

World Glaucoma Association

Intraocular Pressure



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

Intraocular Pressure

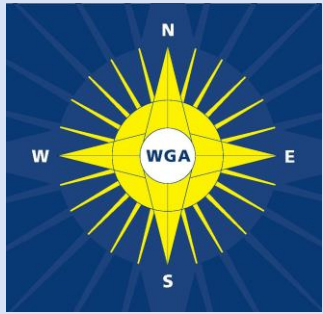
Robert N. Weinreb, James D. Brandt,
David Garway-Heath and Felipe Medeiros

Consensus Series 4



Kugler Publications, The Hague, The Netherlands

The Global Glaucoma Network



Fort Lauderdale, Florida May 5, 2007



The Global Glaucoma Network



Basic Science of Intraocular Pressure

Aqueous flow

1. IOP is determined by contributions from aqueous humor production (measured as aqueous flow), trabecular outflow, uveoscleral outflow and episcleral venous pressure.

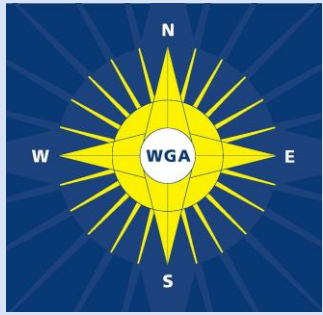


Basic Science of Intraocular Pressure

2. 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.

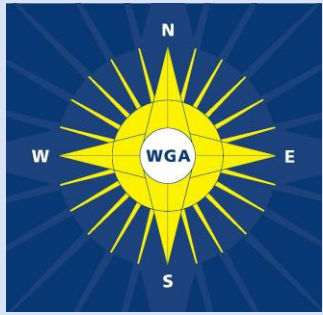


Basic Science of Intraocular Pressure

3. 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.



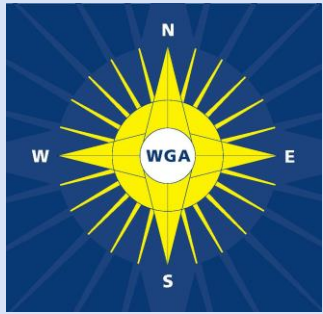
Basic Science of Intraocular Pressure

Trabecular outflow

1. 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 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.



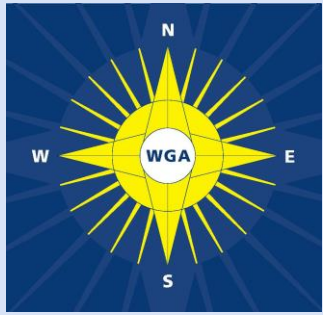
Basic Science of Intraocular Pressure

2. Outflow facility in healthy human eyes is the range of 0.1 to 0.4 $\mu\text{l} / \text{min} / \text{mmHg}$.

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.

3. Outflow facility can be measured with tonography and fluorophotometry. Both methods have inherent limitations associated with their use.

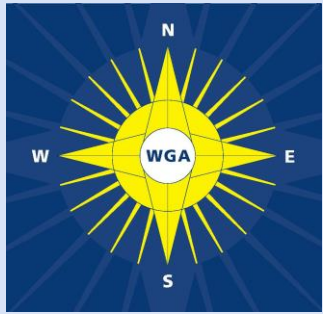


Basic Science of Intraocular Pressure

Uveoscleral outflow

1. The uveoscleral outflow pathway is comprised of the ciliary muscle, supraciliary space, suprachoroidal space, sclera and other less defined areas.
2. 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 an without exfoliation syndrome, increased in uveitis, and unchanged in pigment dispersion syndrome with ocular hypertension

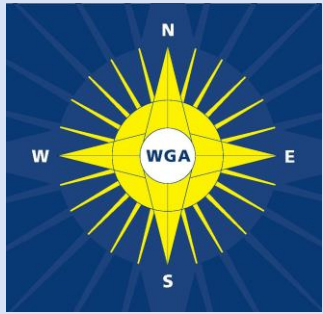


Basic Science of Intraocular Pressure

3. 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



Basic Science of Intraocular Pressure

Episcleral venous pressure

1. Episcleral venous pressure in healthy humans is 8 to 10 mmHg.

Comment: It is affected by body position, inhalation of O₂, 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.



Measurement of Intraocular Pressure

WGA

1. On average, greater central corneal thickness (CCT) results in overestimation of intraocular pressure (IOP) as measured by Goldmann applanation tonometry (GAT).

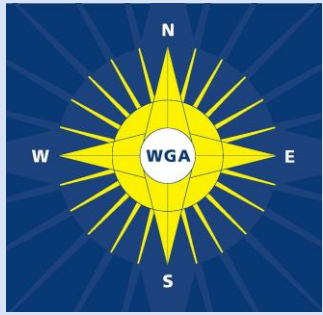
Comment: The extent to which CCT contributes to the measurement error (in relation to other factors) in individual patients under various conditions has yet to be established.



Measurement of Intraocular Pressure

WGA

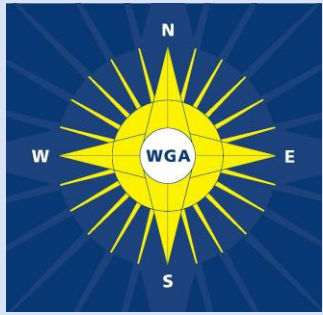
2. Compared to GAT, CCT has a lesser effect on IOP measured by dynamic contour tonometry (DCT) and the ocular response analyzer (ORA) (corneal compensated IOP). CCT has a greater effect on IOP measured by NCT and Rebound Tonometry.



Measurement of Intraocular Pressure

WGA

3. 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.

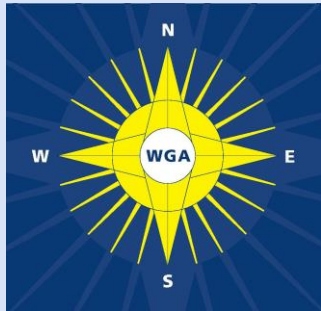


Measurement of Intraocular Pressure

WGA

4. 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)

See comments to this statement on next slide



Measurement of Intraocular Pressure

WGA

Comment to statement 4

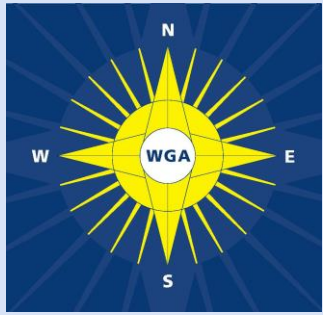
Comment: Under ideal circumstances for measurement, precision figures reported for GAT are:

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



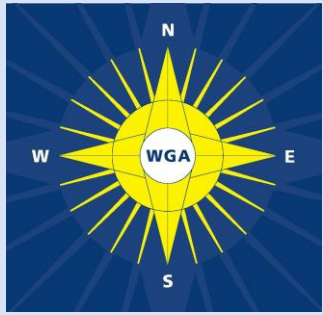
Measurement of Intraocular Pressure

WGA

5. 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 $> \pm 1$ 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.

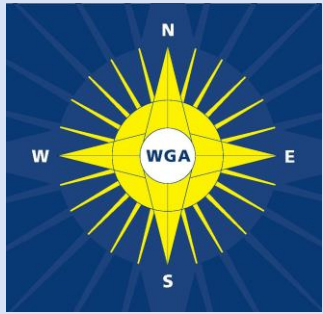


Measurement of Intraocular Pressure

WGA

6. 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 Intraocular Pressure

7. 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.
8. 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.



Measurement of Intraocular Pressure

WGA

9. 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.

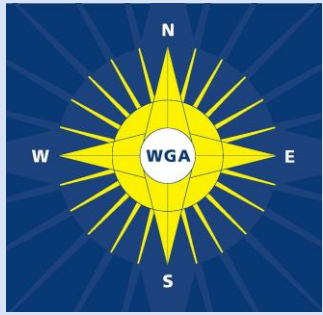


Measurement of Intraocular Pressure

WGA

10. Large amounts of corneal edema produce an underestimation of IOP when measured by applanation tonometry.

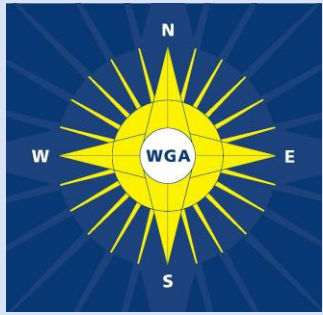
Small amounts of corneal edema (as induced by contact lens wear) probably cause an overestimation of IOP.



Measurement of Intraocular Pressure

11. 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.
12. The wearing of contact lenses on the day when tonometry is performed may lead to an artifactually raised IOP as measured by GAT.

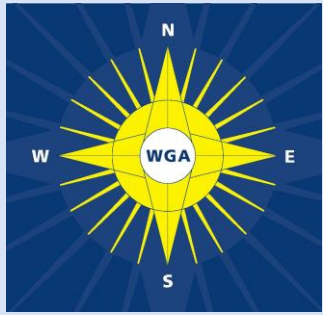
Comment: Contact lens wearing patients should have tonometry performed after having been awake, without contact lenses, for at least two hours for contact lens-induced and diurnal corneal edema to resolve.



Measurement of Intraocular Pressure

13. There are changes in corneal biomechanics following many forms of keratorefractive surgery, associated with a mean fall in IOP as measured by applanation tonometry.

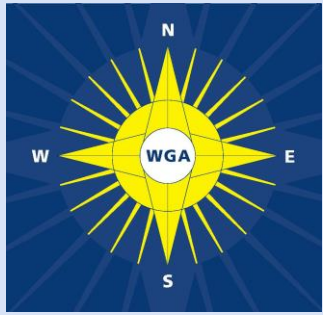
Comment: Although there is a mean fall across patients in measured IOP, there is a wide variability in response.



Measurement of Intraocular Pressure

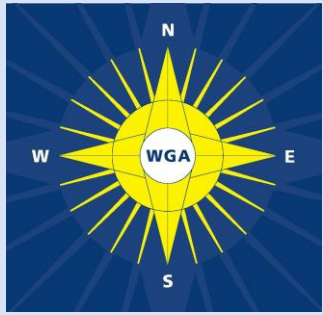
14. DCT and ORA (corneal compensated IOP) may both be less sensitive to changes in corneal biomechanics following keratorefractive surgery and have less variance than standard applanation tonometry.
15. The use of a lid speculum, sedatives and general anesthetics can significantly affect IOP measurement 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.



IOP as a Risk Factor for Glaucoma Development & Progression

1. There is *strong evidence* to support higher mean IOP as a significant factor for the development of glaucoma.
2. There is *strong evidence* to support higher mean IOP as a significant risk factor for glaucoma progression.
3. 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 tends to be correlated with mean IOP.



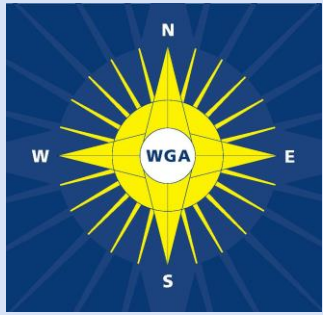
IOP as a Risk Factor for Glaucoma Development & Progression

4. 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.



IOP as a Risk Factor for Glaucoma Development & Progression

5. There is currently *insufficient evidence* to support IOP variation over periods longer than 24 hours as a risk factor for glaucoma development and progression.



IOP as a Risk Factor for Glaucoma Development & Progression

6. Sufficiently low blood pressure, combined with sufficiently high IOP, generates low ocular perfusion pressure and is associated with increased 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.

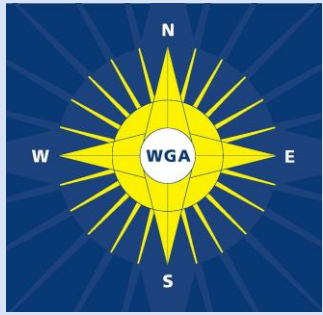


Epidemiology of Intraocular Pressure

1. 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.*

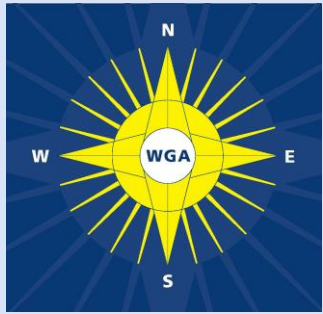
2. Evidence for differences in IOP between blacks and white is contradictory from available populations-based studies.



Epidemiology of Intraocular Pressure

3. Evidence for a relationship between IOP and age is contradictory from available populations-based studies.
4. Evidence for a relationship between IOP and gender is contradictory from available populations-based studies.

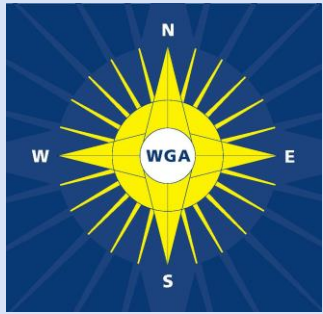
See comments to this statements on next slide



Epidemiology of Intraocular Pressure

5. 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.



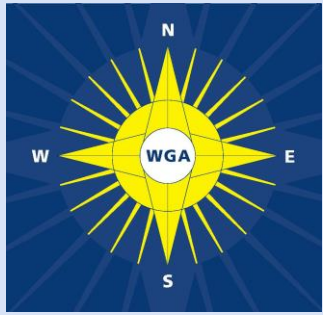
Epidemiology of Intraocular Pressure

6. 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.

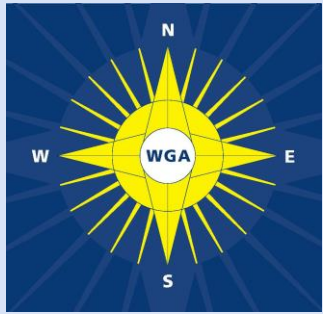
Comment: IOP is higher in eyes with shorter axial anterior chamber depth as a result of pathological angle-closure.

Comment: Corneal radius of curvature is a potential source of measurement error, and should be adjusted for when using an applanation tonometer.



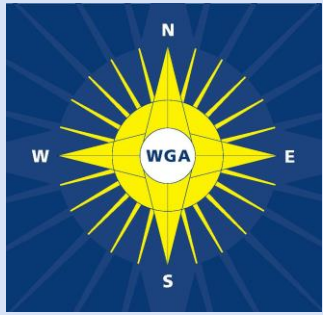
Epidemiology of Intraocular Pressure

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



Clinical Trials & Intraocular Pressure

1. 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.
2. An appropriately-designed clinical trial for efficacy of IOP reduction should specify a clinically significant treatment effect (δ); probability of a type 1 error (α), usually set at 5%, and a desired power (conventionally at least 80%).



Clinical Trials & Intraocular Pressure

3. 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).
4. Clinical trials comparing IOP-lowering efficacy of different treatment should provide 95% confidence intervals for the difference in IOP reduction.



Clinical Trials & Intraocular Pressure

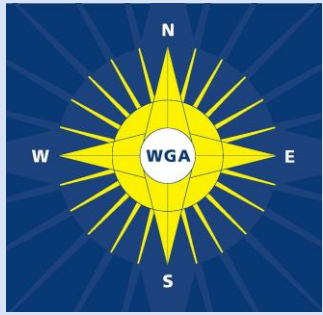
5. Efficacy trials should define *a priori* the clinically meaningful difference for that specific study.

Comment: In addition to IOP-lowering, other factors such as safety and side-effects must be considered in defining a clinically-meaningful difference for that specific study.



Clinical Trials & Intraocular Pressure

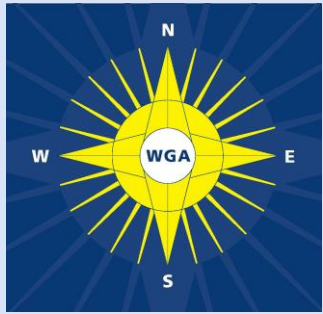
6. Protocols should include *at least* two post-screening IOP measurements acquired on *at least* two different days for calculating baseline IOP, *prior to randomization*.
7. Protocol analyses also should include measurement of baseline IOP, central corneal thickness and type of glaucoma to allow adjustment for these potentially confounding variables when comparing IOP-lowering interventions.



Target IOP in Clinical Practice

1. 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.

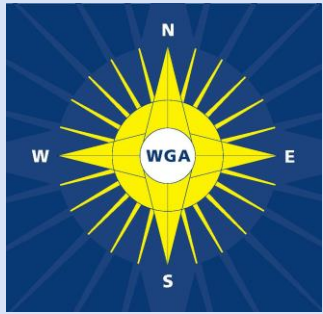


Target IOP in Clinical Practice

2. The determination of a target IOP is based upon consideration of the amount of glaucoma damage, the IOP at which the damage has occurred, and 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.

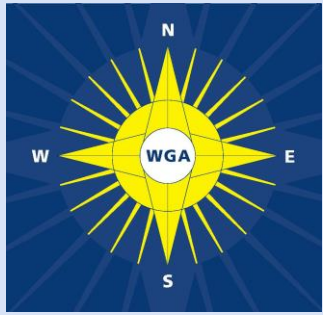
Comment: There is no validated algorithm for the determination of a target IOP. This does not, however, negate its use in clinical practice.



Target IOP in Clinical Practice

3. It is recommended that the target IOP be recorded so that it is accessible on subsequent patient visits.
4. The use of a target IOP in glaucoma requires periodic re-evaluation.

See comments to these statements on next slide



Target IOP in Clinical Practice

Comments to statements 3 and 4

Comment: This entails examination of the optic nerve and assessment of visual function to detect glaucomatous progression, the effect of the therapy upon the patients 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 be lowered or raised.