Why Does IOP Vary:
An Aqueous Humor Dynamics View

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Disclosures

- Aerie Pharmaceuticals Inc. (C, S)
- Allergan, Inc. (C)
- Bausch & Lomb, Inc. (C)
- InjectSense, Inc. (C, O)
- PolyActiva, Pty (C)
- Qlaris Bio, Inc. (C, S)
“Reduction of intraocular pressure is currently the only effective treatment for glaucoma.”
IOP Is Dynamic

• Telemetric monitoring in rabbits

Courtesy of Jay.W. McLaren, Mayo Clinic

Rabbit Intraocular Pressure

15 sec Average every 2.5 min

Intraocular Pressure, mmHg

Circadian Time, hours

Rabbit Intraocular Pressure

Primate Intraocular Pressure

Factors That Affect IOP

- Blinks
- Water
- Food
- Caffeine
- Body position
- Head Position
- Wind instruments
- Hormonal cycles
- Eye movements
- Accommodation
- Tight neck ties
- Pillows
- Circadian rhythms
- Medications
- Blood pressure
- Measurement errors
- Eye rubbing
- Seasons
- Yoga
Circadian Rhythms of IOP
Circadian IOP

Normals

Circadian IOP

Untreated Glaucoma

Circadian IOP: Supine

IOP and Body Position
IOP Varies with Body Position

• Yoga positions can increase IOP two-fold

IOP Varies with Body Position

IOP Increase:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Position 1</th>
<th>Position 2</th>
<th>Position 3</th>
<th>Position 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>79%</td>
<td>48%</td>
<td>28%</td>
<td>25%</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>72%</td>
<td>61%</td>
<td>33%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Effect of Head and Body Position on IOP

- 24 healthy volunteers
- Age: 19 to 47 years (Mean 28.6 ± 8.5 years)
- 7 males, 17 females
- All low myopic (< -4 D)
- Mean refractive error: -2.6 ± 0.8 D
### Measurements

- **Randomization**

<table>
<thead>
<tr>
<th>Sitting</th>
<th>Recumbent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral neck</td>
<td>Supine</td>
</tr>
<tr>
<td>Flexion</td>
<td>Right lateral decubitus</td>
</tr>
<tr>
<td>Extension</td>
<td>Left lateral decubitus</td>
</tr>
</tbody>
</table>

- IOP measured by pneumatonometry
- 5-minute intervals between measurements
Results

<table>
<thead>
<tr>
<th>Body position</th>
<th>IOP (mmHg) (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting</td>
<td>14.8 ± 2.0</td>
</tr>
<tr>
<td>Extension</td>
<td>16.4 ± 2.6</td>
</tr>
<tr>
<td>Flexion</td>
<td>19.7 ± 3.8</td>
</tr>
<tr>
<td>Supine</td>
<td>17.3 ± 2.9</td>
</tr>
<tr>
<td>Right Lateral Decubitus</td>
<td>18.0 ± 2.6</td>
</tr>
<tr>
<td>Left Lateral Decubitus</td>
<td>18.2 ± 2.9</td>
</tr>
</tbody>
</table>

Values are mean of both eyes
Results – Head Position

Values are mean of both eyes

Body position

P<0.001
Results – Head Position

Values are mean of both eyes

Body position

P<0.001
Results – Head Position

P<0.001

Values are mean of both eyes

Body position
Results – Body Position

Values are mean of both eyes

Body position

P<0.001
Results – Body Position

Values are mean of both eyes

Body position

P > 0.05
## IOP in Lateral Decubitus Positions

<table>
<thead>
<tr>
<th>Body Position</th>
<th>IOP (mmHg ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OD</td>
<td>OS</td>
</tr>
<tr>
<td>Right Lateral Decubitus</td>
<td>18.3 ± 2.7</td>
<td>17.6 ± 2.5</td>
</tr>
<tr>
<td>Left Lateral Decubitus</td>
<td>17.7 ± 3.0</td>
<td>18.8 ± 2.8</td>
</tr>
</tbody>
</table>

IOP higher in the dependent eye
Does Body Position Matter?

- Increase in recumbent positions
  - Should glaucoma patients sleep with head elevated?

- Increase in flexion/extensionsion
  - Are extra pillows detrimental?

- Increase in lateral decubitus position
  - Could this contribute to glaucoma asymmetry?

- What causes changes in IOP with body position?
Visual Function in Lateral Decubitus Position

- PERG amplitudes decrease in the dependent eye in LDP
• Clinical significance of IOP changes with body position remain to be determined

• What causes changes in IOP?
Aqueous Humor Dynamics and Body Position
Aqueous Outflow Pathways

Trabecular Pathway

Uveoscleral Pathway
Modified Goldmann Equation

\[ IOP = \frac{Q - U}{c} + P_e \]

Where:

- \( Q \) = aqueous outflow rate
- \( U \) = uveoscleral outflow rate
- \( c \) = outflow facility
- \( P_e \) = episcleral venous pressure
Measurement of Outflow Facility

\[ C = \frac{\Delta V / \Delta t}{\Delta P} \]

- Calculation of outflow facility from Friedenwald equations and tables

\[ y = -0.0009x^3 - 0.0834x^2 + 1.112x + 6.3138 \]

\[ R^2 = 0.9647 \]
Measurement of Aqueous Humor Flow

Fluorescein diluted by aqueous humor

Scanning ocular fluorophotometer

Aqueous humor flow determined from fluorescein clearance

Measurement of EVP

20X magnification

Calculation of Uveoscleral Outflow Rate
Modified Goldmann Equation

Where:

\[ IOP = \frac{Q - U}{C} + P_e \]

or

\[ U = Q - c(IOP - P_e) \]

\( Q \) = aqueous humor flow rate
\( U \) = uveoscleral outflow rate
\( C \) = outflow facility
\( P_e \) = episcleral venous pressure
Aqueous Humor Flow and Body Position

Aqueous Humor Flow and Body Position

- Increase in IOP associated with small decrease in aqueous flow

Table 1. Baseline Characteristics (n=42 eyes)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.6 ± 6.9 yrs</td>
<td>24-45 yrs</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 12</td>
<td>Female 9</td>
</tr>
<tr>
<td>Race</td>
<td>White 16</td>
<td>Other 5</td>
</tr>
<tr>
<td>Concurrent Systemic Medication</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Intraocular Pressure and Outflow Facility

<table>
<thead>
<tr>
<th>Posture</th>
<th>IOP (mmHg)</th>
<th>Facility (µL/min/mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting</td>
<td>17.8 ± 1.7</td>
<td>0.30 ± 0.08</td>
</tr>
<tr>
<td>Supine</td>
<td>19.9 ± 1.6</td>
<td>0.28 ± 0.09</td>
</tr>
<tr>
<td>Change with posture</td>
<td>2.1 ± 1.6</td>
<td>-0.02 ± 0.12</td>
</tr>
</tbody>
</table>

p-value <0.001

0.37

EVP and Body Position

EVP and Body Position

Postural rise in IOP (1.7 ± 1.1 mmHg) not significantly different from the postural rise in EVP (1.4 ± 1.7 mmHg) (p=0.18)

EVP in Supine Position
Circadian Aqueous Humor Dynamics
Nocturnal Changes in Aqueous Flow

Study Population

• 42 healthy, phakic eyes of 21 normal volunteers
• Age: 45 to 76 years (mean 58.2 years)
• 9 males, 12 females
• Regular sleep patterns
Measurements

- **IOP** – Pneumatonometry
  - Model 30 Classic, Mentor

- **Flow** – Anterior chamber fluorophotometry
  - Scanning ocular fluorophotometer

- **Facility** – Digital Schiøtz tonography
  - 4 minutes, 5.5 gram weight

- **EVP** – Objective venomanometry
Protocol

- Measurements adjusted to correspond with sleep time of 11 PM and wake time of 7 AM
- Measurement intervals:
  - Mid-diurnal: 2-4 PM
  - Mid-nocturnal: 2-4 AM
- Comparisons performed using GEE models

Aqueous Humor Flow

Flow Rate ($\mu l/min$)

- **Diurnal**: $2.5 \pm 1.0 \mu l/min$
- **Nocturnal**: $1.3 \pm 0.6 \mu l/min$

(p<0.001)

(mean ± SD)
Intraocular Pressure

<table>
<thead>
<tr>
<th>IOP (mmHg)</th>
<th>Seated IOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diurnal</td>
<td>13.9 ± 3.0 mmHg</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>13.0 ± 1.8 mmHg</td>
</tr>
</tbody>
</table>

p=0.07

(mean ± SD)
Intraocular Pressure

Seated IOP

13.9 ± 3.0 mmHg

13.0 ± 1.8 mmHg

p=0.07

Supine IOP

18.2 ± 3.2 mmHg

17.8 ± 2.3 mmHg

p=0.19

Diurnal

Nocturnal

(mean ± SD)
Outflow Facility

Facility ($\mu l/min/mmHg$)

- Diurnal: $0.23 \pm 0.06 \mu l/min/mmHg$
- Nocturnal: $0.20 \pm 0.06 \mu l/min/mmHg$

$p=0.004$ (mean ± SD)
Episcleral Venous Pressure

7.44 ± 1.79 mmHg (Diurnal)

7.41 ± 2.18 mmHg (Nocturnal)

$p=0.948$

(mean ± SD)
### Uveoscleral Flow Calculation

<table>
<thead>
<tr>
<th></th>
<th>Sitting IOP (mmHg)</th>
<th>Flow (μL/min)</th>
<th>Facility (μL/min/mmHg)</th>
<th>EVP (mmHg)</th>
<th>Uveoscleral outflow (μL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>13.9 ± 3.0</td>
<td>2.5 ± 1.0</td>
<td>0.23 ± 0.06</td>
<td>7.4 ± 1.8</td>
<td>0.94 ± 1.26 (38.0%)</td>
</tr>
<tr>
<td>Night</td>
<td>13.0 ± 1.8</td>
<td>1.3 ± 0.6</td>
<td>0.20 ± 0.06</td>
<td>7.4 ± 2.2</td>
<td>0.07 ± 0.78 (5.6%)</td>
</tr>
<tr>
<td>P</td>
<td>0.07</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>0.95</td>
<td>0.008</td>
</tr>
</tbody>
</table>

\[
U = Q - c(IOP - EVP)
\]

Study Conclusions

• EVP does not change from day to night
• Outflow facility and uveoscleral flow decrease at night
  • Compensates for the decrease in aqueous humor production
  • IOP does not decrease at night
Rabbit Intraocular Pressure

15 sec Average every 2.5 min

Intraocular Pressure, mmHg vs. Circadian Time, hours

One Rabbit

Summary

• IOP elevation with body position due to EVP changes

• Circadian rhythm
  • IOP is highest at night in most individuals
  • IOP elevation is due to body position, decreased uveoscleral flow and decrease in outflow facility
Thank You!