Learning Objectives

- To understand new concepts in IOP measurement and risk assessment
- To understand the various clinical utilities of OCT in Glaucoma diagnosis and monitoring
- To recognise new medication development in glaucoma and what it could mean for your patients

Agenda

- New Technology in glaucoma diagnosis
  - Corneal Hysteresis
  - 24 Hour IOP measurement
  - Home tonometry
  - Electrodiagnostics
- New Treatment in Glaucoma
- Using your OCT smarter:
  - GCC
  - Macular Vulnerability Zone

24-Hour IOP Monitoring

- How do we evaluate IOP if we are only measuring it briefly in office?
  - Currently we make decisions based upon single in-office IOP but patient’s IOP may vary at other times
    - With 24-hour IOP measurement, we will be able to determine your treatment target based on peaks and troughs of IOP
  - 24-hour IOP monitoring systems
    - Better definition of IOP leading to better therapies
    - Personalising glaucoma care

IOP is Higher At Night

![Graph showing 24-hour IOP pattern (ages 40-80) for glaucoma vs. non-glaucoma](image)
Implantable IOP monitor

Check back in 2011

Temporary Continuous IOP Monitoring

- Triggerfish contact-lens system
  - FDA approved March 2016 but not available for sale in US
  - Measures changes in corneal curvature as surrogate for IOP

Triggerfish Contact Lens Monitor

- Provides 24 hour IOP monitoring, including the sleep period
- Takes measurement every five minutes
  - 388 times per day
- At the five minute measurement, obtains 300 data points
  - 10 Hz for 30 seconds
- Main concern is that instrument does not provide IOP measurement
  - Provides change in corneal curvature, based upon peripheral corneal measurement that correlates with change in IOP
  - Detect fluctuations in IOP

Triggerfish Contact Lens 24-Hour IOP Monitoring Device


An Implantable Intraocular Pressure Transducer Initial Safety Outcomes

Leonardi M, MD, PhD, and Towers WJ, Congdon, NG, MD

INTRODUCTION

This is a report of the first implantation of a wireless intraocular pressure transducer (WIT) in a human eye.

METHODS

This was a prospective, nonrandomized study of the safety of the WIT. All patients were aged 18 years or older, and had normal or corrected-to-normal vision.

RESULTS

No complications were noted during the WIT implantation or postimplantation. All preimplantation intracocular pressure measurements were within normal limits.

CONCLUSIONS

The WIT is an alternative method for measuring intraocular pressure in the future.
**Implandata - Permanent Continuous IOP Monitoring**

- Based upon sensors found in tires in cars
- Used automotive technology and modified to fit into eye
- Needed to be smaller and more precise
- Inserted at time of cataract surgery with ring placed in front of IOL
- Sensor powered on by external unit with data sent to device
- Available in Europe

**Self Tonometry**

- Patients would monitor their IOP over time with easy-to-use devices
- Easiest approach in regards to continuous monitoring
- Adapt current device such as Noncontact tonometer or Rebound tonometer
- May be difficult for some patients to perform
- Not easy to obtain 24 hour IOP
- Icare Home Tonometry
  - Waiting FDA approval
  - Person would have device provided from eye doctor to use for 24 hours
  - Measurements sent to eye doctor for review
  - Issue with reimbursement
  - Dependent upon ability of individual to take accurate readings

**Corneal Hysteresis**

- Rigidity of cornea may be associated with the risk of glaucoma development
- Reichert instrument based upon the non-contact tonometer
- Measures corneal response to indentation by rapid air pulse to determine viscoelasticity
- Reduced hysteresis associated with increased risk
- Measures
  - Pressure at applanation (IOP 1) and when cornea becomes flat (IOP 2)
  - Difference between two pressures is termed corneal hysteresis
  - Measure cornea biomechanical properties

**Normal ICH values**

**Summary of published results**

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Kimura, O'Keefe (Ireland)</td>
<td>12.5 ± 1.35</td>
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<tr>
<td>Altshuler et al (China)</td>
<td>10.8 ± 1.5</td>
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<tr>
<td>Wegner et al (Germany)</td>
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<td>Touloukian et al (France)</td>
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<td>Lam et al (Hong Kong)</td>
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<td>Chang (Belgium)</td>
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<td>Gonzalez-Marchena (Portugal)</td>
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<tr>
<td>Hong (Israel)</td>
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<tr>
<td>Catarman (JH)</td>
<td>10.2 ± 1.24</td>
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<tr>
<td>Meltzer (France)</td>
<td>10.26 ± 1.6</td>
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<tr>
<td>Kida et al (JNA 2014 adults)</td>
<td>10.5 ± 1.1</td>
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<tr>
<td>Touboul et al (France)</td>
<td>10.26 ± 1.24</td>
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<tr>
<td>Lam et al (China)</td>
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<tr>
<td>Fontes, et al (Brazil)</td>
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<td>Carbonaro (UK)</td>
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<td>Delannoy (Belgium)</td>
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<td>Gozalez - Mejome (Portugal)</td>
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<td>Kamiya (Japan)</td>
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<td>Kida et al (UK Young Adults 20-30)</td>
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<td>Jung (Korea)</td>
<td>10.7 ± 1.6</td>
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<tr>
<td>Liew et al (Singapore Children)</td>
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</tr>
<tr>
<td>Kimura, O'Keefe (UK Children)</td>
<td>12.5 ± 1.35</td>
</tr>
</tbody>
</table>
New Active Level I CPT Code for Corneal Hysteresis (CH)

- New CPT Code 92145
- Replaces previous Level III 0181T
- Bilateral code (like pachymetry)
- Suggest limiting to once per doctor per patient or no more than once per year

Diagnosis/Treatment

- COAG OU
- PGA 22 OU
- PGA and Combigan Ta 17/16
- Is this low enough?
- Maximum medical therapy?

Primary Open-Angle Glaucoma: Pathophysiology

Electrodiagnostic Testing

- Provides functional assessment of the visual system that supports other parts of the examination
  - Patient may not be able to perform reliable visual field testing
  - May be an early indicator of damage
- Pattern electroretinogram (PERG)
- Visually Evoked Potential (VEP)
The Glaucoma Suspect

A glaucoma suspect is defined as an individual who has an optic nerve or visual field defect suggestive of glaucoma but lacks confirmatory evidence. This includes patients with abnormal visual fields but normal optic nerve head examinations, or visual field defects without optic nerve head changes. They are monitored over time to assess for progression of glaucoma.

PERG is retinal response to a patterned stimulus

- Visual stimulus: checker/bar pattern
- Measures at level of photoreceptors, ganglion cells
- Small signal prone to interference from noise
- While independent of patient motor and cognitive skills (unlike perimetry), PERG requires careful control of fixation, refraction and stimulus distance

2 types:
- 1. Transient PERG
- 2. Steady State PERG

What is ERG

- Measures electrophysiological activity at the retina-photoreceptors
- Objective testing of ganglion cell function

ERG Magnitude (uV)

- Defined as the strength of the PERG signal resulting from the visual stimulus. Larger magnitude numbers are generally generated from healthy eyes, as the contrast level dropped or the stimulus size increased, the magnitude will typically decrease. Initial evaluation of the magnitude should be made using the 24 h/1st results.

<table>
<thead>
<tr>
<th>Magnitude (uV)</th>
<th>HD (F1)</th>
<th>HD (F2)</th>
<th>HD (F3)</th>
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<tbody>
<tr>
<td>Magnitude</td>
<td>2.04</td>
<td>3.58</td>
<td>4.34</td>
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<tr>
<td>Max Haze Ratio</td>
<td>1.02</td>
<td>0.89</td>
<td>0.83</td>
</tr>
<tr>
<td>SNR (dB)</td>
<td>0.03</td>
<td>1.3</td>
<td>2.8</td>
</tr>
<tr>
<td>SNR (dB)</td>
<td>0.00</td>
<td>1.00</td>
<td>2.00</td>
</tr>
</tbody>
</table>

PERG Artifacts

Magnitude(uV) takes into account magnitude and phase variability throughout the test. The more repeatable the magnitude and phase are throughout the test, the closer Magnitude(uV) will be to the Magnitude measured.

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Signal to Noise Ratio (SNR): 9.5 1.3 9.5 0.5
Artifacts: 0 0 0 0

1. Magnitude (uV) for Hc and Lc levels - >1.2uV
2. Magnitude D for Hc and Lc levels - similar 1.2uV
3. Magnitude D/Magnitude ratios - close to 1.00
4. Signal to Noise Ratio (SNR, dB)- 0-10 dB
5. Artifacts
Current Research in ERG

Pattern Electroretinogram in Glaucoma Suspects New Findings from a Longitudinal Study

S. H. booker, Thomas Jobs, and Michael Jack

- Ocular Hypertensionconversion to glaucoma monitor with PERG
- Eyes that converted had low PERG amplitude
- PERG ratio high indicator for conversion
- PERG detects conversion to glaucoma 4 yrs. earlier

Current Research in ERG

Progressive Loss of Retinal Ganglion Cell Function Precedes Structural Loss by Several Years in Glaucoma Suspects


- PERG amplitude with RNFL thickness OCT
- PERG amplitude decrease 50% before RNFL thickness decrease
- "2 yrs. for 10% change in amplitude of ERG" vs. "10 yrs. to see 10% RNFL loss"

Treatment and PERG affect

Progressive Loss of Retinal Ganglion Cell Function Is Hindered with IOP-Lowering Treatment in Early Glaucoma

S. H. Vickers, William J. Pearson, and Victoria Vincent

- Glaucoma suspects treated (prostaglandin or Beta-blockers)
- Treatment slowed slope of PERG from declining compared to no treatment
- Dysfunctional RGC can be reversed

Current Drug Classes

- PGA’s
- Beta Blockers
- Alpha Agonists
- Topical CAI’s
- Combos

Today’s Treatment Algorithms

Glaucoma Agents on the Horizon

- Latanoprostene bunod (NicOx)
- Rho-associated Protein Kinase Inhibitors
  - ROCK inhibitors
- Trabodenoson
- Bimatoprost SR
- Bimatoprost Ring
Latanoprostene bunod 0.24%

- BOL-303259-X (VESNEO)/ VYZULTA
- Collaboration between NiCoX and Bausch
- Nitric Oxide-donating prostaglandin F2-analogue
- PIII US clinical trials- separate pivotal trials
  - APOLO and LUNAR studies complete
  - Also 2 Japanese trials underway
    - JUPITER PIII
    - KRONUS PI

Latanoprostene Bunod: NO-Donating Latanoprost

- NO plays key roles in both health and disease throughout the body, including the eye

Latanoprostene-bunod: Mechanism of Action

- Latanoprostene = latanoprost
  - Increases uveoscleral outflow
- Bunod modification donates nitric oxide
  - Exerts its effect in trabecular smooth muscle
  - Activating cGMP signaling pathway
  - Resulting in trabecular relaxation and increased conventional outflow
- Mechanisms would be expected to additive

Latanoprostene-bunod

- Phase 2 VOYAGER study
  - At highest doses, lowered IOP 1-1.5 mmHg more than latanoprost
  - Most common AE: pain upon instillation

Other NO-Donating Compounds in Development

- NO-donating bimatoprost
- NO-donating carbonic anhydrase inhibitors
  - Dorzolamide
  - Brinzolamide
ROCK Inhibitors

- Rho-associated coil-forming protein kinase
- Inhibitors of ROCK modulate changes in the actin cytoskeleton and cellular motility of the TM
- May lower resistance to aqueous outflow by relaxation of TM and Schlemm’s canal cells
- Hyperemia has been a concern

Rho Kinase Inhibitors

- Several molecules failed clinical trials
- One rho kinase inhibitor (Netarsudil mesylate) in Phase
  - Inhibits the enzyme rho kinase
  - Also inhibits norepinephrine transporter (increases adrenergic activity)
- Potentially lower IOP by three mechanisms
  - Increasing TM outflow
  - Reducing episcleral venous pressure
  - Reducing aqueous production (via NET inhibition)

Netarsudil Mesylate Development

- Two Phase 3 trials completed
  - ROCKET-1
    - Entry IOP >20 mmHg and <27 mmHg
    - N=411
    - 3 months
  - ROCKET-2
    - Entry IOP >20 mmHg and <25 mmHg
    - N=756
    - 12 months (primary efficacy at Month 3, safety through Month 12)
- Similar design
- Randomized to
  - Netarsudil mesylate 0.2% QHS
  - Netarsudil mesylate 0.2% BID (ROCKET-2 only)
  - Timolol 0.5% BID
- Primary endpoint
  - Mean IOP non-inferior to timolol at 800, 1000 and 1600 at Weeks 2 and 6 and Month 3

Netarsudil Mesylate Development

- Phase III studies with mixed results (and not yet published)
- Current development plan is in combination with

<table>
<thead>
<tr>
<th>N=298 total</th>
<th>Latanoprost</th>
<th>Netarsudil mesylate</th>
<th>Fixed combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline IOP</td>
<td>26.0 mmHg</td>
<td>25.4 mmHg</td>
<td>25.1 mmHg</td>
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<tr>
<td>Final IOP</td>
<td>18.4 mmHg</td>
<td>19.1 mmHg</td>
<td>16.5 mmHg</td>
</tr>
<tr>
<td>IOP Reduction</td>
<td>7.6 mmHg</td>
<td>6.3 mmHg</td>
<td>8.6 mmHg</td>
</tr>
</tbody>
</table>

Netarsudil Mesylate Development

- Phase III results (and not yet published)
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ROCK Inhibitors

- Altheos, Inc
  - ATS8535
  - ATS907
- Amakem
  - AMA0076

  * Trial against latanoprost showed superior IOP lowering with this ROCK, and w/o hyperemia which is problematic with ROCK
Trabodenoson

- First in class selective adenosine mimetic
- Entering Phase III US trials
- Hyperemia does not appear to be an issue
- Site of action is TM
- Stimulation of the A1 adenosine receptor in the trabecular meshwork causes a meaningful improvement in metabolic activity there which helps to clear the pathway for the aqueous humor

Next Frontier: Drug Delivery

- Punctal Plug eluting
- Contact lens eluting
- Nanoparticles
- Liposomal processes
- Injectable
- Surgically implanted

Bimatoprost Sustained Release (SR)

- Sustained release formulation of bimatoprost
- Bioerodible implant injected into AC in clinic setting
- Phase 3 study underway comparing SR to timolol

Gel Forming Fornix Gel

- Developed by Selkie Therapeutics
- Administered as an eye drop
- Once it hits lower fornix it forms a gel that provides 30 days of continuous release
- Consists of a thermo-responsive hydrogel carrier with a polymer microsphere loaded (encapsulated) with drug
- Currently looking at a brimonidine platform
  - Reduction of systemic absorption
  - Also looking at PGAs

Micro and Macro Particles

- Ohr Pharmaceuticals
- Injectable
  - Sub Conj
  - Anterior Chamber
- Special attention to steroid induced glaucoma population
- Also GrayBug developing a similar platform
- PRINT Technology by Envisia
**Ohr Microparticle Platform**

**Punctal Plug Eluting Platform**
- Ocular Therapeutix
- Currently has a dexamethasone platform submitted to the FDA
  - Glaucoma would be next
- Release kinetics seem to be a limiting factor at this time

**Contact Lens Eluting Platforms**
- First tried by JNJ about 8 years ago for allergy and possible glaucoma platform
- FDA pushed back on safety and program was pulled
- Mass Eye and Ear working on a new platform that instills the drug in a thin layer on surface of lens similar to the wafer of coloration on a colored contact lens
- Release metrics currently the main hurdle in development

**Mechanism of Action of Today’s Medications**

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