Glaucoma Under Pressure: IOP, BP/OPP and CSFP

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Conflict of Interest Disclosure

I have the following potential conflict(s) of interest to report:

- Receipt of grants/research support: Carl Zeiss Meditec
- Receipt of consultation fees: Carl Zeiss Meditec
- Unpaid Board Member: EyeCarrot Inc.
- Unpaid Board Member: Glaucoma Research Foundation
- Unpaid Advisory Board: Essilor
What Do We Know?

- Metabolic Dysfunction
- Vascular Dysfunction
- Pigmentation
- CSF Pressure
- Intraocular Pressure
- Aging
- Oxidative Damage
- Genetics
- Excitotoxicity

NFL Thinning
RGC Death
Biomechanical and/or Ischemic Stress

Neurodegenerative Injury/Glaucomatous Optic Neuropathy

Oxidative Stress & Mitochondrial Dysfunction

Glial Cell Activation & Dysfunction

Immune Compromise

Flanagan, Rogers & Sivak, 2011.
Glaucoma is:

• A neurodegenerative disease
• The most common neurodegenerative disease
• More common than all other neurodegenerative diseases put together!!
• Alzheimer’s, Parkinson’s, Huntington’s, ALS….
  • 30 million (Exp Gerontology, 2009)
• Glaucoma
  • 60 million (BJO, 2006)
Characterizing the “POAGome”: A bioinformatics-driven approach to primary open-angle glaucoma

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ABSTRACT

Primary open-angle glaucoma (POAG) is a genetically, physiologically, and phenotypically complex neurodegenerative disorder. This study addressed the expanding collection of genes associated with POAG, referred to as the “POAGome.” We used bioinformatics tools to perform an extensive, systematic literature search and compiled 542 genes with confirmed associations with POAG and its related phenotypes (normal tension glaucoma, ocular hypertension, juvenile open-angle glaucoma, and primary congenital glaucoma). The genes were classified according to their associated ocular tissues and phenotypes, and functional annotation and pathway analyses were subsequently performed. Our study reveals that no single molecular pathway can encompass the pathophysiology of POAG. The analyses suggested that inflammation and senescence may play pivotal roles in both the development and perpetuation of the retinal ganglion cell degeneration seen in POAG. The TGF-β signaling pathway was repeatedly implicated in our analyses, suggesting that it may be an important contributor to the manifestation of POAG in the anterior and posterior segments of the globe. We propose a molecular model of POAG revolving around TGF-β signaling, which incorporates the roles of inflammation and senescence in this disease. Finally, we highlight emerging molecular therapies that show promise for treating POAG.

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patients with POAG express significantly higher levels of THBS1 (Supplementary Table 2) (Fatma et al., 2009; Kirwan et al., 2009). Additionally, overexpression of CTGF in rats caused an excess deposition of fibronectin and collagen IV in the TM, causing an increase in resistance to aqueous outflow (Supplementary Table 2) (Su et al., 2013). Therefore, it is conceivable that fresolimumab could attenuate the development of OHT, and quite possibly inhibit the development of the senescent-inflammatory phenotype throughout the eye.

In conclusion, POAG is an incredibly complex neurological disease as evidenced by the many genes implicated in its pathogenesis and in its clinical presentation. It is clear from our study that inflammation and senescence play pivotal roles in the development and progression of this devastating disease. Apart from the administration of IOP lowering drugs, there seems to be ample opportunity to develop novel and effective therapeutics.

![Diagram](Image)

**Fig. 10.** TGF-β and the senescent-inflammatory phenotype in action during POAG. In panel A of the figure we see important cells of the posterior (astrocytes and microglia) and anterior segments (TM cells) of the globe. In healthy eyes, these cells are in a quiescent state. However, an initial insult, such as elevated IOP, triggers inflammatory (or gliotic) responses from these cells causing the release of inflammatory cytokines, including TGF-β. In panel B we see TGF-β interaction with its receptor on the surface of a non-descript cell, which could represent other glia, TM cells, or even RGCs. This triggers SMAD activation which eventually results in the transcription of other inflammatory cytokines as well as senescence-inducing molecules such as CDKN2B. Senescence also contributes to the inflammatory milieu through the SASP. CDKN2B-AS1 may modulate inflammation and senescence by inhibitory interactions with the SMAD complex or CDKN2B directly—however the exact mechanism of action of CDKN2B-AS1 is still unclear. SNPs in the 9p21 region which are associated with POAG may impair the function or expression of CDKN2B-AS1 thus contributing to development and progression of the senescent-inflammatory phenotype.

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Glaucoma is the **second** leading cause of blindness worldwide

- Projected 60.5 million with OAG and ACG in 2010 and up to 79.6 million by 2020
  - 75% of these are OAG
- Leading cause of blindness in African NA, and disproportionately affects women and Asians
  - Women are 59% of all glaucoma (55% of OAG; 70% of ACG)
  - Asians are 47% of those with glaucoma (87% of ACG)
- Bilateral blindness in 2010 in 8.4 million
  - 4.5 million with OAG and 3.9 million with ACG

The number of people with glaucoma worldwide in 2010 and 2020
IOP, CSFP, and OPP Dynamics

Lower Diastolic, Systolic, or Mean Pressure Reduces Perfusion Pressure

Hayreh SS. Trans Am Acad Ophthalmol 1974;78:240-54
Multiple Pressure Model of Glaucoma

This model could explain why patients with NTG tend to have a low systemic BP, and why eyes with normal IOP glaucoma and eyes with high-pressure glaucoma, in contrast to eyes with a direct vascular optic neuropathy, show profound similarities in the appearance of the ONH.
IOP, CSFP, and OPP Dynamics: What Are We Missing in the Clinic?

- The Biometrics
  - IOP
  - CSFP
  - BP/OPP
- The Bioperiodicity
- The Biomechanics
  - Role of Corneal Hysteresis?
  - Effect of aging and disease?
  - What controls ocular biomechanics?
    - “As goes the Sclera so goes the Lamina”
Case: 62 yr old, WF

- No specific complaint
- +ve FH (father)
- Vasospastic symptoms
- No meds
- Diag w MS, 1991
  - numbness in hands
  - single episode of ON 5 yrs previously (OD)

- VA:  OD – 20/30 (hx of amblyopia)
  OS – 20/20+1
- IOP:  13mmHg OU
- CCT:  OD - 515
  OS - 525
Under pressure: a review of normal-tension glaucoma

BY DEREK MACDONALD, OD, FAAO

Introduction
For a disease recognized as a common cause of irreversible vision loss, a universally agreed-upon definition of glaucoma is necessary. Normal-tension glaucoma (NTG) has been defined as POAG with only pressure-dependent optic neuropathy. Indeed, many recommend that the concept of distinct clinical entities be abandoned in favor of viewing glaucoma as a continuum from primarily IOP-dependent (POAG) to IOP-independent (NTG) disease.
Normal tension glaucoma: review of current understanding and mechanisms of the pathogenesis

HE Killer1 · A Pircher1

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Abstract
Normal tension glaucoma (NTG) is an exception in the “glaucoma family” where the major risk factor, increased intraocular pressure, is missing. If not increased intraocular pressure, then what other causes can then lead to glaucomatous optic disc change and visual field loss in NTG? Several possibilities will be discussed. Among them a higher sensitivity to normal pressure, vascular dysregulation, an abnormally high translaminar pressure gradient and a neurodegenerative process due to impaired cerebrospinal fluid dynamics in the optic nerve sheath compartment. There are many excellent review papers published on normal tension glaucoma (NTG). The aim of this paper is therefore not to add another extensive review on NTG but rather to focus on and to discuss some possible mechanisms that are thought to be involved in the pathophysiology of NTG and to discuss the stronger and weaker aspects of each concept. The fact that several concepts exist suggests that NTG is still not very well understood and that no single mechanism on its own might adequately explain NTG.
## Risk Factors & Associations

<table>
<thead>
<tr>
<th>POAG</th>
<th>PACG</th>
<th>NTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race (African, Caribbean)</td>
<td>Race (Chinese, Eskimo, S.Asian)</td>
<td>Race (Japanese)</td>
</tr>
<tr>
<td>Age</td>
<td>Age</td>
<td>Vascular dysregulation</td>
</tr>
<tr>
<td>Family history</td>
<td>Family history</td>
<td>Peripheral vasospasm, e.g. Raynaud</td>
</tr>
<tr>
<td>IOP</td>
<td>Female gender</td>
<td>Migraine</td>
</tr>
<tr>
<td>Perfusion pressure</td>
<td>Anatomy</td>
<td></td>
</tr>
<tr>
<td>NFL Thickness</td>
<td>AC depth</td>
<td>Optic disc hemorrhage</td>
</tr>
<tr>
<td>Myopia</td>
<td>Limbal AC depth (van Herick)</td>
<td>Deficiency in SPCA circulation, suggested by association with:</td>
</tr>
<tr>
<td></td>
<td>Hyperopia</td>
<td>- Myopia</td>
</tr>
<tr>
<td></td>
<td>Lens thickness</td>
<td>- Peripapillary atrophy</td>
</tr>
<tr>
<td></td>
<td>Small radius of corneal curvature</td>
<td>- Nocturnal “dips” in blood pressure</td>
</tr>
</tbody>
</table>

Collaborative NTG Study:

- **Purpose:** Does lowering IOP help NTG?
- **Organized:** 1984 140 eyes (140 pts)
- **Design:** Included better of 2 eyes
  - IOP daytime phasing < 20 mmHg
  - VF progression: 4 of 5 exams
- Excluded advanced disease
Visual fields in NTG are variable
Lowering IOP ≥ 30% slows VF loss
  – Effect is hidden by cataract
  – Can be achieved in more than half of patients medically
Progression reduced from 35% to 12% w. 30% reduction
Risk factors for the progression of NTG:
  – Disc hemorrhage, Migraine, Female
Differences in Rates of Glaucoma among Asian Americans and Other Racial Groups, and among Various Asian Ethnic Groups

Joshua D. Stein, MD, MS,1 Denise S. Kim, BS,1 Leslie M. Niziol, MS,1 Nidhi Talwar, MS,1 Bin Nan, PhD,2 David C. Musch, PhD, MPH,1,3 Julia E. Richards, PhD1,3 Ophthalmology 2011;118:1031–1037

**Purpose:** To determine the incidence and prevalence of different glaucoma types among Asian Americans and other races, and evaluate the hazard for glaucoma among different races and Asian ethnicities.

**Design:** Retrospective, longitudinal, cohort study.

**Participants:** A group of 2,259,061 eye care recipients, aged ≥40, who were enrolled in a US managed-care network in 2001–2007.

![Graphs of hazard ratios for open-angle, narrow-angle, and normal-tension glaucoma](image)

Figure 2. Multivariable Cox regression results. The hazard of developing each glaucoma type for different races is presented (reference group, white). Bars represent 95% CIs.
Differences in Rates of Glaucoma among Asian Americans and Other Racial Groups, and among Various Asian Ethnic Groups

Joshua D. Stein, MD, MS,¹ Denise S. Kim, BS,¹ Leslie M. Niziol, MS,¹ Nidhi Talwar, MS,¹ Bin Nan, PhD,² David C. Musch, PhD, MPH,¹,³ Julia E. Richards, PhD¹,³
An Evidence-Based Review of Prognostic Factors for Glaucomatous Visual Field Progression

Table 4: Prognostic Factors Associated with Glaucon

<table>
<thead>
<tr>
<th>Prognostic Factors</th>
<th>Diagnostic Group</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>OAG</td>
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</tr>
<tr>
<td>Disc hemorrhages</td>
<td>NTG</td>
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<tr>
<td>Baseline visual field loss</td>
<td>OAG</td>
<td>4</td>
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<tr>
<td>Baseline IOP</td>
<td>OAG</td>
<td>3</td>
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<tr>
<td>Exfoliation syndrome</td>
<td>OAG</td>
<td>3</td>
</tr>
<tr>
<td>Central corneal thickness</td>
<td>OAG</td>
<td>3</td>
</tr>
<tr>
<td>OBF resistivity index</td>
<td>OAG</td>
<td>3</td>
</tr>
<tr>
<td>Anticardiolipin antibody in blood</td>
<td>OAG</td>
<td>3</td>
</tr>
<tr>
<td>Peripapillary atrophy</td>
<td>NTG</td>
<td>3</td>
</tr>
<tr>
<td>Previous visual field progression</td>
<td>NTG</td>
<td>3</td>
</tr>
<tr>
<td>Stroke</td>
<td>NTG</td>
<td>3</td>
</tr>
<tr>
<td>Gender</td>
<td>OAG</td>
<td>2</td>
</tr>
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</table>
Table 4: Prognostic Factors Associated with Glaucomatous Visual Field Progression

<table>
<thead>
<tr>
<th>Prognostic Factors</th>
<th>Diagnostic Group</th>
<th>Association</th>
<th>Direction</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>OAG</td>
<td>1=no, 2=possible, 3=probable, 4=definite</td>
<td>Increased</td>
<td>Total</td>
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<td>OAG</td>
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<td>More loss</td>
<td>47</td>
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<tr>
<td>Baseline visual field loss</td>
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<td>3</td>
<td>More loss</td>
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<td>Baseline IOP</td>
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<td>Higher IOP</td>
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<td>Exfoliation syndrome</td>
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<td>Presence</td>
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<td>Central corneal thickness</td>
<td>OAG</td>
<td>3</td>
<td>Thinner</td>
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<tr>
<td>OBF resistivity index</td>
<td>OAG</td>
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<td>Higher index</td>
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<tr>
<td>Anticardiolipin antibody in blood</td>
<td>OAG</td>
<td>2</td>
<td>Higher level</td>
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<tr>
<td>Peripapillary atrophy</td>
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<td>Presence</td>
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<tr>
<td>Previous visual field progression</td>
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<td>3</td>
<td>More progression</td>
<td>2</td>
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<tr>
<td>Stroke</td>
<td>NTG</td>
<td>3</td>
<td>Presence</td>
<td>2</td>
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<tr>
<td>Gender</td>
<td>OAG</td>
<td>2</td>
<td>Female sex</td>
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<td>Cup disc ratio</td>
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<td>Higher ratio</td>
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<td>Age</td>
<td>OAG</td>
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<td>Older age</td>
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<td>Myopic refractive error (spherical equivalent)</td>
<td>OAG</td>
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<td>Higher error</td>
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<tr>
<td>Diabetes</td>
<td>OAG</td>
<td>2</td>
<td>Presence</td>
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<tr>
<td>African descent</td>
<td>OAG</td>
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<td>Presence</td>
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<tr>
<td>Baseline untreated IOP</td>
<td>OAG</td>
<td>2</td>
<td>Higher IOP</td>
<td>6</td>
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<tr>
<td>Disc hemorrhages</td>
<td>OAG</td>
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<td>Presence</td>
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<tr>
<td>Diastolic blood pressure</td>
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<td>Lower pressure</td>
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<td>Systemic hypertension</td>
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<td>Presence</td>
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<td>Recovery rate from cold exposure test</td>
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<td>Lower rate</td>
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<td>Baseline IOP fluctuation</td>
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<td>Higher fluctuation</td>
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<tr>
<td>Migraine</td>
<td>OAG</td>
<td>2</td>
<td>Presence</td>
<td>4</td>
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<tr>
<td>Ocular perfusion pressure (overall)</td>
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<td>Lower pressure</td>
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<tr>
<td>Pulse rate</td>
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<td>Higher rate</td>
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<td>Central corneal thickness</td>
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<td>Presence</td>
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<td>Intracranial scotoma localization</td>
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<td>Presence</td>
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<td>Peripapillary atrophy</td>
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<td>Presence</td>
<td>2</td>
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<td>Normal tension glaucoma</td>
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<td>2</td>
<td>Absence</td>
<td>3</td>
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<tr>
<td>OBF end diastolic velocity</td>
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<td>2</td>
<td>Lower velocity</td>
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<tr>
<td>Systolic ocular perfusion pressure</td>
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<td>Lower pressure</td>
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<td>Absence</td>
<td>1</td>
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<td>Variant of myocilin (mt.1(+))</td>
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<td>Presence</td>
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<td>Red blood cell distribution width</td>
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<td>Threat to fixation</td>
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<td>Presence</td>
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<tr>
<td>Outflow facility/ IOP water drinking test/ diurnal IOP</td>
<td>OAG</td>
<td>2</td>
<td>Presence</td>
<td>1</td>
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<tr>
<td>IOP increase after pupillary dilation</td>
<td>OAG</td>
<td>2</td>
<td>Higher increase</td>
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<tr>
<td>Highest IOP ever recorded before baseline</td>
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<td>2</td>
<td>Higher IOP</td>
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<tr>
<td>Ocular perfusion pressure fluctuation</td>
<td>OAG</td>
<td>2</td>
<td>Higher fluctuation</td>
<td>1</td>
</tr>
</tbody>
</table>

All prognostic factors investigated in the literature are ranked by the strength of their association with visual field progression (third column) and the number of studies investigating each factor (seventh column). The fourth column indicates the direction of association between the prognostic factor and visual field progression. NTG = normal-tension glaucoma, OAG = open-angle glaucoma, IOP = intraocular pressure, OBF = ocular blood flow.
Table 5: Prognostic Factors Without Evidence of an Association with Glaucomatous Visual Field Progression

<table>
<thead>
<tr>
<th>Prognostic Factors</th>
<th>Diagnostic Group</th>
<th>Association</th>
<th>Direction</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of glaucoma</td>
<td>OAG</td>
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<td>-</td>
<td>12</td>
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<td>Atherosclerosis</td>
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<td>Systemic hypertension</td>
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<td>-</td>
<td>11</td>
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<td>Visual acuity</td>
<td>OAG</td>
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<td>Gender</td>
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<td>Hypertensive blood pressure</td>
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<td>Myopic refractive error (spherical equivalent)</td>
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<td>Raynaud’s phenomenon</td>
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<td>-</td>
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<td>Baseline IOP</td>
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<td>-</td>
<td>4</td>
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<tr>
<td>Diabetes</td>
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<td>4</td>
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<td>Migraine</td>
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<td>-</td>
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<td>Smell</td>
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<td>Elastic blood pressure</td>
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<td>-</td>
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<td>Mean diurnal IOP</td>
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<td>Low blood pressure tendency</td>
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<td>-</td>
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<td>Duration of disease</td>
<td>OAG</td>
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<td>-</td>
<td>5</td>
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<td>Diurnal IOP fluctuation</td>
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<td>Right-hand eye</td>
<td>OAG</td>
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<td>-</td>
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<td>Educational level</td>
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<td>Minimum IOP of diurnal variation</td>
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<td>MAP</td>
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<td>Disc size</td>
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<tr>
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<td>OAG</td>
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<td>3</td>
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<tr>
<td>Pigment glaucoma</td>
<td>OAG</td>
<td>1</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Alcohol intake, Family history of diabetes (NTG), OPTN E50K mutation, African descent (NTG), Non-European Descent, Multiple blood values, Diurnal MAP fluctuation, Nocturnal MAP fluctuation, 24-hour MAP fluctuation, Recovery rate from cold exposure test, Finger blood flow, 24-hour peak MAP, 24-hour trough MAP, Lens opacity, Iris color, Previous optic disc change, Postoperative IOP spike ≥ 5 mmHg, Anemia, Asthma, Blood transfusion, Fatigue or weakness, Major surgery, Malnourishment, Muscle tremor or weakness, Psychomotor symptoms, Renal stones, Stroke, Sensorineural hearing loss, Any systemic disease, Tinnitus or diarrhea, Ocular perfusion pressure (WTO), Pupil response, Reflective error in cylinders, Retinal artery narrowing</td>
<td>OAG</td>
<td>1</td>
<td>-</td>
<td>2</td>
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NTG: Normal tension glaucoma; OAG = open-angle glaucoma; IOP = intraocular pressure; OBF = ocular blood flow; MAP = mean arterial blood pressure.

All prognostic factors investigated in the literature are ranked by the strength of their association with visual field progression (third column) and the number of studies investigating each factor (seventh column). The fourth column indicates the direction of association between the prognostic factor and visual field progression. NTG = normal-tension glaucoma; OAG = open-angle glaucoma; IOP = intraocular pressure; OBF = ocular blood flow; MAP = mean arterial blood pressure.
NTG Risk Factors for Progression

- **Definite**
  - Disc Hemorrhage
- **Probable**
  - Peripapillary Atrophy
  - Stroke

- **Possible**
  - Age
  - Systemic Hypertension
  - Migraine
  - CCT
  - Threat to Fixation
  - Recovery from Cold
The primary vascular dysregulation syndrome: implications for eye diseases
Josef Flammer*, Katarzyna Konieczka and Andreas J Flammer

Abstract
Vascular dysregulation refers to the regulation of blood flow that is not adapted to the needs of the respective tissue. We distinguish primary vascular dysregulation (PVD, formerly called vasospastic syndrome) and secondary vascular dysregulation (SVD). Subjects with PVD tend to have cold extremities, low blood pressure, reduced feeling of thirst, altered drug sensitivity, increased pain sensitivity, prolonged sleep onset time, altered gene expression in the lymphocytes, signs of oxidative stress, slightly increased endothelin-1 plasma level, low body mass index and often diffuse and fluctuating visual field defects. Coldness, emotional or mechanical stress and starving can provoke symptoms. Virtually all organs, particularly the eye, can be involved. In subjects with PVD, retinal vessels are stiffer and more irregular, and both neurovascular coupling and autoregulation capacity are reduced while retinal venous pressure is often increased. Subjects with PVD have increased risk for normal-tension glaucoma, optic nerve compartment syndrome, central serous choroidopathy, Susac syndrome, retinal artery and vein occlusions and anterior ischaemic neuropathy without atherosclerosis. Further characteristics are their weaker blood–brain and blood-retinal barriers and the higher prevalence of optic disc haemorrhages and activated astrocytes. Subjects with PVD tend to suffer more often from tinnitus, muscle cramps, migraine with aura and silent myocardial ischaemia and are at greater risk for altitude sickness. While the main cause of vascular dysregulation is vascular endotheliopathy, dysfunction of the autonomous nervous system is also involved. In contrast, SVD occurs in the context of other diseases such as multiple sclerosis, retrobulbar neuritis, rheumatoid arthritis, fibromyalgia and giant cell arteritis. Taking into consideration the high prevalence of PVD in the population and potentially linked pathologies, in the current article, the authors provide recommendations on how to effectively promote the field in order to create innovative diagnostic tools to predict the pathology and develop more efficient treatment approaches tailored to the person.

Keywords: Primary vascular dysregulation, Endothelial dysfunction, Vasospasm, Glaucoma, Retinal venous pressure, Risk factors, Molecular targets, Predictive diagnostics, Targeted prevention, Integrative medical approach
There are several factors potentially reducing the OBF. The vascular dysregulation is one of the main mechanisms invoked. It is defined as the inability of a tissue to maintain a constant blood supply despite changes in perfusion pressure secondary to vascular abnormalities or to the role of local vasospastic/vasodilating agents (Fig. 1).

Also, the blood pressure has a predominant role: several studies reported that low blood pressure was a significant risk factor for visual field defect progression in NTG (Leighton and Phillips, 1972; Okumura et al., 2012). However, the real association between these findings is still debated.

In a recent study in patients with NTG, Abegao Pinto et al. (2012) reported the reduction of blood flow velocities in retrobulbar arteries and in cerebral circulation. They found that, while in healthy individuals there was a linear correlation between vascular pulsatility index and resistive index, this relation was not present in NTG patients. Su et al. (2006, 2008), using the brachial artery ultrasound assessment of endothelium-dependent flow-mediated vasodilation, provided evidence of a generalized endothelial dysfunction in patients with NTG.

The vascular dysregulation in NTG was also related to alterations of local agents. Henry et al. (1999, 2006) documented an altered vascular reactivity to endothelial vasodilators. This should be intended as expression of an impairment of the peripheral endothelium-mediated vasodilatation, Buckley et al. (2002) analyzed cutaneous artery biopsies showing a selective defect in the agonist-mediated release of endothelium-derived vasodilators. These findings support the

**FIGURE 1**
Schematic representation of the risk factors, pathogenesis, and the current therapy of NTG.
*OBF, ocular blood flow.

Normal Tension Glaucoma

• On the “other” end of the continuum of OAGs
  – Mechanism shifts from elevated IOP to independent-IOP factors
    • Vascular? Cerebral Spinal Fluid Pressure?

• Usually a bilateral, slowly progressive condition
  – Evidence that it may progress *slower* than high IOP POAG

• Distinguishing clinical features that frequently differentiate it from high IOP induced POAG
  – *Paracentral* VF defects, greater *PPA*, more *focal rim thinning*

- Vascular theory
- Mechanical theory

8-15 mmHg

30 mmHg +
Habitual IOP and Systemic Blood Pressure

Ocular Perfusion Pressure: \[ \text{M OPP} = \frac{2}{3} \text{MAP} - \text{IOP} \]
\[ \text{DPP} = \text{DBP} - \text{IOP} \]
 Higher IOP Negatively Impacts Perfusion Pressure

 Lower Diastolic, Systolic, or Mean Pressure Reduces Perfusion Pressure

 Lower Perfusion Pressure Is Associated with Increased Risk for Open Angle Glaucoma

 Perfusion Pressure is a Result of A Delicate Balance Between IOP and Blood Pressure

 Hayreh SS. Trans Am Acad Ophthalmol 1974;78:240-54
Diurnal Profile of IOP and MOPP in a Patient with Asymmetric Presentation of Glaucoma

Sehi and Flanagan
OCT Angiography Showing Reduced ONH Blood Flow in Pre-Perimetric Glaucoma

Normal (OS)

Preperimetric Glaucoma (OS)

ONH flow index = 0.159

ONH flow index = 0.125

The Effects of Nocturnal Dip and Blood Pressure Variability on Paracentral Scotoma in Early Open-Angle Glaucoma

Sang Wook Jin¹, Hong Ryung Seo², Seung Soo Rho³, and Sae Heun Rho¹

¹Department of Ophthalmology, Dong-A University Hospital, Busan, Republic of Korea, ²Department of Ophthalmology, Wallace Memorial Baptist Hospital, Busan, Republic of Korea, and ³Department of Ophthalmology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea

ABSTRACT

Purpose: To evaluate the effect of nocturnal dip and blood pressure (BP) variability on paracentral scotoma in early open-angle glaucoma. Methods: The present study included 72 early normal-tension glaucoma (NTG) patients and 34 early primary open-angle glaucoma (POAG) patients. Nocturnal dip and weighted standard deviation (wSD) were determined by 24-hour ambulatory BP monitoring (24-hr ABPM). The mean deviation (MD) and pattern deviation (PD) were measured with visual field. Correlations between nocturnal dip and/or BP variability and paracentral scotoma were assessed using Student’s t-test, Pearson’s correlation test, and linear logistic regression analysis. Results: The systolic and diastolic nocturnal dip and paracentral scotoma occurrence demonstrated a statistically significant correlation in the early NTG group (systolic nocturnal dip: p=0.047, diastolic nocturnal dip: p=0.011). In the early NTG group, the subgroup with paracentral scotoma had a greater nocturnal dip than those patients without paracentral scotoma (systolic nocturnal dip: p=0.000; diastolic nocturnal dip: p=0.000). In the early NTG group, the subgroup with paracentral scotoma had higher wSD of SBP than the patients without paracentral scotoma (p=0.003). In the logistic regression analysis of the factors that can affect paracentral scotoma SBP dip and SBP, wSD appeared to significantly affect the occurrence of paracentral scotoma in the early NTG group. Conclusions: Early NTG patients with paracentral scotoma have nocturnal dip and large BP variability. Therefore, in early glaucoma patients, particularly in early NTG with paracentral scotoma, nocturnal dip and BP variability should be assessed with 24-hr ABPM.

Keywords: 24-hr ambulatory blood pressure, blood pressure variability, early open-angle glaucoma, nocturnal dip, normal tension glaucoma, paracentral scotoma
Association Between Nocturnal Blood Pressure Dips and Optic Disc Hemorrhage in Patients With Normal-Tension Glaucoma

JUNKI KWON, JINYOUNG LEE, JAEWAN CHOI, DAWOON JEONG, AND MICHAEL S. KOOK

The link between optic disc hemorrhages (ODHs) and glaucoma has been extensively explored in various clinical trials and hospital-based studies. A higher incidence of ODHs has been reported in patients with normal-tension glaucoma (NTG) than with high-tension glaucoma (HTG) or normal healthy eyes. One hypothesis for this finding is that NTG may be related to disturbed ocular blood flow (OBF) to the optic nerve head (ONH), owing to vascular structural changes or dysregulation. In this regard, ODH may be one manifestation of vascular dysregulation (VD) and occur more frequently in patients with NTG than in those with other glaucoma types. Recently, several clinical factors associated with ODH observation have been identified in glaucoma patients. A reduction of nocturnal blood pressure (BP) in the range of 10%–20% relative to daytime BP levels is usually observed in normotensive subjects and in the majority of hypertensive patients. This dip is termed “physiologic,” while BPs that exhibit excessive (>20%) or minimal (<10%) dips at night are termed “nonphysiologic” dips. Excessive or minimal nocturnal BP dip has been recognized as a sign of VD and has been found to be associated with glaucoma progression in both NTG and primary open-angle glaucoma (POAG). Our recent research has demonstrated that excessive nocturnal hypotension leading to increased 24-hour fluctuation of BP or ocular perfusion pressure (OPP) is a consistent risk factor for NTG development and progression. Further, Tokunaga and associates and Collignon and associates reported that the lack of a physiologic BP dip at night, as in nondippers, is also associated with glaucoma progression over time. Despite these findings, it remains unknown how ODH and nonphysiologic nocturnal BP dips might be associated with a greater risk of ODH development in NTG patients, as both conditions may be associated with greater likelihoods of subsequent visual field progression (VFP). Therefore, we hypothesized that nonphysiologic nocturnal BP dips are related to ODHs in NTG patients. We retrospectively enrolled 698 NTG eyes of 349 consecutive normotensive patients who were ≥40 years old, underwent 24-hour intraocular pressure and ambulatory BP monitoring in the habitual position, and had ≥5 reliable visual field tests with minimum follow-up of 3 years. NTG patients were classified into 2 groups: “nonphysiologic” dippers, including nondippers and overdippers, and “physiologic” dippers. Odds ratios for the association between the “nonphysiologic” group and ODH were calculated using logistic regression models. Kaplan-Meier analyses were performed to compare outcomes with reference to the presence of ODH for VFP.

RESULTS: Overall, ODH and VFP were detected in 107 (15.3%) eyes and 60 (8.6%) eyes among total 698 eyes, respectively. Overdippers showed a significantly greater frequency of ODH than nondippers or dippers. Being an overdipper was a significant and an independent risk factor for ODH occurrence during follow-up. The rates of VFP were 6%, 7%, and 24% for dippers, nondippers, and overdippers, respectively. Eyes with ODH were associated with greater likelihoods of subsequent VFP than those without. VFP occurred only in eyes with ODH.

CONCLUSIONS: Being an overdipper is a significant risk factor for ODH in NTG eyes. The detection of ODH during follow-up is a potent predictor of future VFP.
1 week later
Case 5: 62 yr old, WF

- No specific complaint
- +ve FH (father)
- Vasospastic symptoms
- No meds
- Diag w MS, 1991
  - numbness in hands
  - single episode of ON 5 yrs previously (OD)

- VA:  OD - 6/9 (hx of amblyopia)  
  OS - 6/6+1
- IOP:  13mmHg OU
- CCT:  OD - 515  
  OS - 525
Why Do I Treat NTG Differently?

**Time to treat:**
- Imaging
  - Photos & NFL
- Repeated Visual Fields
Progression in Glaucoma: EMGT

Treated patients, EMGT

Progression in Glaucoma: EMGT

Untreated patients, EMGT

- 3X normal aging rate: ~0.08 dB/yr
- 90X normal aging rate: ~4 dB/yr
- 12X normal aging rate: ~0.60 dB/yr
Why Do I Treat NTG Differently?

Time to treat:

- Imaging
  - Photos & NFL
- Repeated Visual Fields
- Diurnal IOP
- BP
- CCT
- Target pressure
- When to consider neuroimaging?
Neuroradiologic Screening in Normal-Pressure Glaucoma: Study Results and Literature Review

Journal of Glaucoma 11:279–286
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*Iqbal Ike K. Ahmed, MD, FRCS(C), *Fred Feldman, MD, FRCS(C), †Walter Kucharczyk, MD, FRCP(C), and *Graham E. Trope, MB, PhD, FRCS(C)

Departments of *Ophthalmology and †Medical Imaging, University of Toronto, Toronto, Ontario, Canada

• 4 of 62 NTG
• 0 of 70 progressive POAG
• < 50 years
• VA < 20/40
• ON pallor
• Vertically aligned VF defect
• Poor correlation of S-F progression
• Progression at very low IOP
The Cupped Disc

Who Needs Neuroimaging?

David S. Greenfield, MD, R. Michael Stiatkowski, MD, Joel S. Glaser, MD, Norman J. Schatz, MD, Richard K. Parrish II, MD

**Objective:** To determine the incidence of positive neuroradiologic studies in consecutive patients with glaucoma associated with normal intraocular pressure and to compare the psychophysical and clinical characteristics of these eyes with eyes with disc cupping associated with intracranial masses.

**Design:** Retrospective case-controlled study.

**Participants:** Fifty-two eyes of 26 patients with glaucoma associated with normal intraocular pressure and 44 eyes of 28 control patients with compressive lesions were reviewed.

**Intervention:** The medical records of consecutive glaucoma patients with normal intraocular pressure who underwent brain magnetic resonance imaging or computed tomography scanning as part of a diagnostic evaluation between January 1, 1985, and July 1, 1995, were reviewed. A masked reading of optic nerve photographs and visual fields was performed by one observer. A similar analysis was performed on a control group of consecutive patients with nonglaucomatous optic nerve cupping with known intracranial mass lesions.

**Main Outcome Measures:** The neuroradiologic findings, clinical characteristics, optic nerve head appearance, and patterns of visual field loss were compared between groups.

**Results:** None of the patients diagnosed with glaucoma had neuroradiologic evidence of a mass lesion involving the anterior visual pathway. Compared to control subjects, patients with glaucoma were older ($P = 0.0001$), had better visual acuity ($P = 0.002$), greater vertical loss of neuroretinal rim tissue ($P = 0.0001$), more frequent optic disc hemorrhages ($P = 0.01$), less neuroretinal rim pallor ($P = 0.0001$), and more nerve fiber bundle visual field defects aligned at the horizontal midline ($P = 0.0001$). Visual acuity less than 20/40, vertically aligned visual field defects, optic nerve pallor in excess of cupping, and age younger than 50 years were 77%, 81%, 90%, and 93% specific for nonglaucomatous cupping associated with compressive lesions, respectively.

**Conclusions:** Anterior visual pathway compression is an uncommon finding in the neuroradiologic evaluation of patients with a presumptive diagnosis of normal-tension glaucoma. Younger age, lower levels of visual acuity, vertically aligned visual field defects, and neuroretinal rim pallor may increase the likelihood of identifying an intracranial mass lesion. *Ophthalmology* 1998;105:1866 –1874

**Conclusions:** Anterior visual pathway compression is an uncommon finding in the neuroradiologic evaluation of patients with a presumptive diagnosis of normal-tension glaucoma. Younger age, lower levels of visual acuity, vertically aligned visual field defects, and neuroretinal rim pallor may increase the likelihood of identifying an intracranial mass lesion. *Ophthalmology* 1998;105:1866 –1874
Case: 54yo, Korean W

- IOP – 15/14
- CCT – 540/535
- Gonio – Open to CB, normal approach
- SAP Fields – Threatening fixation

Discs - Inferior temp notch and NFL defect OU
Case: 54yo, Korean W

IOP – 15/14
CCT – 540/535
Gonio – Open to CB, normal approach
SAP Fields – Threatening fixation
**Patient:** Kim, Hee Sun  
**DOB:** Dec/23/1959  
**Sex:** F  
**Patient ID:** 216329  
**Exam.:** Oct/15/2012  
**Diagnosis:** ---  
**Comment:** ---  

**Software Version:** 5.3.2 www.HeidelbergEngineering.com

**OD**

**Asymmetry OD - OS**

**OS**

**Classification OD**

**Classification OS**

**Notes:**

Date: 10/21/12  
Signature:
Asymmetry Analysis Single Exam Report OU
SPECTRALIS® Tracking Laser Tomography

Patient: Kim, Hee Sun
DOB: Dec/23/1959
Sex: F
Patient ID: 216329
Exam.: Oct/15/2012
Diagnosis: ---
Comment: ---

Software Version: 5.3.2 www.HeidelbergEngineering.com

Notes:
Date: 10/21/12
Signature:

OD - OS Asymmetry
Hemisphere Asymmetry
Superior (S) 290
Inferior (I) 270
Total 280

Average Thickness [µm] Superior (S) 295
Total 282
Inferior (I) 270

OS - OD Asymmetry
Hemisphere Asymmetry
Superior (S) 285
Total 282
Inferior (I) 270

Average Thickness [µm] Superior (S) 285
Total 282
Inferior (I) 270

Notes:
Date: 10/21/12
Signature:
Clinical Implications: Systemic Hypotension
Observations on Degenerative Changes Within the Optic Nerve in Patients With Primary Open Glaucoma and Arterial Hypertension: 6-Month Follow-Up

Beata Krasinska, Maciej Banach, Małgorzata Karolczak-Kulesza, Zbigniew Krasinski, Jerzy Głuszek, Andrzej Tykarski.

**Observations on Degenerative Changes Within the Optic Nerve in Patients With Primary Open Glaucoma and Arterial Hypertension: 6-Month Follow-Up**

Beata Krasinska, Maciej Banach, Małgorzata Karolczak-Kulesza, Zbigniew Krasinski, Jerzy Głuszek, Andrzej Tykarski.


**Purpose:** To determine the effect of the time of hypotensive drug administration on the progress of degenerative changes within the optic nerve in patients with hypertension and glaucoma.

**Sample:** Two groups were included in the study:
- Group A, dippers taking drugs in the mornings
- Group B, non-dippers taking drugs both mornings and evenings.

**Results:** After 6 months, Group B showed significant drop in nocturnal DBP (Month 1 = 73.27 vs Month 6 = 67.50 mmHg), nocturnal mean BP (89.34 vs 84.65 mmHg), min. DBP (50.74 vs 44.03 mmHg), nocturnal OPP (43.0 vs 39.73 mmHg), RNFL thickness (131.31 vs 113.12 μm), and retinal blood flow.
Results: After 6 months, Group B showed significant drop in nocturnal DBP (Month 1 = 73.27 vs Month 6 = 67.50 mmHg), nocturnal mean BP (89.34 vs 84.65 mmHg), min. DBP (50.74 vs 44.03 mmHg), nocturnal OPP (43.0 vs 39.73 mmHg), RNFL thickness (131.31 vs 113.12 μm), and retinal blood flow.

Conclusion: Taking hypotensive drugs in the evening may significantly decrease retinal blood flow, cause degenerative changes within the optic nerves, and result in greater loss in the field of vision.
• Use systemic BP meds in the AM to minimize nocturnal hypotension

• Use IOP lowering drugs that lower IOP during the diurnal and nocturnal period

• Avoid IOP meds that lower systemic BP at night (beta blockers, alpha agonists)

Blood pressure and glaucoma: At the crossroads between cardiology and ophthalmology

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2 Department of Ophthalmology, SPKSO Ophthalmic Hospital, Medical University of Warsaw, Poland
3 1st Chair and Department of Cardiology, Medical University of Warsaw, Poland

Abstract
Glaucoma is an optic nerve neuropathy of undetermined cause. Although many mechanisms are thought to be involved in the development and progression of the disease, only an increased intraocular pressure has been established as a clinically significant modifiable risk factor. Nevertheless, up to 40% of patients develop glaucoma without evidence of increased intraocular pressure.

Ample evidence suggests that alterations in the control of arterial blood might negatively affect optic nerve function. However, evidence-based guidelines on the management of arterial blood pressure in glaucoma patients are lacking.

Regrettably, intraocular pressure is generally not included as a secondary end-point in clinical trials on arterial hypertension. Considering the relative simplicity of intraocular pressure measurements and large number of patients included in hypertension studies, the benefits of including intraocular pressure as a secondary end-point could be of a great value for improving care for glaucoma patients. Therefore, closer collaboration between cardiologists and ophthalmologists is needed.

Key words: blood pressure, intraocular pressure, glaucoma, hypertension

Introduction
Glaucoma is a progressive optic nerve neuropathy [1]. It is estimated that by 2040 at least 112 million people will be diagnosed with glaucoma worldwide [2]. Increased intraocular pressure (IOP) is the only modifiable glaucoma risk factor which has been well established in clinical practice [1]. Pharmacotherapy, laser or surgical procedures are utilized to lower IOP and prevent deterioration of visual field defects [1]. However, up to 40% of patients develop glaucomatous neuropathy without any evidence of increased IOP [1]. This observation prompted research into alternative causes of optic nerve damage and abnormal level of arterial blood pressure (ABP) — both too low and too high, was proposed as a possible risk factor [4]. Nevertheless, ophthalmologists are still far from evidence-based management of ABP in glaucoma patients.

In contrast, cardiologists have well established preferred practice patterns on the management of hypertension [5]. The most recent update of these guidelines recommends systolic blood pressure (SBP) between 120 and 129 mmHg as a treatment goal in majority of high-risk patients [5]. Although the SPRINT study proved that a low ABP target significantly decreases mortality, and an intensified approach did not remain without side effects [6]. Acute kidney failure or syncope were reported by SPRINT investigators [6]. Interest-
The Role of Pressures in the Diagnosis and Management of Glaucoma

Lower Diastolic, Systolic, or Mean Pressure Reduces Perfusion Pressure

- IOP
- Perfusion Pressure
- Blood Pressure
- CSF Pressure

Hayreh SS. Trans Am Acad Ophthalmol 1974; 78: 240-54
4-compartment model of optic disc pressure relationships.
The retrolaminar ON is affected by ONSAS, which is connected to the intracranial CSF space. The ONSAS is surrounded by orbit, which may set a minimum ONSAS pressure.
Schematic representation of

A: The CSF spaces surrounding the optic chiasm (intracranial CSF space)
B: The CSF surrounding the optic nerve (orbital CSF space)
   - CSF flows from intracranial (A) into the ONSAS (B)
C: The ONSAS is most narrow in the canalicular region
D: The intraorbital segment of the ONSAS is characterized by broad septae, whereas
E: The retrobulbar segment is characterized by small trabeculae

Owing to the CSF volume gradient the direction of flow is directed from the intracranial SAS to the ONSAS.

With permission from Brain. 2007;130:514-520.
Optic nerve tissue pressure in dogs at various IOP and CSF pressures. Micropipette was advanced from vitreal surface (0 μm) into the optic disk. Note the fall in pressure over 400 to 500 μm corresponding to the lamina cribrosa. Calculation of the pressure gradient can be performed using regression analysis of these data.

Cerebrospinal Fluid Pressure: What Are We Missing in the Clinic?

Jost B. Jonas

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ABSTRACT

The pathogenesis of normal (intracranial) pressure glaucoma has remained unclear so far. As hospital-based studies showed an association of normal-pressure glaucoma with low systolic blood pressure, particularly at night, and with vasculopathic symptoms, it has been hypothesized that a vascular factor may play a primary role in the pathogenesis of normal-pressure glaucoma. That assumption may, however, be overturned by the morphology of the optic nerve head. Eyes with normal-pressure glaucoma and glaucomatous eyes with high-intraocular pressure can show a similarly different appearance of the optic nerve head, including a loss of onemicroscopic rim, a deepening of the optic cup, and an enlargement of parapapillary atrophy. These features, however, are not found in any other vascular optic neuropathy, with the exception of an enlargement and deepening of the optic cup in arteritic anterior ischemic optic neuropathy. One may additionally take into account (i) that it is the trans-lamina cribrosa pressure difference (and not the trans-corneal pressure difference, i.e., the normal intraocular pressure) which is of importance for the physiology and pathophysiology of the optic nerve head; (ii) that studies have shown that the anatomy of the optic nerve head including the intracranial pressure, the anatomy and biomarkers of the lamina cribrosa and peripapillary sclera, extraocular orbital cerebrospinal fluid pressure and the intraocular pressure have been found to be independent of the IOP, and (iii) that clinical studies have reported that patients with normal (intracranial) pressure glaucoma have significantly lower cerebrospinal fluid pressure and a higher trans-lamina cribrosa pressure difference when compared to normal subjects. One may, therefore, postulate that a low cerebrospinal fluid pressure may play a role in the pathogenesis of normal (intracranial) pressure glaucoma. In that view, cerebrospinal fluid pressure becomes an important adjustable parameter in the pathogenesis of normal-pressure glaucoma. A low systemic blood pressure, particularly at night, could physiologically be associated with a low cerebrospinal fluid pressure, which leads to an abnormally high trans-lamina cribrosa pressure difference and, as such, to a different situation if the cerebrospinal fluid pressure is normal and the intracranial pressure is elevated. This model could explain why patients with normal (intracranial) pressure glaucoma tend to have a low systemic blood pressure and why eyes with normal (intracranial) pressure glaucoma and eyes with high-pressure glaucoma, in contrast to eyes with a direct vascular optic neuropathy, show profound similarities in the appearance of the optic nerve head.

Keywords: Cerebrospinal fluid pressure; Glaucoma; Open-angle glaucoma; Normal-pressure glaucoma; Diabetic retinopathy; Retinal vein occlusion; Brain pressure

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The trans-lamina cribrosa pressure difference (and not the trans-corneal pressure difference, i.e. the IOP) is of most importance for the physiology and pathophysiology of the ONH.
Clinical studies reported that patients with NTG had significantly lower CSF pressure and a higher trans-lamina cribrosa pressure difference

Conclusion:
- Low CSF pressure likely associated with NTG
- Low systemic BP, particularly at night, could be associated with a low CSF pressure, which leads to an abnormally high T-LC pressure difference
- Similar to normal CSF pressure and high IOP
- Glaucomatous neuropathy essentially the same in NTG and POAG with ocular hypertension
Clinical studies reported that patients with NTG had significantly lower CSF pressure and a higher trans-lamina cribrosa pressure difference.

**Conclusion:**

- **Low CSF pressure likely associated with NTG**
- **Low systemic BP, particularly at night, could be associated with a low CSF pressure, which leads to an abnormally high T-LC pressure difference**
- **Similar to normal CSF pressure and high IOP**
- **Glaucamous neuropathy essentially the same in NTG and POAG with ocular hypertension**
This model could explain why patients with NTG tend to have a low systemic BP, and why eyes with normal IOP glaucoma and eyes with high-pressure glaucoma, in contrast to eyes with a direct vascular optic neuropathy, show profound similarities in the appearance of the ONH.
Orbital Cerebrospinal Fluid Space in Glaucoma: The Beijing Intracranial and Intraocular Pressure (iCOP) Study

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Objective: Low cerebrospinal fluid pressure (CSF-P) may be involved in the pathogenesis of glaucoma. We measured the optic nerve subarachnoid space width (ONASW) as a surrogate for orbital CSF-P in patients with primary open-angle glaucoma (POAG) with normal and high pressure and a control group.

Design: Prospective observational study.

Participants: The study included 39 patients with POAG; 21 patients had normal pressure (intraocular pressure [IOP] 21 mmHg), and 18 patients had high pressure (IOP >21 mmHg); 21 subjects formed the control group.

Methods: By using magnetic resonance imaging (MRI) with fat-suppressed fast recovery fast spin echo (FRFSE) T2-weighted sequence, we determined the ONASW at 3, 9, and 15 mm posterior to the globe.

Main Outcome Measures: The ONASW and optic nerve diameter.

Results: At all 3 measurement locations of 3, 9, and 15 mm, the ONASW was significantly (P<0.001, P<0.001, and P = 0.003, respectively) narrower in the normal-pressure group (0.67±0.16, 0.55±0.09, and 0.51±0.12 mm, respectively) than in the high-pressure group (0.93±0.21, 0.70±0.12, and 0.62±0.11 mm, respectively) or the control group (0.87±0.15, 0.67±0.07, and 0.61±0.07 mm, respectively). The high-pressure and control groups did not vary significantly at 3, 9, and 15 mm (P = 0.31, P = 0.39, and P = 0.44, respectively). At all 3 measurement locations, ONASW was narrower in the normal-pressure group compared with the high-pressure and control groups after adjustment for optic nerve diameter (P<0.01). Correspondingly, the width of the optic nerve subarachnoid space measured at 3, 9, and 15 mm behind the globe, respectively, was significantly (all P<0.05) associated with IOP after adjustment for optic nerve diameter and visual field defect.

Conclusions: The narrower orbital optic nerve subarachnoid space in patients with POAG with normal pressure compared with high pressure suggests a lower orbital CSF-P in patients with POAG with normal pressure.

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Figure 4. Boxplots showing the differences in the width of the optic nerve subarachnoid space measured at 3 mm (A), 9 mm (B), and 15 mm (C) behind the globe.
Conclusions

TLCPD was significantly associated with the prevalence of NTG in high-teen IOP subjects, but not low-teen IOP subjects, in whom hypertension may be more closely associated. This study suggests that the underlying mechanisms may differ between low-teen and high-teen NTG patients.
Impaired cerebrospinal fluid dynamics along the entire optic nerve in normal-tension glaucoma

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ABSTRACT.
Purpose: To investigate the cerebrospinal fluid (CSF) dynamics along the entire optic nerve (ON) in patients with normal-tension glaucoma (NTG).

Methods: Retrospective analysis of computed tomographic (CT) cisternographies in Caucasian patients with NTG. Fifty-six patients (99 of 112 eyes) fulfilled the diagnostic criteria of NTG and underwent CT-cisternography. Twelve subjects without NTG (24 eyes) served as controls. Contrast-loaded cerebrospinal fluid (CLCSF) density measurements in Hounsfield units (HU) were performed at four defined regions along the ON and in the basal cistern.

Results: In NTG patients, the mean density CLCSF in the bulbar segment measured 76 ± 49 HU right and 88 ± 74 HU left, in the mid-orbital segment 117 ± 92 HU right and 119 ± 73 HU left, in the intracanalicular ON portion 209 ± 106 HU right and 266 ± 118 HU left and in the basal cistern 517 ± 213 HU. The distribution of CLCSF along the ON showed a statistically significant reduction in the intraorbital ON segments in NTG patients compared to controls without NTG with the far largest difference within the retrobulbar segment (150 HU right and 117 HU left; right: p < 0.001, left: p < 0.001).

Conclusion: This study demonstrates a gradual reduction in CLCSF towards the retrobulbar segment in NTG, while in controls without NTG, no reduction in CLCSF was measured within the orbital segments. Impaired CSF dynamics along the ON may contribute to the pathophysiology of NTG.

Key words: cerebrospinal fluid – CT-cisternography – normal-tension glaucoma – optic nerve – optic nerve sheath compartment

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Introduction
Normal-tension glaucoma (NTG), a subset of primary open-angle glaucoma (POAG), is a multifactorial optic nerve (ON) disease characterized by progressive ON fibre and visual field loss despite a normal intraocular pressure (IOP). In contrast to high-tension glaucoma, IOP independent factors must be involved in the pathophysiology of NTG (Mi et al. 2014; Mastropasqua et al. 2014). In the last years, the role of cerebrospinal fluid (CSF) has gained interest. A higher translaminar pressure difference (TLP) has been suggested to be involved in the pathophysiology of glaucomatous damage (Ren et al. 2010; Jonas et al. 2016); however, the exact mechanism causing ON damage is still not understood. Recently, a new hypothesis based on impaired clearance of neurotoxic substances within the ON subarachnoid space (SAS) shifted the focus from mechanical forces to biochemical processes (Wostyn et al. 2017).

Anatomically, the ON can be divided into the orbital ON portion with the bulbar and mid-orbital segments, the intracanalicular and the intracranial ON portion. The ON is enveloped on its entire length by the meninges that confine the SAS which is in direct contact with CSF. The ON-SAS contains a complex system of structural elements (trabeculae, septa and pillars) that differ markedly in number and morphology as well as in diameter within the different ON portions. The narrowest SAS diameter is located within the optic canal (OC) (Killer et al. 2005).

In a recent study (Killer et al. 2012) applying cisternography, our group demonstrated a reduced CSF exchange between the basal cistern and the bulbar segment of the ON in 18 patients with NTG. In this study, we measured the contrast-loaded CSF (CLCSF) in the orbital (bulbar and mid-orbital segment), intracanalicular and intracranial ON portion and in the basal cistern in 56 Caucasian patients with NTG and compared the measurements to a control group of 12 subjects without NTG.

The purpose of this study was to investigate about the CSF dynamics in the SAS of the ON in patients with NTG.
Fig. 1. Measurement regions for contrast-loaded cerebrospinal fluid (CLCSF) density along the entire optic nerve (ON) in patients with normal-tension glaucoma (NTG). Region of interest (ROI) 1: Bulbar segment of the orbital portion, ROI 2: mid-orbital segment of the orbital portion, ROI 3: intracanalicular portion, ROI 4: intracranial portion, ROI 5: basal cistern.

Fig. 2. Measurement of contrast-loaded cerebrospinal fluid (CLCSF) density in the mid-orbital segment of the orbital portion (region of interest 2) of a right optic nerve (ON). Axial (A), sagittal (B) and coronal (C) sections were used. Note the reduction in CLCSF density towards the globe.
Fig. 3. Distribution of contrast-loaded cerebrospinal fluid (CLCSF) along the entire optic nerve (ON) in patients with normal-tension glaucoma (NTG) and controls without NTG. In both NTG patients and controls, there is a decrease in CLCSF density within the canalicular portion [region of interest (ROI 3)]. After the optic canal, the CLCSF density further decreases in the NTG group with its lowest concentration in the bulbar segment (ROI 1) behind the lamina cribrosa. In the control group, the concentration of CLCSF, however, increases again and reaches a peak in the bulbar segment (ROI 1). Region of interest (ROI 1): Bulbar segment of the orbital portion, ROI 2: mid-orbital segment of the orbital portion, ROI 3: intracanalicular portion, ROI 4: intracranial portion. Contrast-loaded cerebrospinal fluid (CLCSF) for CLCSF. HU for Hounsfield units.— NTG patients;— controls.
What do we know?
• Trans-scleral pressure difference
• Low CSF pressure associated with NTG – possibly higher-teen NTG
• Finally provides a reasonable explanation for aspects of NTG
• Implication for venous outflow
What the future may hold

• Proxy clinical measurement
• NASA
  – Problems associated with cerebral and retinal edema
  – VIIP Syndrome

Vision Impairment & Intracranial Pressure

Cerebral Spinal Fluid Pressure
Normal tension glaucoma: review of current understanding and mechanisms of the pathogenesis

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Abstract
Normal tension glaucoma (NTG) is an exception in the "glaucoma family" where the major risk factor, increased intraocular pressure, is missing. If not increased intraocular pressure, then what other causes can then lead to glaucomatous optic disc change and visual field loss in NTG? Several possibilities will be discussed. Among them a higher sensitivity to normal pressure, vascular dysregulation, an abnormally high translaminar pressure gradient and a neurodegenerative process due to impaired cerebrospinal fluid dynamics in the optic nerve sheath compartment. There are many excellent review papers published on normal tension glaucoma (NTG). The aim of this paper is therefore not to add another extensive review on NTG but rather to focus on and to discuss some possible mechanisms that are thought to be involved in the pathophysiology of NTG and to discuss the stronger and weaker aspects of each concept. The fact that several concepts exist suggests that NTG is still not very well understood and that no single mechanism on its own might adequately explain NTG.

Conclusion
Normal tension glaucoma (NTG) is an optic nerve neuropathy that presents with optic disc excavation, visual field loss in spite of intraocular pressure <21 mm Hg. Progressive visual field loss and disc excavation can continue despite of pressure lowering of 30% of IOP. There are however, also a substantial number of patients who do not progress even without treatment. A substantial number of older NTG patients also suffer from Alzheimer's disease, a finding that raises the question whether or not NTG is an early manifestation of a more generalized neurodegenerative disease. At the same time, some NTG patients share features of vascular dysregulation, which raises the question whether NTG is an optic nerve disease in a diseased body. In analogy therefore NTG might be a diseased optic nerve in a toxic CSF environment.

None of the current pathophysiological concepts can explain this intriguing condition on its own. It is most likely that NTG is a complex syndrome consisting of a variety of pathological pathways that may differ between populations and individuals. Further research should focus on translational research that will lead to a more individualized therapeutic approach.