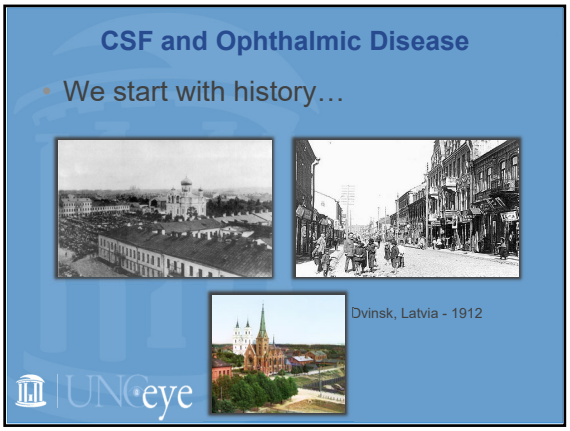

UNC eye
CSF and Ophthalmic Disease:
Only in Your Dreams
David Fleischman, MD
Associate Professor
University of North Carolina
Chapel Hill, NC


CSF and Ophthalmic Disease
We start with history…
Dvinsk, Latvia - 1912
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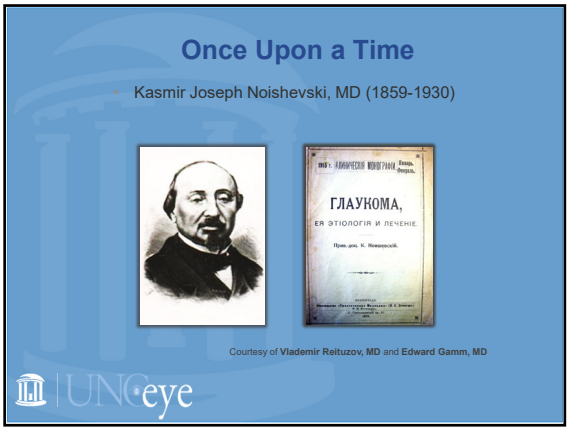
Once Upon a Time
Kasmir Joseph Noishevski, MD (1859-1930)
ГЛАУКОМА,
Courtesy of Vlademir Reituzov, MD and Edward Gamm, MD
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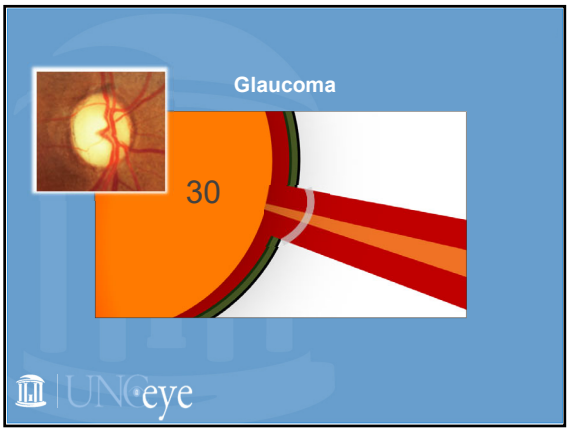
Glaucoma
30
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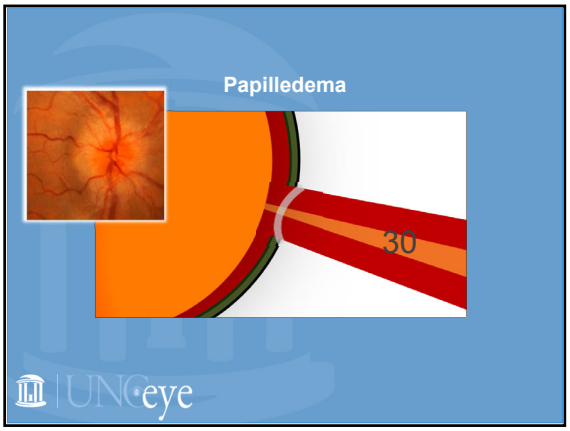
Papilledema
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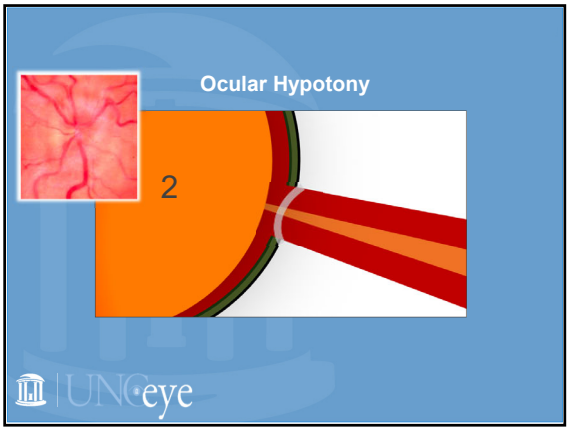
Ocular Hypotony
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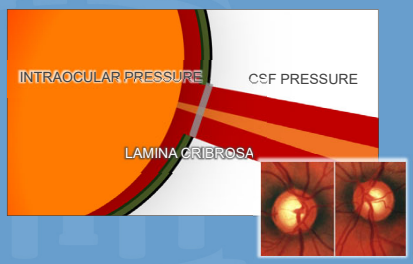
Translaminar Pressure Difference



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A New Theory

- December 15, 1908 during lecture to the Conference of the Military Medical Academy of St. Petersburg, Noishevski raised the question:
  - *"Could it be that the cause of depression papilla of the optic nerve [is] a simple… difference between the pressure inside the eye and inside of the skull, on the assumption that the intraocular pressure, remaining within the normal range, is still more than the intracranial pressure."*
- Noishevski proposed and experimentally proved his hypothesis about glaucoma with pseudonormal pressure:

Courtesy of **Vlademir Reituzov, MD** and **Edward Gamm, MD**

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A New Theory

- In the laboratory of I. Pavlov on January 20, 1910:
  - Black dog named "Gypsy": hole through frontal bone, 10 cm^2 in diameter
  - Observed until February 1910: Gypsy developed "***glaucomatous excavation"***
  - Histologic sections were demonstrated at the St. Petersburg Ophthalmological Society on January 27, 1911

Courtesy of **Vlademir Reituzov, MD** and **Edward Gamm, MD**

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A New Theory

- In the laboratory of I. Pavlov on January 20, 1910:
  - This was highly disputed and largely ignored by many of the prominent glaucoma specialists of the time
  - Many isolated studies and case reports ensued throughout the years
  - *This history came to light in the West through sheer chance!*

Courtesy of **Vlademir Reituzov, MD** and **Edward Gamm, MD**

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Cerebrospinal Fluid Pressure and Glaucoma Reintroduced

- Yablonski (1979):
  - In a cat model, CSFP was lowered to -4 mm Hg
  - One eye cannulated to produce a pressure of 0 mm Hg, while the other eye was unchanged and maintained at a normal pressure

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Cerebrospinal Fluid Pressure and Glaucoma Reintroduced

- Yablonski (1979):
  - After 3 weeks, the uncannulated eye developed optic nerve damage consistent with glaucomatous optic neuropathy
  - The eye that was cannulated and maintained at a low pressure similar to the CSF pressure did not develop optic neuropathy

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Cerebrospinal Fluid Pressure

- Morgan (1995): The influence of cerebrospinal fluid pressure on the lamina cribrosa tissue pressure gradient – *Invest Ophthalmol Vis Sci*
  - CSFP largely determines retrolaminar tissue pressure, therefore, along with IOP, it is of major importance in setting the translaminar tissue pressure gradient
  - Hydrostatic continuity between the optic nerve subarachnoid space and lateral ventricle

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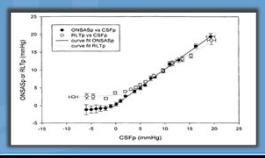
Cerebrospinal Fluid Pressure

- Morgan (1998): The correlation between cerebrospinal fluid pressure and retrolaminar tissue pressure – *Invest Ophthalmol Vis Sci*
  - The TLPG and the retrolaminar tissue pressure (and OSASp) are dependent on CSFP when CSFP is more than -0.5 mm Hg. Below this, **there is no hydrostatic continuity between OSASp and CSFp *(termed the "break point")***



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Cerebrospinal Fluid Pressure

- Morgan (2002): Optic disc movement with variations in intraocular and cerebrospinal fluid pressure – *Invest Ophthalmol Vis Sci*
  - Movement of the optic disc occurs with pressures changes in the low range of the translaminar pressure difference

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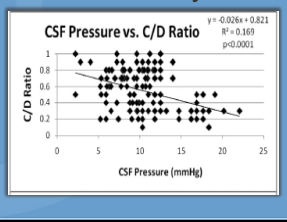
Cerebrospinal Fluid Pressure

- Berdahl (2008): First large-scale retrospective investigation
  - 31,786 patients from Mayo Clinic having undergone LP:
  - **28 POAG patients and 49 controls analyzed**

CSFP is significantly lower in POAG patients compared with non-glaucomatous controls (13.0 mm Hg +/- 4.2 versus 9.2 mm Hg +/- 2.9)



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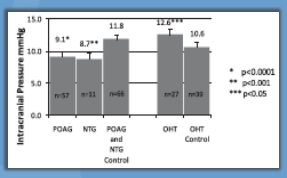
CSFP and Glaucoma: Retrospective Studies

- Berdahl (2008): Follow up retrospective investigation
  - 62,468 patients with LP
  - **57 POAG; 11 NTG; 27 OHT; 105 controls**

POAG:	9.1 mmHg
NTG:	8.7 mmHg
Control:	11.8 mmHg
OHT:	12.6 mmHg
OHT Control:	10.6 mmHg



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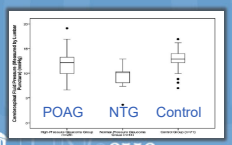
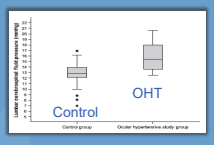
CSFP and Glaucoma: Prospective Studies

- Ren (2010-11): First controlled prospective studies

Prospective Study #1:
- Normal-Tension Glaucoma << High-Pressure Glaucoma < Controls

Prospective Study #2:
- Ocular hypertension >> Control group





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CSFP and Glaucoma

- Big Picture:
  - Normals: normal CSFP
  - POAG: low CSFP
  - NTG: even lower CSFP
    - Explains why IOP reduction is helpful in NTG
  - OHT: higher CSFP compared to normal
    - Counterbalance to IOP

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How important is CSF P to glaucoma?

- If CSFP is important in glaucoma pathogenesis, are there trends in CSFP that explain risk factors for glaucoma?

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R. Rand Allingham, MD (1953-2018)

Cerebrospinal Fluid Pressure Trends

- Fleischman (2012): Cerebrospinal fluid pressure decreases with older age – *PLoS One*
  - 33,932 patients having undergone LP from Mayo Clinic
  - **12,122** met all entry criteria and analyzed

Funding for above study courtesy of… ^^^

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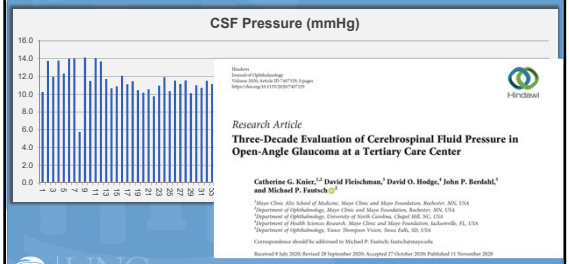
CSFP and Age



Hindawi

Research Article

Three-Decade Evaluation of Cerebrospinal Fluid Pressure in Open-Angle Glaucoma at a Tertiary Care Center

Catherine G. Knier,[1,2] David Fleischman,[3] David O. Hodge,[4] John P. Berdahl,[3] and Michael P. Fautsch[2]

[1]Mayo Clinic Alix School of Medicine, Mayo Clinic and Mayo Foundation, Rochester, MN, USA
[2]Department of Ophthalmology, Mayo Clinic and Mayo Foundation, Rochester, MN, USA
[3]Department of Ophthalmology, University of North Carolina, Chapel Hill, NC, USA
[4]Department of Health Sciences Research, Mayo Clinic and Mayo Foundation, Jacksonville, FL, USA
[5]Department of Ophthalmology, Vance Thompson Vision, Sioux Falls, SD, USA

Correspondence should be addressed to Michael P. Fautsch; fautsch.mayo.edu

Received 8 July 2020; Revised 28 September 2020; Accepted 27 October 2020; Published 11 November 2020

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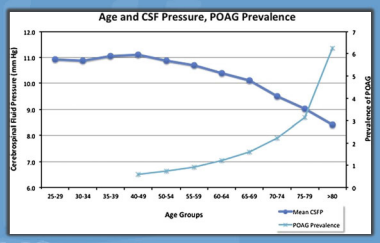
Cerebrospinal Fluid Pressure Trends

- CSF pressure trends and prevalence of glaucoma



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Translaminar Pressure Difference and Glaucoma
Is it really that simple?

- What is the translaminar pressure difference?
- More importantly….
- What is NOT the translaminar pressure difference??

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What is NOT the Translaminar Pressure Difference?

- The translaminar pressure difference is **NOT**:
  - A static number: changes in IOP and CSFp based on positioning, for example
  - IOP minus lumbar spine opening pressure
  - IOP minus intracranial pressure

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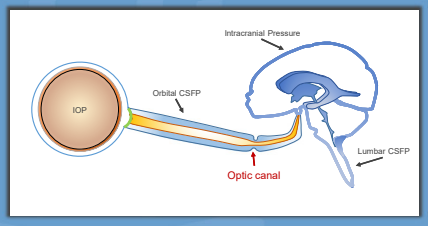
What is NOT the Translaminar Pressure Difference?



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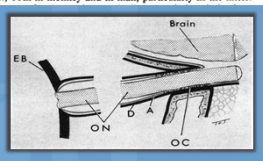
Cerebrospinal Fluid Pressure Relationships

- Hayreh (1964)

orbital part of the sheath. I feel, therefore, that *the region of the optic canal plays a crucial role in the dynamics of conveying the CSFP of the cranial cavity into the optic nerve sheath*, both in monkey and in man, particularly in the latter. Unilateral or



Hayreh SS. Pathogenesis of oedema of the optic nerve (papilloedema): a preliminary report. *Brit J Ophthal* 1964 64:522-43.

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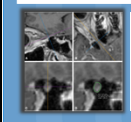
Cerebrospinal Fluid Pressure Relationships

- Bidot (2015 and 2016)

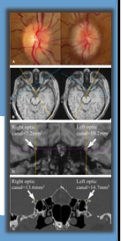
The Optic Canal Size Is Associated With the Severity of Papilledema and Poor Visual Function in Idiopathic Intracranial Hypertension

Samuel Bidot, MD, Lindsay Clough, BA, Amit M. Saindane, MD, Nancy J. Newman, MD, Valérie Biousse, MD, Beau B. Bruce, MD, PhD



Asymmetric Papilledema in Idiopathic Intracranial Hypertension

Samuel Bidot, MD, Beau B. Bruce, MD, PhD, Amit M. Saindane, MD, Nancy J. Newman, MD, Valérie Biousse, MD



Bidot et al. *J Neuro-Ophthalmol* 2015; 35: 31-36.
Bidot et al. *J Neuro-Ophthalmol* 2016; 36: 120-125.

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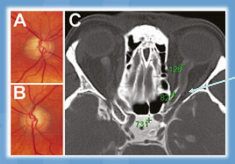
Cerebrospinal Fluid Pressure Relationships

- Killer (2016): Compartmentalization of the orbital CSF space in NTG patients



Look at contrast front

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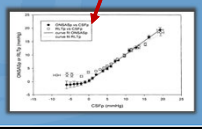
Cerebrospinal Fluid Pressure

- Morgan (1998): The correlation between cerebrospinal fluid pressure and retrolaminar tissue pressure – *Invest Ophthalmol Vis Sci*
  - The TLPG and the retrolaminar tissue pressure (and OSASp) are dependent on CSFP when CSFP is more than -0.5 mm Hg. Below this, there is no hydrostatic continuity between OSASp and CSFp (*termed the* ***"break point"***)



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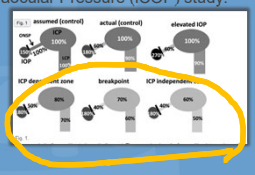
Cerebrospinal Fluid Pressure Relationships

- Hou (2016): Intracranial pressure (ICP) and optic nerve subarachnoid space pressure (ONSP) correlation in the optic nerve chamber: the Beijing Intracranial and Intraocular Pressure (iCOP) study.



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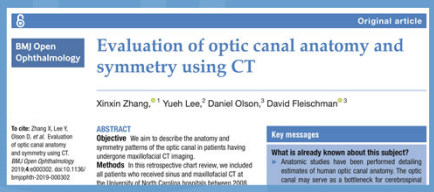
Optic Canal Symmetry

- If optic canal anatomy is important, how likely are normal patients to have asymmetric canals – perhaps explaining asymmetric glaucoma or asymmetric papilledema?



Original article

BMJ Open Ophthalmology

Evaluation of optic canal anatomy and symmetry using CT

Xinxin Zhang,[1] Yueh Lee,[2] Daniel Olson,[3] David Fleischman[3]

To cite: Zhang X, Lee Y, Olson D, *et al*. Evaluation of optic canal anatomy and symmetry using CT. *BMJ Open Ophthalmology* 2019;**4**:e000302. doi:10.1136/bmjophth-2019-000302

ABSTRACT

Objective We aim to describe the anatomy and symmetry patterns of the optic canal in patients having undergone maxillofacial CT imaging.

Methods In this retrospective chart review, we included all patients who received sinus and maxillofacial CT at the University of North Carolina hospitals between 2018

Key messages

What is already known about this subject?

- Anatomic studies have been performed detailing estimates of human optic canal anatomy. The optic canal may serve as a bottleneck for cerebrospinal

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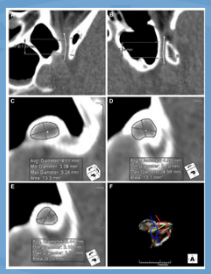
Optic Canal Symmetry



Results Of 335 patients, the mean canal length was 5.61±2.22 mm. The mean minimum area was 11.84±3.11 mm^2. The mean minimum diameter was 3.28±0.55 mm. A total of 39.4% (132/335) of patients had asymmetric canal lengths, 18.8% (63/335) had asymmetric minimum areas, and 12.5% (42/335) had asymmetric minimum diameters. No differences were found between racial groups. The right optic canal was larger than the left (right: 12.12 mm vs left: 11.55 mm, p<0.0001).

Conclusion Optic canal asymmetry is not uncommon. It may affect risk of papilloedema severity, explain cases of unilateral or asymmetric papilloedema and possibly asymmetric glaucoma.

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Let's Catch Up

1. The translaminar pressure difference is the IOP minus the CSFP
2. More specifically, the orbital CSFP, which is not the same as the intracranial CSF pressure
3. Orbital CSFP is different than ICP because of the restriction of the optic canal and the "blind pouch" at the start of the optic nerve
4. Glaucoma may very well be a disease of translaminar imbalance
5. Ocular hypertension patients may have higher CSFP's, thereby protecting them from the harmful effects of increased IOP

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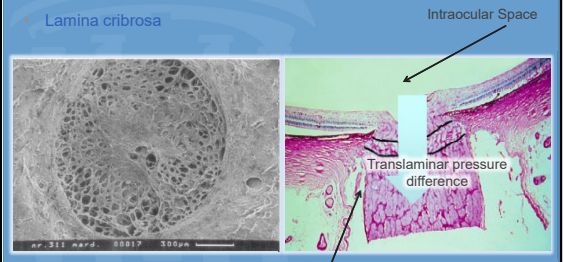
Cerebrospinal Fluid Pressure and Glaucoma

- Lamina cribrosa



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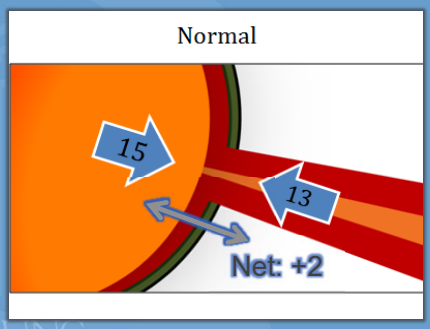
Translaminar Pressure Difference



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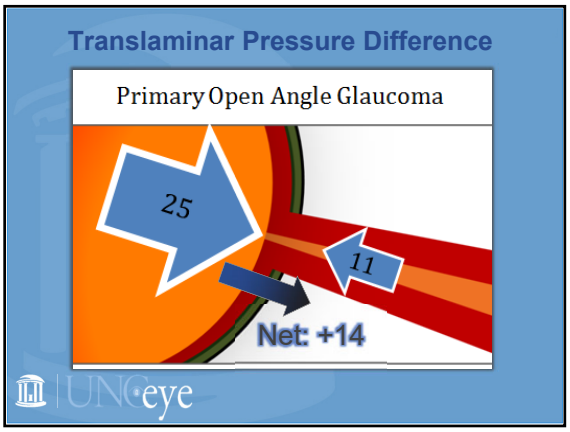
Translaminar Pressure Difference
Primary Open Angle Glaucoma
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Net: +14
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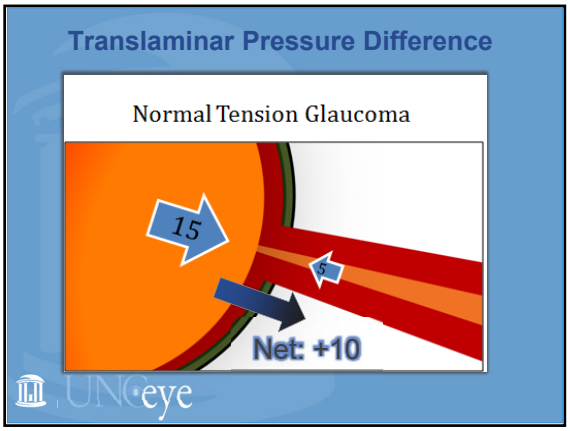
Translaminar Pressure Difference
Normal Tension Glaucoma
15
5
Net: +10
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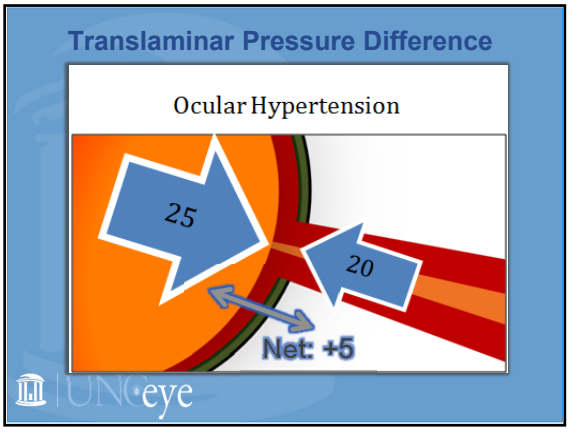
Translaminar Pressure Difference
Ocular Hypertension
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Net: +5
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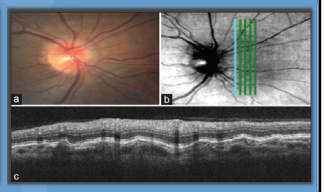
Other Eye Diseases?



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Spaceflight-Associated Neuro-Ocular Syndrome

- First described in 2011 by T. Mader

Comment > Ophthalmology. 2012 Jun;119(6):1290; author reply 1291. doi: 10.1016/j.ophtha.2012.02.024.

Disc swelling and space flight

John Berdahl, David Fleischman, R Rand Allingham, Mike Fautsch

PMID: 22656904 DOI: 10.1016/j.ophtha.2012.02.024

Big grant application here. X!

> Exp Eye Res. 2013 Oct;115:278. doi: 10.1016/j.exer.2012.09.008.

Increasing intraocular pressure as treatment for papilledema

David Fleischman [1], John P Berdahl, Michael P Fautsch, David A Chesnutt, R Rand Allingham

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Idiopathic Intracranial Hypertension

Multicenter Study > Can J Ophthalmol. 2017 Feb;52(1):26-29. doi: 10.1016/j.jcjo.2016.07.021. Epub 2016 Nov 17.

Retrospective analysis of translaminar, demographic, and physiologic parameters in relation to papilledema severity

David Fleischman [1], Jennifer T Perry [2], R Rand Allingham [3], Sandra S Stinnett [3], Gita M Fleischman [4], Syndee J Givre [5], David A Chesnutt [6]

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Holes Ahead

1. While there was a trend towards a statistically significant relationship, overall, the translaminar pressure differential did not explain papilledema severity as expected
2. Is it really all about the pressure?

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Maybe Not the Pressure: The Need for Speed!

Peter Wostyn and colleagues theorized that CSF pressure was likely not responsible for any major effect on the development of or protection against glaucoma, but that CSF flow and velocity was most important.

As the nerve is a highly metabolic tissue, significant waste products are formed and cleared into the CSF space.

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Maybe Not the Pressure: The Need for Speed!

A lack of CSF flow, therefore, would create a buildup of toxic elements that results in optic atrophy.

Fast CSF clearance, on the other hand, would create a hospitable environment for healthy neural tissue, and even increased intraocular pressure would not likely cause damage in these patients.

Visualization of orbital flow by means of **phase contrast** MRI.
Golzan SM, Avolio A, Magnussen J, **Graham SL.**
Annu Int Conf IEEE Eng Med Biol Soc. 2012;2012:3384-7. doi: 10.1109/EMBC.2012.6346691.
PMID: 23366652

Remarkably detected CSF velocities of up to 5cm/s!!!

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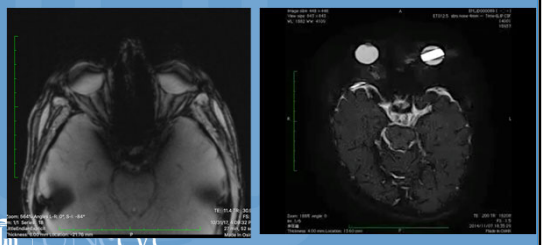
Orbital CSF Imaging

Investigate orbital CSF flow velocities in glaucoma, ocular hypertension, and normals with a 3-Tesla and research 7-Tesla magnet



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Orbital CSF Imaging

Conclusions:

- Unable to replicate Golzan study

- Flow velocities were less than 1 cm/second (in either direction)

- No appreciable difference between OHT/glaucoma/normal could be detected

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Orbital CSF Pressure & Flow

New Research Focus:

Let's figure out orbital CSF pressure

Medium-sized pigs

Lateral orbitotomies to access orbital CSF space while accessing intracranial CSF space, lumbar CSF space

Once access and relationships established, sacrifice the optic canal to create equilibrium in pressure between intracranial compartment and orbital CSF space

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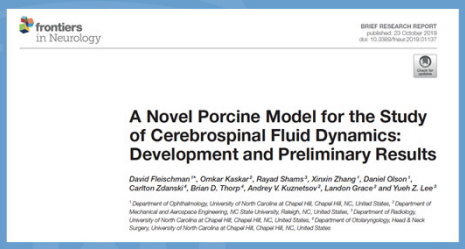
Development of a Model



frontiers in Neurology

BRIEF RESEARCH REPORT
published: 23 October 2019
doi: 10.3389/fneur.2019.01137

A Novel Porcine Model for the Study of Cerebrospinal Fluid Dynamics: Development and Preliminary Results

David Fleischman[1], Omkar Kaskar[2], Rayad Shams[3], Xinxin Zhang[1], Daniel Olson[1], Carlton Zdanski[4], Brian D. Thorp[4], Andrey V. Kuznetsov[3], Landon Grace[2] and Yueh Z. Lee[3]*

[1] Department of Ophthalmology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [2] Department of Mechanical and Aerospace Engineering, NC State University, Raleigh, NC, United States, [3] Department of Radiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [4] Department of Otolaryngology, Head & Neck Surgery, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

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Development of a Model

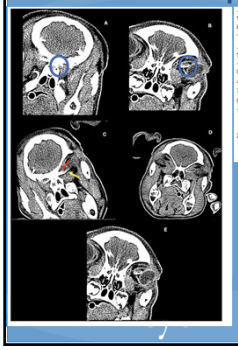

TABLE 1 | Experiment #2: Estimated migration of contrast front vs. time of injection of contrast agent (iopamidol 370).

Experiment #2	
Time from Injection (minutes)	**Location of contrast front**
0	
4	
7	
9	
14	
20	

TABLE 2 | Experiment #3: The pig's head was rotated such that the right orbit was dependent and left orbit was non-dependent.

TABLE 3 | Experiment #3 continued: Following scanning at the 58th min, the head was rotated so that the left orbit was made dependent.

	Head tilt	
Time from Injection (minutes)	**Location of contrast front**	
	Left (Dependent)	
55		
56	63	75.1% inferior, 61.7% superior
57	64	75.5% inferior, 64.8% superior
58	65	83.1% inferior, 66.5% superior
Contrast mig	67	91.1% inferior, 69.3% superior
left orbit, the	69	91.7% inferior, 67.7% superior
superior and	70*	104.2% inferior, 72.6% superior (Bulbous cul de sac filling)
and the right	73*	98.4% inferior, 68.5% superior (Bulbous cul de sac filling)

*Scanning was repeated in the documented intervals and estimated contrast front location described in terms of the percentage of the length of the nerve. The measured linear distance between the optic canal and the right and left globes were 28.91 and 27.55 mm, respectively. *Effectively complete filling.*

Conclusions Thus Far

CSF and maybe its pressure is associated with glaucoma

CSFP is associated with IIH/SANS

CSF moves slowly within the optic nerve

CSF in the orbit is dependent (provided the eye is not moving…)

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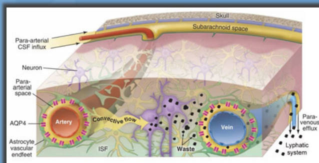
Different Perspective on Role of CSF

This is a system for waste clearance in the central nervous system, first described by Nedergaard and colleagues at the University of Rochester in 2012

Essentially, CSF flows into the paravascular space around cerebral arteries, combines with interstitial fluid and waste products within the parenchyma, and egresses through the venous paravascular spaces back into the CSF space.

The exchange is driven by arterial pulsatility and sleep-induced changes of CNS extracellular spaces (*in particular, stage 3 sleep*).

Glymphatics



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Different Perspective on Role of CSF

Glymphatic flow within the optic nerve may be responsible for the clearance of metabolic waste products and other toxins

But the question is, how does the CSF go into and exit out of the orbital CSF space?

Glaucoma

Evidence for Cerebrospinal Fluid Entry Into the Optic Nerve via a Glymphatic Pathway

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Purpose. The purpose of this study was to determine whether cerebrospinal fluid (CSF) enters the optic nerve via a glymphatic pathway and whether this entry is size-dependent.

Methods. Fluorescent dextran tracers (fluorescein isothiocyanate [FITC]) of four different sizes (10, 40, 70, and 500 kDa) and FITC-ovalbumin (45 kDa) were injected into the CSF of 15 adult mice. Tracer distribution in the orbital optic nerve at 1 hour after injection was assessed in tissue sections with confocal microscopy. Tracer distribution within the optic nerve was studied in relation to blood vessels and astrocytes identified by isolectin histochemistry and glial fibrillary acidic protein (GFAP) immunofluorescence, respectively. Aquaporin 4 (AQP4) immunostaining was performed to assess astrocytic endfeet in relation to CSF tracer.

Results. One hour following tracer injection into CSF, all tracer sizes (10–500 kDa) were noted in the subarachnoid space surrounding the orbital optic nerve. In all cases, 10 kDa ($n = 4/4$) and 40 kDa ($n = 3/3$) tracers were noted within the optic nerve, while 70-kDa tracer was occasionally noted ($n = 1/4$). Tracer found within the nerve was specifically localized between isolectin-labeled blood vessels and GFAP-positive astrocytes or AQP4-labeled astrocytic endfeet. The 500-kDa tracer was not detected within the optic nerve.

Conclusions. To our knowledge, this is the first evidence of a glymphatic pathway in the optic nerve. CSF enters the optic nerve via spaces surrounding blood vessels, bordered by astrocytic endfeet. CSF entry into paravascular spaces of the optic nerve is size-dependent, and this pathway may be highly relevant to optic nerve diseases, including glaucoma.

Keywords: glymphatic, paravascular, perivascular, optic nerve, cerebrospinal fluid, glaucoma

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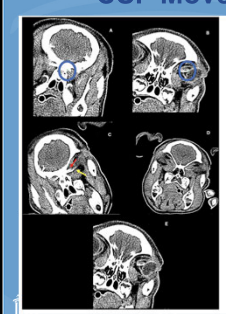
CSF Movement in the Orbit



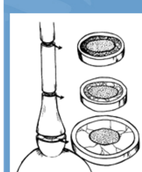


Fig. 5 (Liu and Kahn). Schematic drawing of the optic nerve, its sheath, and the arachnoidal trabeculations. The arachnoidal trabeculations appears to be most dense posteriorly and inferiorly, and sparse anteriorly. There is great individual variation.

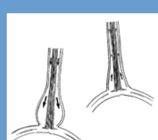


Fig. 6 (Liu and Kahn). Schematic drawing of the bulbous portion of the optic nerve. Cerebrospinal fluid under the intracranial pressure flows in an anterior direction and fills the bulbous portion. As the globe is moved about in the orbit, the bulbous portion is squeezed or massaged by the surrounding orbital tissues. An intermittent higher pressure is created at this point, which reverses the direction of flow.

CSF Movement in the Orbit

What happens during sleep?

What happens during anesthesia?

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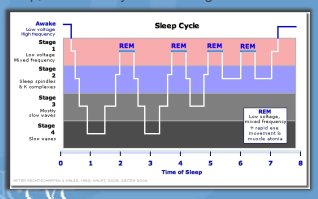
CSF Movement in the Orbit

What happens during sleep?

- During waking hours, natural eye movement likely replenishes orbital CSF

During sleep, there is likely little exchange… until….



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Rapid Eye Movement

Why do we have **Rapid Eye Movement** during REM SLEEP?

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Rapid Eye Movement

Most avian species, all mammals have REMS or paradoxical sleep

Even if….

- Someone is born blind (congenital blindness)
- Someone loses vision

These are the examples that discredit the "*scanning theory*"

So, why do our eyes move around haphazardly when sleeping while the rest of the body is paralyzed?

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Our Theory…

So, why do our eyes move around haphazardly when sleeping while the rest of the body is paralyzed?

Known: Glymphatic clearance is up-regulated by 60% during Stage 3 Sleep (pre-REM)

Mostly Known: CSF likely enters and exits the orbit predominantly through eye movement

Our Theory: REM during Paradoxical Sleep is an evolutionary mechanism to help circulate CSF in and out of the orbit during sleep when the eyes otherwise would be immobile

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Our Theory…

Our Theory: REM during Paradoxical Sleep is an evolutionary mechanism to help circulate CSF in and out of the orbit during sleep when the eyes otherwise would be immobile

Therefore, lack of eye movement would cause damage to the ocular structures over time…

How about **Chronic Progressive External Ophthalmoplegia**?

- The condition is associated with optic nerve atrophy
- Case series of 13 patients at UNC
  - Only patients with long-standing CPEO developed optic atrophy (more details coming soon from Dr. Anne Poulsen and Ayham Abdel)

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Our Theory…

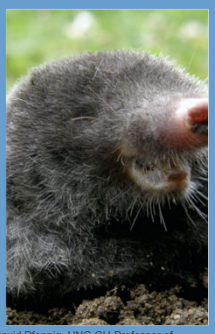
European Mole and Eastern Mole

Nearly sightless

Still maintain paradoxical sleep… BUT:

Evolutionarily denervated cranial nerves to EOMs!

Why would we otherwise bother wasting precious energy if it did not serve an important purpose?*



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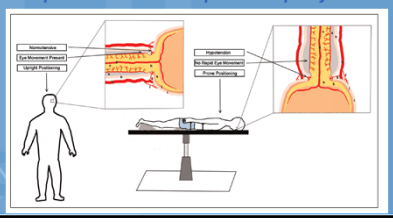
* Discussions with Dr. David Pfennig, UNC-CH Professor of Evolutionary Biology

Our Theory…

Two situations to look at:

REM and Optic nerve health

Periods of ocular immobility such as general anesthesia → *posterior ischemic optic neuropathy*



Our Theory…

REM and Optic nerve health

- In collaboration with Dr. Benjamin Frankfort at Baylor:

C57BL/6 Mouse study:

Botox injections into EOMs of young mice

Follow for one year (approximately half of lifetime)

Sacrifice mice and perform ON axon counts

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Our Theory…

- PION : Pathogenic mechanism
  - Prone positioning for several hours
    - CSF pooling into orbital CSF space
    - Higher local pressures acting on nerve
    - External pressure on pial vessels
    - Patients develop hypotension and blood-loss during surgery
      - Therefore, perfect storm event results in infarction of nerve in area of optic canal
  - Study possibilities:
    - Dynamic nerve imaging with U/S of nerve during spine surgery
  - Countermeasures:
    - Strategic head/body re-positioning for allowing CSF circulation to prevent PION

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In Conclusion

- Imbalance or alterations in CSF can contribute to ophthalmic diseases such as:
  - Glaucoma
  - Spaceflight-associated neuro-ocular syndrome
  - Idiopathic intracranial hypertension
  - Chronic progressive external ophthalmoplegia
  - Posterior ischemic optic neuropathy
- A teleologic perspective to REMS can help us understand the purpose of extra-physiologic functions

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