspondence on copies, supplements, content, advertising, etc. should be directed to:
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

e-IGR.com

IGR Searchable Glaucoma Database

- Huge time saver to stay on top of the most significant glaucoma developments!
- The IGR abstract database holds **over 21,000 abstracts** related to Glaucoma, **all classified**, and some 10% commented on by leading experts.
- **Only glaucoma abstracts**: no false positives to wade through.
- Expert comments from the Editor's Selection are also **fully searchable** and linked to the abstracts.

Accessible, free of charge, to all members of WGA affiliated Glaucoma Societies

Features

- Searches in the abstracts may be limited to those abstracts that are commented on by experts.
- Limit your search or view abstracts by classification.
- Limit your search to (a range) of year(s) of publication
- Find related abstracts with one click of your mouse.
- Browse abstracts by classification, journal or author.
- Use operators to refine your queries and get better search results.

International Glaucoma Review is published as an online journal only.

If you are not yet receiving **IGR online**, we urge you go to the WGA website and supply us with your email address, so you will not miss any of the IGR content.

www.e-IGR.com

Table of contents

Download the IGR Abstract Book Supplement for the 6th World Glaucoma Congress:

Download PDF

Download EPUB

All abstracts are available online in the classified IGR searchable glaucoma database

www.e-IGR.com

The affiliations of the contributors to this issue can be found on www.e-IGR.com.

Please save the date for the 7th

WORLD GLAUCOMA CONGRESS

JUNE 28–JULY 1 2017

HELSINKI

THE GLOBAL GLAUCOMA NETWORK

WWW.WORLDGLAUCOMA.ORG

From the WGA Executive Office

By the time you read this, the 6th World Glaucoma Congress in Hong Kong is taking place. The Program Planning Committee has worked diligently during the last two years to offer the best possible glaucoma meeting. 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, 9 wetlabs and more than 60 courses, there is plenty to learn and interchange.

New this year, the President's Symposium: Glaucoma Innovation and Opportunities, is presenting the state of the art in glaucoma during the inaugural ceremony on 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 symposium entitled 'Tackling Glaucoma in Sub-Saharan Africa' is the start of a new WGA project on glaucoma care in Africa. *IGR*, issue 16-4 will provide you with the outlines of the different presentations during this symposium. In addition, we will be updating you on our plans regarding this project via future *IGR* issues. Do inform us on names of colleagues working in Africa via Mariska van der Veen at the WGA Executive Office (vanderveen@worldglaucoma.org), as we are starting to create a mailing list.

Also the second online-only issue was a success and we are very pleased with this result. The statistics show that the E-pub and E-pdf versions of *IGR* 16-1 & 2 have been downloaded by over 8,000 users and the total number of hits at the *IGR* website is over 280,000 since January 1.

Please 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

The moment your perimeter accelerates clinic flow.
The NEW Humphrey Field Analyzer 3.

NEW!
Liquid Lens Technology

// INNOVATION
MADE BY ZEISS

ZEISS introduces the NEW HFA3 with Liquid Lens technology that combines the power of many lenses into one.* Discover how the new HFA3 is faster, easier and more reliable than ever – and see how Liquid Lens technology works.

- Accelerate clinic flow
- Reduce setup time
- Improve confidence in test results

Visit **www.zeiss.com/HFA3**.

Carl Zeiss Meditec, Inc. 800.342.9821 www.meditec.zeiss.com

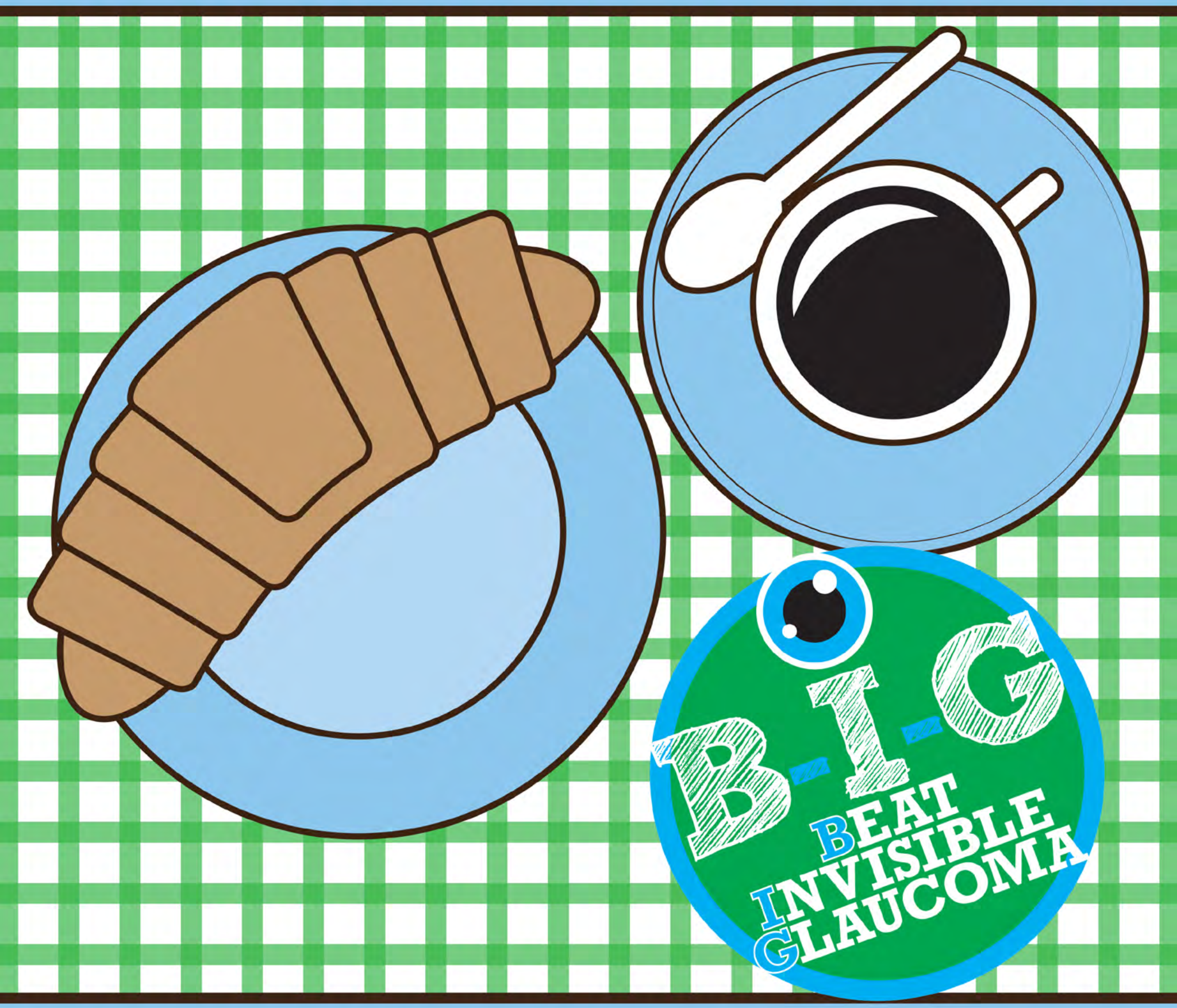
*Some patients may require a separate lens. Liquid Trial Lens available on the HFA3 model 860.

ZEISS
We make it visible.

WORLD GLAUCOMA WEEK 2015

THANK YOU!

World Glaucoma Week 2015 was a great success world wide. With close to 500 activities registered on our website we are very grateful to all the participants!



www.wgweek.net • follow us via facebook or twitter

WORLD GLAUCOMA WEEK 2016

March 6–12, 2016

We have started preparations for World Glaucoma Week 2016 so keep an eye on our website or follow us via facebook or twitter!

www.wgweek.net

Your Special Attention For:

Current concepts in the diagnosis, pathogenesis and management of nonarteritic anterior ischaemic optic neuropathy

Miller NR, Arnold AC
(abstract no. 58732)
Eye 2015; 29: 65-79

Systematic review and meta-analysis on the efficacy of selective laser trabeculoplasty in open-angle glaucoma

Wong MO, Lee JW, Choy BN, Chan JC, Lai JS
(abstract no. 58926)
Survey of Ophthalmology 2015; 60: 36-50

The placebo effect in early-phase glaucoma clinical trials

Sharpe RA, Nelson LA, Stewart JA, Stewart WC
(abstract no. 58932)
Current Eye Research 2014; 0: 1-4

Stem cell therapy for glaucoma: Science or snake oil?

Sun Y, Williams A, Waisbourd M, Iacovitti L, Katz LJ
(abstract no. 58959)
Survey of Ophthalmology 2015; 60(2): 93-105

Ocular and systemic manifestations of exfoliation syndrome

Ritch R
(abstract no. 59242)
Journal of Glaucoma 2014; 23: S1-8

Extracellular, stem cells and regenerative ophthalmology

Wang Y, Xie T
(abstract no. 59247)
Journal of Glaucoma 2014; 23: S30-3

Prospects for gene-environment interactions in exfoliation syndrome

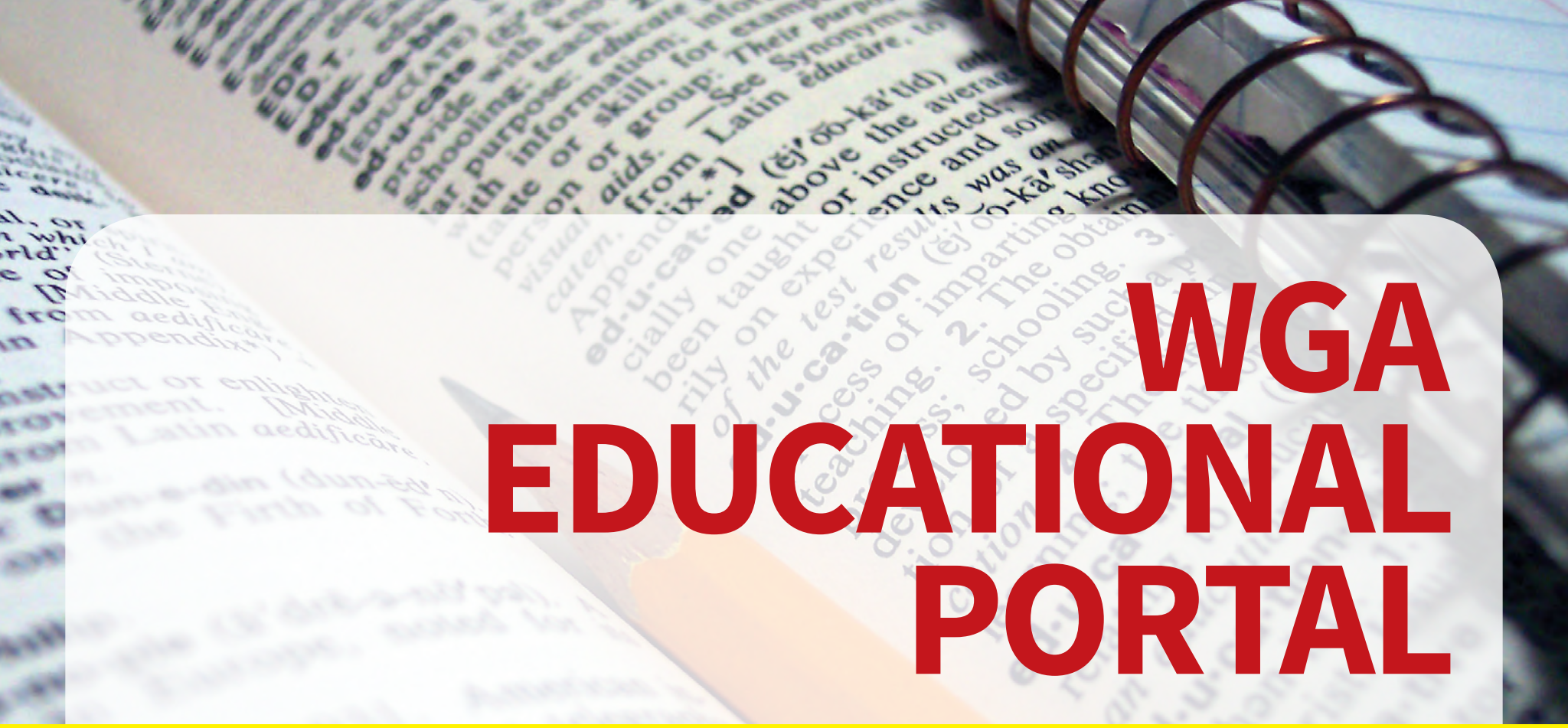
Pasquale LR, Kang JH, Wiggs JL
(abstract no. 59257)
Journal of Glaucoma 2014; 23: S64-7

Measuring rates of structural and functional change in glaucoma

Nouri-Mahdavi K, Caprioli J
(abstract no. 59296)
British Journal of Ophthalmology 2014; 305210

Ophthalmic patients on antithrombotic drugs: a review and guide to perioperative management

Kong KL, Khan J
(abstract no. 595650)
British Journal of Ophthalmology 2014; 306036



WGA EDUCATIONAL PORTAL

Getting the knowledge you want anytime, anywhere!

WGA provides you with the opportunity to view recorded sessions of the 5th and 6th World Glaucoma Congress sessions online via the WGA Educational Portal. Within the next weeks, we will be providing free access to the full content of the 5th **WGC-2013** via the WGA website. Soon after the 6th WGC in Hong Kong, the newly recorded session will be available as well. **WGC-2015** registered participants have free access to view these sessions via the Portal and can listen and watch recorded sessions which they missed during the Congress.

If you were unable to attend **WGC-2015** and you would be interested in registering for the virtual meeting, please contact the Executive Office via info@worldglaucoma.org, so we can provide you with the details.

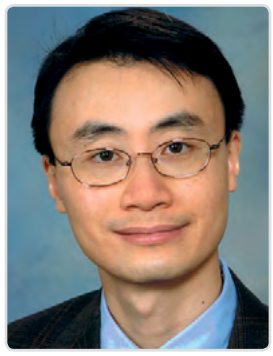
Please do not miss this opportunity of online glaucoma top education and visit the WGA Educational Portal!

Forgot your login details? Please contact wga-eduportal@mci-group.com.

www.worldglaucoma.org

Glaucoma Opinion

Episcleral Venous Pressure



Arthur Sit
Rochester, MN, USA

Episcleral venous pressure (EVP) is an important determinant of intraocular pressure (IOP), but has previously been difficult to measure, resulting in a lack of understanding about its role in modulating IOP. Also, knowledge of its role in the mechanisms of action of glaucoma therapies has been incomplete, resulting in a lack of interest in its potential as a therapeutic target. However, recent advances in our ability to measure EVP may potentially transform our understanding of this parameter.

EVP in aqueous humor dynamics

In addition to its intrinsic role in determining IOP, EVP is also a critical determinant in the calculation of uveoscleral outflow. The modified Goldmann equation describes IOP as being determined by several factors:

$$IOP = EVP + (Q - U) / c$$

where Q is the aqueous humor flow rate, c is the conventional outflow facility, and U is the pressure-insensitive uveoscleral outflow rate. While IOP, EVP, Q and c can be measured non-invasively, U is typically calculated from the modified Goldmann equation. Small errors in EVP can cause much larger errors in the estimate of uveoscleral flow. For example, if IOP = 17 mmHg, Q = 2.3 µL/min, c = 0.22 µL/min/mmHg, and EVP is 8 mmHg, then U would be 0.32 µl/min, or 14% of total aqueous humor outflow. If EVP were erroneously estimated to be 9 mmHg (a 12% error), the estimate of U would be 0.54 µL/min, or 23% of total aqueous humor outflow, an over-estimate of 69%. Despite its significance, difficulty in EVP measurement has resulted in uncertainty about its characteristics, and often an assumption that it has a largely static value.

> The anatomy of the outflow system distal to Schlemm's canal is consistent with a vascular system capable of pressure regulation

Regulation of EVP

Although **it is uncertain if EVP is actively regulated**, the anatomy of the outflow system distal to Schlemm's canal is consistent with a vascular system capable of pressure regulation, with the episcleral vasculature consisting of arteries, veins, and arteriovenous anastomoses.[1-3] One **possible mechanism for the regulation of EVP is the direct modulation of vascular**

resistance in the episcleral venous system. Episcleral vessels, including the veins, stain intensely for smooth-muscle α-actin,[4] which suggests the presence of muscular walls. Since outflow resistance varies with vessel diameter to the fourth power, **relatively small changes in vascular tone may result in venous constriction that increases fluid resistance and EVP**.

Dynamic modulation of the episcleral arteriovenous connections, possibly through nitric oxide signaling, could also alter EVP by controlling the degree to which the episcleral venous system is exposed to the higher pressure arterial system. Funk *et al*.[5] reported that topical administration of a vasodilator and nitric oxide donor (nitroprusside) increased EVP in rabbits, and Zamora and Kiel[6] demonstrated that a nitric oxide synthase inhibitor (N-nitro-L-arginine methyl ester) reduced EVP. These results suggest that vasodilation of the episcleral arteriovenous anastomoses, mediated by nitric oxide, can increase EVP and subsequently IOP.

Measurement of EVP

Measurement of EVP is difficult due to the small caliber of the vessels. Human episcleral veins typically range from 50 to 100 mm in diameter, and less in small animal models. EVP has been measured both invasively and non-invasively. Invasive measurement can be performed by direct cannulation of episcleral veins and indirectly by controlling the pressure in the anterior chamber. With direct cannulation, the small diameter and the low volume of fluid in the vessel preclude direct measurement by a pressure transducer through the cannula. Instead, a 'zero-flow' or 'servo-null' technique is utilized in which the pressure in the cannula is adjusted by using a manometer until fluid stops moving through the cannula in either direction. At that point, the boundary between the blood in the vein and the perfusion fluid oscillates with the cardiac pulse, indicating that the pressure set by the manometer was equal to average venous pressure.[7-9] With smaller animals, such as mice, an alternate, indirect measurement technique is used due to the small size of the episcleral veins.[10,11] Pressure in the anterior chamber is controlled through a glass intracameral needle connected to a water-filled reservoir and pressure transducer, and the intracameral pressure is reduced until blood refluxes into the collector channels and Schlemm's canal. The pressure that allowed blood to reflux is assumed to be equal to the EVP. While these measurements can be very precise, it is not clear how animal EVP compares with human EVP due to differences in body position and possible effects of cannulation on the vascular tone.

Non-invasive measurement of EVP is based on the principle of venous compression. An episcleral vein is identified, a force is applied to the vein with a clear flexible membrane until it collapses, and venous pressure is determined from the pressure in the membrane required to collapse the vessel to a predetermined endpoint. However, vessels do not collapse instantaneously, but collapse gradually over a range of several mmHg of applied pressure. Based on ideal tube laws,[12] and confirmed with animal experiments,[13] EVP is best represented by the pressure that is required to just start the collapse of the episcleral vein. This is a very difficult point to detect manually, and most investigators have assumed an endpoint where visible collapse has occurred. Unfortunately, this can be subjective and likely results in a pressure reading higher than the true EVP, and a wide array of values for mean normal EVP reported in the literature, ranging from 7.6 mmHg to 11.4 mmHg.[14] A recently developed objective technique for EVP measurement utilizes the pressure chamber technique, but combines video imaging synchronized with readings from a pressure transducer.[15] By using image processing techniques, the initial point of episcleral vein collapse can be easily identified. With this technique, mean EVP in normal subjects is typically around 7 mmHg.

Modulation of EVP

Due to the previous lack of objective techniques for measurement, many studies evaluating mechanisms of action for glaucoma therapies assumed a static EVP. **Most human studies that have evaluated existing pharmacologic agents have not found an effect on EVP, but may have been limited by the precision of the measurements.** This includes studies of beta-blockers,[16-18] prostaglandin analogs,[19] carbonic anhydrase inhibitors,[20] and alpha-agonists,[21] which have all reported no change in EVP with medication administration. However, one study of calcium channel blockers indicated that topical verapamil 0.25% reduced EVP by 12% after two weeks of administration three times a day.[22] In that study, EVP also decreased in the control eye, suggesting a systemic effect.

In contrast, animal studies have suggested that EVP can be modified by a variety of pharmacologic agents. Zamora and Kiel[23] reported that topical proparacaine decreased EVP in rabbits when conjunctiva was removed, possibly by blocking efferent neural inputs in the episcleral vasculature. Similarly, Reitsamer *et al*.[24] found that EVP decreased 42% within five to ten minutes after topical application of brimonidine in rabbits. In a study in mice, Millar *et al*. reported that latanoprost reduced EVP by 50%, while betaxolol and brimonidine had no effect on EVP.[25] The reasons for the discrepant results between human and animal studies, as well as different animal models, in unclear and further measurements of EVP using objective measurement methods are needed.

> The physiology of the episcleral vascular plexus suggests that EVP can be modulated, and reduction of EVP may be a viable target for glaucoma therapy

Summary

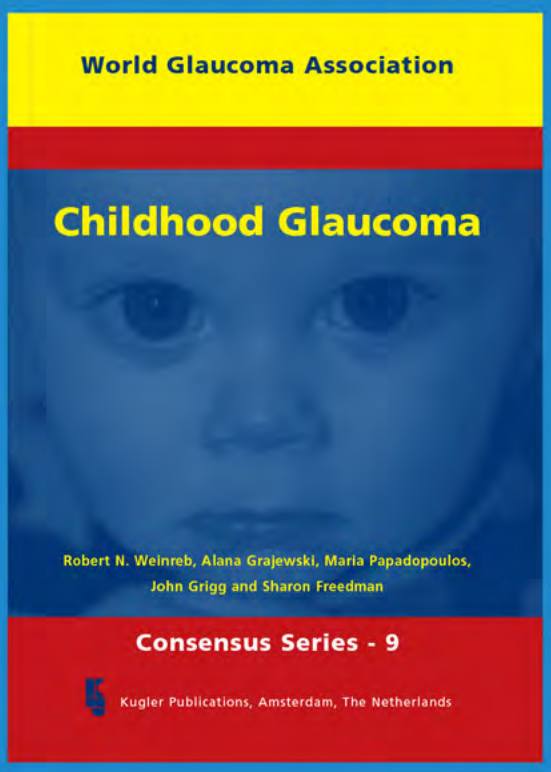
EVP is an important contributor to IOP and assessment of aqueous humor dynamics requires accurate measurements of this parameter. Although past attempts to measure this parameter were limited by the technology available, **current techniques appear able to measure EVP reliable.** The physiology of the episcleral vascular plexus suggests that EVP can be modulated, and reduction of EVP may be a viable target for glaucoma therapy. Animal studies suggest that even some existing therapies may modulate this parameter. While modification of EVP is unlikely to be a primary target for initial therapy of primary open-angle glaucoma, due to the limited amount of IOP reduction possible, it may be a reasonable target for adjuvant therapy or treatment of normal-tension glaucoma patients.

References

1. Ashton N. Anatomical study of Schlemm's canal and aqueous veins by means of neoprene casts. Part I. Aqueous veins. Br J Ophthalmol 1951;35:291-303.
2. Ashton N. Anatomical study of Schlemm's canal and aqueous veins by means of neoprene casts. II. Aqueous veins. Br J Ophthalmol 1952;36:265-267; contd.
3. Ashton N, Smith R. Anatomical study of Schlemm's canal and aqueous veins by means of neoprene casts. III. Arterial relations of Schlemm's canal. Br J Ophthalmol 1953;37:577-586.
4. Selbach JM, Rohen JW, Steuhl KP, Lütjen-Drecoll E. Angioarchitecture and innervation of the primate anterior episclera. Curr Eye Res 2005;30:337-344.

5. Funk RH, Gehr J, Rohen JW. Short-term hemodynamic changes in episcleral arteriovenous anastomoses correlate with venous pressure and IOP changes in the albino rabbit. Curr Eye Res 1996;15:87-93.
6. Zamora DO, Kiel JW. Episcleral venous pressure responses to topical nitroprusside and N-Nitro-L-arginine methyl ester. Invest Ophthalmol Vis Sci 2010;51:1614-1620.
7. Brubaker RF. Determination of episcleral venous pressure in the eye. A comparison of three methods. Arch Ophthalmol 1967;77:110-114.
8. Maepea O, Bill A. The pressures in the episcleral veins, Schlemm's canal and the trabecular meshwork in monkeys: effects of changes in intraocular pressure. Exp Eye Res 1989;49:645-663.
9. Reitsamer HA, Kiel JW. A rabbit model to study orbital venous pressure, intraocular pressure, and ocular hemodynamics simultaneously. Invest Ophthalmol Vis Sci 2002;43:3728-3734.
10. Aihara M, Lindsey JD, Weinreb RN. Episcleral venous pressure of mouse eye and effect of body position. Curr Eye Res 2003;27:355-362.
11. Aihara M, Lindsey JD, Weinreb RN. Reduction of intraocular pressure in mouse eyes treated with latanoprost. Invest Ophthalmol Vis Sci 2002;43:146-150.
12. Shapiro AH. Steady flow in collapsible tubes. J Biomech Eng 1977;99:126-147.
13. Gaasterland DE, Pederson JE. Episcleral venous pressure: a comparison of invasive and noninvasive measurements. Invest Ophthalmol Vis Sci 1983;24:1417-1422.
14. Sit AJ, McLaren JW. Measurement of episcleral venous pressure. Exp Eye Res 2011;93:291-298.
15. Sit AJ, Ekdawi NS, Malihi M, McLaren JW. A novel method for computerized measurement of episcleral venous pressure in humans. Exp Eye Res 2011;92:537-544.
16. Yablonski ME, Zimmerman TJ, Waltman SR, Becker B. A fluorophotometric study of the effect of topical timolol on aqueous humor dynamics. Exp Eye Res 1978;27:135-142.
17. Yablonski ME, Novack GD, Burke PJ, Cook DJ, Harmon G. The effect of levobunolol on aqueous humor dynamics. Exp Eye Res 1987;44:49-54.
18. Schenker HI, Yablonski ME, Podos SM, Linder L. Fluorophotometric study of epinephrine and timolol in human subjects. Arch Ophthalmol 1981;99:1212-1216.
19. Toris CB, Zhan G, Fan S, et al. Effects of travoprost on aqueous humor dynamics in patients with elevated intraocular pressure. J Glaucoma 2007;16:189-195.
20. Kupfer C, Gaasterland D, Ross K. Studies of aqueous humor dynamics in man. II. Measurements in young normal subjects using acetazolamide and L-epinephrine. Invest Ophthalmol 1971;10:523-533.
21. Toris CB, Gleason ML, Camras CB, Yablonski ME. Effects of brimonidine on aqueous humor dynamics in human eyes. Arch Ophthalmol 1995;113:1514-1517.
22. Abreu MM, Kim YY, Shin DH, Netland PA. Topical verapamil and episcleral venous pressure. Ophthalmology 1998;105:2251-2255.
23. Zamora DO, Kiel JW. Topical proparacaine and episcleral venous pressure in the rabbit. Invest Ophthalmol Vis Sci 2009;50:2949-2952.
24. Reitsamer HA, Posey M, Kiel JW. Effects of a topical alpha2 adrenergic agonist on ciliary blood flow and aqueous production in rabbits. Exp Eye Res 2006;82:405-415.
25. Millar C, Clark AF, Pang IH. Assessment of aqueous humor dynamics in the mouse by a novel method of constant flow infusion. Invest Ophthalmol Vis Sci 2010;Sep 22, 2010. Epub ahead of print.

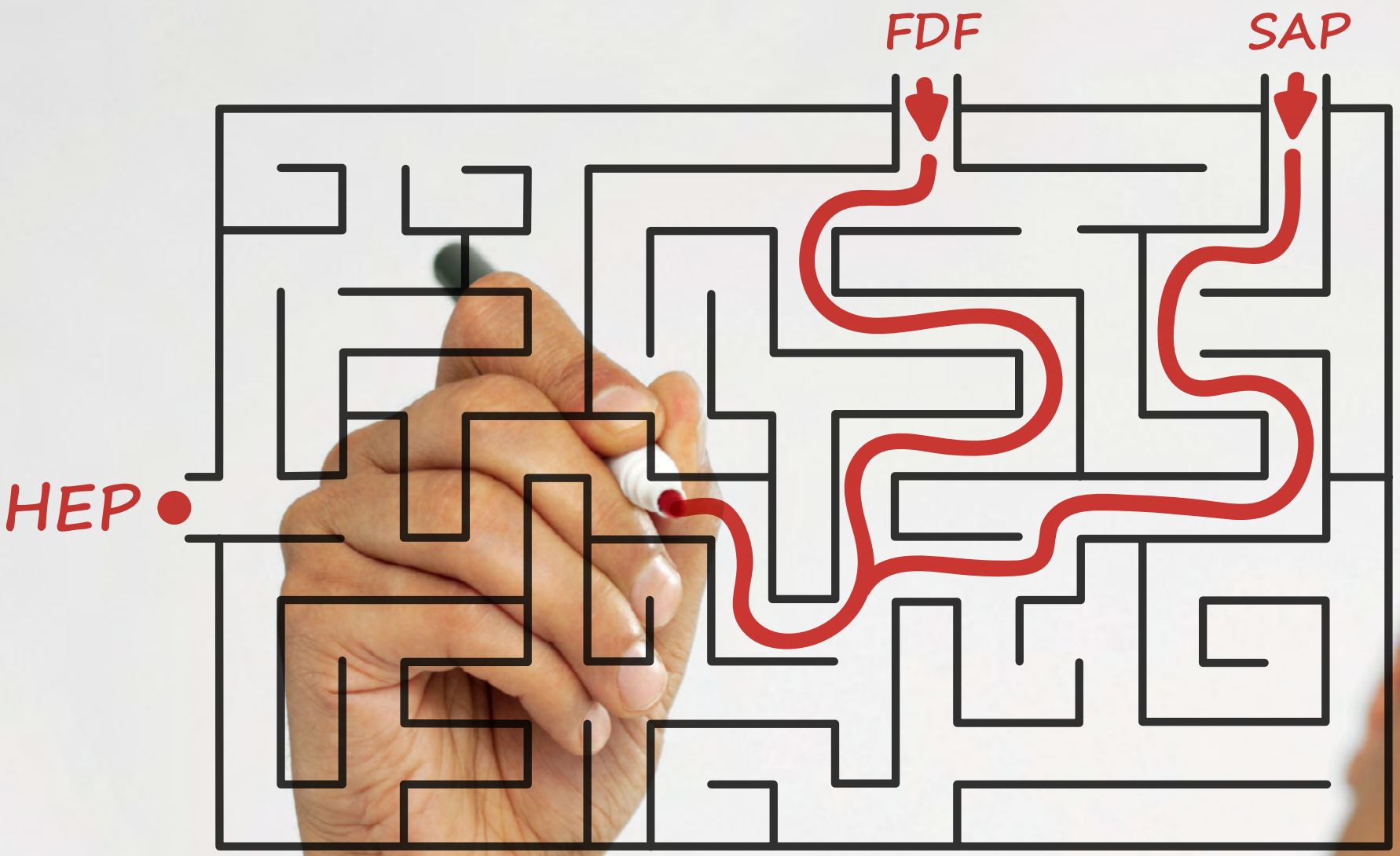
WGA CONSENSUS SERIES



KUGLER PUBLICATIONS
www.kuglerpublications.com

The 2-in-1 Perimeter

Heidelberg Engineering Functional Testing



Heidelberg Edge Perimeter (HEP)

Two test methods in one device:

- White-on-White Perimetry (SAP) for established glaucoma
- Flicker-Defined-Form (FDF) Perimetry for glaucoma suspects

One Software Platform HEYEX for all Heidelberg Engineering devices.

Efficient comparison of structural (SPECTRALIS® OCT) and functional data (HEP).

PeriData

New: Interface to PeriData

HEIDELBERG ENGINEERING

Meeting Highlights

Top Five of the 25th American Glaucoma Society Meeting

Coronado, CA, USA, February 26 – March 1, 2015


Christopher A. Girkin and Steven J. Gedde

• **A common variant of the gene *SIX6*(rs33912345) is associated with global and regional reduction in the retinal nerve fiber layer in a non-glaucomatous Asian population**
(Rand Allingham)
The common variant of SIX6 that is present in 80% of Asians and a large percent of all other populations not only increases risk of POAG but also affects the eyes of those who will never be diagnosed with glaucoma. This is likely the first variant to be discovered that will alter the manner in which we calculate POAG risk.

• **To detect peripapillary perfusion defect in glaucoma using optical coherence tomography (OCT) angiography**
(David Huang)
Visualization of small vasculature in optical coherence tomography (OCT) imagery is limited by the high noise levels inherent to OCT signals. Huang has overcome this barrier through an algorithm that divides each raw A-scan into four *independent* measurement. Split-spectrum amplitude decorrelation angiography (SSADA) algorithm was compared vessel glaucomatous and age-matched healthy eyes, finding an association between it and visual field parameters.

• **New OCT system shows collector channels rapidly open & close with pressure changes: a factor in the persistent distal resistance after MIGS?**
(Murray J. Johnstone)
Ex vivo human limbal segments were examined to evaluate the effects of intraocular pressure pulses. Imaging revealed that collagen septa at collector channel ostia form flap-like openings that close with small pressure changes.

• **Impact of the introduction of generic latanoprost on glaucoma medication adherence**
(Joshua D. Stein)
Using a network containing 8427 eligible patients, adherence rates were compared between persons who continued brand-name PGAs and those who switched to generic latanoprost. Patients who continued brand name PGAs were 39% more likely to have reduced adherence. Improved adherence was associated with lower monthly copay of generic latanoprost and black race.

• **Characteristics of patients who first present with severe-stage glaucoma**
(Victoria Addis)
The characteristics of patients in a large US-managed care network who presented with a severe stage of glaucoma were discussed. Males, Asian Americans, and persons of lower income were more likely to have a severe stage of glaucoma at diagnosis in this patient group with health insurance.

Top Five of the 2nd International Glaucoma Conference Pakistan

Lahore, Pakistan, March 22-23, 2015

Nadeem H. Butt

• **Gonioscopy – A forgotten art**
(Syed Imtiaz Ali, Pakistan)
A presentation covering the basic discussion of how to perform and interpret gonioscopy.. The presentation, mostly targeted for trainees, also emphasized the hands-on practice sessions for better interpretation and understanding.

• **My patients do not take glaucoma medications – why?!**
(Waleed Tantawy, UK)
A presentation, highlighting in detail all the issues related to compliance, adherence and persistence. A comparison of different groups of medications from the point of view of compliance was also presented.

• **Role of IOP control and glaucoma progression**
(Nadeem Hafeez Butt, Pakistan)
The paper highlighted the fundamental concept of IOP as the only modifiable risk factor and covered the literature review as the evidence base proving control of glaucoma progression through control of IOP. Clinical scenarios were also presented in which good control of IOP clearly showed maintenance of visual field and all parameters on OCT.

• **Trabeculectomy made easy**
(Sohaib Mustafa, United Arabic Emirates)
The presentation covered step-by-step trabeculectomy surgery. The difficulties in these steps were highlighted, as well as the solutions.

• **Needling procedures**
(P.S. Mahar, Pakistan)
The presentation showed dissection of fibrotic and failed blebs through various gauge needles. It also covered usefulness of simultaneous or preoperative adjuvants (MMC/5FU). Various surgical scenarios were presented and a needling procedure was demonstrated.

Top Four of the 10th Spanish Glaucoma Society Meeting

Madrid, Spain, March 5-7, 2015

Julian García Feijoo

• Spanish Glaucoma Clinical Practice Guidelines (CPG)

(FJ Muñoz-Negrete, A Azuara-Blanco)

The scientific based evidence about epidemiology, diagnosis and treatment was registered in this CPG. The second CPG on closed-angle glaucoma is available in: Muñoz-Negrete *et al*. GUIDELINES FOR TREATMENT OF CHRONIC PRIMARY ANGLE-CLOSURE GLAUCOMA. Arch Soc Esp Oftalmol 2015; 90:119.

• Initial Treatment for Ocular Hypertension and Glaucoma

(A Azuara-Blanco)

Management options of OHT and the results of a cost-effectiveness study led by Jen Burr (2012) were discussed. Using systematic reviews, validation of the risk calculator for conversion to glaucoma based on the OHTS-EGPS in different cohorts, and economic modelling with a UK perspective it was found that monitoring intervals of 2 years were the most cost-effective option.

• Microglia in mouse retina contralateral to experimental glaucoma exhibit multiple signs of activation in all retinal layers

(Spanish Glaucoma Society Research Award. Presenter: Blanca Rojas)

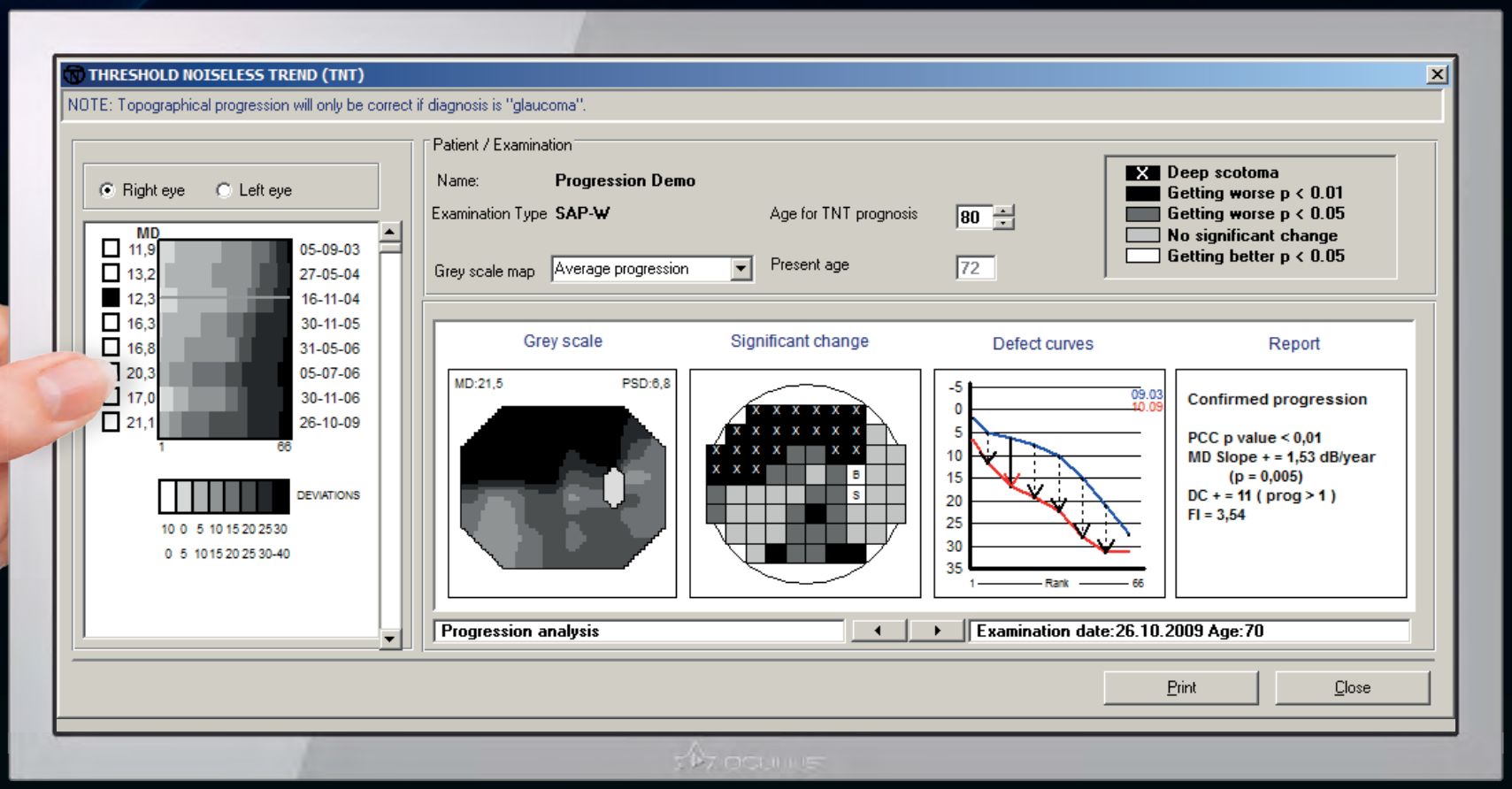
In an experimental model of unilateral laser induced ocular hypertension, retinal microglia exhibited several quantitative and qualitative signs of activation in both the hypertensive and the contralateral eye, although these were stronger in the former. Such activation extended beyond the ganglion cell layer, involving all retinal layers. Differences between the two eyes could help to elucidate glaucoma pathophysiology.

• Optic nerve head hemoglobin levels in chilhood glaucoma patients

(C Mendez-Hernandez)

The Laguna ONhE program determines the optic nerve hemoglobin levels (ONH-Hb) by analyzing conventional fundus images. In this prospective study 66 patients with childhood glaucoma and 68 healthy children were examined. In childhood glaucoma patients the program's glaucoma diagnostic indices and ONH-Hb were abnormal and cup-disc ratio was higher, indicating the diagnostic capacity of this noninvasive procedure in childhood glaucoma.

OCULUS Twinfield®, Centerfield®, Easyfield®



Please note: The availability of the products and features may differ in your country. Specifications and design are subject to change. Please contact your local distributor for details.

Tradition and innovation in visual field measurement – OCULUS perimeters bring you the best of both worlds

Come and see the NEW OCULUS Smartfield Perimeter at WGC 2015, Hong Kong

- Optimized SPARK test strategy for fast and reliable examinations
- Unique Glaucoma Staging Program (GSP) based on pattern recognition in support of early disease detection
- Threshold Noiseless Trend (TNT) for high sensitivity progression analysis

www.oculus.de

OCULUS®

Glaucoma Dialogue

In this section, a published manuscript of import and potential impact for discussion will be selected. It also provides a forum for manuscripts that some might judge to be controversial or where further discussion of the experimental models or data is warranted. Solicited comments of experts will be sent to the authors of a selected manuscript for a response. Both comments and responses will be published in IGR in their entirety. This should provide interesting information for our readership that is not otherwise available from the published manuscript.

Robert N. Weinreb, Chief Editor

Article 1

59479 Induced pluripotent stem cells restore function in a human cell loss model of open-angle glaucoma, Abu-Hassan DW, Li X, Ryan EI, Acott TS, Kelley MJ, Stem Cells 2015;33(3):751-761

Comments

Comment by Terete Borras, Chapel Hill, NC, USA

The authors of this manuscript report a breakthrough finding that could open the door to the use of stem cells for the treatment of glaucoma. They have put together a well thought out procedure to differentiate induced pluripotent human stem cells (iPSC) to trabecular meshwork cells in culture, graft them into the trabecular meshwork tissue in perfused post-mortem human eyes and obtain restoration of their homeostatic response to pressure. The study is important for several different reasons. The continuously referred to as well-established phenomenon of loss of TM cellularity with age and in glaucoma is still based on two to three studies that are now about thirty years old. Although not their primary goal, their technology could provide a handle to revisit and confirm or not an important old finding, which has not been done. But the true importance is the feasibility of a potential new treatment.

The study comprises two arms. In one, the authors use commercially available human iPSC to show that they can be differentiated into cells which exhibit all morphological and molecular characteristics of trabecular meshwork cells. The cultured cells express the correct stem and trabecular cell markers before and after differentiation, and are able to regain their phagocytic property. In the second part of the study, they show that their new cells can be transplanted to *ex vivo* living human tissue and acquire one of the key functional properties of the tissue, that of regulating pressure. All these results could only be achieved due to the vast knowledge and experience of the group in trabecular meshwork biology and physiology. They were able to pay attention to every relevant detail. Cell differentiation occurred when using not only conditioned cell media but also conditioned extracellular matrix (ECM). A system to deplete a controlled number cells *in situ* was carefully developed by the use of saponin, which eliminates the cells but leaves behind their ECM. All controls, including using Q-dots to trace transplanted cells, perfusing undifferentiated dermal fibroblasts and showing size of the frontal sections are in place. One wished though, that details about their tissue processing (frozen sections?) and beams blue autofluorescence had been added. At times, the quantification and localization of the green live cells is not so clear (Fig. 1 B & C). One also wishes that in addition to the normalization of flow to baseline levels, the difference in outflow resistance between the saponin-treated and normal tissues could be seen. Would just the ECM presence matter?

Without resting importance to the relevance of proving and grafting truly differentiated HTM cells in the whole intact tissue, I would see the result as pretty obvious. **The cells determine the function of the whole tissue. Less cells, less function. Add more cells and now you see the function. It might not be that the remaining cells have lost their homeostatic ability, but just that it is a matter of detection, or that a reduced number of cells are not able to amount the response levels that the entire tissue requires.**

A new beginning that would allow addressing many questions regarding the involvement of cells and ECM in outflow facility regulation, as well and more important, allow thinking on a potential autologous cell treatment for glaucoma. A well-deserved congratulations to the group.

Comment by Yiqin Du, Pittsburgh, PA, USA

Abu-Hassan and colleagues reported a research study about cell treatment to repopulate the cellularity of the trabecular meshwork (TM) and restore the intraocular pressure (IOP) homeostatic response to high pressure in an anterior segment organ culture system.

Under normal conditions, the outflow pathway responds to high pressure and increases flow rate to maintain IOP at normal range, maintaining a certain flow of uL/min/mmHg (outflow facility). When the response is compromised, IOP may increase.

The authors conducted an acute TM cell depletion model by perfusing saponin to destroy a portion of the TM cells. Using an optimized concentration of saponin to perfuse for seven

minutes, the percentage of TM cells remaining was comparable to that present in glaucomatous TM. Repopulation of the damaged TM cells in the organ culture model by applying primary TM cells or TM-like cells induced from iPSCs could restore the IOP homeostatic function. In contrast, other cell types, such as dermal fibroblasts, not-differentiated iPSC embryoid bodies and human umbilical vein endothelial cells, did not restore the homeostasis. iPSCs were induced into TM-like cells by culture on extracellular matrix (ECM) produced by TM cells and in a medium conditioned by TM cells for 30 days.

Although still in a preliminary phase, this is a remarkable study which opens a door for cell-based therapy to replenish the TM and regulate IOP using autologous cells. It has been previously shown that TM cellularity reduction is associated with open-angle glaucoma. There was previously no direct evidence to show that cellular replacement to the TM could restore normal outflow facility and regulate IOP. Abu-Hassan and colleagues conducted the experiment to show that **exogenous TM cells or TM-like cells derived from iPSCs could integrate to all layers of the TM tissue and restore the IOP homeostatic function.**

But there is still a long way to go in order to translate TM cell transplantation for clinical treatment of glaucoma. The TM cell death induced by saponin treatment is an acute response whereas the cellularity reduction in glaucoma is a chronic process with ECM changes in the outflow pathway. The authors detected cell death in glaucomatous TM tissue. It is unclear if the TM cells continuously undergo apoptosis and necrosis while self-regeneration is ongoing or altogether absent in glaucoma patients. On the other hand, is there TM cell apoptosis and necrosis and what is the self-regeneration condition and potential in normal population?

In this study, perfused exogenous cells were able to restore TM function in such a short period. The cell replacement is an acute cellular attachment rather than chronic remodeling. What are the mechanisms for the restoration? Did the cells deposit any specific ECM, which is essential to regulate IOP, in such a short period? To have an *ex vivo* or *in vivo* model mimicking the chronic glaucoma pathology is still challenging and function of repopulated cells on the ECM remodeling and outflow regulation needs to be explored.

Again, this study is a short-term observation. For long-term effects and considering the lifespan of transplanted cells, what cell types are the best: primary TM cells, stem cells from TM, progenitors of TM cells derived from iPSCs, or fully differentiated TM-like cells from iPSCs?

There is a concern about the differentiation efficiency from iPSCs to TM-like cells. iPSCS, similar to embryonic stem cells, are in the very early immature stage. On the other hand, TM cells are functionally fully differentiated cells. There are many cell developmental stages between them. Simply induction in one step would be ideal, but the efficiency is also a big concern.

Along the cell-based therapy, there is still huge work to do. But this study is exciting in validating the concept that cellular repopulation of the diseased TM could restore outflow homeostasis and control IOP.

Comment by Michael Fautsch, Rochester, NY, USA

TM cells play an essential role in IOP homeostasis by sensing changes in the outflow pathway. Reduction in TM cell number is believed to be a factor that contributes to loss of IOP regulation in POAG. However, this has not been examined experimentally until now. In the study by Abu-Hassan *et al*., the investigators observed that cultured human anterior segments have an IOP homeostatic response, returning IOP to normal following manual elevation of pressure by increasing the flow rate. They developed a model in human anterior segment cultures where TM cell number can be artificially reduced using saponin, a natural detergent found in many plants. In this cell depletion model, the investigators showed that reduction of TM cell number inhibited the anterior segment cultures ability to adjust outflow resistance to pre-elevated IOP levels. The investigators went one step farther and showed that reseeding the cell depletion cultures with primary TM monolayer cells repaired the cultures ability to restore normal pressure following a pressure elevation challenge. Non-TM cells such as human umbilical vein endothelial cell (HUVEC) or embryoid bodies from induced pluripotent stem cells (iPSCs) were ineffective in a similar study. The investigators also differentiated human iPSCs into TM-like cells, confirming their likeness by the presence of several markers that are present in mature TM cells, but not in iPSCs such as CHI3L1, Wnt1, α3 integrin and Aqp1. Functionally, the TM-like cells were phagocytic like mature TM cells. Similar to primary human TM cells, these iPSC derived TM-like cells also repopulated the TM and restored IOP homeostasis. These findings provide valuable information regarding the ability to establish TM-like cells from iPSCs and functionally perform similar activities to mature TM cells. This study is potentially seminal in the fact that the investigators have shown convincingly that TM cells are essential to maintaining IOP homeostasis.

> The investigators have shown convincingly that TM cells are essential to maintaining IOP homeostasis

In addition, **the ability to differentiate iPSCs cells into TM-like cells and show these cells are also capable of maintaining IOP homeostasis provides strong evidence that development of cell based strategies to treat POAG are feasible**. Future studies to define culture based methods to reproducibly differentiate iPSCs to TM cells are warranted as this technology will enable clinicians to utilize autologous transplantation, since iPSCs can be derived from skin fibroblasts.

Comment by Paul Kaufman, Madison, WI, USA

Over thirty years ago, several research groups reported that in humans the number of cells in the TM declined with age,[1] and that in POAG either the decline accelerated or the affected individuals started out with fewer cells early in life.[2]

Subsequently, other groups reported that actomyosin contractility and TM and inner wall SC endothelial cellular and overall TM/SC contraction/relaxation were important regulators of outflow resistance and could be manipulated pharmacologically to therapeutic advantage in glaucoma.[3] More recently, still others have elucidated signaling mechanisms emanating from mechanical distention and mechanico-reception in the TM that promote a homeostatic drive toward a set point for outflow resistance and thereby for intraocular pressure (IOP).[4]

The current authors have provided another quantum leap forward in our understanding of the outflow physiology, pathophysiology and perhaps glaucoma therapeutics. They were able to deplete cells from the TM in cultured perfused human anterior segments and show that outflow resistance increased, and then perfuse those depleted anterior segments with cultured HTM cells and show restoration of normal resistance. Most astonishing and important, they showed that iPS cells derived from skin fibroblasts and then perfused into depleted segments assumed the characteristics of TM cells and restored the elevated resistance to normal and also restored the normal homeostatic response to an increased perfusion/elevated IOP.

> iPS cells derived from skin fibroblasts and then perfused into depleted segments assumed the characteristics of TM cells and restored the elevated resistance to normal and also restored the normal homeostatic response to an increased perfusion/elevated IOP

The latter raises the exciting possibility of **stem-cell therapy for glaucoma by restoring normal function to an aging, diseased trabecular meshwork using the patient's own iPS cells – a truly personalized therapy that bypasses the need for a genetic understanding of the disease**, as well as perhaps bypassing the need for topical IOP-lowering medication, laser treatment or surgery, with all their pitfalls. Obviously this will not be all-or-none for many patients, but it would be a huge advance.

I would quibble with a few points in the article: 1) Dismissing gene therapy as a therapeutic strategy because of the complexity of glaucoma genetics is the same mistake that gene hunters for this disease often make, namely that one cannot tweak a compensatory mechanism genetically to therapeutic advantage without ever knowing what has misfired genetically. 2) The authors have historically focused their research on the ECM, and view the ECM as central to understanding TM physiology and glaucoma pathophysiology in that light. It is equally likely that TM cell and organ contractility/relaxation are at least as important, and of course the

possibilities for interactions between these 'players' are infinite. And this does not even get into the realm of the 'poor people' and those who believe that resistance lies primarily in the inner canal wall endothelium rather than the outer JCT. Perhaps we should be (re)generating SC inner wall cells rather than or in addition to TM cells in our poor, aging, sick conventional outflow pathway! However, these are side issues in the present context of a seminal piece of work.

References

1. Alvarado J, Murphy C, Polansky J, Juster R. Age-related changes in trabecular meshwork cellularity. Invest Ophthalmol Vis Sci 1981;21(5):714-727.
2. Alvarado J, Murphy C, Juster R. Trabecular meshwork cellularity in primary open-angle glaucoma and nonglaucomatous normals. Ophthalmology 1984;91(6):564-579.
3. Tian B, Geiger B, Epstein DL, Kaufman PL. Cytoskeletal involvement in the regulation of aqueous humor outflow. Invest Ophthalmol Vis Sci 2000;41:619-623.
4. Stamer WD, Lei Y, Boussommier-Calleja A, Overby DR, Ethier CR. eNOS, a pressure-dependent regulator of intraocular pressure. Invest Ophthalmol Vis Sci 2011;52(13):9438-9444.

Response by the original authors

We would like to thank Dr. Weinreb and the IGR editorial team for selecting our paper for discussion and the reviewers for their thoughtful and generous comments recognizing the therapeutic potential of patient-specific stem cells for IOP control in glaucoma.

We should clarify a few points mentioned by the reviewers, which are very relevant to outflow pathway biology and to glaucoma, but were perhaps unclear since they were not the central focus of this stem cell restoration study aimed at a broader audience.

First, in all of these flow studies, saponin treatment, which removed approximately 30% of outflow pathway cells, did not directly change the outflow facility or the outflow resistance. Immediately after perfusion pressures were increased from 1x to 2x for saponin-treated or controls, outflow facility was not different, i.e., doubling the perfusion pressure doubled the outflow rate.

Second, with the functional cells present, either in the controls, which had not been saponin-treated, or with TM or TM-like iPS added back, the 2x pressure challenge triggered a slow increase in the outflow facility, and therefore a decrease in the outflow resistance, which only became apparent and significant after at around 24 hours. This is the classic IOP homeostatic response that we have described in detail in a recent review.[1] In this review, we argued that the ability of outflow pathway cells to sense pressure elevations and to respond by adjusting the outflow resistance to restore the IOP to within a narrow acceptable range is the reason that most people do not ever develop glaucoma.

We interpret these two observations to mean: 1) that outflow pathway cells are not the outflow resistance, since their presence or absence does not change outflow facility. This supports the idea that juxtacanalicular extracellular matrix provides most of the outflow resistance; and 2) a sufficient number of functional TM and/or Schlemm's canal inner wall endothelial cells are absolutely essential to regulate and maintain the outflow resistance over time within acceptable IOP ranges.

Since it can be argued that the loss of an active functional IOP homeostatic response is a hallmark of most of glaucoma, we think these studies argue for the relevance of the observation by

Alvarado, et. al., that outflow pathway cell loss is increased in glaucoma.[2]

References

1. Acott TS, Kelley MJ, Keller KE, et al. Intraocular pressure homeostasis: maintaining balance in a high-pressure environment. *Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics* 2014;30:94-101.
2. Alvarado J, Murphy C, Juster R. Trabecular meshwork cellularity in primary open-angle glaucoma and nonglaucomatous normals. *Ophthalmology* 1984;91:564-579.

Article 2

59604 Short-term enhancement of visual field sensitivity in glaucomatous eyes following surgical intraocular pressure reduction, Wright TM, Goharian I, Gardiner SK, Sehi M, Greenfield DS, American Journal of Ophthalmology 2015;159(2):378-385

Comment by Ivan Goldberg, Sydney, Australia

In this prospective, case-controlled cohort study of 30 eyes of 30 glaucoma patients who underwent trabeculectomy or insertion of a glaucoma drainage device compared with 41 eyes of 28 patients who continued stably on medical therapy, Wright and co-workers set out to determine whether or not intra-ocular pressure (IOP) reduction improved visual field (VF) sensitivities in the short-term. Matched for age and VF mean deviation, the two groups were followed with serial VFs for three months post-surgery or for 18 months with ongoing stable medications.

Whereas surgery reduced IOP from a group mean of about 18 to 10 mmHg, stable medical treatment maintained cohort mean IOP at about 13.7 mmHg.

Localized VF sensitivities were recorded for all tested points, for 16 central and for 36 peripheral points. In the operated eyes, an average of six of all points improved compared with three in the medical group; for the central 16, 1.8 points improved following surgery compared with 0.8 without and for the peripheral 36, 4.6 points improved compared with 2.6. With VF sensitivity fluctuations, as anticipated, some points also deteriorated: again more often in the surgical versus the medical group, suggesting greater variability following surgery.

In the surgery versus medical groups, VF Mean Deviation improved in ten eyes versus six and Pattern Standard Deviation, in nine eyes versus three.

Asked the investigators: what clinical parameters were associated with VF improvements in the surgery group? Favorable were trabeculectomy over glaucoma drainage device, an associated improvement in ocular perfusion pressure (OPP) and greater improvement in eyes with worse pre-surgical damage. Factors that seemed to play no part included eye laterality, patient age, baseline IOP or absolute IOP reduction achieved.

As quoted by the authors, despite the relatively small sample size, the presence of some

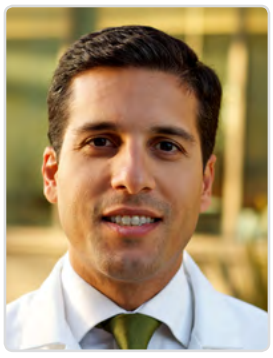
confounders and the lack of an established baseline VF sensitivity variability, these results support Spaeth's report that IOP reduction leads to an improved VF sensitivity[1] as well as the suggestion by Caprioli[2] and by Musch *et al*.[3] that the most damaged areas of the VF seem to show the most benefit. These findings also conform with similar indications of partial reversibility of glaucoma damage when assessed electro-physiologically.

At any one time in a glaucoma-affected eye there would seem to be populations of retinal ganglion (RGCs)and their support cells that are fully functional, that are dysfunctional but redeemable if a noxious element is reduced or removed, that are irreversibly damaged and non-functioning and are at various stages of degeneration. Surgical reduction of IOP would seem to allow dysfunctional RGCs to return to more normal activities, at least in the short term.

This all seems to underline the complex relationship between IOP levels and VF sensitivities. Nonetheless, to have potential reversibility of glaucoma damage result from risk factor (IOP) reduction is exciting and promising, particularly from a neuroprotection perspective

References

1. Spaeth GL. The effect of change in intraocular pressure on the natural history of glaucoma: lowering intraocular pressure in glaucoma can result in improvement of visual fields. Trans Ophthalmol Soc U K 1985;104:256-264.
2. Caprioli J. Glaucoma: a disease of early senescence. Invest Ophthalmol Vis Sci 2013;54 54(14):ORSF60-7.
3. Musch DC, Gillespie BW, Palmberg PF, Spaeth G, Niziol LM, Lichter PR. Visual field improvement in the Collaborative Initial Glaucoma Treatment Study. Am J Ophthalmol 2014;158(1):96-104.



Comment by Kaweh Mansouri, Geneva, Switzerland

The hypothesis that significant IOP reduction can lead to visual field (VF) improvement in glaucoma has been discussed for decades. It is based on the putative reversal of retinal ganglion cell (RGC) dysfunction when IOP is lowered. In 1985, Dr George Spaeth laid the scientific foundation for this theory by suggesting it as an outcome measure for glaucoma treatment.[1] Ever since, and disconcertingly, solid evidence for a phenomenon that many of us clinicians, albeit sporadically, observe has been lacking.

Skeptics point to the *regression to the mean* effect as an explanation for cases of observed VF "improvement" after successful surgery. Similar to IOP-based decisions, surgery is often recommended when VFs seem to have worsened. Given an additional stochastic element in VF series, it would then be expected that in some patients fields would improve, *i.e.* regress back to the mean.

Recently, the subject of VF restoration after IOP-lowering versus regression to the mean, or simply due to variation, was addressed in a re-analysis of the collaborative initial glaucoma treatment

study (CIGTS).[2] (see Comment by Dr Kouros Nouri-Mahdavi, IGR 16-2). The authors found the percentage of participants showing substantial VF improvement (by 3dB or more) over time to be similar to that showing VF loss through 5 years after initial treatment. They demonstrated an association with lower mean and minimum IOP. If VF improvement had been entirely due to regression to the mean or random variation, there such a correlation would be highly unlikely.

In the present study, Wright *et al*. attempted to examine this hypothesis by designing a prospective study comparing surgical IOP reduction with medically controlled eyes with stable IOP. Eyes that underwent surgery had their baseline IOP reduced from a mean of 18.0 ± 6.7 mmHg to 9.9 ± 4.7 mmHg. They found that a greater number of these eyes had improved PSD at the three-month follow-up visit (30%, respectively) than the control group (7%). Similarly, surgical eyes had a greater number of test locations improving, while MD was not statistically significantly different. Contrary to the CIGTS data, and despite a 0.04 higher number of improving test locations per mmHg lower baseline IOP, no 'dose-response relationship' between IOP change and VF improvement was observed.

Interestingly, a 'risk factor' for VF improvement was a higher postoperative mean ocular perfusion pressure. Also, the fact that both groups retained a similar number of locations with deteriorating VF sensitivities (4.8 vs 6.4, p = 0.433) may give credence to the putative explanation for VF improvement, namely that it corresponds to restoration RGC function in borderline damaged areas but not in severely damaged ones.

Despite a greater number of phakic eyes in the control (average age 67 years), the authors addressed the potential for cataract bias by excluding patients with visual acuity below 20/30. Despite their best attempts to create a strong study design, there were shortcomings that weaken (but in my mind not seriously so) the findings: a short follow-up period of three months for the surgical group and, most importantly, the absence of a sufficient number of fields to confirm the suspected enhancement in sensitivity. Helping partially in alleviating the first issue was a secondary analysis comparing three-month surgical to the six-month follow-up of controls: surgical patients still had significantly more test locations with improved sensitivity.

Encourage clinicians to offer glaucoma patients cautious words of hope that some degree of loss may be recoverable

This report adds to a growing body of evidence demonstrating that VF progression does not have to be a one-way street in all patients. What are the clinical implications from this important study? From my perspective, it is 1) to **never take any VF change for granted and to seek (re) confirmation, even in cases of improvement, despite an uphill battle with reimbursement authorities; 2) to encourage clinicians to offer glaucoma patients cautious words of hope that some degree of loss may be recoverable; and possibly 3) resort to surgery earlier in our clinical decision-making process.**

References

1. Spaeth GL (1985) The effect of change in intraocular pressure on the natural history of glaucoma: lowering intraocular pressure in glaucoma can result in improvement of visual fields. Trans Ophthalmol Soc U K 104 (Pt 3): 256-264.
2. Musch DC, Gillespie BW, Palmberg PF, et al. Visual field improvement in the collaborative initial glaucoma treatment study. Am J Ophthalmol 2014;158:96-104 e102.

Comment by Shamira Perera, Singapore

This study supports our long-held suspicions about the enhancement of visual field that occurs after surgical reduction of intraocular pressure (IOP) in eyes with glaucomatous optic neuropathy.

This mimics the observed retinal nerve fiber layer changes following IOP reduction alongside reversal of optic disc cupping. Clinically, it would be interesting to see if this improvement is noticeable or useful to the patient at this stage of field loss. We know that in more advanced disease the improvements are sustained and distinctly observable. This study showed no clear relationship between the degree of IOP lowering and the improvement in visual field sensitivity. Previous studies have been inconclusive on this point and no biologically plausible theory exists to explain how this might occur.

The fact that only 30% had an improvement in Pattern Standard Deviation despite the dramatic IOP lowering to 10mmHg certainly suggests that the number of potentially salvageable retinal ganglion cells (RGCs) vary from patient to patient irrespective of the stage of disease. Unfortunately, we know little about this group of RGCs. Notably, a similar number of patients in each group had worsening eyes or worsening points indicating some RGCs will deteriorate and atrophy inevitably. Newer methods of imaging with spectral domain Optical Coherence Tomography (OCT) that concentrate on the ganglion cell complex may be able to map the patterns of visual field improvement to structural changes. It would seem logical that the last affected areas would be more likely to improve, but that would need a more technical analysis.

Further research could use automated pointwise linear regression of the visual field on the two groups. The Progressor software (Medisoft, Ltd, Leeds, UK) is a sophisticated tool to characterize the changes and how they evolve with time, but it requires more than five visual fields.

The profile of the IOP changes in both groups would have been useful to know, as it is likely that the flatter IOP after surgery would be beneficial to the recovery of the RGCs. In the absence of this, the authors, attribute the mechanism to be via an improvement in ocular perfusion pressure. The authors should be commended on their robust methodology and analysis which addresses the learning effect and the authors acknowledge that some of the visual improvement may reside in an improved ocular surface.

Whilst longer longitudinal studies would help expound the relationship between IOP and VF enhancement, the authors have opened up the potential role for using localized changes in visual sensitivity as a potential biomarker for salvageable RGC function. Current options of the Pattern Electro Retinogram are impractical for routine use and OCT is reportedly less sensitive for early disease. This biomarker may be used to test the response to IOP lowering of various modalities.

Response by the original authors

We are grateful to the reviewers for their positive comments regarding our study. The concept of visual field (VF) improvement following intraocular pressure (IOP) reduction has existed for decades.[1] In clinical practice there are patients that describe subjective improvement in vision after glaucoma surgical intervention, which has often been dismissed by physicians given widespread disbelief that such improvement may occur. The growing body of evidence[2,3] demonstrating enhancement of visual function after IOP reduction supports electrophysiological data using pattern electroretinogram[4] and offers promise for the development of biomarkers of RGC function for use in research trials and clinical practice.

We describe a statistical method for identifying repeatable improvement in VF test locations using a glaucoma change probability strategy. At present, commercially available VF testing algorithms for glaucomatous change detection are engineered soley to detect progression. For example, the Glaucoma Progression Analysis™ (GPA, Carl Zeiss Meditec, Dublin CA) was introduced in 2004 and employs statistical criteria to compare VF locations on the pattern deviation probability map of follow-up VF exams compared to the average of 2 baseline exams. An automated analysis identifies progressing test locations that show change greater than the expected variability in pattern deviation (at the 95% significance level). Improving VF test points are not identified using GPA software. However, it is interesting to note that an earlier generation of change detection software entitled Glaucoma Change Probability™ (GCP, Carl Zeiss Meditec, Dublin, CA) did identify statistically "improving" test locations on follow up VF exams compared to baseline, but confirmation was not required.

Our study, along with others, demonstrates that short-term improvement in visual function does occur after IOP reduction in glaucomatous eyes. Dysfunctional RGCs may represent a viable treatment target for glaucoma, and biomarkers should be identified to measure both biological improvement and deterioration in RGC function. Although long-term data is necessary, as described by the reviewer, this data may "encourage clinicians to offer glaucoma patients cautious words of hope that some degree of loss may be recoverable."

References

1. Spaeth GL. The effect of change in intraocular pressure on the natural history of glaucoma: lowering intraocular pressure in glaucoma can result in improvement of visual fields. Trans Ophthalmol Soc U K 1985;104(Pt 3):256-64.
2. Caprioli J. Glaucoma: a disease of early senescence. Invest Ophthalmol Vis Sci 2013;54:ORSF60-7.
3. Musch DC, Gillespie BW, Palmberg PF, et al. Visual Field Improvement in the Collaborative Intitial Glaucoma Treatment Study. Am J Ophthalmol 2014;158:96-104.
4. Sehi M, Grewal DS, Goodkin ML, Greenfield DS. Reversal of retinal ganglion cell dysfunction following surgical reduction of intraocular pressure. Ophthalmology 2010;117:2329-36.

DEDICATED to changing the **Glaucoma** landscape

We believe everyone should have the best possible vision throughout their lives.

As the leader in eye care, Alcon is dedicated to changing the glaucoma landscape through a focus on **science, innovation and leadership,** and by developing a glaucoma portfolio designed to address unmet patient needs at all stages of the disease.

We are committed to long-term investments in research and development in order to advance the treatment of patients living with glaucoma and reduce the burden of disease around the world.

Visit Alcon at booth **34** during the World Glaucoma Congress to learn more.

Alcon®
a Novartis company

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

Epidemiology

Glaucoma Prevalence

Comment by Ningli Wang, Beijing, China

58821 The prevalence of primary angle closure glaucoma in adult Asians: a systematic review and meta-analysis, Cheng JW, Zong Y, Zeng YY, Wei RL, PLoS ONE 2014; 9: e103222

Primary angle closure glaucoma (PACG) is a major cause of visual morbidity in Asia, with higher prevalence in Asians compared to Caucasians or black populations.[1,2] Therefore, it is important to estimate the burden of PACG in Asia. With the better control of PACG, the increasing prevalence of myopia and the changing of lifestyle, the number of PACG patients is supposed to be decreased through the two decades in Asia, but is that really the case? Also, before the emergence of International Society of Geographical and Epidemiological Ophthalmology (ISGEO) definition for PACG,[3] the prevalence rates reported in different studies may not be accurate and comparable. Therefore, it is necessary to re-evaluate the prevalence of PACG in Asia, using the same definition of cases.

Cheng *et al*. did a systematic review and meta-analysis to summarize available population-based studies reporting prevalence values in Asians, to estimate an overall prevalence of PACG consistent with the ISGEO definition. **Twenty-nine studies were included and the highest pooled**

prevalence rates of PACG were 1.19% in the Japan group and 1.10% in the China group, followed by 0.97% in the Middle East group, 0.66% in the South East Asia group and 0.46% in the India group. And a high prevalence rate was strongly associated with an older age and a higher proportion of female gender. Also, they found a strong variability of PACG prevalence rates by ethnic group.

This systematic review provides a current estimate of PACG prevalence in Asian populations based on data of 29 published studies conducted through the period of 2000 to 2013, which provide important information about the burden of PACG in Asia nowadays and may help decide the appropriate policies on prevention and treatment.

References

1. Cook C, Foster PJ. Epidemiology of glaucoma: what's new? Can J Ophthalmol 2012;47(3):223-226.
2. Quiley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006;90(3):262-267.
3. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol 2002;86(2):238-242.

Anatomical structures

Angle configuration changes

Comment by Noel Chan, Hong Kong, China

58618 Longitudinal changes of angle configuration in primary angle-closure suspects: the Zhongshan Angle-Closure Prevention Trial, Jiang Y, Chang DS, Zhu H, Khawaja AP, Aung T, Huang S, Chen Q, Munoz B, Grossi CM, He M, Friedman DS, Foster PJ, Ophthalmology 2014;121:1699-1705

Laser peripheral iridotomy (LPI) is considered a standard treatment in acute or chronic angle closure glaucoma.[1] However, without prior history of primary angle closure (PAC), the benefit of LPI in asymptomatic eyes with narrow angles has been inconclusive. The Zhongshan Angle-Closure Prevention trial was initiated in 2008 to shed light in this area and hopefully help guide future management of primary angle closure suspects (PACS). In this longitudinal cohort of 775 PACS subjects, one eye of each participant was randomized to receive LPI while the fellow eye remained untreated and served as a control. Changes in angle configuration between the two eyes were compared at two weeks, six months and 18 months after LPI using gonioscopy and anterior segment optical coherence tomography (AS-OCT). This was a well-conducted study with strengths including large sample size, randomization, uniform cohort, control with fellow eye and reasonable follow-up duration. The use of ASOCT for angle assessment also ensured more objective and reproducible measurements.

> "This [study] has provided further evidence to the existing theory that non-pupil block mechanisms play a considerable role in causing PAC."

Two weeks after LPI, treated eyes were found to have a wider drainage angle than control eyes or baseline. Together with a significant reduction in iris curvature, the results further proved the effect of LPI in eliminating pupil block mechanism. This result was expected and consistent across existing literature.[2-4] However, **six months after LPI, the angle width decreased over time in all treated eyes while the untreated eyes experienced a decrease in angle width in a more rapid fashion** (1.2°/year versus 1.6°/year). This has provided further evidence to the existing theory that non-pupil block mechanisms play a considerable role in causing PAC.[5] Not surprisingly, **25% of treated eyes in this study were found to have persistent angle closure despite successful iridotomies**.

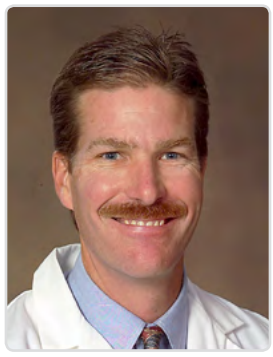
One of the interesting results from this study was a significant increase in AS-OCT angle width in both treated and untreated eyes at two weeks post-LPI. Despite the postulated explanation of systemic absorption of pilocarpine administered prior to laser, there was no significant

difference in pupil diameter observed before and two weeks after LPI in both groups. Another interesting finding was that, compared with controls, treated eyes had significantly greater lens vault at 18 months post-LPI. The authors suggested that apart from aging, LPI might have additional effect on the crystalline lens, especially the contour of its anterior surface. Although the study has demonstrated beneficial effect of LPI in angle widening in PACS eyes, some of these interesting results were yet to be answered. I look forward to the authors' follow-up studies investigating any difference in the development of PACG between the two eyes.

References

1. Saw SM, Gazzard G, Friedman DS. Interventions for angle-closure glaucoma: an evidence-based update. Ophthalmology 2003;110:1869-1879.
2. Lim LS, Aung T, Husain R, et al. Acute primary angle closure: configuration of the drainage angle in the first year after laser peripheral iridotomy. Ophthalmology 2004;111:1470-1474.
3. How AC, Baskaran M, Kumar RS, et al. Changes in anterior segment morphology after laser peripheral iridotomy: an anterior segment optical coherence tomography study. Ophthalmology 2012;119:1383-1387.
4. He M, Friedman DS, Ge J, et al. Laser peripheral iridotomy in primary angle-closure suspects: biometric and gonioscopic outcomes: The Liwan Eye Study. Ophthalmology 2007;114:494-500.
5. Kumar RS, Baskaran M, Chew P, et al. Prevalence of plateau iris in primary angle closure suspects. Ophthalmology 2008;115:430-434.

Outflow pathways



Comment by Daniel Stamer, Tucson, AZ, USA

58977 Anatomic changes in Schlemm's canal and collector channels in normal and primary open-angle glaucoma eyes using low and high perfusion pressures, Hann CR, Vercnocke AJ, Bentley MD, Jorgensen SM, Fautsch MP, Investigative Ophthalmology and Visual Science 2014;55:5834-5841

Resistance generation by the conventional outflow tissues sets intraocular pressure (IOP). While a great deal of progress has been made towards better understanding the regulation of resistance by the trabecular meshwork, little attention has been paid to resistance control distal to the inner wall of Schlemm's canal; where 25-50% of total outflow resistance is generated. Using micro-CT imaging of human eyes from normal and primary open-angle glaucoma (POAG) donors, Hann *et al*. compared anatomic changes in Schlemm's canal (SC) and collector channels (CC) of eyes subjected to normal and elevated perfusion pressures.

> It is important to know whether drugs that soften conventional outflow tissues like rho kinase inhibitors restore function of valve-like collector channel ostia.

In response to an IOP of 20 mmHg (elevated), results show that SC volume and CC orifice area of normal eyes decreased, while the number of observable CCs significantly increased by 26%. In contrast, the number of observable CCs did not change in POAG eyes perfused at 20 mmHg. Moreover, there were a significantly greater number of CC occlusions observed in POAG versus normal eyes at elevated IOP. These parameters were not different between normal and POAG eyes perfused at 10 mmHg.

The investigators hypothesize that as SC collapses at elevated IOPs, a reserve population of CCs is mechanically exposed, acting like a relief valve. In POAG, such a compensatory mechanism may be diminished or lost due to stiffness and/or architectural changes in conventional outflow tissue properties associated with disease. These ideas are supported by data from other laboratories, and if true add to the number of dynamic pressure-dependent processes that work together in the conventional outflow tract to maintain intraocular pressure within a narrow range over a lifetime. Looking forward, it would be interesting to attempt visualization of these valve-like structures in real time, and explore strategies to restore their functionality in POAG. Equally important is to know whether drugs that soften conventional outflow tissues like rho kinase inhibitors restore function of these valve-like CC ostia.

RNFL and disc hemorrhage

Comment by Gustavo de Moraes, New York, NY, USA

58890 Changes in retinal nerve fiber layer thickness after optic disc hemorrhage in glaucomatous eyes, Hwang YH, Kim YY, Kim HK, Sohn YH, Journal of Glaucoma 2014;23:547-552

In this retrospective longitudinal study, Hwang *et al*. investigated changes in one retinal nerve fiber layer thickness (RNFLT) measured with spectral-domain optical coherence tomography (sdOCT) after optic disc hemorrhage (DH) in glaucomatous eyes. They included patients with a single or recurrent DH in only one eye and selected a control group of glaucomatous eyes without DH, but who underwent three sdOCT scans with a one-year interval. Event-based significant RNFLT change was defined if it exceeded the 95% confidence interval of test-retest variability calculated from the control group in clock-hour sectors 6, 7, 8, 10, 11, and 12. They tested the hypothesis that RNFLT loss is spatially-consistent with the location of DH, and that this loss is more significant in DH eyes than their fellow non-DH eyes after one and two years of DH detection. They also investigated factors associated with a significant RNFL loss in DH eyes.

The authors found that **among eyes with DH, 38.5% showed decrease in RNFLT and 6.2% showed increase in RNFLT one year after DH detection. After two years, however, 58.5% showed decrease in RNFLT and no eye showed increase in RNFLT.** Among fellow non-DH eyes, 4.6% and 15.4% showed decrease in RNFLT pne and two years after DH detection, respectively. **Factors significantly associated with RNFLT loss in DH eyes were recurrent DH and thicker RNFLT at the time of the first sdOCT measurement.**

Although the literature on DH and glaucoma progression is thorough, Hwang et al. added new information on its structural features. Notably, significant RNFLT changes could be detected as early as one year after DH detection. This is a great advantage over standard achromatic perimetry (SAP), which requires more frequent testing during a longer follow-up periods due to its inherent larger variability. An important strength of the study was that the authors used the sdOCT test-retest repeatability at each clock-hour of eyes with stable glaucoma to define significant change. Manufacturers should provide these values from their reference databases to help clinicians improve their ability to detect progression in practice.

Laminar displacement

Comment by Claude Burgoyne, Portland, OR, USA

59467 Factors affecting plastic lamina cribrosa displacement in glaucoma patients, Jung KI, Jung Y, Park KT, Park CK, Investigative Ophthalmology and Visual Science 2014;55:7709-7715

The phenotype of human glaucoma[1] spans from '*shallow*' through 'deep' forms of 'cupping'. '*Senile sclerotic*'[2] cupping classically occurs in elderly eyes that demonstrate '*shallow*' enlargement of the cup, pale rims and peripapillary atrophy. What determines, and can we predict, the eye-specific phenotype an ocular hypertensive eye will manifest as it becomes detectably '*glaucomatous*'? **In this report Jung *et al*.,** add to two previous retrospective analyses,[3,4] (one their own),[3] and a third that was prospective,[5] which **find age to be inversely related to SDOCT-determined laminar depth in glaucoma subjects** within an analysis that controls for IOP and severity of damage (visual field MD and or retinal nerve fiber thickness). A similar relationship was present in their previous study[3] of a small group of primary open angle glaucoma patients (but not within a larger group of normal tension glaucoma subjects). Ren *et al*.[4] found age to inversely correlate to laminar depth within high risk ocular hypertensive and early glaucoma subjects. Unlike the present report, neither of the prior studies found strong relationships to initial or treated IOP. These data suggest that ONH 'aging' increases ONH structural stiffness and also that structurally stiff eyes of all ages will deform less for a given level of IOP insult. These findings are important because they contribute to a scientific explanation of phenotype that will allow us to predict the appearance a given eye will demonstrate at a given level of IOP. Study limitations (as in all like it) include the fact that neither the actual IOP nor the actual age at the time of IOP elevation (and/or initial laminar deformation), can be known. Nor has this (or any) study, determined ONH structural stiffness at the start of the study and then longitudinally assessed laminar deformation while controlling for the level of IOP at which the deformation occurs.

References

1. Broadway DC, Nicolela MT, Drance SM. Optic disk appearances in primary open-angle glaucoma. Surv Ophthalmol 1999;43(Suppl 1):S223-243.
2. Jonas JB, Grundler A. Optic disc morphology in 'age-related atrophic glaucoma'. Graefes Arch Clin Exp Ophthalmol 1996;234:744-749.
3. Rho CR, Park HY, Lee NY, Park CK. Clock-hour laminar displacement and age in primary open-angle glaucoma and normal tension glaucoma. Clin Experiment Ophthalmol 2012;40:e183-189.
4. Ren R, Yang H, Gardiner SK, et al. Anterior lamina cribrosa surface depth, age, and visual field sensitivity in the Portland Progression Project. Invest Ophthalmol Vis Sci 2014;55:1531-1539.

5. Yang H, He L, Gardiner SK, et al. Age-related differences in longitudinal structural change by spectral-domain optical coherence tomography in early experimental glaucoma. Invest Ophthalmol Vis Sci 2014;55:6409-6420.

Retrochiasmal optic pathways

Comment by Ahmed El-Rafei, Cairo, Egypt

58936 A topographical relationship between visual field defects and optic radiation changes in glaucoma, Kaushik M, Graham SL, Wang C, Klistorner A, Investigative Ophthalmology and Visual Science 2014;55:5770-5775

Recent advancements in diffusion tensor imaging has enabled the reconstruction and characterization of the brain white matter fibers. This imaging technique has been utilized to segment and to evaluate the visual pathway in different pathologies. The study by Kaushik et al. used diffusion tensor imaging to investigate the secondary effects of primary open angle glaucoma on the optic radiations (OR). **Reduction in OR size and fractional anisotropy, in addition to elevated radial and mean diffusivities, are reported in this paper as consequences of glaucoma.** These results are in agreement with recent studies suggesting that the integrity of OR fibers are compromised in the presence of glaucoma. Moreover, this study differentiates the glaucoma induced OR changes corresponding to retinal hemifields with and without visual defects. **A significant rarefaction of the OR associated with the affected hemifields in comparison to unaffected hemifields was shown**. Nevertheless, no significant difference was observed in DTI-derived measures between affected and unaffected ORs.

> The findings of this study add to the growing evidence from recent studies suggesting the trans-synaptic nature of degeneration caused by glaucoma

The findings of this study add to the growing evidence from recent studies suggesting the trans-synaptic nature of degeneration caused by glaucoma. The authors suggested a possible explanation for the retained fiber bundles in the unaffected OR in that it may be due prolonged loss of the axons projected from the retinal ganglion cells. This hypothesis, if confirmed, could be extremely important for the potential preservation of the cerebral fiber tracts of the visual pathway by neuroprotective agents. However, it needs further investigation by performing a comprehensive study that includes large number of subjects, reliability analysis for identifying OR, and higher DTI-image resolution. In addition, this study demonstrated that DTI-indices show similar sensitivity to severe and early glaucoma damage from affected and unaffected hemifields, respectively. Therefore, DTI-metrics could provide an additional mean to early detect glaucoma.

Basic Science

Aqueous oxygen levels

Comment by Malik Kahook, Denver, CO, USA

59630 Central corneal thickness correlates with oxygen levels in the human anterior chamber angle, Siegfried CJ, Shui YB, Bai F, Beebe DC, American Journal of Ophthalmology 2015;159(3):457-462

Central corneal thickness (CCT) is an important metric that has been validated as a risk factor for developing glaucomatous optic neuropathy. Siegfried and colleagues report a connection between thinner corneas and increased partial pressure of oxygen (pO_2) in the anterior chamber angle of patients undergoing cataract and/or glaucoma surgery. **They propose that alterations of oxygen distribution in some patients may result in formation of reactive oxygen species in the anterior chamber and eventually oxidative stress that leads to alteration in outflow facility.** If their findings hold true in the next stages of preclinical and clinical testing, this would be the first validated physiologic link between thin CCT and development of open-angle glaucoma. These findings also raise the prospect of introducing new therapies in the field of glaucoma that directly address oxidative stress in the anterior segment and aqueous outflow system of the eye.

Neuroprotection

Comment by Jeffrey Goldberg, San Diego, CA, USA

59230 Neural stem cell-based intraocular administration of ciliary neurotrophic factor attenuates the loss of axotomized ganglion cells in adult mice, Flachsbarth K, Kruszewski K, Jung G, Jankowiak W, Riecken K, Wagenfeld L, Richard G, Fehse B, Bartsch U, Investigative Ophthalmology and Visual Science 2014;55:7029-7039

In this article, Flachsbarth and colleagues report on experiments in which they used neural stem cells transduced to express ciliary neurotrophic factor (CNTF) as a delivery vehicle to look

for retinal ganglion cell (RGC) neuroprotection and regeneration after optic nerve crush injury. **Compared to injected control neural stem cells not expressing CNTF, those expressing CNTF showed significantly higher levels of RGC survival and optic nerve axon regeneration up to four months after injury**. Of note, loss of RGCs appears to have been stabilized by three months after injury, suggesting a long term halt to RGC loss may be possible. Comparison between control cells and no cells would have been interesting, as various stem cell populations have previously been demonstrated to produce considerable levels of neurotrophic factors without transduction of additional genes. It was also interesting to note the relatively weakregenerative response at four months, with few axons traveling long distances.

> An important question for the future might be to directly explore bolus versus sustained delivery, and sustained delivery by viral vectors versus by cell transplant

CNTF has a long history in the preclinical literature of promoting survival and regeneration of RGCs in various models of optic nerve injury from mice to monkeys. Delivery has ranged from bolus injections, repeat bolus injections, to viral transduction of retinal cells. How does the current paper compare to other CNTF delivery experiments? Perhaps comparison to the human experimental use of encapsulated cell technology in Neurotech's NT501 device is worth considering. The NT501 device secretes approximately 20 ng/day. In this paper, CNTF secretion in culture was estimated at approximately 90 ng/10^5 cells/day in these experiments. An important question for the future might be to directly explore bolus versus sustained delivery, and sustained delivery by viral vectors versus by cell transplant.

Overall, this paper adds to an already considerable body of literature on the use of this neurotrophic factor to promote RGC survival and regeneration, and further supports the premise of translating this promising candidate towards possible human use.

Comment by Miriam Kolko, Roskilde, Denmark

59266 The Novel Rho Kinase (ROCK) Inhibitor K-115: A new candidate drug for neuroprotective treatment in glaucoma, Yamamoto K, Maruyama K, Himori N, Omodaka K, Yokoyama Y, Shiga Y, Morin R, Nakazawa T, Investigative Ophthalmology and Visual Science 2014;55:7126-7136

Increasing evidence exists on Rho Kinase (ROCK) inhibitors as a novel class of pharmacological agents to slow down glaucomatous progression. ROCK inhibitors have been shown to offer distinct applications relevant to glaucoma management, including significant IOP-lowering effects, increased ocular blood flow, and promotion of retinal ganglion cell (RGC) survival and axonal regeneration. The present study identifies the ROCK inhibitor, K-115 as a new candidate drug for neuroprotective treatment in glaucoma. A model of optic nerve crush (NC) is used and

the authors identify an increased survival of RGCs after NC injury in mice treated with K-115. Moreover, the authors identify ROS production in RGCs after NC and show reduced ROS levels after K-115 treatment. The mechanism of action is suggested to be due to a reduced NAPDH oxidase 1 (NOX1) expression and the authors suggest that K-115 inhibits oxidative stress through NOX-1-induced axonal injury. Even though the study is of great interest and shows promise of K-115 as a neuroprotective treatment option for glaucoma caution should be taken to make to extensive conclusions. The main concern is the use of NC as a model. NC is not glaucoma and the mechanism of RGC death may not resemble glaucomatous damage.

> Optic nerve crush is not glaucoma and the mechanism of RGC death may not resemble glaucomatous damage

Nevertheless, ROCK inhibitors are encouraging as a new treatment strategy for glaucoma. In this matter K-115 has recently been approved and launched for ocular hypertension in Japan. Although the approval was based on a significant IOP-lowering effect future clinical studies will clarify its potential additional neuroprotective effects.

Scleral properties

Comment by Chris Leung, Hong Kong, China

59507 Age- and race-related differences in human scleral material properties, Grytz R, Fazio MA, Libertiaux V, Bruno L, Gardiner S, Girkin CA, Downs JC, Investigative Ophthalmology and Visual Science 2014;55:8163-8172

Investigation of scleral material properties has provided valuable insights into the risk factors and pathogenesis of glaucoma. With 40 European and 22 African donor eyes, Grytz and colleagues recorded three-dimensional displacements of posterior scleral shells during inflation tests; fitted parameters of scleral material properties, which included the crimp angle (a global microstructural measure that define collagen fibril crimping), the shear modulus, the elastic modulus and other parameters that define the local variation in the anisotropic collagen architecture into a computational model that matched the predicted displacements with the experimental deformation measurements; and evaluated the impact of age and race on the scleral material properties. **The key findings are that the posterior sclera is less compliant in donors of African than European descent and that there is age-related reduction in posterior scleral compliance.** The authors suggested these age- and race- related differences may be consequential to an increase in collagen cross-linking, and/or loss of the elastin-driven recoil (which were captured in the model by an increase in shear modulus and a decrease in collagen fibril crimp angle) in the aged and persons of African descent. Although age- and race- related differences in scleral material properties have been previously reported, this study is unique in

incorporating parameters at multiple scales, from displacement measurements obtained from inflation tests (macro-level) to computational analysis of the collagen fibril crimp (micro-level), thereby providing an informative approach to study the effect of age and race on the overall scleral compliance. Of note, interpretation of the model requires careful examination of the assumptions. For example, that the stiffness and microstructural parameters are assumed to be constant throughout the sclera and that the crimp angle is not a direct measurement but based on an inverse computational analysis. Inflation tests were performed within 48 hours postmortem but the hydration status of the sclera (which is also related to age) during the measurement is unknown. More important, it remains unclear to what extent the overall scleral compliance impacts the biomechanical responses of the peripapillary sclera and the lamina cribrosa at different levels of intraocular pressure. Nevertheless, this study is an important addition to the literature and has opened up new opportunities to investigate the relationship between tissue material properties and optic nerve degeneration in glaucoma.

Scleral properties may impact glaucoma damage

Comment by Ernst Tamm, Regensburg, Germany

59292 Experimental scleral cross-linking increases glaucoma damage in a mouse model, Kimball EC, Nguyen C, Steinhart MR, Nguyen TD, Pease ME, Oglesby EN, Oveson BC, Quigley HA, Experimental Eye Research 2014;128:129-140

Intraocular pressure acts as a mechanical load that produces stress and strain to the glial and connective tissues in region of the optic nerve head. There is evidence that both human glaucoma and animal models of glaucoma lead to an increased scleral stiffness. The goal of the study was to determine whether scleral stiffening as observed in human glaucoma is a beneficial adaptation or rather a detrimental contributor to optic nerve injury. To follow up on this very critical question, Kimball and colleagues designed a clever experimental approach. Offbred CD1 mice were treated with three subconjunctival injections of 0.5 M glyceraldehyde (GA) in one week, a treatment that is known to increase the stiffness of the mouse sclera by collagen crosslinking. Next, high intraocular pressure glaucoma was induced by bead injection into the anterior chamber. GA treatment did not cause obvious structural or functional defects, but lead to a steeper pressure-strain behavior of the sclera indicating increased stiffness. Most intriguingly, **GA-treated eyes had greater retinal ganglion cell (RGC) axon loss from elevated intraocular pressure than either buffer-injected or control eyes.** Clearly, this appears to be the first report that experimental alteration of the sclera, by cross-linking, increases susceptibility to RGC damage in mice. The important next step will be to identify the cellular and molecular mechanisms that are behind scleral stiffening in human glaucoma, and TGF-β signaling appears to be a likely candidate. A very likely cause for the higher activity of TGF-β signaling that was observed in the optic nerve heads of human patients with glaucoma is the intraocular pressure-induced strain

in the optic nerve head extracellular matrix. Transmission of cell force via integrins is known to be one major mechanism to activate latent TGF-β from extracellular matrix stores.

> TGF-β signaling might be the common mechanism that causes both aqueous humor outflow and optic nerve head changes in glaucoma, an unifying concept that might open new and novel causative pathways for therapy

Mechanical activation of latent TGF-β is more efficient with higher cell forces and extracellular matrix stiffening. Quite intriguingly, there is substantial evidence that higher activity of TGF-β signaling and of its downstream mediator connective tissue growth factor is the causative factor behind the increased stiffness of trabecular meshwork and Schlemm's canal endothelium that is observed in human glaucoma and is thought to be a causative factor for the increase in outflow resistance. TGF-β signaling might be the common mechanism that causes both aqueous humor outflow and optic nerve head changes in glaucoma, an unifying concept that might open new and novel causative pathways for therapy.

Source of VEGF in neovascular glaucoma

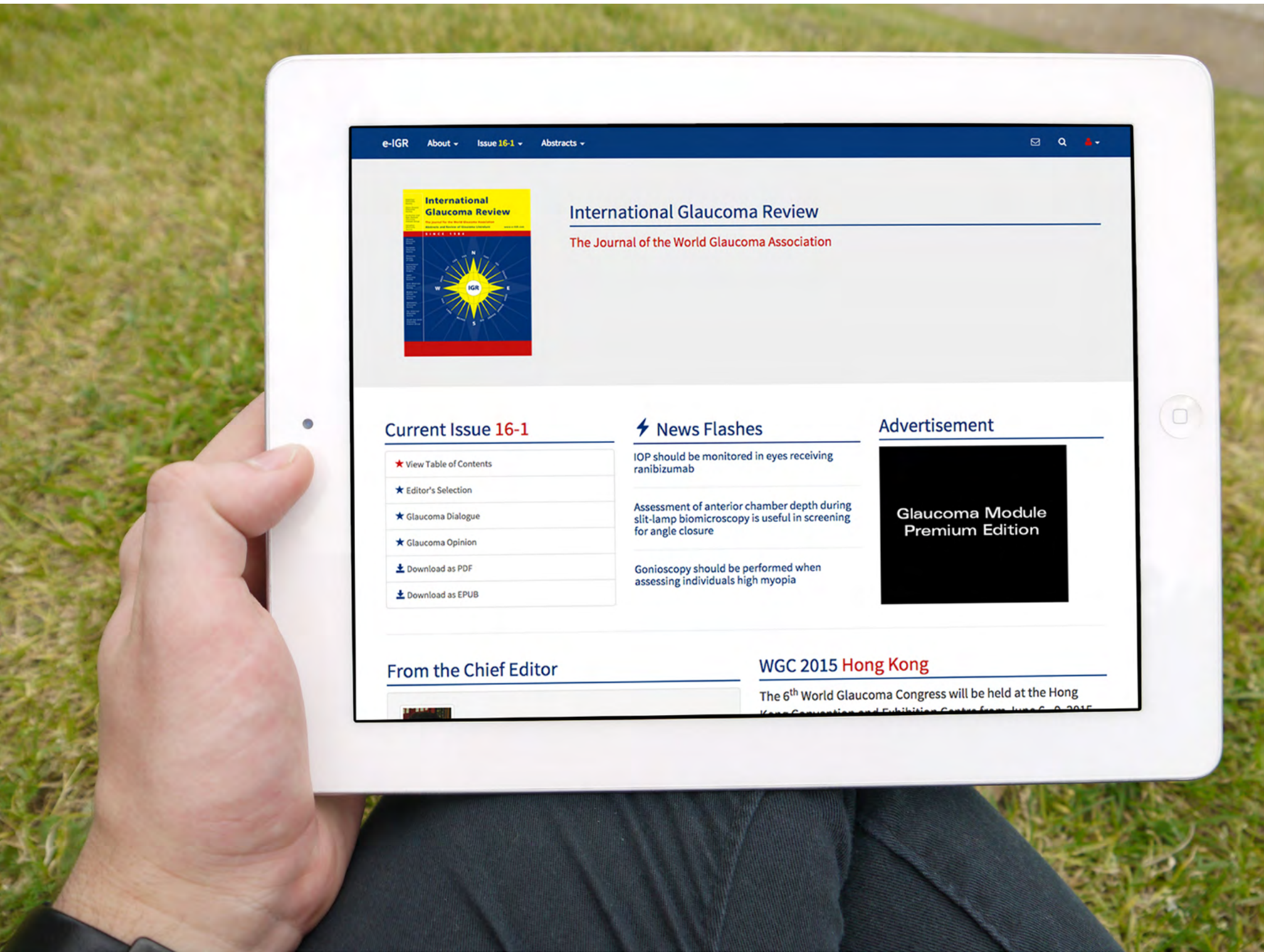
Comment by Tina Wong, Singapore

58858 Human ciliary epithelium as a source of synthesis and secretion of vascular endothelial growth factor in neovascular glaucoma, Chalam KV, Brar VS, Murthy RK, JAMA ophthalmology 2014;132:1350-1354

The effective treatment of neovascular glaucoma lies in the cause and site of elevated VEGF secretion. Most commonly the retinal pigment epithelium to secrete VEGF into the vitreous humor, and diffusing into the aqueous humor, in response to a hypoxic or ischaemic event. Appropriate treatment with pan retinal photocoagulation reduces the local tissue hypoxia by destroying the retinal cells responsible for secreting VEGF as well as stimulating angiogenic inhibitors. The authors observed though that despite extensive PRP, iris neovascularisation and therefore elevated IOP persisted in some individuals. Through the application of Nd:YAG laser cyclophotocoagulation or cyclocryotherapy, complete regression of iris neovacularization was noted in these eyes. This prompted Chalam *et al*. to investigate the ciliary epithelium as another source of VEGF and explain the angiogenic response following treatment from the two laser types.

The authors evaluated the expression of VEGF in human enucleated eyes with intractable neovascular glaucoma with no light perception previously treated with standard PRP,

using *in situ* hybridization and immunohistochemical staining. Positive staining for VEGF expression was found in all affected eyes compared to healthy control cadaver eyes. **The authors conclude that the ciliary epithelium to be an important source of VEGF** and proposed that cyclophotocoagulation should be considered in high-risk eyes to prevent the secretion of VEGF from the ciliary epithelium which can lead to a poorer prognosis in eyes that are already sick. The results of the study prove to be an important step to improving current clinical management of neovascular glaucoma. It also provides an insight into greater understanding of the cellular events that occur in response to global ischaemia or hypoxia. It would be most interesting to further evaluate this idea with a prospective study.



Clinical Examination Methods

Factors affecting IOP

Comment by Jost Jonas, Heidelberg, Germany

59047 A longitudinal study of age-related changes in intraocular pressure: the Kangbuk Samsung Health Study, Zhao D, Kim MH, Pastor-Barriuso R, Chang Y, Ryu S, Zhang Y, Rampal S, Shin H, Kim JM, Friedman DS, Guallar E, Cho J, Investigative Ophthalmology and Visual Science 2014;55:6244-6250

This is very large health-screening center-based longitudinal examination mostly of employees of large companies in Korea over a period of eight years. Intraocular pressure (IOP) was measured by automated noncontact tonometers which changed during the follow-up period (2002-2004: TX-10; Canon, Tokyo, Japan; 2005-2008: TX-F; Topcon, Itabashi, Tokyo, Japan; 2009 onward: CT-80; Topcon). **Including 281,238 adult Korean men and women into the investigation, the authors reported that IOP was inversely associated with age.** For men, this inverse association was observed throughout the entire age range, while for women it was evident only in younger (< 30 years of age) and older (≥ 60 years of age) women, with no association in women aged 30 to 59. The strength of the study is very large sample size and long follow-up over eight years. Limitations of the study are that it was health-care center-based mostly including employees of companies, and more importantly that associations between IOP and blood pressure, body height and body mass index were statistically not fully taken into account. To cite an example, differences between Koreans and Westerners in the association of IOP with age may be caused by inter-ethnic differences in age-related changes in body mass index, body height and blood pressure. In view of the high qualities of the study, the authors may be encouraged to further explore statistically the potential influence of these potentially confounding factors.

IOP fluctuation

Comment by Tony Realini, Morgantown, WV, USA

59370 Asymmetry of habitual 24-hour intraocular pressure rhythm in glaucoma patients, Liu JH, Weinreb RN, Investigative Ophthalmology and Visual Science 2014;55:7398-7402

Professors Liu and Weinreb at the University of California, San Diego have reported the results of an analysis of fellow-eye symmetry of 24-hour IOP curves in three groups: healthy younger people, healthy older people, and untreated glaucomatous older people. In general, **the two healthy groups exhibited reasonable symmetry of mean 24-hour IOP, timing of peak IOP, and amplitude of IOP, while the glaucoma group exhibited substantially less symmetry of these parameters.** Asymmetry of IOP in fellow glaucomatous eyes limits the validity of inferring IOP behavior in one eye based on observations in the fellow eye.

> This result critically undermines the validity of the monocular therapeutic drug trial

There are a number of important clinical implications of this finding. Firstly, this result critically undermines the validity of the monocular therapeutic drug trial, in which one eye is treated and the fellow eye left untreated in an attempt to distinguish between therapeutic and spontaneous IOP change. The monocular trial requires symmetric IOP variation between fellow eyes in order for the untreated fellow eye to serve as a control for the treated eye. The monocular drug trial has largely fallen out of fashion, although efforts have been made to restore its utility by considering diurnal or even 24-hour IOP curves before and after treatment. The current study demonstrates that even these modifications of the monocular drug trial are unlikely to improve its performance. Secondly, and more timely and relevant, is the significance of this finding in the era of continuous 24-hour IOP monitoring. Triggerfish contact-lens based 24-hour IOP assessment is technically noninvasive but is far from user-friendly: an uncomfortable contact lens, an unsightly antenna taped to the face around the eye, a cord attaching it to a recorder worn on a belt or in a pocket and fraught with risk for entanglement during sleep. There will be great temptation to conduct this test unilaterally and make the assumption that the output represents IOP behavior bilaterally. Based on the results of this study, such a temptation should be resisted.

RGC loss and disc hemorrhage

Comment by Ki Ho Park, Seoul, South Korea

58999 Estimated rates of retinal ganglion cell loss in glaucomatous eyes with and without optic disc hemorrhages, Gracitelli CP, Tatham AJ, Zangwill LM, Weinreb RN, Liu T, Medeiros FA, PLoS ONE 2014; 9: e105611

In contrast to the previous studies on structural and functional changes in glaucoma associated with disc hemorrhage, the current study has introduced a new concept of retinal ganglion cell (RGC) loss estimation in glaucoma patients with or without disc hemorrhage. RGC number estimation was proposed by Medeiros *et al*. in a series of previous reports. Even though the formulas for RGC number estimation have been derived empirically in studies on a primate model of glaucoma, they have been validated with human cohorts.

The authors found the rate of RGC loss to be twice as fast in their disc hemorrhage group (22,233 cells/year) than in their no-hemorrhage group (10,704 cells/year). In the latter group, no disc hemorrhage was detected during follow up (average: 3.74 ± 0.85 years). Also associated with faster rates of progression was a higher mean IOP during follow-up. Even after adjusting for confounding variables, however, the effect of disc hemorrhage on the estimated RGC loss rate remained significant. Overall, the study supports the current evidence that the presence of disc hemorrhage should be considered to be an indicator of increased risk of faster optic nerve damage in glaucoma.

> The rate of RGC loss is two-times faster in the disc hemorrhage group than in the no-hemorrhage group (in which no disc hemorrhage was detected during follow up)

The study has limitations, in that (1) there might have been cases of missed detection of disc hemorrhage; and (2) the recorded hemorrhages occurred at any time during the rate calculation period, not at the beginning. Nonetheless, this new approach does strengthen the existing evidence on the association of hemorrhage with the rate of glaucoma progression.

It will be interesting to focus the current study into the regional rate of RGC loss after developing a new formula for estimated regional RGC number or using additional tool such as regional RGC layer and inner plexiform layer thickness analysis in disc hemorrhage cases.

References

1. Medeiros FA, Lisboa R, Weinreb RN, et al. A combined index of structure and function for staging glaucomatous damage. Arch Ophthalmol 2012;130:1107-1116.
2. Medeiros FA, Zangwill LM, Anderson DR, et al. Estimating the rate of retinal ganglion cell

loss in glaucoma. Am J Ophthalmol 2012;154:814-824.
3. Medeiros FA, Zangwill LM, Bowd C, Mansouri K, Weinreb RN. The structure and function relationship in glaucoma: implications for detection of progression and measurement of rates of change. Invest Ophthalmol Vis Sci 2012;53:6939-6946.
4. Kim KE, Yoo BW, Jeoung JW, Park KH. Long-Term Reproducibility of Macular Ganglion Cell Analysis in Clinically Stable Glaucoma Patients. Invest Ophthalmol Vis Sci 2015; March 31. [Epub ahead of print]

Ruling out glaucoma based on VF indices

Comment by Nomdo Jansonius, Groningen, The Netherlands

59182 Role of visual field reliability indices in ruling out glaucoma, Rao HL, Yadav RK, Begum VU, Addepalli UK, Choudhari NS, Senthil S, Garudadri CS, JAMA Ophthalmology 2015;133(1):40-44

Rao *et al*. studied the influence of the visual field reliability indices (fixation loss [FL] and false-positive [FP] and false-negative [FN] response rates) on the ability of standard automated perimetry (SAP) to rule out glaucoma in glaucoma suspect patients. In this study, glaucoma suspect patients were patients referred by general ophthalmologists because of a suspected optic disc – that was in the end deemed normal by glaucoma specialists**. Suspects with a high FN response rate were found to have more often an abnormal SAP (Humphrey field analyzer SITA standard 24-2) test result, based on the glaucoma hemifield test and the pattern standard deviation (PSD)**. FL and FP response rate were not associated with the SAP classification.

At first sight, these results are surprising. As the authors mention, FN response rate is supposed to be related to the presence and severity of glaucoma and to have little influence on the test result. FP response rate, on the other hand, is considered to be the most important indicator of visual field reliability. This was recently confirmed in a longitudinal study reporting that the FP response rate had a strong influence on the SAP mean deviation (MD) whereas the role of the FN response rate was negligible (Junoy Montolio *et al*. IOVS 2012).

The lack of influence of the FP response rate in the current study might be related to the very low median FP response rate of only 1%. The association between a high FN response rate and an abnormal SAP test result triggers the question if these cases were really normal – or is the combination of an elevated FN response rate, an abnormal glaucoma hemifield test, and an abnormal PSD pointing to early glaucoma? Only longitudinal follow-up of either the discs or the fields could settle this issue. The study relies on the assumption that disc abnormalities always precede visual field abnormalities. However, population-based studies have shown that glaucoma with field abnormalities preceding disc abnormalities is not rare (Czudowska et al 2010).

RNFL and Psychophysical performance

Comment by Pradeep Ramulu, Baltimore, MD, USA

58843 Glaucomatous retinal nerve fiber layer thickness loss is associated with slower reaction times under a divided attention task, Tatham AJ, Boer ER, Rosen PN, Della Penna M, Meira-Freitas D, Weinreb RN, Zangwill LM, Medeiros FA, American Journal of Ophthalmology 2014;158:1008-1017.e2

Prior work has demonstrated that drivers with glaucoma demonstrate driving difficulties and are more likely to be at fault for a motor vehicle accident. A general assumption, supported by some evidence, is that these driving problems were primarily the result of vision loss, *i.e.*, the inability to observe threats presenting in their peripheral vision.

In the current cross-sectional study, **Tatham and colleagues observe that a specific driving simulator metric (reaction time to a peripheral stimulus) was worse with greater retinal nerve fiber loss as defined by SD-OCT**. Reaction time was measured during a divided attention task in which patients were asked to negotiate a series of curves while maintaining lane position or follow a car moving at varying speed at a fixed distance. Performance of both central tasks was similar amongst patients with and without glaucoma, while reaction time to peripheral stimuli was slower amongst glaucoma patients, and was noted to be progressively slower with lower rNFL thickness. Of note, slower reaction times were only found when low contrast peripheral stimuli, likely near the threshold of perceptibility, were presented and were not observed for medium or high contrast stimuli.

The authors' findings raise an interesting question: Why would rNFL thickness predict reaction time independent of VF loss severity? One possibility is that rNFL thickness predicts visual abilities (i.e., motion detection) not evaluated in SAP. Alternately, a growing literature suggests that rNFL thickness may be lower in Alzheimer's dementia and early stages of cognitive loss, in which case the observed findings may reflect the ability of OCT to predict cognitive ability. Further research is needed to distinguish these possibilities, and to establish the extent to which OCT may be used to predict functional outcomes independent of standard visual metrics.

Clinical Forms of Glaucoma

Secondary glaucoma

Comment by Malik Kahook, Denver, CO, USA

59338 Refractory open-angle glaucoma after neodymium-yttrium-aluminum-garnet laser lysis of vitreous floaters, Cowan LA, Khine KT, Chopra V, Fazio DT, Francis BA, American Journal of Ophthalmology 2015;159:138-143

Nd:YAG vitreolysis for floaters is a non-FDA approved treatment modality that has been linked with serious adverse events such as cataract formation and retinal detachment.

> Nd:YAG vitreolysis for floaters is a non-FDA approved treatment modality

While cases of transient elevation in intraocular pressure (IOP) have been reported after this procedure, the incidence of chronic elevation in pressure is not known. Cowan and colleagues report two cases (three eyes) of significant IOP elevation after Nd:YAG vitreolysis that required escalation of medical/laser therapy and, in two eyes, invasive surgery. The pathophysiology of the IOP elevation is not clear and would be difficult to surmise from the information provided in this report. Furthermore, the small number of eyes included in this report, and retrospective nature of the data collection, makes it difficult to generalize the findings to all patients undergoing this procedure. Nevertheless, it is important to consider this potential complication when counseling patients who are considering this treatment modality for vitreous floaters.

Glaucoma and Systemic Diseases

IOP fluctuation in patients with thyroid eye disease

Comment by Eytan Blumenthal, Jerusalem, Israel

58958 Twenty-four-hour intraocular pressure patterns in patients with thyroid eye disease, Parekh AS, Mansouri K, Weinreb RN, Tafreshi A, Korn BS, Kikkawa DO, Clinical and Experimental Ophthalmology 2015;43(2):108-114

Parekh and colleagues evaluated the safety, tolerability and diurnal IOP patterns obtained in patients with active thyroid eye disease (TED), using the Sensimed Triggerfish contact lens, a novel device sensitive to changes in corneal curvature and circumference. Intraocular pressure-derived corneal geometrical changes are captured by a strain gauge embedded within this unique contact lens. The generated electrical signals are transferred to a microprocessor, and then wirelessly transferred to a patched periorbital antenna and finally to a portable recorder. The device is set to capture 300 data points within a 30-second interval period, repeated every five minutes. Data is expressed in 'arbitrary units', hence, trends, peaks and circadian patterns can be identified, rather than actual IOP measurements in mmHg.

> Recognizing patterns of IOP circadian rhythms may better assist in choosing the most appropriate therapy, as well as monitoring the success of therapies applied

In this prospective study, the more proptotic eye of ten TED patients was measured during a 24-hour interval. Safety was good, with only mild conjunctival hyperemia, occasional superficial punctate keratitis and blurred vision, all transient to the period the contact lens was placed on the eye. Tolerability was good, at 1.5 (on a 1-10 discomfort score). Of interest, three patients were measured both pre- and post-orbital decompression surgery.

Regarding the circadian patterns observed, **a peak was found at early morning (around 6:30 am) in half the patients.** Analyzing the wake-sleep and sleep-wake transitions (which also coincide with the sitting-supine and supine-sitting postural changes) **a notable change found was a significant decrease of the signal in the morning, transitioning from the sleep-supine to the wake-sitting position.**

This study assists in identifying 24-hour IOP patterns in various secondary glaucomas and conditions known to affect the IOP. Recognizing patterns of IOP circadian rhythms may better assist in choosing the most appropriate therapy, as well as monitoring the success of therapies applied.

POAG and Dementia

Comment by Francesca Cordeiro, London, UK

59457 Associations between primary open angle glaucoma, Alzheimer's disease and vascular dementia: record linkage study, Keenan TD, Goldacre R, Goldacre MJ, British Journal of Ophthalmology 2015;99(4):524-527

For a number of years, there has been speculation that there may be a link between Alzheimer's Disease (AD) and POAG. However, despite increasing evidence of possible common molecular mechanisms underlying the two diseases, epidemiological studies have shown conflicting results. Recently, Keenan and Goldacre have explored this further using the method of record linkage that the authors have previously applied to AMD and AD, as also for assessing trends in trabeculectomy and cataract surgery in England.

In record linkage, data relating to successive care episodes are brought together per patient, enabling analysis across multiple episodes of care across specialties. Data in this study came from English national hospital episode statistics (HES) through the NHS Information Centre and the Oxford record linkage group. In this analysis, the authors used a complete data set from all hospitals in England from 1999 to 2011, looking specifically at hospital admissions.

Eighty-seven thousand six hundred and fifty-eight POAG, 251 703 AD and 217 302 vascular dementia cohorts were compared to a reference cohort (> 2.5 million people). **The findings suggested that the risk of AD following a diagnosis of POAG was not elevated (rate ratio 1.01), whilst that of vascular dementia after POAG was modestly elevated (with rate ratio 1.10)**. The likelihood of a hospital record of POAG following AD or vascular dementia was very low, with rate ratios 0.28 and 0.32.

> The question as to whether or not there is a definitive link between AD and POAG remains unanswered

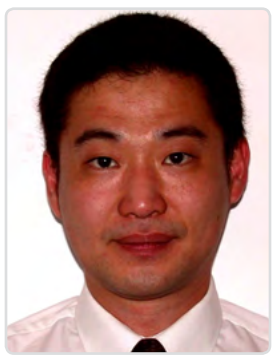
Whilst this is an interesting result, it is important to consider several factors. Firstly, although there are major advantages in the use of record linkage not least of which is related to cost, there are real drawbacks, the most important in this study being inclusion only of hospital admissions. Hence, only patients who were admitted into hospital or for day-case surgery were included. As the authors themselves admit, 'this methodology will not capture all patients with POAG in England, particularly those treated over a long period exclusively with medical therapy' – in other words, the majority of patients attending glaucoma follow-up.

Secondly, record linkage is dependent on the reliability and appropriateness of HES-entered diagnostic codes, and this has long been an issue, especially given the over-burdening of the

NHS with administrative duties. Moreover, sub-coding problems such as with NTG or even Glaucoma Suspect may occur, as well as those associated with AD and other forms of dementia. Mis-coding would therefore represent a significant issue in the analysis.

POAG and AD are neurodegenerative, chronic and progressive diseases associated with irreversible neuronal cell loss. Both primarily affect the elderly, with a strongly age-dependent incidence, and as life expectancy increases, their burden will escalate. As they share similar pathological processes, and potential treatments, the question as to whether or not there is a definitive link between AD and POAG remains unanswered. This study highlights the need for further good and prospective epidemiological data in the field.

POAG and Glucose metabolism disorders



Comment by Minguang He, Guangzhou, China

59521 Diabetes, glucose metabolism, and glaucoma: the 2005-2008 national health and nutrition examination survey, Zhao D, Cho J, Kim MH, Friedman D, Guallar E, PLoS ONE 2014; 9: e112460

There is some evidence suggesting an association of diabetes and open-angle glaucoma (OAG). **Zhao and his colleagues confirmed this association (odds ratio = 2.12, 95%CI: 1.23~3.67) whereas they also reported that diabetes with five years or longer duration had much higher odds (OR=3.90, 95%CI: 1.63~9.32) to be associated with OAG, based on the sample from NHANES study.** In this study, diabetes and pre-diabetes were ascertained by a robust definition based on fasting plasma glucose, Hb1Ac and medical history. The potential problem is on the diagnosis of glaucoma where all cases were ascertained by self-reported questionnaire. Given the fact that over 50% of glaucoma might be undiagnosed in the community even in the US population, this definition on glaucoma would probably lead to substantial misclassification. Interestingly, the analysis also suggested a somehow dose-response effect on the association of glaucoma and fasting glucose and metabolism markers. This further supports the biological association between diabetes and OAG. The study is able to deliver an important public health message: in the routine annual eye check-up for diabetic patients, physicians should not only look for diabetic retinopathy but also pay attention to glaucoma, people with longer duration of diabetes would have even greater risk of developing glaucoma.

Comment by Paul Healey, Westmead, Australia

In 1997 I authored a paper which reported a positive association between Diabetes and glaucoma in the Blue Mountains Eye Study[1]. This stood in contrast to a report two years earlier from the Baltimore Eye Survey which did not find any evidence for an association[2]. We could find no clear indications of bias in either study, leaving us with the somewhat unsettling conclusion that data were inconsistent. Numerous subsequent studies were also inconsistent. Inconsistency is the worst outcome of multiple investigations as it neither offers direction for scientific research nor allows us to advise our patients. One approach to shed light on such dichotomy is the systematic review and meta-analysis which seeks to increase power by pooling like cohorts as well as showing relative results weighted for power. This is the approach taken by Zhao et al in a recent paper in JAMA Ophthalmology. The key to a good meta-analysis is to cast a wide net for studies, exclude poor quality or non-generalizable results, weight based on study quality and analyze like studies together. Zhao et have done a good job in this respect, identifying 47 cross-sectional, case-control and longitudinal studies of almost 3 million individuals from many parts of the world. Point estimates of relative risk ranged from strongly positive (4.20) to moderately negative (0.61). Most studies reported positive point estimates but many were not statistically significant. In general smaller studies reported stronger associations, a common manifestation of publication bias. But the overwhelming evidence was for a positive association when pooled by study type or dose-response. Consistent (though weaker) positive associations were also found with intraocular pressure or ocular hypertension. The authors found that **risk of glaucoma increases by 5% for each year since diagnosis of diabetes with an overall risk of about 1.5 compared to individuals without diabetes**. This is an almost identical finding of an earlier meta-analysis conducted on 12 studies in 2004. So did we need another meta-analysis? This one included more studies and importantly more higher quality studies published since the previous paper. Do we need more studies investigating whether an association exists between diabetes and glaucoma? Probably not. Rather, given the weak association with IOP we need research into how a vascular disease caused by a neuroprotectant can lead to neurodegeneration.

References

1. Mitchell P, Smith W, Chey T, Healey PR. Open-angle glaucoma and diabetes: the Blue Mountains Eye Study, Australia. Ophthalmology 1997;104:712–8.
2. Tielsch JM, Katz J, Quigley HA, et al. Diabetes, intraocular pressure, and primary open-angle glaucoma in the Baltimore Eye Survey. Ophthalmology 1995;102:48–53.

Medical treatment

Long-acting drug delivery

Comment by Jose-Maria Martinez de la Casa, Madrid, Spain

59114 Targeted delivery of antiglaucoma drugs to the supraciliary space using micronee-dles, Kim YC, Edelhauser HF, Prausnitz MR, Investigative Ophthalmology and Visual Science 2014;55:7387-7397

Glaucoma is a chronic disease that requires chronic treatment. Two important problems that may result in deficient glaucoma control are patient non-adherence to treatment and the low bioavailability of topical drugs.

In this article, Kim *et al*. assess the efficiency of the supraciliary injection of anti-glaucoma agents as an alternative to topical administration such that the drug is delivered closer to its site of action. Their study was carefully designed with strict control of some of the variables that could affect intraocular pressure readings such as the type of anaesthetic used and prior calibration of the rebound tonometers used in the study.

Their results show that the targeted delivery of anti-glaucoma drugs using micro-needles in the New-Zealand White rabbit enables a significant reduction in the dose used. For one of the drugs tested, sulprostone, **the dose needed for a similar pharmacodynamic response to that achieved via its topical administration was around 100-fold lower,** while for the other drug tested, brimonidine, this dose was 115-fold lower. Thus substantial differences exist between the two routes of administration even if we consider that the supraciliary formulation contained as vehicle 2% carboxymethylcelullose to increase the viscosity and therefore the persistence of the drug following its injection.

Future work is needed to assess the efficacy and safety of this administration route in humans. **The method proposed seems an interesting option that opens an array of possibilities to improve the performance of anti-glaucoma treatment.** Finding formulations that given by this route will enable the controlled release of drugs could substantially improve the quality of life of patients with glaucoma.

Surgical treatment

Current trends in surgery

Comment by Rupert Bourne, Cambridge, UK

59097 Recent trends in glaucoma surgery in Scotland, England and Wales, Murphy C, Ogston S, Cobb C, MacEwen C, British Journal of Ophthalmology 2015; 99(3):308-12.

Murphy *et al.* present the numbers of trabeculectomy and aqueous shunt procedures performed over 20 years from 1993 to 2012 in England, Scotland and Wales. **Highest rates of trabeculectomy were achieved in 1995, followed by a sharp decline by a factor of three until 2000. Since then, rates have remained stable** at approximately 33 trabeculectomies per 100,000 population aged 60+ years. The authors noted that **numbers of aqueous shunts, a much more infrequently performed operation throughout, began to rise in 2003 with a steep rise from 2009 to 2012** (2012: four shunts per 100,000 aged 60+ yrs). By 2012, the ratio of trabeculectomy to aqueous shunt was 10:1 in this age group. In children, a national trend towards increased use of aqueous shunts and decreased use of trabeculectomy was observed, in 2012, the ratio was 2:1.

> trabeculectomy still remains an important surgical option for glaucoma despite growing numbers of alternative laser and shunt procedures

This work followed a robust methodology involving national hospital statistics. Although errors can and do occur with validity of diagnostic/operative coding, and these statistics only include the state-run National Health Service, it is likely that we are seeing a valid picture of national trends, which fits with similar observations in the United States[1] and Canada,[2] where tube implantation has become increasingly popular.

The trabeculectomy rate among those aged 60+ years remains static since 2000 yet the population in this age group increased by 18% between then and 2012, so the crude numbers of trabeculectomies performed per year continued to rise. Although the numbers of aqueous shunts implanted is much smaller, they are becoming more commonly used and this may reflect a growing perception that the role of shunts is not only limited to refractory glaucoma. The same explanation may underly the observation also made by this study, that ciliary body laser photocoagulation procedures had doubled between 2003 and 2012 in this older age group. Against this surgical backdrop, a 67% increase in NHS prescriptions for glaucoma occurred between Yr2000 (4.8 million) and 2012 (7.9 million) in the United Kingdom![3]

The national surgical picture painted by this study is an important resource for commissioners of care in the UK's National Health Service where the demands on resources are increasingly

intense. It demonstrates that trabeculectomy still remains an important surgical option for glaucoma despite growing numbers of alternative laser and shunt procedures, and emphasizes the importance of maintaining adequate resources for glaucoma surgery that includes high standards of surgical training.

References

1. Ramulu P, Corcoran K, Corcoran S, et al. Utilization of various glaucoma surgeries and procedures in medicare beneficiaries from 1995 to 2004. Ophthalmol 2007;114:2265-2270.
2. Campbell R, Trope G, Rachmiel R, et al. Glaucoma laser and surgical procedure rates in Canada: a long-term profile. Can J Ophthalmol 2008;43:449–453.
3. Connor AJ, Fraser SG. Glaucoma prescribing trends in England 2000 to 2012. Eye (Lond) 2014;28(7):863-869.

Laser trabeculoplasty

Comment by Karim Damji, Ottawa, Ontario, Canada and Lisa Heckler, Montreal, Quebec, Canada

59573 Efficacy of selective laser trabeculoplasty in primary angle-closure glaucoma: a randomized clinical trial, Narayanaswamy A, Leung CK, Istiantoro DV, Perera SA, Ho CL, Nongpiur ME, Baskaran M, Htoon HM, Wong TT, Goh D, Su DH, Belkin M, Aung T, JAMA Ophthalmology 2015;133(2):206-212

This first-of-its-kind RCT compared the efficacy of SLT with a prostaglandin analog (PGA) travaprost in patients with primary angle closure (PAC) or PAC glaucoma (PACG) who have undergone previous laser iridotomy and in whom the trabecular meshwork was visible for at least 180°.[1] This is an important question given the burden of PAC associated blindness globally, and difficulties with cost, adherence and toxicity related to glaucoma medications. A previous study by Ho also looked at SLT in PACG patients and was prospective but not controlled.[2]

In this well-powered three-center unblinded study, 50 patients were randomized to SLT and 50 to medication. SLT included pre-treatment with brimonidine and pilocarpine, and post-treatment with prednisolone. Analysis was based on intent to treat. **At six months, there was excellent follow-up and no differences between the SLT and PGA arms in IOP reduction** (4.0 vs. 4.2 mmHg or 16.9% vs. 18.5% respectively). More patients in the PGA group achieved IOP ≤ 21 mmHg without additional medications vs. the SLT group (84% vs. 60%). In the SLT group one patient had an IOP spike and no patients developed additional PAS; in the PGA group one patient had allergic conjunctivitis and another uveitis. **A 4.8% decrease in endothelial cell count (ECC) was noted in the SLT arm vs. a mean increase of 0.4% in the medication arm.**

The authors excluded secondary causes of angle closure but do not mention exfoliation syndrome, which can result in a combined mechanism glaucoma in some patients. SLT was repeated at the one- or three-month follow-up if there was less than 20% reduction in IOP; this may have been premature given that it can take two to four months for the full effect of SLT after treatment.[3,4]

This study provides convincing evidence that at six months SLT is as effective as a PGA in treating high IOP in PAC patients after iridotomy, albeit with a 5% decline in ECC. Longer follow-up and further study will be needed to better elucidate its role in this patient population.

References

1. Narayanaswamy A, Leung CK, Istiantoro DV, et al. Efficacy of selective laser trabeculoplasty in primary angle-closure glaucoma: a randomized clinical trial. JAMA Ophthalmol 2015;133(2):206-212.
2. Ho CL, Lai JS, Aquino MV, et al. Selective laser trabeculoplasty for primary angle closure with persistently elevated intraocular pressure after iridotomy. J Glaucoma 2009;18(7):563-566.
3. Latina MA, Sibayan SA, Shin DH, Noecker RJ, Marcellino G. Q-switched 532-nm Nd:YAG laser trabeculoplasty (selective laser trabeculoplasty): a multicenter, pilot, clinical study. Ophthalmology 1998;105(11):2082-2088; discussion 2089-2090.
4. Nagar M, Luhishi E, Shah N. Intraocular pressure control and fluctuation: the effect of treatment with selective laser trabeculoplasty. Br J Ophthalmol 2009;93(4):497-501.

Trabeculectomy ab interno

Comment by Julian Garcia Feijoo, Madrid, Spain

59017 Outcomes of ab interno trabeculectomy with the trabectome after failed trabeculectomy, Bussel II, Kaplowitz K, Schuman JS, Loewen NA, British Journal of Ophthalmology 2015;99(2):258-262

Filtering surgery is still the 'gold standard' as it is very effective, but is linked to complications. In the past years new surgical techniques aiming to minimize the ocular trauma and the impact on the quality of life have been developed. Some of these, known as MIGS, aim to increase the outflow enhancing the physiological drainage pathways.[1] Trabectome is one of these bleb-less procedures and its mechanism of action is the ablation of the trabecular meshwork,[2] so to succeed the downstream conventional drainage system should be intact. However there is controversy regarding the theoretical efficacy of these procedures after failed conventional filtering surgery.

The objective of the paper is to address the role of trabectome after failed trabeculectomy.[3] These are challenging patients for a technique like this, as it has been reported that after a functional trabeculectomy the flow is directed to the bleb, inducing/causing the atrophy of the conventional outflow system.[4,5] The authors hypothesized that, by removing the diseased meshwork and subendothelial plaques, conventional outflow might be restored, if not completely to a certain level. Moreover they think that, as the TM could be more damaged in more advanced cases, the IOP reduction could even be greater than in patients with early disease.

> A prospective study analyzing a homogeneous population (glaucoma diagnosis, stage…) and considering factors that may influence the results is needed to help identify the type of patients who could benefit the most from this surgery

So the study addresses a relevant question and of interest that challenges some of our believes. They have analyzed two subgroups of patients, one underwent Trabectome alone (AIT. N: 58) and the other trabectome plus cataract (Phaco-AIT. n: 15). In the AIT group mean IOP was reduced from 23.7 ± 5.5 to 16.2 ± 3.9 mmHg (28% mean reduction, $p < 0.01$) and the number of medications was reduced from 2.8 ± 1.2 to 2.0 ± 1.3 ($p < 0.01$) at one year. In the phaco-AIT group, the mean IOP was reduced from 20.0 ± 5.9 to 15.6 ± 5.1 mmHg (19% mean reduction, $p = 0.11$). More interestingly, the authors provide the success rate according to different criteria, **by using the criteria of IOP < 18 mmHg and 20% IOP reduction the one-year success rate is of 53% in the AIT group and 54% in the Phaco-AIT group**.

They have stratified the patients according to the VF Include patients with early, moderate, advanced glaucoma stage, and when VFs could not be categorized, due to non-glaucomatous VF changes, or unreliable test performance by software assessment, exams were categorized as 'other'. But a significant proportion of patients were included in this group: 47% of the Phaco-AIT patients and 24% of the AIT alone patients.

The study has some limitations, is retrospective and the study group not only includes POAG patients, but patients with other glaucoma diagnose. As there are many factors that could have an impact on the success rate more information baseline characteristic of the population, on the follow-up of the trabeculectomy (time to failure, re-introduction of adjunctive therapy…) and a clear definition of the glaucoma stage is missed.

A prospective study analyzing a homogeneous population (glaucoma diagnosis, stage…) and considering factors that may influence the results is needed to help identify the type of patients who could benefit the most from this surgery. Some of these factors could be the survival time of the previous trabeculectomy, time of complete or qualified success, total period of time from the trabeculectomy to the trabectome surgery.

But the conclusion of the author is fair and so it seems that this technique could be a viable option for patients after a failed trabeculectomy. If these results will be confirmed, we could raise the question of if other MIGS procedures aiming to bypass the trabecular meshwork could also be beneficial. There are obvious and marked differences between trabectome and these techniques, so even though the conclusion of this study does not apply directly to them, this study might open a window that for many was closed.

References

1. Saheb H, Ahmed I. Micro-invasive glaucoma surgery: current perspectives and futures directions. Curr Opin Ophthalmol 2012;23:96-104.
2. Francis BA, See RF, Rao NA, et al. Ab interno trabeculectomy: development of a novel device (Trabectome) and surgery for open-angle glaucoma. J Glaucoma 2006;15:68-73.
3. Bussel II, Kaplowitz K, Schuman JS, Loewen NA, Trabectome Study Group. Outcomes of ab interno trabeculectomy with the trabectome after failed trabeculectomy. Br J Ophthalmol 2015;99:258-262.
4. Lütjen-Drecoll E. Functional morphology of the trabecular meshwork in primate eyes. Prog Retin Eye Res 1999;18:91-119.
5. Johnson DH, Matsumoto Y. Schlemm's canal becomes smaller after successful filtration surgery. Arch Ophthalmol 2000;118:1251-1256.

Aqueous drainage devices

Comment by Franz Grehn, Würzburg, Germany

59586 Five-year treatment outcomes in the Ahmed Baerveldt comparison study, Budenz DL, Barton K, Gedde SJ, Feuer WJ, Schiffman J, Costa VP, Godfrey DG, Buys YM, Ophthalmology 2015;122(2):308-316

This paper reports the five-year results of a randomized prospective study comparing the outcome of Ahmed Glaucoma Valve Implant (AGV) versus the 350 mm^2 Baerveldt Glaucoma Implant (BGI). Primary outcome was failure rate as defined by the study protocol (inadequate IOP control without re-operation, reoperation, explantation, persistent hypotony, loss of light perception). Secondary outcome measures were IOP, visual acuity, glaucoma medications, and complications. The protocol was designed according to the 'Guidelines on Design and Reporting of Surgical Trials' of the World Glaucoma Association.

Out of 276 patients (eyes) entering the study at beginning, 174 (87 in each group) completed the five-year follow-up. **Similar rates of surgical success were observed with both implants.** In general, the BGI produced greater IOP reduction and a lower rate of glaucoma reoperation than the AGV, but the BGI was associated with twice as many failures because of safety issues.

The detailed results of this study allow further insight in the differences of outcomes of the two implants.

The Kaplan Meier success survival rates were virtually identical during the first four years with a non-significant difference at five years (44.7% in the AGV group and 39.4% in the BGI group). The IOP of the AGV group was reduced from 29.6 ± 10.1 mmHg at baseline to 14.7 ± 4.4 mmHg, and the IOP of the BGI from 28.3 ± 9.3 mmHg at baseline to 12.7 ± 4.5 mmHg at the five-year follow-up visit, respectively. This difference was significant even if adjusted for the lower baseline IOP of the BGI. The AGV patients had more inadequately controlled IOP or reoperations as compared to the BGI group, counting as failures (AGV 80% of all failures vs. BGI 53% of all failures). However, the **BGI had more sight-threatening complications – 25 (47% of failures) vs. 11 (20% of failures).** One possible bias discussed in the paper was lower failing IOP before re-operation in the AGV group (20.0 vs. 23.0 mmHg). This might have increased the number of re-operations (counted as failures) in the AGV group. In the AGV group 20.8% compared with 8.6% in the BGI group underwent reoperation for glaucoma during five years of follow-up.

The number of **complete successes at five years was nine (8%) in the AGV group compared with 14 (14%) in the BGI group** (P = 0.27). This demonstrates a general need of additional medication in tube implants and outlines the very low rates of complete success. In trabeculectomy, even after five years of follow-up, the complete success rate is considered considerably higher by most surgeons.

The cumulative probability of qualified (with or without medications) success, defined as IOP ≤ 17 mmHg and reduced IOP by at least 20%, was 39.6% in the AGV group and 53.9% in the BGI group (P = 0.048) at five years.

There was a significant decrease in Snellen VA in both treatment groups during the five years of follow-up. Approximately 43% of subjects lost two or more lines of Snellen VA. There was no significant difference in logMAR Snellen VA between the two groups at five years. In neovascular glaucoma, at five years, the cumulative proportion of patients who progressed to NLP in the AGV group was 28.3% compared with 51.1% in the BGI group (P = 0.030). The authors also report that compared with the three-year study results, there were no additional subjects in the AGV group who lost two or more lines of vision, but there were eight additional subjects in the BGI group who lost two or more lines of vision.

In summary, the BGI seems more effective in providing long-term IOP control than the AGV implant (2 mmHg lower). However, the BGI had a higher number of inadequately low IOPs and also a considerable number of phthisis cases. Therefore, averaging the IOP of all cases may have shifted the mean value towards lower IOPs in the BGI group. However, with the WGA success criteria that define a bimodal IOP cut-off, the BGI still provides higher rates of IOP control.

> Both the ABC and AVB Studies observed significantly greater long-term IOP reduction and less need for glaucoma medical therapy with the BGI compared with the AGV, with similar success rates after three years of follow-up

The major challenge of the comparison is the balance between IOP results and safety issues. Although the AGV had more reoperations and needed more additional medication, which may have a major impact on quality of life of the patient, the BGI was more challenged with severe safety issues such as phthisis, loss of light perception, hypotony, and implant explantation. Safety differences may be more relevant for complictated cases such as neovascular glaucoma (which would favor AGV), whereas in less complicated cases the safety aspects are less frequent and IOP control becomes more important (which would favor BGI).

One important aspect is the postoperative hypertensive phase in ligated BGI tubes that only open after approx. six weeks, whereas the AGV will better control the IOP in the early postoperative phase. Therefore, the BGI may have advantages when the risk profile of an individual case is lower.

The present study does not explicitly report corneal endothelial counts, which would be a surrogate of corneal impact. However, in Table 5 of the paper, three of 36 cases (8%) of AGV and ten of 38 (26%) cases of BGI were reported to have more than two Snellen lines visual deterioration due to corneal problems of various reasons.

The general results of the ABC study are also in accordance with the AVB study, the other comparative tube implant study. Both the ABC and AVB Studies observed significantly greater long-term IOP reduction and less need for glaucoma medical therapy with the BGI compared with the AGV, with similar success rates after three years of follow-up.

Comment by Tanuj Dada, New Delhi, India

59347 *In vivo* testing of a novel adjustable glaucoma drainage device, Villamarin A, Stergiopulos N, Bigler S, Mermoud A, Moulin A, Roy S, Investigative Ophthalmology and Visual Science 2014;55:7520-7524

Villamarin *et al*. report on the *in vivo* testing of a novel noninvasively adjustable glaucoma drainage device (AGDD). The AGDD is designed to drain aqueous with a resistance to outflow that can be externally regulated.

The implant is inserted surgically under a scleral flap and contains a mechanism that allows for a variable compression of the tube, altering its cross-sectional area and thus changing the fluidic resistance using an external magnet. In the present study AGDD was implanted on one eye of seven white normotensive rabbits for a duration of four months with the other eye serving as control. **The IOP dropped significantly when the AGDD was opened from its fully closed (maximum outflow resistance) to fully opened (minimum outflow resistance) position.**

> Safety issues which need to be investigated include magnetic resonance imaging (MRI) compatibility and the influence of an external magnetic field on the device resistance

Although this is an exciting new technology to regulate postoperative IOP and prevent hypotony in glaucoma filtering surgery there are several inherent limitations on its use in penetrating glaucoma filtering surgery. The study evaluated the efficacy AGDD in IOP reduction in normotensive eyes and not in glaucomatous eyes, for which it is actually intended. The IOP was reported only with fully open or closed positions of the device and there was no control/gradient of outflow reported with change of device resistance. Despite being implanted in a closed position there was a transient hypotony in the early postoperative period. A very large (7 x 7 mm) sclera flap was used and the resistance to outflow may vary with the number and tension of sutures used to close the sclera flap. Safety issues which need to be investigated include magnetic resonance imaging (MRI) compatibility and the influence of an external magnetic field on the device resistance. Finally, a four-month postoperative follow-up is too short because episcleral and subconjunctival fibrosis will eventually limit the aqueous outflow and reduce the efficacy of the device making the adjustable outflow technology redundant in the long term.

Despite these limitations this is a commendable innovation which may also have potential in the prevention of early hypotony if coupled with non-valved glaucoma drainage devices.

Comment by Nitin Anand, Gloucester, United Kingdom

59347 *In vivo* testing of a novel adjustable glaucoma drainage device, Villamarin A, Stergiopulos N, Bigler S, Mermoud A, Moulin A, Roy S, Investigative Ophthalmology and Visual Science 2014;55:7520-7524

In an experimental study, Villamarin and colleagues implanted an adjustable glaucoma drainage device (AGDD) made of deformable silicone, in seven white New-Zealand rabbit eyes. The device body was implanted under a seven-by-seven mm limbal scleral flap, with the nozzle inserted into the anterior chamber and a distal outlet for drainage into the subconjunctival space. In the device body is an asymmetrically placed magnet and a peripheral deformable tube that can be progressively compressed by rotating the magnet. Thus, the angular position of the magnetic disk defines the length of the tube that is compressed. An external control unit (CU) can rotate the magnet without touching the device The CU also has a compass that indicates the position of the magnet.

The implanted device was opened with the CU once a month for four months. **IOP dropped in all eyes each time the implant was opened from a mean of 11.2 mmHg (range 7-17 mmHg) to 4.8 mmHg (4-7 mmHg). The IOP dropped by 8 mmHg even in the third to fourth month.** Histopatholgy was reassuring, with a mild granulomatous reaction around the device in most eyes.

The study has significant translational implications. In eyes with a low propensity to fibrosis, it can be implanted like the Express shunt to allow for an anterior filtration bleb. IOP can be titrated keeping it in the high normal range in the early postoperative period. If adjuvant Mitomycin C is used, the ability to regulate flow may be of great advantage in the long-term. Late hypotony could possibly be reversed simply by completely closing the device.

The AGDD may be used in conjunction with various implants designed to direct flow posteriorly like the Baerveldt or Molteno implant. Regulating the early IOP is problematic with these implants. Surgeons use various permutations of intraluminal sutures, external suture ligatures and slits in the tube to regulate IOP. The AGDD may offer a solution. The device may be closed or partially open in the early postoperative period depending on the IOP. Early hypotony and IOP spikes, two persistent problems for tube surgeons, could possibly be eliminated. Another possible innovation may be to design an AGDD with a longer nozzle to enable more posterior implantation and drainage.

The short follow-up is a limitation of rabbit eye experimental studies. The article alludes to trials with the device on human eyes and these are eagerly awaited.

Industry News

Humphrey Field Analyzer 3 from ZEISS

The new Humphrey® Field Analyzer 3 (HFA3) from ZEISS, is the next generation in visual field testing and analysis. The HFA3 is designed to accelerate clinic flow while delivering the same gold-standard testing strategies and test patterns.

ZEISS

We make it visible.

The New HFA3 provides a streamlined and faster workflow with an array of new features designed to:

- Reduce setup time with a single trial lens. Using liquid pressure, the new Liquid Trial Lens™ instantly delivers each patient's refractive correction with the touch of a button.*
- Save time with an intuitive new SmartTouch™ interface, which reduces the number of steps required for the technician to start a perimetry exam.
- Accelerate clinic flow with equipment that can be learned quickly and operated easily.
- Improve confidence in test results with RelEYE™, which allows doctors to instantly review the patient's eye position, at any stimulus point. RelEYE data is available on the instrument and when reviewing test results with FORUM® Glaucoma Workplace.
- Simplify test administration, with an easy-to-use kinetic graphical user interface with a full 180-degree field of view.

**Some patients may require a separate lens. Liquid Trial Lens available on the HFA3 model 860.*

Carl Zeiss Meditec, Inc.

Website: www.zeiss.com/hfa3

Icare Home - Self-tonometry is here

icare FINLAND

Now IOP monitoring is possible at home with the new, easy to use **Icare HOME** tonometer.

Iop self-monitoring anywhere, anytime

- Improved cost and clinic efficiency
- Better care and patient comfort
- More reliable data

The world-wide established and renowned rebound technology by **Icare** guarantees quick, effortless and effective IOP measurements. **Icare Finland** supports IOP phasing studies by supplying loaner **Icare HOME** devices.

For more information, please contact Mr. Jouni Onnela: jouni.onnela@icarefinland.com

www.icaretonometer.com

We acknowledge the unrestricted educational grants of our:

Glaucoma Industry Members

Alcon®

ALLERGAN

Associate Glaucoma Industry Members

ZEISS
We make it visible.

HEIDELBERG ENGINEERING

A Clear Vision For Life™
Santen
SANTEN PHARMACEUTICAL CO., LTD.
http://www.santen.com

TOPCON
CONNECTING VISIONS

Supporting Glaucoma Industry Members

Aeon Astron Europe B.V., AqueSys Inc., Bausch + Lomb, EyeTechCare, Glaukos, Haag Streit AG, Icare Finland Oy, Implandata Ophthalmic Products GmbH, Lumenis Vision, NeoMedix Corporation, Oculus, Optovue Inc., Otsuka, Pfizer, Senju, Sensimed AG, Tomey

The Global Glaucoma Network

The Journal of the World Glaucoma Association

Santen

A Clear Vision For Life®

Headquartered in Japan, Santen specializes in research & development, manufacturing and marketing of ophthalmic and anti-rheumatic pharmaceuticals to protect and improve people's eyesight and health. Since its foundation in 1890, Santen has accumulated scientific knowledge and organizational capabilities for over 120 years. We are advancing our operations not only in Japan but also in Europe, the U.S. and Asia. Our products are now sold over 70 countries. Santen will continue to contribute to society, working primarily for the benefit of patients and their loved ones.

WGC HONG KONG 2015
Please visit Santen Booth #33

SANTEN PHARMACEUTICAL COMPANY
http://www.santen.com

www.e-IGR.com

News flashes

- ★ Reduction of EVP may be a viable target for glaucoma therapy
- ★ iPS cells restore the normal homeostatic response to and elevated IOP
- ★ Is some degree of loss recoverable in glaucoma?
- ★ The trans-synaptic nature of degeneration caused by glaucoma
- ★ Recognizing patterns of IOP circadian rhythms may better assist in choosing the most appropriate therapy
- ★ Whether or not there is a definitive link between AD and POAG remains unanswered

Published by the World Glaucoma Association in collaboration with
Kugler Publications, Amsterdam, The Netherlands