Nocturnal Considerations in Glaucoma Management

Goals for this morning....

- Review ocular perfusion pressure and its relationship to glaucoma
- Discuss nocturnal changes to IOP, pathophysiology, and impact on glaucoma management
- Discuss efficacy of current glaucoma treatments during nocturnal period
- Review nocturnal hypotension and its relationship to glaucoma development and progression

**Perfusion Pressure (PP)**

- Difference between arterial and venous pressure
- Maintain blood flow to organ/tissue
- Surrogate measurement blood flow

**Ocular Perfusion Pressure (OPP)**

- Venous pressure approximately = IOP
- Perfusion Pressure = Arterial BP - IOP
  - Systolic PP = systolic BP - IOP
  - **Diastolic PP = diastolic BP – IOP**

  *Reflects vascular status at optic disk*

**DPP = Diastolic BP – IOP**

Low diastolic blood pressure or relatively high IOP decreases DPP

*At night, potential for BOTH*

1) IOP increase
2) BP decrease

**Ocular Perfusion Pressure**

- Risk factor NEW glaucoma damage
- Risk factor progression ESTABLISHED glaucoma
- Defective autoregulatory mechanism

*Low diastolic perfusion pressure* associated with OAG studies in US, Europe, Caribbean, and Asia
Risk Factors for Incident Open-angle Glaucoma
The Barbados Eye Studies

Low DPP (< 55 mm Hg) 3 times increased risk developing OAG
-Mean DPP: 53.2 mmHg healthy vs 53.8 mmHg glaucoma

Hypertension, Perfusion Pressure, and Primary Open-angle Glaucoma
A Population-Based Assessment Baltimore Eye Survey

Diastolic Perfusion Pressure < 30 mm Hg
Risk of POAG 6 times higher vs DPP > 50 mm Hg

Vascular Risk Factors for Primary Open Angle Glaucoma
The Egp-A-Neusmark Study

4297 patients Rural Italy

Lower DPP (< 68 mm Hg) associated marked, progressive increase frequency glaucoma

Clinical and Epidemiologic Research
Distribution of Ocular Perfusion Pressure and Its Relationship with Open-Angle Glaucoma: The Singapore Malay Eye Study

3261 Ethnic Malays
2.5% OAG in Malays 40 - 80 years old
Mean IOP 15.3 mm Hg
ONLY 17% IOP > 21

Low DBP and DPP (<56 mmHg) OAG risk factors

Vascular Mechanism in Glaucoma


Case
• 89 year old caucasian male
• Low Tension Glaucoma diagnosed 2003
• Pachymetry: 490 um OU
• Medications: Travatan Z qhs and Alpha TID OU
• Medical History:
  – Sleep Apnea w/ CPAP use
  – Hypertension, Anemia

IOP history

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Pressures well controlled over past 12 years, mostly single digits, ~30% reduction.

Diurnal fluctuation? Balanced IOP checks AM and PM during that period.

Based on IOP alone, would predict little to no progression over this period??

2003 vs 2014

2006

2012
Blood pressure readings from 2000 to 2011

Diagnosed with LTG in 2003
-first visit to eye clinic

Poor perfusion pressure?

What would your next management step be for this patient?

1. Assuming no C/I, add additional IOP lowering drop (Trusopt or convert to Combigan)
2. Refer to OMD for filtration or laser surgery
3. No change to treatment, continue to monitor with visual fields and pressure checks

Other questions to consider…..

- Would your management plan change if…..
  - Patient was 65 instead of 89?
  - Patient was currently taking blood pressure medication(s) at night? Discontinue?? Switch to AM?

Management Dilemma

- Glaucoma patients w/ VF progression despite low IOP during office visits
  - No visible benefit, side effects
  - Patient ability to instill drops?
  - Number of drops per day?
  - Drops only prior to office visit? Refill schedule?
  - Washout Effect?
  - IOP fluctuation????
  - Not really LTG?

Greater role IOP-dependent mechanisms??

- **Sporadic** IOP measurements 2-4x / year
- Unpredictability single IOP measurements
- Treatment and management decisions
- Office diurnal curve
  - Serial tonometry
  - IOP checks in AM or PM

Are we getting the FULL clinical picture?
Beyond Office Hours

- What happens to IOP when office is closed?
- Nocturnal IOP – 3 AM pressure check?
  - Admit patient hospital/academic center
  - Trained personnel
  - Inconvenient
  - $$$
  - Not practical

Why is 24 hour IOP measurement important in glaucoma?

“It is highly likely that nocturnal IOP, such as diurnal IOP, may contribute to the worsening of glaucoma”

Glaucoma is a 24 hour disease!!

Day: Sitting
Night: Supine

IOP fluctuates
IOP higher nocturnally

“In absence of 24 hour IOP monitoring, exercise caution when extrapolating results of isolated IOP measurements to clinical management of glaucoma”

Clinical Utility of Intraocular Pressure Monitoring Outside of Normal Office Hours in Patients With Glaucoma

Mean peak 24 hr IOP 16.8 mm Hg vs 14.7 mm Hg during office hours

Mean 24 hr IOP fluctuation 6.9 mm Hg vs 3.8 mm Hg during office hours

69% patients highest IOP measured OUTSIDE office hrs. Immediate Tx change 36% patients

Higher peaks + wider IOP fluctuation outside clinic

Contact Lens Sensor: Triggerfish

24-Hour Intraocular Pressure Rhythm in Patients With Untreated Primary Open Angle Glaucoma and Effects of Selective Laser Trabeculoplasty

1 month med washout
- Nocturnal Acrophase
- SLT decrease IOP but no change 24 hr pattern

Graph untreated glaucoma patient 24 hour IOP
NTG vs Nonglaucoma patients

**Highest IOP during sleep**
- 57.1% NTG (Prostaglandin, BB)
- 91.7% nonglaucoma

NTG larger IOP fluctuations

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**Upright vs Horizontal**

- **Supine position**: IOP increase average 3-4 mm Hg, both normal and GLC eyes regardless of time of day

Glaucoma patients more likely greater IOP rise after changing to supine position

Greater variation w/ advanced disease!

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**What might cause IOP increase in the supine position?**

Corneal properties?
Studies on CCT, CH, CRF no difference AM vs PM

**THEORY:**
Redistribution of body fluid → Choroidal vascular congestion → *Rise in episcleral venous pressure (EVP)*

0.83 mm Hg rise EVP ~ 1 mm Hg rise in IOP

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**Prone vs Supine Position**

20 Healthy patients

Prone position IOP >> Supine position IOP
IOP (27 mm Hg vs 13 mm Hg) before surgery

After 5-6 hours surgery prone position, IOP increased
40 mm Hg vs. 31 mm Hg supine position

**Mechanism:**
A/C shallows 2/2 gravity
Spine Surgeries

- 10 fold increased risk Ophthalmic injury
  - CRAO, posterior ischemic optic neuropathy
- Risk Factors vision loss
  - Hypotension
  - Anemia
  - Patient positioning
  - Time of surgery
- Mean arterial pressure (MAP) = average BP
  - Deliberately decreased during spine surgeries to decrease bleeding, improve visibility surgery site

Effect of Head Position on Intraocular Pressure During Lumbar Spine Fusion
A Randomized, Prospective Study

Control group – surgery neutral position, face parallel to operating table
Experimental group – neck extended w/ face 10 degree inclined to table
IOP and blood pressure measured during surgery
  - perfusion pressure drop → ischemic optic neuropathy

<table>
<thead>
<tr>
<th>Head elevation w/ prone position</th>
<th>LOWER IOP vs neutral</th>
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<tr>
<td>Supine Neutral</td>
<td>14.24 mmHg</td>
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<tr>
<td>Prone initial</td>
<td>23.96 mmHg</td>
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<tr>
<td>Prone operation</td>
<td>27.59 mmHg</td>
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<td>10 degrees</td>
<td>13.98 mmHg</td>
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<td>Prone operation</td>
<td>22.21 mmHg</td>
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<tr>
<td>Prone operation</td>
<td>23.33 mmHg</td>
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Dark-Room Prone-Position Test

- 37 eyes intermittent angle closure
  - Repeated, brief, episodes angle closure
  - Mild symptoms, elevated IOP
- Prone position, dark room x 45 minutes
- **100%** patients had IOP increase
- 28 of 37 eyes (75.5%) had positive test (> 8 mmHg)
- Range IOP elevation 4 to **35 mm Hg**

Sleeping on your side?

- Popular sleep position takes most stress off back
- Direct pressure on globe → increased IOP during sleep
- **78%** agreement between eye larger C/D and preferred sleeping side

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Statistically significant effect sleep side on IOP: Higher IOP consistently ipsilateral eye w/ and w/o CPAP Tx

Effect of Lateral Decubitus Position on Intraocular Pressure in Glaucoma Patients

892 patients w/ bilateral glaucoma

IOP worse glaucoma eye >> IOP better eye SUPINE position

-Latent Asymmetric IOP (1.6 mmHg)

NTG (74% patients in study): 66% prefer sleep side WORSE glaucoma

High Tension Glaucoma: 71.9% prefer sleep side WORSE glaucoma

Habitual sleep position may be associated with greater VF loss in glaucoma

Effect of Lateral Decubitus Body Posture on Anterior Chamber Angle in Healthy Subjects: An Anterior Segment Optical Coherence Tomography Study

Left lateral decubitus shallow AC

OD temporal angle

OS nasal angle

GRAVITY

-Lens tilt

-Aqueous movement

Intraocular Pressure Curves of Untreated Glaucoma Suspects and Glaucoma Patients in Sitting and Lateral Decubitus Positions Using the Goldmann Applanation Tonometer

41 patients

91.5% eyes IOP increase in LDP vs sitting, increase higher dependent eye

68% IOP increase 2-5 mmHg

23.5% IOP increase 6-12 mmHg

Timely identification patients w/ excessive postural IOP elevation could affect management and prevent VF loss

Besides glaucoma medications, can we lower IOP in our patients while they sleep?

As cool as the other side of the pillow

Initial IOP increases in supine position neutralized by adopting semi-reclined position that raised the head
17 glaucoma patients, controlled IOP, new disc hemorrhages

Measure IOP q 2 hours sleep laboratory:
1 night lying flat, 1 night 30-degree head-up w/ wedge pillow

Mean IOP average 3.2 mmHg lower
30-degree head-up position vs flat position

94% (16 of 17) patients lower IOP head-up position

Ophthalmology 2010; 117: 1348-1351
J Glaucoma 2014; 23: 282-287

Prospective, nonrandomized comparative case series, 30 patients
15 glaucoma, 15 non-glaucoma

IOP measurements
supine vs 20 degree head up position w/ wedge pillow
IOP mean 1.51 mmHg lower (9% reduction)

83.3% lower mean IOP 20 degree head up

Head-up position =
Effective, inexpensive, noninvasive adjunct method IOP reduction

Ophthalmology 2012; 119: 987-991

Lateral decubitus position
IOP increases lower eye

IOP neck flexion >> IOP neck extension

Clinical application
Too many pillows?

Optom Vis Sci 2016; 93: 1163-1170

IOP elevations may not be detected in office
Avoiding IOP-elevating postures/habits help glaucoma patients

Clinical applications:
1/3 of life spent sleeping
Glaucoma can progress during sleep periods
Measure IOP supine position – TP, pneumotonometry

Potential Sleep Recommendations

- Sleep on back rather than on your stomach
  - Especially narrow angle patients
- Sleep with head slightly elevated w/ wedge pillows

Optometry 2010; 117: 1348-1351
Compared to IOP while sitting:
- Position 1: 12 mmHg higher
- Position 2: 10 mmHg higher
- Position 3: 6 mmHg higher
- Position 4: 4 mmHg higher

IOP drops back down within 2 min of returning to sitting position.

Mean 15 mmHg increase in IOP immediately after assuming headstand posture.

Management After Midnight

How effective are current medications at curbing nocturnal IOP fluctuations?

Latanoprost (square) sustained 24-hour IOP lowering
Beta Blocker (triangle) limited efficacy

Diurnal and Nocturnal Effects of Brimonidine Monotherapy on Intraocular Pressure

Alphagan TID x 4 weeks: Diurnal IOP significantly lower

NO statistically significant change in IOP vs baseline during the nocturnal period

Effect of Timolol, Latanoprost, and Dorzolamide on Circadian IOP in Glaucoma or Ocular Hypertension

Timolol more effective during the day, but poor nocturnal efficacy, only ~ 1/2

Latanoprost uniform circadian IOP reduction

Dorzolamide less effective than latanoprost, but significant reduction nocturnal IOP

20 patients, 1 month period Tx with each med
**Comparing Diurnal and Nocturnal Effects of Brinzolamide and Timolol on Intraocular Pressure in Patients Receiving Latanoprost Monotherapy**

- Only CAI lower IOP during nocturnal period

**Meta-analysis of 24-Hour Intraocular Pressure Studies Evaluating the Efficacy of Glaucoma Medicines**

- Only Carbonic anhydrase inhibitors (CAI) lower IOP during nocturnal period
- Dorzolamide reduce mean IOP 16% daytime vs 21% nighttime
- Carbonic anhydrase inhibitors ONLY class better NIGHTTIME than daytime efficacy

**Why the difference at night??**

- Reduction circulating catecholamines, **natural decrease AQ flow nocturnal period ~50%**
- Drop targeting AQ production less effective at night
  1. Beta Blocker,
  2. Alpha 2 Agonist

**GLC Surgery and Nocturnal IOP**

- **Laser trabeculoplasty** → lower diurnal variation

- Agarwal study of 40 eyes with ALT
  - Diurnal range decreased 7.9 mm Hg to 3.2 mm Hg

- Laser trabeculoplasty reduced IOP during nocturnal period more consistently than diurnal
Consider surgery w/ nocturnal IOP fluctuations

Nocturnal Hypotension
- Sleep, decrease sympathetic nervous system
- Protective against CV mortality
- ~10-15% NATURAL drop BP in 2/3
- Overdippers > 20% BP decrease
- Add BP Medications?
- ~15-25% individuals > 40 years old
- Risk factor glaucoma development / progression
  - Poor autoregulation
  - Ischemic optic nerve
  - Diastolic - IOP

BP considerations
- White Coat Syndrome
  - Increased BP in presence of doctors/nurses
  - Over-treatment and over-reduction of BP
  - Greater decrease in perfusion during day and more importantly. NIGHT

BP medication schedule??

Back to our patient ....

In-office BP readings from 2000 to 2011

IOP increases outside office hours – worse PP
Potential for lower BP outside of office hours?

Nocturnal Hypotension
- Orthostatic Hypotension
  - CC: Floaters or “fireflies”
  - Posture changes
    - TV, sitting up after nap/sleep
    - Experience AM or PM?
    - After taking BP medications?
  - Weakness, fainting, vasovagal
    - Drop instillation
    - Goldmann
    - Reclined BIO

Hypotension in your chair

BP considerations
- BP monitor patients w/ AION, POAG, NTG
- Patients taking anti-HTN drugs
  - Worse VF deterioration with lower night time systolic/diastolic BP
  - Evening dose anti-HTN med worsens nocturnal hypotension
Systemic Antihypertensive Medication and Incident Open-angle Glaucoma

- **Rotterdam Study**: only patients on BP meds had association low perfusion pressure and glaucoma
- 4-5 times greater chance OAG DPP < 50 mmHg vs DPP > 65 mmHg
- Increased risk OAG calcium channel blockers

Blood Pressure Medications and PP

- **Risk Factors for Optic Disc Hemorrhage**
  - Migraine, thin neuro rim, Beta Blockers (HR 5.58)
  

- **Risk Factors for VF Progression**
  - Age, lower mean OPP, BP Medications (HR 2.53)
  

- Normal DBP result of Tx treatment increased rim thinning → Caution with aggressive HTN Tx

Nocturnal Systemic Hypotension Increases the Risk of Glaucoma Progression

Association Between Nocturnal Blood Pressure Dips and Optic Disc Hemorrhage in Patients With Normal-Tension Glaucoma

Duration/Magnitude MAP 10 mmHg below daytime MAP, “Predictor VF progression

- Overdippers significant greater frequency 
  - Worsening VF defects, more dranage hemes

Low nocturnal BP, spontaneous or 2/2 medications

Optometry 2014; 121: 2004-2012

- VF progression 24% vs 7% vs 6%

DPP = Diastolic BP – IOP

- At night, potential for BOTH
  - IOP increase
  - BP decrease

Which risk factor is more important with regards to perfusion?

Optic Nerve Head Blood Flow Response to Reduced Ocular Perfusion Pressure by Alteration of Either the Blood Pressure or Intraocular Pressure

- 12 primates
  - IOP at 10 mmHg, while reduce BP by pentobarbital
  - IOP increase from 10 to 50 mmHg, while BP maintained

ONH blood flow MORE susceptible to OPP drop caused lowering the BP!
Poor perfusion pressure during nocturnal period….

What about **sleep quality**?

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### Obstructive Sleep Apnea (OSA)

- Pauses in breathing during sleep
  - Few seconds to minutes
  - 5 to 30 per hour
  - Men >> Women
  - Characterized by:
    - *Snoring*
    - *Restless sleep*
    - *Daytime sleepiness*
    - 40% obese individuals
  - Large tonsils or tongue constrict airway
  - Fat tissue in neck
  - Increased w/ DM 2, smoking

### OSA and Glaucoma

- 212 POAG, prevalence sleep-disordered breathing **47.6%**
- Meta-Analysis of Association of Obstructive Sleep Apnea With Glaucoma
- Obstructive Sleep Apnea and Increased Risk of Glaucoma: A Population-Based Matched-Cohort Study
  - Ophthalmology 2013; 120; 1559-1564
- J Glaucoma 2016; 25: 1-7
- OSA = risk factor for Glaucoma!

### Obstructive Sleep Apnea and Retinal Nerve Fibre Layer Thickness: A Meta-analysis

- Xiaoying Zhao, MD, Chong-Chong Ye, MD, Bo-Cheng Zhang, MD,
  Hai Zheng, MD, Ping-Ping Liu, MD, and Qin Li, MD, PhD

1034 eyes, six studies
- OSA associated w/ RNFL thickness
- Greater severity OSA = greater RNFL loss

### Normal Tension Glaucoma in Patients With Obstructive Sleep Apnea/Hypopnea Syndrome

- Po-Chen Liu, MD*; Michael Naftolin, MD, FACOS; J. Chin Chong, MD, FAC\(\text{*}\)
- J Glaucoma 2011; 20: 553-558

209 OSA patients, 7.1% prevalence NTG
- Higher prevalence moderate/severe cases OSA

### Continuous Positive Airway Pressure (CPAP)

- Keeps airway open during sleep
- Prevents apneas, reduces snoring

Does CPAP therapy affect IOP and glaucoma?
**Pathophysiology: Vascular**

- Disrupted autoregulation blood flow
  - Hypoxia
  - Hypercapnia - excessive CO₂
- Disrupted blood flow – LESS blood
  - Hypotension during apneas
- Direct hypoxic injury – LESS O₂ in blood
  - O₂ desaturation due to apneas
- All cause *ischemic* optic nerve damage

**OSA in your exam chair**

- Glaucoma patients/ suspects: Medical Hx
- Ask questions
  - Sleeping problems?
  - Daytime drowsiness?
  - H/O Snoring?
- CPAP/BI-PAP/Mouth guard safest, most effective Tx, but not a cure

**Open-Angle Glaucoma and the Risk of Erectile Dysfunction**

*A Population-based Case-control Study*

ED patients 2.85 fold greater risk POAG diagnosis vs controls

Vascular pathophysiology for glaucoma development
Positive association between severity of ED and severity of glaucoma OR = 2.58

Criticism of OPP

- Blood pressure accurate?
  - Brachial arterial pressure does NOT equal ocular arterial pressure
- Cause or the effect?
  - Reduction in blood flow may not be cause of glaucoma
- Is increased BP and blood flow beneficial?
  - No evidence currently
- Common things are common
- **DO NOT overrate perfusion pressure!!**

The Future

- "Is it really true that there was a time when glaucoma diagnosis relied exclusively on IOP measurements once every 3 months in office?"
- 24 hour IOP assessment
  - Enhance IOP data, guide glaucoma Tx/manage
  - IOP sensitive contact lens

Glaucoma is a 24 hour disease

Manage Accordingly!!