NORMAL-TENSION GLAUCOMA: A NOCTURNAL DISEASE
SLEEP AND POSITION

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Classification of the Glaucomas

- Until recently, there has been little concern regarding causative mechanisms
- POAG was considered a single disease, rather than many genetically different variations
- Traditional classification of the glaucomas into primary and secondary types should be replaced with a scheme that provides a better working foundation for the new concepts of etiology, mechanisms, diagnosis, and therapy
- POAG better described as “Idiopathic” open-angle glaucoma
- IOP exists on a spectrum
- NTG formerly considered rare
“Normal-Tension Glaucoma”

- NTG useful basically for dividing patients for comparison between groups looking at risk factors and outcomes.
- Risk factors for NTG can also exist anywhere across the spectrum.

- Estimated 20% to 35% of OAG in USA
- 90% in Japan, 80% in Korea, 50% in Hong Kong
- Tajimi Eye Study: Reported prevalence of glaucoma 3.9%. 92% had NTG

Iwase et al. Ophthalmology 2004;111:1641

“Normal-Tension Glaucoma”

- NTG/MTG/HTG categorization, conceptually inaccurate
- Really speaking of risk factors in addition to or other than IOP
- Other risk factors not limited to patients with IOP <22 mmHg
My Current Concept

- “Normal-tension glaucoma” is basically a nocturnal disorder
- Mechanisms other than IOP are often associated with systemic abnormalities
- Risk factors are additive, whether “NTG” or “HTG”

SLEEP

- All animals sleep. Fish sleep. Insects sleep. Squid and octopuses sleep. Jellyfish and nematodes sleep (recently discovered)
- Sleep is necessary to maintain CNS physiological function, remodelling of synapses, neural plasticity, brain growth, and rejuvenation of brain metabolism and function
REM Sleep – about 25% of total sleep

- Increased cerebral metabolic activity
- CNS excitation (dreaming)
- Intermittent eye movements
- Decreased motor activity
- Decreased ventilation
- Decreased postural tone
- Decreased heart rate
- Decreased blood pressure
- Autonomic variability
- Cardiorespiratory instability

SLEEP APNEA

Changes in cardiovascular physiology balanced by autoregulatory mechanisms to maintain homeostasis

In OSAS, this balance is upset, leading to decreased oxygenation and sympathetic activation

Obstructive – 80% - greatly underdiagnosed and highly treatable. Compromised ocular blood flow

Keep in mind – elastic tissue
SLEEP APNEA

• OBSTRUCTIVE
  breathing briefly and repeatedly interrupted during sleep
  “apnea” – breathing pause lasts ≥10 seconds; happen
  many times a night
  Muscles in back of throat fail to keep the airway open,
  despite attempts to breathe. Usually supine.
  Associated with snoring
  Men = 2x women

• CENTRAL (1%) - brain fails to control breathing properly
during sleep
• MIXED (19)
• PEDIATRIC

Sleep Apnea – Risk Factors

• Middle-aged men
• Obesity
• Neck girth >17” in men, 16” in women
• Upper airway abnormalities
• Large tongue, Small jaw
• Snoring, Sinus problems
• Alcohol, sedatives
• Insomnia
• Hypoxia
• Allergies
• GI reflux
• Family history
Obstructive Sleep Apnea Syndrome (OSAS)

- The typical NTG patient is a thin, myopic woman with cold hands and feet (and sleeps with socks on), low blood pressure (need 24 hour BP), decreased thirst, and increased sense of smell (Now termed Flammer Syndrome)

- OSAS is common in NTG, e.g. Japan, which does not fit the classic description.

- I have many patients without fatigue, snore lightly, are thin, and have severe OSAS on polysomnography.

- Therefore, the classic description is wrong.

Conditions with compromised ocular blood flow

- Sleep apnea
- Systemic, nocturnal, orthostatic hypotension
- Defective autoregulation
- Supine IOP rise
- Vasospasm / migraine / Raynaud’s
- High myopia
- Atrial fibrillation (OSAS, OAG, XFS)(XFS and OSAS?)
- Globe pressure during sleep
- Low intracranial pressure
- Endothelin abnormalities
Sleep Apnea – Ocular Associations

- NAION*
- Papilledema – ↑ ICP*
- Glaucoma
- Floppy eyelid syndrome
- Blepharitis
- Keratoconus
- Retinal vascular tortuosity
- Diabetic retinopathy (several recent reports)
- Central serous chorioretinopathy
- Ptosis
- Papillary conjunctivitis
- Filamentary keratitis

Floppy eyelid syndrome

- Easily inverted lid with papillary conjunctivitis
- 90% of patients with FES have OSAS
- 31.5% of OSAS pts had FES in one series
  
  Kadyan A et al; Eye 2010;24:843-850

- Loss of elastin fibers with upregulation of elastolytic proteases in tarsal plates
- Ischemia/reperfusion injury can lead to upregulation of MMPs
Sleep Apnea – Systemic Associations

- Hypertension
- Stroke
- Epilepsy
- Atrial fibrillation*
- Impaired sympathetic tone
- Cerebral and coronary vascular disease*
- Congestive heart failure
- Metabolic and cognitive dysfunction
- Endothelial dysfunction and coagulopathies
- Oxidative and inflammatory stress
- Excessive daytime sleepiness
- Decreased productivity and quality of life

Sleep Apnea and Gout

- Medicare sample 2006-2012 comprising 10,448,472 person-years of followup in a cohort of 1.7 million adults ≥65 y/o
- Association of development of OSAS 2x greater in patients with gout.
  Singh & Cleveland, Clin Sleep Med 2018; Epub Aug 30
- Patients ≥18 y/o with OSAS 1990-2010 followed through 2015.
  Patients with OSAS twice as likely to develop gout compared to those without OSAS, weighted toward greater BMI
  Blagojevic-Bucknall et al, Arthritis Rheumatol 2018, Epub Aug 30
Other Recent Associations

- Nasal lavage obtained in 575 patients with OSAS for microbiome composition and biomarkers for inflammation (inflammatory cells, IL-8, and IL-6)
- Severity of OSAS correlated with differences in microbiome diversity and composition
- Differences found in microbiota associated with inflammatory markers. Wu et al, Am J Respir Crit Care Med 2018; Epub July 3

- Increased volume of hippocampus and amygdala and decreased thickness in bilateral temporal regions associated with cognitive deficiency in older patients with OSAS. Cross et al, Eur Respir J 2018; Epub July 4

OSAS and NTG

- Polysomnography in 16 NTG patients
- OSAS in 0/2 < age 45, 3/6 age 45-64, and 5/8 > age 64
- Concluded NTG high risk for OSAS and should undergo PSG
  Mojon et al: Ophthalmologica 2002; 216:180

- 209 OSAS and 38 controls
- NTG in 12 OSAS (5.7%) vs 0 in controls

- More and more studies are showing VF defects, RNFL thinning, and VEP/PERG abnormalities in normotensive patients with moderate to severe OSAS and no previously known glaucoma

References available on request
OAG in OSAS

- Mayo Clinic
- 100 patients with moderate to severe OSAS
- 27 had OAG
- Presence of glaucoma did not correlate with sex, BMI, or apnea-hypopnea index (AHI)
- Positive association with age

Sleep Apnea and Glaucoma

- POAG more common in OSAS and vice versa
- OSAS more common in NTG than in HTG
- Decreased ocular blood flow in OSAS
- Severity of OSAS proportional to severity of glaucomatous damage
Obstructive Sleep Apnea Syndrome (OSAS)

- Activates renin-angiotensin system
- Increased levels of ET-1
- Oxidative stress, increased lipid peroxidation and ROS, decreased antioxidant capacity
- Inflammatory condition evidenced by elevated CRP, NF-kB, TNF-a, ICAM-1, VCAM-1, IL-6, E-selectin
- All of these are associated with glaucoma
- All (?) improve with CPAP

Mean Ocular Perfusion Pressure (MOPP)

- OSAS may alter blood flow to the optic nerve head and, in alone or combination with other predisposing factors, lead to decreased MOPP.
- Additive risk factors
  - Low nocturnal blood pressure
  - Positional changes – supine, lateral decubitus
  - Low CSF pressure
  - Other systemic ischemic disease
Continuous Positive Airway Pressure (CPAP)

- Restores normal IOP rhythm
  - Pepin et al, Arch Ophthalmol 2010;128:1257
- Increases IOP
  - Kiekens et al, IOVS 2008;49:934
- Visual field stabilization? (2 small papers, 6 patients)
- Reduces elevated soluble cell adhesion molecules ICAM-1, E-selectin, NFkB, CRP
- Reduces fibrinogen, clotting time, and platelet hyperaggregability
- Improves visual acuity in patients with diabetic macular edema and OSAS
  - Mason et al, Respiration 2012;84:275

MOST IMPORTANT – OXYGENATION

Sleep Apnea and Glaucoma - Treatment

Currently no approved drug treatment for OSAS
  - Carley et al: Pharmacotherapy of Apnea by Cannabinimetic Enhancement, the PACE Clinical Trial: Effects of Dronabinol in Obstructive Sleep Apnea. Sleep 2018;Epub Jan 1

- Phase II PACE Trial. 73 pts with OSA randomized to placebo, 2.5 mg or 10 mg dronabinol hs up to 6 weeks.
- 10 mg/day produced highest satisfaction with treatment. Reduced AHI, Epworth Sleepiness Scale vs placebo.
- Paper did not mention glaucoma, but we may conclude that cannabinoids are potentially good for both diseases.
Ocular Surface Disease

- Ocular Surface Disease Questionnaire: 13% in nonOSAS, 23% mild, 46% moderate, and 57% severe
- Schirmer: 11mm in no OSAS, 10 mm mild, 8 mm moderate, 7 mm severe
- Gradual decrease in tear breakup time
- Gradual increase in corneal staining
- Advocate polysomnography in patients with FES and dry eye complaints

Acar et al: Sleep Breath 2013;17:583

Take Home Messages

- Sleep history on all glaucoma patients
- Get sleep history in patients with NAION, keratoconus, severe ocular surface disease
- Ask about snoring (ask person the patient sleeps with)
- Check for floppy eyelid syndrome

- If suspect OSAS, get PSG. If you don’t suspect it and patient w NTG progressing, get it anyway

- Periodic eye exams in patients with moderate to severe OSAS.

- The more we test, the more we find.
Globe Pressure During Sleep

- IOP measured with device placed between dependent eye and pillow in normotensive subjects

- 78% agreement between eye with larger C/D and preferred side for sleeping (P<0.001) in patients with symmetric IOP

- Mean IOP 22 ± 5 mmHg, peak 40±11 mmHg
  - Korenfeld & Dueker, ARVO 1994

- Confirmed in our asymmetric NTG patients

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Globe Pressure During Sleep

- 30 eyes of 15 healthy volunteers
- Icare PRO rebound tonometer
- IOP measured sitting, supine, right and left LDP
- Additional IOP measurements taken with dependent globe against a latex pillow
- IOP increase significantly greater with the eye against the pillow compared to other groups
  - Kim HS, Park KH, Jeoung JW: Acta Ophthalmol 2013 Epub Apr 23

- I consider this topic of great importance and continuous IOP monitoring lends itself to key studies in this area
Globe Pressure During Sleep

- Specially developed electronic pressure sensor attached to lid of right eye of 11 patients with POAG and 11 controls.
- Measurements performed in simulated sleep position on a comfortable pillow, with and without protective glasses.
- Mean IOP increased by estimated 19.6 mmHg in patients and 28.00 in controls.
- With glasses, mean estimated IOP decreased again by 16.3 mmHg in patients and 25.1 mmHg in controls.
- Conclude protective glasses abolished IOP rise in supine position with face turned toward pillow.

Van Meurs et al, Is a pillow a risk factor for glaucoma? Acta Ophthalmol 2018;Epub Oct 8

Position change

- Sitting (A)
- Supine (B)
- Lateral decubitus (C)
- Compressed against pillow (D)

Ki Ho Park, MD
Contact with the eyeball and forearm/arm

Possibly dangerous: increases IOP

<table>
<thead>
<tr>
<th>Baseline IOP by GAT</th>
<th>OD 13.1±2.7 mmHg; OS 12.5±2.3 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak IOP during sleep:</td>
<td></td>
</tr>
<tr>
<td>1. Sleep with OD on forearm: 38.9 ± 26.0 mmHg</td>
<td></td>
</tr>
<tr>
<td>Sleep with OS on forearm: 47.5 ± 34.6 mmHg</td>
<td></td>
</tr>
<tr>
<td>2. Sleep with OD on the arm and OS on the forearm:</td>
<td></td>
</tr>
<tr>
<td>OD: 24.5 ± 12.9 mmHg, OS: 38.4 ± 22.0 mmHg</td>
<td></td>
</tr>
<tr>
<td>3. Sleep on the bridge of nose and forehead:</td>
<td></td>
</tr>
<tr>
<td>OD: 14.8 ± 4.2 mmHg, OS: 13.6 ± 3.1 mmHg</td>
<td></td>
</tr>
</tbody>
</table>

Results greatly vary among subjects possibly due to the difference in the location of the eye ball relative to the bony orbit.
Importance of 24-Hour IOP Measurement

Most patients peak outside of normal office hours

Peak IOP is related to glaucoma progression

IOP increases in the supine position

Average supine IOP during nocturnal/sleep period significantly higher than average sitting IOP during diurnal/wake period in untreated glaucoma patients

Liu et al: IOVS 2003;44:1586

Effect of dependent eye on IOP and asymmetric damage

Kim et al: Ophthalmology 2013;120:731

Continuous 24h IOP monitoring with a contact lens sensor
24 hr IOP/BP – 32 pts

- All pts considered well controlled but continuing to progress
- Mean office IOP 14.7±3.2 mmHg
- Mean peak IOP 16.8±3.2 mmHg
- Mean fluctuation office hrs 3.8±2.3 mmHg
- Mean fluctuation over 24 hr 6.9±2.9 mmHg

24 hr IOP/BP – 32 pts

- In 11 eyes of 7 patients, peak IOP recorded in supine position at 6 a.m.
- IOP fluctuation greater in NTG patients
- Pilocarpine 2% qhs reduced early morning IOP spike
Sleep Position

- 17 patients with controlled IOP and new DH underwent diurnal IOP and BP

- During sleep period, mean IOP 3.2 mmHg greater in supine position than in 30° position (16/17 patients)

- Reduction was 30% or more in 6/17 patients

- No differences in BP or OPP between the two positions


We have a lot of people sleeping on 20 degree wedge pillows

Sleep Position and OSAS

- 27 patients with OSAS and 25 normal controls

- IOP measured 10 min after sitting, immediately and at 30 min on supine position, and immediately after sitting

- Increase in mean IOP from sitting to supine in OSAS significantly greater than in controls.

Fang et al, Graefes Arch Clin Exp Ophthalmol 2018;256:783
Sleep Position – Lateral Decubitus

- 38 eyes of 19 healthy young subjects
- IOP measured by Tono-Pen supine and in lateral decubitus positions
- IOP rose significantly in dependent eyes but not fellow eyes on assuming LC position at 5 min and persisted at 30 min
- IOP decreased again on return to supine position


IOP Varies with Body Position

<table>
<thead>
<tr>
<th>Position</th>
<th>Normal 79%</th>
<th>Glaucoma 72%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ardha Mukha Svanasana</td>
<td>48%</td>
<td>61%</td>
</tr>
<tr>
<td>2. Ustrasana Position</td>
<td>28%</td>
<td>33%</td>
</tr>
<tr>
<td>3. Halasana Position</td>
<td>25%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Nocturnal Hypotension

- Blood pressure follows a diurnal pattern, as does IOP
- Nadir usually around 2:00-3:00 a.m.
- Decreased BP leads to decreased ocular perfusion
- Normal dippers - 10%
- Underdippers - stroke, silent cerebral infarct, NAION
- Overdippers - NTG

Nocturnal Hypotension

- Low BP leads to more rapid progression of glaucoma
  - Sachsenweger R. Klin Mon Aug 1963;142:625
- Greater nocturnal decrease in BP in NTG
  - Meyer et al, BJO 1996;80:864
- Duration and magnitude of drops in nocturnal BP below the daytime mean arterial pressure predict progression in NTG.
- Treated hypertensive NTG patients with sustained BP dips are at greater risk of progression than normotensive NTG patients.
  - De Moraes et al, ARVO, AOS, WGC 2013

- Overdipping AND an IOP rise is potentially dangerous for glaucoma patients. Argues for continuous monitoring of both IOP and BP.
Nocturnal Hypotension

- Patients using β-blockers had greater nocturnal decrease in diastolic BP, lower minimum diastolic BP, and lower minimum heart rate
  - Hayreh et al, Ophthalmologica 1999;213:76-96

Risk Factors for Visual Field Progression in the Low-pressure Glaucoma Treatment Study

CARLOS GUSTAVO DE MORAES, JEFFREY M. LISBAMAN, DAVID S. GREENFIELD, STUART K. CARDINER, ROBERT RITCH, AND THEODORE KRUPIN, ON BEHALF OF THE LOW-PRESSURE GLAUCOMA TREATMENT STUDY GROUP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotension vs. hypertension</td>
<td>1.20</td>
<td>0.99 to 1.48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age (per decade older)</td>
<td>1.41</td>
<td>1.06 to 1.90</td>
<td>.020</td>
</tr>
<tr>
<td>Use of systemic antihypertensives</td>
<td>2.53</td>
<td>1.32 to 4.87</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Mean ocular perfusion pressure during follow-up (per mm Hg lower)</td>
<td>1.21</td>
<td>1.12 to 1.31</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

HR = hazard ratio.
*Variables were entered in the model if P < .05 and removed if P > .10 in the saturated multivariate model.
Mean Ocular Perfusion Pressure (MOPP)

- Larger MOPP fluctuation correlated with glaucoma damage in NTG

- Overdippers had marked circadian fluctuation, which was the most consistent risk factor for glaucoma severity and progression in NTG
  
  - Sung et al: IOVS 2009;Epub May 27
No alcohol

Average Nocturnal MAP = 92.3 mmHg

Nocturnal MAP is below the average daytime MAP 45% of the time

Alcohol

Average Nocturnal MAP = 90.7 mmHg
Mean Ocular Perfusion Pressure (MOPP)

- Large, sustained BP dips associated with VF progression in NTG
  - De Moraes et al, AGS, March 2013
- 85 NTG patients BP monitored q30min x 48 hours q6months
- 24% of patients progressed over 5 year follow-up
- Total time that MAP during sleep was lower than daytime MAP was significant predictor of progression
- Significant association of MD progression also with asthma and systemic beta-blocker therapy
- Overtreatment of HBP may lead to glaucomatous damage
Take Home Messages

• Nocturnal systemic hypotension may be a modifiable risk factor in glaucoma

• NTG patients (or any patient with apparent IOP control) who continue to progress despite substantial IOP lowering should have 24-hour BP monitoring and polysomnography.

• The relationship between nocturnal (asleep) and daytime MAP is of great value to determine the risk of progression in NTG

• Take home: monitor 24 hour BP in all NTG
• Move hs medications to a.m.

Practical Applications

• Cerebral ischemia, renal damage, and myocardial infarction exhibit evidence of parallel insult from systemic nocturnal hypotension

• Collaboration with colleagues in other fields is important for glaucoma management
Caution

• Patients with HBP should not take medications in the evening

• Patients with NTG should perhaps not take β-blockers in the evening

Questions

• Should patients sleep with head elevated, e.g. with wedge pillows?

• IOP may be higher in supine position, but what about BP and OPP?

• All these observations are not necessarily applicable only to NTG. Patients with HTG whose IOPs are supposedly “controlled” but progress may have additional risk factors
Atrial Fibrillation

• 17% of glaucoma patients vs 8% of controls

• Severe VF defects in 70% of glaucoma patients with AF vs 42% without AF

Endothelin

• 21 amino-acid polypeptide, one of most powerful vasoconstrictors known.

• Elevated plasma ET-1 in Japanese NTG patients
  - Sugiyama et al, Surv Ophthalmol 1995;39:S49

• Elevated in sleep apnea
  - Saarileinen et al: Endothelium 1997;5:185

• Plasma ET-1 elevated in progressing glaucoma patients vs non-progressing. Causative vs secondary phenomenon?
  - Emre et al, Br J Ophthalmol 2005;89:60-63

Endothelin

• Bosentan (Tracleer, Actelion Pharmaceuticals)
  - dual endothelin receptor antagonist marketed for treatment of pulmonary hypertension

• 500 mg bid x 8 days in POAG and age/sex matched normals

• Retinal blood flow increased up to 45% in both groups
Platelet Aggregability

- Higher in POAG patients with VF progression than patients without progression and glaucoma suspects
- Abnormal in 17/22 NTG and 5/13 HTG Japanese patients
- Increased aggregability in sleep apnea
  - Naughton et al, Curr Heart Fail Rep 2006;3:183

Neuroimaging

- Patients with NTG had greater diffuse cerebral small vessel ischemic changes on MRI than controls
- More NTG patients with silent cerebral infarct on CT scanning showed progression (65.6% of SCI+ and 45.9% of SCI-)
NEUROIMAGING

- Not routinely indicated in NTG
- Reserve for patients in whom the disc and visual field findings do not correlate and/or are inconsistent with glaucomatous damage
- Newer imaging modalities – fMRI, diffusion tensor imaging, may change all this

SAS and Cerebral Hemodynamics

- Patients with severe OSAS have changes in cerebral blood flow velocity and vascular compliance (transcranial Doppler sonography)
- Abnormal cerebrovascular reactivity and increased arterial stiffness
- Cerebral autoregulation impaired in OSAS
- Severity correlated to severity of OSAS
CSF Pressure in Glaucoma

43 patients with OAG: 14 NTG, 29 HTG
71 controls: Peripheral neuropathy (16); unilateral NAION: (39); multiple sclerosis (4); unilateral optic neuritis (12)

Lumbar CSF pressure significantly lower in NTG vs HTG or controls

Extent of VF loss negatively correlated with height of CSF pressure and positively correlated with trans-lamina cribrosa pressure difference


Cerebrospinal Fluid Pressure: Lower in the Normal-Pressure Glaucoma Group

Courtesy of Jost Jonas
Conjecture

- Do disc hemorrhages occur at night?
- Are they associated with OSAS?

THINK ABOUT GLAUCOMA AS

- An ocular manifestation of systemic disease
- Optic nerve and visual field damage as a final common pathway of different diseases and risk factors that affect the eye
- Glaucoma is a brain disease, which in the past was mostly associated with eye disease, but no longer
Muchas Gracias
TREATMENT

- No time for details of supplements (antioxidants, mitochondrial protectants, low grade anti-inflammatory compounds)

- These make up a large component of treatment of patients with NTG