Glaucoma 2012
Managing Challenging Glaucoma Problems—Merging Art and Science

Subspecialty Day
2012
Chicago
November 9 – 10

Under Pressure®

Program Directors
Wallace LM Alward MD and
Thomas W Samuelson MD

In conjunction with the American Glaucoma Society
McCormick Place
Chicago, Illinois
Saturday, November 10, 2012

Presented by:
The American Academy of Ophthalmology

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AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

Dear Colleague:

On behalf of the American Academy of Ophthalmology and the American Glaucoma Society (AGS), it is our pleasure to welcome you to Chicago and Glaucoma 2012: Managing Challenging Glaucoma Problems—Merging Art and Science.

As co-chairs of the Glaucoma Subspecialty Day Program Planning Group, we are honored to have planned this year's meeting. The goal for this year's Glaucoma Subspecialty Day is to deliver clinically relevant information for clinicians. We want both general ophthalmologists and specialists to walk away with new tools. We worked very hard to get the best speakers from all over the world and the best moderators to engage these speakers in meaningful conversation. We anticipate that this will be an extraordinary educational event.

We have built in plenty of time for audience response and feedback. For the first time ever, participants will be able to text in their questions during the discussion periods. And several of the surgical cases will be presented as "point-counterpoint" to allow for lively debate. Highlights include the pathophysiology of glaucomatous vision loss, the latest advances in medical and surgical therapy for glaucoma, and surgical devices and complications.

We are excited to have Mildred M G Olivier MD as the AGS Subspecialty Day Lecturer. Her talk is entitled "The Global Impact of Glaucoma: Addressing Care in Developing Countries." Dr. Olivier speaks from vast personal experience. She has focused much of her outreach effort on Haiti. Her involvement began many years before the devastating earthquake and has continued throughout the aftermath of that disaster. Her story will provide insight into managing glaucoma in developing countries.

In an effort to put together innovative and interesting Subspecialty Day meetings in the future, we request that you assist us by completing the evaluation. We carefully review all comments to better understand your needs, so please indicate the strengths and shortcomings of today's program.

Again, we welcome you to Glaucoma 2012: Managing Challenging Glaucoma Problems—Merging Art and Science. We hope you find it educational and enjoyable.

Sincerely,

Wallace L M Alward MD
Program Director

Thomas W Samuelson MD
Program Director

Glaucoma 2012 Contents

Electronic version of Syllabi available at
www.aao.org/2012syllabi

CME Credit

Academy's CME Mission Statement

The purpose of the American Academy of Ophthalmology's Continuing Medical Education (CME) program is to present ophthalmologists with the highest quality lifelong learning opportunities that promote improvement and change in physician practices, performance or competence, thus enabling such physicians to maintain or improve the competence and professional performance needed to provide the best possible eye care for their patients.

2012 Glaucoma Subspecialty Day Meeting Learning Objectives

Upon completion of this activity, participants should be able to:

- Describe innovations in the diagnosis and management of glaucoma within their historical context
- Compare new ideas regarding the pathophysiology of glaucomatous vision loss
- Evaluate the current status of optic disc and retinal nerve fiber layer imaging and its role in diagnosing and managing glaucoma
- Demonstrate familiarity with current issues in medical and surgical therapy for glaucoma
- Identify and manage glaucoma surgical complications

2012 Glaucoma Subspecialty Day Meeting Target Audience

This activity has been designed to meet the educational needs of general ophthalmologists, glaucoma specialists and other ophthalmologic subspecialists, and allied health personnel who are involved in the management of glaucoma patients.

2012 Glaucoma Subspecialty Day CME Credit

The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The American Academy of Ophthalmology designates this live activity for a maximum of 7 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Before processing your requests for CME credit, the Academy must verify your attendance at Subspecialty Day and/or the Joint Meeting. In order to be verified for CME or auditing purposes, you must either:

- Register in advance, receive materials in the mail and turn in the *Final Program* and/or *Subspecialty Day Syllabus* exchange voucher(s) onsite;
- Register in advance and pick up your badge onsite if materials did not arrive before you traveled to the meeting;
- Register onsite; or
- Use your ExpoCard at the meeting.

CME Credit Reporting

Grand Concourse Level 2.5; Academy Resource Center, Hall A - Booth 508

Attendees whose attendance has been verified (see above) at the 2012 Joint Meeting can claim their CME credit online during the meeting. Registrants will receive an e-mail during the meeting with the link and instructions on how to claim credit.

Onsite, you may report credits earned during Subspecialty Day and/or the Joint Meeting at the CME Credit Reporting booth.

Academy Members: The CME credit reporting receipt is not a CME transcript. CME transcripts that include 2012 Joint Meeting credits entered onsite will be available to Academy members on the Academy's website beginning December 3, 2012.

NOTE: CME credits must be reported by Jan. 16, 2013. After the 2012 Joint Meeting, credits can be claimed at www.aao.org/cme.

The Academy transcript cannot list individual course attendance. It will list only the overall credits spent in educational activities at Subspecialty Day and/or the Joint Meeting.

Nonmembers: The Academy will provide nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity, but it does not provide CME credit transcripts. To obtain a printed record of your credits, you must report your CME credits onsite at the CME Credit Reporting booths.

Proof of Attendance

The following types of attendance verification will be available during the Joint Meeting and Subspecialty Day for those who need it for reimbursement or hospital privileges, or for nonmembers who need it to report CME credit:

- CME credit reporting/proof-of-attendance letters
- Onsite Registration Form
- Instruction Course Verification

Visit the Academy's website for detailed CME reporting information.

The American Glaucoma Society (AGS) Subspecialty Day Lecture

The Global Impact of Glaucoma: Addressing Care in Developing Countries

Saturday, November 10, 2012
11:43 AM – 12:13 PM

Mildred M G Olivier MD

Mildred M.G. Olivier, M.D., is Associate Professor at Rosalind Franklin University of Medicine and Science, and Associate Clinical Professor at Midwestern University. She is the CEO and founder of the Midwest Glaucoma Center. She received her bachelor's degree from Loyola University and her medical degree from Rosalind Franklin University. She completed her residency at Columbia University/Harlem Hospital Center and her fellowship at the Kresge Eye Institute.

Dr. Olivier is a veteran of frequent medical missions to Haiti since 1993. She was a key member of the Task Force on Haiti Recovery following Haiti's earthquake in January, 2010. She has served on the Advisory Council of the National Eye Institute, the Women's Task Force, and the Women and Diversity Committee at ARVO. She is an AAO delegate to the AMA. She is past chair of the Education and Training Committee on the Commission to End Health Disparities. Dr. Olivier serves on the board of Prevent Blindness America and is past chair of its scientific committee. She is president of the Chicago Glaucoma Society, and is active in the American Glaucoma Society and on the board of the American Glaucoma Society Foundation. Dr. Olivier is president-elect for 2013 of Women in Ophthalmology.

Dr. Olivier presented on the AAO/PAAO Task Force for Haiti Recovery and Organizational Collaboration at the World Glaucoma Conference in Berlin. She is published in major, peer-reviewed journals and co-authored the Glaucoma Section in *Clinical Eye Atlas*. She co-authored the book, *Maintaining the Target Intraocular Pressure*.

Dr. Olivier's work has earned various honors including the American Glaucoma Society's Humanitarian Award (2012), AAO's Secretariat Award (2011), AMA's Dr. Nathan Davis Award for International Medicine (2011), the Pan-American Congress of Ophthalmology's Benjamin F. Boyd Humanitarian Award (2011), and Prevent Blindness America's Person of Vision Award (2010).

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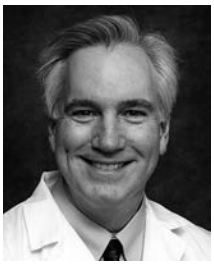

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Glaucoma 2012: Managing Challenging Glaucoma Problems—Merging Art and Science

In conjunction with the American Glaucoma Society

SATURDAY, NOVEMBER 10, 2012

7:00 AM	REGISTRATION/ MATERIAL PICKUP/ CONTINENTAL BREAKFAST		
8:00 AM	Welcome and Introductions	Wallace L M Alward MD	
8:02 AM	American Glaucoma Society Introduction	Jeffrey M Liebmann MD*	
8:04 AM	Announcements	Thomas W Samuelson MD*	
Section I:	**Apparent Worsening**		
	Moderator: Christopher A Girkin MD		
8:08 AM	Case Presentation and Audience Response	Christopher A Girkin MD	
8:13 AM	Correlating Ganglion Cell Loss and Perimetric Change	Keith R Martin MD*	1
8:20 AM	Incorporating Perimetric Rate of Change	Joseph Caprioli MD FACS*	3
8:27 AM	Incorporating Structural Rate of Change	Felipe A Medeiros MD*	6
8:34 AM	Does Early Glaucoma Affect the Central 10 Degrees?	Donald C Hood PhD*	8
8:41 AM	Pitfalls in Interpreting Spectral Domain OCT	Sanjay G Asrani MD*	10
8:48 AM	Panel Discussion and Q&A		
9:03 AM	Audience Response		
Section II:	**Progression at Normal Pressures**		
	Moderator: Kuldev Singh MD MPH*		
9:06 AM	Case Presentation and Audience Response	Kuldev Singh MD MPH*	
9:11 AM	Pressure Fluctuation: In the Lab and in the Clinic	Arthur J Sit MD*	12
9:18 AM	Effect of Cerebrospinal Pressure	Jost B Jonas MD*	15
9:25 AM	Contribution of the Lamina Cribrosa in Glaucoma Susceptibilty	John C Morrison MD	18
9:32 AM	Blood Pressure and Sleep Apnea	Donald L Budenz MD MPH*	20
9:39 AM	How I Treat Patients Progressing at Low IOPs	David S Greenfield MD*	22
9:46 AM	Panel Discussion and Q&A		
10:01 AM	Audience Response		
10:04 AM	REFRESHMENT BREAK and JOINT MEETING EXHIBITS		
Section III:	**Narrow Angles**		
	Moderator: Harry A Quigley MD*		
10:45 AM	Audience Response	Harry A Quigley MD*	
10:48 AM	Could Your Primary Open-Angle Glaucoma Patient Have Chronic Angle Closure?	Paul J Foster FRCS*	24
10:55 AM	Anterior Segment Imaging	Joel S Schuman MD*	26

* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.

11:02 AM	Gonioscopy in the Clinic and the OR	Douglas J Rhee MD*	30
11:09 AM	When to Consider Lensectomy for Angle Closure	David S Friedman MD MPH*	32
11:16 AM	Not All Angle Closure Is Pupillary Block	Tin Aung FRCS PHD*	33
11:23 AM	Panel Discussion and Q&A		
11:38 AM	Audience Response		

The American Glaucoma Society Subspecialty Day Lecture

Moderator: Jeffrey M Liebmann MD*

11:41 AM	Introduction of the Lecturer	Jeffrey M Liebmann MD*	
11:43 AM	The Global Impact of Glaucoma: Addressing Care in Developing Countries	Mildred M G Olivier MD*	35
12:13 PM	Presentation of the Award	Jeffrey M Liebmann MD*	
12:14 PM	LUNCH and JOINT MEETING EXHIBITS		

Section IV: A Need for Glaucoma Surgery (With or Without Cataract)

Moderator: Dale K Heuer MD*

1:30 PM	Introduction	Dale K Heuer MD*	
1:32 PM	Advocating for Patients	Thomas A Graul MD*	36
1:37 PM	Late Breaking Development: How Will the Trabecular Micro-bypass Approval Impact Glaucoma Management?	E Randy Craven MD*	38
1:45 PM	The Case for Angle Surgery	Robert N Weinreb MD*	39
1:51 PM	The Case for Trabeculectomy	Philip P Chen MD*	41
1:57 PM	The Glaucoma Filtration Device Mini-shunt Has Been a Positive Development	Marlene R Moster MD*	43
2:03 PM	The Glaucoma Filtration Device Mini-shunt: I Don't Get It	Robert M Feldman MD*	45
2:09 PM	The Case for Tube Shunts	Steven J Gedde MD*	47
2:15 PM	The Case for Cataract Surgery Alone	Steven L Mansberger MD MPH*	49
2:21 PM	Cases and Panel Discussion		
3:07 PM	Audience Response		
3:10 PM	REFRESHMENT BREAK and JOINT MEETING EXHIBITS		

Section V: Intraoperative Challenges

Moderator: Richard K Parrish II MD*

3:52 PM	Broken Capsule/Vitreous Loss	Louis D Skip Nichamin MD*	50
3:59 PM	Use of Intraoperative Endoscopy	Brian A Francis MD*	52
4:06 PM	Loose IOLs	Iqbal K Ahmed MD*	53
4:13 PM	Not Enough Conjunctiva	Cheryl L Khanna MD	54
4:20 PM	Panel Discussion and Q&A		
4:40 PM	Audience Response		

* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.

Section VI:	**Avoiding and Treating Postoperative Complications**		
	Moderator: Eydie G Miller-Ellis MD*		
4:43 PM	Bleb Leak With or Without Infection	Gloria P Fleming MD	56
4:50 PM	Failing Bleb	Jonathan S Myers MD*	58
4:57 PM	Painful Bleb	Ronald Leigh Fellman MD OCS*	60
5:04 PM	VEGF Inhibitors and Glaucoma Surgery	Cynthia Mattox MD FACS*	61
5:11 PM	Panel Discussion and Q&A		
5:24 PM	Audience Response		
5:27 PM	Closing Remarks	Wallace L M Alward MD	
5:30 PM	ADJOURN		

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Correlating Ganglion Cell Loss and Perimetric Change

Keith R Martin MD

Progressive loss of retinal ganglion cells (RGC) is a key feature of glaucoma and is associated with characteristic structural and functional changes seen in the condition. Perimetry is the functional test used most widely in the diagnosis and monitoring of glaucoma. The relationship between perimetric performance and RGC loss is thus highly clinically relevant. The current generation of glaucoma imaging devices mostly uses measures of optic disc topography and/or retinal nerve fiber layer thickness as surrogates for RGC loss. Over the years, however, many attempts have been made to correlate direct measures of ganglion cell density with perimetry. These studies have generally been challenging to conduct and interpret because they have often relied on attempts to correlate post mortem retinal histology with premortem visual field tests, either in humans[1,2] or monkeys.[3,4]

Does RGC Loss Precede Perimetric Change?

Classic studies by Quigley and co-workers[1,2] have frequently been interpreted as suggesting that 25%-35% loss of RGC is associated with visual field loss. However, one of the clearest findings from this work was the degree of variability, even between normal subjects, in RGC counts at any given eccentricity. Indeed, the estimated total RGC count in normal individuals varied by a factor of two. It should be remembered in interpreting any study that "loss" of RGC relative to a population average is not the same as "loss" of RGC over time by an individual. Thus, it should be no surprise that a proportion of glaucoma subjects studied by Quigley had abnormal visual fields with statistically "normal" RGC numbers. Clearly, longitudinal data on how RGC density changes over time is key to understanding the relationship between RGC loss and perimetry, and this is not possible in post mortem human studies.

In studies by Harwerth and co-workers,[3,4] the relationship between RGC loss and perimetric change has been investigated in a monkey glaucoma model where IOP elevation can be initiated at a defined time in one eye with the other eye used as a control. As monkeys can be trained to perform impressively reliable automated perimetry, and as experiments can be terminated after different durations of experimental glaucoma, measurement of the correlation between RGC loss and perimetric changes can be achieved. These studies have shown that RGC counts and perimetric performance are tightly correlated as long as appropriate measurement scales are used and other factors such as the effect of aging and eccentricity are considered. While these studies have sometimes been interpreted as suggesting that structural changes occur before changes in function, and they often do, a clear finding was that perimetric defects can also sometimes occur in the presence of relatively normal RGC density.

In the clinical domain, where optic disc imaging has often been used as a surrogate for RGC loss, large clinical trials have shown that whether detectable structural or functional changes occur first is extremely variable. For example, in the Early Manifest Glaucoma Trial a visual field endpoint was reached before a structural change in 86%, compared to 35% in the Ocular Hypertension Treatment Study. However, these results should be interpreted with care, given the widely different criteria used for structural and functional changes in clinical studies.[5]

Key Messages

1. RGC loss in glaucoma is associated with a variety of structural changes that can be measured and that correlate with perimetric change.

Individual RGC bodies in the retina cannot currently be quantified directly with commercially available instruments but surrogate measures such as optic disc topography, nerve fiber layer thickness, and more recently, thickness of the macular retinal ganglion cell complex have been shown to correlate well with RGC loss. Direct imaging of RGC bodies is possible in the lab using fluorescent labels, and techniques exist to label cells undergoing apoptosis that may help with the quantification of RGC loss clinically the future.

2. Measurements of NFL thickness and optic disc topography appear to correlate relatively well with ganglion cell loss and perimetry, but different structural measures may not necessarily co-vary simultaneously.

As an example, it is becoming clear that even for a relatively clearly defined structure such as the retinal nerve fiber layer, different instruments may detect different aspects of pathology. For example, recent work by Fortune and co-workers, presented at ARVO this year, has shown that scanning laser polarimetry may detect nerve fiber layer changes earlier than OCT. The proposed mechanism is related to possible cytoskeletal changes that occur before axonal loss that can be detected by SLP but not OCT. Structural measures of RGC features by different techniques are not necessarily interchangeable.

3. Structural measures of RGC sickness prior to loss could be very useful.

It may seem that the quantification of RGC body survival should be the main aim of a structural test in glaucoma, but it may be extremely valuable to have tests that can assess RGC injury prior to death. Recent studies suggest that the contrast sensitivity of ultrahigh-resolution OCT may allow the detection of subcellular changes that correlate with neuronal health or possibly even with neuronal activity.[6] Cellular structures and processes amenable to imaging that could give an indication of neuronal dysfunction prior to death include cytoskeletal components, axonal transport, early events in the apoptotic cascade, and possibly electrical function using voltage-sensitive dyes. The ability to detect sick RGCs at a stage when rescue is still possible would be extremely attractive, and correlation of such measures with perimetry would be very interesting.

4. We still need both structural and functional measures clinically.

Either structural or functional measures may be more useful at different stages of the glaucomatous disease process. Thus, structural changes may be very useful early in the disease as an indica-

tor of progression in the presence of normal standard automated perimetry. In contrast, the current generation of structural tests may be less valuable than perimetry late in the disease, when further RGC structural attrition may be difficult to detect structurally but causes progressive loss of function.

5. Combined structure–function indices are evolving rapidly and are likely to be widely used in future.

Current work in this area will be reviewed by Medeiros later in this session.[7,8]

References

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7. Garway-Heath DF, Poinoosawmy D, Fitzke FW, Hitchings RA. Mapping the visual field to the optic disc in normal tension glaucoma eyes. *Ophthalmology* 2000; 107(10):1809-1815.
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Incorporating Perimetric Rate of Change

Joseph Caprioli MD FACS

The measurement of rates of change in glaucoma help to identify those patients who are deteriorating quickly and to distinguish them from those who are worsening slowly.[1] The fast progressors may require suitably aggressive treatment while the slow progressors might be spared the expense and morbidity of unnecessary treatments. This topic is particularly important for an aging population with limited resources for medical care. Advancing damage in glaucoma can be measured by structural or functional changes, the latter most often estimated with perimetric measurements. In this presentation, we address the measurement of rates of damage with standard achromatic automated perimetry. Our goals are to develop a method to reliably measure the rate of functional decline in glaucoma, to use it to identify the fast progressors, and to provide clinically useful forecasts of the disease to help guide treatment. To be useful, the method should perform well across the entire range of disease severity.

The many problems with measuring rates with perimetry are well known. Mainly, these include a low signal-to-noise ratio, the requirement of multiple tests to reduce the noise, the requirement of confirmatory tests to validate the signal, and an inherent lack of external validation to evaluate any new method. A method to estimate global rates of visual field progression in glaucoma, the visual field index (VFI), has been presented by Bengtsson and Heijl.[2] The index is weighted more heavily toward the central visual field in proportion to the cortical representation of vision, is normalized to the entire range of visual field function, and provides some predictive capability as a linear extrapolation of the index.[3] It requires the use of proprietary, stored normative data and assumes a linear rate of worsening. A shortcoming of the global indices in general is the lack of any spatial information with regard to the regions of the visual field showing faster progression.

We hypothesize that progression in glaucoma is frequently nonuniform and that it is possible to identify a faster spatial component for visual field decay that can be distinguished from the remaining test locations that have a slower rate of decay. The latter frequently include components related to aging and media opacity, although in some cases the slow component may indeed represent true glaucomatous progression.[4] To test this hypothesis, we have developed a novel method to measure visual field decay with a large cohort of glaucoma patients with long-term follow-up. The method identifies visual field locations progressing at the fastest rates, provides a method to spatially separate test locations demonstrating slower progression from those showing faster progression, and predicts future visual field measurements with appropriate confidence intervals while preserving spatial information.[5] This approach has subsequently been validated in a separate, large group of glaucoma patients with long-term follow-up.[6]

An example of the analysis is given in Figures 1 and 2. This approach provides a statistically and clinically reasonable method to develop approximations of rates of worsening of glaucoma patients, and can be entirely automated for rapid retrieval and evaluation of serial visual field data. It provides a method to (1) isolate the faster and slower components of decay in the visual fields of an individual glaucoma patient, (2) identify those patients who are considered fast progressors for more intensive scrutiny and care, and (3) predict, with preservation of spatial information and with appropriate confidence intervals, the future outcome of the visual field.

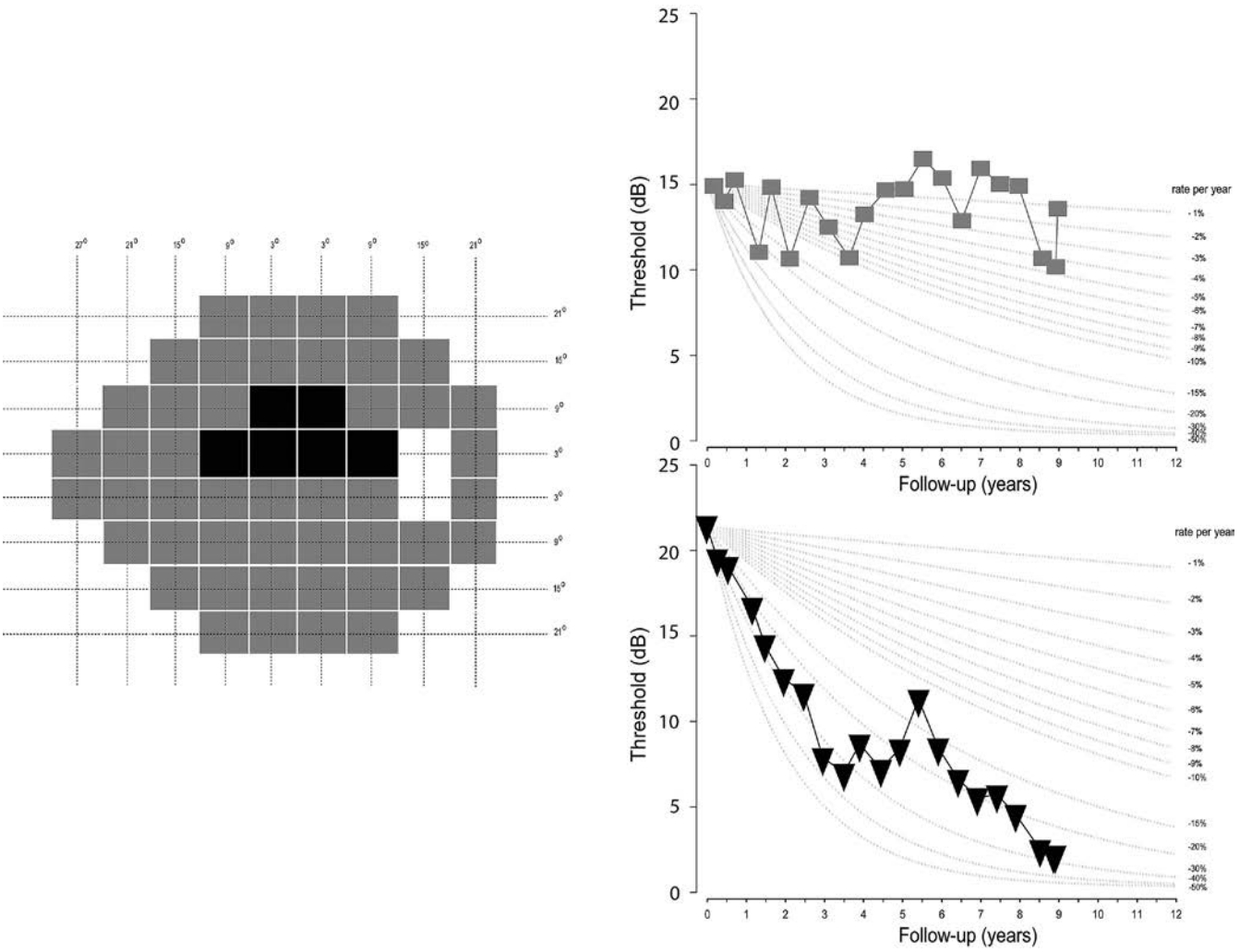

Figure 1. The partition of test location rates of decay into "slower" and "faster" components. The gray scale on the left shows the spatial distribution of test locations assigned to faster and slower components of exponential decay. The graphs on the right show the time course of the faster and slower components separately, superimposed on a grid that quantifies the rate of exponential decay. In this example the average slow component rate is 0%/year, while the average faster component rate is 30%/year.

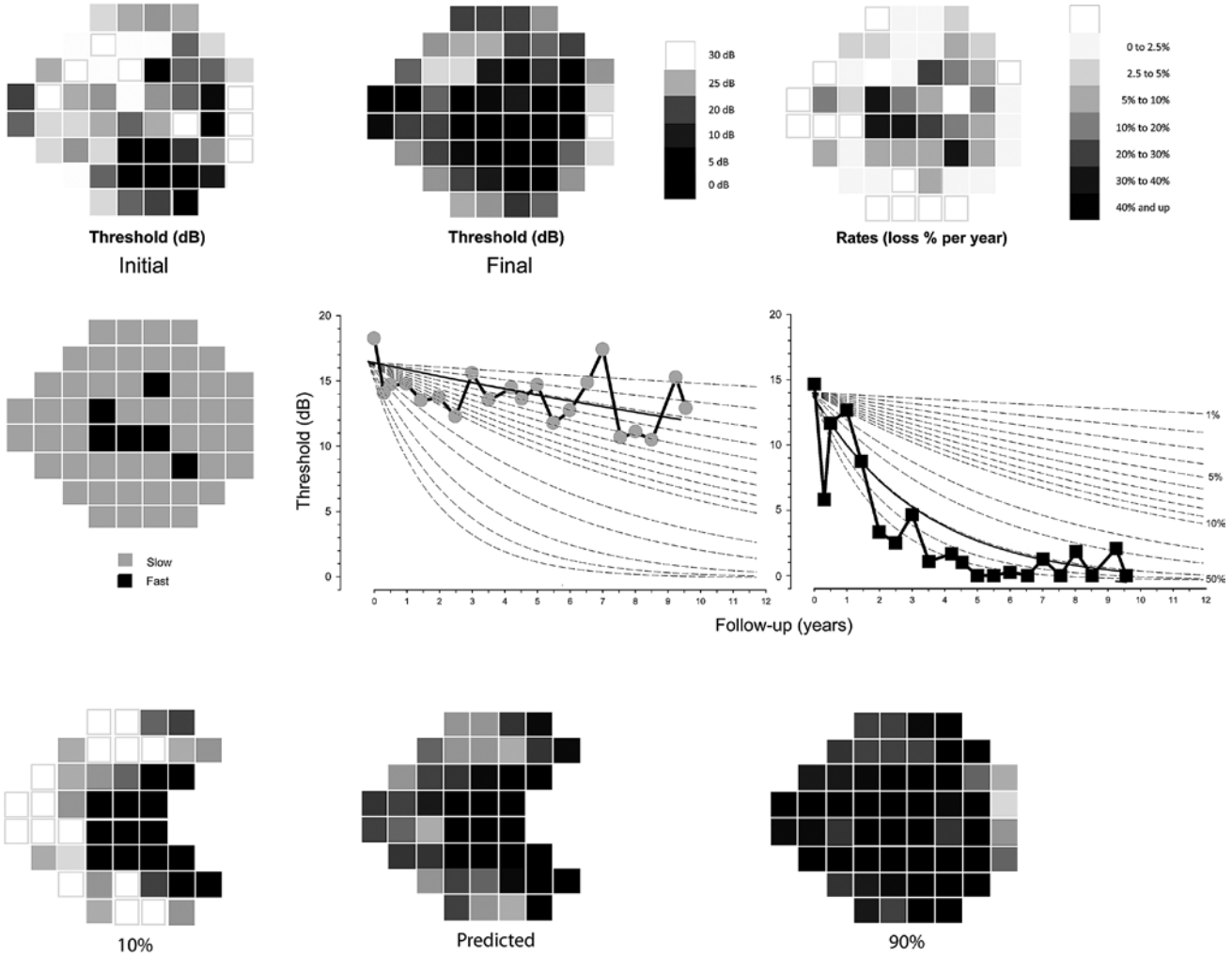

Figure 2. An example of a visual field rate and prediction display that summarizes the behavior of the visual field in a typical glaucomatous eye and provides predictions of future behavior of the visual fields. Top left: grayscale of the initial visual field in the series. Top middle: grayscale of the grayscale of the final visual field in the series. Top right: grayscale of the rate of decay (%/year) at each test location. Middle left: spatial partition of the visual field into slower (gray) and faster (black) components. Middle and middle right: average rates of decay of the slower (gray) and faster (black) components superimposed on gridlines for exponential decay. Bottom row: gray scale predictions for the visual field thresholds at final follow-up for the 10th percentile, 50th percentile (median), and 90th percentile confidence intervals; predictions were calculated based on the regression slopes derived from the first half of follow-up.

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Incorporating Structural Rate of Change

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Glaucoma treatment should be directed toward slowing down the rate of change to a level where disability from the disease will be unlikely during the remaining projected years of life.[1] Therefore, an accurate and precise determination of the rate of change is essential to guide aggressiveness of therapy and need for follow-up. Although rates of change are frequently assessed using standard automated perimetry (SAP), sole reliance on SAP to assess rates of change may result in underestimation of rates of neural damage in early to moderate stages of the disease.[2] This may result in delayed diagnosis and underestimation of the risk of developing functional impairment. Over the past few years, several longitudinal studies have shown that imaging technologies can provide reliable, objective, and quantitative estimates of rates of structural progression in glaucoma that can easily be incorporated into clinical practice.[3] Most studies have shown that straightforward strategies such as assessment of global average retinal nerve fiber layer thickness or measurements of neuroretinal rim area over time seem to perform well for assessment of rates of change.

Frequent disagreements are seen when structural and functional tests are used to monitor glaucoma patients for progression, and this has led to confusion in the literature and among clinicians. These disagreements, however, are easily reconciled when one understands the nature of the structure and function relationship in the disease.[4] The apparent disagreement between structural and functional measurements of the disease seem to be largely derived from the different algorithms and measurement scales, as well as the different variability characteristics of the tests commonly used to assess structural and functional losses. Therefore, the question should not be whether structural damage precedes functional damage or vice versa, but rather which characteristic of progression in the disease is detectable with currently available methods.

While SAP has relatively low sensitivity to identify progression at initial stages of the disease, currently available methods for structural assessment often perform poorly to identify change at advanced stages of damage.[4] Approaches combining structure and function can take advantage of the different performance of these tests according to the stage of damage in order to provide a reliable method for detecting change throughout the spectrum of the disease. It is important to emphasize that an optimal method for detecting glaucomatous progression not only should give an indication of whether or not the eye is changing over time, but also should estimate the rate of deterioration. Although most glaucoma patients will show some evidence of progression if followed long enough, the rate of deterioration can be highly variable among them.[5-9] While most patients progress relatively slowly, others have aggressive disease with fast deterioration that can eventually result in blindness or substantial impairment unless appropriate interventions take place. The use of rates of change as the outcome variable may also result in decreased sample size requirements compared to the use of categorical classifications in clinical trials evaluating glaucoma progression.

Several recent approaches have been described integrating structural and functional information for improving diagnosis, staging, and detection of glaucoma progression. These approaches range from use of Bayesian statistical methodologies[10,11] to the development of combined indexes integrating structural and functional measurements.[12,13] A combined structure and function index (CSFI) has been described by Medeiros et al[14] with the purpose of merging the results of structural and functional tests into a single index that could be used for diagnosis, staging, and detecting glaucomatous progression. The index uses estimates of retinal ganglion cell (RGC) counts obtained by previously derived empirical formulas. The estimates of RGC counts are obtained from two sources: one structural, retinal nerve fiber layer thickness assessment OCT; and one functional, standard automated perimetry. These estimates are then combined using a weighted average to provide a single estimate of the RGC count for a particular eye. For each eye, the CSFI represents the percent estimate of RGC loss compared with the age-expected number of RGCs. By combining structural and functional tests into a single estimate of RGC loss, the index provides a very intuitive parameter to be used in clinical practice. The CSFI has been shown to perform better than isolated structural and functional parameters for diagnosing and staging glaucomatous damage. Estimates of RGC counts from a combination of structural and functional tests have been shown to be able to detect glaucomatous progression and estimate rates of disease deterioration.[12] In a longitudinal study of 213 eyes followed for an average of 4.5 years, 47 (22.1%) showed statistically significant rates of RGC loss that were faster than the age-expected decline. The mean rate of RGC loss in these eyes was -33369 cells/year (range: -8332 cells/year to -80636 cells/year). In addition, estimates of RGC losses detected a significantly larger number of progressing eyes compared to isolated measures of function and structure at the same specificity level.[12]

In conclusion, a large amount of evidence has accumulated with regard to the beneficial role of incorporating results from imaging instruments in clinical practice. Approaches combing structural and functional information seem to offer great promise in improving our ability to better diagnose, stage and detect glaucomatous progression over time.

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Does Early Glaucoma Affect the Central 10 Degrees?

Donald C Hood PhD

I. Visual Field Studies

A. For some time, the literature has indicated that early glaucoma sometimes affects the central 10° (the macula). For example:

1. Aulhorn and Harms[1] reported a "spot-like" defect in the central 10° that developed into an accurate. See their Figure 10.
2. Drance[4] showed an arcuate defect that approached close to fixation. See his Figure 4.
3. Heijl and Lundovist,[5] using automated perimetry, examined the earliest defects in 45 eyes showing progression from normal to abnormal visual fields. They found early damage in the central 5°, especially in the upper field. See their Figure 1.

B. However, the visual field evidence also suggests that early damage to the central 10° is relatively common. For example:

1. Aulhorn and Karmeyer[2] examined the visual fields of 400 eyes with early glaucoma (their stage II). They found that the central ±5 to 7° of the upper visual field was among the most affected regions. These defects could extend to within 1 degree of fixation. See their Figure 3.
2. Langerhorst et al[8] prospectively obtained 10-2 (2° grid, ±10° field) and 30-2 (6° grid, ±24°) visual field data on 121 patients who were suspects or showed signs of early glaucoma. Of these, 36.4% of the hemifields showed abnormalities in the central 10° on the 10-2, as compared to 48.4% on the 30-2. In addition, the damage was rated as severe, or more severe, on the 10-2 visual fields in 55.2% of the abnormal hemifields.
3. Traynis et al,[14] in a similar study, found that 53.0% and 58.5% of the hemifields in eyes with 24-2 mean deviations (MD) better than -6 dB were abnormal on the 10-2 and 24-2, respectively, and 15.7% of the hemifields normal on the 24-2 visual fields were abnormal on the 10-2.
4. Schiefer et al[11] reported that over 50% of eyes with mild to moderate glaucoma had defects within the central ±3°.

C. Early damage of the macula is often, if not typically, arcuate in nature.

1. Dr. Robert Ritch first suggested to us that initial macular visual field defects often resemble a "comma" or a partial comma (unpublished talk).
2. There are a number of isolated examples in the earlier literature of small arcuate or comma-like defects close to fixation.[1-4]
3. Early damage to the macula is probably more often, if not typically, arcuate in shape.[7,11,12,14]

D. Macular damage found in the upper, as opposed to lower, visual field tends to be more common, more severe, and closer to fixation and the midline.[2,5,6,9,11,12]

II. Lessons From OCT

A. Early damage affects the macula: Retinal ganglion cell (RGC) layer thickness in the macula is significantly reduced in glaucoma suspects whose visual fields are classified as normal.[6,13]

B. RGC layer thinning is more severe in the inferior retina (upper visual field).[6]

C. Macular damage is largely arcuate in nature.[6]

D. Local loss of macular sensitivity is associated with local RGC loss if the displacement of RGC near the fovea is taken into consideration.[10]

E. The major RGC thinning due to glaucoma falls within the location of the central 4 points tested by the 24-2 (6° grid) test pattern.[6]

III. A Schematic Model of Macular Damage[6]

A. Assumptions

1. Wiring assumption: There is an asymmetric pattern of projections from the superior and inferior macular retinal ganglion cells (RGCs) to the optic disc.
   a. The superior macular RGCs, as well as the RGCs in a small cecocentral central region of the inferior macular, project to the temporal quadrant of the disc.
   b. Most of the RGCs in the inferior macular region project largely to the inferior quadrant to a region near the border of the temporal and inferior quadrants.

B. Vulnerability assumption: The probability of glaucomatous damage at the disc increases from the center of the temporal quadrant (9 o'clock for the right eye) toward the superior and inferior poles.

C. The model and visual fields: The model provides an explanation for:

1. The arcuate nature of macular visual field defects
2. The greater severity of upper visual field (inferior retinal) defects

3. The shape of the preserved macular region in some patients with severe glaucomatous loss[15]

IV. Conclusions and Clinical Implications/Suggestions

A. Summary

1. Early macular damage is common.
2. The macular RGC damage is largely arcuate in nature and associated with damage in the inferior quadrant and the lower portion of the temporal quadrant of the disc.
3. It is poorly sampled by the 24-2 (6° grid) test pattern.

B. Clinical implications

1. At a minimum, if there is any hint of macular problems on the 24-2 (6° grid) or in the patient's history, perform a test with a finer grid.
2. Preferably, the 24-2 (6° grid) test pattern should be replaced with one that better samples the central 10°.

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Pitfalls in Interpreting Spectral Domain OCT

Sanjay G Asrani MD

Introduction

In the last decade, our utilization of imaging technology for glaucoma has increased dramatically,[1] and we have come to rely upon data from these imaging devices to help us in differentiating normal from glaucoma. Future studies may demonstrate their utility as an objective measure of detecting progression. Spectral domain OCT is one such common modality. Many of us depend on the classification provided by the machine for the retinal nerve fiber layer (RNFL), macular thickness, or the optic nerve head as normal or abnormal. We also need accurate and reproducible measurements of retinal thickness or its sublayers to utilize it for disease progression.

Recognition of artifacts is critical for intelligent interpretation of the data. Many artifacts can occur in the measurement of the retina in disease states such as uveitis, epiretinal membranes, diabetic retinopathy, or macular degeneration.[2-5] However, even in the absence of retinal pathology, artifacts do occur.

Types of Artifacts

Operator dependent artifacts

- Acceptance of images with poor signal strength
- Improper RNFL circle placement
- OCT image not being in the center of the acquisition window. This results in cut off of innermost layers of the retina thus resulting in extremely low values of RNFL.

Patient/ocular pathology-dependent artifacts

- Decentration errors resulting from poor fixation by the patient
- In the presence of multifocal IOLs, the OCT line-scanning ophthalmoscope images can show wavy horizontal artifacts. Gaps between the wavy horizontal artifacts are wider in the center of the image and narrower in the periphery, matching the diffractive rings on the surface of such IOLs.[6]
- Myopic eyes with longer axial length are associated with a higher percentage of abnormal diagnostic classifications since the RNFL normative databases are typically adjusted only by age but not by axial length or refractive error.[7] Myopic eyes are also associated with many other artifacts such as difficulty in acquiring a good image due to excessively long axial length or myopic retinal schisis, affecting peripapillary RNFL thickness.
- Prominent posterior hyaloid, epiretinal membranes, and partial vitreous detachments create abnormal hyperreflective bands inward of the normal retinal boundary. The algorithm may identify the abnormal bands as the retinal boundary resulting in an overestimation of retinal thickness.[3]

Machine or post-image processing artifacts

- In the absence of an eye tracking system, a new artifact type related to patient eye movement is likely to occur when some cross-sectional retina images are shifted superiorly or inferiorly compared with adjacent images without corresponding shifts of the retina segmentation lines. These artifacts result in characteristic motion waves in the inner limiting membrane and retinal pigment epithelium layer maps that may be mistaken for either true retinal pathologic features or significant algorithm error.[2]
- Misidentification of the retinal boundaries. This is commonly seen in eyes with prominent posterior hyaloid, those with high myopia, or those with significant media opacities due to poor image quality.
- The effect of head tilt: In the absence of software to control for head tilt, significant artifacts may ensue with as little as 8 degrees of head tilt. A right head tilt causes statistically significant superior-temporal RNFL thickening, inferior-temporal RNFL thinning, superior outer macular thickening, and inferior outer macular thinning. A similar left head tilt induces superior-temporal RNFL thinning, inferior-temporal RNFL thickening, superior outer macular thinning, nasal outer macular thickening and inferior outer macular thickening.[8]

Clinical interpretation artifacts

- Localized losses of RNFL or macular thickness classified as normal due to averaging of thickness values by quadrant, sector or hemisphere
- Failure to recognize nonglaucomatous patterns of loss such as those seen in nonarteritic ischemic optic neuropathy, retinal dystrophies, hemiretinal vein occlusion, post lateral geniculate body strokes, optic neuritis, or in toxic, nutritional and infectious causes of optic atrophy
- Failure to recognize the effect of partial posterior vitreous detachment causing traction-related thickening and then subsequent thinning of the peripapillary RNFL over time
- Degradation of RNFL and ganglion cell layer without collapse of retinal structure in early stages of cellular loss

Summary

Ophthalmic imaging is an important adjunct to clinical diagnosis, but the results from imaging devices must be assessed critically relative to artifacts of imaging and the limitations of the technology and its normative databases. We need to avoid making therapeutic decisions based on thickness measurements without first assessing scans for artifacts. Manually correcting segmentation errors is time consuming and perhaps impractical in a busy clinical setting, but doing so in specific areas of interest may promote more accurate RNFL or retinal thickness measurements and better clinical care.

Ultimately, OCT imaging for glaucoma remains a rapidly developing field, and continued improvements in software and segmentation algorithms may provide increasingly reliable retinal images and quantitative thickness data.

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Pressure Fluctuation: In the Lab and in the Clinic

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Introduction

Variations in IOP have long been known, with Sidler-Huguenin first reporting diurnal variations in 1898.[1] IOP fluctuation has been suggested as an independent risk factor for glaucoma. However, the evidence in the literature is inconclusive, and the nature of IOP fluctuations is incompletely understood. In this presentation we will discuss the patterns of IOP fluctuation as measured under laboratory conditions and in clinical studies, and its role in glaucoma pathogenesis. We will also discuss emerging technology that may help to better understand IOP fluctuations.

Definition of IOP Fluctuation

For the purposes of this presentation, we will discuss 4 types of IOP fluctuation. First, "circadian IOP variations" will be used to discuss the normal circadian pattern that individuals experience through a 24-hour period. Second, "short-term IOP fluctuations" will be used to describe IOP changes within a 24-hour period, which will include random as well as circadian changes. Third, "long-term fluctuations" will be used to describe the variations that occur in IOP measured over multiple office visits. Finally, we will discuss positional changes in IOP that occur with alterations of body posture.

IOP Fluctuations in Animals

IOP varies rapidly and constantly when measured on a continual basis in animal models. McLaren et al[2] used an implantable pressure sensor in rabbits to allow continuous telemetric monitoring of IOP. They found that IOP undergoes virtually constant short-term fluctuations with heart rate, eye position, lid position, breathing patterns, physical activity, and application of external tonometers, among other factors. The clinical significance of these variations, which last a few seconds or less, is unknown but likely minimal. Rabbits also demonstrated a circadian rhythm in IOP, with pressure on average higher in the nocturnal period than in the diurnal period. More recent work from Downs et al[3] demonstrated similar rapid IOP fluctuations in nonhuman primates. However, their studies did not demonstrate a clear circadian pattern.

IOP Fluctuations in Humans

Circadian IOP fluctuations

It can be clinically difficult to separate random IOP fluctuations from the normal circadian pattern in an individual patient. However, using a sleep laboratory and IOP measurements every 2 hours, Liu et al[4] have shown that IOP is highest in the nocturnal period when measured in the physiologic positions (sitting while awake, supine while asleep). This pattern persists for both normal subjects and glaucoma patients. The nocturnal elevation in IOP combined with the drop in systemic blood pressure that normally occurs during sleep may result in compromise of optic nerve head perfusion in susceptible individuals. In support of this concept, Graham et al[5] have shown that glaucoma patients with exaggerated nocturnal declines in blood pressure had significantly greater disease progression rates. As well, Sung et al[6] found that circadian variation in ocular perfusion pressure was the most consistent prognostic factor for progression in normal-tension glaucoma patients. However, true "sleeping" IOP cannot be measured at this time.

Short-term IOP fluctuations

Bergea et al[7] investigated the correlations of IOP parameters with visual field progression in capsular (exfoliation) and simple (primary open-angle) glaucoma. They defined IOP fluctuation as the mean of the daily IOP range obtained during diurnal curves obtained every 2 months for 2 years. They found that both mean IOP and IOP fluctuations were correlated with visual field progression in exfoliation glaucoma. However, neither factor was associated with progression in primary open-angle glaucoma patients, who tended to have lower IOP. Asrani et al[8] also investigated short-term fluctuations by using home self-tonometry in open-angle glaucoma patients. They found that, based on Cox proportional hazard models, IOP fluctuation was a significant risk factor for progression while mean IOP was not.

Long-term IOP fluctuations

Evidence for the clinical significance of long-term IOP fluctuations in glaucoma typically comes from ad hoc secondary data analyses of large clinical trial databases. The results from these analyses are inconclusive.

Nouri-Mahdavi et al[9] performed a post hoc analysis of the data from the Advanced Glaucoma Intervention Study (AGIS). They defined IOP fluctuation as the standard deviation of IOP at all visits after the initial surgery in the study protocol. IOP fluctuation was found to be a significant risk factor for visual field progression. However, one of the issues with this study was that the data before and after visual field progression were included, along with patients who had additional surgical procedures to reach the predetermined target of 18 mmHg. These factors may have contributed to the IOP fluctuations in patients who were progressing. In a subsequent study using the AGIS cohort, Caprioli and Coleman[10] addressed this issue by limiting the follow-up to the period before visual field progression and excluding patients with multiple surgical procedures. Patients were also stratified into terciles based on the mean IOP and IOP fluctuation. The authors found that IOP fluctuation was significantly associated with visual field progression in the low mean IOP tercile, but not the high mean IOP tercile.

In contrast to the AGIS results, Bengtsson and Heijl[11] did not find and any statistically significant relationship between diurnal IOP fluctuation and visual field progression in 90 patients of the Malmö Ocular Hypertension Study, where IOP fluctuation was calculated based on the range of IOP. Of note, IOP fluctuations were significantly correlated with mean IOP, with IOP fluctuations increasing 0.17 mmHg for each 1-mmHg increase in mean IOP. Similarly, Bengtsson et al[12] analyzed the data from the Early Manifest Glaucoma Trial (EMGT) and found that mean IOP was a significant factor for glaucoma progression (based on visual field or optic disc criteria). However, IOP fluctuation,

defined as the standard deviation of IOP from all visits, was not a significant factor.

Medeiros et al[13] investigated this issue using the data on untreated ocular hypertension patients in the Diagnostic Innovations in Glaucoma Study (DIGS). IOP fluctuations were defined as the standard deviation of all available IOP measurements for each eye. Defining glaucoma conversion as the development of visual field loss or optic disc damage, they found that mean IOP was a significant risk for conversion in both univariate and multivariate models, but IOP fluctuation was not a significant risk factor in either model.

To integrate these disparate results, Caprioli[14] has suggested that IOP fluctuation is a significant risk factor for glaucoma progression in patients with low IOP, but when IOP is high, then mean IOP is the predominant risk factor. Other potential explanations include a nonlinear response to IOP changes, with greater importance at higher IOP, or the need to measure IOP fluctuation as percentage change instead of absolute change.[15] Further research is required to clarify the role of long-term IOP fluctuation in glaucoma.

IOP Fluctuations With Body Position

IOP has long been known to vary with body position, increasing from the sitting to the supine position. However, measurement sequence can affect the magnitude of the change in IOP. As well, IOP in other body positions is incompletely understood. A recent study from our laboratory compared IOP in 6 head and body positions using a randomized sequence of measurements in healthy subjects.[16] We found that in the sitting position, neck flexion and extension both resulted in an increase in IOP compared with having the neck in a neutral position. In all recumbent positions, including supine, right and left lateral decubitus positions, IOP was higher than sitting with the neck in a neutral position. As well, lateral decubitus positions resulted in a higher IOP in the dependent eye than in the nondependent eye. IOP measured while sitting with the neck in a neutral position (the typical position for a slitlamp examination) resulted in the lowest IOP measurements.

While these results cannot necessarily be extrapolated to glaucoma patients, they do demonstrate the need to further understand the role of positional IOP in glaucoma pathogenesis.

Progress Toward Continuous IOP Monitoring in Humans

Complete understanding of the role of IOP fluctuations in glaucoma pathogenesis will ultimately require the development and use of continuous IOP monitoring devices in humans. While this has been a long-standing goal, with efforts spanning over 50 years, recent progress in the field suggests that clinical devices may be imminent.[17]

Two basic strategies for continuous IOP monitoring exist. Temporary continuous IOP monitoring would involve a noninvasive device that can be placed on the eye to obtain an IOP pattern over a 24-48 hour period. Permanent continuous IOP monitoring would involve a pressure sensing implant within the eye that could be powered externally to provide long-term data. These devices would likely have complementary indications, and devices that occupy an intermediate stage may be developed.

For temporary continuous IOP monitoring, human data are available from 2 devices. First, the Triggerfish system from Sensimed AG (Lausanne, Switzerland) is a contact lens–based system that measures the change in corneal radius of curvature with changes in IOP.[18] While it is currently not calibrated to provide true IOP readings, it does produce 24-hour IOP patterns that are very similar to sleep laboratory data.[19] This device is currently available in Europe and is undergoing trials in the United States. A second device, using the principle of dynamic contour tonometry, has been demonstrated in a prototype device to provide data similar to a slitlamp-mounted dynamic contour tonometer.[20]

Currently, multiple companies and groups are developing permanent continuous IOP monitoring systems, including AcuMEMS, Inc. (Menlo Park, Calif., USA) and Implandata Ophthalmic Products GmbH (Hannover, Germany). At this time, only data from animal testing are available in the literature.[21]

Conclusions

Fluctuations in IOP occur continuously over both short and long time intervals and with changes in body position. The evidence for the role of IOP fluctuation as an independent risk factor in glaucoma is currently mixed, stemming from the inability to measure IOP continuously, the lack of a standard definition for IOP fluctuation, variable patient populations, and the use of retrospective data. The future development of continuous IOP monitoring systems, along with the design of studies to specifically address these issues, will help clarify the nature of IOP fluctuations and their role in glaucoma pathogenesis.

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Effect of Cerebrospinal Pressure

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Introduction

The pathogenesis of glaucomatous optic neuropathy has not completely cleared yet, in particular in view of the observation that patients with glaucoma can markedly differ in the level of IOP. It is the purpose of this presentation to discuss some aspects from the morphologic appearance of the optic nerve head that may be of potential interest for the discussion of the pathogenesis of glaucomatous optic nerve damage.

Neuroretinal Rim

In none of the vascular optic neuropathies (except for arteritic anterior ischemic optic neuropathy) is there a loss of the neuroretinal rim, which keeps its physiological shape despite losing retinal ganglion cell axons. This is in distinct contrast to glaucoma.[2] The discrepancy between the loss of neuroretinal rim in all types of glaucoma, including normal-pressure glaucoma, and the preserved rim in the vascular optic neuropathies, the normal color of the remaining rim in glaucoma in contrast to the pale color of the existing rim in eyes with a vascular optic nerve damage, the finding that the loss in neuroretinal rim in normal-pressure glaucoma is related to the height of the IOP,[4] the finding that the location of the deepest part of the optic cup in normal-pressure glaucoma spatially correlates with the location of the most marked perimetric loss,[5] and the finding that lowering of IOP is therapeutically helpful in normal-pressure glaucoma[6] may all point against a primarily vascular pathogenesis in normal-pressure glaucoma.

Parapapillary Atrophy

Beta zone of parapapillary atrophy can be found in all types of chronic open-angle glaucoma, including normal-pressure glaucoma. In contrast, none of the vascular optic neuropathies, including arteritic anterior ischemic optic neuropathy, show an enlargement of beta zone or an increased frequency of beta zone.[7]

Optic Disc Hemorrhages

Hospital-based studies have shown that eyes with normal-pressure glaucoma have significantly more frequent and larger disc hemorrhages than eyes with high-pressure glaucoma.[8,9] They also showed that the size of the hemorrhage is larger in eyes with normal-pressure glaucoma than in eyes with high-pressure glaucoma.[10] It has been discussed that the difference in the frequency of detected disc hemorrhages between high-pressure glaucoma patient groups and normal-pressure glaucoma patient groups was due to the difference in IOP between high-pressure glaucoma and normal-pressure glaucoma. Assuming that the size of the leaking part in the vessel wall is similar in both glaucoma groups, then the amount of blood leaking out of the vessel into the adjacent tissue depends on the transmural pressure difference. The latter is the difference between the blood pressure in the vessel and the pressure in the surrounding space, ie, the IOP. Taking into account the lower IOP in the normal-pressure glaucoma eyes than in the high-pressure glaucoma eyes, just the difference in IOP between both glaucoma groups may be reason enough for larger disc hemorrhages, which take a longer time to be absorbed and have a higher chance to be detected by ophthalmoscopy.

Thinning of the Retinal Arteries

Thinning of the retinal arteries (arterioles) in a diffuse and localized manner has been described in eyes with glaucoma, and it has been suggested that the amount and location of the reduction in the arteriolar diameter may be correlated with the amount and location of glaucomatous optic nerve damage.[11] The retinal arteriolar caliber reduction has been found in eyes with normal pressure as well as in eyes in high-pressure glaucoma. Since, however, the localized and generalized thinning of the retinal arterioles can be found in any type of optic nerve damage,[12,13] the reduction in the arteriolar diameters is not pathognomonic for glaucoma in general nor for normal-pressure glaucoma in particular but may at least partially be a secondary phenomenon due to the loss of retinal tissue and the consequently reduced demand for blood supply.

Phenotyping of the Chronic Open-Angle Glaucomas According to the Morphology of the Optic Nerve Head

Analyzing the morphology of the optic nerve for differences between subgroups of chronic open-angle glaucoma may lead to various phenotypes, such as the highly myopic type of (primary) open-glaucoma,[14] and the age-related atrophic type of open-angle glaucoma. The juvenile high-pressure glaucoma type is characterized by a relatively young age of the patients (usually less than 40 years at the time of the first diagnosis), with a steep and deep cupping, a relatively small parapapillary atrophy (beta zone), and an apparently diffuse loss of retinal nerve fiber layer. At a closer look, however, multiple small, localized retinal nerve fiber layer defects become apparent that can mimic a diffuse loss. The so-called focal type of normal-pressure glaucoma may typically be found more in females than in males, with an age of about 45 to 65 years; the patients tend to have a low arterial blood pressure and to report some vasospastic symptoms. The optic disc can show a relatively deep and steep cupping, rim notches, disc hemorrhages, marked localized retinal nerve fiber layer defects, and parapapillary atrophy. The location of the deepest part of the optic cup in normal-pressure glaucoma spatially correlates with the location of the most marked perimetric loss. In selected examples, there was a strikingly similar appearance in the appearance of the optic nerve head between eyes with open-angle glaucoma and high IOP and eyes with normal IOP. Correspondingly, monkey experiments performed by Hayreh have shown that monkeys with experimental high-pressure glaucoma develop localized retinal nerve fiber layer defects, what formerly was believed to be typical for normal-pressure glaucoma.

The questions arose: Why, despite marked differences in IOP between eyes with high-pressure glaucoma and eyes with normal-pressure glaucoma, both glaucoma subtypes could have

a sometimes strikingly similar optic nerve head appearance? And how one may explain the marked differences in the optic nerve head appearance between eyes with normal-pressure glaucoma and eyes with any (other) vascular optic neuropathy, if normal-pressure glaucoma was supposed to have a (partially) vascular pathogenesis?

It was suggested that one may consider looking beyond the lamina cribrosa. The bottom of the optic cup on the inner surface of the optic nerve head is formed by the lamina cribrosa. On its outer surface, the lamina cribrosa faces the anterior region of the optic nerve. The main functions of the lamina cribrosa are to allow the retinal ganglion cell axons and the central retinal vein to leave the eye, to allow the central retinal artery to enter the intraocular space, and to stabilize the IOP by forming a barrier between the intraocular space and the extraocular space. Due to the barrier function, the lamina cribrosa prevents a major leakage of aqueous humor from the intravitreal space into the retrobulbar cerebrospinal fluid space surrounding the retrobulbar part of the optic nerve. Since the lamina cribrosa forms the border between the intraocular space with a higher pressure and the retrobulbar space with a lower pressure, a pressure gradient exists across the lamina cribrosa as difference of IOP minus pressure in the retrobulbar cerebrospinal fluid space. This trans lamina cribrosa pressure gradient is of importance for ocular diseases in which the pressure on one or on both sides of the lamina cribrosa is either abnormally high or abnormally low.[16,17] An abnormal pressure gradient influences the physiology of the optic nerve fibers with their orthograde and retrograde axoplasmic flow. Also for glaucomatous optic nerve damage, one may discuss that not the transcorneal pressure difference (which usually has been called ("intraocular pressure") but the translamina cribrosa pressure difference and the translamina cribrosa pressure gradient may be important.

The translamina cribrosa pressure gradient depends on the pressure difference and the distance between the intraocular compartment and the retrobulbar fluid-filled compartment. The distance between both compartments markedly depends on the thickness of the lamina cribrosa. Consequently, the thinning of the lamina cribrosa in highly myopic eyes may be one of the reasons that glaucoma susceptibility is increased in highly myopic eyes. In addition, histomorphometric studies have shown that in non-highly glaucomatous myopic eyes the lamina cribrosa gets thinner in an advanced stage of the disease. This glaucoma-related thinning of the lamina cribrosa may be one of the reasons why the risk for further glaucoma progression in eyes with advanced glaucoma is increased. More than 30 years ago, Volkov pointed out that a low cerebrospinal fluid pressure could pathogenetically be associated with glaucomatous optic neuropathy. The same idea had already been expressed earlier by Szymansky and Wladyczko. In a similar manner, Yablonsky, Ritch, and Pokorny observed marked glaucomatous changes in normotensive eyes of cats in which the intracranial pressure was reduced to 5 cm H_2O below the atmospheric pressure, while artificially hypotensive eyes did not show such changes.[18] Consequently, Berdahl and colleagues found in a retrospective chart review that the mean cerebrospinal fluid pressure was significantly higher in nonglaucomatous patients than in open-angle glaucoma patients, and that ocular hypertensive subjects had significantly higher cerebrospinal fluid pressure.[19] In a similar manner in a recent prospective study, the lumbar cerebrospinal fluid pressure was significantly lower in the normal-IOP glaucoma group (9.5 ± 2.2 mmHg) than in a high-IOP glaucoma group (11.7 ± 2.7 mmHg) or a control group (12.9 ± 1.9 mmHg).[20] The translamina cribrosa pressure difference was significantly ($P < .001$) higher in the normal-IOP glaucoma group (6.6 ± 3.6 mmHg) and the high-IOP glaucoma group (12.5 ± 4.1 mmHg) than in the control group (1.4 ± 1.7 mmHg). In multivariate analysis, the amount of glaucomatous visual field loss was mainly associated with the translamina cribrosa pressure difference ($P = .005$) while IOP and cerebrospinal fluid pressure as single parameters were not significantly ($P > .50$) associated with perimetric loss. In the control group, cerebrospinal fluid pressure was significantly correlated with both systolic blood pressure ($P = .04$) and IOP ($P < .001$). Since the IOP is physiologically associated with blood pressure,[21] the translamina cribrosa pressure difference was not significantly ($P = .97$) related with the blood pressure.

The correlation between all 3 pressure parameters, ie, cerebrospinal fluid pressure, blood pressure, and IOP, may suggest a systemic mechanism simultaneously influencing all three of them. It may explain why arterial hypertension, although associated with elevated IOP, was not associated with glaucoma in population-based studies. One may assume that the elevation in IOP was compensated by the increase in cerebrospinal fluid pressure, so that the translamina cribrosa pressure difference remained unchanged. This assumption was supported by the study of Ren and colleagues,[20] in which the translamina cribrosa pressure difference was not significantly ($P = .97$) related to blood pressure. The correlation between the cerebrospinal fluid pressure and arterial blood pressure supports clinical observations that patients with normal-pressure glaucoma tend to have low blood pressure. It was the reason to postulate a vasogenic pathogenesis of normal-pressure glaucoma. If, however, a low blood pressure is associated with a low cerebrospinal fluid pressure, a barotraumatic pathomechanism in normal-pressure glaucoma with an elevated translamina cribrosa pressure gradient may become likely. In a parallel manner, the translamina cribrosa pressure difference was not significantly associated with the arterial blood pressure.[20] If one considers the translamina cribrosa pressure difference as being the driving force for optic nerve damage in glaucoma, the lack of an association between the translamina cribrosa pressure difference and the systemic arterial blood pressure may contradict the notion that a vascular insufficiency in the optic nerve head may play a major primary role in the pathogenesis of glaucomatous optic nerve fiber loss.

In conclusion, a primary vasogenic pathogenesis of glaucomatous optic neuropathy may be contradicted by the morphology of the optic nerve head, since normal-pressure glaucoma eyes and high IOP glaucoma eyes can show a similar appearance of the optic nerve head. These features are not found in any (other) vascular optic neuropathy (except for arteritic anterior ischemic optic neuropathy). Other factors that may be taken into account are (1) the translamina cribrosa pressure difference (instead of the transcorneal pressure difference [ie, the so-called IOP]) is of importance for the physiology of the optic nerve head; (2) a physiologic association exists between arterial blood pressure, cerebrospinal fluid pressure, and IOP; and (3) patients with normal (intraocular-) pressure glaucoma had significantly lower cerebrospinal fluid pressure and a higher translamina cribrosa pressure difference when compared to normal subjects. One may, therefore, discuss that a low (orbital) cerebrospinal fluid pressure may be associated with normal (intraocular-)pressure glaucoma. A low systemic blood pressure, particularly at night, could physiologically be associated with a low cerebrospinal fluid pressure, which leads to an abnormally high translamina cribrosa pressure difference and as such to a similar situation

as if the cerebrospinal fluid pressure is normal and the IOP is elevated. This model could explain why patients with normal (intraocular-)pressure glaucoma tend to have a low systemic blood pressure, and why eyes with normal (intraocular-)pressure glaucoma and eyes with high-pressure glaucoma, in contrast to eyes with a direct vascular optic neuropathy, show profound similarities in the appearance of the optic nerve head.

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Contribution of the Lamina Cribrosa in Glaucoma Susceptibility

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Clues to the potential that the lamina cribrosa contributes to glaucoma susceptibility reside in its anatomy, its composition, and the apparent association between this anatomy and retinal ganglion cell (RGC) loss in glaucoma and aging.

Grossly, the lamina cribrosa spans the scleral opening at the back of the eye, through which the optic nerve fiber bundles exit the eye to form the optic nerve. At this point, the bundles of unmyelinated RGC nerve fibers, now separated by astrocyte processes, appear to perforate the lamina, which consists of a series of connective tissue plates that are oriented across this opening.[1] Careful analysis has shown that the laminar plates, or beams, consist of connective tissue and vascular tissue. The connective tissue components of the lamina include interstitial collagen types I and III, which provide strength and resistance to deformation from elevated IOP.[2] The lamina also has resiliency, due to the presence of elastin. Although the role of this elastic tissue is unclear, it is likely required to maintain the basic organization of the lamina and optic nerve head throughout life in the face of constantly changing IOP caused by vascular pulsation, eye movement, eye rubbing, and circadian fluctuation in IOP.[3]

Another important component of the lamina cribrosa is the capillaries within the laminar beams, which are responsible for nutrition of axonal bundles. Composed of capillary endothelium resting on a basement membrane, these generally are situated within the beams, leaving a variable distance for diffusion of oxygen and nutrients between the capillaries and the axons.[2] This supply connection between capillaries and axons is likely aided by the presence of glial astrocytes. Closely associated with the laminar connective tissue by their own basement membranes, astrocytes appear to line the laminar beams and serve as an interface between adjacent beams and the axon bundles.[4] They are closely interconnected to each other by tight junctions and send numerous processes into the bundles of unmyelinated axons, where they provide intimate contact with individual axons. In this manner, a single astrocyte will contact many axons, and each axon is likely to be contacted by numerous astrocytes. Because the astrocyte cell bodies are themselves oriented across the scleral opening and intimately contact the laminar beams, they are well positioned to respond to stresses and strains induced within the lamina and peripapillary sclera induced by fluctuating IOP. These responses to tissue strain most likely occur through integrins, specialized cell-tissue junctions that connect the extracellular environment with the intracellular cytoskeleton. In this manner, changes in extracellular forces can induce numerous intracellular responses, including cell division, changes in cytoskeletal organization, and cell motility.[5]

The above considerations clearly indicate that the lamina cribrosa, with its connective tissue, vascular, and cellular components, is well positioned to contribute to axonal susceptibility. However, clear proof of this potential is indirect.

First, the lamina cribrosa appears to be the primary site of glaucomatous axonal injury.[6] Axonal transport obstruction from elevated IOP, with buildup of mitochondria and organelles, has long been noted at the level of the lamina in glaucoma and in models of experimentally elevated IOP.[7] In addition, the typical pattern of glaucomatous cupping, axonal injury, and visual field loss appears to concentrate at the superior and inferior regions of the optic nerve head. Because these regions are often noted to have thinner, more sparse laminar beams, this suggests that some features of these regions may contribute to increased susceptibility, leading to initial axonal injury. Several potential mechanisms may contribute to this. These include greater posterior movement with elevated IOP and potentially less physical protection for axons, and even direct mechanical injury. Increased biomechanical influences associated with this may also induce astrocyte responses, via the above-mentioned integrins. Potentially, these responses could result in astrocytes no longer being able to perform their regular functions, which include maintenance of laminar organization and providing energy support and ion homeostasis to the unmyelinated axon bundles.

In addition, because the superior and inferior regions have fewer laminar beams, the intervening laminar "pores," which are occupied by axon bundles, will be larger. As a result, these regions may receive less overall blood flow, with greater distances between laminar capillaries and axons, which may compromise nutrient delivery.

It is recognized that eyes with more advanced glaucomatous optic nerve damage are likely to be more susceptible to subsequent injury, and that, with greater injury, progressively lower IOP is required to prevent further vision loss.[8] Changes within the lamina cribrosa from elevated IOP are likely potential contributors to this phenomenon. Structural disorganization of the lamina, due to failure of laminar beams and disinsertion from the adjacent sclera, along with deposition of extracellular matrix material within laminar pores, will all alter functional properties of the lamina as a biomechanical structure.[9,10] Alterations of elastin, with elastosis, will further reduce resiliency of the tissue and normal response to IOP fluctuation.[11] Cell proliferation, astrocyte migration, and loss of normal astrocyte-axon contacts in response to elevated IOP will progressively alter axonal metabolic support.[12] Concurrent activation of all of these phenomena may accelerate increased susceptibility with increased injury, as alterations in the biomechanical behavior of the lamina cribrosa may directly affect astrocytic responses to further fluctuations in IOP.

Age is another factor strongly associated with glaucoma, and normal-tension glaucoma (NTG) is more frequently described in the elderly, implying that age is associated with increased susceptibility.[13,14]

Several aging changes within the lamina may explain this. These include increased content of structural collagen types I and III, as well as elastin within the laminar beams, which appear enlarged.[15] This results in a "stiffer" lamina, with reduced compliance to fluctuations in IOP.[16] While this behavioral difference has clearly been documented in both human and experimental glaucoma, a biomechanical explanation of why this would result in greater axonal susceptibility is unclear, aside from potential compromise of capillary patency, as they would be surrounded by stiffer, less compliant connective tissues.[17] However, thickness and density of capillary and astrocyte basement membranes, which are composed of collagen IV and laminin, tends to also be increased in aging. This may increase the diffusional barrier of

nutrients to the axonal bundles, thus increasing their susceptibility to IOP.

Additional indirect evidence for the contribution of the lamina to IOP susceptibility can be seen in the thickness of the lamina associated with NTG. OCT studies using enhanced depth imaging demonstrate that laminar thickness is less in primary open-angle and NTG eyes, compared to normal controls.[18] In addition, laminar thickness was found to be thinner in NTG patients with disc hemorrhage than in those without disc hemorrhage. In both instances, greater glaucomatous injury (and potentially greater susceptibility) appears to be associated with a thinner lamina. This suggests that the thinner lamina may provide less structural support, resulting in greater movement from fluctuating IOP and greater effects on axonal bundles. However, these considerations—in conjunction with the understanding that the elderly eye, which also demonstrates increased susceptibility, has an apparently stiffer lamina—suggest that factors beyond simple mechanical behavior of the lamina, such as aging changes of astrocytes, axon bundles and even RGCs,[19] also influence susceptibility in the elderly eye.

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Blood Pressure and Sleep Apnea

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Blood Pressure and Glaucoma

Numerous studies have demonstrated a positive correlation between glaucoma and blood pressure.[1-3] Specifically, large population-based studies have demonstrated that systemic hypertension is slightly more prevalent in primary open-angle glaucoma patients. The difficulty with many of these studies lies in how authors define open-angle glaucoma as well as systemic hypertension. There is no clear relationship between systemic blood pressure and open-angle glaucoma damage. In fact, recent studies evaluating the relationship between blood pressure and glaucoma damage have demonstrated positive, negative, and even no association between blood pressure and glaucoma.[4-7]

Although high blood pressure has been shown to be associated with glaucoma, low ocular perfusion pressure and low systolic blood pressure are also known risk factors for glaucoma. Many individuals feel that nocturnal hypotension plays a role in the development and progression of glaucoma.[7] This bimodal distribution of risk factors (both high and low blood pressure) demonstrates some of the challenges in studying the relationship of glaucoma and blood pressure. Moreover, there is no consensus among authors which blood pressure measurements matter—systemic, diastolic, or MAP.[4-7] One possible theory that explains epidemiologic evidence for low blood pressure and chronic hypertension as risk factors for glaucoma focuses on the concept of ocular perfusion pressure and blood flow as a unifying concept. Low blood pressure results in low perfusion pressure, which results in reduced blood flow to the optic nerve, and chronic hypertension results in atherosclerotic changes to the blood vessels of the optic nerve, thus resulting in reduced blood flow to the optic nerve as well.

To date, no studies have definitively demonstrated the utility of clinical monitoring of blood pressure and glaucoma management. As such, it remains unclear whether ophthalmologists should monitor blood pressure in the clinic, at night, throughout the day, or perhaps at all.[8]

Ocular Perfusion Pressure

Ocular perfusion pressure (OPP) is defined as the difference between the arterial blood pressure and the intraocular pressure (IOP), which is considered a substitute for the venous pressure. To be more specific regarding blood pressure measurements, one should use mean perfusion pressure as opposed to systolic or diastolic pressure, as the latter two values can fluctuate greatly. Mean perfusion pressure (MPP) is defined by the following equation:[4,5]

MPP = 2/3 MAP – IOP

MAP = DBP + 1/3(SBP – DBP)

SBP = systolic blood pressure

DBP= diastolic blood pressure

IOP = intraocular pressure

Changes in ocular perfusion may lead to ischemia of the optic nerve and poor perfusion of the tissues within and around the optic nerve. Although many individuals feel that open-angle glaucoma has an unknown etiology, some authors feel that glaucomatous optic neuropathy could be an ischemic optic neuropathy. In fact, the "vascular hypothesis" is based on the premise that abnormal optic nerve perfusion plays a major role in the pathogenesis of glaucoma.[4]

Sleep Apnea[9]

Walsh and Montplaisir[10] are credited with first describing the association between glaucoma and sleep apnea in 1982. Since then, a number of studies have demonstrated a higher prevalence of sleep apnea in patients with glaucoma[11-15] and vice versa.[16-19] The precise mechanism of this association is not known, but the theory that repeated episodes of hypoxia during sleep due to bouts of sleep apnea is the most compelling. In addition, several studies have found an association between sleep apnea and thinner nerve fiber layer measurements even in subjects without glaucoma.[20,21] At least two studies have failed to demonstrate an association between these two diagnoses.[22,23]

Conclusions

Patients with progressive glaucoma at "normal" IOP as measured in the office are an enigma. Further IOP lowering may require aggressive intervention such as surgery to get the IOP in the single digits, which is often difficult to do without lowering IOP into a range that can cause hypotony and accompanying adverse effects such as maculopathy and corneal folds. If non-IOP related factors such as low blood pressure or sleep apnea are contributing to progression in these patients, we may be exposing our patients to undue risk. If ocular perfusion pressure is one of the final common pathways linking low blood pressure to glaucoma risk, then lowering IOP, which also improves ocular perfusion pressure, would still be expected to reduce the risk from low blood pressure. With regard to sleep apnea, this condition should be treated regardless of its purported effect on glaucoma, and if there is a relationship, then this treatment should reduce the risk of glaucoma and its progression. Additional research is needed in both of these areas to provide new treatment strategies for clinicians.

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How I Treat Patients Progressing at Low IOPs

David S Greenfield MD

I. Overview

A. Although an artificial construct, "normal-tension glaucoma" (NTG) is a term widely used to classify the disease in patients with glaucomatous optic neuropathy with or without visual field loss whose pressures are within the 95th percentile of the normal distribution of IOP measurements in the healthy population (IOP < 22 mmHg using Goldmann applanation tonometry).

B. The Collaborative Normal-Tension Glaucoma Study Group (CNTGS) has provided detailed information regarding the effect of IOP reduction on the natural history of NTG.[1,2]

1. One eye per each of 145 subjects with NTG was randomized either to 30% IOP reduction or no treatment (control).

2. Randomization criteria included documented progression of visual field (VF) defects, new disc hemorrhage, or field defects that threatened fixation.

3. IOP lowering demonstrated to be of proven therapeutic benefit[3]

C. Unclear relationship between IOP and NTG

1. IOP is not significant independent predictor of progression in untreated NTG.[2]

2. Some eyes progress despite significant IOP lowering.

3. Some eyes do not progress despite observation.

D. Progression may occur in patients at normal or low IOP.

II. Many factors influence retinal ganglion cell health.[4]

A. Elevated IOP

B. Blockade of neurotrophins and other target-derived factors

C. Excessive glutamate stimulation

D. Aberrant immunity

E. Ischemia

F. Inflammatory cytokines

III. My Approach to Patients Progressing at Low IOP

A. Confirm suspected VF progression

B. Glaucomatous vs. nonglaucomatous optic nerve damage

C. Establish the level of IOP responsible for progressive VF loss

D. Management options

1. Surgical IOP lowering

2. Nonsurgical IOP lowering

3. Other

IV. Ancillary Diagnostic Testing

A. Neuroimaging

Anecdotal reports of occult intracranial mass lesions exist that simulate NTG[5-8]

1. Stewart and Reid[9] reported compressive intracranial lesions in 2 of 53 patients (3.8%) referred for evaluation of NTG. In another study,[10] 8 of 141 subjects (5.7%) suspected of having glaucoma by optic nerve screening were found to have intracranial lesions.

2. In a series of glaucoma patients who underwent neuroimaging between 1985 and 1995,[11] none were found to have evidence of anterior visual pathway compression.

B. Carotid blood flow and laboratory evaluation

1. Referral to a vascular laboratory to exclude clinically significant carotid occlusive disease has been suggested in the evaluation of patients with NTG.

2. Laboratory testing has been proposed to rule out anemia, hyperviscosity syndromes, diabetes, hyperlipidemia, or cranial arteritis.

3. Pilot data from 20 patients with NTG and primary open-angle glaucoma who underwent carotid Doppler ultrasonography, serum laboratory testing (erythrocyte sedimentation rate, complete blood count, VDRL, FTA-ABS), and scanning laser Doppler flowmetry demonstrated no differences among these two groups of patients.[12]

4. Sedimentation rate should be performed in older patients with a history of abrupt visual loss or other symptoms suggestive of cranial arteritis; carotid studies are warranted in patients with symptoms of transient visual loss or ocular signs of embolic phenomenon or ocular ischemia.

V. Nonsurgical Management

A. Most patients respond to medical therapy and laser trabeculoplasty: 50% nonprogressive.

B. High risk for single-digit IOP

1. High myopia

2. Elderly (age > 90)

3. Anticoagulation therapy

VI. Surgical Management

A. Young age

B. Rapid progression

C. Progression at IOP ≤ 12 mmHg

D. Monocular patients with favorable risk-benefit ratio

E. Threat to fixation

VII. The Low-pressure Glaucoma Treatment Study (LoGTS)

A. The Low-pressure Glaucoma Treatment Study[13-15] is a multicenter, double-masked, prospective, randomized clinical trial that aimed to investigate visual field outcomes in low-pressure glaucoma patients treated either with a topical beta-adrenergic antagonist (timolol maleate 0.5%) or alpha2-adrenergic agonist (brimonidine tartrate 0.2%).

B. The results of this trial revealed that subjects randomized to topical brimonidine 0.2% had better preservation of visual function than those receiving timolol 0.5% despite similar IOP levels.

C. A significantly higher rate of ocular allergy requiring discontinuation from the study was observed in eyes receiving brimonidine (20%) compared to timolol (4%).

D. LoGTS[13-15] is the first trial to compare the ability of 2 topical glaucoma medications to preserve visual function. It is unclear, however, whether the differences in outcome were due to different mechanisms of drug action.

E. Validation of a neuroprotective mechanism of action requires additional basic science and clinical research to confirm these results prior to altering current clinical patient care paradigms.

VIII. Conclusions

A. Complex disease

B. IOP-dependent and independent mechanisms

C. IOP reduction only proven therapy

D. Most patients respond to nonsurgical therapy.

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Could Your Primary Open-Angle Glaucoma Patient Have Chronic Angle Closure?

Paul J Foster MD PhD

The simple answer is yes—some people who have narrow but apparently open drainage angles will experience iridotrabecular contact (ITC). In some of these people, obstruction to aqueous outflow is sufficient to cause intermittent or sustained elevations in IOP. Determining who will develop significant ITC remains a challenge for clinicians. However, identifying people who will suffer primary angle closure (PAC) disease is important, as the early and intermediate phases of the disease respond well to quick and generally safe interventions, which appear to prevent catastrophic deterioration to late-stage disease. Identifying PAC disease is crucial in optimizing care for all our patients.

Current data suggest that risk factors, prognosis, and optimal management pathways differ considerably between primary open angle-closure glaucoma (POAG) and primary angle-closure glaucoma (PACG). In population surveys, people with PACG are more often blind than are those who suffer from POAG, implying that PACG is a more visually destructive disease. Angle-closure glaucoma accounts for 50% of all glaucoma blindness.[1]

Optimal initial management should be tailored according to the diagnosis. POAG patients typically receive topical medication, or possibly laser trabeculoplasty. In contrast, PACG management is directed (after addressing initially elevated IOP in acute cases) at reversing ITC by laser iridotomy ± laser iridoplasty. The management pathways for both POAG and PACG are aimed at preventing progressive loss of retinal ganglion cells by controlling IOP. While fluctuation in IOP is a presumed risk factor for progression in POAG, intermittent and acute angle closure almost certainly results in far greater IOP variation.

Ultrasound biomicroscopic (UBM) studies show that laser iridotomy results in reversal of ITC in 75% of cases.[2] A systematic review of benefits of laser iridotomy suggested that this is effective in preventing acute angle closure (AAC) in fellow eyes of those people who have suffered an episode of symptomatic IOP rise.[3] Long-term follow-up paints a less optimistic picture. In Singapore, at an average of 6 years after suffering AAC, 18% of eyes were blind, and at least half had visual dysfunction from either glaucoma or unoperated cataract.[4] However, among fellow eyes incident glaucoma occurred at an average of 1%/year, with 80% of eyes retaining good vision over the same 6-year period. Of those that had reduced vision, unoperated cataract accounted for over half of all visual deficits.[5] This suggests that with ophthalmic attention prior to the onset of AAC, the prognosis for retention of vision is good.

The challenge remains how to detect those at high risk of PAC, and to offer treatment for those benefits that exceed risks. In the detection of people with PAC disease, clinical assessment of the angle is an essential skill, primarily requiring expertise in gonioscopy. Limbal chamber depth assessment (the van Herick test) is an extremely helpful adjunct to gonioscopy. These clinical skills may be supplemented by anterior segment imaging, employing either UBM or OCT, although these are not essential in making clinical management decisions.

When assessing temporal limbal chamber depth, the finding of iridocorneal contact (ie, grade 0) is a hard physical sign that "trumps" gonioscopic findings, if gonioscopy indicates a narrow but open angle. The act of putting a gonioscope onto the eye and exposing the eye to sufficient illumination to assess the angle may in some cases reverse the presence of ITC.

In a patient with an apparently open angle, determining if angle-closure mechanisms may be responsible, in part or in whole, for their glaucoma, one question must be answered: is there any evidence of iridotrabecular contact, either current or previous? The initial examination should be carried out in the darkest conditions practically possible, and in particular, keeping the illumination of the eye to an absolute minimum. During the initial phase of gonioscopic examination, a 1-mm long beam should be regarded as the absolute maximum. The vertical beam should be kept very narrow and horizontally offset for examination of superior and inferior angles. For nasal and temporal angles, the >1-mm beam should be horizontal and vertically offset.

Gonioscopy is the core skill for detection of angle closure. As in most other aspects of medical practice, more is missed from not looking than not knowing. Gonioscopy is mandatory in all new cases where glaucoma or ocular hypertension is considered possible and should be repeated periodically. Identifying ITC on gonioscopy points strongly toward angle closure as a significant component in a milieu of glaucoma risk factors. Even in the presence of an open angle, evidence of pathological angle closure can be found. Studies in East Asians found primary peripheral anterior synechiae in 8%-12% of eyes with a geometric angle width graded as 20°. In those with a 10° angle, PAS rates were seen in 17% to 31% of people in two different populations (Singapore and Mongolia, respectively).[6]

The reason for this apparently contradictory state of affairs is that is almost certainly a consequence of the inherent variability in angle configuration that is seen with variation in illumination.[7] Also relevant is the difference in classification of angle status that is seen between OCT and gonioscopy; OCT tends to grade more angles as occluded than does gonioscopy.[8] Which technique should be regarded as the reference standard is currently unclear. However, the ability to perform OCT imaging in near dark conditions and the fact that no corneal contact is involved makes it plausible that OCT imaging is able to identify true in vivo relationships with greater accuracy than gonioscopy. This does not mean that OCT is essential for accurate diagnosis, but it does suggest that reaching the correct diagnosis may require greater skill and thoughtful interpretation of clinical findings. Pigment smudging on the surface of the trabecular meshwork is an additional useful sign of the presence of angle-closure disease.[9]

Eyes that suffer angle closure tend to be smaller than average. The anterior chamber again tends to be shallower in people with angle closure than without. Anterior chamber depth (ACD) has been explored as a method of population screening, but data on the performance of this test suggest the performance of the test will vary significantly between populations, even in Asia. The performance of biometry in predictive risk stratification is currently unproven. A positive family history of angle closure is a marker for elevated risk.[10]

Symptoms are a poor guide to the presence or absence of PAC disease.[11] The presence of "typical" symptoms of angle closure in people without any sign of the disease means that closed ques-

tioning seeking these typical symptoms will misidentify a large number of normal people as angle-closure suspects. The bulk of angle-closure disease in Asians is chronic, asymptomatic. Clinical experience suggests that the situation is similar in whites. Ultimately, careful examination and detection of clinical signs currently appears to be the best way of identifying people who have primary angle closure disease.

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Anterior Segment Imaging

Joel S Schuman MD

I. Detection of Angle Closure
  A. Gonioscopy
    1. Established technique
      a. Direct
      b. Indirect
    2. Validated
    3. Inexpensive technology
    4. Requires examiner skill
      a. To perform
      b. To interpret
    5. Contact technique
  B. Ultrasound biomicroscopy (UBM)
    1. Developed by Pavlin, Sherar, and Foster
    2. 50- to 100-MHz transducers incorporated into a B-mode clinical scanner
      a. Higher-frequency transducers provide finer resolution of more superficial structures.
      b. Lower-frequency transducers provide greater depth of penetration with less resolution.
      c. Commercially available units operate at 20-80 MHz.
      d. At 50 MHz, lateral resolution is ~50 µm and axial resolution is ~25 µm.
      e. Tissue penetration is approximately 4-5 mm.
    3. Image acquisition technique is similar to traditional immersion B-scan ultrasonography.
      a. Scanning is performed with the patient in the supine position.
      b. A fluid containing silicone condom is placed over the transducer and on the eye or a plastic eye cup is inserted between the lids holding methylcellulose or normal saline coupling medium.
      c. To maximize the detection of the reflected signal, the transducer should be oriented so the scanning sound beam strikes the target surface perpendicularly.
    4. The normal eye
      a. Cornea, anterior chamber, posterior chamber, iris, ciliary body, and anterior lens surface can be easily recognized.
      b. Scleral spur is the only constant landmark, allowing us to interpret UBM images in terms of morphological status of the anterior chamber angle, which is the key for analyzing the angle pathology.
      c. Scleral spur can be located where the corneal endothelial border meets the interface line between sclera and ciliary body.
      d. Iris has roughly planar configuration with slight anterior bowing, and the anterior chamber angle is wide and clear.
      e. Morphological relationships among the anterior segment structures alter in response to a variety of physiological stimuli (ie, accommodative targets and light); maintaining a constant testing environment is critical for cross-sectional as well as longitudinal comparison.
    5. Established technique
    6. Validated
    7. Expensive technology
    8. Requires examiner skill
      a. To perform
      b. To interpret
  C. Anterior segment OCT (AS-OCT)
    1. First OCT reported by Huang and coauthors in 1991.
    2. First AS-OCT reported by Izatt and colleagues with ~800-nm light.
      a. 10-micron resolution of cornea, anterior chamber, iris, and lens
      b. Poor visualization of angle structures due to poor penetration of light at this wavelength through sclera
    3. Later reported using 1300-nm light by Radhakrishnan and coauthors
      a. Good visualization of the anterior chamber angle
      b. Poor visualization of structures posterior to the iris
    4. Nolan and colleagues, Singapore study
      a. 304 eyes of 200 subjects examined by a masked observer
      b. Subsequently imaged with the commercial prototype AS-OCT device
      c. AS-OCT sensitivity 98%; specificity, 55%
        i. More subjects appeared closed on OCT than on gonioscopy.

ii. No automated quantitative algorithms

iii. Lower illumination when using the OCT than when using gonioscopy

iv. Anterior segment distortion by gonioscopy (wider appearing angles)

v. Different landmarks to define angle closure

5. Swept-Source OCT

a. 1300 nm

b. High speed

c. Greater scan depth than conventional SD-OCT

d. Can measure anterior and posterior corneal powers, elevation, and pachymetry

6. Reproducibility of AS-OCT

a. 4Optics AS-OCT

b. Intraobserver coefficient of variation

i. 6% for anterior chamber angle (ACA)

ii. 4% for AOD500

c. Interobserver coefficient of variation

i. 11% for ACA

ii. 8% for AOD500

7. Results similar to gonioscopy for nasal and temporal ACA

8. Eyelids can create difficulty in scanning of superior and inferior ACA.

9. New technique

10. Expensive technology

11. Requires little examiner skill to perform, but skill is required for the interpretation.

12. Higher image resolution than UBM

13. Noncontact

D. Scheimpflug photography

1. Commercially available

2. Expensive technology

3. Requires little examiner skill to perform, but skill is required for the interpretation.

4. Noncontact

5. Angle recess is not visualized.

6. Structures posterior to the iris are not visualized.

II. Quantitative and Qualitative Assessment of Angle Closure

A. There are several semiquantitative methods for gonioscopic anterior chamber angle description.

1. Shaffer

a. Grades I–IV

b. I = closed

c. IV = open

2. Scheie

a. Grades I–IV

b. I = open

c. IV = closed

3. Spaeth

a. Grades appearance of angle and iris

i. Angle of insertion

ii. Configuration of iris: "r," which is regular, "s," which is steep, or "q," which is queer or backward bowing.

iii. Level of iris insertion: A = anterior to Schwalbe line, B = behind Schwalbe line but anterior to scleral spur, C = posterior to scleral spur (ie, scleral spur visible, but not ciliary body), D = ciliary body visible, and E = large amount of ciliary body visible

b. Apparent insertion point of the iris as well as the true location of iris insertion (after manipulation or compression)

c. Amount of pigmentation in the angle at 12 o'clock: none, just visible (grade = 1), more visible, but mild (grade = 2), moderately dense (grade = 3), and dense (grade = 4)

d. Presence or absence of peripheral anterior synechiae (PAS)

B. UBM and AS-OCT quantitative measures

1. Angle opening distance: 250 and 500 microns anterior to the scleral spur

2. Angle recess area: 750 microns anterior to scleral spur

3. Acceleration

4. Y-intercept

5. Trabeculo-iris space area

6. Trabeculo-iris contact length

III. Accuracy and Precision of Angle-Closure Assessment

A. Little data exist

B. Gonioscopy is an imperfect gold standard.

C. UBM has coefficient of variation of ~10% for analysis of a single image, but a high variability from scan to scan.

D. AS-OCT shows coefficients of variation of ~5% intraobserver and ~10% interobserver.

E. AS-OCT sensitivity, 98%; specificity, 55%

IV. Mechanisms of Angle Closure and Provocative Testing

A. Pupillary block is detectable using gonioscopy, UBM, or AS-OCT.

B. Only UBM offers visualization of structures posterior to iris.

1. UBM permits assessment of ciliary body, supraciliary space, peripheral lens, and zonules, as well as haptics and other foreign bodies.

2. UBM permits definitive classification of mechanism of angle closure.

C. Dark room testing is cumbersome and questionable using gonioscopy and IOP assessment.

D. UBM and AS-OCT dark room testing offer rapid and dynamic assessment of the anterior chamber angle and its potential for occlusion.

V. Patient Education Regarding Angle Closure

A. UBM and AS-OCT provide a tangible and visible image of the relationships of the anterior chamber structures.

B. Images produced by UBM and AS-OCT showing angle closure, whether under normal or provocative conditions, are powerful tools in educating patients.

1. Nature of their disease

2. Necessity for treatment or opportunity for observation

VI. Other Applications of Anterior Segment Imaging

A. Tumor detection and longitudinal evaluation for change

B. Corneal evaluation

C. Assessment of aqueous outflow system

Selected Readings

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Gonioscopy in the Clinic and the OR

Douglas J Rhee MD

Historical Notes[1]

Trantas is credited for coining the term "gonioscopy" when visualizing the angle in an eye with geratoglobus by indenting the limbus. The first goniolens was introduced by Salsmann in 1914 and improved upon by Koeppe in 1919. The Goldmann gonioprism was introduced in 1938.

Introduction

Gonioscopy has always been critical to the diagnosis and classification of the different subtypes of glaucoma, but it is now even more important in light of the numerous new surgical procedures that rely upon visualization and proper recognition of the angle structures. The goniolens eliminates the internal reflectance of the cornea by placing the lens-air interface at a different angle. Gonioscopy can be either direct or indirect.

Direct goniolenses allow visualization of the angle structures "directly" in the line of sight of the observer—that is, to view the nasal angle structures, the examiner is looking toward the nasal part of the eye. Indirect gonioscopy utilizes a mirrored surface to view the angle 180 degrees away from the line of sight of the observer—that is, to view the nasal angle structures, the examiner looks toward the temporal mirror of the gonioprism.

There are numerous versions of contact goniolenses (see Table 1).

Techniques

Direct Gonioscopy

These are generally used with the patient in the supine position with a second hand-held biomicroscope. The advantages of direct gonioscopy are experienced in patients with nystagmus or irregular corneas, where it provides a panoramic evaluation of the angle. Direct goniolenses are more commonly used in the operating room.

Specific lenses

Koeppe lens

This is the prototypical goniolens which is available in different diameters and radii of posterior curvature and is generally utilized for diagnostic purposes either in the operating room or clinic. A fluid bridge is needed as the inner radius of curvature is steeper than the cornea. A handheld biomicroscope with separate illuminator (eg, Barkan's device) or portable slitlamp can be used with the patient in the supine position.

Table 1. Contact Lenses for Gonioscopy

Lens	Notes
Direct	
Koeppe	Prototypical lens
Richardson-Shaffer	Small Koeppe lens for use in infants
Layden	For gonioscopic examination in premature infants
Barkan	Prototypical surgical goniolens
Thorpe	Surgical and diagnostic lens for operating room
Swan-Jacob	Surgical goniolens
Indirect	
Goldmann 1-mirror	Mirror inclined at 62 degrees
Goldmann 3-mirror	1 mirror for gonioscopy, 2 for retinal examination
Zeiss 4-mirror	All 4 mirrors inclined at 64 degrees; Posner and Sussman 4-mirror lenses are modified Zeiss lenses with an attached handle or handheld, respectively
Thorpe 4-mirror	All 4 mirrors inclined at 62 degrees requiring fluid bridge
Ritch trabeculoplasty lens	4 gonioscopy mirrors with 2 inclined at 62 degrees and 2 included at 59 degrees
Latina trabeculoplasty lens	1 mirror angled at 62 degrees

Table is adapted from Allingham RR, Damji KF, Freedman S, Moroi SE, Rhee DJ, eds. "Gonioscopy and other techniques for assessing the anterior segment," in *Shields Textbook of Glaucoma*, 6th ed. Wolters Kluwer/Lippincott Williams & Wilkins, Philadelphia; 2011: table 3.1, ch. 3, p 42.

Barkan lens

This lens also requires a fluid bridge and is held onto the surface of the eye through positioning holes (see Figure 1). Generally used in the operating room. The most common application is for goniotomy.

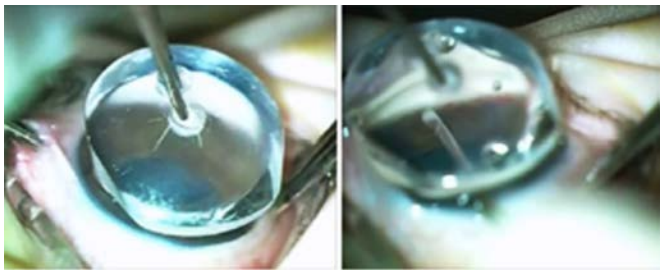

Figure 1. Barkan lens being held with a Castroviejo 0.12 forceps during a goniotomy procedure. The assistant is gripping the superior and inferior lateral rectus muscle insertions. Image left shows the placement of the lens on the eye. Image right shows use of the lens during the incision of the trabecular meshwork.

Swan-Jacob lens

This lens requires a fluid bridge and is attached to a handle. There are modified Swan-Jacob lenses that have a small notch underneath to provide more room for instruments that are inserted through corneal wounds (see Figure 2).

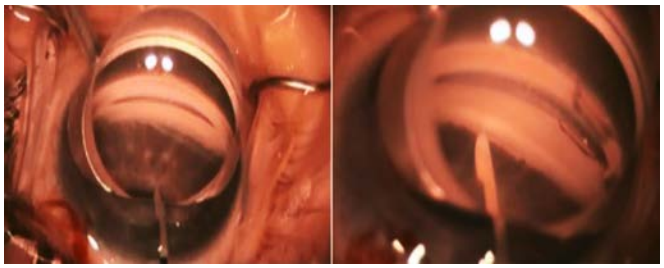

Figure 2. Modified Swan Jacob lens being used during a goniotomy procedure. Image left shows the placement of the lens on the eye. Image right shows use of the lens during the incision of the trabecular meshwork. Tilting the head away from the surgeon assists in obtaining the proper angle to visualize the angle.

Indirect Gonioscopy

Goldmann lenses require a fluid bridge due to a radius of curvature that is steeper than the anterior surface of the cornea. Zeiss, Posner, and Sussman lenses have a radius of curvature that is similar to the cornea. Four mirrored lenses allow the evaluation of the entire angle without rotation of the lens. The advantages of indirect gonioscopy are that the patient is in the upright position and these lenses can be used at the slitlamp biomicroscope. Lenses that have a similar radius of curvature to the anterior cornea allow for the technique of indentation gonioscopy to be performed; thus, these lenses are the preferred method for the clinical evaluation of narrow angles.

Angle Anatomy

Proper identification of the angle structure is critical for diagnosis and therapeutic interventions such as laser trabeculoplasty and angle surgery. The Schwalbe line is the junction between the Descemet membrane and the trabecular meshwork. The trabecular meshwork has a pigmented and a nonpigmented portion. The scleral spur is the attachment of the ciliary body to the sclera and is seen as a prominent white line between the ciliary body face and the pigmented trabecular meshwork. The ciliary body face is posterior and is the insertion of the iris root to the ciliary body. The width of the band depends on the level of the iris insertion and is generally wider in myopic and with pigment dispersion syndrome eyes (see Figure 3).

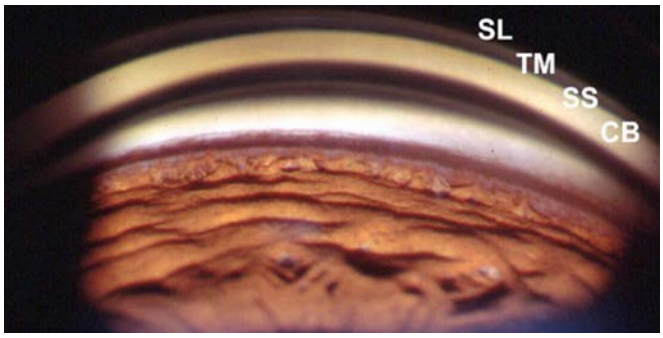

Figure 3. Angle anatomy of a normal and wide open anterior chamber angle. SL = Schwalbe line; TM = trabecular meshwork; SS = scleral spur; CB = ciliary body face. This angle would be classified as IV by the Schaefer system; D40r 4+ PTM by the Spaeth system.

During gonioscopy, the different angle structures can be divided into 2 groups: (1) a fixed portion that includes the Schwalbe line, the trabecular meshwork, and the scleral spur and (2) a mobile portion that includes the anterior-superior face of the ciliary body and the iris insertion along with its last fold.

Indentation gonioscopy involves gently applying pressure on a Zeiss style goniolens to increase the IOP within the anterior chamber to move the iris/lens posteriorly. This technique can reveal a hidden trabecular meshwork in a narrow angle. In a hypopigmented angle, indentation gonioscopy can help reveal the iris insertion point.

Technique Tips

- Gently place the lens on the eye. Don't press too hard; this can create folds in the cornea and distort your view.
- The light should be perpendicular to the mirror of the goniolens.
- If you are having trouble seeing angle structures due to the curvature of the iris, ask the patient to look slightly into the side being evaluated (ie, away from the mirror you are looking at).
- Use indentation gonioscopy to help identify the insertion of the iris root and locate the scleral spur.

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Other Helpful Resources

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When to Consider Lensectomy for Angle Closure

David S Friedman MD MPH PhD

I. Evidence That the Lens Is an Important Determinant of Angle Closure
   A. Theoretical models
   B. Epidemiologic studies
   C. Anterior segment OCT findings

II. Clinical Research Looking at Cataract Extraction in Acute Angle Closure
   A. Early case series demonstrating benefit
   B. Randomized clinical trial from Hong Kong shows a large long-term benefit of early cataract surgery in acute angle closure, especially for patients presenting with high IOP.
   C. Not clear when the safest time is to do the surgery; trying to prevent development of peripheral anterior synechiae

III. Clinical Research Looking at Cataract Extraction in Chronic Primary Angle Closure
   A. Initial Cochrane review in 2006 found no randomized trials to support cataract surgery to lower eye pressure in primary angle-closure glaucoma.
   B. Case series indicate some eye pressure lowering with cataract surgery alone.
   C. One randomized clinical trial from Hong Kong with 2.5 years follow-up found lower eye pressure when comparing cataract surgery and trabeculectomy to cataract surgery alone.
   D. Average decrease in eye pressure for treated patients with baseline IOP around 18 only about 2 mmHg with cataract surgery alone.
   E. Some patients in combined trabeculectomy and cataract surgery group developed hypotony.

IV. EAGLE Trial will answer the question of clear lens extraction for early primary angle-closure glaucoma.
   A. Either established glaucoma or high eye pressure
   B. Randomized to either topical therapy or clear lens extraction
   C. Subjects being enrolled in Asia, Europe, and Australia
   D. Follow-up is for 3 years from randomization
   E. Enrollment complete, results likely available in the next 2 or 3 years.
   F. Measuring quality of life as well as economic implications of the 2 treatment arms

V. Practical Recommendations
   A. Early cataract removal after acute angle closure attacks reduces the need for medications to control eye pressure; consideration should be given to early cataract surgery, especially in patients presenting with very high eye pressures.
   B. Cataract extraction in established primary angle-closure glaucoma can lower the eye pressure substantially, but average eye pressure lowering is not large.
   C. Clear lens extraction for primary angle-closure glaucoma is being studied in a large randomized trial. Results will guide clinical decision making once they are available in the next few years.

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Not All Angle Closure Is Pupillary Block

Tin Aung FRCS PhD

Primary angle-closure glaucoma (PACG) is a major form of glaucoma worldwide.[1] Angle closure occurs due to obstruction of the trabecular meshwork by the iris, resulting in impaired aqueous outflow and causing an increase in IOP.

Pupillary block is considered to be the primary mechanism for angle closure.[2,3] In pupillary block, there is resistance to aqueous flow from the posterior to anterior chamber at the level of the pupil, creating a pressure gradient that causes bombe of the peripheral iris and closure of the angle. Laser peripheral iridotomy (LPI) is the standard first-line treatment for angle closure as it relieves this pressure differential, flattens the iris, and widens the angle, thereby relieving pupillary block.

Recent advances in imaging techniques such as anterior segment OCT (AS-OCT) and ultrasound biomicroscopy (UBM) have aided in identifying non-pupil block mechanisms that may be responsible for a significant proportion of angle closure, as well as novel anatomical factors associated with this condition.

Plateau Iris

Plateau iris configuration, defined as a closed angle on gonioscopy, with a flat iris plane and a normal central anterior chamber depth (ACD),[4] is one example of non-pupil block mechanisms. In eyes with plateau iris, a large ciliary body and/or anteriorly directed ciliary processes have been shown to hold the peripheral iris in apposition to the trabecular meshwork.

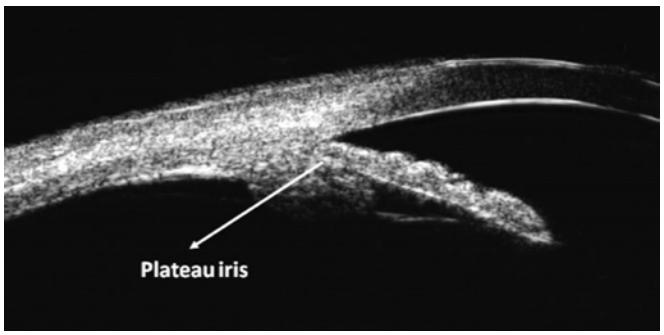

Figure 1. Plateau iris.

Using standardized UBM criteria, it has been shown that more than 30% of eyes have plateau iris in the presence of a patent LPI.[5,6] The Liwan Eye Study also reported a high rate of plateau iris configuration in primary angle closure suspect eyes (60%) in at least 1 quadrant, among a Chinese population.[7]

A thick peripheral roll of the iris also predisposes to angle closure.

Altered Physiology/ Dynamic Factors

There is increasing recognition that physiological factors, such as increase in iris volume with pupil dilation and choroidal expansion, may also have a role in angle closure. Eyes with angle closure were found to lose less iris volume compared with controls during pupil dilation (P = .008). The dynamic behavior was proposed to be due to movements of extracellular fluid between the iris stroma and the anterior chamber. The inherent tendency to lose less or even gain volume during dilation in eyes at risk of angle closure is possibly a contributing factor in the development of the disease.[8,9]

Choroidal effusion (or uveal or ciliochoroidal effusion) is an abnormal accumulation of fluid in the suprachoroidal space due to an imbalance of pressure differentials. It has been hypothesized that choroidal expansion is another mechanism for angle closure and may precede and even precipitate an acute attack of the condition.[10] In eyes with no transvitreous resistance, it is proposed that any choroidal expansion would be balanced by increasing aqueous outflow, without iris or lens movement. However, as the vitreous has limited capacity to transmit fluid, there can be anterior movement of the compressed vitreous, iris, and lens when transvitreous flow is restricted. In small eyes predisposed to angle closure, choroidal expansion leading to increased vitreous cavity pressure may be a contributing cause.[10] Choroidal effusion has been demonstrated to be more prevalent among those with acute, rather than with chronic, angle closure.[11,12]

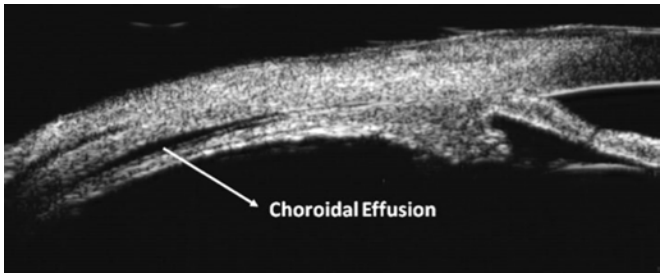

Figure 2. Choroidal effusion.

Anatomical Factors Associated With Angle Closure

Established ocular risk factors for angle closure include a shallow central anterior chamber depth (ACD), short axial length (AL), and a thicker and more anteriorly positioned lens. Demographic risk factors for the condition include female sex, older age, and East Asian ethnicity. Among these, a shallow ACD is regarded as a cardinal risk factor for the condition. However, population-based data suggest that only a small proportion of subjects with shallow ACD ultimately develop PACG.

Novel anatomical risk factors for angle closure that have recently been identified through imaging studies using AS-OCT include smaller anterior chamber width (ACW),[13] area, and volume,[14] thicker iris with greater curvature and area,[15] and an increased lens vault (LV).[16]

By using customized analysis software, such as the ZAAP (Zhongshan Angle Assessment Program; Guangzhou, China), various AS-OCT-based parameters can be easily obtained from AS-OCT scans.

A smaller ACW implies a smaller anterior chamber volume, which may cause angle crowding.[13] A greater iris curvature, area,

and thickness were observed to be independently associated with angle closure, after adjusting for other known associated biometric parameters. A thicker peripheral iris could crowd the angle, especially in morphologically predisposed eyes, such as those with shallow ACD.[15]

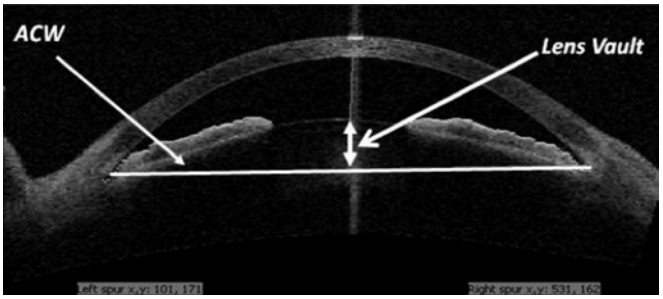

Figure 3. Lens vault.

LV, a recently described AS-OCT parameter that measures the amount of lens that is located anterior to the plane of the scleral spurs, has been found to better quantify the relationship of the lens with respect to the anterior chamber angles.[16] A greater LV was observed to be strongly and possibly independently associated with an increased risk of angle closure.[16,17] Many eyes with angle closure have a large lens vault, and the effect of this parameter may not be overcome by LPI alone.

Conclusions

Although pupillary block is the main mechanism for angle closure, the role of non-pupil block factors is increasingly recognized. With a wider availability of imaging tools, there is a better understanding of risk factors and mechanisms involved in angle closure. An interplay of multiple anatomical and physiological factors may be involved in angle closure pathogenesis.

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The Global Impact of Glaucoma: Addressing Care in Developing Countries

Mildred Marie Gerard Olivier MD

I. Introduction: Magnitude of Glaucoma

II. Organizations Impacting Ophthalmology

III. My story: Haiti Making a Change

IV. Our Story: Challenges—Are we ready?

A. Education – Underserved Populations

1. Residency – Training the trainer
2. Local ophthalmologist – Continuing medical education

B. U.S. community

1. Delivery systems

a. Individual

b. Institutions

c. Global electronic

V. Motivating Others

Young ophthalmologist – Investing in the future

VI. Advocacy: How can we use our experience to help others in other countries?

Building partnerships to work within other countries.

VII. Detection and Management

VIII. Research

A. St. Lucia

B. Laser study

C. Surgical intervention

XVI. AGS Foundation: Making a Change

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2012 Advocating for Patients

Thomas A Graul MD

Ophthalmology's goal in protecting quality patient eye care remains a key priority for the Academy. As health care delivery evolves, with narrowing practice margins making efficiency of increasing importance, all Eye M.D.s should consider their contributions to the following three funds as (a) part of their costs of doing business and (b) their individual responsibility in advocating for patients:

1. OPHTHPAC® Fund
2. Surgical Scope Fund (SSF)
3. State Eye PAC

While the Academy fully supports the concept of an "integrated eye care delivery team," it also remains firm on defining appropriate roles for the various eye care providers as demonstrated via its Surgery by Surgeons campaign.

OPHTHPAC® Fund

OPHTHPAC is a crucial part of the Academy's strategy to protect and advance ophthalmology's interests in key areas, including physician payments in Medicare as well as protecting ophthalmology from federal scope of practice threats. Established in 1985, today OPHTHPAC is one of the largest and most successful political action committees in the physician community. In 2010, Politico highlighted OPHTHPAC as one of the most successful health PACs in strategic giving in the 2010 election. By making strategic election campaign contributions and independent expenditures, OPHTHPAC helps us elect friends of ophthalmology to federal leadership positions, ultimately resulting in beneficial outcomes for all Eye M.D.s. For example, 20 physicians, including 2 ophthalmologists, were elected to Congress in 2010. Thanks to the OPHTHPAC contributions made in the 2007-2010 timeframe, ophthalmology realized an 8% increase in Medicare payments (other specialties experienced significant decreases). Among the significant impacts of OPHTHPAC:

- Averted significant cuts to Medicare payments due to the Sustainable Growth Rate (SGR) formula
- Protected Practice Expense increases for ophthalmology when attacked by other specialties
- Exempted ultrasound from imaging cuts
- Protected the in-office ancillary services exception
- Secured physician exemption from Red Flag (creditor) rules
- Secured reversal of a CMS decision to cut reimbursement for Avastin
- Delayed Medicare penalties dates in health reform law
- Secured appointment of full-time ophthalmology national program director in the Department of Veterans Affairs

Leaders of the American Glaucoma Society (AGS) are part of the American Academy of Ophthalmology's Ophthalmic Advocacy Leadership Group (OALG), which has met for the past five years in the Washington, DC, area to provide critical input and to discuss and collaborate on the American Academy's advocacy agenda. As 2012 Congressional Advocacy Day (CAD) partners, the AGS ensured a strong presence of glaucoma specialists to support ophthalmology's priorities as over 350 Eye M.D.s had scheduled CAD visits to members of Congress in conjunction with the Academy's 2012 Mid-Year Forum in Washington, DC. The AGS remains a crucial partner to the Academy in its ongoing *federal* and *state* advocacy initiatives.

Surgical Scope Fund (SSF)

At the state level, the Academy's Surgery by Surgeons campaign has demonstrated a proven track record. While Kentucky was an outlier, the Academy's SSF has helped 33 state / territorial ophthalmology societies reject optometric surgery language. The Academy's Secretariat for State Affairs, in partnership with state ophthalmology societies, battled optometry across the country in 2011 to protect patient access to quality medical surgical care. Several ophthalmic subspecialty societies also provided critical support when called upon. Although there was a setback in Kentucky, ophthalmology derailed O.D. surgery initiatives in 7 states and achieved its first proactive victory in Oklahoma.

The SSF is a critical tool of the Surgery by Surgeons campaign to protect patient quality of care and our collective fund to ensure that optometry does not legislate the right to perform surgery. The Academy relies not only on the financial contributions via the SSF by individual Eye M.D.s but also the contributions made by ophthalmic state, subspecialty and specialized interest societies. The AGS contributed to the SSF in 2011 and the Academy counts on its contribution in 2012.

With last year's passage of legislation in Kentucky that allowed optometrists to perform laser surgery, the American Academy of Ophthalmology's partnership with ophthalmic subspecialty and state societies in the Surgery by Surgeons campaign became even more important in protecting quality patient eye care across the country. The Academy's Secretariat for State Affairs redoubled its efforts with "target" states, including Tennessee and others, while adding professional media training to the resources provided to prepare Eye M.D.s in advance of any anticipated legislative or regulatory move.

State Eye PAC

State ophthalmology societies can not count on the SSF alone—equally important is the presence of a strong state Eye PAC, which provides financial support for campaign contributions and legislative education to elect ophthalmology-friendly candidates for the state legislature. The Secretariat for State Affairs strategizes with state ophthalmology societies on target goals for state eye PAC levels.

Action Requested: Advocate for Your Patients!!

PAC contributions are necessary at the state and federal level to help elect officials who will support the interests of our patients. Academy SSF contributions are used to support the infrastructure necessary in state legislative / regulatory battles and for

Surgical Scope Fund	OPHTHPAC® Fund	State EyePAC
Scope of practice at the state level	Ophthalmology's interests at the federal level – Support for candidates for US Congress	Support for candidates for State House and Senate
Lobbyists, media, public education, administrative needs	Campaign contributions, legislative education	Campaign contributions, legislative education
Contributions: Unlimited	Contributions: Limited to $5,000	Contribution limits vary based on state regulations
Contributions are 100% confidential	Contributions above $200 are on the public record	Contributions are on the public record

public education. Contributions across the board are needed. SSF contributions are completely confidential and may be made with corporate checks or credit cards—unlike PAC contributions, which must be made by individuals and which are subject to reporting requirements.

Please respond to your Academy colleagues who are volunteering their time *on your behalf* to serve on the OPHTHPAC* and SSF** Committees, as well as your state ophthalmology society leaders, when they call on you and your subspecialty society to contribute. Advocate for your patients now!

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Late Breaking Development: How Will the Trabecular Micro-bypass Approval Impact Glaucoma Management?

E Randy Craven MD

NOTES

The Case for Angle Surgery

Robert N Weinreb MD

I. What is angle surgery?

Ab interno approach to outflow pathways (ie, trabecular meshwork or uveoscleral outflow pathway)

II. What ab externo approaches address aqueous outflow?

A. Trabecular meshwork

B. Uveoscleral outflow

III. Background

A. It is widely believed that the trabecular meshwork is the major site of aqueous outflow. The juxtacanalicular tissue and the inner wall of the Schlemm canal are major sites of resistance to outflow within the trabecular meshwork.[1]

B. Several studies have suggested that the uveoscleral outflow route accounts for as much as 50% of total outflow in healthy eyes.[1] It contributes less with aging.

C. It is remarkable, however, how little we know about the outflow pathways and their pathophysiology.

1. Is the Schlemm canal a canal or a virtual space?
2. Does it have circumferential or radial flow?
3. Are the collector channels sites of resistance and are they different (or change) with aging or in individuals with glaucoma?
4. Are there individual differences in where the major site(s) of outflow resistance is located?

IV. Compared with conventional surgical approaches, angle surgery (ab interno) has several theoretical advantages and disadvantages.

A. Advantages

1. No incision of conjunctiva or Tenon tissue
2. Sutureless
3. For most procedures, there is no bleb.
4. Can be performed relatively quickly

B. Disadvantages

1. There may be need for procedure to be performed under gonioscopic visualization. Appropriate training with intraoperative gonioscopy is needed.
2. Like other surgical procedures that employ devices, there is additional cost for the device.
3. Targeting locations outside of the nasal area may be problematic.
4. Cost-effectiveness of these procedures and how they compare with standard ones is not known.

V. Not all procedures are the same with respect to their IOP-lowering effect.

A. It is important to keep in mind that some procedures may not be sufficiently effective to justify their use except in certain individuals.

Patients with advanced glaucoma have lower target IOPs and need maximum IOP lowering.

Patients with mild disease have higher target IOPs and also might from mild IOP lowering.

B. As examples:

1. A device that is placed in the inner trabecular meshwork might not achieve a low IOP. Flow of fluid still is restrained by the resistance in the juxtacanalicular meshwork. Moreover, the IOP will never be lower than the episcleral venous pressure.

Minimally invasive glaucoma surgery (MIGS) should not be synonymous with minimally effective glaucoma surgery (MEGS)

2. A device that is placed in the Schlemm canal will bypass the resistance of the inner meshwork and juxtacanalicular trabecular meshwork, but will not achieve an IOP lower than episcleral venous pressure.
3. A full thick drainage device might maximally lower IOP similar to a trabeculectomy. It is independent of episcleral venous pressure and it might be possible to achieve a single digit IOP.
4. A device within the uveoscleral outflow pathway that has the potential to lower the IOP below that of the episcleral venous pressure and achieve a single digit IOP.

VI. General Considerations: Well-Designed Clinical Trials Are Needed[3]

A. Randomized to determine safety and efficacy, and compare their results and complications with those of established procedures

B. Comply with the CONSORT checklist for reporting

C. Broad-based study populations to develop widely applicable and generalizable new information

D. Benefits and risks should be compared with those of established interventions. Participation of concurrent controls, rather than historic ones.

E. A priori establishment of study endpoints (including assessment optic disc structure and function), definition of success and surgical complications

VII. Perspective on What We Know and What We Do Not Know

A. The location of increased resistance to aqueous outflow in a particular individual is not known.

1. Is it in the juxtacanalicular trabecular meshwork/inner wall of Schlemm canal for all individuals?

2. If it varies, then placing a device that addresses only one site of resistance would not be expected to work in all cases. Such variability is consistent with the uniformly excellent results (in the absence of episcleral scarring) with trabeculectomy, Ex-PRESS, and glaucoma drainage devices, as each of them bypasses the outflow pathway regardless of the specific site of resistance.

B. How much variability is there in the precise placement of a device from patient to patient? At the current time, it is not possible to reliably know that one has placed the device where it is intended to be placed.

A surgeon needs to individualize his or her approach to a particular patient and choose a procedure that is most likely to be effective for them.

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The Case for Trabeculectomy

Philip P Chen MD

Cairns introduced trabeculectomy in 1968 as a method to allow aqueous access to the Schlemm canal. It was not intended to result in bleb formation, but later reports noted that subconjunctival aqueous drainage with bleb formation produced good outcomes.[1] Trabeculectomy gained widespread acceptance despite postoperative IOP that was higher than after full-thickness procedures, because it had markedly fewer postoperative complications and less ocular morbidity than full-thickness procedures.[2]

Improvements Over Time

Trabeculectomy has continued to evolve, resulting in improved postoperative control of IOP and fewer serious short- and long-term complications. Experiments with the antimetabolite 5-fluorouracil (5-FU) led to its use in glaucoma filtering surgery. The Fluorouracil Filtering Surgery Study showed in a randomized clinical trial that trabeculectomy with 21 postoperative subconjunctival injections of 5-FU was superior to trabeculectomy without 5-FU in pseudophakia or after a previous failed trabeculectomy.[3] Chen later reported high trabeculectomy success rates using intraoperative application of the alkylating antibiotic mitomycin C (MMC) in cases at high risk for surgical failure.[4] The efficacy of MMC-augmented trabeculectomy in IOP reduction and the efficiency of intraoperative MMC application has led to the vast majority of American Glaucoma Society members choosing to use MMC over 5-FU as adjunct to trabeculectomy, including for primary trabeculectomy in low-risk eyes.[5]

Other important improvements in trabeculectomy technique included the titration of aqueous outflow in the postoperative period with laser lysis of scleral flap sutures[6] or placement of releasable scleral flap sutures.[7] These maneuvers significantly reduced the incidence of early postoperative overfiltration and its associated complications (hypotony, shallow or flat anterior chambers, choroidal effusions).

However, routine use of antifibrosis agents with the traditional limbus-based conjunctival flap can result in blebs that are thin or cystic and prone to leakage. Bleb leak is a known risk factor for bleb-related infection, including blebitis and bleb-related endophthalmitis.[8] To reduce this risk, some authors have championed use of fornix-based conjunctival flaps, along with other modifications such as a larger scleral flap and application of MMC over a larger surface area.[9] These steps can result in "improved" bleb appearance: thicker and more diffuse, with posterior extension. Recent studies have shown fornix-based trabeculectomy may be associated with a lower risk of bleb leak and infection.[10,11]

Comparison With Other Glaucoma Surgeries

Trabeculectomy has remained the benchmark for glaucoma surgery for the last several decades owing to its favorable safety profile and long-term IOP-reducing capability.[12] For patients undergoing initial glaucoma surgery, recent surgical techniques such as nonpenetrating deep sclerectomy[13] and viscocanalostomy[14] have offered the advantage of fewer postoperative complications. However, the considerably longer learning curve and surgical time for these procedures, combined with similar or slightly worse IOP results, has limited their use.

Newer angle surgeries also show promise, with reduced complications compared with trabeculectomy.[15] However, published reports on these surgeries have repeatedly found postoperative IOPs in the 15-17 mmHg range,[15] which might not be sufficient control for patients with normal-tension glaucoma or moderate-to-advanced glaucoma. At the time of this synopsis, only two of these techniques have been compared directly with trabeculectomy. One retrospective, single-surgeon study of canaloplasty and trabeculectomy reported similar outcomes (no significant differences) at 1 year, although IOP, medication use, and reoperation rates for glaucoma were all lower with trabeculectomy.[16] Canaloplasty shares many of the same surgical steps as viscocanalostomy (ie, it is time consuming), yet in up to 34% of surgeries, successful 360-degree cannulation was not possible.[15] Another angle surgery, ab externo trabeculotomy, caused notably fewer postoperative complications than trabeculectomy in a case-control study, but its success rate at 2 years was significantly worse than trabeculectomy.[17]

The Tube Versus Trabeculectomy (TVT) Study showed the Baerveldt implant (350 mm^2) had a lower failure rate and required fewer reoperations for glaucoma than MMC trabeculectomy in eyes with pseudophakia or a previous failed filter.[18] However, 31% of the failures in the trabeculectomy arm were due to hypotony, which may be amenable to several methods of revision surgery.[19-21] After 5 years of follow-up more patients in the trabeculectomy arm (n = 37) were using no glaucoma medications than in the Baerveldt arm (n = 18), making trabeculectomy arguably the better choice in patients with limited ability to use medical therapy due to allergic reactions, side effects, or known nonresponse. In addition, it remains unclear if the TVT study results can be generalized to other tube shunt devices, such as the Ahmed valve; randomized trials such as the Ahmed-Baerveldt Comparison and Ahmed Versus Baerveldt studies have shown the Baerveldt has an IOP advantage over the Ahmed, and indeed one earlier randomized trial found equal IOP and success rates between primary Ahmed valve and trabeculectomy after 3 years of follow-up.[22]

When IOP control is inadequate after trabeculectomy, revision may be performed using either transconjunctival needling revision at the slitlamp[23] or open revision in the operating room,[24] with high success rates. These relatively simple procedures can extend the life of a suboptimally functioning trabeculectomy remarkably and repeatedly, to great patient benefit. Few other glaucoma surgeries can claim this advantage.

Trabeculectomy is far from perfect. However, prospective studies of trabeculectomy have shown that most early postoperative complications are relatively minor, are usually transient, and are of little consequence to long-term outcomes.[25] Late postoperative complications such as hypotony and bleb leaks are also amenable to surgical repair, albeit at the cost of IOP control in perhaps 5%-10% of cases.[20] Devastating complications such as bleb infection, though relatively rare,[10] still remain too frequent; current refinements in technique as discussed above may help to significantly lower the risk.[9-11]

Innovations that improve safety and outcomes of glaucoma surgery are welcomed by all glaucoma surgeons, and perhaps someday the trabeculectomy will become a relic of the past. Until that time, it will remain a mainstay of the glaucoma surgical armamentarium for most patients needing substantial, long-term IOP reduction to reduce the risk of going blind from glaucoma.

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The Glaucoma Filtration Device Mini-shunt Has Been a Positive Development

Marlene R Moster MD

Introduction

It is well known that trabeculectomy has always been the gold standard in lowering IOP since 1968. However, we are well aware of some of the negative issues involved with trabeculectomy surgery.

There are issues with the surgery itself:

- Bleb-related issues
- Issues related to failure
- There is no standardization with trabeculectomy regarding the removal of the internal block. This leads to too much variability during the surgery.

What we need is a move toward standardization.

Exploring the Technical Issues

After the trab block is removed, there is a "trampoline" effect where the chamber collapses and the iris comes up to block the wound. This is a problem in high myopes with poor scleral rigidity.

This is also a problem with patients starting off with high IOP at risk for choroidal detachment (IOP going from high to low without control).

The Ex-PRESS shunt eliminates some of the variability.

How? By delivering a consistent 50 micron flow of aqueous so an immediate posterior bleb forms

The Ex-PRESS does not causing a trampoline effect so the chamber does not collapse during the surgery. An iridectomy is not necessary since the iris does not "plug up" the Ex-PRESS.

Key Questions

How are some of the steps similar to a trabeculectomy?

- A scleral flap is still necessary as the Ex-PRESS is placed under it so there will be no erosion.
- Secure suturing is a must as to avoid hypotony.
- Closure with either a fornix or a limbal based flap must be water tight.

In what situations does the Ex-PRESS give us an edge?

- If the first trab has failed, why do the same exact thing again?
- The Ex-PRESS allows for a nasal or temporal placement with the possibility of lowering the IOP without having to put in a large silicone tube (glaucoma drainage device).
- In patients who are moderate to high myopes , or who have had prior scarring
- In patients who had corneal grafts with open angles and high IOP (Ates, 86% success in grafts at 1 year)
- In patients who have had vitrectomies, or are pseudophakic and need IOP lowering
- In patients who already had a failed trab and are not good candidates for a large tube

Why is an Ex-PRESS more reliable in these situations?

Because the flow is immediate, constant, posterior, with formation of microcysts within the bleb, often by Day 2.

We need to have options when we treat glaucoma. But does the Ex-PRESS lower the IOP? What is the evidence?

De Jong L, et al. 5-year efficacy and safety analysis of the EX-PRESS device vs. trabeculectomy. 2011.

- 39 patients in each group , prospective, randomized; Ex-PRESS vs. trab. 5 year follow-up.
- EX-PRESS device provided better IOP control vs. trabeculectomy during the first 3 years
- EX-PRESS device patients had less IOP controlling medications and needed fewer surgical interventions compared with trabeculectomy.
- Overall, EX-PRESS device implantations are more effective than standard trabeculectomy for the treatment of medically uncontrolled primary open-angle glaucoma during first 3 years.

Kanner EM, et al. EX-PRESS Device Under Scleral Flap Alone or Combined with Phaco Cataract Surgery. 2009.

- Retrospective chart review of 345 eyes
- Significant reduction in IOP and medications. At 3 years after surgery, surgical success was 94.8% and 95.6% in the Ex-PRESS and combined groups, respectively (P = .948). Compared with baseline values, the postoperative IOP and number of glaucoma medications were significantly lowered in both groups. The change from baseline IOP was significantly greater after Ex-PRESS implant alone compared with combined surgery (P < .001). EX-PRESS device is effective and well tolerated for long term both alone and combined with cataract procedure.

Good TJ, Kahook MY. One-year retrospective analysis: assessment of bleb morphologic features and postoperative outcomes after Ex-Press drainage device implantation versus trabeculectomy EX-PRESS® Device vs Trabeculectomy Patients. 2011.

- IOP equal at 6 months, then slightly higher for EX-PRESS device at 1 year and the final follow-up visit (P = .004 and P = .008, respectively).
- Unqualified success 77.14% (EX-PRESS Device) vs. 74.29% (Trab) (P = 1.00)
- Fewer postoperative visits for EX-PRESS device 6.05 vs. 8.23 in first 3 months (P < .000)
- There were fewer cases of early postoperative hypotony and hyphema and quicker visual recovery in the Ex-PRESS group.

N Geffen, et al. MRI safe: evaluation of EX-PRESS device safety at 3 Tesla. 2011.

- 3 Tesla is the most common MRI exposure to patients.
- No perceptible movement within the anterior chamber
- Embedded friction was greater than the magnetic force applied.
- *The EX-PRESS device is likely safe up to 3 Tesla due to ocular tissue resistance.*

Why do I like it?

- Because it works
- Patients vision recovers quickly and IOP can be brought down into the low teens.

Is it for everyone with glaucoma?

No, nothing is. There is no one "perfect" procedure to date.

However, there have been over 40,000 Ex-PRESS devices implanted worldwide. *As glaucoma surgeons it is imperative that we have surgical options available to us so we can tailor the surgery to the needs of each individual patient.*

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The Glaucoma Filtration Device Mini-shunt: I Don't Get It

Robert M Feldman MD

I. The First Thing I Learned in Clinics in Medical School

When evaluating whether to perform a new procedure, use a new drug, or order a test, the first question is always: Does it make sense to work the way it is purported to?

II. Problems With Trabeculectomy

A. Blebs

B. Hypotony early

C. Hypotony late

D. Late infection

III. Problems With Implants

A. Extrusion

B. Malposition

C. Accelerated endothelial cell loss

IV. Combine Trabs With Tube in One Procedure to Reduce the Problem and Increase the Success

V. Concept 1

A. The Ex-PRESS Mini-shunt as a flow restrictor

1. Does the flow restrictor make sense?

2. Should the Ex-PRESS Mini-shunt restrict flow to the correct parameters?

B. A flow restrictor should allow fluid to leave the eye but maintain a nonhypotonous IOP with only atmospheric pressure outside the eye.

1. Prevent flat chambers

2. Prevent early and late hypotony

3. Prevent decompression retinopathy

4. Potentially prevent snuff out

C. If we define IOP of < 5 mmHg as hypotony, there should be a 5-mmHg differential across the shunt (see Figure 1).

D. A 200-micron tube offers no resistance at the rate of aqueous production (±2 microliters per minute).

E. A 50-micron tube offers at best 3 mm of pressure differential across the tube at body temperature.

1. If the pressure in the bleb is 0 (air pressure), then the most IOP that can be maintained by the tube is 3 mmHg in the anterior chamber.

2. 3 mmHg IOP is hypotonous.

a. Can go flat

b. Can get choroidals

F. If the tube supplied adequate resistance then there would be no need for scleral flap to prevent these complications.

G. A well-constructed scleral flap can create as much resistance over a sclerostomy as it can over an Ex-PRESS Mini-shunt.

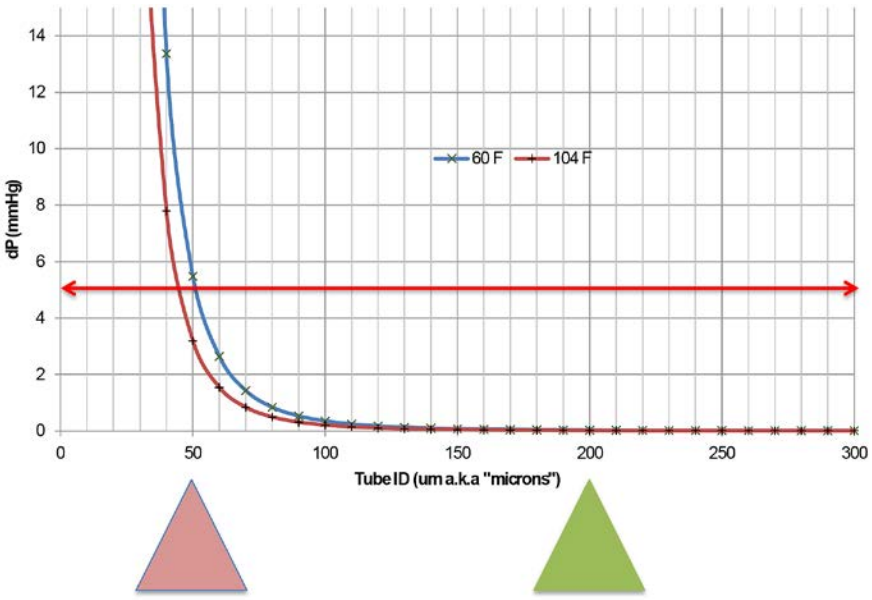

Figure 1. Pressure differential by tube diameter.

H. So what is the point?

1. No iridectomy? Are they needed in pseudophakic eyes or deep eyes with trabeculectomy?
    a. An Ex-PRESS Mini-shunt is not indicated in narrow angles where an iridectomy is required for a trabeculectomy.
2. Standardize the sclerostomy
    a. The sclerostomy size is not what is responsible for resistance.
    b. Resistance is regulated by the amount and tension of overlap of the scleral flap to the scleral bed.
3. A large hole under a large scleral flap may have the same resistance as a small hole under a small flap.
4. Regulating the size is irrelevant unless you standardize to the same precision of the scleral flap tension.

I. So does the Ex-PRESS Mini-shunt pass the first rule of new procedures?

VI. Concept 2

A. What does the literature say?

1. Mid- to long term
    a. Efficacy
    b. Safety

B. Success can't be determined in a glaucoma surgery in less than 1 year.

VII. The Glaucoma Filtration Device Mini-shunt: I Don't Get It

The Case for Tube Shunts

Steven J Gedde MD

Introduction

Tube shunts (also known as aqueous shunts, glaucoma drainage implants, glaucoma drainage devices, and setons) are being used with increasing frequency in the surgical management of glaucoma. Medicare claims data have shown a 184% increase in tube shunt surgeries and a concurrent 43% decrease in the number of trabeculectomies performed between 1995 and 2004.[1] Practice patterns in glaucoma surgery have also been evaluated with sequential surveys of the American Glaucoma Society (AGS) membership, and selection of tube shunts as the preferred surgical approach increased from 17.5% in 1996[2] to 50.8% in 2008.[3] Several factors have likely contributed to the growing popularity of tube shunts as an alternative to trabeculectomy.

Advantages of Tube Shunts

Tube shunt surgery offers multiple advantages over trabeculectomy and other glaucoma procedures.

Versatile procedure with broad surgical indications

Tube shunts have traditionally been reserved for eyes at high risk for failure with standard filtering surgery, such as refractory secondary glaucomas (eg, neovascular glaucoma) or extensive conjunctival scarring. The Tube Versus Trabeculectomy (TVT) Study is a multicenter randomized clinical trial comparing the safety and efficacy of tube shunt implantation with trabeculectomy with mitomycin C (MMC) in patients with prior cataract and/or glaucoma surgery.[4,5] Tube shunt placement was shown to be a viable surgical option in a patient population at lower risk for surgical failure than has historically had this procedure. Results from the TVT Study prompted another prospective clinical trial comparing tube shunt surgery to trabeculectomy with MMC in eyes without previous ocular surgery (ie, the Primary Tube Versus Trabeculectomy Study). If a surgeon is to become proficient in one glaucoma procedure, tube shunt surgery allows for the management of a broader range of patients than any other glaucoma procedure (ie, from primary surgery in low-risk eyes to reoperations in refractory glaucomas).

Marked IOP reduction

The goal of glaucoma surgery is to decrease IOP adequately to prevent progressive optic nerve damage. Several microinvasive glaucoma surgeries (MIGS) have recently been introduced into clinical practice.[6] While these newer procedures may have a lower rate of surgical complications, they do not appear to be as effective at lowering IOP as trabeculectomy or tube shunt surgery. Recent multicenter randomized clinical trials have shown that profound and persistent IOP reduction to the low teens can be achieved with tube shunts.[4,7,8]

Predictable surgical results

Glaucoma surgical trials typically define success in terms of reduction of IOP to a specified range without the need for a glaucoma reoperation or loss of light perception vision.[9] Therefore, the rate of surgical success may be considered as a predictor of a procedure's effectiveness in achieving a desired result. Figure 1 shows a higher success rate with tube shunt surgery relative to trabeculectomy with MMC in the TVT Study throughout 5 years of follow-up.[4] The superior success of tube shunts was observed over a broad range of IOP criteria defining success and failure.

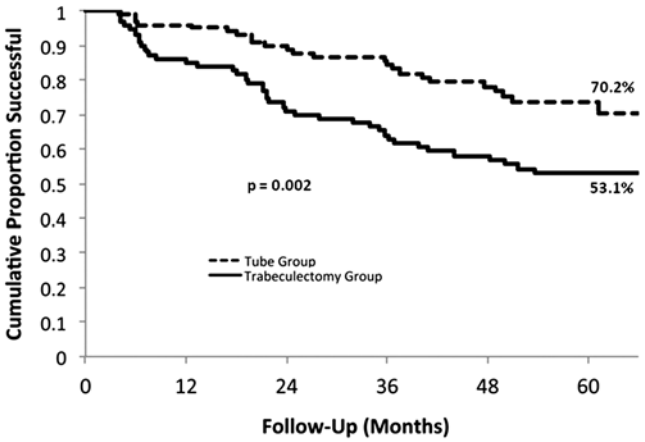

Figure 1. Kaplan-Meier plots of the cumulative probability of success in the TVT Study.

Avoidance of bleb-related complications

There has been a growing concern within the ophthalmic community about bleb-related complications associated with trabeculectomy. The cumulative risk of bleb leaks, bleb infections, and bleb dysesthesia has prompted many surgeons to seek alternative surgical approaches. The bleb seen after tube shunt placement is thick-walled and located in the equatorial region of the globe. It is very different in character from the thin-walled, perilimbal bleb created by a trabeculectomy (especially when an adjunctive antifibrotic agent is used), and it is less prone to bleb-related problems. It is noteworthy that the rate of postoperative complications was higher after trabeculectomy with MMC compared with tube shunt surgery in the TVT Study, including bleb leaks and dysesthesia.[5]

Ease of surgical implantation

The surgical technique used in tube shunt implantation has become standardized, and very little variation is needed between individual patients. In contrast, trabeculectomy requires significant intraoperative manipulation to establish the desired rate of aqueous filtration at the scleral flap for a specific patient. Tube shunt surgery is a procedure that requires less finesse and is more forgiving than trabeculectomy.

Less intensive postoperative care

The ultimate success of a trabeculectomy depends heavily on postoperative care. Laser suture lysis and subconjunctival 5-fluorouracil injections are common interventions that may be critical to achieving a good surgical result. The outcome of tube shunt surgery is less influenced by postoperative manipulations. As a

result, less frequent follow-up visits are needed after tube shunt surgery compared with guarded filtering surgery.

Conclusions

Tube shunts have historically been relegated to the treatment of refractory glaucomas. However, the surgical indications for these devices are broadening, and this is reflected in an increase in the number of Medicare beneficiaries who are receiving tube shunts and in shifts in surgical practice patterns among AGS members. The TVT Study supports the expanded use of tube shunts beyond only patients at high risk of filtration failure. Tube shunts produce marked IOP reduction to a lower level than is generally achieved with MIGS, while avoiding the bleb-related complications associated with trabeculectomy. The operation has become standardized and reproducible, and it also requires less postoperative care than trabeculectomy. Although it is not a perfect procedure, a compelling case can be made for the use of tube shunts in the surgical management of glaucoma.

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The Case for Cataract Surgery Alone

Steven L Mansberger MD MPH

I. Cataract Surgery and IOP
   A. Previous studies suggest that cataract surgery lowers IOP in normal and glaucoma patients.
   B. IOP reduction is generally proportional to presurgical IOP.
   C. Most studies used only a single preoperative IOP, were retrospective, and did not include untreated patients.
   D. Differential bias due to ocular hypotensive medications

II. What did the Ocular Hypertension Treatment Study (OHTS) study show?
   A. The OHTS study only includes data from the Observation Group who underwent cataract surgery.
   B. Excluded eyes
      1. Combined cataract/trabeculectomy surgery
      2. Glaucoma treatment (ocular hypotensive medications, laser iridotomy, or trabeculoplasty)
      3. Less than 1 pre- or postoperative IOP measurement
      4. Included both eyes if eligible.

III. OHTS Study Methods
   A. Split point: Study visit date when cataract surgery reported
   B. IOP (preoperative and postoperative): Mean IOP of the 3 visits prior or after cataract surgery
   C. Control Group: One randomly selected eye from participants who had not undergone cataract surgery and met the same inclusion and exclusion criteria

IV. OHTS Study Results
   A. 16.5% drop in IOP with cataract surgery (23.9 + 3.2 SD) vs. 19.8 + 3.2 SD, $P < .001$).
   B. At 36 months, mean postop IOP is still below preop IOP.
   C. Trend for increasing IOP (Slope = 0.05, $P < .001$).
   D. IOP in Control Group changed slightly (23.8 + 3.6 SD vs. 23.4 +3.9 SD, $P < .001$).
   E. 11.1% had an increase in IOP.
   F. 71.4% had a decrease in IOP by 10% or more from preop IOP.

V. Previous Studies
   A. Shingleton (*J Glaucoma.*, 2006)
      1. 150 patients with glaucoma, glaucoma suspects, and without glaucoma
      2. Mean decrease in IOP of 1.5 mmHg in all 3 groups at 3 years
   B. Poley (*J Cataract Refract Surg*. 2008; 2009)
      1. Reported IOP changes with average follow-up of 4 years
      2. The higher the preoperative IOP, the greater the reduction in IOP after cataract surgery.
         a. 6.5 mmHg drop with preop IOP 23-31 mmHg
         b. 1.6 mmHg drop with preop IOP 15-17 mmHg
   C. Samuelson (*Ophthalmology* 2011)
      1. At 12 months, IOP reduction of 8.5 mmHg with cataract surgery alone in a group of patients with ocular hypertension and early glaucoma
      2. However, 35% were back on IOP-lowering medications.

VI. How do we decide between cataract alone vs. combined cataract and glaucoma surgery?
   A. Glaucoma: 60% will have 10-mmHg IOP rise after surgery (Krupin, *Ophthalmology*, 1989)
   B. Normal eyes: 70% with IOP > 31 mmHg (Rainer, *Ophthalmology*, 2005)

VII. If at End Stage Glaucoma or High Risk
   A. Check IOP 5 hours later (Browning, et al. *J Cataract Refract Surg*., 2002).
   B. Judicious viscoelastic and cortex removal
   C. Consider a miotic (cholinergic).
   D. Intracameral carbachol

VIII. Summary
   A. Perform a glaucoma surgery if poor adherence, wants to stop glaucoma medications, or at high risk of vision loss.
   B. Cataract surgery lowers IOP by 17% in untreated ocular hypertension patients.
   C. Mean reduction in IOP persists for more than 3 years.
   D. Not randomized to surgery so we are unable to compare results to treatments of increased IOP (meds, laser, surgery).

Broken Capsule/Vitreous Loss

Louis D "Skip" Nichamin MD

I. General Philosophy
II. The "Good News"
III. High-risk Patients
  A. Elderly and debilitated
  B. Extreme refractive errors
  C. History of trauma
  D. Exfoliation syndrome
IV. Prevention
  A. Employ pupilloplasty techniques
  B. Adequate-sized capsulorrhexis
  C. Thorough hydrodissection
  D. Groove deeply
  E. Groove with sufficient power
  F. Irrigation/aspiration (I/A): "Don't let up"
V. When a Problem Arises
  A. Stop.
  B. Evaluate.
  C. Choose the best course.
  D. Slowly and thoroughly execute the appropriate treatment.
VI. Recognition
  A. Easy during I/A
  B. Subtle during phaco
    1. Anterior chamber or posterior chamber deepens
    2. Inability to rotate lens
    3. Lens tilt
    4. Loss of followability
VII. Goals
  A. Remove remaining lens material.
  B. Perform a complete anterior vitrectomy.
  C. Avoid enlarging the posterior capsular tear and preserve as much capsule as possible.
VIII. Goal: Avoid Enlarging the Posterior Capsule Tear
  A. Dry or low infusion technique
  B. Maintain a closed-chamber environment.
  C. Generous use of viscoelastic is necessary.
  D. When possible, perform a posterior capsulorrhexis.
IX. Your "Best Friends"
  A. Viscoelastic
  B. Lens glide
X. Nucleus Management
  A. Viscoelastic to support nucleus and tamponade vitreous
  B. Determine if adequate support exists for further phaco
  C. Convert if necessary . . . *extrude*, do not *express*.
  D. Lens glide to support nucleus
XI. Cortex Removal
  A. Viscoelastic to tamponade vitreous and mobilize cortex.
  B. Begin away from tear, and strip toward it.
  C. Intermittent vitrectomy
  D. Manual technique allows *complete* removal.
XII. Vitrectomy Technique
  A. Goals
    1. Avoid enlarging tear by dry or low flow technique.
    2. Only remove vitreous anterior to posterior capsule.
    3. Do this without conveying excess vitreoretinal traction forces.
  B. Bimanual (AC) vitrectomy:
    1. Separate infusion from cutting/aspiration
    2. Infusion cannula placed through side-port
    3. Low flow/infusion—AC maintenance aided by viscoelastic
    4. Low vacuum/high cutting rate
    5. In limited cases, no infusion (dry technique)
    6. Remember, a closed chamber requires *watertight* incisions
  C. The vitrectomy "kit"
    1. Disposable 20-gauge posterior vitreous cutter
    2. An infusion cannula (Storz E-4421)
    3. Viscoat
    4. Phacoglide (Visitec)
    5. MVR blade
    6. 9-0 nylon suture

XIII. IOL Insertion

A. Carefully examine integrity of remaining capsule

B. Utilize viscoelastic and lens glide, avoid IOL rotation

C. Bag fixation for small tears

D. Bag fixation for zonular dialysis (haptic toward dialysis). Consider an endocapsular ring.

E. If posterior capsulorrhexis is possible, precede with bag fixation.

F. Sulcus fixation for large tears with haptics *away* from tear

G. Place optic posterior to intact anterior capsulorrhexis (T. Nuehann).

H. When in doubt, suture into sulcus.

XIV. The Dropped Nucleus

A. Nucleus loss into anterior vitreous

1. Visible and easily reached
2. Support with viscoelastic and second instrument
3. Capture in AC and remove

B. Nuclear loss into posterior vitreous

1. Do not attempt to "float" up.
2. Consult with vitreoretinal surgeon.
3. If lens fragment is very dense, delay placement of IOL.

Use of Intraoperative Endoscopy

Brian A Francis MD

I. Introduction
   A. Glaucoma
   B. Glaucoma treatment options
   C. Cyclophotocoagulation procedures background
   D. Endoscopic diode laser instrumentation
II. Basic Science
   A. Histopathology of endoscopic cyclophotocoagulation (ECP)
   B. Contrast with other cyclophotocoagulation procedures
III. Patient Selection for ECP
   A. Types of glaucoma
   B. Severity of disease
   C. Combined with cataract extraction
   D. Use after prior glaucoma surgeries
IV. Surgical Technique of ECP
   A. Anterior approach
   B. Combined with cataract extraction
   C. Pars plana approach
   D. ECP plus
V. Clinical Results of ECP
   A. Primary procedure
      1. With or without cataract extraction
      2. Vs. trabeculectomy
      3. Vs. tube shunt
   B. Refractory glaucomas
   C. Pediatric glaucomas
VI. Endoscopic cilioplasty (ECPL) for plateau iris
VII. Endoscopic-Assisted Anterior Segment Procedures
   A. Angle procedures
      1. Cyclodialysis cleft repair
      2. Iridodialysis repair
      3. Goniosynechialysis
      4. Trabecular surgery
   B. Anterior segment and ciliary sulcus procedures
      1. IOL surgery
         a. IOL repositioning
         b. Secondary IOL
      2. Hypotony evaluation and treatment
      3. Tube shunt implantation
      4. Ciliary sulcus suture placement
VIII. Endoscopic-Assisted Posterior Segment (Retinal) Procedures
   A. Diabetic Retinopathy
      1. Vitreous hemorrhage
      2. Traction retinal detachment
      3. Retinal ablation
   B. Rhegmatogenous retinal detachment
   C. Proliferative vitreoretinopathy
   D. Retinopathy of prematurity
   E. Posterior dislocation of lens material and implant
   F. Intraocular foreign body
   G. Endophthalmitis
   H. Hypotony and cyclitic membrane
IX. Conclusions

Loose IOLs

Iqbal K Ahmed MD

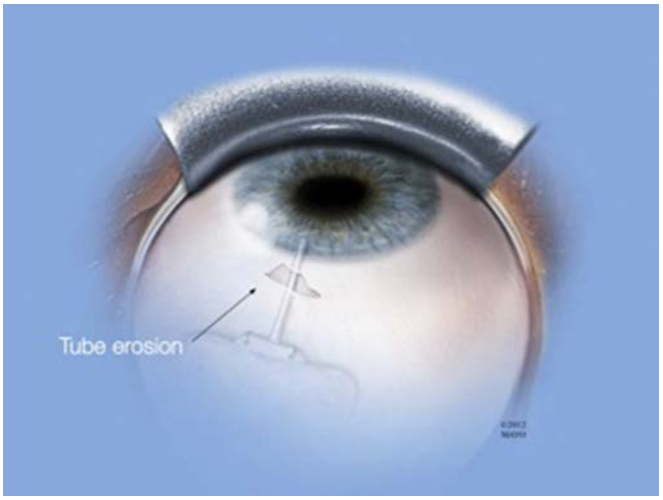
NOTES

Not Enough Conjunctiva

Cheryl L Khanna MD

What are the options available to address glaucoma drainage device erosion, bleb leaks, and multiple intraoperative conjunctival buttonholes when conjunctiva is inadequate?

Tube Exposure Repair: Evidence-Based Medicine



Tube erosion: Case presentation #1

- 54-year-old female with history of BB injury left eye 1960 seen at Mayo Clinic Rochester
- Penetrating keratoplasty left eye
- Uveitic glaucoma left eye
- Underwent Ahmed + Baerveldt left eye
- Vision 20/60 left, IOP left 11
- Tube exposure left eye
- Limited conjunctiva with history of injury, scleral malacia, multiple surgeries with extensive scarring

Method of tube exposure repair: Is there a consensus? Options for conjunctiva

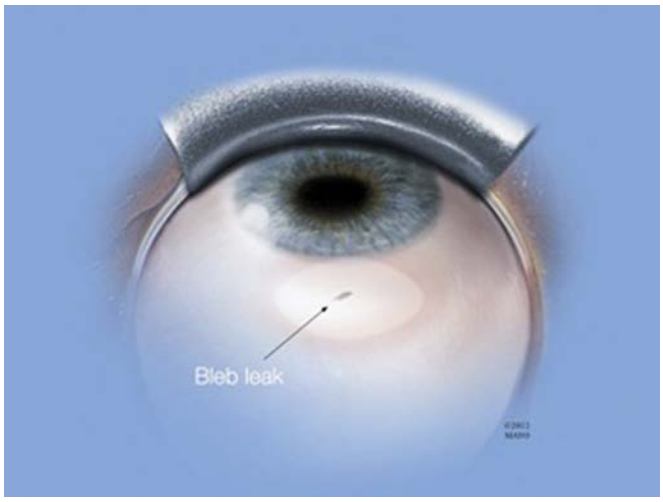
- Primary closure
- Autologous conjunctival graft
- Amniotic membrane

Method of tube erosion repair

- Two components of repair
- Graft over tube
- Conjunctival repair

Method of Repair Chosen in Case Presentation #1

Bleb Leak Repair: Evidence-Based Medicine



Bleb leak: Case presentation #2

- 70-year-old male with open-angle glaucoma with maximum IOP 30/33
- Trabeculectomy with mitomycin C 0.1 mg/cc both eyes
- Three years post-trabeculectomy, patient developed adenovirus membranous conjunctivitis
- Bleb leak noted in left eye post conjunctivitis
- Conjunctival advancement performed
- Retraction of conjunctiva with recurrent bleb leak occurred

Case Presentation #3

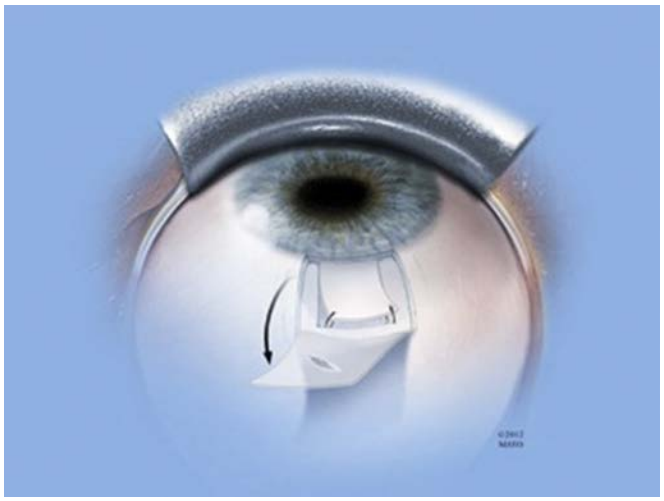
- 68-year-old female with iridocorneal endothelial syndrome status post trabeculectomy twice in left eye
- Blebitis left eye
- Bleb leak noted after resolution of blebitis
- Visual acuity 20/20, Ta 10 left eye

Algorithm for bleb leak repair

- Bleb leak repair with conjunctival advancement
  - Decreased surgical time
  - Cost-effective
  - Short-term less persistent leak compared to amniotic membrane
  - Long-term 92% success
- Bleb leak repair with amniotic membrane
  - Good success in patients with inadequate conjunctiva
  - Long-term success only slightly lower than conjunctival advancement
  - Fewer vascular blebs

Method of bleb revision in case presentations #2 and #3

Intraoperative Button Holes: Evidence-Based Medicine



Intraoperative button holes: Case presentation #4

- 83-year-old Vietnamese woman with thin conjunctiva
- Resident case
- Trabeculectomy with mitomycin C 0.1 mg/cc
- Multiple intraoperative conjunctival button holes

Options for repair

- Direct repair with BV75-4 on 10-0 nylon
- Fibrin glue
- Amniotic membrane

Amniotic membrane as a conjunctival substitute

- Preserve conjunctiva
- Enhances rapid epithelialization

Clinical considerations with amniotic membrane

- Which form of amniotic membrane is best? Cryo preserved vs. dehydrated
- What are the available thicknesses of amniotic membrane?
- What is the ideal orientation of amniotic membrane?
  - Epithelial side up
  - Stromal side up
  - Folded or layered amniotic membrane
- What is the best method of amniotic membrane attachment?
  - Glue vs. sutures
  - Choices of fibrin glue

Selected Readings

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Bleb Leak With or Without Infection

Gloria P Fleming MD

I. Introduction

The trabeculectomy, or some modification thereof, continues to be the gold standard for primary glaucoma filtering surgery. The use of antimetabolites, mitomycin C (MMC) or 5-fluorouracil, has enabled the surgeon to prolong the lifespan of the bleb by minimizing postoperative scarring and eventual failure. However, associated risks of antimetabolite use can include bleb leaks, which can occur early or late, with or without infection.

II. Symptoms

A. Asymptomatic

B. Tearing

C. Blurred vision

D. Pain/discomfort

III. Recognizing Signs of a Bleb Leak

A. Normal to low IOP

B. Low to flat bleb

C. Seidel positivity

D. Surrounding injection

E. Normal to shallow anterior chamber

F. Descemet folds

IV. Early-Onset Bleb Leak

A. Timing/occurrence: Within the first 3 months postoperatively

B. Incidence: Overall incidence may be underestimated, as many leaks are asymptomatic and overlooked.

C. Etiology

1. Wound dehiscence
2. Conjunctival button hole
3. Inadequate conjunctival closure
4. Suture track defects

D. Management

1. Small leak
   a. Observation: May close spontaneously
   b. Reduce aqueous outflow through conjunctival defect
      i. Topical aqueous suppressants
      ii. Oral aqueous suppressants
   c. Topical antibiotics
   d. ± cycloplegics
   e. Protective eye shield
2. Larger, more brisk leak
   a. Large diameter bandage contact lens
   b. Autologous blood injection
   c. Tissue adhesives
   d. Cyanoacrylate glue
   e. Trichloroacetic acid
   f. Slitlamp needle closure
   g. Surgical revision

V. Late-Onset Bleb Leak

A. Timing/occurrence: Beyond 3 months postoperatively

B. Incidence

1. Increases progressively with time[1]
2. 5-year probability of development almost 20%[2]

C. Signs: Similar to early-onset leaks; however, may have normal IOP and elevated blebs

D. Predisposing factors

1. Adjunctive use of antimetabolites: Bleb leaks are 3 times more frequent following trabeculectomies with MMC than 5-fluorouracil.[3]
2. Avascular, thin-walled, cystic blebs
3. "Ring of steel" fibrosis
4. Full-thickness procedures[1]

E. Associated risks

1. Hypotony
2. Hypotony maculopathy
3. Serous choroidal effusions, choroidal hemorrhage
4. Bleb-related infections: Late-onset bleb leaks are a significant risk factor for the development of bleb-related infections; increasing the risk by 26% compared with controls.[4]

F. Management

1. There is no universally accepted consensus on management intervention. Rather, management decisions should be patient specific and individualized based on consideration of several factors:
   a. Character and size of bleb leak
   b. Severity of glaucoma
   c. Status of fellow eye

d. Prior episode or potential risk of bleb-related infection

e. Adherence to medical advice and follow-up care

2. Options

a. Observation

b. Conservative: aqueous suppressants, bandage contact lens, pressure patch, Simmons shell, symblepharon ring, cyanoacrylate glue, trichloroacetic acid, autologous fibrin glue

c. Bleb manipulations: autologous blood injection, MMC needling, compression sutures

d. Laser procedures

e. Surgical revision

G. Potential complications: bleb-related infections

1. Blebitis

2. Endophthalmitis

VI. Conclusion

Bleb leaks following glaucoma filtering surgery can occur at any time in the postoperative period and are more frequent following antimetabolite-augmented procedures. Complications arising from a leak can have potentially vision-threatening results, including blebitis and endophthalmitis. Management strategies are not universal and should be individualized and weighed against potential secondary complications of initiated intervention.

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Failing Bleb

Jonathan S Myers MD

I. Bleb Failure

Early Failure vs. Late Failure

II. Bleb Descriptors

A. Height

B. Extent

C. Vascularity

D. Thickness of tissue

E. Microcysts

F. Leaks

G. Heme

III. Early Postop Evaluation (see Table 1)

Table 1. Early Postop Bleb Evaluation

IOP	Bleb	Issue
Low	Low	Leak
		Reduced aqueous
Low	High/Large	Overfiltration
High	Low	Tight flap
High	High	Encapsulation
		Tight flap (uncommon

IV. Specific Scenarios

A. Early vascularity and thickening

1. More steroid: Consider injection if compliance issues are insurmountable
2. More antimetabolite: Postop 5-fluorouracil (5-FU) and mitomycin C (MMC) are not well studied in the setting of intraoperative antimetabolite use.
3. Earlier suture lysis?
   a. More flow helps prevent scarring and fibrosis. But . . .
   b. Hot eyes more predisposed to aqueous shut down and hypotony.

B. Leaks (covered by prior presentation)

1. Less steroid
2. Aqueous suppressant
3. Bandage contact lens
4. Suture
5. Revision
6. Also:
   a. Glue
   b. Cautery
   c. Bleb needling or suture lysis to redirect flow posteriorly

C. Flat bleb, high IOP

1. Episcleral fibrosis is the most common cause of failure.
2. Digital compression seems to help early on.
   a. Stretches tissues
   b. Flushes plugs of hemorrhage and fibrin
   c. Less effective later
3. Suture removal/laser suture lysis
   a. Too early leads to more grief
   b. Too late is ineffective
4. Bleb needling

D. Fibrin and hemorrhage

1. TPA (tissue plasminogen activator) breaks down fresh fibrin.
2. 6-25 μg dose in anterior chamber (AC)
3. Longstanding fibrin not cleared
4. Rebleed a definite possibility if recent hemorrhage

E. Iris to the ostium

1. May follow shallow chamber episode
2. Digital compression will force iris further into sclerostomy!
3. Look at ostium with gonioprism first.
4. Greater risk if no peripheral iridectomy (PI)
   a. Pilocarpine
   b. Argon or YAG Laser
   c. Needle at slitlamp through needle track
   d. Paracentesis track: risk destabilizing chamber
5. Operating room: enlarge PI?
6. Clear cornea approach vs. full revision

F. Encapsulation

1. Usually goes away on its own, although patients may require long-term medications
2. Aqueous suppressants to temporize

3. Reduce steroids?
4. Needle?
   a. If IOP too high for nerve in short term

G. Late failure
1. Typically fibrosis
   a. Still worth looking on gonio
3. Aqueous suppressants first
4. Bleb needling
5. Full revision
6. Tube shunt
7. Cilioablation

V. Bleb Needling
A. Appearance of bleb matters
B. Decreasing success
1. Encapsulation
2. Central avascular zone/ring of steel
3. Completely flat
4. Thick, "beefy" conjunctiva

VI. Bleb Needling: OR vs. Office Considerations

Table 2. Bleb Needling: OR vs. Office

Issue	Favors
Patient comfort	OR
Control of patient	OR
Access and visibility	OR
Options if things go awry	OR
Test flow/deepen AC	OR
Viscoelastic	Either
Full revision	OR
Convenient for patient	Office
Avoids admitting defeat	Office

VII. Needling Instrumentation Choices
A. 30-gauge needle
1. No need to suture entry
2. Good control
3. Less aggressive
B. 25-gauge needle
1. No need to suture distant entry
2. Good control
3. More aggressive
C. MVR blade
1. Need to close entry: suture or cautery
2. Less forgiving if applied to unintended tissue
3. Very, very effective
D. Viscoeastic: an option to prevent shallow chamber if trab really opened up by needling

VIII. Antimetabolites for Needling
A. None: Safe
B. 5-FU: More effective, greater hypotony risk
C. MMC: Very effective, greatest hypotony risk
D. MMC: One technique
1. 50/50 mixture MMC 0.4 mg/ml with lidocaine 1% nonpreserved/MPF
2. 30-gauge needle
3. Inject subconjunctivally but not subtenons 8-10 mm posterior to the limbus at 12 o'clock.
4. Massage with blunt 18-gauge cannula or blunt instrument into superior 180 degrees of bulbar conjunctiva.

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Painful Bleb

Ronald Leigh Fellman MD OCS

I. Introduction and Scope of the Problem

II. Bleb Dysesthesia

- A. Definition
- B. Etiology
- C. Associated problems
  1. Overhanging bleb
  2. Visual compromise

II. Management

- A. Conservative (nonsurgical)
- B. Surgical options
  1. Resurface bleb
  2. Bleb needling
  3. Bleb window cryopexy
  4. Bleb revision with conjunctival advancement
  5. Closure of filtration site and simultaneous tube surgery

VEGF Inhibitors and Glaucoma Surgery

Cynthia Mattox MD

There are 2 major categories where VEGF inhibitors such as bevacizumab (Avastin) and ranibizumab (Lucentis) can be of use in glaucoma surgery:

1. Avoiding postoperative complications: Anti-VEGFs and neovascular glaucoma
2. Treating postoperative complications: Anti-VEGFs to improve postoperative bleb function

Neovascular Glaucoma

Background

In the setting of retinal ischemia in eyes with vascular occlusions or diabetic retinopathy, production of VEGF is upregulated and abnormal concentrations are found in the vitreous and aqueous humor. The presence of VEGF stimulates angiogenesis and fibroblast proliferation, and these intraocular effects can be blocked by the administration of anti-VEGF agents intravitreally, intracamerally, and even via subconjunctival injection.

Clinical use of anti-VEGFs in neovascular glaucoma

Numerous case series and publications have described the rapid clinical improvement in eyes with anterior segment neovascularization after injection of anti-VEGFs, typically with bevacizumab 1.0-1.25 mg intravitreally. The anterior segment neovascularization of the iris and angle clinically regresses and pain control improves within 1 week, although histopathological studies reveal that the abnormal vessels remain present in the trabecular meshwork and iris, but they are collapsed and less permeable after treatment.

In the recent evolution of understanding about the use of anti-VEGFs in the setting of neovascular glaucoma, several findings become apparent:

- The half-life of the anti-VEGFs in the eye is relatively short (days to weeks), and repeated injections and preferably panretinal photocoagulation (PRP) are required to prolong the inhibition of VEGF in ischemic eyes, which need continued monitoring.
- Eyes that have developed massive angle infiltration with new vessels or peripheral anterior synechiae are unlikely to have significant IOP-lowering after anti-VEGF treatment. Eyes that have early new vessel formation may be cured of their neovascular glaucoma by prompt anti-VEGF and PRP treatment.
- Eyes that are unlikely to show IOP improvement with the use of anti-VEGF agents will still have improved perioperative morbidity with reduction in the incidence or severity of hyphema, postoperative inflammation, and intraoperative bleeding with trabeculectomy or glaucoma drainage implants.
- Similarly, anti-VEGF agents will reduce pain and anterior segment neovascularization more rapidly in eyes undergoing transscleral cyclophotocoagulation (TSCPC) after PRP, although the IOP-lowering outcomes of TSCPC may be similar to eyes not receiving anti-VEGF.

Postoperative Bleb Function

Background

Excessive subconjunctival fibrosis will cause trabeculectomy failure. VEGF levels are elevated in the aqueous of glaucoma eyes, even prior to surgery. VEGF has been shown to stimulate Tenons fibroblast proliferation, as well as to induce angiogenesis and scar formation after trabeculectomy. Anti-VEGF agents such as bevacizumab have been shown to block these effects and fibroblast cytokine release in animal models and in vitro. While current antifibrotic agents like mitomycin C and 5-fluorouracil are effective in modulating wound healing after trabeculectomy, they cause widespread fibroblast cell death that can lead to complications such as avascular blebs, late bleb leak, and endophthalmitis. The hope is to find agents like anti-VEGFs that will modulate wound healing postoperatively yet allow for better bleb morphology, increasing long-term safety.

Clinical studies of anti-VEGFs in glaucoma surgery

Few studies have been published. Table 1 summarizes the available literature at the time of this monograph (July 2012).

These early studies do not show superiority of bevacizumab or ranibizumab over mitomycin C in either IOP success or near-term bleb morphology in contemporary fornix-based trabeculectomy. But questions remain about the optimal dose, route of administration: intravitreal vs. intracameral vs. subconjunctival, timing, and duration of the use of anti-VEGFs with glaucoma surgery.

Table 1.

Author/Journal/Year	No. of Eyes	Protocol	Followup / Outcomes	Results
Grewal/*Ophthalmology*/ 2008	12, POAG, CACG	Case series, pilot study. Trab + subconjunctival injection bevacizumab intraop 1.25 mg	6 months. Complete success = IOP 6 to 16 mmHg, no meds + 30% lower. Qualified success = IOP of ≤ 16 mmHg with 1 or fewer IOP-lowering medication.	11/12 eyes success. No adverse effects to eye or bleb. Some increased bleb vascularity after 3 months.
Kahook/*Am J Ophthalmol.*/ 2010	10, POAG	Randomized, masked pilot study, 2 groups: 1. Trab + MMC + ranibizumab intravit, intraop injection 0.5mg 2. Trab + MMC alone	6 months. Bleb morphology. Complete success = 5 > IOP < 22, + 30% lower, no meds. Qualified success = 5 > IOP < 22, + 30% lower, on meds.	All eyes qualified success. Ranibizumab eyes had more diffuse, less peripheral vascularity of blebs.
Sengupta/*J Glaucoma.*/2011	38, POAG, CACG	Phaco-trabs, single-site. Randomized, masked, 3 groups: 1. MMC, 2. Intraoperative sponge-applied bevacizumab 1.25 mg. 3. Subconjonctival bevacizumab injections ×2 perioperatively and at 1 week postop, 1.25mg each.	6 months. Complete success = no meds + IOP < 18 +20% lower. Qualified success = 1 med + IOP < 18 +20% lower. Bleb morphology.	MMC: 60% complete success Sponge bevacizumab: 90% complete success Subconjunctival bevacizumab: 60% complete success. Trend for bevacizumab groups to develop increased bleb vascularity at 6 months compared to 1 month.
Sedghipour/*Clin Ophthalmol.*/2011	37, POAG, secondary OAG	Trabs, randomized, masked. 1. Trab + intraoperative subconjunctival injection bevacizumab 0.2 mg 2. Trab + subconjunctival injection saline placebo	3 months. Mean IOP comparison.	No significant difference in mean IOP at any time point.

(table continues)

Table 1. (continued)

Author/Journal/Year	No. of Eyes	Protocol	Followup / Outcomes	Results
Mahdy/*J Glaucoma*./2011	60 eyes of 48 patients age 1-6 years old with congenital phakic glaucoma	Randomized, masked, 3 groups: 1. Ahmed + intraoperative subconjunctival injection bevacizumab 1.25 mg 2. Ahmed + MMC sponge 3. Ahmed alone	12 months. Complete success = IOP ≤ 21 and ≥ 10, no meds. Qualified success = ≤ 21 and ≥ 10, on meds.	Complete success: bevacizumab 70%[a] MMC 80%[a] No adjunct 60% Failures: Bevacizumab 20% (4 cases of encysted bleb) MMC 10%[b] (2 eyes with scleral erosion beneath plate) No adjunct 40% (8 cases of encysted bleb)
Nilforushan/*Am J Ophthalmol*./2012	36, POAG PXFG	Randomized, 2 groups: 1. Trab + MMC 2. Trab + bevacizumab intraoperative subconjunctival injection 2.5 mg	6 months minimum. Bleb morphology. Complete success = IOP ≤ 21 or > 5, + 20% lower, no meds. Qualified success = IOP ≤ 21 + 20% lower, on fewer meds than preop.	All eyes complete or qualified success, except 1 eye in MMC group had IOP of 4. Significantly lower mean IOP in MMC eyes, months 1-6. Similar bleb morphology at 6 months.
Zarnowski/*Acta Ophthalmol*./2011	2 eyes, 1 patient	Case report. Use of topical bevacizumab eye drops 5 mg/ml beginning on Day 15 postop in addition to usual care.	4 and 6 months.	Authors felt bevacizumab helped improve bleb characteristics and success in a failing bleb.
Bochmann/*BMC Ophthalmol*./2011 Switzerland protocol description for topical ranibizumab	Plan for Phase 1 (5 eyes) Phase 2 (50 eyes) POAG, PXFG, PG	Phase 1: Phaco trab + MMC + ranibizumab eye drops 2 mg/ml Phase 2: randomized phaco trab MMC ± ranibizumab eye drops	6 months. Safety, IOP success, bleb morphology	No results.

Abbreviations: POAG indicates primary open-angle glaucoma; CACG, chronic angle-closure glaucoma; OAG, open-angle glaucoma; PXFG, pseudoexfoliation glaucoma; PG, pigmentary glaucoma; trab, trabeculectomy; MMC, mitomycin C.

[a]Significant compared to no adjunct.

[b]Additional 6 eyes in MMC group had tube exposure.

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Morphosys AG, Munich: C
SOOFT SpA Montegiorgio, Italy: C,L
Zeiss-Meditec: S

Cheryl L Khanna MD
None

Jeffrey M Liebmann MD
Alcon Laboratories, Inc.: C
Allergan, Inc.: C
Carl Zeiss Meditec: S
Diopsys Corp.: C,S
Glaukos Corp.: S
Heidelberg Engineering: S
Merz Pharmaceuticals, Inc.: C
National Eye Institute: S
New York Glaucoma Research Institute: S
Optovue, Inc.: C,S
Quark Pharmaceuticals, Inc.: C
SOLX, Inc.: S
Topcon Medical Systems: S

Steven L Mansberger MD MPH
Allergan: C,L
Glaukos Corp.: C
Santen, Inc.: C
Merck: S

Keith R Martin MD
Allergan: L

Cynthia Mattox MD FACS
AHRQ: S
Alcon Laboratories, Inc.: S
National Eye Institute: S
Transcend: S

Felipe A Medeiros MD
Alcon Laboratories, Inc.: C,L,S
Allergan: C,L
Carl Zeiss Meditec: L

Eydie G Miller-Ellis MD
Alcon Laboratories, Inc.: C
Allergan, Inc.: C
Merck & Co., Inc.: C

John C Morrison MD
None

Marlene R Moster MD
Aeon Astron: S
Alcon Laboratories, Inc.: C,L,S
Allergan: C,L,S
Genentech: S
iScience: L
Ista Pharmacuticals: C,L
Merck & Co., Inc.: C,L
Solx: L
TissueTech, Inc.: S

Jonathan S Myers MD
Alcon Laboratories, Inc.: C,L
Allergan, Inc.: C,L,S
Aquesys: S
Aton Pharma Inc.: C
Diopsys, Inc.: S
Glaukos Corp.: S
Haag Streit: L
Inotek: C,S
Merck & Co., Inc.: L,S
Sucampo Pharma Americas, Inc.: C

Louis D Skip Nichamin MD
3D Vision Systems: C,O
Abbott Medical Optics: C
Allergan, Inc.: C
Bausch + Lomb Surgical: C
Eyeonics, Inc.: C,O
Foresight Biotherapeutics: C
Glaukos Corp.: C
Harvest Precision Components: O
iScience: C,O
LensAR: C,O
PowerVision: C,O
RevitalVision, LLC: C,O
SensoMotoric Instruments: C
WaveTec Vision System: C,O

Mildred M G Olivier MD
Alcon Laboratories, Inc.: C,L
Allergan, Inc.: L
National Eye Institute: S
Santen, Inc.: C

Richard K Parrish II MD
Alimera Sciences, Inc.: C
AqueSys: C,O
Bausch + Lomb Surgical: C
Glaukos Corp.: C,O
InnFocus, Inc.: O
Innolene LLC: O
Merck & Co., Inc.: C
QLT, Inc.: C

Harry A Quigley MD
Carl Zeiss Meditec: C
Genentech: C
Merck & Co., Inc.: C
Ono, Inc.: C
Sensimed: C
Sucampo: C

Douglas J Rhee MD
Alcon Laboratories, Inc.: C,S
Allergan, Inc.: C,S
Merck & Co., Inc.: C
Santen, Inc.: C

Thomas W Samuelson MD
Abbott Medical Optics: C
AcuMems: C
Alcon Laboratories, Inc.: C,L
Allergan, Inc.: C
AqueSys: C
Endo Optiks, Inc.: C
Glaukos Corp.: C,O
Ivantis: C
Merck & Co., Inc.: C
Ocular Surgery News: C
QLT Phototherapeutics, Inc.: C,O
Santen, Inc.: C
SLACK, Incorporated: C

Joel S Schuman MD
Carl Zeiss Meditec: P
National Eye Institute: S
SLACK, Incorporated: C
Vindico, Inc.: C

Kuldev Singh MD MPH
Alcon Laboratories, Inc.: C
Allergan, Inc.: C
Bausch + Lomb Surgical: C
iScience: C
Ivantis: C
Santen, Inc.: C
Transcend: C

Arthur J Sit MD
AcuMEMS: C
Alcon Laboratories, Inc.: C
Allergan: C
Glaukos Corp.: C,S
Sensimed AG: C

Robert N Weinreb MD
Alcon Laboratories, Inc.: C,L
Allergan, Inc.: C,L
Altheos: C
Bausch + Lomb: C
Heidelberg Engineering: S
Humphrey Zeiss: C,L
Merck & Co., Inc.: C,L
National Eye Institute: L,S
Nidek, Inc.: S
Novartis Pharmaceuticals Corp.: S
Optovue: C,S
Othera Pharmaceuticals Inc.: C
Sensimed: C
Solx: C
Topcon Medical Systems: C,S

Presenter Index

* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.