Challenges in Ophthalmology

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Outline

• Introduction to Eye Anatomy
• Selected Challenges in Ophthalmology
• Questions / Brainstorming
General Anatomy

- The eye has three distinct layers or “tunics”:
  - outer “fibrous” tunic (cornea and sclera)
  - middle “vascular” tunic (iris, ciliary body, and choroid)
  - inner “nervous” tunic (retina)

Source: NEI - NIH
General Anatomy

Source: NEI - NIH
Light Pathway

Source: NEI - NIH
Challenge #1
Corneal Ectasias

- Ectasia (distension or expansion of a hollow organ)
  - Keratoconus Disease
  - Post LASIK Ectasia
Keratoconus

- Corneal disease
- Unknown etiology
- Corneal protrusion and thinning
- Bilateral
- Asymmetric
- If left untreated, up to 20% of patients will require a corneal transplant
Diagnosis

- Topographical Maps
- Pachymetrical Maps (corneal thickness)
Classical Treatments

• Glasses
• Contact lens
• Corneal rings
• Keratoplasty (Corneal transplant)
Keratoconus

Genetic Predisposition
  +
Environmental Stimuli

Risk Factor
- Eye Rubbing

Protective Factors
- Aging
- Smoking
- Diabetes
1970s


1990s

- **Chemical**: Glutaraldehyde; Karnovsky Solution
- **Photochemical**: Riboflavin + Light

Riboflavin (Vit. B2)

1879 – Lactochrome (Alexander Blyth)
1934 – Synthesized (Richard Kuhn)

**Formula:** C17H20N4O6

**IUPAC ID:** 7,8-Dimethyl-10-[(2S,3S,4R)-2,3,4,5-tetrahydroxypentyl]benzo[g]pteridine-2,4-dione

**Molar mass:** 376.36 g/mol

**Melting point:** 536° F (280° C)
Photochemical Cross-linking

Generates cross-links not only between collagen molecules but also between proteoglycan core proteins.
2003 - Germany

Riboflavin/Ultraviolet-A–induced Collagen Crosslinking for the Treatment of Keratoconus

GREGOR WOLLENSAK, MD, EBERHARD SPOERL, PhD, AND THEO SEILER, PhD, MD

2006 - Italy

Parasurgical therapy for keratoconus by riboflavin–ultraviolet type A rays induced cross-linking of corneal collagen

Preliminary refractive results in an Italian study

Aldo Capovia, MD; Stefano Baniocchi, MD; Cosimo Masson, MD; Claudio Taccetti, MD; Tommaso Cappelli, MD

2008 – Brazil & Australia

Reticulação do colágeno corneano com radiação ultravioleta e riboflavin para tratamento do ceratocone: resultados preliminares de um estudo brasileiro

Corneal collagen crosslinking with riboflavin and ultraviolet radiation for keratoconus treatment: preliminary results of a Brazilian study.

A Randomized Controlled Trial of Corneal Collagen Cross-linking in Progressive Keratoconus: Preliminary Results

Christine Wittp, Silvia, MD; Mark Whiting, FRANZCO; Ecosse Lamoine, PhD; Richard G. Lindsay, BScOptom; Luana J. Sullivan, FRANZCO; Grant R. Snelson, FRANZCO

04/18/2016

FDA approves Corneal Crosslinking for treating progressive Keratoconus

Corneal Collagen Crosslinking (CXL)

- Stops Progression in > 92% of patients
- Mild Improvement in Vision
Corneal Collagen Crosslinking (CXL)

- Remove the corneal epithelium
- Apply riboflavin drops every 2 minutes for 30 min to saturate the cornea
- UVA 3 mW/cm² for 30 minutes
Video

UV-X Crosslinking
What to expect?

- Topography flattening
  (Decreasing KMAX: 0.7 to 2.0 diopters)

- Vision improvement
  (BSCVA: 0.5 to 1.5 Snellen lines)
Biomechanical Effects

Ex Vivo

Uniaxial Test

Biomechanical Effects
*Ex Vivo*

AFM Nanoindentation
Biomechanical Effects

*In Vivo*

**CORVIS ST®**

- Air Jet
- High Speed Camera
- Analyze Corneal Deformation

Biomechanical Effects

*In Vivo*

**CORVIS ST®**

- Confounded by biomechanical responses from surrounding tissues.

- Airjet displaces the aqueous fluid within the anterior chamber causing movement of the iris and lens, as well as the entire eye into the orbit.
Biomechanical Effects

In Vivo

Optical Coherence Elastography

• Clinical devices are under development

• Micro Air-Pulse Stimulator (MAPS) to produce discrete tissue excitation that is synchronized with a high resolution phase-sensitive OCT imaging system

Biomechanical Effects

*In Vivo*

**Brillouin Microscopy**

- Clinical devices are under development
- Continuous-wave laser light at 780 nm (0.7 mW)
- Light Scattering

Scarcelli G, Yun SH.

LASIK Safety Guidelines

Corneal Thickness
- Pre-op > 500 μM
- Post-op > 400 μM with a Residual Stromal Bed > 250 μM

Post-LASIK Ectasia incidence 0.05% to 0.25%

Form Fruste Keratoconus?
Forme Fruste Keratoconus (FFK)

• 10% of patients seeking LASIK are refused.

• 180,000 Keratoconus cases in America.

• 1 to 2% of the population may fit into the FFK or keratoconus suspect category. (3 to 6 Million patients in the USA are considered at risk if they were to seek LASIK consultation)
Challenge #2
Corneal Ulcers

• Microtrauma followed by infection = Infectious keratitis (corneal ulcers)
  – US: 75,000 per year
  – India: 840,000 per year

• Current Standard of Care
  – Topical antimicrobials
    (up to 1 year may be required if Acanthamoeba)
What is the unmet clinical need?

- Blindness secondary to corneal ulcers
  - Resistant/aggressive infections
  - Patient compliance challenges
  - Lack of access to medications

1.5 - 2 million per year

Challenge #3
Floaters

wikipedia.org/wiki/Floater
Vitreous Body

- 98% water
- 2% collagen and hyaluronan

Source: NEI - NIH
Floaters

- **Primary**
  - Light scattering in bundles of collagen fibers (crosslinking of collagen) and lacunaes (liquid zones devoid of collagen fibrils)
  - Crosslinking and vitreous liquefaction increases with age.

- **Secondary**
  - Light scattering in proteins, amyloid or cells from vitreous hemorrhage, retinal tear, inflammatory conditions or intravitreal injections.
Prevalence of Symptons

Prevalence of vitreous floaters in a community sample of smartphone users.


Up to 76% of smartphone users
### Prevalence of Ultrasonic Findings

**Table 1. Ultrasonic findings in the vitreous body at various ages**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Patients</th>
<th>Eyes</th>
<th>Homogenous</th>
<th>Degeneration +</th>
<th>Degeneration ++</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–20</td>
<td>31</td>
<td>34</td>
<td>34</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>21–40</td>
<td>86</td>
<td>117</td>
<td>111/95%</td>
<td>6/5%</td>
<td>–</td>
</tr>
<tr>
<td>41–50</td>
<td>35</td>
<td>53</td>
<td>43/81%</td>
<td>10/19%</td>
<td>–</td>
</tr>
<tr>
<td>51–60</td>
<td>44</td>
<td>71</td>
<td>26/37%</td>
<td>37/52%</td>
<td>8/11%</td>
</tr>
<tr>
<td>61–70</td>
<td>39</td>
<td>67</td>
<td>4/6%</td>
<td>55/82%</td>
<td>8/12%</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>55</td>
<td>102</td>
<td>15/15%</td>
<td>66/65%</td>
<td>21/20%</td>
</tr>
</tbody>
</table>

Treatment Options

- **Vitrectomy** – high success in removing the floaters, but increased risk of complications such as cataract, retinal tear, retinal hemorrhage.
- **Yag Laser Vitreolysis** – Can be used to treat opacities that are far from the retina. Lysis of fibers into smaller pieces or displacement from visual axis. Nothing is removed from the eye.
- **Pharmacological Vitreolysis** – 7 agents have failed. Ocriplasmin is the only one approved for vitreomacular adhesion.
Challenge #4
Intravitreal Medication Delivery
Age-related macular degeneration

Source: NEI - NIH
Diabetic macular edema
Challenge #5
Chronic Ocular Hypotony

- IOP < 5 mmHg
- Too little fluid production
  or
- Too much fluid outflow
Challenge #6
Long-Duration Space Flights

• Post-Flight CSF pressure is elevated in majority
• Loss of hydrostatic drainage
• Optic disc edema
Table 2. Summary of ophthalmic changes from seven affected long-duration mission crewmembers. Data from [7,16].

<table>
<thead>
<tr>
<th>Ophthalmic Condition</th>
<th>Total Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic nerve sheath distension</td>
<td>6/7 (86%)</td>
</tr>
<tr>
<td>Nerve fiber layer thickening</td>
<td>6/7 (86%)</td>
</tr>
<tr>
<td>Optic disc edema</td>
<td>5/7 (71%)</td>
</tr>
<tr>
<td>Posterior globe flattening</td>
<td>5/7 (71%)</td>
</tr>
<tr>
<td>Hyperopic shift in one or both eyes by $\geq+0.50$ diopters</td>
<td>5/7 (71%)</td>
</tr>
<tr>
<td>Choroidal folds</td>
<td>4/7 (57%)</td>
</tr>
<tr>
<td>Elevated postflight CSF pressure (indicative of increased ICP)</td>
<td>4/7 (57%)</td>
</tr>
<tr>
<td>Cotton wool spots</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>Decreased intraocular pressure ($IOP$) postflight</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>Tortuous optic nerve</td>
<td>2/7 (29%)</td>
</tr>
</tbody>
</table>

Translaminar Pressure Gradient

- Normally: IOP ~5 mmHg more than ICP
  - IOP 15 mmHg vs ICP 10 mmHg

- Space Flights (reversed)
  - IOP 15 mmHg vs ICP 20 mmHg

- IOP: intraocular pressure
- ICP: intracranial pressure
Choroidal thickening

Source: NEI - NIH
Choroidal thickening

- All have Choroidal Thickening in Flight

Thin

Thick
Choroidal thickening

- Post flight, some cases return and even get thinner choroidal measurements; other cases never return to baseline
Challenges

- Corneal ectasias
- Corneal ulcers
- Floaters
- Intravitreal drug delivery
- Ocular hypotony
- Long-duration space flights
Thank you

University of California, San Francisco