World Glaucoma Association

Intraocular Pressure

Robert N. Weinreb, James D. Brandt,
David Garway-Heath and Felipe Medeiros

Consensus Series 4

Kugler Publications, The Hague, The Netherlands

INTRAOCULAR PRESSURE

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Reports and Consensus Statements of the 4th Global AIGS Consensus Meeting on Intraocular Pressure

edited by

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Kugler Publications/Amsterdam/The Netherlands

ISBN 10: 90-6299-213-7
ISBN 13: 978-90-6299-213-3

Distributors:

For the USA and Canada:
Pathway Book Service
4 White Brook Road
Gilsum, NH 03448
U.S.A.
email: pbs@pathwaybook.com

For all other countries:
Kugler Publications
P.O. Box 20538
1001 NM Amsterdam, The Netherlands
Telefax (+31.20) 68 45 700

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This publication is the fourth of a series on Consensus meetings in Glaucoma under the auspices of the Assocation of International Glaucoma Societies

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Robert N. Weinreb

James D. Brandt

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Felipe A. Medeiros

FOREWORD

Intraocular Pressure is the subject for the fourth Consensus report published under the auspices of the AIGS, now renamed as the World Glaucoma Association (WGA). It seems like yesterday (November, 2003) that the inaugural AIGS Consensus meeting was held in San Diego to discuss *Glaucoma Diagnosis*. Since then we have had annual consensus reports on *Open Angle Glaucoma Surgery* and *Angle Closure and Angle Closure Glaucoma*. Each of them has been preceded by several months of active participation in our Project Forum E-Room (beginning in January, 2007 for the IOP Consensus) by expert members of the various consensus committees. As done with prior reports, the preliminary document was circulated to each of the member societies of the WGA, and additional comments were solicited for the document. Each member Society also was invited to send a representative to attend the consensus meeting that was held in Fort Lauderdale, Florida on May 5, 2007. The report then was discussed extensively during the Consensus Meeting and Consensus Statements were revised following these discussions.

Intraocular Pressure is a topic that touches the essence of our subspecialty. Its measurement is a vital aspect of glaucoma diagnosis and treatment. For now, it is the only modifiable risk factor. Measurement of IOP is a relatively recent – one century – addition to our diagnostic armamentarium. Even though the measurement of IOP is relatively simple, it is by no means uncomplicated. The greatest limitation is probably the paucity of measurements that are obtained in practice. Although continuous IOP measurement is on the horizon, it still is not ready for clinical practice.

Arriving at a consensus often can be circuitous and filled with compromises. However, this opportunity is used to critically assess the evidence and develop consensus points. The reader will find this consensus report instructive, practical, and thought-provoking. Moreover, it has great potential to impact patients, both individually and collectively, through both their care and research.

Robert N. Weinreb
Erik L. Greve


Association of
International Glaucoma Societies
May 5, 2007, Fort Lauderdale, FL, USA
Intra Ocular Pressure
AIGS
CONSENSUS
Consensus Meeting
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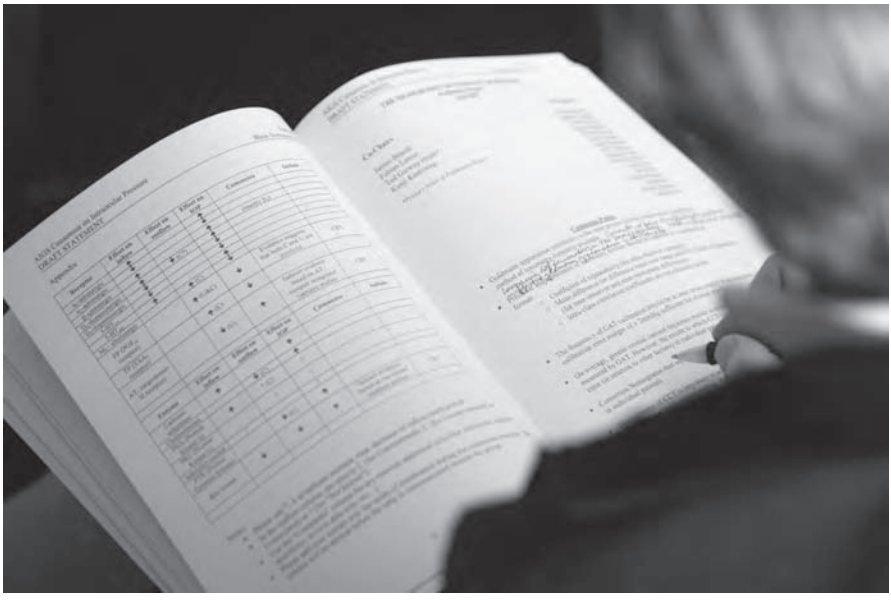

PREFACE

This is the fourth glaucoma consensus held under the auspices of the AIGS, now renamed as the World Glaucoma Association (WGA). We anticipate that the discussion and conclusions from this consensus will have broad impact, as the relationship between IOP and the disease is fundamental to the care of glaucoma patients worldwide. As with the previous consensus meetings on Glaucoma Diagnosis, Open-Angle Glaucoma Surgery and Angle-Closure Glaucoma, this consensus report was developed over several months in an interactive internet system. The Consensus faculty, consisting of leading authorities on various aspects of IOP from throughout the world, has met in Fort Lauderdale on May 5, 2007 to discuss the reports and refine the consensus points.

In the 1980s, health policy researchers from outside ophthalmology challenged the most closely-held beliefs in our field. They pointed out that an objective review of the extant literature provided little evidence that IOP bore a strong risk relationship to glaucoma, and furthermore that there was even less evidence that lowering IOP was of any benefit in the treatment of the disease. Ophthalmology responded with over two decades of groundbreaking clinical and basic research. Multi-center clinical trials like the AGIS, OHTS, EMGT and CNTGS leave no doubt that IOP is a primary risk factor for the disease and that lowering IOP is beneficial in a majority of our patients. Basic research, in particular animal models of elevated IOP and glaucomatous damage, form another intellectual cornerstone establishing the relationship of IOP to the disease.

And yet… over the last decade we have begun to acknowledge that the relationship of IOP to the disease is not as clear-cut as we like to believe. Indeed, our ability to even measure IOP accurately has come into question, with the recognition that central corneal thickness significantly affects tonometry. What should we be measuring? Random IOP? IOP fluctuation? Nocturnal IOP? How should IOP be studied in clinical trials? How should clinicians use IOP in the care of individual patients?

Obtaining consensus on how IOP should be measured and used in the care of patients and in performing clinical research is a daunting task. As with the previous AIGS consensuses, the IOP consensus is based on the published literature and expert experience. Although consensus does not replace and is not a surrogate for scientific investigation, it does provide considerable value, in particular when the desired evidence is lacking. The goal of this consensus was to establish what we 'know' and what we 'need to know' to better understand the role of IOP in glaucoma. We hope that this consensus will serve as a benchmark of our understanding in 2007, and that it will be revised and improved with the emergence of new evidence.

James D. Brandt
Ted Garway-Heath
Makato Araie
Robert N. Weinreb

Attendees of the IOP Consensus held on May 5, 2007 in Fort Lauderdale, Florida.

Name tags.

Caroline Geijssen in final preparation for the meeting

Paul Palmberg and Caroline Geijssen

Bernard Scwartz and Erik Greve

Program committee discussing consensus points

Makoto Aihara reading examining the consensus points

Networking and discussion during a break.

Discussion continued informally during lunch.

BASIC SCIENCE OF INTRAOCULAR PRESSURE

Ernst Tamm

Ernst R. Tamm, Carol Toris, Jonathan Crowston, Arthur Sit, Sheng Lim, George Lambrou and Albert Alm

Contributors: Makoto Aihara, Jonathan Crowston, Ian Grierson, Megumi Honko, Doug Johnson, Paul Kaufman, George Lambrou, Sheng Lim, John Liu, Elke Lütjen-Drecoll, Doug Rhee, John Samples, Arthur Sit, Ernst R. Tamm, Carol Toris

Consensus points

Aqueous flow

- IOP is determined by contributions from aqueous humor production (measured as aqueous flow), trabecular outflow, uveoscleral outflow and episcleral venous pressure.
- Aqueous flow has a distinctive circadian rhythm, being lower at night than during the day.
  Comment: Aqueous flow is not affected by exfoliation syndrome, pigment dispersion syndrome, primary open angle glaucoma, or ocular hypertension.
  Comment: Aqueous flow is reduced by diabetes mellitus and myotonic dystrophy.
- The best technique to measure aqueous flow in humans is by fluorophotometry.
  Comment: Limitations and assumptions associated with fluorophotometry include:
  – a rate of diffusion of fluorescein into the iris, limbal vessels and tear film is assumed;
  – fluorescein is distributed uniformly throughout the anterior chamber and cornea;
  – a lens-iris barrier is present to block the egress of the tracer into the posterior chamber;
  – short-term fluctuations in aqueous flow of less than 30 minutes are not detectable.

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Trabecular outflow

- The trabecular outflow pathway is comprised of the trabecular meshwork, the juxtacanalicular connective tissue (JCT), the endothelial lining of Schlemm's canal, the collecting channels and aqueous veins.
  Comment: Normal outflow resistance resides in the inner wall region of Schlemm's canal (SC), including JCT and inner endothelial lining of SC. Cells in the trabecular meshwork influence the hydraulic conductivity of the inner wall region and outflow resistance by modulating extracellular matrix turnover and/or by actively changing cell shape.
  Comment: Trabecular outflow is under the influence of ciliary muscle tone.
- Outflow facility in healthy human eyes is in the range of 0.1 to 0.4 μl/min/mmHg.
  Comment: Outflow facility is reduced in primary open angle glaucoma, ocular hypertension, and exfoliation and pigment dispersion syndromes with accompanying ocular hypertension.
  Comment: In chronic open-angle glaucoma there is an increase in extracellular material in the juxtacanalicular connective tissue and decrease in number of pores in Schlemm's canal endothelium.
- Outflow facility can be measured with tonography and fluorophotometry. Both methods have inherent limitations associated with their use.

Uveoscleral outflow

- The uveoscleral outflow pathway is comprised of the ciliary muscle, supraciliary space, suprachoroidal space, sclera and other less defined areas.
- Uveoscleral outflow is 25-57% of total outflow in young healthy humans and uveoscleral outflow decreases with aging.
  Comment: Uveoscleral outflow is reduced in ocular hypertension with and without exfoliation syndrome, increased in uveitis, and unchanged in pigment dispersion syndrome with ocular hypertension.
- In clinical studies, uveoscleral outflow is calculated from the modified Goldmann equation.
  Comment: Inherent variability is great and reproducibility is fair.
  Invasive methods to measure uveoscleral outflow are:
  1. The tracer collection method;
  2. The indirect isotope method.

Episcleral venous pressure

- Episcleral venous pressure in healthy humans is 8 to 10 mmHg.
  Comment: It is affected by body position, inhalation of O_2, application of cold temperature and treatment with vasoactive drugs.

Comment: Episcleral venomanometry is used in clinical studies. This measurement is difficult to make and highly variable.

Comment: Direct cannulation is used in animal studies. This is an accurate, but invasive method.

Determinants of intraocular pressure

IOP is determined by the production, circulation and drainage of ocular aqueous humor. Parameters involved in the maintenance of IOP are aqueous flow, outflow facility, uveoscleral outflow and episcleral venous pressure.

Aqueous flow in health and disease

Aqueous flow averages about 2.9 µl/min in young healthy humans and 2.2 µl/min in octogenarians.[1] The difference between these values is a reduction of about 2.4% per decade. The age-related aqueous flow reduction does not appear to be of clinical significance. Aqueous flow also has a distinctive circadian rhythm. The flow rate at night during sleep is only 43% of the rate during the morning after awakening.[2]

The formation of aqueous humor involves several steps: a) Blood flowing to the ciliary processes; b) Ultra-filtration of plasma into the tissue spaces of the ciliary processes; c) Energy-dependent active secretion of aqueous from the non-pigmented epithelial cells into the posterior chamber of the eye against an oncotic pressure gradient. This creates a strong osmotic gradient and water follows the ions into the intercellular space. Nutrients and other substances necessary for the survival of the lens and cornea are added to this fluid by diffusion.

Drugs such as carbonic anhydrase, β-adrenergic antagonists and α_2-adrenergic agonists lower the intraocular pressure by reducing the aqueous flow rate, while others such as prostaglandins analogues and cholinergic drugs might cause a slight increase in aqueous production rate, but the effects are not clinically significant.

Aqueous flow does not appear to be affected by exfoliation syndrome, pigment dispersion syndrome, primary open angle glaucoma, or ocular hypertension.[1]

Intraocular inflammation may increase aqueous flow. However, this is difficult to quantify, as the breakdown of the blood-aqueous barrier makes fluorophotometry inaccurate by: a) increasing the amount of diffusional loss of fluorescein through iris vessels; and b) the increased concentration of proteins in the anterior chamber bind the fluorescein particles thus affecting its clearance. Experimental studies in primates with induced iridocyclitis found that the aqueous flow was reduced by half compared to control eyes,[3] but human studies on Fuchs' uveitic syndrome were equivocal.[4] In glaucomatocyclitic crisis,[5] aqueous flow is probably normal, but flow measurements may be inaccurate due to the presence of flare in the anterior chamber.

Aqueous flow can be altered in systemic diseases. In diabetes mellitus, aque-

ous flow may be reduced in correlation with the severity of diabetic retinopathy, age of onset, duration of diabetes and patient age. In myotonic dystrophy with ocular hypotony, it appears that aqueous flow is reduced, but this is not sufficient to account for the low IOP.[1]

Measurement of aqueous flow

The most practical technique of measuring aqueous flow in humans is by fluorophotometry using topical fluorescein as initially described by Jones and Maurice.[6] This method has some assumptions and a few limitations but it is a very well established method with good reproducibility.[7] The technique has been used in monkeys and for the most part, effects of various factors (drugs, aging) are similar between monkeys and humans.

Aqueous flow can be measured directly by assessing the rate of clearance of a tracer from the anterior segment. Under steady state conditions, aqueous flow is assumed to be equivalent to the rate of aqueous humor production. A corneal depot of fluorescein is established using topically applied drops. Fluorescein from the cornea diffuses into the anterior chamber, mixes with aqueous humor and drains through the anterior chamber angle.

The fluorophotometer measures fluorescein concentrations in the cornea and anterior chamber based on amount of fluorescence by an excitation light. Total fluorescein mass in the anterior segment is the product of the fluorescein concentrations in the cornea and anterior chamber and their respective volumes. Aqueous flow rate is calculated by measuring the mass of fluorescein lost from the cornea and anterior chamber over a time interval, divided by the average concentration in the anterior chamber.

Although aqueous flow rate can be calculated by measuring intraocular pressure, outflow facility, and episcleral venous pressure, along with some assumptions about non-pressure dependent flow, fluorophotometry is generally more reproducible with fewer sources of measurement error than tonography or episcleral venomanometry.

There are a number of limitations and assumptions associated with fluorophotometry. First, a rate of diffusion of fluorescein into the iris, limbal vessels and tear film must be assumed. Second, fluorescein is distributed uniformly throughout the anterior chamber and cornea. Third, a lens-iris barrier is present to block the egress of the tracer into the posterior chamber. This makes fluorophotometry unreliable in pseudophakia or in eyes with previous iridotomy or iridectomy as well as in eyes with a dilated pupil. A further limitation is that fluorophotometry necessarily measures aqueous flow over a time interval. Because of the rate of fluorescein clearance and the limits in precision of fluorescence, measurement intervals are at least 30 minutes in human studies. Short-term fluctuations in aqueous flow of less than 30 minutes would not be detected.

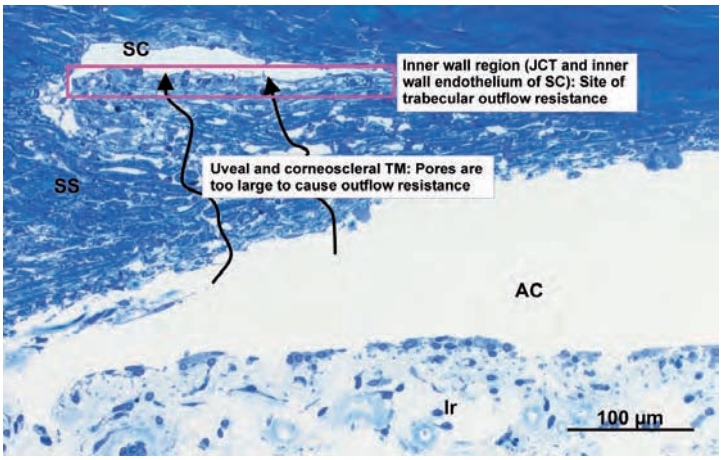

Fig. 1. Light micrograph of the chamber angle (semithin section, Richardson's stain; photography by Ernst R. Tamm). Black arrows indicate the outflow pathways of the aqueous humor through the trabecular meshwork (TM). The boxed area indicates the inner wall region. TM = trabecular meshwork; JCT = juxtacanalicular connective tissue; SC = Schlemm's canal; SS = scleral spur; AC = anterior chamber; Ir = iris.

Trabecular outflow

The trabecular outflow pathway is comprised of the trabecular meshwork (consisting of the uveal and corneoscleral meshworks), the juxtacanalicular connective tissue, the endothelial lining of Schlemm's canal, the collecting channels and aqueous veins. After having passed through the trabecular outflow pathways, aqueous humor drains into the episcleral venous system. Experimental evidence and theoretical predictions indicate that little if any significant trabecular outflow resistance in the normal eye is found in the uveal and corneoscleral meshwork, Schlemm's canal, or the collector channels and aqueous veins. In contrast, there is considerable evidence that normal aqueous humor outflow resistance resides in the inner wall region of Schlemm's canal.[8,9]

The inner wall region is comprised of the inner wall endothelium of Schlemm's canal, its basement membrane, and the adjacent juxtacanalicular (cribriform, subendothelial) connective tissue. The exact structural location of trabecular outflow resistance in the inner wall region is unclear. As of today, there is active debate and research regarding the specific role of the inner wall endothelium of Schlemm's canal or the juxtacanalicular connective tissue for the formation of trabecular outflow resistance.

The inner wall endothelium has one of the highest hydraulic conductivities in the body, comparable only to that of fenestrated endothelia. In addition, it allows passage of microparticles 200-500 nm in size. The most likely explanation for this is the presence of micron-size pores in the inner wall endothelium,

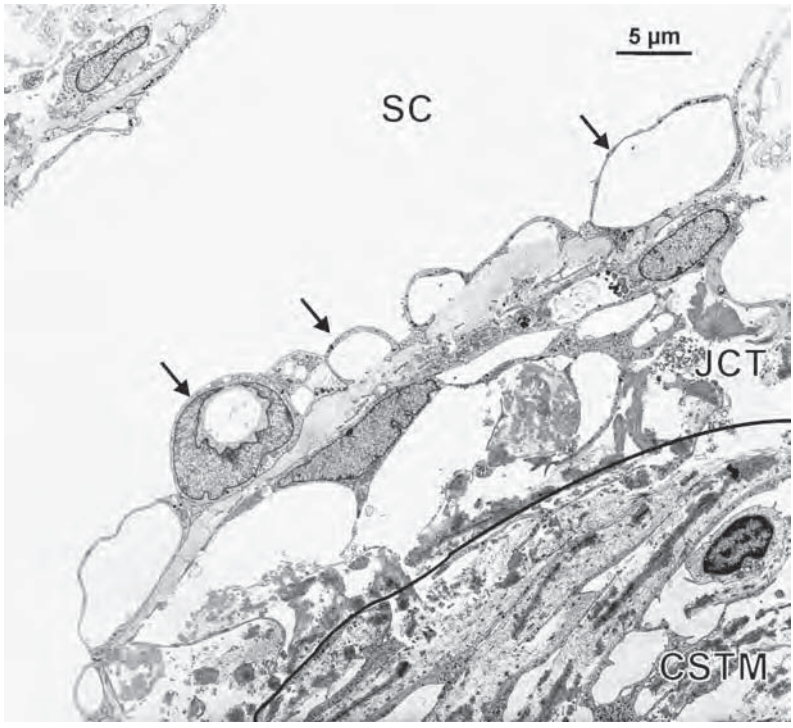

Fig. 2. Electron micrograph of the inner wall region (photography by Ernst R. Tamm). The black line separates the corneoscleral trabecular meshwork (CSTM) from the juxtacanalicular connective tissue (JCT). Arrows indicate the inner wall endothelium of Schlemm's canal (SC). The endothelium forms characteristic outpoutchings ('giant vacuoles') in response to aqueous flow.

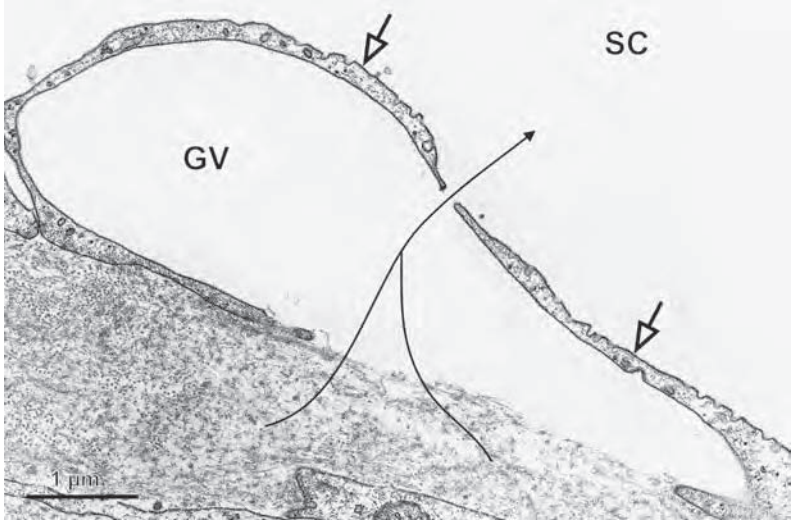

Fig. 3. Electron micrograph of an inner wall cell (open arrows) of Schlemm's canal (SC) endothelium (photography by Ernst R. Tamm). The black arrow indicates the flow of aqueous humor through a pore in the endothelial cell. The pore is associated with a giant vacuole (GV) that forms in response to aqueous flow.

which have been identified by scanning and transmission electron microscopy. The fluid resistance generated by the pores in electron microscopy specimens accounts for only a small fraction of the measured trabecular outflow resistance. However, more recent experiments indicate that the number of pores increases with the amount of fixative perfused through an enucleated eye and that the total number of pores identified by electron microscopy is likely smaller in the living eye.

The juxtacanalicular connective tissue has many open spaces that should serve as pathways for aqueous humor. Morphometric analyses combined with theoretical calculations indicate that these apparently open spaces would generate an insignificant fraction of outflow resistance, unless they are filled with extracellular matrix material.[10] Indeed, more extracellular matrix was seen with quick-freeze deep-etch electron microscopy than with conventional electron microscopy.[11] The amount of extracellular matrix in the juxtacanalicular tissue increases with age. So far, specific extracellular components in the open spaces of the juxtacanalicular connective tissue that are responsible for aqueous humor outflow resistance have not been identified. Funneling of aqueous humor into the pores of the inner wall endothelium may result in a greater outflow resistance since the fluid would pass through a smaller volume of extracellular matrix.

There is experimental evidence that cells in the trabecular meshwork very likely influence the hydraulic conductivity of the inner wall region and outflow resistance by modulating extracellular matrix turnover[12] and/or by actively changing cell shape and altering the geometry of the aqueous humor outflow pathways.[13,14] In addition, trabecular outflow is under the influence of ciliary muscle tone, as the anterior tendons of the muscle are connected with extracellular fibrils in the juxtacanalicular region and to the inner wall endothelium. Ciliary muscle contraction mechanically deforms this region in such a manner as to decrease the region's overall resistance to fluid flow.

Outflow facility in health and disease

Outflow facility in healthy human eyes is in the range of 0.1 to 0.4 µl/min/mmHg.[15-19] By tonography or perfusion of enucleated human cadaver eyes, trabecular outflow resistance has been shown to increase with aging.[20] No age-related changes have been observed by fluorophotometry.[18]

IOP lowering drugs that increase outflow facility are cholinergic agonists and some adrenergic agonists.[21,22] Prostaglandin analogues also appear to increase outflow facility.[23-25]

Outflow facility is reduced in primary open angle glaucoma, ocular hypertension, and exfoliation and pigment dispersion syndromes with accompanying ocular hypertension. When IOP is normal in these syndromes, outflow facility is normal.

A characteristic structural change of the trabecular outflow pathway in chronic open-angle glaucoma is an increase in extracellular material in the juxtacana-

licular connective tissue.[26] The material is referred to as sheath-derived plaque material, as it involves mainly the sheaths of elastic fibers which form a network underneath the endothelial lining of Schlemm's canal. While the amount of sheath-derived -plaque material correlates with glaucomatous axonal damage in the optic nerve, it does not correlate with intraocular pressure indicating that the material alone is not causative for the increase in trabecular outflow resistance in chronic open-angle glaucoma.[27] Another structural change in chronic open-angle glaucoma involves the number of pores in Schlemm's canal endothelium, which is decreased significantly from normal eyes, even after accounting for the volume of fixative perfused.[28] A specific molecular and/or structural component and/or functional mechanism that is responsible for increased trabecular outflow resistance in chronic open-angle glaucoma has not been identified.

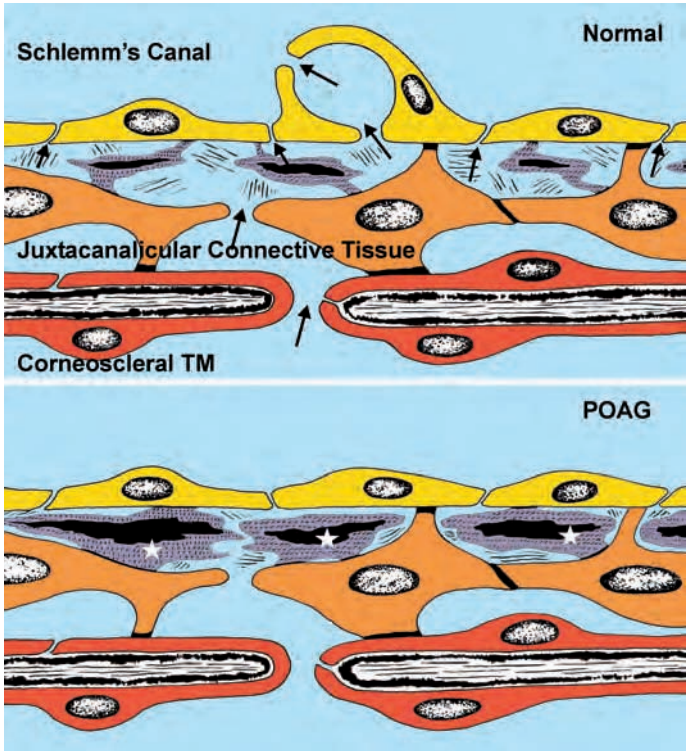

Fig. 4. Schematic drawing of the outer parts of the trabecular meshwork (TM) in normal eyes and in those with POAG. Aqueous humor enters the juxtacanalicular connective tissue (JCT) and flows into Schlemm's canal through pores in the endothelial lining that are often associated with giant vacuoles (arrows). In POAG, the pathways for the aqueous humor in the JCT become smaller, as there is an increase in extracellular plaque material that mainly derives from the thickend sheaths of the JCT elastic fibers (asterisk). (From Tamm 2004, in Glaucoma Therapy, Eds. Shaarawy and Flammer, published by Martin Dunitz, Taylor and Francis Group, London and New York.)

Measurement of outflow facility

There are several techniques for quantifying outflow facility. In clinical studies, tonography and fluorophotometry are used. Tonography includes trabecular outflow facility, uveoscleral outflow facility (considered to be small) and pseudofacility (also considered to be small) in the measurement. Tonography measures a reduction in IOP from application of a weight over two to four minutes, and estimates a corresponding change in aqueous flow. The fluorophotometric method directly measures IOP and aqueous flow and a change in IOP and aqueous flow following application of an aqueous flow suppressant. Although this measurement avoids pseudofacility and scleral rigidity, the measurement takes several hours to complete and is more variable than tonography. Also it does not work well in ocular normotensive volunteers who do not have much change in aqueous flow and IOP by the aqueous flow suppressant.

Tonography and fluorophotometry also are used in animal studies but the methods were designed for human eyes and work best in humans who do not require anesthesia for the measurement. Invasive methods are used often in animal studies, including two-level constant-pressure perfusion. The invasive methods have inherently less variability than the non-invasive techniques, but anesthesia and insertion of needles into the anterior chamber precludes their use in living human eyes, although the methods can be used in enucleated human cadaver eyes. The invasive nature of the perfusion methods precludes their frequent repetitive use at short intervals in animals. Further, to measure trabecular, rather than simple total facility, involves more complex techniques, with higher variability.

Uveoscleral outflow

Compared to the trabecular outflow pathway, the uveoscleral outflow pathway is anatomically less well defined and understood. This pathway also has been called ‘nontrabecular’, ‘uveo-vortex’ or ‘unconventional’. The significance of this drainage pathway was first described by Anders Bill, who observed that large tracers, as markers of bulk flow, exited the anterior chamber through the ciliary body into the supraciliary space and out through the sclera into the extraocular tissues.[29] Fluid in this pathway ultimately drains into the lymphatic system. It should be stressed that, normally, most constituents of aqueous flow probably never pass through the sclera but are absorbed into the suprachoroidal space.

Uveoscleral outflow often is described as pressure independent because uveoscleral outflow does not depend on intraocular pressure to the same extent as trabecular outflow. However, no flow is pressure independent. There is a pressure gradient, although very small, for flow from the anterior chamber into the supraciliary space and suprachoroidal space. Bill initially observed the relative pressure-independence of uveoscleral outflow in the primate eye, in which uveoscleral outflow changed little at IOPs from the normal to high range (11-35 mmHg).[30] It is not known how such a change in intraocular pressure affects the

pressure gradient between the anterior chamber and the suprachoroidal space, but the effect is probably small explaining the seeming 'pressure-independence' of uveoscleral flow. When IOP is sufficiently low (4 mmHg in monkey eyes), uveoscleral outflow is pressure-dependent.

Uveoscleral outflow in health & disease

Calculated uveoscleral outflow is 25-57% of total aqueous flow in young healthy subjects 20-30 years of age and it decreases as one ages.[31-33] Uveoscleral outflow is reduced in ocular hypertension with and without exfoliation syndrome, and increased in uveitis. It is unchanged in pigmentary dispersion syndrome and unknown in diabetes and primary open-angle glaucoma.[3,19,34,35] Clinically available IOP lowering drugs that increase uveoscleral outflow are prostaglandin analogues and some adrenergic agonists.[31,33,36-38]

Uveoscleral outflow methods of measurements

In clinical studies, uveoscleral outflow is calculated from the modified Goldmann equation. Inherent variability is great and reproducibility is fair. New noninvasive techniques are needed to improve accuracy. These are not yet available.

More accurate methods to measure uveoscleral outflow are invasive and used only in research animals. Two methods are available. 1). The tracer collection method involves infusing a radioactive or fluorescent tracer into the anterior chamber at a specific pressure and for a specific time. The eyes are enucleated and the amount of tracer found in the uvea and sclera during that time is used to calculate uveoscleral outflow. The sacrifice of the animal makes this method non-repeatable. 2). The indirect isotope method involves infusing a radioactive tracer in the anterior chamber and monitoring the appearance rate of the tracer in the blood (an indication of trabecular outflow) and the disappearance rate of tracer from the anterior chamber (an indication of aqueous flow). Uveoscleral outflow is calculated as the difference between aqueous flow and trabecular outflow. This method does not involve sacrifice of the animal and changes in uveoscleral outflow can be assessed over time.

Episcleral venous pressure

Episcleral venous pressure in healthy humans is in the range of 7 to 14 mmHg,[39] with values between 9 and 10 mmHg being reported most often. This is the only component of aqueous humor dynamics that is affected by body position. Episcleral venous pressure increases by 3.6 mmHg by changing body position from seated to supine. This pressure appears to be relatively stable when body position does not change and the magnitude of any change in episcleral venous pressure is relatively small. A change in episcleral venous pressure of 0.8 mmHg corresponds to a change in IOP of 1 mmHg. Episcleral venous pressure also

Table 1. Summary of receptor and enzyme effects on aqueous humor dynamics

Receptor	Effect on inflow	Effect on outflow	Effect on IOP	Comments
α_1-adrenergic	↑		↑	
α_2-adrenergic	↓		↓	
β-adrenergic	↑		↑	(mainly β_2)
D_1-dopaminergic	↑	↓ (C?)	↑	
D_2-dopaminergic	↓		↓	
5-HT_{1A}	↓		↓	
5-HT_{2A}	↑		↑	
M_3-cholinergic		↑ (C)	↓	
FP (PGF_{2a} receptor)		↑ (U&C)	↓	Evidence suggests that both C and U are involved[41]
TP (TXA_2 receptor)		↑ (C)	↓	
AT_1 (angiotensin II receptor)		↓ (U)	↑	Indirect evidence based on AT_1 receptor antagonist (sartans) studies[42]

Enzyme	Effect on inflow	Effect on outflow	Effect on IOP	Comments
Carbonic anhydrase	↑		↑	
Cholinesterase		↓ (C)	↑	
PKA (Protein Kinase A)	↑	? (C)	?	
PTK (Protein Tyrosine Kinase)		↓ (C)	↑	
Rho kinase	↓	↓	↑	Indirect evidence based on rho kinase inhibitor studies[43]

- ↑, ↓ indicate increase or decrease of inflow/outflow/IOP
- Abbreviations in the outflow column, C = Conventional, U = Unconventional or Uveoscleral, ? = "Not known"
- The Comments column includes any relevant additional info (like references, species-specificity, *in-vivo* data only, etc…)

is affected by inhalation of O_2, application of cold temperature and treatment with vasoactive drugs.

Episcleral venous pressure is difficult to measure. Visualization of an appropriate vessel and determination of the precise pressure at which the vessel collapses are the major problems with the measurement. Reproducibility is poor. Episcleral venomanometry is used in clinical studies.[40]

Issues requiring further attention

1. The issue of the pressure independence of uveoscleral outflow was discussed extensively. The value of the facility of uveoscleral outflow is low, but it is believed by some to be increased by topical prostaglandins. There is little direct evidence supporting the prostaglandin effect. This is more of a basic science than a clinical issue, but elucidating this and other factors affecting aqueous humor dynamics will help explain syndromes, drugs and surgeries that affect IOP.

2. A possible increase in permeability of iris vessels in diseases such as diabetes and exfoliation syndrome may interfere with the measurement of aqueous flow. Effects of flare on the measurement of aqueous flow need to be studied further to answer the question: To what extent does a disease violate the assumptions behind the techniques used to study aqueous humor dynamics?
3. Is there a diurnal or seasonal rhythm of outflow facility or uveoscleral outflow? Evidence suggests that there is no nocturnal change in outflow facility in young healthy subjects. How is the normal rhythm affected by various diseases?
4. The mechanism of inflow needs further discussion.
a. Neural and hormonal factors, beta-adrenergic, catecholaminergic mechanisms
b. Role of carbonic anhydrase, Na/K ATPase, etc.
c. Central nervous system centers such as suprachiasmatic nucleus, the center of clock genes and light perception.
d. blood flow, oncotic pressures, osmotic pressures

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Ernst Tamm presenting the section on basic science

Basic science consensus panel. From left to right: Jonathan Crowston, George Lambrou, Sheng Lim, Carol Toris and Achim Krauss.

From left to right: Makoto Araie, Ted Garway-Heath, Robert N. Weinreb, James Brandt and Ernst Tamm.

Basic science consensus panel: From left to right: Makoto Aihara, Jonathan Crowston, George Lambrou, Sheng Lim, Carol Toris and Achim Krauss.

Presentation of consensus points for the basic science section.

MEASUREMENT OF INTRAOCULAR PRESSURE

Ted Garway-Heath, Aachal Kotecha, Fabian Lerner, Volkan Dayanir, Jamie Brandt, Jay Pepose, David Pye, Cynthia Roberts, Ahmed Elsheikh and Nathan Congdon

Ted Garway-Heath

Contributors: Andreas Boehm, Jamie Brandt, Nathan Congdon, Volkan Dayanir, Ahmed Elsheikh, Ronnie George, Ted Garway-Heath ,Daniel Grigera, Jesper Hjortdal, Kenji Kashiwagi, Aachal Kotecha, Fabian Lerner, Jeffrey Liebmann, Baskaran Mani, Felipe Medeiros, Jay Pepose, David Pye, Cynthia Roberts, Sunil Shah, Robert Stamper, Lingling Wu

Consensus points

- On average, greater central corneal thickness (CCT) results in overestimation of intraocular pressure (IOP) as measured by Goldmann applanation tonometry (GAT).
  Comment: The extent to which CCT contributes to the measurement error (in relation to other factors) in individual patients under various conditions has yet to be established.
- Compared to GAT, CCT has a lesser effect on IOP measured by dynamic contour tonometry (DCT) and the ocular response analyzer (ORA) (corneal compensated IOP). CCT has a greater effect on IOP measured by NCT and Rebound Tonometry.
- Currently we have insufficient evidence comparing different tonometers in the same population. However, there are some data to suggest that Goldmann applanation tonometry is more precise (lowest measurement variability), compared to other methods.
- Precision and agreement of tonometry devices should be reported in a standardized format:
  – Coefficient of repeatability (for intra-observer variation)
  – Mean difference (or difference trend over range) and 95% limits of agreement (for inter-observer and inter-instrument differences)

Intraocular Pressure, pp. 17-54
edited by Robert N. Weinreb, James D. Brandt, David Garway-Heath and Felipe A. Medeiros

Comment: Under ideal circumstances for measurement, precision figures reported for GAT are:
- Intraobserver variability: 2.5 mmHg (two readings by the same observer will be within this figure for 95% of subjects)
- Interobserver variability: ± 4 mmHg (95% confidence limits either side of mean difference between observers)
- In clinical practice these figures may be considerably higher
- Intra-class correlation coefficients are not clinically useful

- Currently there are no data to support a specific frequency of calibration verification for GAT.
  Comment: The frequency for verification of GAT calibration of at least twice yearly is suggested.
  For clinical research, a verification error > ± 1 mmHg should be the threshold to send the tonometer for recalibration; the threshold for clinical practice may be higher and requires a cost-benefit analysis.
- Correction nomograms that adjust GAT IOP based solely on CCT are neither valid nor useful in individual patients.
  Comment: a thick cornea gives rise to a greater probability of an IOP being over-estimated (and a thin cornea of an IOP being under-estimated), but the extent of measurement error in individual patients cannot be ascertained from the CCT alone.
- Measurement of CCT is important in assessing risk for incident glaucoma among ocular hypertensives in the clinical setting, though the association between CCT and glaucoma risk may be less strong in the population at large.
- The corneal modulus of elasticity likely has a greater effect on GAT IOP measurement error than CCT, especially with corneal pathology and after corneal surgery.
  Comment: The corneal modulus of elasticity increases with age, thus generating artifactual increases in Goldmann tonometry with age.
  Comment: A higher modulus of elasticity is associated with greater stiffness.
- Consideration of corneal visco-elasticity is essential for determining the ocular mechanical resistance to tonometry and hence improving the accuracy of IOP measurement.
  Comment: Corneal aging affects the visco-elasticity of the tissue and adds another layer of complexity to determining the mechanical resistance of the cornea to tonometry.
- Large amounts of corneal edema produce an underestimation of IOP when measured by applanation tonometry.
  Small amounts of corneal edema (as induced by contact lens wear) probably cause an overestimation of IOP.
- To obtain a GAT measurement, which is relatively unaffected by daytime changes in CCT, the patient should desirably have been awake with his/her eyes open for at least two hours prior to the measurement being made.

- The wearing of contact lenses on the day when tonometry is performed may lead to an artifactually raised IOP as measured by GAT.
  Comment: contact lens wearing patients should have tonometry performed after having been awake, without contact lenses, for at least two hours for contact lens-induced and diurnal corneal edema to resolve.
- There are changes in corneal biomechanics following many forms of keratorefractive surgery, associated with a mean fall in IOP as measured by applanation tonometry.
  Comment: Although there is a mean fall across patients in measured IOP, there is a wide variability in response.
- DCT and the ORA (corneal compensated IOP) may both be less sensitive to changes in corneal biomechanics following keratorefractive surgery and have less variance than standard applanation tonometry.
- The use of a lid speculum, sedatives and general anesthetics can significantly affect IOP measurement in children, and tonometers vary in their accuracy in pediatric eyes.
  Comment: The clinician should adopt a consistent protocol for the measurement of IOP in children so that through experience the 'normal' range for their protocol can be determined.

A. Techniques

i. Physics and engineering assumptions underlying tonometric techniques

Tonometers covered in this section:
1. Goldmann applanation tonometry
2. Pneumotonometry (ocular blood flow tonometry)
3. Non-contact tonometry
4. Tonopen
5. Pascal Dynamic Contour tonometer
6. Rebound tonometry

The minimum requirements and the design compliance procedures for tonometers intended for routine clinical use are specified in the International Organization for Standardization, report 8612.[1]

1. Goldmann applanation tonometry

Tonometer principle
The Goldmann applanation tonometer (GAT) was introduced in 1957 by Hans Goldmann and Theo Schmidt. The optimum design for the tonometer tip was derived from empirical experimentation.[2] The Imbert-Fick principle, which is often quoted as being used to determine the tonometer dimensions by Goldmann, was in fact invoked to explain the theory behind applanation tonometry. The

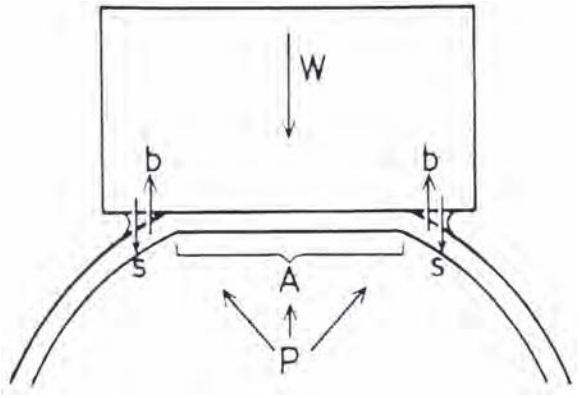

Fig. 1. Representation of forces involved during applanation tonometry. (Key: W = tonometer force; s = surface tension of pre-corneal tear film; P = intraocular pressure; A = area of applanation; b = corneal rigidity/ resistance to bending.)

Imbert-Fick principle states that the pressure *(P)* of a body of fluid encapsulated within a sphere is directly proportional to the force *(W)* required to applanate an area *(A)* of the sphere:

$$W = PA \tag{1}$$

The principle assumes that the surface encapsulating the sphere under examination is infinitely thin, perfectly elastic, perfectly dry and perfectly flexible and that the only force being exerted upon it is the force from the applanating surface. In reality, none of these are true when applied to the cornea.

Goldmann recognised that having a finite corneal thickness, a measurable corneal rigidity and the capillary attraction forces of the pre-corneal tear film would affect the accuracy of the tonometer. It was also acknowledged that a variation in central corneal thickness (CCT) would affect the accuracy of intraocular pressure (IOP) readings, but it was felt that in the absence of corneal pathology, the CCT did not vary much around 500 μm. Based on these assumptions, a modification of the Imbert-Fick principle was devised that included factors to consider the resistance of the cornea to applanation and the surface tension of the tear meniscus surrounding the tonometer prism during measurement:

$$W + s = PA + b \tag{2}$$

Where W = tonometer force; s = surface tension of pre-corneal tear film; P = intraocular pressure; A = area of applanation; b = corneal rigidity/ resistance to bending (see also Fig. 1).

With this formula it was determined that on applanating an external corneal area of approximately 7.35 mm^2, the effects of corneal rigidity and tear film surface tension forces would cancel (Fig. 1). In addition, a force of 0.1 grams

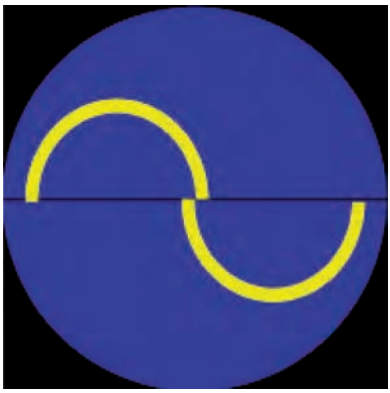

Fig. 2. Correct mire alignment in GAT

would correspond to an IOP of 1 mmHg.

Operating procedure
The GAT is available as a slit-lamp mounted or hand-held device. Correct usage is given in the operating manual.[3] Corneal anaesthesia is required. The use of fluoroscein sodium is a prerequisite for correct IOP reading: the tears fluoresce in a colbalt blue light, making it easier to determine the area applanated. The slit lamp illumination arm is positioned at an angle to the observation arm to maximise illumination of the tonometer head. The instrument is brought closer to the eye until corneal contact is made. When viewed through the slit lamp, a biprism within the tonometer tip splits the image seen into two semicircular rings. The height of the slit lamp is raised or lowered so that the semi-circles are equal in size. A dial on the side of the tonometer is adjusted to vary the force applied to the eye. This causes a movement of the rings towards or away from each other. The correct area is applanated when the inner edges of the semi-circles touch (Fig. 2).

2. Pneumatonometry

Tonometer principle
The principle of using a pneumatic device to measure IOP was first described by Durham and coworkers in 1964,[4] with modifications being developed by Langham in 1969.[5] The pneumatonometer is a contact applanation tonometer that consists of four main components:

- A sensor that responds to IOP when applied to the cornea;
- A transducer that converts the pneumatic signal to an electrical signal;
- A combined amplifier and recorder that amplifies the signal and provides a readout of the signal recorded;
- An air supply unit that supplied compressed air to the tonometer probe.

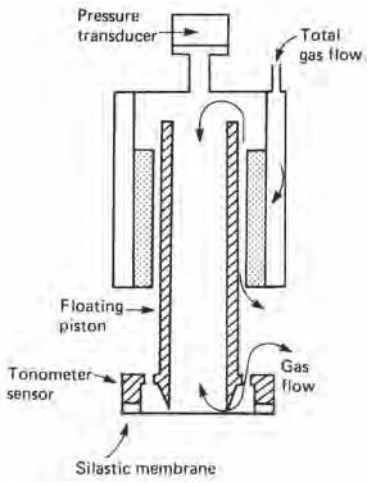

Fig. 3. Principle of pneumatonometer probe (adapted from Langham5)

The probe has a hollow central tube flanked circumferentially by side exhausts. The probe tip is covered by a flexible inert silicone elastomer diaphragm (Silastic membrane) which comes into contact with the cornea. A constant flow of air is passed through the central tube, forcing a small gap between the diaphragm and probe edge forcing air out through the side exhausts. When placed against cornea, the force of air eventually results in the cornea being applanated to the edge of the probe, forcing the membrane gap to close. Air pressure within tube rises until it balances the IOP and membrane mechanics of the cornea, at which point air can escape. At this point, the air pressure within the tube is proportional to the IOP (Fig. 3). The pneumatonometer is also able to measure the fluctuations in IOP caused by the cardiac cycle. These variations are manifestations of ocular blood flow and are recorded as the ocular pulse amplitude (OPA).

Operating procedure

The OBF tonometer is a slit-lamp mounted device and requires corneal anaesthesia prior to IOP measurement. A disposable tip is placed over the pneumatic probe. When the probe tip is in contact with the cornea, a whistling sound indicates good contact. The pitch varies with the ocular pulse. A minimum of 7 cycles is required for an adequate OBF reading.

Up to 20 subjects should be examined to obtain sufficient experience with the device.[6]

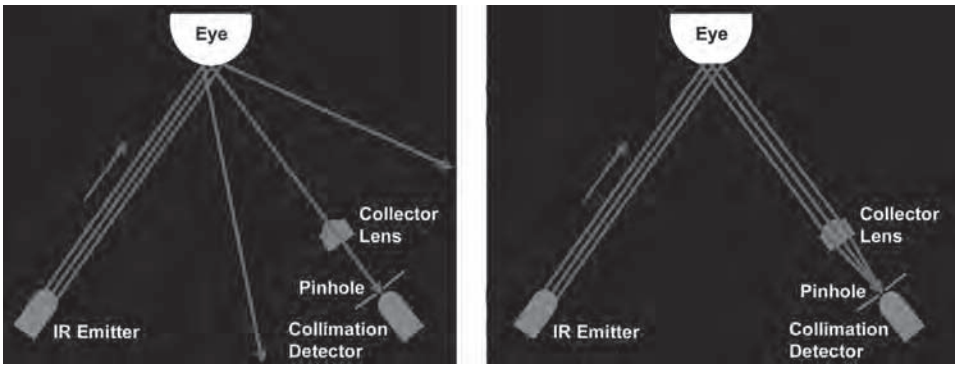

Fig. 4a and b. Non-contact tonometer principle.

3. Non-contact tonometry

Tonometer principle

The non-contact tonometer (NCT) was developed by Grolman in the early 1970's and uses a jet of air to applanate the anterior corneal surface.[7]

The system consists of a central air plenum flanked either side by a light emitter and detector. When the cornea is in the resting state, light emitted is scattered by the convex corneal surface. As the pressure of the air pulse directed to the cornea increases to deform the cornea, the corneal surface behaves like a plane mirror reflecting light to the detector. At the point of maximal light detection, when the cornea is completely applanated, the instrument switches off the air pressure pulse (Fig. 4a and 4b).

The first generation NCT's determined IOP from the time it took for the air jet to applanate the cornea. With the introduction of the pressure transducer in the late 1980's, the instrument was refined so that the IOP was determined from the actual air jet pressure required to applanate the cornea.[8] This facilitated the use of a more gentle airjet that could be ramped and terminated when the point of applanation was reached.

Corneal anaesthesia is not necessary. In addition, particularly with the newer generation models, the NCT is simple to use and requires minimal training to master.

The Reichert Ocular Response Analyser (ORA)

The Ocular Response Analyzer (ORA; Reichert Corporation; New York, USA) measures the corneal response to indentation by a rapid air pulse. The principles of the ORA are based on those of non-contact tonometry. A metered air-pulse is directed at the cornea until an applanation event is reached. This first 'force-in' applanation acts as a trigger to switch off the air-pulse, after a small further increase in air pressure which causes a degree of corneal indentation. The air pressure steadily reduces until it is completely removed. The instrument makes

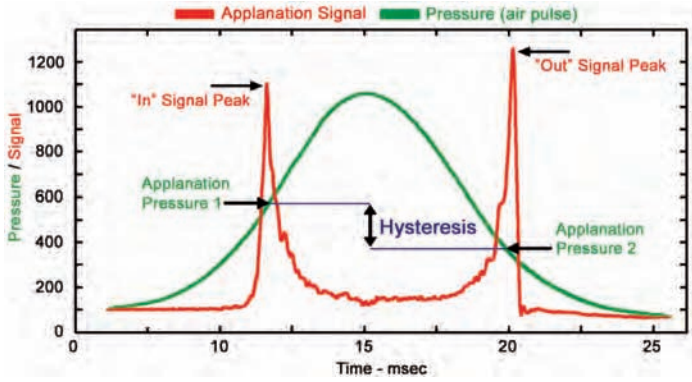

Fig. 5. Signal/applanation plot from Reichert ORA. The difference between the 'inward' applanation and 'outward' applanation is termed *corneal hysteresis*. (Copyright © 2004 Reichert Inc.)

two measurements – the force required to flatten the cornea as the air pressure rises ('force-in' applanation, P1) and the force at which the cornea becomes flat again as the air pressure falls ('force-out' applanation, P2). The second applanation occurs at a lower pressure than the first, and this has been attributed to the dampening effects of the cornea. The difference between the two pressures is termed *corneal hysteresis* (Fig. 5). Corneal hysteresis is a direct measure of the biomechanical properties of the cornea and may more completely describe the contribution of corneal resistance to IOP measurements than CCT alone.[9,10]

The ORA produces two measurements of corneal biomechanical properties, corneal hysteresis (CH) and the corneal response factor (CRF). Whilst CH represents the absolute difference between the applanation pressures P1 and P2, the CRF is derived from the formula (P1- *k*P2), where *k* is a constant. It has been suggested that CH predominantly reflects the viscous properties of the cornea, whilst CRF better reflects the elastic properties.[11]

4. The Tono-pen

Tonometer principle

The Tonopen is based on the principle of the MacKay-Marg tonometer. The device consists of a central 1.02-mm diameter moveable plunger surrounded by a larger footplate. Pressing the instrument tip against the cornea activates a strain gauge that senses the force generated by the plunger to applanate the central cornea. As the rest of the tonometer comes into contact with the cornea, the force exerted on the plunger reduces until the plunger is flush with the footplate. The effect of corneal rigidity is transferred to the surrounding footplate and at that point the force exerted on the plunger is considered to be only the IOP. This change in force generates a waveform tracing which is analysed by a microprocessor.

Operating procedure
The device requires corneal anaesthesia for measurements. Disposable tips are changed between patients. The Tonopen is hand held and positioned upon the central cornea. When the instrument has generated a satisfactory waveform, an audible click is sound, and the operator repeats small pecking movements onto the cornea until six to ten readings are accepted. These are automatically averaged and a digital display provides the final reading along with the percentage variability between the highest and lowest value.[12]

5. The Pascal® Dynamic Contour Tonometer

The Pascal® Dynamic Contour Tonometer (DCT; Swiss Microtechnology® AG, Port, Switzerland) was first introduced in 2002. The design purpose was to develop a non-invasive and direct method for IOP measurement that would be relatively unaffected by the inter-individual variations of corneal biomechanics. The tonometer is a non-applanating, slit-lamp mounted, contact tonometer (Fig. 6).

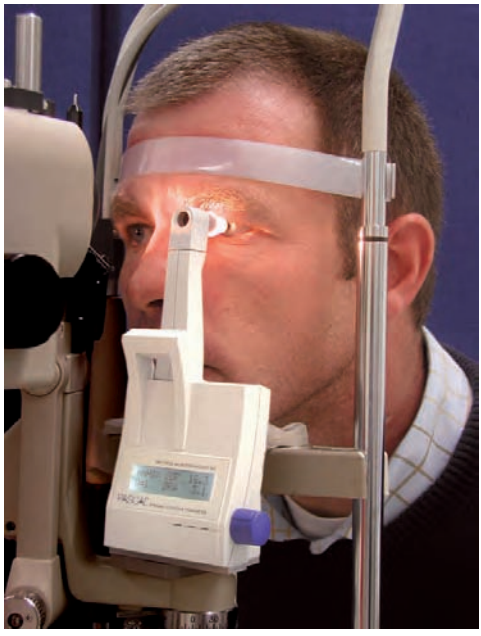

Fig. 6. Pascal DCT

Tonometer principle
The principle is based on contour matching, which assumes that if the eye were enclosed by a contoured, tight fitting shell, the forces generated by IOP would act on the shell-wall. Replacing part of the shell-wall with a pressure sensor would enable measurement of these forces and therefore the IOP.[13]

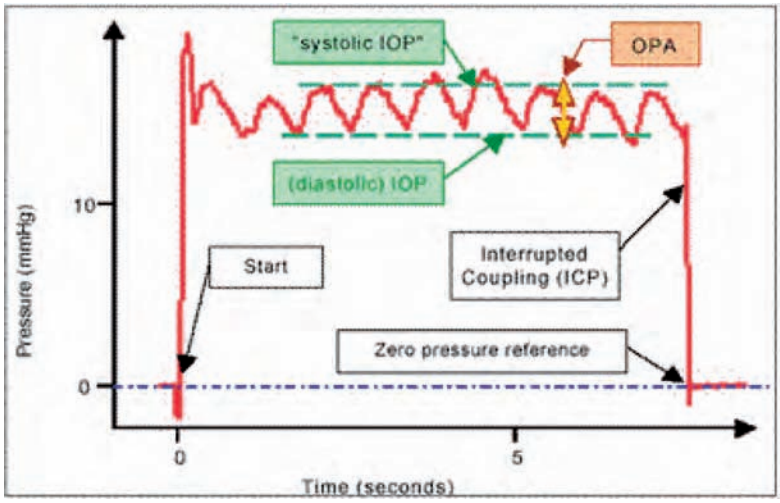

Fig. 7. Pressure curve from DCT recording. The instrument displays the diastolic IOP and ocular pulse amplitude.

The DCT has a contoured tonometer tip surface that aims to match the contour of the cornea. The radius of curvature of the tip is 10.5 mm with a contact surface of approximately 7 mm diameter. A piezoresistive pressure sensor of diameter ~1.2 mm is integrated flush within the contour surface, enabling trans-corneal measurements of the anterior chamber fluid pressure. The tip is mounted into housing, similar to that used for GAT, which provides a constant appositional force of 1 g.

IOP readings are sampled at 100 Hz and data are computed with a resolution of 0.1 mmHg.

The *diastolic* IOP is displayed on a LCD screen within the housing. The dynamic sampling of IOP also yields pressure curves from which the OPA is determined (Fig. 7). The OPA value displayed on the LCD screen is a peak-to-peak difference of the average systolic IOP and average diastolic IOP, in units of mmHg. The DCT provides an audible signal, the pitch of which modulates regularly, indicating pulse oscillations.

Operating procedure

Corneal anaesthesia is required. A disposable silicone tip is placed on the tonometer head, and is changed between patients.

A minimum of five cardiac cycles need to be recorded for an adequate reading, although between five and eight cycles is recommended. Once adequate measurements are obtained, the LCD display will generate an IOP and OPA value (in mmHg), and a ‘quality score’. Readings of value ‘1’ and ‘2’ only should be accepted, although the manufacturer reports that readings up to quality ‘3’ are acceptable. Readings of ‘4’ or ‘5’ should be discarded.

6. Rebound tonometry

Tonometer principle

Rebound tonometry uses a dynamic electromechanical method for measuring IOP. The device consists of two coils, a solenoid propelling coil and a sensing coil positioned around a central shaft containing a lightweight magnetised probe. The application of a transient electrical current to the solenoid coil propels the probe to the cornea. This movement of the magnetised probe induces a voltage within the system which is monitored by the sensor, allowing the speed and direction of probe movement to be determined. As the probe impacts cornea, it decelerates and rebounds from surface; deceleration is less at low compared with high IOPs and consequently the higher the IOP.

A commercially available rebound tonometer, the ICare, became available in 2003.[14]

Operating procedure

No corneal anaesthesia is required. The instrument is a hand-held device and on activation of the measurement button automatically takes 6 readings of IOP, automatically discarding the highest and lowest reading before presenting a digital readout of the average IOP.

ii. Tonometer calibration verification

Calibration verification of GAT

GAT is the reference standard for measuring IOP. As with all machines, GAT needs proper periodic calibration. The calibration procedure is covered in the Goldmann Applanation Tonometer Instruction Manual.[3]

- Technique: GAT comes with a steel weight bar that has a stationary base and a slide. The slide has marks for 0 (the middle mark), 2 (marks on both sides of the middle mark) and 6 (marks that are most distal) grams (corresponding to 0, 20 and 60 mmHg) on it. The calibration is done for 0, 20 and 60 mmHg by mounting the steel weight bar slide into its home on the side of the GAT.

  0 mmHg calibration: Steel weight bar may or may not be used since not mounting the steel weight bar corresponds to 0 gr weight. If the steel weight bar is used, the slide is adjusted so that the middle mark on the bar corresponding to 0 mmHg is aligned with the mark on the stationary base. With the tonometer tip mounted, the GAT dial is turned and stopped at the 0 mmHg mark. The dial is then first turned to +0.5 mmHg where the tonometer tip is expected to tilt towards the patient and then turned to –0.5 mmHg where the tonometer tip is expected to tilt towards the examiner.

  20 mmHg calibration: The steel weight bar slide is slided towards the examiner and stopped at the next closest mark corresponding to 2 gr (20 mmHg). The GAT dial is turned and stopped at the 20 mmHg mark. The dial is then first turned to +0.5 mmHg where the tonometer tip is expected to tilt

towards the patient and then turned to -0.5 mmHg where the tonometer tip is expected to tilt towards the examiner.

60 mmHg calibration: The steel weight bar slide is slided towards the examiner and stopped at the most distal mark corresponding to 6 gr (60 mmHg). The dial is then first turned to +1.0 mmHg where the tonometer tip is expected to tilt towards the patient and then turned to -1.0 mmHg where the tonometer tip is expected to tilt towards the examiner.

- Magnitude of calibration verification error: The calibration verification error, recommended by the manufacturer should ideally be within ± 0.5 mmHg. The SEAGIG guidelines suggest ± 2 mm Hg is acceptable.[15] Anything outside this range should be considered faulty and the tonometer sent for re-calibration. Wessels and Oh reported 81% out of 185 tonometers used by sole practitioners were within ± 0.5 mmHg.[16] While Sandhu and colleagues reported 0 to 10.3% tonometers at ± 0.5 mmHg error range in institutional tonometers.[17] In the longitudinal study by Sandhu, calibration drift was evaluated. Tonometers were sent for re-calibration if the verification error (range about a mid point) was greater than ± 0.5 mmHg. Ten of 29 tonometers (34%) had drifted outside this range over a 1-month period. Seventeen of 33 (52%) drifted outside this range over the next 3-month period. Calibration drift has been reported to be related to tonometer usage.[16] Tonometer calibration drift is, therefore, a problem and regular calibration verification is recommended.

  Frequency of calibration verification: There is little guidance as to how often the calibration error checks should be made. Once a year or twice yearly checks have been suggested in the literature. The frequency of calibration verification should probably be greater where tonometer usage is greater. The manufacturer recommends calibration verification at monthly intervals.[3] Additional verification (checks) should be performed in the case of suspected faulty readings or if the tonometer has been improperly handled (for instance, dropped).

Calibration of Tono-Pen

- Technique: The transducer end of the Tono-Pen is pointed downward and the button is rapidly depressed twice. A ‘beep’ sound is heard and the display reads ‘CAL’. In about 15 seconds another ‘beep’ sound is followed by the ‘UP’ display. Transducer end is pointed upwards. If the calibration is good, the display will read ‘Good’. If the Tono-Pen does not pass the calibration, the display will read ‘bAd’ in which case the calibration procedure should be repeated.
- Frequency of calibration (manufacturer’s recommendation): Calibration must be performed whenever batteries are replaced or after an unsuccessful calibration. Calibration procedure must also be routinely performed once daily prior to instrument use, or whenever indicated by the LCD display.

Calibration of Non-Contact Tonometer (NCT)

- Technique: Special tools and equipment are needed for the calibration of a non-contact tonometer and it is recommended to be performed by trained personnel.
- Frequency of calibration (manufacturer's recommendation): Recommended calibration schedule is every two years.

Issues requiring further attention

- Specific guidelines should be set as to how the clinician should consider IOP obtained with GAT in relation to CCT.
- Specific guidelines should be set for the role of the three most commonly used tonometers, namely GAT, Tono-Pen and NCT, with regard to their use in the clinical setting (*e.g.*, glaucoma follow-up, IOP screening in the outpatient clinic, corneal diseases, etc).
- Specific guidelines should be set for the frequency of calibration and the amount of error that is clinically acceptable.
- The impact of calibration error on clinical outcomes needs to be evaluated.
- A recommendation should be made for the dilution of fluorescein solution hence many clinics prepare their own solutions. It should be made clear if fluorescein strips can reliably be used for GAT IOP measurements and if yes what should be the concentration of the solution that they are made of.

iii. Sterilization techniques

Recommendations for cleaning and disinfecting the GAT prism are given in the instructional manual.[3]

Various techniques have been described to disinfect contact tonometers, and guidelines vary country by country. Swabbing the tip of applanation tonometers with 70% isopropyl alcohol is effective to disinfect previously inoculated Herpes Simplex Virus Type 1.[18] Using 70% isopropyl alcohol or 3% hydrogen peroxide to wipe the tips of the tonometers is effective against previously inoculated Herpes Simplex Virus Type 1, Herpes Simplex Virus Type 2, and Human Immunodeficiency Virus (HIV) Type 1.[19] These two methods are also effective in removing Adenovirus type 8 from Goldmann tonometer and pneumatonometer tips.[20]

A Clinical Alert jointly issued by the American Academy of Ophthalmology, the National Society to Prevent Blindness and the Contact Lens Association of Ophthalmologists provided recommendations for ophthalmic practice in relation to the HIV virus.[21] Regarding Goldmann-type tonometers, immediate cleaning after use of the tonometer tip with an alcohol soaked sponge, followed by drying for at least 1-2 minutes before next use was recommended. More stringent recommendations include cleaning the tip with household bleach. The prism of the tonometer is removed and immersed in a 1:10 solution of household

bleach for five minutes. This is followed by washing the tip under running water and dried before next use. The disinfecting solution should be changed at least once daily. Soaking the entire tip may remove the color of the etched calibration marks.

Soaking the tonometer head for five minutes in 70% isopropyl alcohol may damage the prism of the tonometer.[22] Depending on the kind of alcohol, its concentration and the duration of exposure, soaking in alcohol may result in degradation of the material resulting possibly in cracks or other damage of the tonometer tip. Consequently sharp edges or contamination in the cracks (that cannot be cleaned) could harm the patient. Therefore, the surface of the tonometer prism should be checked before each use, and the manufacturer recommends that prisms should be exchanged after a maximum of two years of use.

Possible transmission of variant Creutzfeldt-Jakob disease (vCJD) through remnants of corneal epithelial cells,[23] or proteins[24] in the surface of the reusable tonometer tips has also been considered. Wiping or washing the tonometer significantly reduced the number of cells and protein carry-over, however these methods did not eliminate the cells completely.[23,24]

Disposable covers for the tips of the tonometers have also been described,[25,26] as well as disposable prisms.[27] The UK Medical Devices Agency recommended wherever practical, "single patient use" of devices that touch the eye.[28] While the use of disposable prisms is in good agreement on average with standard GAT, measurements made with silicone shields tend to be higher than conventional GAT.[26,29]

B. Precision and Accuracy

i. Precision

'Accuracy' refers to how close tonometry measurements are to true IOP. 'Precision' refers to how repeatable are the measurements. Both inaccuracy and imprecision will cause the measured IOP to deviate from the true IOP.

Precision is affected by patient and technician factors such as human/instrument error, ocular pulse, etc. This section deals with observer (clinician/technician) related imprecision. Ocular- and patient-related sources of error are dealt with under heading 4, below. It is useful to consider observer-related imprecision from two view-points: intra-observer variability and inter-observer variability. The comparison of reported studies is made difficult by differences in statistical analyses employed.

1. Intra-observer variability

Limited data are available that compare the precision of various tonometers in the same population.

Tonnu *et al*. reported the repeatability of GAT and three other tonometry

Table 1. Repeatability coefficients for various tonometers

	Repeatability coefficient
Goldmann applanation tomometry[30]	2.2 to 2.5 mmHg
Dynamic Contour Tonometry[31]	2.6 to 3.2 mmHg
Non-contact tonometry[30]	3.2 mmHg
Ocular Blood Flow Tonography[30]	3.7 mmHg
TonoPen[30]	4.3 mmHg

methods, quantified with the 'repeatability coefficient' (two readings by the same observer will be within the repeatability coefficient for 95% of subjects) – see Table 1.[30]

Limited data are available for the DCT. Kotecha reported repeatability coefficients for a prototype DCT – see Table 1.[31]

Repeatability coefficients for the ORA and Rebound Tonometer have yet to be published.

Thus, with respect to data currently available, there is some suggestion that measurement precision is greatest with GAT. The precision of tonometers making measurements in very short period (NCT and Rebound Tonometers) are lower because, at least in part, of the effect of IOP variation with the cardiac cycle (ocular pulse amplitude). These tonometers may sample to the IOP at different times in the cardiac cycle with each measurement.

2. Inter-observer variability

The 95% limits of agreement between different observers measuring IOP with the same instrument in the same subjects have been reported to be ± 2.2 to 3.8 mmHg for GAT[30, 31] and ± 5.1 mmHg for a prototype DCT.[31]

3. Tonometer agreement

The agreement studies between different tonometers, in the same patients, provide two metrics: bias (mean difference) and limits of agreement. The bias is affected by calibration differences and sources of error that have a differential effect on the compared tonometers. The bias may vary across the range of IOP. The limits of agreement (either side of the bias) give an indication of the combined measurement error of the compared tonometers.

a. Bias:

On average, DCT tends to give higher IOP readings than GAT, by 0.7 to 2.3 mmHg.[31,32]

IOP by NCT is, on average, similar to GAT. NCT tends to be lower than GAT at low IOP and higher than GAT at higher IOP (Tables 3 and 4 in reference 30). The 'cornea corrected' IOP value of the ORA is similar to GAT values across the range.[33]

Most reports suggest that the TonoPen gives slightly lower readings than GAT (Table 4 in reference 30).

The IOP measurements of the OBF tonograph are, on average, very similar to GAT measurements. OBF readings tend to be lower than GAT at low IOP and higher than GAT at higher IOP (Tables 3 and 4 in reference 30).

The IOP measurements of the Rebound Tonometer tend to be slightly higher than GAT measurements, by 0.6 to 1.6 mmHg.[34, 35]

b. 95% Limits of Agreement:
Reported values (limits either side of the bias) are: DCT ± 5.6 mmHg,[31] NCT between ± 2.2 and ± 7.1 mmHg (most around ± 5.0 mmHg),[30] ORA 'cornea corrected' IOP ±5.4 to ± 6.0 mmHg,[10,33] TonoPen ± 4.5 to ± 8.3 mmHg (most around ± 6.0 mmHg),[30] OBF tonograph between ± 4.6 and ± 7.7 mmHg,[30] and Rebound Tonometer ± 4.2 to ± 6.8 mmHg.[36,37]

Areas requiring further attention

- More studies of the intra- and inter-observer variation of the newer tonometry devices, compared with GAT in the same population, are needed.

4. Sources of error
In addition to variations in 'material properties' of the cornea and corneal curvature (discussed in the section on 'accuracy', below), GAT measurements are potentially affected by corneal astigmatism, magnitude of capillary attraction, and tear film fluorescence.

- When the GAT prism is oriented horizontally, with-the-rule regular *corneal astigmatism* over 4 D will result in an underestimate of IOP and against-the-rule astigmatism, an overestimate of IOP.[38] A practical way to overcome this problem is to take two successive measurements, one with the prism oriented horizontally and the other vertically and then simply take the average of the two. An alternative method, suggested for patients with a 3 D or greater astigmatism, is to orient the axis of the tonometer tip 43° (this angle is marked on the Goldmann tonometer prism holder with a red line) to the major axis of astigmatism (in minus cylinder).

  In irregular corneal astigmatism GAT mires will be distorted and reproducible results may not be obtained.[39] The use Tono-Pen could be suggested in such corneas since it seems to be less affected by ocular surface abnormalities.[40,41]
- *Magnitude of capillary attraction* is affected inversely by the radius of liquid in contact and the angle of contact between the tears and the GAT tip. The radius of contact (between the tonometer tip and cornea, at the edge of the prism; *s* in Fig. 1) is greater with wide mires and lesser with thin mires, corresponding to proportionate overestimation and underestimation. To get consistent readings, rings of uniform size should be achieved at each applanation. The width of the fluorescein ring around the contact position of

the measuring prism should be approximately 1/10 of the diameter of the applanation surface (0.3 mm).[3]

If there is paucity of tear film, putting in an extra drop of topical anesthetic may help. If there are excessive tears, then the tip should be wiped and the measurement repeated. If tears keep flowing, especially from the upper marginal tear film, the upper lid may be retracted avoiding excessive pressure on the globe.

In theory, the angle of contact is greater in steep corneas, therefore decreasing capillary attraction and leading to overestimation of IOP, although this is unlikely to have clinical importance.

- Adequate *tear film fluorescence* is needed for the clear visualization of the contact point between the GAT tip and the cornea. Anything that causes hypofluorescence will cause misinterpretation of the contact point leading to underestimation of IOP. Clinically significant reduction of fluorescence can result from excessive tearing.
- *Digit preference* is a subconscious bias towards numbers that end in certain digits. Most frequent preferences are made to figures that end in 0, 5, or even numbers. The preference is individual specific and does not seem to be removed with education.[42]
- *Posture*: IOP is influenced by posture. IOP is higher in the supine position when compared with the sitting position, in young healthy adults, in healthy ageing individuals, and in untreated open-angle glaucoma patients.[43-45] Total inversion of the body, results in a significant and rapid rise in IOP, both in normal individuals and glaucoma patients.[46,47] This is probably due to an increased episcleral venous pressure, although other factors such as orbital congestion and possibly congestion of the uvea and redistribution of fluids inside the eye may also play a role.
- *Obesity:* measuring the IOP with the Goldmann tonometer in obese patients may give high readings. This may be due to simultaneous thorax compression and breath-holding, increasing the venous pressure and thus causing transitory rises of IOP. In overweight patients, measurement of IOP with a Perkins hand-held applanation tonometer is recommended to avoid transitory elevations of the IOP during Goldmann tonometry.[48]
- *Valsalva maneuver/necktie use:* Situations associated with the Valsalva maneuver, such as straining, or playing a wind instrument have been associated with elevated IOP,[49] however high individual variability has also been reported.[50] Elevated episcleral venous pressure associated with the Valsalva maneuver has been implicated as a possible mechanism. A rise in IOP, measured with Goldmann applanation tonometry, both in normal subjects and glaucoma patients has been reported associated with the use of a tight necktie.[51] In this setting, elevated venous pressure has also been implicated as a possible mechanism. However, another report failed to identify a rise of IOP associated with a tight necktie when measured with the Tonopen, and postulated that this rise may be due to neck retroflection that is associated with the position at the slit-lamp with Goldmann tonometry.[52]

- *Eyelid squeezing*: attempted eyelid closure during tonometry may be an important source of error. In a study performed in normal subjects, attempted eyelid closure increased IOP measured both with Tonopen and with Goldmann applanation tonometry (GAT).[53] With the Tonopen, mean IOP increase was 1.9 ± 2.7 mmHg (range: -2 to +9 mmHg), and with GAT mean increase was 1.5 ± 2.0 mmHg (range: -2 to +8 mmHg).[53] Attempted eyelid closure increased IOP in patients with normal tension (NTG) and with high tension open-angle glaucoma (HTG).[54] Attempted eyelid closure increased IOP in NTG by a mean of 3.9 ± 2.0 mmHg (range: 2 to11 mmHg) when measured with GAT, and by a mean of 4.2 ± 2.7 mmHg (range: 1 to 14 mmHg) when measured with the Tonopen.[54] In eyes with HTG, attempted eyelid closure increased IOP 4.1 ± 2.1 mmHg (range: 1 to 9 mmHg) measured with GAT, and 4.5 ± 2.0 mmHg (range: 2 to 11 mmHg) when measured with the Tonopen.[54]

ii. Accuracy

1. Central corneal thickness

Measurement error

All forms of tonometry currently available are affected by CCT, however, the effect of CCT on DCT IOP measurement is about half that of the CCT effect on GAT IOP measurement.[31,55,56] The 'cornea corrected' measurement of the ORA (IOPcc) is less affected by CCT than GAT; two studies have reported a weak, non-significant association between IOPcc and CCT.[10,33] Forms of tonometry that indent the cornea very rapidly (such as NCT and Rebound Tonometry) are significantly more affected by CCT.[57,58] This is due to the cornea's viscoelastic properties.

The table on next page (taken from Tonnu and colleagues[57]) summarizes the literature for the effect of CCT on IOP measurements taken with GAT, NCT, OBF and the TonoPen.

Most population studies suggest that CCT accounts for between 1% and 6% in the variation of GAT IOP and 7% to 12% in the variation of NCT IOP.[57] In the study by Ku and colleagues,[55] CCT accounted for almost 14% of the variation in GAT. The IOP measured in a population will vary as a result of factors that affect measurement accuracy (such as CCT) and precision and as a result of variation in true IOP.

In the clinic, we are interested in the accuracy and precision of the tonometry (and less in the between-individual component of variability). To isolate the contribution of CCT to measurement error, two types of study are possible: to compare tonometers differentially affected by CCT (and material properties) or to compare GAT with true IOP (manometry study).

Available data suggest that DCT is about 50% less affected by CCT than GAT.[31,55,56] Yet only 5% to 14% of the measurement differences between GAT and DCT can be accounted for by CCT. Presumably other factors, including

Table 1. Increase in IOP (mmHg) for every 10 μm-increase in CCT. Summary of previous findings regarding effect of CCT on IOP measurements. (From Tonnu and colleagues[57])

Author	Study type	Country	GAT	Tono-Pen	OBF	NCT
This study	Clinic based	United Kingdom	0.28	0.31	0.38	0.46
Ko *et al*, 2004[6]	Clinic based	Taiwan	0.37		0.47	0.63
Siganos *et al*, 2004[36]	Clinic based	Greece	0.26			0.39
Bhan *et al*, 2004[5]	Clinic based	United Kingdom	0.23	0.10	0.28	
Gunvant *et al*, 2004[21]	Clinic based	United Kingdom	0.27		0.48	
Morgan *et al*, 2003[12]	Clinic based	United Kingdom			0.30	
Shimmyo *et al*, 2003[22]	Clinic based	United States	0.16			
Eysteinsson *et al*, 2002[23]	Population based	Iceland				0.22 (M) 0.28 (F)
Dohadwala *et al*, 1998[4]	Population based	Indian subcontinent		0.29 (M) 0.12 (F)		
Foster *et al*, 2003[24]	Population based	Singapore	0.15 (R) 0.18 (L)			
Foster *et al*, 1998[25]	Population based	Mongolia	0.18 (R) 0.24 (L)			
Wolfs *et al*, 1997[38]	Population based	Netherlands	0.19			
Nemesure *et al*, 2003[39]	Population based	Barbados	none			
Feltgen *et al*, 2001[16]	Manometry	Germany	none			
Foster *et al*, 2000[17]	Manometry	Singapore	none			
Ehlers, 1975[1]	Manometry	Denmark	0.71			

M, male; R, right-eye; F, female; L, left eye.

corneal material properties and imprecision, account for much of the rest of the differences. Importantly, in the study by Kotecha,[31] subject age explained about the same proportion of the GAT/DCT differences as did CCT, indicating that other parameters may be as important as CCT. Medeiros has reported an age effect on ORA IOPcc measurments.[33] It has been established that corneal stiffness is significantly associated with subject age.[59]

Manometric studies potentially contribute valuable data. In the study by Kohlhass and colleagues,[60] a single observer measured the IOP with a Perkins applanation tonometer at each of three IOP levels, set by manometry. Around 80% of the measurement error could be accounted for by CCT. Once CCT was accounted for, the measurement error was ± 1.5 mmHg in 90% of eyes. This value of ± 1.5 mmHg is close to the repeatability coefficient of about 2.5 mmHg for GAT (two readings by the same observer will be within the repeatability coefficient for 95% of the subjects).[30] The implication of this is that, in this study, virtually all the measurement error was accounted for by CCT and measurement imprecision, leaving almost no room for other factors that we know affect IOP measurement error. Perhaps the restricted age range in this population undergoing cataract surgery may explain the failure to observe an age effect in measurement error.

Although it is known that CCT does significantly affect GAT IOP measurement *on average*, its contribution to the measurement error *in individual patients* is unknown and may not be that large.

Most population studies find the relation between CCT and GAT measurement error is about 2.5 mmHg per 100 microns CCT.[57] The recent manometry study found the error to be about 4.0 mmHg per 100 microns CCT.[60] The 95% confidence intervals for CCT in a population span about 120 microns,[56] so the variation in measured IOP due to CCT, between these extremes, is likely to be about 3.0 to 4.8 mmHg. Measurement imprecision (95% confidence intervals for between-observer variation) for GAT is about ± 2.5mmHg, or 5.0mmHg between extremes.[30] Thus, the error due to CCT is likely to exceed the imprecision only towards the extremes of CCT. Obviously, the error due to CCT is systematic and that due to imprecision is random, but the comparison puts the magnitude of the effect in context.

Areas requiring further attention

- The contribution of factors, such as the corneal material properties, on the accuracy of tonometry needs to be determined.
- The accuracy of new tonometers, such as the DCT and ORA, needs to be determined.

CCT as a 'risk factor'

The Ocular Hypertension Treatment Study (OHTS)[61] and the European Glaucoma Prevention Study (EGPS),[62] clinic-based, randomized trials of treatment versus no treatment among a large cohort of persons with ocular hypertension, found thinner CCT to be an independent risk factor for incident glaucoma. Subsequent clinic-based studies have reported thinner CCT as a risk factor for advanced glaucoma damage, the progression of existing field damage, and the presence of abnormal SWAP fields among persons with normal white-on-white perimetry. However, population-based studies in Sweden[63] and Barbados have failed to detect an association between CCT and indices of glaucoma damage. The reasons for this inconsistency between clinic and population-based studies are not well understood, but it may be that the association between CCT and glaucoma risk is more pronounced among subjects with thicker CCT. Those with thicker CCT may be less common in the population as a whole than in the clinical setting.

That CCT is found to be a *statistically* independent risk factor does not necessarily mean that CCT *is* an independent risk factor. In multiple variable analyses, the effect of one variable can be evaluated after controlling for covariates. However, statistics cannot take into account the fact that the measurement of the variable was inherently affected by another covariate. In other words, it is not possible in the OHTS or EGPS analyses, to completely separate the effect of IOP and CCT. This is because IOP was measured by GAT and the GAT

measurement is affected by CCT in ways we do not yet fully understand. For instance, the interaction of CCT, corneal elastic properties and true IOP may result in non-linear associations of IOP measured by GAT and CCT. To truly evaluate whether CCT is an independent risk factor, IOP measurements would need to be obtained by a method independent of CCT.

Racial variation in CCT has been reported as well, with lower average CCT having been observed among persons of African descent than for Europeans,[64] for example. Persons from Southern India also appear to have thinner CCT on a population basis.[65] It is possible that thinner CCT among certain races may partly explain their increased burden of risk for glaucoma. OHTS, for example, found that increased glaucoma incidence among African American ocular hypertensive patients was entirely explained by thinner CCT and larger cup-to-disc ratio. However, these are reported *associations* and causation cannot necessarily be inferred.

The reasons for the association between CCT and glaucoma risk are not well understood. It has been hypothesized that IOP is systematically underestimated in persons with thinner CCT, leading to less aggressive treatment. Alternatively, it has also been suggested that thinner CCT may be an indicator of a less robust ocular coat elsewhere in the eye, particularly in the area of the optic nerve, and may thus have a direct association with glaucoma damage, not mediated through IOP.

Limited studies of hysteresis, an indicator of the visco-elasticity of the cornea, have suggested that persons with more deformable corneas may be at greater risk for glaucoma damage, when adjusting for CCT, in a clinic setting.[66] In the formula describing wall strain, increased strain is associated not only with a thinner wall, but also a longer axial length. Population studies in Australia,[67] Sweden and China[68] have all found highly myopic eyes to be at greater risk for glaucoma. Histologic studies have also found that the lamina cribrosa of long eyes is thinner than in shorter eyes. Thus, the relationship between glaucoma risk, eye wall composition/deformability and biometric factors such as wall thickness and axial length is a complex one, with much remaining to be elucidated.

Areas requiring further attention

- Is increased risk for glaucoma among persons with thinner CCT mediated through under-estimation of IOP or due to associated differences in the ocular coat elsewhere in the eye which directly increase risk for glaucoma? As a corollary question, will iatrogenic reduction in corneal thickness (*e.g.*, refractive surgery) affect long-term glaucoma risk?
- Why do population studies not bear out the clinically-observed association between CCT and glaucoma risk? Is a thinner CCT a risk for glaucoma progression?
- How do other biometric factors such as axial length, and eye-wall compositional factors such as hysteresis, interact with CCT.

IOP 'correction' nomograms

The enthusiasm with which the ophthalmic community has embraced pachymetry as part of the glaucoma exam was based in part on the belief that measurements of CCT would provide more accurate Goldmann applanation tonometry (GAT) estimates of IOP through an easily-applied 'adjustment' nomogram. Using such nomograms in individual patients has not been validated and has the potential to lead ophthalmologists astray in their clinical decision-making.

In arguing this point, it is worthwhile to ask two related questions: First, is it even possible to accurately adjust GAT measurements using CCT alone, and second, even if we *could* improve the accuracy of GAT measurements, would this represent a significant advance in patient care?

We don't have the right 'correction nomogram'

No clinically-validated 'correction algorithm' exists for adjusting GAT based on CCT alone. The earliest table suggesting a systematic adjustment to GAT based on CCT is that of Ehlers from the 1970s.[69] The clinician should be cautious in extrapolating Ehlers' findings to general clinical practice. His study was based on a small number of eyes (29) that included a relatively narrow range of CCTs (450 to 590 μm) measured optically.[69] The interested reader is referred to a detailed exploration of the mechanical characteristics of the cornea and the role of CCT and Young's Modulus in GAT error by Orssengo & Pye[70] and Liu & Roberts.[71]

These engineering models of the cornea suggest that variations in the material properties of the cornea (*i.e.*, Young's modulus, inherent stiffness and/or viscoelastic properties) likely dwarf the effect of CCT on GAT measurements.[70,71] These models suggest that if the material properties of the cornea were constant, variations in CCT from the mid-400s to mid-600s would explain only some ± 3 mmHg in variance from 'true' (directly-measured) IOP. These same models suggest that variations in material properties of the cornea (known to vary by several orders of magnitude) could explain ± 15 mmHg in variance from 'true' IOP. For example, a 625 μm cornea that is clinically healthy and has been thick since birth likely behaves very differently than a cornea that is thickened by subclinical endothelial dysfunction. In the latter case, a thicker, slightly edematous cornea may in fact measure *lower* by GAT than expected.

Recall that in a linear regression, just as many data points lie above the regression line as below – the data points above the line need to be 'corrected' downwards, those below 'corrected' upwards. Thus it is entirely possible that in correcting GAT by a fixed, linear correction nomogram, the ophthalmologist can be wrong both in the magnitude of the adjustment but also in its direction. Is this supported by real data? Well, when one looks at the limited published data from directly-cannulated eyes, one can't help but be struck by the fact that the fit of the data is relatively tight at lower CCTs but becomes a very poor fit above about 550 μm. One plausible interpretation of this finding is that at lower

CCTs one is dealing with a population of corneas with relatively homogeneous material properties, but at higher CCTs one is dealing with a much more heterogeneous population. For this reason no generalized 'correction nomogram' can ever adequately adjust IOP without knowing much more about the individual cornea being applanated. Again, depending on which nomogram you use, if you 'correct' GAT measurements only for CCT, you may be off by quite a bit (and even in the wrong direction!).

Diabetes – A useful analogy

If we in fact *could* adjust GAT measurements to improve their accuracy, would this represent a big advance? Among chronic diseases, glaucoma is remarkable in that its primary risk factor, IOP, is measured only rarely and mostly randomly, perhaps a few times a year in most patients. This state of affairs has been unchanged for well over a century. The measurement of blood sugar for the management of diabetes, however, has evolved during that same period from random, crude measurements of urinary and blood glucose to fasting blood sugar, glucose tolerance tests, glycosylated hemoglobin and affordable computerized portable glucometers. If diabetes management was still in the era of random blood sugar measurements, would improving the accuracy of these measurements improve the care of diabetic patients? Not really. No one today manages diabetes with random blood sugar measurements, no matter how accurate, and yet that is what we are doing, by analogy, in glaucoma.

Just as today's astute clinician recognizes that optic discs come in 'small, medium and large', allowing the ophthalmologist to interpret disc configurations accordingly, a basic recommendation can be made to categorize corneas as 'thin, average or thick', and incorporate this knowledge into the overall clinical picture of an individual patient to better target and titrate the treatment of glaucoma. Trying to be more accurate than this is not supported by clinically-validated studies and may lead to erroneous clinical decisions.

Areas requiring further attention

- Nomograms that integrate CCT and biomechanical factors (*e.g.*, hysteresis) may more accurately refine estimates of IOP and prove useful in clinical practice**.**

2. Corneal curvature

A cornea with steeper *curvature* needs to be indented more to produce the standard area of contact. Therefore, more force must be applied against a steep cornea than against a flat cornea, resulting in a higher value of the measured IOP. Theoretically[71] and on clinical grounds,[56,72] GAT IOP measurements are not clinically significantly affected by changes in corneal curvature. IOP measurements by DCT may be more affected by corneal radius of curvature.[56]

3. Corneal biomechanics

Elasticity

The modulus of elasticity of the cornea, one measure of biomechanical properties, has been theoretically shown to have a greater effect on IOP measurement error than either curvature or thickness.[71] The current scientific and clinical focus on corneal thickness is due to the ease with which CCT can be measured in the clinic, compounded by the current lack of a commercial device with the ability to measure corneal elasticity *in vivo*. This can be considered analogous to Goldmann's focus on the potential error caused by variation in corneal curvature, since that could be measured in the clinic at the time he was developing his tonometer, and thickness could not. CCT is likely positively correlated to corneal elasticity in normal populations, with a more complicated relationship in the case of pathology or after corneal surgery.

Young's modulus of elasticity is defined as the ratio of the stress (load per unit area) and the strain (displacement per unit length). Therefore, a material with low modulus will exhibit greater deformation for a given stress than a material with high modulus. The experimentally determined values of Young's modulus reported in the literature for the cornea vary widely, ranging from 0.01 to 10 MPa.[73-75] In addition, the majority of corneas available for experimental testing are post-mortem corneas of advanced age. The distribution of elasticity in a normal population of wide age ranges has not been measured. Despite this, the variability in the reported experimental data is vast, most likely due to variation in experimental techniques. However, the most accurate interim conclusion, at this point in time, is that there is a great deal yet to be learned regarding corneal elasticity *in vivo*.

It is known that the cornea stiffens as it ages, and it has been reported that Goldmann-measured IOP also increases with age. However, it may be that true IOP is stable, and that increasing corneal stiffness is what is driving the increased measured IOP, even in the absence of a change in CCT.

Issues requiring further attention

- *In vivo* measurement of corneal elasticity.
- Understanding the relationship between corneal thickness, corneal thickness profile, and elasticity in normal, post-surgical and diseased eyes; as well as the impact on IOP measurement
- Understanding the complex biomechanical corneal structure in refractive surgery.

Visco-elasticity

It is important to distinguish elasticity from viscoelasticity. The elastic response of the cornea to an applied force has no time-dependent component. The viscoelastic response, on the other hand, has a time-dependent component, meaning that both the magnitude and the rate at which a force is applied will affect the

corneal response. The cornea has clear visco-elastic behaviour; it stiffens under fast load application, creeps under constant stress and exhibits hysteresis with unloading. Visco-elasticity makes corneal behaviour difficult to understand and quantify since any material model obtained experimentally is dependent on the rate of loading adopted and the number of preceding load cycles.[59] Furthermore, corneal visco-elasticity is known to change with age, leading to a gradual decline in hysteresis[10] (the difference in behaviour under loading and unloading conditions) and stiffening of corneal tissue.[59]

Visco-elasticity makes the determination of corneal biomechanics, which influence IOP measurement in tonometry, difficult. Earlier studies that attempted to quantify corneal material properties reported values of Young's modulus (a measure of tissue stiffness) within a wide range; with the highest reported value more than two orders of magnitude larger than the lowest value.[71] One of the main reasons for this wide scatter is the use of different load rates, with tests adopting faster load rates reporting higher values of Young's modulus. Unfortunately, it is not possible to use these results to accurately assess the effect of load rate, and hence visco-elasticity, on corneal material properties due to other variations in the experimental setups or test procedures adopted.

The evident influence of corneal material properties on the accuracy of IOP measurement makes it essential to quantify the effect of visco-elasticity. It is not sufficient to quantify the material properties under a specific load rate since different tonometry techniques load the cornea with different rates. For instance, the Schiotz tonometer, GAT, DCT, tono-pen and similar contact tonometers involve slow load application, while non-contact tonometers, such as the ORA, and the Rebound tonometer, use a much faster, truly dynamic, load application. For this reason it is important that corneal material properties are determined under both static (slow) and dynamic (very fast) load application rates. With the corneal stiffness determined under these conditions, its effect on IOP measurement can be quantified and eliminated.

The effects of age on visco-elasticity are also important and should be quantified. First, there appears to be a reduction in the variation of material stiffness with load rate as the cornea gets older. Second, there is evidence that ageing leads to reductions in corneal hysteresis, a parameter which directly affects IOP measurement using the ORA. Both these effects have been observed in recent experimental and clinical studies but have not been quantified yet.

Although no commercial technology exists to measure corneal elasticity *in vivo*, there is technology available that reports to provide a measure of corneal viscoelasticity. The ORA outputs two parameters, corneal hysteresis (CH) and corneal resistance factor (CRF). Both of these parameters are viscoelastic in nature, and neither can be accurately interpreted as elasticity. However, CRF was empirically derived to correlate with CCT, and is therefore 'weighted' by elasticity, even though it is still affected by the viscoelastic properties of the cornea. In addition, a material which exhibits low corneal hysteresis can have either high or low elastic modudus, depending on the associated viscosity.

Therefore, it is not accurate to interpret low hysteresis as either low elasticity or low viscosity.

Issues requiring further attention

- Quantify corneal visco-elasticity and in particular the change in material properties associated with the range of load rates adopted in tonometry.
- Quantify the effect of age on corneal visco-elasticity and the implications on corneal hysteresis. This latter parameter is particularly important for non-contact tonometry using the ORA.

C. Special considerations

i. Corneal disease and surgery

1. Contact lenses and corneal oedema

Contact lenses

There are a number of contact lenses currently available. The lenses can be soft, hard or a mixture of both. Contact lenses can be manufactured from a large range of materials with varying properties, although many of the currently available materials have good oxygen permeability.

Contact lenses are worn for a variety reasons, including refractive, cosmetic, ocular disease management and for altering corneal shape. Each of these lens types can be worn according to differing wearing schedules and replacement strategies.

Patients tend to have poor recollection of their contact lens care and management strategies, in particular which contact lens solutions they are supposed to use with their lenses. Solutions designed for use with soft contact lenses can produce ocular irritation and, at worst, corneal infection as evidenced by a recent product recall.

Contact lenses can produce changes in corneal shape and/or corneal thickness, and there is evidence that many soft contact lens wearers may develop corneal oedema throughout the day as a result of lens wear.[76]

If corneal oedema is present, relatively low levels of oedema should resolve within two hours after lens removal and eye opening,[77] although there is evidence that the corneas of long term contact lens wearers may take an average of 15 days of non lens wear to provide accurate pachymetry results.[78]

After overnight contact lens wear, the cornea appears to be capable of removing 8% of the induced oedema throughout the day.[77] However, most work in this area has been conducted with young adults who are the most common contact lens wearing group. The response of older corneas to contact lens induced oedema is not fully understood.

Silicone hydrogel contact lenses should provide sufficient oxygen to the cornea

to prevent corneal oedema during the day,[79] although there may be differences in the performance of lenses as a result of overnight wear.[80]

There is some evidence that accurate applanation tonometry results can be obtained through soft contact lenses worn by patients.[81]

Corneal oedema

Large amounts of corneal oedema produce a lower IOP result when the IOP is measured with applanation tonometry.

There is a diurnal variation in CCT, and this can be quite variable from one patient to another. The central cornea is thicker on eye opening after sleep, and decreases in thickness in an exponential fashion over the following two hours providing the eye remains open. In normal eyes, CCT stays relatively constant for the remainder of the day whilst the patient is awake.[82]

Diurnal IOP, measured with applanation tonometry, is usually highest immediately upon eye opening.

In young adults, the changes in IOP, measured with applanation tonometry, and the changes in CCT which occur after eye opening after sleep, decay at a similar rate over a two-hour period.[83] In young adults, the increase in CCT does not appear to solely explain the increased IOP measurement on eye opening.[84] It is likely that the IOP has increased during sleep but also that the corneal behaviour has changed as a result of the corneal swelling.[83]

In young adults, thick soft contact lenses have been used to produce similar levels of corneal swelling as are experienced diurnally. The data suggest that low levels of oedema may produce a stiffening of the corneal tissue which would artificially elevate applanation tonometry results. As the cornea swells beyond six to ten percent, the cornea may behave as a softer tissue, artificially lowering the IOP applanation tonometry measurements.[85]

There is evidence to suggest that the corneas of older people may become stiffer with age, and this may affect the manner in which the corneas of older patients behave diurnally. How this may affect tonometry measurements is currently unknown.[59] The corneas of older patients may deswell at a slower rate to young normals, and how this may affect applanation tonometry measurements of IOP is yet to be determined.

It is not definitively known at this time whether IOP values obtained with new tonometers such as the Pascal[86] or ORA are totally unaffected by corneal swelling in the clinical environment, although some reports are promising.

Refractive surgery

Following many forms of keratorefractive surgery, including LASIK, LASEK, and PRK, there is a mean decline in measured IOP using static tonometry.[87,88] This is true even in surgeries that produce minimal change in CCT, such as radial keratotomy and hyperopic LASIK.[2] IOP measurement by NCT is likely to result in the greatest under-estimation of IOP following refractive surgery.[89] This reflects the changes in corneal biomechanics and elasticity, which can have

an overriding effect on IOP measurement, in addition to changes in corneal curvature.[71] In general, the greatest predictor of average IOP fall following keratorefractive surgery is the mean preoperative IOP.[90] In general, a similar depth of ablation will result in a greater decline in static IOP measurement following LASIK than surface ablation, while the latter is associated with a greater decline in corneal hysteresis.

Large population studies of patients undergoing LASIK indicate that while the mean IOP declines, there may be an *increase* in IOP measurement in a substantial number of patients following surgery, when patients have been long off steroids.[91] In addition, the change in recorded IOP may vary with wound healing postoperatively.[89] This may reflect the complexity of corneal biomechanics following keratorefractive surgery, which is the composite of nonuniform regional pachymetry, varied corneal hydration and curvature, and altered states of collagen crosslinking, which may be affected by age and associated conditions (*e.g.*, diabetes[92]).

Studies comparing static (*e.g.*, Goldmann), dynamic (e.g. PASCAL dynamic contour) and non-contact tonometry (Ocular response analyzer), demonstrate that these two latter forms of tonometry are less sensitive to changes in corneal biomechanics and show small, clinically irrelevant changes following LASIK and LASEK, with less variance than Goldmann tonometry.[11]

Issues requiring further study

- A better understanding of the impact of different forms of keratorefractive surgery on IOP measurement using various devices.
- A better understanding of how corneal hysteresis, corneal resistance factor and other corneal biomechanical metrics define and relate to corneal viscoelasticity and elasticity.
- The impact of both corneal and non-corneal ocular tissue in influencing IOP measurement with different devices following refractive surgery.
- The impact of age, collagen crosslinking and wound healing on IOP measurement following keratorefractive surgery.

Keratoprosthesis

The most common indications for keratoprostheses are patients with Stevens-Johnson syndrome, ocular cicatricial pemphigoid, severe chemical burns and end-stage dry eye.[93] It is likely that many such eyes have altered biomechanical properties prior to placement of the keratoprosthesis and this can effect IOP measurement, particularly with devices (such as Goldmann tonometry) that may be more sensitive to such effects.

Measurement of IOP after placement of the keratoprosthesis may be particularly problematic, and glaucoma is not an uncommon sequelae. For type II Doane-Dohlman keratoprosthesis that traverse the eyelid, most ophthalmologists have

relied on digital palpation techniques.[93] Studies of tactile assessment of IOP in eyes without corneal pathology have revealed little correlation with Goldmann applanation values and while demonstrating high specificity, missed 29% of eyes with Goldmann applanation pressures over 30 mmHg.[94] One study suggested that a transpalpebral tonometry device had lower deviations from Goldmann IOP than tactile palpation, but was not a suitable substitute for Goldmann because of large interobserver and intraobserver variations.[95] While some have applied McKay-Marg tonometers to the sclera of patients with a type I Doane-Dohlman keratoprosthesis, Dohlman suggests that this technique has little utility, and that the TonoPen and pneumatonometry tended to overestimate IOP.[1] Some investigators suggested that following keratoprosthesis patients with VEP perimetry might represent a more reliable methodology for glaucoma monitoring.[96]

The measurement of IOP in patients with more flexible keratoprostheses[97] or artificial corneas made of hydrophilic polymers (such as AlphaCor, comprised of PHEMA where host cells migrate and insinuate within the keratoprosthesis[98]) has not been systematically evaluated. An *in vitro* study of the Aachen-flexible keratoprosthesis in an artificial anterior chamber suggested that tonometry could be performed with a modified Schiotz device, and showed similar readings with a TonoPen and Goldmann tonometer,[97] but no manometric studies have been performed in patients. While investigators have applied Schiotz tonometers adjacent to the limbus of patients with AlphaCor artificial corneas,[98] as well as TonoPen, electronic tonometers, phosphene tonometers and pneumatonometers,[99] there have been no validation studies in this setting.

Other types of prosthetic devices that are implanted within the cornea include Intacs, which are hexagonal PMMA segments of variable thickness, placed between the corneal stromal lamellae in pockets at approximately 2/3 corneal thickness. Whereas the initial use of these devices was for treatment of low myopia, they are now more frequently placed in an effort to stabilize eyes with keratoconus or post-LASIK ectasia. Such eyes already have markedly altered biomechanical characteristics before pocket formation and Intacs placement, and IOP in such eyes pre- and post-operatively may be more accurately assessed using devices less sensitive to altered corneal properties, such as the Pascal dynamic contour tonometer or Ocular Response Analyzer. The few studies on normal non-ectatic myopic eyes with Intacs, indicate that there is a small mean decline in Goldmann IOP compared to the unoperated contralateral eye of -0.5 ± 1.8.mmHg at six months, without marked changes in CCT and an average of -1.87 dioptric fall in central keratometry.[100] TonoPen measurements were similar over the central and paracentral cornea of eyes with Intacs and there were no statistical differences with Goldmann tonometry measured centrally, but Tono-Pen measurements of IOP directly over the Intacs were unreliable as were Goldmann measurements obtained paracentrally. Goldmann measurements directly over the Intacs segments gave elevated readings in the 40 to 60 mmHg range.[101] Some patients with keratoconus and Intacs have also been treated with riboflavin and UV-A crosslinking of corneal collagen,[102] which will also alter corneal viscoelasticity and impact IOP measurement.

Corneal inlays are being developed for treatment of presbyopia, which are placed within corneal flaps or tunnels. The effect of the inlay on corneal biomechanical properties is unknown, but single case studies of corneal flap creation itself without either laser or inlay have shown a drop in Goldmann correlated IOP, and lesser change in corneal compensated ORA IOP readings.[103]

Issues requiring further attention

- Controlled manometric studies comparing different IOP measurement in eyes undergoing keratoprostheses
- Comparison of IOP measurement with different devices following keratoprostheses and correlation with other methods of monitoring glaucoma progression

ii. Tonometry in children

The estimation of IOP in pediatric patients is made difficult by the same issues addressed elsewhere in this consensus document such as CCT, material properties of the eye and varying assumptions underlying different tonometry techniques. Further complicating IOP measurement in younger children is the need for interventions not usually employed in adults – sedation and/or general anesthesia, and the frequent need for a lid speculum.

The normal distribution of IOP among children appears to be lower than that for adults using GAT,[104] and increases with age. The underlying explanation for this finding is unknown, and may represent changes in underlying physiology (*e.g.*, aqueous humor dynamics) or age-related differences in the biomechanical properties of the cornea (*e.g.*, CCT and visco-elastic properties). The distribution of CCTs appears to mimic that in adults, with children characterized as 'ocular hypertensives' having thicker corneas than do age-matched normals, and African-derived children having thinner corneas than their Caucasian counterparts.[105] Children who have undergone surgery for congenital cataract have thicker corneas than phakic controls.[106]

The question of whether one tonometer is superior to the others in pediatric patients is unresolved. Bordon and colleagues suggest that the Tonopen is sufficiently accurate for use in pediatric patients,[107] whereas Eisenberg *et al.*, in an *in vivo* and *in vitro* study comparing Perkins, Pneumatonometry and Tonopen, determined that Perkins tonometry underestimated IOP and that Pneumatonometry was the most accurate in pediatric eyes.[108]

The measurement of IOP in an uncooperative child frequently requires the use of a speculum to gain access to the eye; this is associated with an increased measurement of approximately 4 mmHg.[109] Sedation and/or general anesthesia is often necessary. While benzodiazepine sedatives are thought not to affect IOP,[110] intravenous and inhaled anesthetics affect IOP rapidly. IOP measurement after intravenous ketamine HCl, long thought to raise IOP acutely,[111] is now thought

to more closely mimic awake IOP.[112] Inhaled and intravenous general anesthetics in widespread use, such as IV propofol and inhaled sevoflurane, rapidly lower IOP within minutes of induction.[112, 113] During an examination under anesthesia, the clinician must measure IOP consistently and early in the anesthetic to gain the most useful clinical information.

iii. Pregnancy

IOP decreases during pregnancy both in normal and ocular hypertensive women.[114,115] The reduction in IOP is progressive from the first to the third trimester. Regarding patients with preexisting glaucoma, an analysis of 28 eyes of 15 patients, showed stable IOP in 16 eyes (57.1%), increased IOP without visual field progression in five eyes (17.9%) and progressive visual field loss with either stable or increased IOP in five eyes (17.9%). In two eyes data were inconclusive due to medication noncompliance and previous severe loss of visual field.[116]

The decrease in IOP is probably multifactorial. An increase in outflow facility without a change in aqueous humor formation has been shown. [117, 118] A decrease in episcleral venous pressure may also be involved.[119]

iv. Menstrual cycle

In a study of 1459 women, it was found that IOP varies during menstrual cycle, however these variations were not statistically significant.[120, 121] Postmenopausal women have higher IOP than women of the same age that are still menstruating (mean IOP: 16.07 ± 0.36 vs. 15.4 ± 0.38 mmHg, $p < 0.05$).[122]

v. Exercise

Weight lifting increases IOP, both while holding breath and while breathing normally.[123] IOP decreases after jogging in athletes and untrained subjects,[124] and also after bicycling in young subjects.[125] Different types of exercise have been shown to lower IOP in healthy young adults.[126] IOP declines in acute, dynamic exercise in proportion to the intensity but not the duration of the exercise.[127,128] Possible mechanisms explaining this include hypocapnia,[129] elevated plasma colloid osmotic pressure,[130] and levels of lactate in the blood.[128]

vi. Acupuncture

Besides anti-glaucoma medications, laser, or surgery, some doctors and patients (for example in China) may be interested in complementary and alternative medicine such as acupuncture. Acupuncture is a method of traditional Chinese medicine based on the belief that health is determined by a balanced flow of vital life energy (called qi or chi) present in all living organisms. This energy circulates in the body along 12 major energy pathways called meridians. Each meridian contains over 1000 acupoints that can be stimulated to alter the flow

of qi. With the use of special needles inserted just under the skin at these acupoints, an acupuncturist attempts to correct or rebalance the flow of energy to treat disease. The special needle can be inserted in single acupoint or in a series of acupoints within one meridian.

Ralston observed a decrease in IOP in experimentally induced glaucoma in dogs following acupuncture.[131] Dabov *et al*. reported that three of eight patients had a 'lowering' of IOP after acupuncture measured by a Maklakow's tonometer.[132] However, two separate case series of 33[133] and 18[134] patients with glaucoma found that most patients had no change in IOP. Up to now, there have been 41 papers showing the effect of acupuncture on IOP/glaucoma published in Chinese. All measurements of IOP in these studies were by Schiøtz tonometry. Liu measured IOP before and five minutes after single acupuncture in 40 normal subjects (79 eyes) without glaucoma and ocular hypertension.[135] IOP was lowered in 49 eyes, increased in eight eyes, and there was no change in 22 eyes. Mean IOP was significantly lowered 1.61mmHg. Wu *et al*. treated 120 patients with primary open angle glaucoma with acupuncture. They inserted needles in fourteen acupoints for fourty minutes for each patient and measured IOP and blood pressure (BP) before and immediately after the acupuncture.[136] IOPs after acupuncture (24.9 ± 0.9) were significant lower than the baseline (33.7 ± 1.1) ($p < .001$). Both systolic and diastolic blood pressure after acupuncture (150 ± 3, 96 ± 1) was also significantly lower than at baseline (163 ± 4, 101 ± 2) ($p < .001$). This indicates that acupuncture reduces IOP, but the effect may be partly due to the decline of BP.[136] However, all studies showed the short-term effects on lowing IOP and the long effect of acupucture is still unknown. Also, the acupuncture methods uses in the various studies differed. A prospective placebo-controlled study is required to verify the effect of acupuncture on IOP.

vii. Flat anterior chamber

Measurement of IOP in the presence of a flat chamber may be unreliable, as was shown in a study in cadaver eyes, done with the Goldmann applanation tonometer, the tonopen, and the pneumatonometer.[137] Comparison with manometric readings did not correlate with any of the three tonometers.

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Ted Garway-Heath presenting the section on measurement of intraocular pressure.

Consensus panel. From left to right: Fabian Lerner, Felipe Medeiros, Kengi Kashiwagi, Nathan Congdon and Cynthia Roberts

From left to right: meeting co-chairs-Robert N. Weinreb, James Brandt and Ted Garway-Heath.

IOP consensus points being presented by Ted Garway-Heath.

Consensus development panel discussing the section on measurement of intraocular pressure (James Brandt, Franz Grehn, Robert N. Weinreb, Kuldev Singh, Neeru Gupta, Ted Garway-Heath-front, left to right- and Erik Greve and Jonathan Crowston –back, left to right)

Robert Ritch commenting on measurement of intraocular pressure

IOP AS A RISK FACTOR FOR GLAUCOMA DEVELOPMENT AND PROGRESSION

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Consensus points

- There is *strong evidence* to support higher mean intraocular pressure (IOP) as a significant risk factor for the development of glaucoma.
- There is *strong evidence* to support higher mean IOP as a significant risk factor for glaucoma progression.
- IOP is more variable in glaucomatous than in healthy eyes, but both 24-hour IOP fluctuation and IOP variation over periods longer than 24 hours tend to be correlated with mean IOP.
- There is currently *insufficient evidence* to support 24-hour IOP fluctuation as a risk factor for glaucoma development or progression.
  Comment: 24 hour IOP measurements are comprised of day-time (diurnal) and night-time (nocturnal) periods.
  Comment: Diurnal IOP is generally highest after awakening and decreases during the day-time period.
  Comment: Posture is an important variable in the measurement of IOP; IOP in the sitting position is generally lower than in the supine position.
- There is currently *insufficient evidence* to support IOP variation over periods longer than 24 hours as a risk factor for glaucoma development and progression.

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- Sufficiently low blood pressure, combined with sufficiently high IOP, generates low ocular perfusion pressure and is associated with increased open-angle glaucoma (OAG) prevalence in cross-sectional studies.
  Comment: Physiologic IOP variation occurs in regular rhythmic cycles. Regular IOP peaks and valleys are normal, and compensatory mechanisms are in place to preserve the integrity of the tissue and the organism.
  Comment: The peaks and troughs in circadian IOP and blood pressure do not necessarily occur simultaneously.

1. Mean IOP as a risk factor for glaucoma

Intraocular pressure has been consistently demonstrated to be associated with incidence, prevalence and progression of glaucoma. Below, we summarize the current evidence from major studies with regards to the relationship between IOP and risk of glaucoma development and progression.

Clinical trials: Mean IOP as a risk factor for glaucoma development

There is strong evidence to support higher mean IOP as a risk factor for the development of glaucoma. The evidence comes from prospective, multi-center, randomized clinical trials and also from smaller prospective studies. While some studies have not found higher IOP levels to be associated with risk of glaucoma development, these studies in general had less-well defined end-points and may have lacked the power to detect significant associations.

The *Ocular Hypertension Treatment Study (OHTS)*[1] has provided the best evidence with regards to the role of IOP as a risk factor for glaucoma development. In the OHTS, 1636 ocular hypertensive patients were randomized to either observation or treatment and followed for a median time of 72 months. Ocular hypertension was defined based on the presence of qualifying IOP between 24 mmHg and 32 mmHg in one eye and between 21 mmHg and 3 2 mmHg in the other eye, gonioscopically open angles, normal visual fields and normal optic discs. Participants randomized to medication began treatment to achieve a target IOP of 24 mmHg or less and a minimum of 20% reduction in IOP from the average of the qualifying IOP and IOP at the baseline randomization visit. At baseline, mean IOP was 24.9 ± 2.6 mmHg and 24.9 ± 2.7 mmHg in the treated and observation groups, respectively. The average IOP reduction in the treated group was 22.5% ± 9.9% compared to 4.0% ± 11.6% in the observation group. At 60 months, the cumulative probability of developing POAG was 4.4% in the medication group compared to 9.5% in the observation group, which translates into a 54% relative reduction in the risk of developing POAG with treatment.

A subanalysis of the OHTS data including only African-American participants (25% of the original cohort) showed that the percentage developing POAG during follow-up was significantly lower in the treated group (8.4%) compared to the observation group (16.1%).[2] The protective effect of medication among

African-American participants (hazard ratio = 0.50) was not different from its protective effect among other participants (hazard ratio = 0.36; P= 0.40 for race interaction). Therefore, in the OHTS, IOP reduction was significantly associated with lower POAG incidence regardless of race.

In the analysis of baseline predictive factors for development of POAG, 1 mmHg higher baseline IOP was associated with a 10% higher risk of developing POAG during follow-up, after adjustment for other predictive factors in a multivariate model.[3] For this calculation, baseline IOP was calculated from four to six baseline IOP measurements per eye.

The *European Glaucoma Prevention Study (EGPS)*[4] was also designed to investigate whether the onset of POAG can be prevented or delayed in ocular hypertensive patients by medical hypotensive therapy. Inclusion criteria for the EGPS were similar to the OHTS, requiring participants to have normal visual fields and normal optic discs at baseline. However, qualifying IOP had to be between 22 mmHg and 29 mmHg in at least one eye on two consecutive measurements taken at least two hours apart. There were no inclusion or exclusion criteria defined in the study protocol as regards the IOP in the fellow eye.[5] The EGPS randomized 1081 patients to treatment with dorzolamide or placebo, with a planned follow-up of five years. However, only 64% of patients randomized to dorzolamide and 75% of the patients randomized to placebo completed the study. Mean IOP at baseline was 23.4 mmHg and 23.5 mmHg in the dorzolamide and placebo groups, respectively. Mean IOP reduction at 5 years was 22.1% in the dorzolamide group and 18.7% in the placebo group. At the completion of the study, there was no statistically significant difference in the cumulative probability of developing POAG between patients randomized to dorzolamide versus placebo (13.4% versus 14.1%, respectively; HR = 0.86; 95% CI: 0.58-1.26).

Several reasons have been proposed to explain the conflicting results between the OHTS and EGPS, including regression to the mean effects, lack of target IOP and selective loss to follow-up.[6, 7] In the OHTS, a target IOP lowering of at least 20% below baseline was required in the treatment group, and investigators were free to use any and all commercially-available medications to reach that goal. In contrast, patients in the EGPS were treated with dorzolamide only, regardless of its effectiveness. Therefore, part of the non-significant differences between the dorzolamide and placebo groups in the EGPS may be due to dorzolamide's relatively modest efficacy in lowering intraocular pressure. A 'regression to the mean' effect was also apparent in the EGPS, causing an IOP reduction to occur in both the dorzolamide and placebo groups. In the EGPS only 2 eligibility IOP measurements were required and were permitted to take place on the same day, separated by at least 2 hours. It is likely that for some patients, measurements were taken when the IOP was minimally higher due to diurnal fluctuations. Because treatment was initiated without rechecking untreated IOP at other visits, the next IOP would be, on average, more likely lower than baseline, regardless of any treatment effect. Interestingly, although mean IOP at baseline was relatively similar in the OHTS and EGPS studies

(24.9 and 23.6 mmHg, respectively), there was a large difference in distribution of IOP between the two studies. Approximately 65% of EGPS participants would not have been eligible for inclusion in the OHTS because their IOPs would be considered too low. In the EGPS, the same physician who adjusted the mires recorded the IOP level. Physicians also had the knowledge of the 22 mmHg cutoff for study inclusion, which can introduce significant bias. Also of note is that patients with higher IOP levels were more likely to withdraw from the study, which resulted in subjects with lower levels of IOP completing the trial and an apparently misleading sustained decrease of IOP over time both in dorzolamide and placebo groups.

Despite the fact that the EGPS could not find significant differences between dorzolamide and placebo groups on the rate of POAG development, its results are compatible with higher IOP being a risk factor for POAG incidence. A 1 mmHg higher baseline IOP was associated with 18% higher risk of developing POAG (HR = 1.18; 95% CI: 1.06 – 1.31; P = 0.002) in a multivariable model containing age, presence of cardiovascular disease, CCT and presence of pseudoexfoliation.[8]

In the pooled analysis of the OHTS and EGPS control groups (1319 patients followed without treatment), 1 mmHg higher baseline IOP was associated with 9% higher risk of developing POAG (HR = 1.09; 95% CI: 1.03 to 1.17), after adjustment for age, central corneal thickness, baseline vertical C/D ratio and baseline pattern standard deviation.[9] It is important to note that even for this pooled analysis, the 95% confidence interval was still relatively large, ranging from 1.03 to 1.17. That is, each 1 mmHg increased IOP could be associated with 3% increased risk up to 17% increased risk.

Clinical trials: Mean IOP as a risk factor for glaucoma progression

There is strong evidence to support higher mean IOP as a risk factor for progression of disease in individuals with glaucoma.

The *Early Manifest Glaucoma Trial (EMGT)*[10] was designed specifically to evaluate the effect of IOP-lowering treatment on progression of glaucoma. The EMGT enrolled 255 newly diagnosed, previously untreated, open-angle glaucoma patients who had reproducible visual field defects at baseline (median MD = -4dB). Patients with advanced visual field loss or IOP greater than 30 mmHg at baseline were excluded. Patients were randomized to 360º trabeculoplasty plus betaxolol versus no treatment. Eyes stayed in their allocation arms unless significant progression occurred. If the IOP in treated eyes exceeded 25 mmHg at two consecutive follow-ups or 35 mmHg in control eyes, latanoprost was added. Patients were followed for a median of six years, with excellent retention. Baseline IOP in treated and untreated groups were 20.6 ± 4.1 mmHg and 20.9 ± 4.1 mmHg, respectively. Mean IOP reduction was 25% in the treated group, with no changes in the control group. At study closure, the proportion of patients who developed progression was significantly larger in the control versus the treatment group (62% versus 45%, respectively; HR = 0.60; 95%

CI: 0.42 – 0.84; P = 0.003). Differences between treated and untreated patients remained when results were stratified by baseline IOP level (< 21 mmHg or ≥ 21 mmHg), degree of visual field damage, age or presence of exfoliation.

In the analysis of predictive factors for progression of glaucoma in the EMGT, each 1 mmHg higher baseline IOP increased the risk of progression by 5% (HR = 1.05; 95% CI: 1.01-1.10).[11] Also, each 1 mmHg IOP decrease with treatment (baseline IOP minus 3-month follow-up IOP) was associated with a 10% reduction in the chance of progression (HR = 0.90; 95% CI: 0.86 – 0.94; P<0.001). When the mean IOP over all follow-up visits was analyzed, each 1 mmHg mean IOP was associated with 13% higher risk of progression (HR = 1.13; 95% CI: 1.07-1.19; P<0.001). Results were consistent in multivariate models adjusting for other risk factors.

The *Collaborative Normal Tension Glaucoma Study (CNTGS)*[12] enrolled 230 patients with unilateral or bilateral normal tension glaucoma characterized by glaucomatous cupping and a defined type of visual field defect and a median IOP of 20 mmHg or less in 10 baseline measurements (with no recorded IOP above 24 mmHg).[12] Eyes were randomized to no treatment or to have IOP reduced by 30% by medical or surgical intervention. Mean IOP at baseline was 16.9 ± 2.1 mmHg and 16.1 ± 2.3 mmHg in the treated and control groups, respectively. Mean IOP during follow-up was 10.6 ± 2.7 mmHg and 16.0 ± 2.1 mmHg, respectively. Significantly fewer eyes progressed in the treated group versus the control group (12% versus 35%).

In an analysis of risk factors associated with progression in the CNTGS, however, the untreated baseline median intraocular pressure was not significantly related to the rate of progression. According to the CNTGS authors,[13] this discrepancy could be potentially explained by the fact that the rate of progression could be related not to the absolute level of IOP, but to the amount by which the IOP exceeds the damage threshold of a particular individual. The amount of excess could be unrelated to the presenting baseline IOP in NTG patients. Therapeutic lowering of the pressure would reduce the IOP relative to the damage threshold and slow the rate of progression.

Other prospective clinical trials have also provided evidence that IOP is a risk factor for glaucoma progression. However, it is important to note that these trials were not originally designed to specifically address the relationship between IOP reduction and glaucoma progression.

The *Advanced Glaucoma Intervention Study (AGIS)*[14] was a long-term study designed to evaluate the clinical course of medically uncontrolled OAG by two surgical treatment sequences. Of 591 patients, 789 eyes were randomized to a treatment sequence of (1) argon laser trabeculoplasty, trabeculectomy and trabeculectomy (ATT); or (2) trabeculectomy, argon laser trabeculoplasty and trabeculectomy (TAT). To be eligible for the AGIS, eyes had to meet specific criteria consisting of combinations of uncontrolled IOP with medications, glaucomatous visual field defect and/or optic disc damage. During follow-up, surgical interventions were supplemented by medical therapy with the goal of reducing IOP to less than 18 mmHg. One of the AGIS reports[14] examined

the relationship between control of IOP and visual field deterioration. In the so-called Associative Analysis, eyes were divided according to the percent of visits for which the eye presented IOP less than 18 mmHg. Eyes were assigned to one of four categories: 100% (group A), 75% to less than 100% (group B), 50% to less than 75% (group C) and 0 to less than 50% (group D). The mean IOP over the six years of follow-up was 12.3 mmHg in group A, 14.7 mmHg in group B, 16.9 mmHg in group C and 20.2 mmHg in group D. Eyes in group A had mean changes from baseline in visual field defect score close to zero. Patients in groups B, C and D had progressively more changes in visual field compared to group A. At seven years of follow-up, eyes in group D had an estimated worsening of 1.93 (95% CI: 0.82 – 3.05) units of visual field defect score compared to eyes in group A, after adjustment for potentially confounding covariates.

In the analysis of predictive factors for progression of visual field loss in the AGIS, each 1mmHg higher mean IOP level at the first 18 months of follow-up was associated with a 0.10 increase in visual field defect score during the rest of follow-up (P = 0.002), after adjusting for race, assigned intervention sequence, age, diabetes, gender, reference IOP and reference visual field defect score.[14]

It is important to note that although AGIS results support a relationship between IOP and rate of glaucoma progression, the secondary analyses described above involved non-randomized groups that had potentially imbalanced covariate values. However, results were consistent even after adjustment for potentially confounding covariates using statistical methods.

The *Collaborative Initial Glaucoma Treatment Study (CIGTS)*[15] randomized 607 patients with newly diagnosed OAG to medical versus surgical treatment. Each patient was assigned a target IOP that was a function of baseline IOP and a reference visual field, so that patients with more severe disease were required to have more IOP lowering. Average MD of baseline visual fields was -5dB. Patients assigned to the medical arm were treated with IOP-lowering treatments at the discretion of the treating physician, whereas patients assigned to the surgical arm underwent trabeculectomy (with 5-FU at the discretion of the surgeon). Average baseline IOPs were 27 mmHg and 28 mmHg in the surgical and medical group, respectively. IOP was reduced, on average, by approximately 48% and 35% in the surgical and medical group, respectively. Visual fields were graded using a defined protocol (increasing scores reflecting increasing VF loss and ranging from 0 to 20). Both groups had, on average, minimal changes in visual field scores over time. Repeated measures analysis of variance modeling adjusting for visual field score at baseline, age, race, gender and diagnosis showed that initial surgery resulted in 0.36 unit worse visual field score than initial medical treatment (P = 0.003); however, when the influence of cataract was included in the model, the difference decrease to 0.28 units (P = 0.07). The greater lowering of mean IOP in the surgically treated group apparently was of no further benefit in CIGTS patients. However, a subsequent analysis of longer-term results did reveal a better outcome for the surgical group in a subset of subjects with a greater degree of initial visual field loss.[16]

When contrasted to the EMGT, however, results from the CIGTS seem to indicate that a substantial reduction of IOP decreases the rate of glaucoma progression. Both studies included patients with relatively early glaucoma at baseline (average MD was -4dB in EMGT and -5dB in CIGTS), although different methods were used to assess visual field progression. In the medically treated patients in the CIGTS an IOP reduction of approximately 35% resulted in no net visual field loss, whereas in the EMGT, an average IOP reduction of 25% resulted in 45% of the patients developing visual field loss over time. Whereas in the CIGTS, medical treatment was aggressive to reduce the IOP to the target level, a fixed treatment protocol was used in the EMGT. The mean ± SD IOP reduction from baseline IOP in the EMGT was -4.5 ± 3.4 mmHg, that is, assuming a normal distribution, approximately 25% of the patients had IOP reduction less than 2 mmHg with treatment and approximately 35% had IOP reduction less than 3 mmHg. The suboptimal IOP reduction in many patients is likely to be related to the high rate of visual field progression in the EMGT.

2. IOP fluctuation as a risk factor for glaucoma

IOP varies over time. This variation is predictable under certain conditions – for example, a conserved 24-hour rhythm exists, and fellow eyes often exhibit symmetrical 24-hour IOP variability. IOP can also vary from this predictable pattern due to many physiological and environmental factors, or variation may reflect abnormal regulation of IOP due to disease of the inflow/outflow system. At the present time, there is no useful tool to continuously monitor normal variations and spontaneous fluctuations of IOP in a real life situation. Based on studies in sleep labs and using home tonometry, the normal range of daily physiological fluctuation is believed to be ± 5 mmHg.[17,18]

24-Hour IOP fluctuation

Tonometry performed over a 24-hour period may be subdivided into diurnal (daytime) and nocturnal (nighttime) measurements. 24-hour IOP fluctuation may be due to changes in aqueous humor formation, trabecular outflow, uveoscleral outflow, and/or other as yet unidentified mechanisms in aqueous humor dynamics. Although 24-hour tonometry has the potential to provide much more information about IOP in the individual patient than does isolated office-hour tonometry, performing 24-hour IOP measurements is unrealistic in most office settings.

Several patterns of 24-hour IOP fluctuation have been identified in glaucomatous as well as in healthy eyes.[17] Diurnal IOP is generally higher in the morning and lower is the evening. During the diurnal period, IOP fluctuates more in glaucoma patients than in healthy individuals.

Nocturnal IOP data is limited, and is derived predominantly from sleep laboratories. Analogous to ambulatory blood pressure monitoring, it is important

to account for postural effects to fully understand 24-hour and nocturnal IOP measurements. Sitting and supine IOP readings are significantly different; IOP in while sitting is generally lower than when measured in a supine position.

Long-term IOP variation

Long-term IOP variation is defined as the variability of IOP observed over time, and is generally acquired at various daytime hours during multiple office visits occuring over weeks, months or years. Long-term IOP variation comprises both the cyclical 24-hour fluctuation as well as variation over the longer term; thus long-term IOP variation may reflect both normal aging as well as the disease process, *e.g.*, gradually rising IOP as outflow is progressively impaired.

The extent to which long-term variation reflects the underlying 24-hour rhythm may be minimized by taking measurements at the same time of day at each visit; conversely, a broader picture of long-term IOP variation may be gained by obtaining as many measurements as possible over multiple visits at random times of the day.

IOP variability in glaucoma

IOP tends to vary most in angle closure glaucoma (ACG) due to intermittent closure of the angle, and in secondary open-angle glaucomas such as pigmentary and exfoliation syndromes, most likely as a consequence of intermittent dispersion of pigmentary material onto the trabecular meshwork. IOP variability tends to increase also in primary open-angle glaucoma (POAG); the extent of fluctuation appears to closely correlate with mean IOP level.[19-21] Despite several reports regarding the clinical relevance of IOP fluctuation in POAG, as of today there are limited and generally inconsistent results concerning the actual risk for the onset or progression of POAG associated with either 24 hour fluctuation or long-term variability.[22]

Clinical trials: Long-term IOP variation as a risk factor for glaucoma

Two studies recently addressed the relationship between long-term IOP variation and the progression of glaucoma with conflicting results. In a *post-hoc* analysis of AGIS data, Nouri-Mahdavi *et al*.[23] found that long-term IOP fluctuations were a statistically significant risk factor associated with visual field progression. Long-term IOP variation was calculated as the standard deviation of all available IOP measurements during follow-up, after the initial surgical procedure. In a multivariate logistic regression model, each 1 mmHg higher IOP SD was associated with 31% higher odds of developing progression. According to the study, eyes with an IOP SD < 3 mmHg remained stable over time, whereas eyes with an IOP SD ≥ 3 mmHg demonstrated significant progression.

As part of the EMGT, Bengtsson *et al*.[19] did not find long-term IOP variation to be associated with visual field progression. The definition of long-term

IOP variation was also based on the standard deviation of IOP measurements over time. However, IOP measurements were only included up to the date of progression (for progressors) or last follow-up visit (for non-progressors). The analysis involved 255 patients with a median follow-up time of 8 years. Mean long-term IOP fluctuations were 2.02 mmHg and 1.78 mmHg in patients who progressed and in patients who did not progress, respectively. In a multivariate Cox regression model, IOP variation was not a significant risk factor for progression (adjusted HR = 1.0; 95% CI: 0.81-1.24; P = 0.999). The model adjusted for mean IOP, age, baseline IOP, presence of exfoliation, severity of visual field loss at baseline and whether one or both eyes were eligible for the study. Mean IOP was significantly associated with risk of progressive visual field loss. Each 1 mmHg higher mean IOP was associated with 11% increase in risk. Similar results were identified when treated and control patients were analyzed separately.

Several factors have been proposed to explain the different results with regards to the role of IOP fluctuation in the EMGT and the AGIS,[22] including different study designs, different populations and different outcome criteria. Although both studies calculated long-term IOP variation as the standard deviation of measurements over time, the AGIS calculations of IOP variation included measurements obtained after progression had occurred, whereas in the EMGT, measurements were obtained only up to the study endpoint. After progression occurred, it is possible that treatment would have been intensified and resulted in further IOP lowering and a consequent increase in IOP variation. This could have resulted in spurious positive relationship between IOP fluctuation and risk of progression in the AGIS investigation. In fact, when the EMGT data was re-analyzed including post-progression IOP measurements in the calculation of fluctuation, the authors also found IOP fluctuation to be related to progressive visual field damage.[19]

Both the AGIS and the EMGT included only patients with definite glaucoma diagnosis at baseline. It is possible that the role of long-term IOP variation as a risk factor for glaucoma development may be different than for glaucoma progression. Results from the OHTS in this regard have not yet been published.

The EGPS did not find long-term IOP variation to be significantly associated with the risk of conversion from ocular hypertension to glaucoma. Long-term IOP variation was also calculated as the standard deviation of mean IOP over time. In the univariate analysis long-term IOP fluctuation had a HR = 0.87 per 1 mmHg higher (95% CI: 0.70-1.09; $p = 0.23$). In the multivariate model, adjusting by inter-current factors such as disc hemorrhage, diabetes, systemic hypertension, systemic diuretics, systemic ACE inhibitors, treatment arm and all the baseline predictive factors (age, CCT, PSD, vertical c/d ratio, vertical c/d ratio asymmetry), mean IOP was significantly associated with glaucoma conversion (adjusted HR = 1.12 per 1mmHg higher; 95% CI: 1.03 to 1.22; $p = 0.007$).[24]

A recent report from the *Diagnostic Innovations in Glaucoma Study (DIGS)* by Medeiros *et al.*[25] involved 126 ocular hypertensive patients followed for an

average time of seven years. They did not find long-term IOP variation to be significantly associated with the risk of conversion from ocular hypertension to glaucoma. All patients in the study had high intraocular pressure (>22mmHg), normal optic discs and normal visual fields at baseline. Conversion to glaucoma was defined based on the development of repeatable visual field loss or progressive change to the optic disc as evaluated by stereophotographs. Forty eyes of 31 subjects developed POAG during follow-up. Long-term IOP variation was calculated as the standard deviation of IOP measurements over time. In a multivariate model adjusting for age, CCT, PSD, vertical cup/disc ratio and mean IOP, long-term IOP variation was not significantly associated with glaucoma conversion (adjusted HR = 1.08 per 1 mmHg higher; 95% CI: 0.79 to 1.48; P = 0.620). Mean IOP was significantly associated with glaucoma conversion (adjusted HR = 1.20 per 1 mmHg higher; 95% CI: 1.06 to 1.36; P = 0.005).

In the *Malmö Ocular Hypertension Study*, Bengtsson and Heijl[26] followed high risk ocular hypertensive patients for ten years as part of a prospective investigation in order to compare the rates of development of glaucomatous visual field loss in patients treated with timolol compared to placebo. Patients were followed every three months with Goldmann tonometry measurements obtained at 8:00am, 11:30am and 3:30pm. No association was found between parameters measuring long-term IOP variation and the risk of glaucoma development.

In designing or evaluating studies of the relationship between IOP fluctuation and risk of glaucoma development and progression, it is important to recognize that variation is usually correlated with the level of mean IOP. Eyes with higher mean IOP tend to have higher variation. Therefore, when developing multivariate models to investigate the risk attributable to long-term IOP variation, it is important to adjust for mean IOP level.

Clinical trials: 24-Hour IOP fluctuation as a risk factor for glaucoma

A few investigators have explored the role of 24-hour IOP fluctuation and the risk of glaucoma progression. Asrani *et al*.[27] found that diurnal IOP fluctuation, as measured by home self-tonometry, was a significant risk factor for progression. In their study, patients were recruited to perform home tonometry – measurements were obtained at baseline and their association with risk of progression over time was investigated. This important study has some limitations – a large number of patients were excluded due to loss of follow-up, no pre-defined criteria for visual field progression were used and the predictive effect of IOP measurements obtained during follow-up was not taken into account. Nonetheless, the authors found a significant hazard ratio for diurnal IOP fluctuation in a model adjusting for office IOP (mean of two measurements at baseline), age, race, gender and severity of visual field loss at baseline.

Approaching the issue differently, Liu and colleagues[28] performed IOP measurements at a sleep lab over the 24-hour period in both untreated glaucoma patients and healthy subjects, and did not find any significant difference in 24-hour IOP fluctuations between these two groups, suggesting that larger diurnal

IOP fluctuations are not strongly associated with a glaucoma diagnosis. It is clear that larger, prospective longitudinal studies evaluating the predictive ability of 24-hour IOP measurements for development or progression of glaucoma are needed to confirm or refute this hypothesis.

3. Provocative testing

The search for a clinically-useful provocative test in glaucoma, analogous to a cardiac stress test or glucose tolerance test, has been sought for many decades. Ideally, such a test would identify those individuals at highest risk of developing glaucoma or progressing. Both steroid and water-drinking tests were first introduced in the 1950s and 1960s.[29] The steroid provocative test has proven to be of limited value in screening patients for glaucoma. The ability of IOP response to a topically-applied synthetic steroid to predict the development of glaucomatous visual field loss was not as good as the predictive power of a multivariate model that included patient age, race, baseline IOP, baseline outflow facility, baseline cup/disk ratio, and systemic hypertension. At the present time, steroid provocative testing has been abandoned.

The water-drinking test (WDT) has the potential to evaluate the eye's ability to deal with an extrinsically-induced transient elevation in IOP. Susanna and co-workers have used the WDT to compare the efficacy of hypotensive drugs,[30] the likelihood of glaucoma progression [31] and its correspondence to worse visual field mean defect.[32] As suggested by Brubaker,[33] the WDT may be a clinically useful test for assessing the status of the ouflow of aqueous humor, as it is a relatively easy way to quantify the eye's ability to prevent and dampen pressure spikes.

Although the WDT is technically simple and could be deployed for general clinical use, further studies are necessary to validate the test in clinical practice.

4. IOP in relation to blood pressure (ocular perfusion pressure)

As described above, different clinical and epidemiological studies have demonstrated a strong correlation between the level of intraocular pressure and the prevalence and incidence of glaucomatous damage. Glaucoma occurs in eyes with 'normal' IOP (the range of IOP found in 95% of eyes without disease), but with increasing frequency as the IOP increases, without a clearly defined cut-off level below which the eye is safe and above which the eye is certain to be harmed. The occurrence of glaucomatous damage therefore seems to depend on the susceptibility of an individual optic nerve head (ONH) structure to a given level of IOP.[34, 35] The existence of patients who develop glaucoma despite low levels of IOP and also those primary open angle glaucoma that continue to progress despite IOP lowering treatments suggests that there are contributing

pathogenic factors other than IOP that may sometimes dominate. Abnormal ocular blood flow physiology and large variation of ocular perfusion pressure (IOP in relation to BP) are among the suggested risk factors for the damage to the ONH structure in glaucoma.[36-40]

Mean ocular perfusion pressure (MOPP)

Ocular perfusion pressure is the driving force for the blood circulation in the eye and is defined as the difference between the mean arterial blood pressure (MAP) and venous pressure. The venous pressure in the eye should be marginally higher than the intraocular pressure (IOP) for the vein to maintain an open lumen for blood circulation. Therefore, the perfusion pressure for intraocular vessels is often estimated as the mean ophthalmic arterial pressure (arbitrarily defined as 2/3 the brachial arterial pressure) minus the venous pressure, which is approximately the IOP. The mean ocular perfusion pressure (MOPP) is estimated from the mean brachial arterial pressure and IOP with the formula:[41]

$$MOPP = \frac{2}{3}\,[DBP + \frac{1}{3}\,(SBP - DBP)] - IOP,$$

where *DBP* and *SBP* are the brachial diastolic and systolic blood pressures respectively.

Diurnal MOPP

IOP and BP and, therefore, MOPP have physiologic circadian variations, but the peaks and troughs in circadian IOP and BP do not necessarily occur simultaneously. In fact, there are times during the day such as early hours of morning during which high IOP coincides with relatively low BP and results in low ocular perfusion pressure.[17,39] In healthy individuals, the ocular blood flow is autoregulated through the change in the resistance of vessels to keep the tissue blood flow and metabolic activity stable, thus preserving the integrity of the tissue in the face of changes in MOPP.[41] If the autoregulatory system is faulty or if the minimum perfusion pressure reaches a threshold beyond which the metabolic activity is interrupted, periods of inadequate perfusion might happen that result in ischemia. If the ischemia is prolonged, there will be local tissue necrosis, or ganglion cell apoptosis may be triggered. It has been demonstrated that those with perfusion pressure lower than 50 mmHg are at a greater risk for OAG and at 30 mmHg the risk is four times greater.[42,43]

Population-based studies and ocular perfusion pressure

Several population-based studies have demonstrated the association between low perfusion pressure and risk of glaucoma. The results of the Baltimore Eye Survey indicated that lower perfusion pressure was strongly associated with an increased prevalence of POAG, and that POAG was associated with an altera-

tion in factors related to ocular blood flow and a breakdown of autoregulation.[43] The Baltimore Eye Survey also found that systemic hypertension was protective in early glaucoma, possibly due to an increase in ocular perfusion pressure. However, late in hypertension, the risk of glaucoma was increased and it was suggested that vascular sclerosis reduced blood flow despite an elevated blood pressure.[44] The Barbados study[45] found that lower perfusion pressure at baseline increased the adjusted relative risk of OAG approximately three-fold, and both the Egna-Neumarkt Study[42] and Proyecto VER[46] demonstrated that reduced diastolic perfusion pressure was an important risk factor for POAG.

Issues requiring further attention

IOP and IOP Fluctuation/Variation

- What IOP parameter (mean IOP, IOP fluctuation, peak IOP or area under IOP curve) best relates to the risk of glaucoma development and progression? How can a study be designed to investigate this issue?
- How to best characterize the relationship between IOP fluctuations and risk of glaucoma development?

IOP, Blood Pressure and MOPP

- Is the incidence of glaucoma associated with the magnitude of the ocular perfusion pressure variation (absolute change or percentage change), a sustained level of low perfusion pressure or the amount of time spent below a critical threshold?
- Are there critical times during the day that sampling of IOP and BP are more important in order to get a clear idea about the range of fluctuations of perfusion pressure, or are short-interval measurements across 24 hours sufficient to identify the perfusion pressure fluctuations?
- Is the rate of progression in an individual titrated by the level of IOP, and indirectly by the level of MOPP or by the amount of change?
- Do brief periods of insufficient ocular perfusion pressure lead to brief periods of ischemia within the optic nerve head or lamina cribrosa, such that there is reperfusion injury to axons, to support tissues (astroglia or lamina cribrosa), or both?
- Do brief periods of sufficient ischemia to axon segments in the region of the optic disc interfere with retrograde transport of trophic factors such that ganglion cell apoptosis is triggered?
- Does the sensitivity of a glaucomatous eye increase over time in response to (a sustained or episodes of) low perfusion pressure along with glaucoma progression or does it remain the same?
- How does the presence of systemic hypertension or its treatment affect the

ocular perfusion pressure in glaucoma patients at different age or hypertension levels?

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James Brandt presenting the section on IOP as a risk factor

Consensus panel to discuss variation of IOP. From left to right: Kouros Nouri-Mahdavi, Roberto Vessani, Felipe Medeiros, Yasuaki Kuwayama and Esther Hoffman

Consensus panel to discuss variation of IOP. From left to right: Esther Hoffman, Michel Kook, John Liu and Tony Realini

Remo Susanna presenting the section on variation of IOP

Rohit Varma commenting on IOP as a risk factor

Douglas Anderson commenting on IOP as a risk factor

John Liu and Remo Susanna discussing consensus points on variation of IOP

John Liu (left) and Kouros Nouri-Mahdavi (right)

From left to right: Makoto Araie, Ted Garway-Heath, Robert N. Weinreb and James D. Brandt

EPIDEMIOLOGY OF INTRAOCULAR PRESSURE

Anne Coleman

Anne L. Coleman, Louis Pasquale, Christopher Girkin, Rupert Bourne, Aiko Iwase

Contributors: Rupert Bourne, Anne L. Coleman, Paul Foster, David Friedman, Christopher Girkin, Aiko Iwase, David Mackey, Louis Pasquale, Rohit Varma, Tetsuya Yamamoto, Lingling Wu

Consensus points

- Self-described race is a poor summary of human biodiversity.
  Comment: Self-described race still contains important information that both correlates well with genetic measures of ancestry and disease risk *on a populations basis.*
- Evidence for differences in IOP between blacks and white is contradictory from available populations-based studies.
- Evidence for a relationship between IOP and age is contradictory from available populations-based studies.
- Evidence for a relationship between IOP and gender is contradictory from available populations-based studies.
- Studies with similar methodology comparing differences in IOP between multiple racial groups allowing direct comparisons generally have not been performed.
  Comment: IOP appears lower in Asian populations than populations with European and African ancestry, however direct comparisons have not been made.
- Variations in study designs and IOP measurement techniques limit comparison of mean IOPs across racial, ethnic and regional strata.
  Comment: Very few population-based surveys have included important biomarkers such as CCT that may effect the measured IOP.
  Comment: IOP is higher in eyes with shorter axial anterior chamber depth as a result of pathological angle-closure.
  Comment: Corneal radius of curvature is a potential source of measurement error, and should be adjusted for when using an applanation tonometer.

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edited by Robert N. Weinreb, James D. Brandt, David Garway-Heath and Felipe A. Medeiros

- There is a strong positive relationship between IOP and OAG, although prevalent and incident OAG cases occur commonly at IOP < 22 mmHg.

Executive summary

Epidemiology is the study of the distribution, determinants, and frequency of disease or characteristics in *groups* of persons or in populations. This information is used to improve our understanding of prevalence, incidence, pathogenesis, and treatment of diseases. Because diseases such as open-angle glaucoma are not randomly distributed throughout a population, factors that influence this distribution may provide valuable clues as to what factors are important in diseases. Intraocular pressure is a risk factor that is causally related to open-angle glaucoma and may provide valuable information regarding the distribution and frequency of open-angle glaucoma. The goal of this section is to evaluate what we currently know about the distribution and associations of intraocular pressure (IOP) from population-based studies and to explore whether open-angle glaucoma should be categorized into two separate diseases using an IOP cut-off of 21 or 22 mmHg.

Epidemiology is not only the study of diseases but also a scientific discipline that provides study designs and analytical tools for evaluating population-based and clinical studies. Throughout this consensus statement the authors tried to carefully select studies that very clearly defined their study population, used standardized definitions, had a sufficiently high participation rate and provided enough detail that the study could be repeated by different investigators, if so desired. One of the biggest challenges was how we handled race/ethnicity. In most epidemiological studies, race/ethnicity are self-reported and there was concern that this may be inadequate. Although there are certainly weaknesses in self-describe race, as there are with the measurement of any explanatory variable in epidemiology, self-describe race does have genetic underpinnings (*i.e.*, self-describe race clusters pretty tightly with ancestry determined by SNP analysis- there are multiple references), and the clear relationship between this demographic variable with multiple disease states cannot be ignored. The Seminole article often quoted by Rosenberg NA, Pritchard JK, Weber JL *et al*. clearly states in the discussion that for most epidemiologic studies self-describe race is an adequate surrogate for genetically described race (by Single Nucleotide Polymorphisms or SNPs). For example, although self-reported blacks in the United States are largely of mixed race, genetic admixture analyses show clear differences between self-reported blacks and whites, indicating that self-reported race provides a means for identifying distinct groups (Burchard EG, Ziv E, Coyle N, *et al*. The importance of race and ethnic background in biomedical research and clinical practice. N Engl J Med 2003; 348: 1170-5.) When using a large number of markers, genetically distinct groups can be almost completely inferred from self-reported race. (Tang H, Quertermous T, Rodriguez B, *et al.* Genetic structure, self-identified race/ethnicity, and confounding in case-control

Table 1A. Summary of published population-based studies on IOP

First author	Year	Ethnicity	Country	Project name (or location)	Age range	Partici-pation rate (%)	No of sample	IOP(mmHg)	Subjects	Comments
Arkell *et al.*	1987	Eskimos	USA		15 yrs ≤	84	1686	13.6(MB) 13.8(WB)	All	
Foster *et al.*	1998	Mongolian	Mongol	(Hovsgol)	40 yrs ≤	94.2	1000	12.8(MR) 12.6(ML) 12.4(WR) 12.6(WL)	All	
Dandona *et al.*	2000	India	India	the AndhraPradesh Eye Disease Study	30 yrs ≤	85.4	2522	15.4(MWB)	Non-glau-coma	
Foster *et al.*	2003	Chinese	Singapore	the Tanjong Pagar Study	40-79	71.8	1232	15.3(MR) 15.4(WR)	All 40 yrs	
Ramakrishnan *et al.*	2003	India	India	the Aravind comprehen-sive Eye Survey	40 yrs ≤	93	5150	14.5(MWB)	Non-glau-coma 40 yrs	
Iwase A *et al.*	2004	Japanese	Japan	The Tajimi Study	40 yrs ≤	78.1	3120	14.6MWR) 14.5(MWL)	All	
Hashemi *et al.*	2005	Iranian	Iran	The Tehran Eye study	all ages	70.3	4565	14.5(MWB) 14.4(MB) 14.5(WB)	All	
Raychaudhuri *et al.*	2005	Indian	India	the West Bengal Glau-coma Study	50 yrs ≤	83.1	1594	13.8(MWR) 13.7(MWL)	Non-glau-coma	
Rahman *et al.*	2004	Bengalese	Bangladesh	Bangladesh Study	35 yrs ≤	65.9	2347	15.0(MWR) 15.0(MWL)	All	
Bourne RRA	2003	Thai	Thailand	(Rom Klao)	50 yrs ≤	88.7	701	13.4(MWR)	All right	
Shiose *et al.*	1991	Japanese	Japan	Japan Nation Wide	40 yrs ≤	50.5	8126	13.1(MB) 13.4(WB)	Non-glau-coma	NCT,Participation ratio was low (50.6%), NTG:IOP<21
Hsin-Yi *et al.*	2005	Chinese	Taiwan	The Shihpai Eye Study	65 yrs ≤	66.6	1361	12.7(MB) 13.3(WB)	All	NCT
Xu *et al.*	2006	Chinese	China	The Beijing Eye Study	40-101	83.4	4439	16.1(MWB)	All	NCT
Salmon *et al.*	1993	MIX	South Africa	(Western Cape)	40 yrs ≤	82.7	987	17.0(NB) 17.0(WB)	All	

Table 1A. Continued.

First author	Year	Ethnicity	Country	Project name (or location)	Age range	Participation rate (%)	No of sample	IOP(mmHg)	Subjects	Comments
Wallace *et al.*	1969	Black	Jamaica	(Jamaica)	35-74 yrs	84.9	574	16.8(MR) 16.5(ML) 16.5(WR) 16.4(WL)	Non-glaucoma	
Mason *et al.*	1989	Black	West Indies	(St Lucia)	30 yrs ≤	87	1679	17.7(MWB)	All	
Tielsch *et al.*	1991	Black White	USA	Baltimore Eye Survey	40 yrs ≤	79.2	5308	16(MWB, Black) 17.2(MWB, White)	Non-glaucoma	
Leske *et al.*	1997	Black Mixed White	West Indies	The Barbados Eye Study	40-84 yrs	84	4631?	18.1(MWR, Black) 17.7(MWR, Mixed) 16.2(MWB, White)	Non-glaucoma	
Buhrmann *et al.*	2000	Black	Tanzania	(Kongwa district)	40 yrs ≤	90	3268	15.7(MWR) 15.4(MWL)	All	tonopen. NTG≤22
Rotchford *et al.*	2002	Black	South Africa	(Kwazulu-Natal)	40 yrs ≤	90.1	1005	14.2(MWR) 14.2(MWL)	All	
Rotchford *et al.*	2003	Black	South Africa	The Temba Glaucoma Study	40 yrs ≤	74.9	839	13.7(MWR) 13.6(MWL9)	Non-glaucoma	
Quigley *et al.*	2001	Hispanic	USA	Proyect VER	40 yrs <	72	4774	15.6(MWB)	Non-glaucoma	
Anton *et al.*	2004	Hispanic	Spain	The Segovia Study	40-79 yrs	89.6	510	14.3(MWB)	All	
Leibowitz etal	1980	White	USA	Framingham Study	65 <		5223	16.5(MB) 16.6(WB)		
Hollows *et al.*	1966	White	UK	Hollows &Graham	40-74 yrs	91.9	4231	15.9(ML) 16.6(WL)	Non-glaucoma	
Coffey *et al.*	1993	White	Ireland	Roscommon Glaucoma Survey	50 yrs ≤	99.5	2186	14.6	All	
Tielsch *et al.*	1991	White	USA	Baltimore Eye Survey	40 yrs ≤	79.2	5308	17.2	Non-glaucoma	

Klein *et al.*	1992	White	USA	Beaver Dam Eye Study	43-96 yrs	83.1	4926	15.3(MR) 15.5(WR)	All	
Rochtchina *et al.*	2002	White	Australia	The Blue Mountain Eye Study	59 yrs ≤	82.4	3654	16.0(MWB)	Non-glau-coma	
Dielemans *et al.*	1995	White	Netherlands	The Rotterdam Study	55-95 yrs	79.7	5673	14.7(MWR) 14.5(MWL) 14.6(MWB)	All	
Giuffre *et al.*	1995	White	Italy	The Casteldaccia Eye Study	40 yrs ≤	67.3	1062	15.1(MWR) 15.2(MWL)	All	
Boroni *et al.*	1998	White	Italy	The Egna-Neumarkt Study	40 yrs ≤	73.9	4297	15.1(MB) 14.9(WB)	All	
Weih *et al.*	1998	White	Australia	The Melbourne Visual Impairment Project	40 yrs ≤	83	3271	14.3(MWR)	Non-glau-coma	Tonopen/ GAT
Kozobolis	2003	W	Greece	Greece	40 yrs <	85.2		16.3(MWR) 16.2(MWL)	All	
Hirvela *et al.*	1995	White	Finland	(Finland)	70 yrs ≤	89	500	16.2(MWR) 16.5(MWL)	All	

(MR): Men right eyes, (ML): Men left eyes, (MB): Men both eyes, (WR): Women right eyes, (WL): Women left eyes, (WB): Women both eyes, (MWR): Men and women right eyes, (MWL): Men and women left eyes, (MWB); Men and women both eyes.

Table 1B. Summary of published population-based studies on OAG

First author	Year	Ethnicity	Country	Project name (or location)	Prevalence of OAG (Crude)	Standardized prevalence of OAG (%)*	NTG/ OAG (%) #	Prevalence of NTG (Crude) **	Expected prevalence of NTG(%)##	Standardized prevalence of NTG (%) *
Arkell *et al.*	1987	Eskimos	USA		0.06					
Foster *et al.*	1998	Mongolian	Mongol	(Hovsgol)	0.5					
Dandona *et al.*	2000	India	India	the Andhra-Pradesh Eye Disease Study	1.9	3.4	59.3	1.1		2.1
Foster *et al.*	2003	Chinese	Singapore	the Tanjong Pagar Study	1.8					
Ramakrishnan *et al.*	2003	India	India	the Aravind comprehensive Eye Survey	1.2	1.3		0.87		
Iwase A *et al.*	2004	Japanese	Japan	The Tajimi Study	3.9	3.5	92.3	3.6		3.2
Raychaudhuri *et al.*	2005	Indian	India	the West Bengal Glaucoma Study	3	3				
Rahman *et al.*	2004	Bengalese	Bangladesh	Bangladesh Study	1.2	2.1				
Bourne RRA	2003	Thai	Thailand	(Rom Klao)	2.3					
Shiose *et al.*	1991	Japanese	Japn	Japan Nation Wide	2.5	3.5	79.0	2		2.7
Salmon *et al.*	1993	MIX	SouthAfrica	(Western Cape)	1.5	1.5				
Wallace *et al.*	1969	Black	Jamaica	(Jamaica)						
Mason *et al.*	1989	Black	West Indies	(St Lucia)	8.8	8.1	36.0		2.9	
Tielsch *et al.*	1991	Black	USA	Baltimore Eye Survey	4.2	4.2	>50			
Leske *et al.*	1997	MIX	West Indies	The Barbados Eye Study	7.1	5.3				
Buhrmann *et al.*	2000	Black	Tanzania	(Kongwa district)	3	3.2	75.0		2.4	
Rotchford *et al.*	2002	Black	SouthAfrica	(Zulus)	2.8	2.3	57.1	1.6	1.3	

Rotchford *et al.*	2003	Black	SouthAfrica	The Temba Glaucoma Study	3.7						
Quigley *et al.*	2001	Hispanic	USA	Proyect VER	2	1.7	80.0	1.6	1.4		
Varma *et al.*	2004	Hispanic	USA	LALES	4.7	5	82.0	3.9	4.1		
Anton *et al.*	2004	Hispanic	Spain	The Segovia Study	2	1.5					
Leibowitz *et al.*	1980	White	USA	Framingham Study							
Hollows *et al.*	1966	White	UK	Hollows &Graham	0.43		35.0	0.15			
Coffey *et al.*	1993	White	Ireland	Roscommon Glaucoma Survey	1.9	1.6	36.6	0.7	0.6		
Tielsch *et al.*	1991	White	USA	Baltimore Eye Survey	1.1	0.7	>50				
Klein *et al.*	1992	White	USA	Beaver Dam Eye Study	2.1						
Rochtchina *et al.*	2002	White	Australia	The Blue Mountain Eye Study	3	1.3					
Dielemans *et al.*	1995	White	Netherlands	The Rotterdam Study	1.1	0.8	38.9		0.3		
Giuffre *et al.*	1995	White	Italy	The Casteldaccia Eye Study	1.2		38.5				
Boroni *et al.*	1998	White	Italy	The Egna-Neumarkt Study	2	1.6		0.6		0.4	
Weih *et al.*	2001	White	Australia	The Melbourne Visual Impairment Project	1.8	1.3	76.2	1.4	1.0		
Kozobolis	2003	White	Greece	Greece	85.2	1.7	9.7	0.27	0.2		
Hirvela *et al.*	1995	White	Finland	(Finland)	5.4						

* Standardized according to the age distribution of World Population
** Calculated by prevalence of OAG (crude) X number of OAG subjects with IOP
Number of OAG subjects with IOP ≤ 21mmHg (NTG)/total number of OAG subjects
Calculated by standardized prevalence of OAG X NTG/OAG

association studies. Am J Hum Genet 2005; 76: 268-75.) Lastly, while evolutionary genetics shows us that there are true genetic racial differences, these differences are very small compared to inter-individual differences, which is why you need hundreds of SNPs to accurately define ancestral groups and only a dozen or so markers to define an individual.

Epidemiology of IOP by region

a. North America

Five contemporary North American surveys measured IOP with Goldmann applanation tonometry in three distinct racial/ethnic groups: European-derived Caucasians,[1,2] Latinos[3,4] and people of African descent[2,5] (Table 2). There is no consensus on the relation between race, ethnicity and IOP based on these studies. Among participants without glaucoma, people of African descent in east Baltimore (16.0 ± 4.2 mmHg (N = 4453 eyes)) had significantly lower mean IOP than their Caucasian neighbors (17.3 ± 3.3 mmHg (N = 5682 eyes); $p < 0.001$). In contrast, African-derived subjects in Barbados had higher IOP (18.1 ± 4.8 mmHg (N = 4286 subjects)) than a small sample of their European-derived Caucasian counterparts (16.2 ± 3.1 mmHg (N = 118 subjects)). In the Barbados Eye Study, being of African descent was associated with 5 times increased risk of having IOP > 21 mmHg even after adjusting for age, sex and glaucoma status. There are no North American glaucoma surveys comparing Latinos to people of other ethnicities drawn from the same population.

Interestingly, the standard deviation of IOP measured in the North American glaucoma studies was approximately 3.4 mmHg for the Caucasian populations surveyed (Table 2). The standard deviation for the two studies among Latinos was 3.2 mmHg. In Barbados among a small group of mixed race (based on right eyes of 184 subjects) the standard deviation of IOP measurements was higher (3.7 mmHg). The largest standard deviations were reported for people of African descent. Even after excluding those with glaucoma, the standard deviation among African-derived people in east Baltimore was 4.2 mmHg. In Barbados, the standard deviation for IOP measurement was even higher (4.8 mmHg). The statistical or biologic significance of this observation is unclear.

Mean IOP in North American glaucoma surveys ranged from 14.4 mmHg among Latinos living in Los Angeles, California to 18.1 mmHg among African-derived people residing in Barbados. Very little is known about central corneal thickness in population-based studies at this time. The consensus of evidence does not support a positive relation between increasing IOP and older age. There are no studies to address the relation between ethnicity and IOP. There is no consensus on whether African-derived people have higher IOP than European-derived people living in North America. There seemed to be higher variance in IOP among blacks living in Baltimore or Barbados compared to other US populations but this requires further study. There are no North American studies

Table 2. Summary of North American population-based surveys of intraocular pressure

Study location	Race/ ethnicity	Sample size	% Female	Age range	Eye studied	Mean IOP [SD]
Los Angeles, CA[5]	Latino	2157	61.7	40-95	Either*	14.4 [3.2]
Nogalas/Tuscon, AZ[7]	Latino	4774	61.2	40-90+	Both	15.6 [3.2]
Beaver Dam, WI[8]	Caucasian	4856	56	43-86	Right	15.3 [3.4] male‡ 15.5 [3.4] female
Baltimore, MD[11]	Mixed	5308	?	40-80+	Both	17.2 [3.3] white** 16.0 [4.2] black
Barbados[12]	Mixed	4601	61.1	40-84	Both	18.1 [4.8] black‡ 17.7 [3.7] mixed 16.2 [3.1] white

* One eye per subject was chosen randomly.
** Subjects in both racial groups with glaucoma were excluded.
‡ This estimate includes all subjects.

of the relation between biometric parameters and IOP. Finally there is a strong positive relation between IOP and OAG, although prevalent and incident OAG cases occur commonly at IOP < 22 mmHg.

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b. South America

In a PubMed search, no population-based studies in South America were found that were relevant to this consensus statement. Pubmed was accessed on April 18, 2007. The search words used were 'South America and eye pressure and population-based', 'South America and intraocular pressure and population-based' and 'South America and eye and population-based'.

c. Japan

Previous papers about the intraocular pressure (IOP) in Japanese population pointed out that IOP in Japanese was lower than those in white and black people in western countries. The reported mean IOP was 13.6 mmHg by Shiose *et al.* (Jpn J Ophthalmol 1991; 35: 135-55) and 11.9 mmHg by Nomura *et al.* (Ophthalmology 1999; 106: 2016-22). According to Shiose *et al*. IOP in adult Japanese is correlated negatively with age and positively with myopic refraction. In these studies, however, IOP was measured using a non-contact pneumotonometer and the study designs were not population-based in the strict sense of the word. In the Tajimi Study, it was found that the value of the mean IOP with the Goldmann applanation tonometer (GAT) in an adult Japanese older than 40 yrs old (14.5 mmHg) is lower than those reported in the Baltimore Eye Survey (17.2 mmHg in White, 16.0 mmHg in Black), the Barbados Eye Study (18.7 mmHg), the Beaver Dam Eye Study (15.3 mmHg), Proyect VER (15.6 mmHg) or the Andhra Pradesh Eye Disease Study (15.6 mmHg), and similar to those reported in Singapore (the Tanjon Pagar Study) (14.5 mmHg), the Tehran Eye Study (14.5 mmHg), the Segovia Study (14.3 mmHg), the Roscommon glaucoma survey (14.6 mmHg) or the Rotterdam Study (14.8 mmHg), and higher than those reported in northwest Alaska (13.6 mmHg), northern Mongolia (12.8 mmHg), the West

Bengal Glaucoma Study (13.8 mmHg) or Thailand (13.3 mmHg). Further, the Tajimi Study revealed that the most common type of glaucoma in Japanese adults is normal tension glaucoma (OAG with IOP ≤ 21mmHg at the screening) and the second common type is primary angle closure glaucoma (PACG).

d. Africa

Methodology
Population-based studies were selected from this region. All were required to have used Goldmann tonometry for IOP measurement. Where available, summary data was extracted regarding age, race, gender and IOP, and the relation between IOP and open-angle glaucoma (OAG). (Summary data presented in Table 1A and 1B.)

Ghana
A population-based study[1] involved measurement of IOP among 1843 subjects aged ≥ 30 years with Tonopen/Perkins.All glaucoma cases were measured with Perkins. Twenty-one percent of POAG patients had an IOP of less than 22 mmHg and 94% of all glaucomas were undiagnosed. A further case-control study[2] involved patients newly diagnosed with POAG from the population-based study[1] mixed with newly diagnosed patients in two hospitals in Accra. The case-control design compared IOP (and other factors) in cases (patients with advanced disease: glaucomatous appearance of the optic nerve head with cup/disc (c/d) ratio > 0.8 in one or both eyes and repeatable extensive visual field loss including absolute scotoma(s) within five degrees of fixation in the same eye) versus controls (c/d ratio of 0.5 or greater in one or both eyes or a difference of 0.2 or more between c/d, and no absolute scotomas within 20 degrees of fixation of the visual field in either eye). Patients with IOP > 31 mmHg were about three times more likely to present late with advanced glaucoma than those with lower IOP. This is the only such study from Africa to report the IOP association with late presentation but concurs with findings of some non-African studies[3-5] and the Barbados Eye Study.[6]

An earlier study of applanation IOPs in 600 Ghanaians in Accra[7] (population-based although minimal details given of sampling strategy), aged 16-77 years, reported among non-glaucomatous eyes, a range of IOP of 5-28 mmHg, a mean of 15.5 mmHg, median 16 mmHg, and standard deviation 3.70 mmHg (*i.e.*, mean ± 2SDs: 8.1 mmHg to 22.9 mmHg). They reported a slight reduction in IOP after the 50-55 year age group (possibly related to smaller sample size in older age groups). There was no significant difference between mean IOP in males and females (t statistic = 0.17, $p > 0.5$).

Gambia
In the Gambian national study,[8] 50% of the POAG were reported as normal-tension type.

Tanzania

A population-based study in the Kongwa district of Tanzania[9] examined 3268 (90%) of 2641 eligible people over the age of 40 years. Mean ± SDs of IOPs in the right and left eyes were 15.7 ± 4.3 mmHg and 15.4 ± 4.5 mmHg, respectively (3195 persons; $P > 0.05$). These values were not altered when those defined with glaucoma were removed. The distribution was skewed towards higher IOP and the 97.5th percentile was 24 mmHg. The mean IOP was similar for men (15.5 ± 4.0 mmHg) and for women (15.6 ± 4.2 mmHg; $P > 0.05$). IOP level among those classified with glaucoma was higher in older age groups ($P = 0.04$), although the estimated increase with age was modest (-.25 mmHg/decade) in univariate linear regression analysis. Systolic blood pressure was positively associated with IOP ($P = 0.0001$) but age was not.

Bophuthatswana

A population-based study[10] surveyed Tswana people of the Northern Cape, one of the largest population groups of Southern Africa, who populate Botswana, Bophuthatswana and various areas of South Africa. One thousand five hundred three adults aged ≥ 30 years were examined. The distribution of IOP in the sample was not published, however, 28 patients (1.8%) were diagnosed with open-angle glaucoma, 2 (7.1%) of whom had an IOP < 21mmHg. Ocular hypertension was diagnosed in 9.9% of the sample (8.4% of 30-39-year olds and 12.1% of those aged ≥ 70 years.

South Africa

A population-based study in the Western Cape province of South Africa[11] examined 987 (83%) of 1194 eligible people aged ≥ 40 years. Mean (± SD) IOP was 17.0 ± 4.7 mmHg for men and 17.0 ± 4.5 mmHg for women. The 95th percentile was 23 mmHg. 67% of those diagnosed with chronic open-angle glaucoma had elevated IOP (> 21 mmHg) or a history of previous IOP elevation.

The Temba Glaucoma Study[12] was a population-based survey in urban South Africa that examined 839 (74.9%) subjects among 1120 enumerated adults aged ≥ 40 years. Mean Goldmann IOP in the right and left eyes of nonglaucoma subjects was 13.7 mmHg (Sd, 3.6 mmHg) and 13.6 mmHg (SD, 3.6 mmHg), respectively. The 97.5th percentile right IOP level was 21 mmHg. An IOP below this level was present in 11 (36%) of 31 subjects with POAG.

A population-based study in northern Kwazulu-Natal Province in South Africa[13] involved 1005 adults (90.1% response rate) aged ≥ 40 years of Zulu ethnic origin. Mean Goldmann IOP was 14.2 ± 4.2 mmHg (95% CI, 13.9-14.5 mmHg) for all right eyes for which applanation tonometry was recorded (n = 928) and 14.2 ± 4.1 mmHg (95% CI, 14.0-14.5 mmHg) for all left eyes (n = 914). When glaucoma cases were excluded, the mean values became 13.9 ± 3.4 mmHg (95% CI,13.7-14.1 mmHg) for both right and left eyes. A characteristic right-skewed Gaussian distribution of Goldmann IOP in eyes not classified as glaucomatous was seen. Of the 1790 healthy eyes, 3.5% had an IOP above 21 mmHg (2 SDs

above the mean in this population), and in 40 (4.6%) of 870 healthy subjects, the IOP was above 21 mmHg in at least 1 eye (defines an ocular hypertensive case). Sixteen (57.1%) of 28 cases of POAG had an IOP ≤ 21 mmHg.

Table 3. Summary data from population-based studies of Africa and South Asia

Study location	Race/ Ethnicity	Sample size examined (response rate)	% female	Age range	Eye studied	Mean IOP [SD]
AFRICA						
Ghana[7]	Ghanaians	600 (unpublished)	49.7	16+	Mean	15.5 [3.8] men 15.5 [3.6] women
South Africa[11]	Cape people	987 (83)	60.2	40+	Mean	17.0 [4.7] men 17.0 [4.5] women
South Africa[12]	Bantu	839 (74.9)	66.6	≥40	Right Left	13.7 [3.6] 13.6 [3.6]
South Africa[13]	Zulu	1005 (90.1)	72.1	≥40		
Tanzania[9]	Tanzanians	3268 (90)	55.4	>40	Right Left	15.7 [4.3] 15.4 [4.5] 15.5 [4.0] men 15.6 [4.2] women
SOUTH ASIA						
Bangladesh[14]	Bengali	2347 (66)	48	35+	Right left	15.0 [3.7] 15.0 [4.4]
India[15]		972 (50.3)	59	30-60	Right & left	15.5 [3.6]
India[16]		3934 (81.9)	55.1	40+		14.2 [3.3]
India[17]		5150 (93.0)	54.5	40+		14.1 mmHg to 14.7 mmHg (SD: 3.3 to 4.0)
India[18]		2522 (85.4)	53.4	30+		15.4 [3.3]
Pakistan[19]		16507 (95.5)*	46.7	40+	right	11.8 [3.4] men 12.1 [3.4] women

*1:5 of consecutively examined subjects aged ≥40 years were measured by Goldmann tonometry.

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e. South Asia

Methodology

Population-based studies were selected from this region. All were required to have used Goldmann tonometry for IOP measurement. Where available, summary data was extracted regarding age, race, gender and IOP, and the relation between IOP and open-angle glaucoma (OAG).

Bangladesh

A population-based study in Dhaka,[1] the capital city of Bangladesh, examined 2347 adults aged ≥ 35 years among 3562 eligible subjects (66% response rate). Goldmann tonometry measurements gave a mean of 15 mmHg with standard deviation of 3.7 mmHg in right eyes and 4.4 mmHg in left eyes. The 97.5th percentile was 22 mmHg for either eye and 99.5th percentile, 32 mmHg for right eyes and 45 mmHg for left eyes.

India

The Vellore Eye Survey[2] was situated in the state of Tamil Nadu in southern India. Nine hundred seventy-two (50% of eligible population) persons, aged 30-60 years, were examined. IOP recordings were available from 97% of right and left eyes. Mean IOP in the right and left eyes was 15.5 mmHg (SD, 3.6 mmHg). IOP was greater than 21 mmHg in 62 eyes of 40 persons.

The Chennai Glaucoma Study,[3] also in Tamil Nadu, examined 3934 (81.9%) of 4800 enumerated subjects aged ≥40 years. Among non-glaucomatous eyes, mean IOP was 14.2 mmHg ± 3.3 mmHg.

The Aravind Comprehensive Eye Survey[4] examined 5150 (93%) of 5539 eligible subjects aged ≥ 40 years. Forty-five (52.3%) of the 86 subjects with POAG had IOP < 21 mmHg. Ocular hypertension was present in 57 subjects (1.1%; 95% CI, 0.84, 1.4). There was no significant difference in IOP across age groups. Among non-glaucomatous subjects, mean IOP (SD) varied from 14.1 mmHg to 14.7 mmHg (SD, 3.3 to 4.0) within 10 year age-groups.

The Andhra Pradesh Eye Disease Study (APEDS)[5] assessed 2522 persons (85.4% of those eligible) aged ≥ 30 years in the urban population of Hyderabad. Mean IOP was 15.4 mmHg (SD, 3.3 mmHg; upper 95% CI, 21.9 mmHg). Ocular hypertension (IOP > 22 mmHg) was present in 0.32% of this sample. Eighteen (67%) of 27 cases of definite POAG had IOPs below 22 mmHg.

Pakistan

The Pakistan National Blindness & Visual Impairment Survey[6] examined 16,507 adults (95.5% of those enumerated) aged ≥ 30 years in a nationally representative population-based sample. Goldmann tonometry was performed on 1:5 consecutive subjects aged ≥ 40 years. Of 1867 right eyes, mean IOP was 11.9 mmHg (SD, 3.4 mmHg). Significantly higher IOPs were recorded among women (mean, 12.1 mmHg) than among men (mean, 11.8 mmHg). There was no significant effect of age on IOP. This IOP data is in preparation for publication.

Summary

The mean IOP of population-based surveys performed in Africa ranged from 13.6 mmHg among the Bantu people of South Africa to 17 mmHg among the Cape people of the same country. Within South Asia, the range varied between 12.0 mmHg in Pakistan to 15.5 mmHg in India.

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f. China

Because studies have used different tonometers to measure the IOP, the mean IOP of the Chinese population ranges from 12.9 mmHg (non-contact) to 15.2 mmHg (Tonopen). In two population-based studies, there was a decrease in the mean IOP with age in individuals 50 years and older. In Zhao's study in China

(Zhao *et al*. Zhonghua Yan Ke Za Zhi 2002; 38: 335-9), 9481 eyes (subjects: 4880) had their IOPs measured with a Perkins Tonometer. Eyes diagnosed with glaucoma or as suspicious for glaucoma, or with a corneal opacity or atrophy of the eyeball were excluded. The mean IOP in the population was 13.53 mmHg (SD = 2.20).

In the Shihpai Eye Study (Lin HY, Hsu WM, Chou P, *et al*. Arch Ophthalmol 2005; 123: 381-6), 1361 study participants had their IOPs measured with a non-contact tonometer. Their mean IOP was 12.9 mmHg (SD = 3.1). The IOP decreased significantly ($P < .001$) with age. It decreased from 13.3 ± 3.0 mmHg in participants aged 65 to 69 years, to 11.6 ± 2.8 mmHg in those 80 years and older. Women had significantly higher IOPs than men ($P < .001$). In the multivariate regression analysis, decreasing age, female sex, increasing systolic blood pressure, a history of diabetes, and alcohol drinking were significantly associated with increasing IOP.

g. Europe

All subjects residing in the Egna-Neumarkt area of Alto Adige region (Northern Italy) and over 40 years of age were invited to undergo an ophthalmologic examination. Of a total of 5816, 4297 subjects were examined (73.9% overall participation rate). Mean IOP increased with age, and was slightly higher in men (15.14 mmHg) than in women (14.94 mmHg). While in the Casteldaccia Eye Study, IOP was measured in 1062 middle-aged and elderly subjects of a small Sicilian town, enrolled in a population-based survey. The mean IOP was 15.1 ± 3.7 mmHg without interocular or sex differences. A small, but significant age-dependent increase of IOP was found.

In the Reykjavik Eye Study in Iceland, a population-based random sample of 415 male and 510 female Caucasians aged 50 years and older had central corneal thickness (CCT) and the radius of central cornea (CC) measured with Scheimpflug anterior segment photography and IOP measured with air-puff tonometry. The mean IOP of right eyes was 15.1 mmHg (SD 3.3) among men and 15.8 mmHg among women (SD 3.1), which was statistically significant. The mean radius of the CC for male right eyes was 7.78 (SD 0.60) and for females 7.62 (SD 0.58), which was also statistically significant. Mean CCT for male right eyes was 0.528 mm (SD 0.041) and for females 0.526 mm (SD 0.037), $p > .05$. Linear regression analysis showed no relationship between the radius of CC and IOP while linear regression analysis of the relationship between CCT and IOP suggested higher IOP measurements with thicker corneas. IOP was found to be independent of age.

In the first 3062 Caucasian subjects aged 55 years or older in the Rotterdam Eye Study who were examined, the mean IOP was 14.6 mmHg (median 14.0 mmHg) with Goldmann Applanantion tonometry. The IOP did not change significantly with age and was 0.3 mmHg lower in females compared to males, which was statistically significant.

h. Australia

The Blue Mountains Eye Study assessed 3654 residents aged 49+ years during 1992-1994. Intraocular pressure was measured using Goldmann applanation tonometry. Subjects with glaucoma, those currently on glaucoma medications and those with a history of cataract surgery were excluded. The IOP was reliably measured in 3260 subjects. Mean IOP was 16.0 mmHg with no significant difference found between men and women ($P < 0.89$). No evidence was found of an independent age affect on IOP.

In the Melbourne Visual Impairment Project, a two-site population-based cross-sectional study in Australia, mean IOP in the right eyes of 4744 Caucasian subjects was 14.7 mmHg using the tonopen.

Gender effects

The role of gender in POAG is controversial with several studies showing no gender difference in disease prevalence[11-13] and a few others showing slightly more disease in males.[6,7] Establishing gender trends in IOP or POAG risk would be very important for generating biological hypothesis regarding POAG pathogenesis. Among Caucasians living in Wisconsin, female gender was associated with higher IOP in multivariate analysis.[1] Yet in longitudinal follow-up gender was not related to IOP change.[9] Among African-derived people living in Barbados, IOP was similar between men and women at baseline.[5] After nine years of follow-up, male gender was associated with higher IOP in multivariate analysis.[10] No study accounts for menopausal status or postmenopausal hormone use in women. Accounting for menopausal status may be important as the Rotterdam Eye Study found early menopause was positively associated with POAG.[14] Use of postmenopausal hormones among postmenopausal women participating in population-based surveys of IOP may be important because some clinical studies suggest that postmenopausal hormone use is associated with lower IOP in follow-up.[15-19] At the current time studies performed in North America offer no consensus on the relation between gender and IOP.

In Africa and South Asia, gender differences in IOP were only reported in two studies. The Tanzanian study[9] found no significant gender difference while the Pakistan study[19] reported higher IOPs in women. In Australia, mean IOP was 16.0 mmHg with no significant difference found between men and women ($P < 0.89$).

In China, there is no consensus on whether one gender or the other has a lower mean IOP. In Zhao's study, females had a lower mean IOP (male: 13.69 [2.35], female 13.40 [2.42], $p < 0.01$) while in He's study, females had a higher mean IOP (15.0 [3.2], female15.4 [3.1], $p = 0.025$) compared to males.

Age effects

Primary open-angle glaucoma (POAG) is a strongly age-related disease[6-8] and thus the relation between chronologic age and IOP is important to understand. Among white subjects aged 43 to 86 living in Wisconsin, there was no relation between age and IOP in cross-sectional[1] and longitudinal analysis[9] after controlling for a host of other factors. Among African-derived people aged 40 to 84 living in Barbados, a cross-sectional analysis suggested IOP increased with age[5] but longitudinal data from the same population showed a more complex relation between age and IOP.[10] Only patients in the 50-59 year old age group demonstrated an increase in IOP after nine years of follow-up. Among blacks older than 60, there was a non-significant decrease in IOP after nine years of follow-up. Overall, the consensus of the data available from North American studies does not support the notion that IOP increases with age. It will be interesting to see if the lack of a positive relation between IOP and age is seen in other populations. If the trend holds it would suggest that the age-related nature of POAG is not mediated via an increase in IOP with age.

Limited published data exists for either Africa or Southeast Asia regarding the relation between age and IOP. Of the surveys that have published such information, the Pakistan national survey[19] and the Tanzanian study (non-glaucomatous subjects in multiple variable analysis that included systolic blood pressure)[9] found no significant relationship.

In China, there was a tendency for mean IOP to decrease by age in the study by Zhao (Table 4). As mentioned previously, the mean IOP in 9481 eyes (4880 subjects), whose IOP was measured with a Perkins tonometer, was 13.53 mmHG.

Table 4. Mean normal intraocular pressure (IOP) among the Chinese

Age (years)	Men		Women		Total		μ volume (comparing men and women)
	Eyes	IOP (± s)	Eyes	IOP (± s)	Eyes	IOP (± s)	
50~	859	14.10 ± 2.29	1387	13.80 ± 2.40	2246	13.91 ± 2.36	2.96**
55~	871	13.83 ± 2.23	950	13.62 ± 2.41	1821	13.72 ± 2.33	1.93
60~	862	13.73 ± 2.54	1048	13.56 ± 2.45	1910	13.63 ± 2.49	1.48
65~	706	13.68 ± 2.29	836	13.11 ± 2.40	1542	13.37 ± 2.37	4.76**
70~	511	13.29 ± 2.21	600	12.95 ± 2.25	1111	13.10 ± 2.24	2.53*
75~	38	12.88 ± 2.48	312	12.67 ± 2.60	550	12.76 ± 2.55	0.96
80~	149	13.01 ± 1.92	152	12.29 ± 2.16	301	12.65 ± 2.08	3.06**
Total	4196	13.69 ± 2.35	5285	13.40 ± 2.43	9481	13.53 ± 2.20	5.88**

* $p<0.05$ **$p<0.01$

In Xu's study in China, The mean IOP of men decreased with age. Women did not have this tendency, although the mean IOP was lowest in women age > 70 years.

Ethnicity and race

While it is clear that the prevalence and incidence of glaucoma is higher in individuals with African Ancestry, solid evidence through large population-based studies have provided conflicting findings as to the relationship between IOP and African self-reported ancestry. These studies included the St Lucia Study (1,679 Afro-Caribbean),[1] the Baltimore Eye Survey (5,308 Subjects, 45% black),[2] the Barbados Eye study (4,631 subjects, 93% black),[3] a large survey conducted in six villages in Tanzania (3,268 subjects, East African),[4] the Temba Glaucoma study (1120 subjects, all Blacks in North West Province, South Africa)[5] and in Hlabisa district, Northern KwaZulu-Natal Province, South Africa (1115 subjects, 1005 examined, all of Zulu ethnic origin).[6] It should be noted that none of these studies included measures of central corneal thickness, which can of course have a profound effect on the 'true' IOP, and risk of developing glaucoma.

Only the Baltimore Eye Survey and the Barbados Eye Survey compared racial groups within the same study. Sommer *et al*. reported that while there was no racial difference in IOP between blacks and white with glaucoma,[7] in patients with untreated glaucoma, whites had a higher IOP than blacks indicating that there may be a greater vulnerability to glaucomatous injury in black populations at similar IOP levels. However, level of IOP was used as a referral criterion for additional clinical examination. The mean IOP was similar but slightly higher ($p < 0.001$) in whites [17.17 (SD 3.35)] compared with blacks [16.00 (SD 4.18) at the time of screening, excluding those with POAG.

Conversely, the Barbados Eye Survey found a higher mean IOP in the black population compared to the whites. The mean IOP in blacks was 18.7 (5.2 SD), in whites (16.5 (3.0 SD), and in mixed individuals it was 18.2 (SD 3.8). However, only 7% of the sampled populations was white.

Several studies did not directly compare the IOP between racial groups. The St Lucia study found a mean IOP of 17.7 (4.3 SD) in Afro-Caribbean individuals. In the studies conducted in Africa, the mean IOP was 13.6 (3.6 SD) and 13.7 (3.6 SD) for the right and left eyes respectively in the Temba Glaucoma Study, 14.2 (4.2 SD) and 14.2 (4.1 SD) in the right and left eye respectively in the Zulu population study in South Africa, and 15.7 (SD 4.3) and 15.4 (SD 4.5) in Tanzania. However, directly comparing these populations is difficult, due to differences in study design and IOP measurement techniques. For example, the three studies conducted in Africa all used the Tonopen, while the St.-Lucia study used Perkins hand-held applanation tonometry.

In the Los Angeles Latino Eye Study, the mean intraocular pressure for the entire population (2157 participants of whom the majority self-reported that they were Mexican- American ethnicity) with the Goldmann Applanation tonometer was 14.4 mmHg ± 3.2. This intraocular pressure is lower than that reported in the Baltimore Eye Survey for African Americans and whites. In Proyecto VER, the average IOP was 15.6 mmHg ± 3.2. This is similar to the average IOP found in whites in the Beaver Dam Eye Study.

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Oculometric effects (*e.g.*, axial length, refractive error)

IOP is associated with narrower drainage angle width. This association is independent of the extent of peripheral anterior synechiae.[1] This association is probably a reflection of the association between pathological angle-closure and higher IOP. Treatment of angle-closure by laser iridotomy does not alter axial AC depth but does reduce intraocular pressure in 'suspect' and established cases of angle closure.[2] This reflects the fact that pathological angle-closure occurs in the peripheral anterior chamber. Axial ACD is a surrogate measure of peripheral ACD.

There are no other significant associations between IOP and either axial length or radius of corneal curvature.[3,4] In this context it is not surprising that no association has been observed between CCT and either anterior scleral thickness or axial length.[5] Corneal astigmatism is believed to affect the accuracy of IOP estimates made with Goldmann applanation tonometry. Haag-Streit recommend that the prism is rotated so that the axis of the minus cylinder on the prism graduation corresponds to the red mark on the prism holder, if the corneal astigmatism is greater than 3.0 D.

One thousand two hundred forty-two residents of Hovsgol Province, Northern Mongolia, 10 to 87 years of age, participated in a study by Foster and colleagues. The CCT was measured using an optical pachymeter in all subjects. The IOP was measured using a Goldmann-type applanation tonometer. There was a highly significant decrease in CCT with age: 5 microns/decade in men and 6 microns/decade in women (both, $P < 0.0001$). A highly significant positive correlation was identified between IOP and CCT. Linear regression analysis suggests that between the ages of 40 and 80 years, an increase in CCT of 10 microns is associated with an increase in IOP measurements of 0.18 mmHg in right eyes (95% confidence interval, 0.12-0.25) and 0.24 mmHg in left eyes (95% confidence interval, 0.17-0.31). The authors calculate that interindividual differences in CCT may produce a difference in measured IOP of between 2.3 and 3.1 mmHg. (Foster PJ, Baasanhu J, Alsbirk PH, *et al*. Central corneal thickness and intraocular pressure in a Mongolian population. Ophthalmology 1998; 105: 969-73.)

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Glaucoma prevalence above and below 22 mmHg – NTG vs POAG

Population-based studies show that among patients with open-angle glaucoma (OAG), IOP is commonly < 22 mmHg.[3, 6, 12,13] For example, only 20% of persons with OAG had IOP > 22 mmHg in Proyecto VER.[3] Among participants who were previously undiagnosed with glaucoma but who met criteria for OAG in the Los Angeles Latino Eye Study, the mean IOP was 17.0 mmHg and only 15% of these persons had IOP > 21 mmHg.[13] Since the prevalence of OAG is highly age-dependent, it is very helpful to create prevalence rates which are standardized to the age-distribution of the world population. This was done for three studies: the Tajimi Study, the study by Shiose *et al.*, the Andhra Pradesh Eye Disease Study and the Egna-Neumarkt Study. In these studies, the prevalence of NTG standardized to the age-distribution of the world population was 3.2 or 2.7 % in Japanese (≥ 40 yrs), 2.1 % in Indians (≥ 30 yrs) and 0.4% in Italians (≥ 40 yrs), respectively. In contrast to the Egna-Neumarkt Study, in the Rotterdam Eye Study, 38.9% of subjects with glaucoma had IOPs less than 21 mmHg. In addition, in Africa and South Asia, several studies reported a considerable proportion of POAG cases where the IOP was within the 'normal' range. Among the South Asian studies, APEDS[18] reported that 67% of POAG cases had IOPs below 22 mmHg, in Aravind,[17] 52% were below 21 mmHg. Among the African studies, 33% of OAG cases in the Mamre study,[11] 36% of those in the Temba Glaucoma Study,[12] 57.1% of those in the study in Kwazulu-Natal,[13] and 21% of the cases in the Ghana study[1] had an IOP of 21 mmHg or less. In the study from Bophuthatswana,[10] 7.1% of POAG subjects had an IOP of less than 21 mmHg. One study in China showed 56.7% of the subjects with POAG had IOPs lower than 21mmHg.

Nonetheless, even among subjects with IOP < 21 mmHg, the risk of OAG increased positively with IOP. For example, in Baltimore MD, using subjects with IOP ≤ 15 mmHg as the reference group, the relative risk of OAG was 2.0 for those with IOP between 16-18 mmHg and 2.8 for those with IOP between

19-21 mmHg.[2] Thus, the relative risk of OAG increases with the magnitude of IOP, even when IOP is well within the 97.5 percentile for the population. Furthermore, in east Baltimore, the risk of OAG rose dramatically as IOP increased above 21 mmHg. Finally, the four-year incidence of OAG in Barbados was 1.2% for subjects with baseline IOP < 21 mmHg while it was 9.1% for those with baseline IOP > 21 mmHg.[6]

Because of the large percentage of subjects with glaucoma and IOPs less than 21 mmHg in several of the world's population-based studies, there is no consensus on whether there is actually a distinctive disease labeled normal tension glaucoma. However, it is important to realize that IOP may be a crude way to categorize OAG into normal tension glaucoma and higher pressure open-angle glaucoma. Until we obtain more accurate and valid methods of phenotyping the different types of open-angle glaucoma, categorizing subjects with IOP may be currently the most efficient and accurate way to distinguish two of the phenotypes of open-angle glaucoma.

The different screening and definitional criteria of the studies may explain the different results in these population- based studies around the world to a great degree. If we really wish to make valid comparisons, it is necessary to carry out these studies with the same study design, methodology, and criteria.

Topics for further research and discussion

1. Why is there a difference in the prevalence of open-angle glaucoma among ethnic groups when there is no consensus that there is a difference in mean IOP among ethnic groups and IOP is a risk factor for open-angle glaucoma?
2. Does Japan have a greater prevalence of Normal Tension Glaucoma or OAG with IOPs less than 21 mmHg?
3. Studies with similar methodology comparing differences in IOP between multiple racial groups allowing direct comparisons need to be performed.
4. Do Mexican Americans or Latinos have lower mean IOPs than Europeans or African Americans?
5. Because of the high prevalence of OAG in eyes with IOP < 21 mmHg, is there such an entity as 'normal tension glaucoma' that is a different disease than OAG with IOP ≥ 21 mmHg?

Louis Pasquale presenting section on epidemiology of intraocular pressure.

From left to right: Ted Garway-Heath, Robert N. Weinreb, James Brandt and Louis Pasquale

Robert N. Weinreb commenting on epidemiology of intraocular pressure

Consensus panel for epidemiology of IOP. From left to right: Tetsuo Yamamoto, Aiko Iwase and Christopher Girkin

Linda Zangwill and Ted Krupin discussing consensus points on epidemiology of intraocular pressure

CLINICAL TRIALS AND INTRAOCULAR PRESSURE

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Consensus points

- The type of clinical trial (*i.e.*, Phase II, III, or IV) influences the study design and subsequent considerations of treatment groups, recruitment criteria, and power.
- An appropriately-designed clinical trial for efficacy of IOP reduction should specify a clinically significant treatment effect (delta); probability of a type 1 error (alpha), usually set at 5%, and a desired power (conventionally at least 80%).
- Clinical trials in related disease areas should strive to use similar designs and outcome measures to facilitate meta-analysis (*i.e.*, a pooling of results of independent trials).
- Clinical trials comparing IOP-lowering efficacy of different treatments should provide 95% confidence intervals for the difference in IOP reduction.
- Efficacy trials should define *a priori* the clinically meaningful difference for that specific study.
  Comment: In addition to IOP-lowering, other factors such as safety and side-effects must be considered in defining a clinically-meaningful difference.
- Protocols should include *at least* two post-screening IOP measurements acquired on *at least* two different days for calculating baseline IOP, *prior to randomization*.
- Protocol analyses also should include measurement of baseline IOP, central corneal thickness and type of glaucoma to allow adjustment for these potentially confounding variables when comparing IOP-lowering interventions.

Intraocular Pressure, pp. 105-116
edited by Robert N. Weinreb, James D. Brandt, David Garway-Heath and Felipe A. Medeiros

Study designs for clinical trials

The broad aim of a clinical trial is to provide evidence on whether a new intervention is safe and/or effective. Clinical trials may be designed to identify appropriate dosing regimens for new treatments, to identify potential side effects, to provide preliminary estimates of efficacy, or to carry out a formal comparison of a new treatment with a standard one. Results from each type of trial provide information that affects the risk-benefit ratio of a new treatment. This aim can be achieved by three broad types of trials: a) dose-finding and preliminary efficacy trials (Phase I and Phase II); b) efficacy trials (Phase III); and c) management trials (Phase IV). As the consensus group is focused on clinical trials to compare intraocular pressure (IOP) lowering therapies, we will restrict our discussion to Phase-III and Phase-IV trials.

Types of clinical trials

Efficacy trials (Phase III)

A Phase-III clinical trial is a controlled trial comparing a new treatment to a standard treatment (or, in some cases, a placebo). Phase-III trials are designed to provide firm evidence of the efficacy of an intervention. Typically, Phase-III trials are conducted with formal adherence to a study protocol defining eligibility, treatment, and outcome assessment. Often, eligibility criteria limit enrollment to high-risk, compliant subjects. The interventions are administered according to strict protocols and patients are closely monitored for adherence to study protocol and compliance with treatment. Patients are followed using a defined schedule with standardized assessment of outcomes and adverse events. The analysis of a Phase-III trial is specified before the trial begins and is conducted to compare specific outcome measures at defined time points. Because the design of Phase-III trials requires specific eligibility criteria and relatively homogeneous patient populations, their results may not always be generalizable to a more general population.

Management trials (Phase IV)

The Phase-IV trial is a large-scale trial designed to evaluate the effectiveness of a treatment in a real-world situation. The goal of Phase-IV trials is to estimate the effectiveness of a treatment administered under typical clinical circumstances and include a broad sample of patients with the target disorder (*i.e.*, not restricted to the high risk groups often recruited for Phase-III trials). Treatment is usually administered as in routine clinical care, rather than via a tightly standardized and monitored protocol. Patient compliance is monitored, but special interventions to improve compliance are not necessarily part of the trial, and clinician adherence to the study protocol is of necessity not as closely monitored as in a Phase-III trial.

For glaucoma, as for many health conditions, there is a need for management trials worldwide. Such trials have particular relevance to the resource-starved

'developing' country scenarios of Asia and Africa, where follow up to therapy is suboptimal with consequent effects on the management of glaucoma. Investigators planning a Phase-IV trial must consider additional factors, usually not addressed during the Phase-III trial, including the cost and availability of the medications, issues with distribution, and the common situation in which subsidies for medication costs during the course of a trial may be reduced or absent after the trial. In a setting where cost is a primary consideration, a clinical trial designed to detect equivalence of treatments (*i.e.*, a non-inferiority trial (see below)) may be needed to assess cheaper generic versions of medications. A further consideration is whether non-medical approaches may ultimately result in better outcomes for patients in the developing country setting. A combined efficacy and management trial may be an important next step for researchers to consider after a conventional (medical) treatment comparison trial has identified potential new therapies.

For Phase-IV trials, the end points of interest include not only clinically important differences from a clinician perspective (decreased IOP or reduced progression) but also quality of life and cost-benefit measures.

Clinical trial designs

When planning a clinical trial, the relative merits and disadvantages of different designs should be compared before an appropriate design is chosen for the clinical trial. For readers evaluating a published clinical trial, it is important to assess whether the chosen design is appropriate to answer the scientific and medical questions proposed in the trial.

Parallel group design

In a parallel group design, each patient receives one and only one treatment, assigned by a formal randomization scheme. Each treatment arm is then monitored using the same protocol until the end of the study. The most familiar parallel-group design involves a comparison of two treatments (*e.g.*, a new drug versus placebo or a new drug versus standard treatment). The parallel group design is the most commonly used trial design for Phase-III trials.

Crossover design

In this design, each subject is randomized to a sequence involving two or more treatments with a washout period between interventions. The simplest crossover trial is the two-treatment (A and B), two-period design. In this design, there are two treatment periods and subjects are randomized to receive either A followed by B or B followed by A. However, more complex crossover designs may be employed in various clinical circumstances. For a valid crossover trial, the relevant effects of the medications being evaluated should develop fully within the treatment period and the effects should dissipate completely during the planned washout period.

Crossover designs have potential advantages. Because the subject acts as

her/his own control for comparing the interventions, and the within-subject variability is usually less than between-subject variability, the required sample size for a crossover trial will usually be lower than for a comparable parallel-groups design. Another potential advantage of crossover designs is that patient recruitment may be easier because all subjects receive all treatments under investigation. Sometimes patients may be unwilling to accept a no-treatment arm, but may be willing to delay therapy to the second treatment period. On the other hand, administering two or more treatments to every subject may require more time and be more inconvenient, discouraging participation. Also, crossover trials may increase the likelihood of dropouts, due to the longer trial duration compared to parallel-design studies or due to exposure to more treatments, increasing the chance of side effects.

In crossover designs, carryover effects may have a substantial impact on the results, resulting in biased and possibly specious conclusions. A carryover effect means that the first-period treatment affects the response to the second-period treatment, either by altering the underlying physiology or by not having dissipated in the washout period. Carryover effects can be minimized by a sufficiently long washout period between treatments. If the washout period is too short, the latter treatment period will be biased by carryover effects from the earlier treatment. If there is carryover, the investigator will observe the simultaneous effect of two treatments and attribute it only to the most recently administered one. If there are differences in the carryover effects between the two treatments being evaluated, the design can lead to biased estimates of treatment effects. For clinical trials evaluating IOP-lowering therapies, a wash-out period of four weeks has generally been used. However, the required wash-period may vary with the type of medication and it is possible that the effects of some IOP-lowering medications may persist beyond four weeks.[1]

Analysis must specifically address carryover and calendar (treatment by period interaction) effects. If any are detected, analyses should be restricted to the underpowered, but appropriate, analysis of the first time period only. It must be noted, however, that these effects may not be detectable with certain crossover designs (treatment-by-period interaction is indistinguishable from carryover effect in an AB/BA trial).[2] Because of the many technical issues involved in design and analyses of cross-over trials, and the limited settings in which they can be used, this type of clinical trial has been used relatively infrequently in glaucoma.

Types of comparisons

Superiority trials

A superiority trial is a trial with the primary objective of demonstrating that the response to an investigational treatment is superior to another (active control or placebo). An acceptable clinical margin of superiority has to be *pre-defined* and is essential to estimate a sample size. Most clinical trials involving IOP-lowering treatments are designed to show superiority of one treatment over another

(or over placebo). However, it should be recognized that a non-significant test result for the standard null hypothesis (of no difference between treatments) in a superiority trial does not allow the conclusion that the two treatments are equivalent. For example, suppose that a clinical trial is designed to compare two drugs A and B in order to demonstrate that drug A is significantly better in lowering IOP than drug B. If the study founds that the null hypothesis cannot be rejected, that is, that mean IOP reduction of drug A is not significantly different than that of drug B, this might not constitute evidence implying that drug A is equivalent or non-inferior to drug B. Here, lack of evidence of a difference is not evidence of lack of a difference. It is possible that the power of the study was not adequate to detect a meaningful difference between the two treatments; consequently, an incorrect conclusion of equivalence might be drawn by the unwary reader.

Non-inferiority trials

A non-inferiority, or equivalence, trial is designed to show that the response to two or more treatments differs by a clinically unimportant margin that is *pre-defined*. Non-inferiority trials may be useful to test new treatments that are expected to have similar efficacy to current ones, but may offer advantages such as fewer side effects, easier administration or lower cost. An example would be a non-inferiority trial comparing a fixed combination of two ocular hypotensive drugs compared to the concomitant application of the individual components. A non-inferiority trial would be the appropriate design for head-to-head testing of cheaper generic formulations available in third world countries. It is important to note, however, that non-inferiority trials are not conservative, that is, flaws in the design or conduct of the trial will tend to bias the results towards a conclusion of equivalence. For example, poor compliance during the trial will bring the results of the two treatments close together and favor a conclusion of noninferiority or equivalence.

Sample size and power calculations in randomized clinical trials

In comparative clinical trials, the null hypothesis usually represents no difference between treatments, whereas the alternative hypothesis is chosen to be the smallest difference of clinical importance between treatments. For example, in a clinical trial comparing a new drug A with a standard drug B, the null hypothesis could be stated as no difference in IOP-lowering effect between the two drugs. The alternative hypothesis could be that the IOP-lowering reduction of the new drug A is different than that of drug B by at least 1.5 mmHg, for example. Following hypothesis definition, the size of the trial is planned to yield a high probability of rejecting the null hypothesis if the alternative hypothesis is true.

Hypothesis testing in clinical trials is set in a framework of testing a null hypothesis and an alternative hypothesis: In this framework, two types of erroneous conclusions are possible (Fig. 1). First, investigators can conclude that

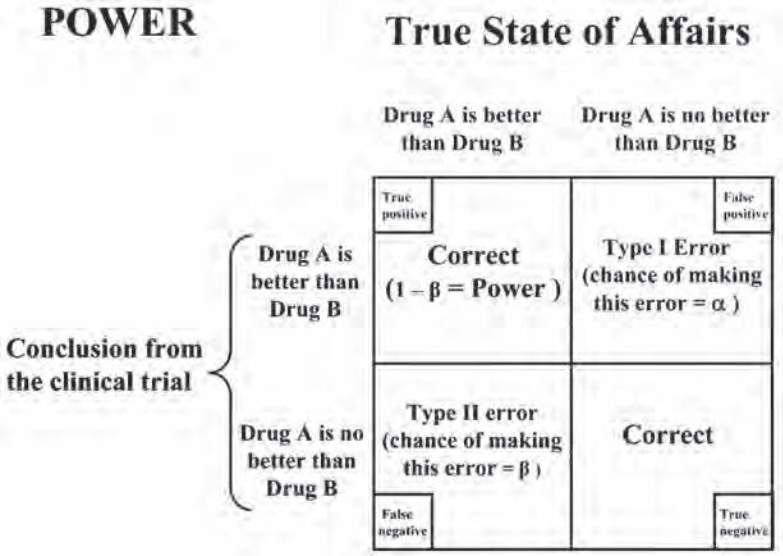

Fig. 1. Types of error in hypothesis testing.

two treatments differ when in fact they don't (*i.e.*, the null hypothesis of no treatment difference is true). This is referred to as a type-I error and can also be described as a false-positive conclusion. The probability of a type-1 error, termed alpha, is specified before the trial and is usually set at 0.05, meaning that investigators desire a 5% or less chance of making a false-positive conclusion. The other type of error (type II) involves a false-negative conclusion, *i.e.*, concluding that two treatments do not differ when in fact they do (*i.e.*, the null hypothesis of no treatment difference is false). The probability of a type-2 error, termed beta, is also specified before the trial begins and is conventionally set to 0.20, which means that the investigators desire a 20% or smaller chance of making a false-negative conclusion. Type-2 errors are of particular interest because they allow the trial to be designed to have a specific probability, or power (1-beta) of correctly rejecting the null hypothesis. Power is a critical consideration in trials because if a statistically significant difference is not found, it could be argued that there was an insufficient sample size to detect a difference of interest (*i.e.*, the study was underpowered).

Sample-size calculations for clinical trials are based on several considerations: the type-1 error rate (alpha), the desired power, the variation in the outcome measure, the treatment group allocation proportions, and the difference between groups that is to be detected.

A relatively recent development in clinical trials is meta-analysis, or the combination of results from independent trials. This combination has the potential to dramatically increase power, but also depends on the studies using

standardized methodologies for recruitment, treatment, and outcome monitoring. A well-designed and conducted clinical trial should be capable of providing results that can later be combined in meta-analyses, even though the trial in itself may have low power.

Post-hoc power calculations

It is relatively common in the medical literature to see post-hoc power calculations in order to interpret tests with statistically nonsignificant results. These post-hoc calculations purportedly compute the power of the study to detect the observed difference found (the 'observed power') after a clinical trial has been completed. The observed power, however, will be less than (1-beta) if the observed difference is smaller than the alternative hypothesis used to plan the study (*i.e.*, the hypothesized difference between groups on which the sample size calculations were based). Power calculations after the trial is completed are therefore pointless, since the power is by definition smaller than the (1-beta) value on which the sample size calculations were based. Post-hoc power calculations are only appropriate if they relate to subgroup analyses of the enrolled patients, or if a new endpoint, not specified in the analysis plan, is reported. At the conclusion of a clinical trial, the estimated treatment effect and its variability (confidence interval) are known and the power of the trial is reflected in the width of the confidence interval.

What should readers look for in a clinical trial paper?

When evaluating a report from a clinical trial, in addition to methodological issues (design, descriptions of the patient population, exclusion/inclusion criteria, randomization methods, treatment and monitoring protocols, and analysis plan, etc.), readers should look for a clear description of the sample size calculations. It is important to review the assumptions used for these calculations such as type-I error (α), type-II error (β), and the treatment effect of interest. Is the planned effect size clinically significant? A clinical trial comparing two drugs to lower IOP might have been designed to have sufficient power to detect a difference of 3 mmHg between treatments. However, the reader might find that 2 mmHg would be more appropriate. The reader should also examine the confidence intervals for treatment effects to determine whether a clinically significant effect has been excluded.

Bayesian theory provides a distinct approach to statistical analysis. A Bayesian approach allows the specification of prior probabilities (*i.e.*, beliefs about treatment efficacy) and then interprets the data in terms of its impact on the prior probabilities. Although this approach is not widely used, it may be advantageous in some settings and enjoys theoretical support among many statisticians. Although Bayesian theory as applied to clinical trials is beyond the scope of the current document, its application in design and analysis are worth exploring.

Statistical versus clinical significance

Investigators sometimes place unwarranted importance on a statistically significant result by implying that such a result is also clinically important. A statistically significant *P*-value means that there is only a small probability that the observed difference between groups could have arisen if there were truly no difference between groups. However, the small p-value does not provide information about the magnitude or importance of the observed difference.

While assessment of clinical significance is based on the assumption that the results are statistically significant, statistically significant results are not always clinically important. In a clinical trial, clinical significance can be defined as the magnitude of increase in the investigational treatment's efficacy, relative to the control treatment, that would be considered sufficiently important to be recognized as a therapeutic advantage. Clinical importance may be suggested when the result is statistically significant and the estimated treatment effect exceeds some pre-specified amount.

Statistical significance is determined objectively using mathematical models, whereas clinical significance is more subjective and depends on the opinion of the investigators, experts in the field, or previously acquired experience on the subject. For IOP-lowering treatments in glaucoma, it has been generally accepted that a difference of at least 1.5 mmHg between two treatments would represent a clinically significant difference. It is important to note that the value of what constitutes a clinically significant difference needs to be established before the beginning of the clinical trial, to appropriately target the sample size calculations to ensure that a statistically significant result will also be clinically relevant. For example, with a very large sample size, one might find that a difference as small as 0.5 mmHg between two IOP-lowering treatments could be found to be statistically significant, even though such a small difference in IOP reduction would be clinically unimportant. As stated by DeMets and Califf, "fueled by a sufficient mass of patients, eventually even the smallest difference in outcome cannot escape the pull of a statistical black hole."[3] On the other hand, a trial with insufficient sample size might find that a difference as large as 3 mmHg between two treatments would not be statistically significant.

To make inferences about clinical significance, the magnitude of the observed difference between the experimental and control groups should be expressed using confidence intervals. The confidence interval (CI) gives a measure of the precision (or uncertainty) of study results for making inferences about the population. For practical purposes, a 95% CI can be defined as the range of values of a test statistic that has a 95% chance of containing the true value.

Confidence intervals can help readers evaluate the clinical importance of results published in a study. In clinical trials comparing IOP-lowering efficacy of two drugs, the investigators should report the 95% CI of the difference in efficacy. For example, suppose that the mean difference in IOP reduction between two drugs A and B (A minus B) was reported as 2.8 mmHg, with a 95% CI ranging from 2.1 mmHg to 3.5 mmHg. In this case, the lower limit of the

95% CI is above the minimal acceptable clinically significant difference of 1.5 mmHg, which means that drug A is likely to be clinically superior to drug B in terms of efficacy. On the other hand, if the 95% CI for the difference ranged from 1.0 mmHg to 4.6 mmHg, the superiority of drug A could not be claimed as definitive, as the lower limit of the 95% CI interval would be below the minimal acceptable clinically significant difference of 1.5 mmHg.

Specific issues related to clinical trials in glaucoma

1. What should be the endpoint for clinical trials in glaucoma?

Traditionally, clinical trials of drugs used for glaucoma treatment have used reduction of intraocular pressure as the endpoint. However, in this circumstance, IOP is used as a surrogate for the definitive outcome, which would be progression or development of the disease. A surrogate outcome is one that is measured in place of the biologically definitive or clinically most meaningful outcome. In this sense, IOP is a surrogate in clinical trials of glaucoma treatment in the same way that blood pressure or cholesterol levels are surrogates in clinical trials for cardiovascular disease. The validity of IOP as a surrogate depends on the certainty that the elevated IOP is causative of optic nerve damage in glaucoma patients, that the IOP can be determined reliably with the type of measurements commonly used, and that lower IOP will result in better outcome in the long term.

There are some benefits and limitations of using IOP as a surrogate in clinical trials.

Benefits:

– Use of IOP as a surrogate makes clinical trials more efficient by reducing the duration and costs. Due to the slow progression rate of glaucoma, many years of trial would be necessary in order to compare the effect of different treatments on the outcome of disease. Also, the sample size requirement for a trial using the definitive outcome would be much larger than one using IOP as a surrogate.
– The interval between treatment and definitive outcome is long in glaucoma, so there is opportunity for intercurrent events to confound the assessment of outcomes.
– Clinical trials using the surrogate may sometimes offer a clearer picture of the effects of treatment than clinical trials employing the definitive outcome. Due to a lack of more precise ways of defining glaucoma progression, we have to rely on assessment of visual field or optic disc progression to evaluate the outcome. Both of these assessments may be prone to greater variability than IOP.
– Ethical acceptability. Leaving a patient untreated or with placebo for a few

months is certainly more ethically acceptable than leaving untreated for many years and waiting to develop visual field progression.

Limitations:

- Validity of IOP as a surrogate: The central issue of the relationship between IOP changes and glaucoma status has not yet been fully characterized, despite numerous studies. We know that many patients with high IOP never develop glaucoma and that others do not experience progressive glaucomatous damage. We also know that glaucoma can progress even if IOP is low. It is hoped that the incorporation of CCT in clinical trials using IOP as a surrogate measure for glaucomatous damage could potentially clarify this relationship.
- The possibility that treatment affects the true outcome through a mechanism that does not involve the surrogate – in the case of glaucoma, a particular treatment could have an effect on disease outcome by other means then IOP, such as changes in blood flow or neuroprotection. These effects may not be adequately captured in clinical trials that look only at IOP reduction.
- Trials using IOP as a surrogate measure may not have sufficient follow-up time to detect side effects that appear with chronic use of medications.

2. What is an adequate sample of 'baseline' IOP in clinical trials evaluating IOP-lowering therapies?

Prior to approval of a particular ocular hypotensive medication, regulatory agencies (Federal Drug Administration, European Union) will use IOP lowering as the outcome of interest for efficacy. Baseline IOP is defined as the intraocular pressure measured prior to an IOP-lowering intervention and is one of the key components to determine IOP response in clinical trials.

Before assessing baseline IOP, prior IOP-lowering medication should have had an adequate wash-out period. IOP is measured with a calibrated Goldmann applanation tonometer on a slit-lamp biomicroscope. After topical anesthesia and fluorescein have been instilled, the IOP measurement is ideally performed by two individuals: an operator who adjusts the tonometer dial and a reader who reads and records the results. The reading in mmHg is rounded to the next higher integer. Each reading is repeated, and if the two measurements differ by more than 2 mmHg, a third reading is taken. The baseline IOP at that time may be determined by the median of the two or three measurements.[4-6]

Because of the tendency for intraocular pressure measurements to fluctuate, a tenet of accurately measuring a factor includes repeating the measurement. The baseline or 'reference' IOP measurement should be made on at least two separate days, following eligibility measurements and prior to randomization. Diurnal fluctuations may also influence single IOP readings. Although we do not know the most important time-points, published studies suggest that three time-points (morning, afternoon and early evening) may provide sufficient information for the purposes of a large clinical study.

Multiple IOP measurements also reduce the potential for regression to the mean, which may falsely augment the perceived IOP response in a clinical trial.[7] Regression to the mean is a recognized event in clinical studies when evaluating treatment effects. It occurs because an unusually large random measurement error (resulting in an overestimate of the true value of IOP) is unlikely to recur at a later measurement. With follow-up measurements, therefore, IOP measurements tend to become closer to the true value. A decrease due to random measurement error cannot be distinguished from a true decrease in IOP, therefore this phenomenon may augment the apparent response to an ocular hypotensive medication, especially when a group with higher baseline IOP is compared to a group with a lower baseline IOP.

Even when a protocol minimizes regression to the mean, controlling for differences in baseline intraocular pressure is important in medication response studies. Patients with higher IOP on average have larger physiological reductions in IOP in response to an ocular hypotensive medication. For example, the OHTS study showed that higher baseline IOP was strongly correlated with greater IOP reduction after four to six weeks of a one-eyed trial.[8,9]

Observer and recruitment bias may also alter the accuracy and reliability of baseline intraocular pressure. For example, recruitment bias may occur if an investigator adjusts intraocular pressure slightly upwards to reach the qualifying IOP of a study. Upon follow-up, the IOP response would then be speciously increased. Observer bias may occur if the investigator only reports IOP measurements closest to the hash marks on the tonometer reticule, such as 10, 12, 14, etc. mmHg. The Ocular Hypertensive Treatment Study protocol attempted to minimize these biases. The protocol required an examiner to adjust the tonometer reticule without looking at it, while observing the tonometer mires through the slit lamp. A second person recorded the IOP measurement.

In addition to baseline IOP and the methods of determining it, the two other variables important to collect as part of a clinical trial include central corneal thickness (CCT) and type of glaucoma (such as pigmentary dispersion, pseudoexfoliation). Similarly, studies may differentiate between glaucoma and ocular hypertension patients. Two recent studies from the OHTS suggest that a thinner CCT is more likely to result in a greater IOP response to topical beta adrenergic antagonists and prostaglandin.[8,9] The reasons for this difference are not known. Brandt *et al*.[8] postulated that thicker corneas have higher rigidity which reduces the ability to measure a decrease in IOP by applanation tonometry. Another explanation, decreased diffusion of ocular hypotensive medication into an eye with a thicker cornea, is possible but less likely due to known high concentrations of active medication in the anterior chamber.[10-12]

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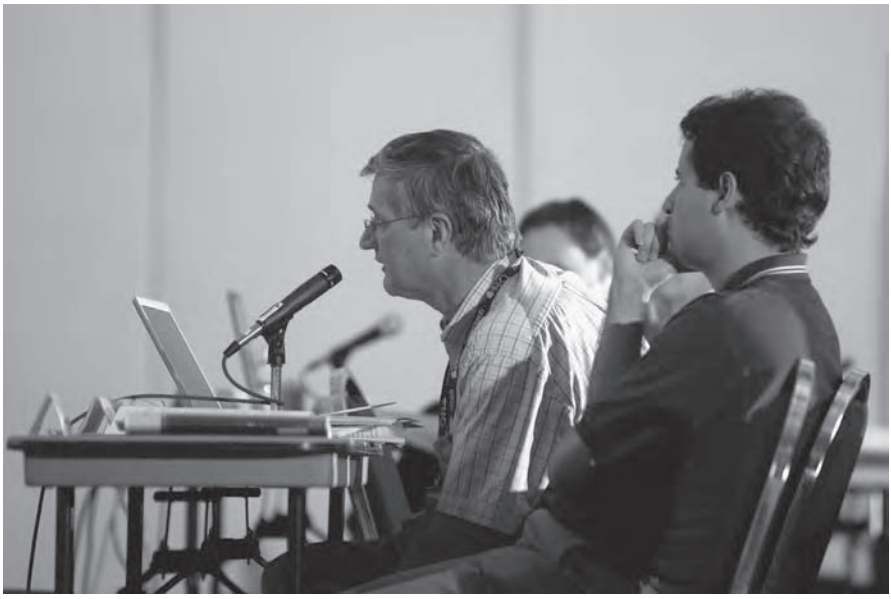
Felipe Medeiros presenting the section on clinical trials and intraocular pressure



Anders Heijl

Mike Patella and Murray Fingeret discussing the section on clinical trials and IOP

From left to right: David Friedman, Tin Aung, Tony Wells and Keith Barton

Chris Leung (left) and George Spaeth (right)

Paul Palmberg (left) and Harry Quigley (right)

TARGET IOP IN CLINICAL PRACTICE

Henry Jampel

Henry Jampel

Contributors: Augusto Azuaro Blanco, Daniel Grigera, Henry Jampel, Jeff Liebmann, Jonathan Myers, Shan Lin, Ravi Thomas, Kuldev Singh, Michele Lim, Ivan Goldberg, Doug Anderson, Neeru Gupta, Young Kwon

Consensus points

- The target IOP is the IOP range at which the clinician judges that progressive disease is unlikely to affect the patient's quality of life.
  Comment: The burdens and risks of therapy should be balanced against the risk of disease progression.
- The determination of a target IOP is based upon consideration of the amount of glaucoma damage, the IOP at which the damage has occurred, the life expectancy of the patient, and other factors including status of the fellow eye and family history of severe glaucoma.
  Comment: At present, the target IOP is estimated and cannot be determined with any certainty in a particular patient.
  Comment: There is no validated algorithm for the determination of a target IOP. This does not, however, negate its use in clinical practice.
- It is recommended that the target IOP be recorded so that it is accessible on subsequent patient visits.
- The use of a target IOP in glaucoma requires periodic re-evaluation.
  Comment: This entails examination of the optic nerve and assessment of visual function to detect glaucomatous progression, the effect of the therapy upon the patient's quality of life, and whether the patient has developed any new systemic or ocular conditions that might affect the risk/benefit ratio of therapy.
  Comment: During the re-evaluation, it is essential to determine whether the IOP target is appropriate and should not be changed, or that it needs to lowered or raised.

Intraocular Pressure, pp. 121-125
edited by Robert N. Weinreb, James D. Brandt, David Garway-Heath and Felipe A. Medeiros

Justification for the use of target intraocular pressure (IOP)

Patients who have glaucoma are at risk of developing damage to their vision, and this may impact their quality of life (QOL). As physicians, our goal is to maintain patients' overall quality of life, balancing the burdens of therapy against the risk of disease. The IOP is related both to a person's risk of developing glaucoma[1] and to their risk of progressive damage.[2-6] Furthermore, lowering IOP therapeutically has been shown to reduce the risk of the development of glaucoma[1] and the risk of progressive vision loss.[2-6] Clinical trials have also identified other factors that may influence a patient's risk of developing glaucoma, or of progressive glaucomatous damage, such as age, optic nerve status, visual field status, and corneal thickness.[1,5,6]

The concept of a target IOP recognizes that IOP reduction is a goal of glaucoma therapy, because of IOP's relation to the patient's risk for progressive disease, and therefore may be used as a surrogate for the real goal of maintaining each patient's overall QOL to the greatest extent possible. The 'threshold for treatment IOP' is a related concept and refers to the IOP at, or greater than, that therapy would be started in an untreated individual. At present, neither the target IOP nor the threshold to treat IOP can be determined with any certainty in a particular patient.

The clinician must thoroughly evaluate the patient's overall situation and may determine a target IOP and use that as a guideline for therapy in the short or long term. This target may be readjusted (see below) based on the patient's clinical course, including response and reactions to therapeutic interventions as well as his/her ocular status, and overall life events. The use of a target IOP does not just provide for efficiency in patient care, but more importantly helps to maintain consistency in a chronic course of treatment and monitoring.

The clinician must individualize treatment to each patient and his/her specific characteristics and overall situation. The art of caring for glaucoma involves incorporating a complex body of information in determining therapeutic goals and choices as well as accepting that some information is not available prospectively. The patient's particular ocular condition will influence the risk to their QOL from glaucoma. Non-ocular factors, including but not limited to, systemic health and life expectancy, ability to adhere to therapy and follow-up, the degree to which a therapy – medical or surgical – affects their quality of life, and cost of therapy, also must play a role in the assessment of the patient's treatment goals. The patient should be a partner in these decisions to the extent that he/she is able and willing, and the patient's individual wishes and views will often determine the therapeutic goals and choices.

It should be emphasized that the target IOP is only an estimate, and must be continually reassessed in relation to the patient's condition, needs, and wishes. The target IOP merely reflects a goal set by the treating clinician, based on estimated measures of the patient's risk and the current understanding of glaucoma. Some patients will continue to have unacceptable rates of disease progression despite apparent achievement of their target IOP, and many who do not achieve

their target IOP will not be adversely affected by their glaucoma. Therefore, in many cases, clinicians may choose not to advance treatment in patients who have not met their target IOP, always balancing the burdens of therapy against the risks of glaucoma.

Establishing a target in clinical practice

Definition of target IOP

The target IOP may be defined in different ways. The European Glaucoma Society guidelines define Target IOP as 'an estimate of the mean IOP obtained with treatment that is expected to prevent further glaucomatous damage.' Others may argue that we cannot halt glaucoma damage but only reduce the rate of progression. Therefore an alternative definition might be 'an estimate of the mean IOP at which the risk of decreased vision-related quality of life due to glaucoma exceeds the risk of the treatment.' There is no 'correct' definition, and the definition may vary for each physician and each patient.

Determination of target IOP

Steps in the estimation of target IOP may vary, but should include the following steps:

1. *Estimating the amount of glaucoma damage.* This is based upon both structural and functional assessment.
2. *Estimating the damaging IOP.* One should make the best clinical assessment possible as to what the likely IOP was at which damage has already occurred. In some instances, multiple IOP measurements may help determine a baseline IOP and hence influence the initial determination of the target IOP.
3. *Estimate the patient's life expectancy.* In general, the longer the patient's life expectancy, the lower the target IOP will need to be. Actuarial tables can be helpful, keeping in mind that any given patient may live much longer or shorter than the mean. When in doubt, err on the side of estimating a longer life expectancy. Nevertheless, on average, 40 year olds and 90 year olds may be treated differently.
4. *Consideration of the other risk factors for progression.* Other proposed risk factors include severe damage in the other eye, family history of blindness from glaucoma, etc.
5. *Guesstimate the Rate of Progression* of glaucoma damage, either disc and/or fields, based upon the assessment of damage that has already occurred versus time.

Once steps 1-5 are complete, the treating physician may opt to choose an absolute IOP level for the target (*e.g.*, IOP of 11 mmHg in a young individual with advanced damage that seemed to occur at relatively low IOP), or a percentage

reduction in IOP determined by the risk of progression estimated from steps 1-3 (*e.g.*, 20% reduction for mild glaucoma in an elderly individual and 40% reduction in a young person with moderate damage and significant IOP elevation).

A prior assessment of the rate of progression is valuable to help the discussion with the patient regarding the aggressiveness of the treatment.

Recording the target IOP

If one elects to use the target IOP as a guide to IOP lowering therapy, it needs to be recorded in the medical record. Not only does this make it more convenient for the physician to judge if the therapy is having its intended effect, it also saves the physician from having 'to reinvent the wheel' on every visit. Provisos include avoiding the potential pitfalls of ignoring the truly important clinical data-how is the patient?, how is the patient's visual function, and hesitating to modify the target pressure because it has been written down (but on paper, not in stone). The written target should be intended as a reminder of the previously estimated ideal pressure range and not as a binding agreement.

Re-evaluation of target IOP

The use of a target IOP in glaucoma requires periodic re-evaluation. During the re-evaluation, the physician will conclude that either the target is appropriate and should not be changed, that the target needs to lowered, or that the target should be raised.

Re-evaluation entails the detection of the presence or absence of glaucomatous progression, the effect of the therapy upon the patient's QOL, and whether the patient has developed any new systemic illness that might affect the risk/benefit ratio of therapy or likely to greatly shorten life expectancy.

The presence or absence of progression is determined by serial assessment of the optic nerve head and/or retinal nerve fiber layer and of the functional damage on perimetric testing.

The effect of therapy upon a patient's QOL is determined through talking to the patient as well as ocular and physical examination. For instance, if the patient's eyes are red or wheezing is noted at the slit lamp the physical observation can be a tip off to a QOL-decreasing therapy. Examples of systemic illnesses that might affect the re-evaluation of target IOP would include the development of asthma requiring cessation of beta-blocker therapy, or a diagnosis of pancreatic cancer. In such instances, the target pressure might be raised, particularly if it were to reduce the burden of therapy (*e.g.*, need for a glaucoma operation).

One cannot reassess the target IOP unless one is aware of what the target IOP is. This is best accomplished by have a record of the target IOP in the medical record. Without such a record, there is the danger of losing sight of the initially determined IOP and assume the patient's current pressures are adequately controlled. A potential tool for avoiding such a mistake includes some graphical or serial form of recording IOP in conjunction with other information such as target IOP, when medications were started and stopped, whether surgery was

performed, visual field indices, and results of image analysis. This is an area in which an electronic medical record can be a great help, by bringing the power of graphical display and integration of multiple pieces of data to the forefront making it easier for one to make decisions based on a complex set of information. Whenever a change in the target IOP is made, the date of the change and the new target IOP should also be recorded.

Topics for future research/discussion

1. Suggest that all clinical trials involving IOP lowering report as an outcome the distribution of eyes achieving a pre-determined target IOP. This would require the establishment of a target IOP upon entrance into the trial. This outcome would supplement more conventional outcomes such as % of eyes with IOP lower than 18 mmHg, or % of eyes with at least a 25% reduction of IOP.
2. Perform a randomized clinical trial in which half of a cohort of newly diagnosed glaucoma patients have their target IOP determined and readily available to the clinician and the other half are managed without an explicitly determined target IOP. Determine if one group had less progressive glaucoma damage and/or less diminution to their health-related quality of life.

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DISCLOSURES

Nothing to disclose/no industry connection to this material
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