Pressure Values

Normal-tension Glaucoma Patients with Different Intracranial Pressure Values

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Purpose: To assess differences in neuroretinal rim area (NRA) and ocular hemodynamic parameters in normal-tension glaucoma (NTG) patients with different intracranial pressure (ICP) values.

Methods: 40 patients (27.5% men, 72.5% women) with NTG (age 61.1(11.5) years) were included in the prospective study. During the study the intraocular pressure (IOP), non-invasive IOP, retrobulbar blood flow (RBF) and confocal laser scanning tomography for optic nerve disc (OND) structural changes were assessed. Non-invasive IOP was measured using novel two-depth Transcranial Doppler device (Vitamed UAB, Kaunas, Lithuania), technology based on simultaneous blood flow signals in intracranial and extracranial segments of the ophthalmic artery (OA). RBF was measured using Color Doppler imaging (CDI; Accuvix, Seoul, Korea) in the OA and central retinal (CRA) arteries, assessing peak-systolic (PSV) and end-diastolic (EDV) velocities, and calculated resistance index (RI).

Based on statistical mediana patients were divided into 2 groups for comparison: patients with ICP ≥ and < than 8.3 mmHg. The level of significance p<0.05 was considered significant.

Results: NTG patients had mean ICP 8.8(2.5) mmHg, IOP 13.6(2.1) mmHg, OND size 2.25(0.6) mm2, NRA 1.17(0.35) mm2. Lower ICP was correlated with decreased NRA (r=0.51, p=0.001).

NTG patients with lower ICP (N=20) had significantly lower NRA 1.02(0.3) mm2, than NTG patients with higher ICP (N=20) 1.31(0.3) mm2 (p=0.002), though there were no significant difference in OND size (accordingly, 2.22(0.5) and 2.30(0.6) mm2, p=0.57) and IOP (accordingly, 13.5(2.4) and 13.7(1.8) mmHg, p=0.58). NTG patients with lower ICP had statistically significantly lower OA blood flow velocities (PSV 28.7(8.0), EDV 6.9(3.0) cm/s), compared to NTG patients with higher ICP (accordingly, 35.5(10.2) and 9.4(4.1) cm/s), p=0.04.

Conclusions: Normal-tension glaucoma patients with lower ICP had decreased neuroretinal rim area and ocular hemodynamic parameters, compared to patients with higher ICP. Further studies are needed to analyze the involvement of ICP in normal-tension glaucoma management.

Commercial Relationships: Lina Siaudvytyte, None; Ingrida Januleviciene, None; Akvile Daveckaitė, None; Arminas Raguškas, None; Laimonas Bartusis, None; Alon Harris, None

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Ocular Hemodynamic Parameters and Neuroretinal Rim Area in Normal-tension Glaucoma Patients with Different Intracranial Pressure Values

ARVO 2015 Annual Meeting Abstracts

Program Number: 4126 Poster Board Number: B0135
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The Association of Intraocular Pressure and Visual Function in Papilledema from Idiopathic Intracranial Hypertension

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Purpose: Idiopathic intracranial hypertension (IIH) frequently manifests as papilledema associated with visual loss. Recent studies suggest that increased intraocular pressure (IOP) may counteract the effect of elevated intracranial pressure (ICP) at the level of the lamina cribosa, possibly mitigating damage to axonal transport and subsequent visual function. The current retrospective, cross-sectional, paired-eye, comparison study aimed to test the hypothesis that eyes with increased IOP are associated with superior visual function in those with papilledema secondary to IIH.

Methods: A consecutive series of newly diagnosed patients with IIH from a single Neuro-ophthalmology specialist practice between January 2006 and January 2014 were assessed. Included subjects had baseline bilateral IOP measurements obtained by Goldmann applanation tonometry and concurrent Humphrey Visual Field (HVF) perimeter. Major exclusion criteria were any previous treatment for IIH (ICP-lowering surgery, medical therapy >1 month in duration), a record of any asymmetric ocular comorbidity, or the presence of atrophic papilledema. Patients were divided into two groups for analysis. The first group had symmetric IOPs (+/-1 mmHg) bilaterally whereas the second group had asymmetric IOPs (>=2mmHg) between eyes. All comparisons were performed between each pair of eyes, with the primary outcome being Mean Deviation (MD) as measured by the HVF analyzer.

Results: A total of 77 patients were assessed for inclusion. Forty-four patients were analyzed, with 31 in the symmetric group and 13 in the asymmetric group. Baseline demographic features were similar between both groups. In the group with symmetric IOPs, there was no significant difference in MD (p = 0.89). In the group with asymmetric IOPs, there was a significant difference in MD (p = 0.007). Specifically, the eyes with the higher IOP (mean, 15.77 SD 2.52 mmHg) had less visual loss (MD: -5.72 SD 7.13 dB) compared to the fellow eyes with lower IOP (mean, 12.77 SD 2.92 mmHg) and greater visual loss (MD: -7.04 SD 7.66 dB).

Conclusions: Patients presenting with papilledema from IIH with asymmetric IOPs display better visual function in the eye with higher IOP. This observation suggests that IOP may be a factor in the pathophysiology of visual loss from IIH. Further investigation into this relationship is warranted.

Commercial Relationships: Gary L. Yau, None; Martin W. ten Hove, None

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Correlation between Optic Disc Examination, Symptoms and findings of Intracranial Pressure (ICP) Monitoring for Pediatric Patients and its Clinical Implications

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Purpose: To investigate whether optic disc edema and symptoms of increased ICP (e.g. headache or visual obscurations) correlate with the findings of ICP monitoring in a pediatric population. We predict that findings of ICP monitoring correlate with both disc edema and symptoms.

Methods: A retrospective chart review was performed of Vanderbilt Children’s Hospital records for patients under 19 years old who underwent 24-hour continuous ICP monitoring with an
intraparenchymal Codman ICP monitoring system between 1998 and 2014, and in whom at least 1 year of ophthalmology follow-up was available. 25 patients met entry criteria. Patients were categorized based upon the presence of symptoms suggestive of elevated ICP and disc appearance.

**Results:** None of the 25 patients who underwent continuous intraparenchymal ICP monitoring developed complications from the procedure. Of 8 patients with symptoms but a normal disc on exam, only two patients had elevated ICP; of 9 patients with symptoms and disc edema, 8 had elevated ICP; 3 patients had symptoms with disc atrophy, of which only 1 patient had elevated ICP; 5 patients were asymptomatic with suspected pseudo-disc edema, and all 5 had normal ICP. To evaluate this categorial data, a Chi Squared test was used (p<0.0014). In each patient with elevated ICP, intervention with ventriculoperitoneal shunt followed monitoring. Patients with disc edema compared to patients with normal discs showed a trend toward elevated ICP which was not statistically significant (p=0.2043). The presence of symptoms among patients with disc edema was highly correlated with elevated ICP, and conversely, asymptomatic patients with suspected pseudo-disc edema were highly correlated with normal ICP (p=0.0030). The two-tailed Fisher’s exact test was used to draw statistical comparisons between groups of this study.

**Conclusions:** In asymptomatic patients with suspected pseudo-disc edema, ICP monitoring has the ability to potentially differentiate true disc edema from pseudo-disc edema based upon symptoms. ICP monitoring may also be helpful in determining actual ICP symptomatistics patients with a normal disc exam. This study provides important correlates in guiding decision making for when to initiate ICP monitoring in the pediatric population in the setting of suspected elevated intracranial pressure.

**Commercial Relationships:** Matthew Zhang, None; Matthew Hollar, None; Noel Tulipan, None; Sean Donahue, None

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**Qualitative assessment of cerebrospinal fluid movement in the orbital subarachnoid space: An optimization study**

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**Purpose:** The role of cerebrospinal fluid (CSF) dynamics in diseases of the optic nerve, like glaucoma, is coming under increasing scrutiny. In this study we examine the use of magnetic resonance imaging (MRI) as an approach to evaluate CSF movement and flow patterns within the periorbita subarachnoid space (POSAS) as a function of head and body position.

**Methods:** After informed consent was obtained, 2 healthy male volunteers aged 27 years (volunteer A) and 49 years (volunteer B), were recruited to participate in the optimization of imaging parameters for the purposes of quantitative analysis and characterization of CSF flow in the optic nerve sheath. Subjects were studied using a 1.5-T MRI scanner (EXCELART/Vantage; Toshiba, Tochigi, Japan) equipped with quadrature-detected –Head SPEEDER phased array coils (5 channels). CSF fluid movement within the POSAS was studied using cardiac-gated, non-contrast MRI spin labeling, time–spatial labeling inversion pulse (Time-SLIP) with single-shot fast spin echo (SS-FSE) and conventional FSE techniques. The patients were positioned in supine, right- and left-lateral decubitus, and prone positions.

**Results:** POSAS was consistently asymmetric in subject A and symmetric in subject B. The POSAS was consistently larger in the prone position compared to the supine position in both subjects. No significant difference was grossly noted in both lateral decubitus positions. CSF in the POSAS demonstrated movement in response to eye motion. In a static position, CSF movement was detected by Time-SLIP imaging, but was not pulsatile. Motion artifact and small target size reduced image quality.

**Conclusions:** This pilot study suggests that CSF movement in ostensibly normal subjects occurs in response to gravity and is motion-dependent. This supports the notion that CSF within the optic nerve sheath moves, similar to other areas within the subarachnoid space. We also noted that the POSAS symmetry in ostensibly normal subjects varies. The results of this optimization study will be used to quantify these findings and to begin looking at a larger number of subjects, both normal and those with diseases that affect the optic nerve like glaucoma.

**Commercial Relationships:** David Fleischman, None; Mitsue Miyazaki, None; Shinya Yamada, None; R R. Allingham, None

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**Presentation Time:** 8:30 AM–10:15 AM

**How accurate are cerebrospinal fluid pressure estimates using a formula derived from clinical data?**

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**Purpose:** There is growing interest in the role of cerebrospinal fluid pressure (CSFP) as a contributing factor in the pathogenesis of glaucoma. Currently, the only known way to measure CSFP is by lumbar puncture, an invasive procedure. Recently, a method to estimate CSFP using a regression formula was proposed by Jonas et al, PLos One, 2014. We compared this formula with one of our own design using a large medical record dataset.

**Methods:** The regression formula proposed by Jonas et al, derived from a Chinese dataset in Beijing (CSFP[mm Hg] = 0.44 x Body Mass Index[kg/m2] + 0.16 x Diastolic Blood Pressure[mm Hg] – 0.18 x Age[Years] – 1.91) was tested on a Mayo Clinic database containing the medical records of patients having undergone lumbar puncture at the Mayo Clinic (Rochester, MN) between 1996 and 2010 (n = 4378). Half of the patients were selected randomly to comprise a training sample and the remaining patients were used for validation. Using the training sample, a new general linear model was derived with similar physiologic parameters to those utilized by Jonas et al and fit to the validation sample to test CSFP prediction. Intraclass correlation (ICC) was used to assess predicted and actual CSFP in the validation data set.

**Results:** The Beijing study’s ICC between training and validation group was 0.71. The Beijing regression equation poorly predicted CSFP in the Mayo dataset (ICC=0.14 [0.11-0.17]). The regression formula obtained from the Mayo training set was: CSFP[mm Hg] = 9.620 + 0.080 x Body Mass Index[kg/m2] – 0.042 x Age – 0.926 x Sex[F] + 0.0262 x Diastolic blood pressure[mm Hg]. The ICC between Mayo predicted and actual CSFP in the validation sample was 0.28 (95% CI=0.24, 0.32).

**Conclusions:** The equation derived for predicting CSFP from a prospective study in Beijing, China fared poorly against a large, retrospective dataset from the Mayo Clinic. The Mayo regression formula performed better, but still failed to accurately predict CSFP. The possible differences may be due to the retrospective nature of the Mayo Clinic dataset, differences in the populations studied, and differences in LP technique. We conclude that caution should be exercised in using estimated CSFP derived from clinical data.
Dynein, Kinesin and Morphological Changes in Optic Nerve Axons in a Rat Model with Cerebrospinal Fluid Pressure Reduction
Qian Liu, Zheng Zhang, Ningli Wang. Beijing Institute of Ophthalmology, Beijing Tongren Hospital, Beijing, China.

**Purpose:** To examine the influence of experimentally reduced cerebrospinal fluid pressure (CSFP) as compared to elevated intraocular pressure (IOP) on axonal morphology and motor proteins in retinal ganglion cells (RGCs).

**Methods:** The experimental study included 30 rats which underwent cerebrospinal fluid drainage for 6 hours, 30 rats which unilaterally underwent IOP elevation for 6 hours, and 30 rats in a control group with changes neither in IOP nor CSFP. Six hours after baseline, the animals were sacrificed and the eyes were histologically and immunohistochemically examined.

**Results:** Both, in the high-IOP group and in the low-CSFP group as compared to the control group, RGC axons became abnormally dilated and accumulating vesicles. The high-IOP group and the low-CSFP group as compared to the control group showed immunohistochemically an accumulation of dynemin IC at the optic nerve and retinal ganglion cells (RGCs).

**Conclusions:** Sustained ICP reduction caused a decrease in RGCs and optic nerve axons in the rat IVC model. The rat IVC model can be an effective tool to investigate and establish the role of ICP as an important contributory factor in the pathophysiology of glaucoma.

**Commercial Relationships:** Uttio Roy Chowdhury, None; Bradley H. Holman, Michael P. Fautsch.

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**Presentation Time:** 8:30 AM–10:15 AM

Optic nerve and retinal ganglion cells (RGCs).

**Purpose:** Intracranial pressure (ICP) has recently gained importance as a risk factor for glaucomatous neuropathies. We have developed a rat intraventricular cannula (IVC) model which allows lowering and real-time monitoring of ICP for extended periods of time. The purpose of this study was to evaluate the health of retinal ganglion cells (RGC) and optic nerve axons following long-term lowering of ICP.

**Methods:** Stainless steel cannulae (20 gauge) were surgically implanted in Brown Norway rats (n=3, retired breeders, age ≥8 months, weight >300 g). Through a flexible metal tether, the cannula was connected with PE60 tubing to a 3 way stopcock and a pressure transducer. A syringe column containing artificial cerebrospinal fluid (CSF) was attached in parallel. ICP was reduced by lowering the syringe column below head level in 1-2 cm increments. Flat mounted retinas were stained and RGCs counted and averaged from 12 specific predetermined regions across 4 quadrants. Optic nerve axons were counted and averaged from 3 separate toluidine blue stained 0.5 µm plastic sections of optic nerve head at 1 mm beyond the globe. All values were compared to either a normal rat or a sham control, where the syringe column was maintained at head level.

**Results:** ICP was reduced by 53.7 ± 3.3% for approximately 60 days. Reduction of ICP was well tolerated by all rats with no apparent discomfort or weight loss. Experimentally lowered ICP caused significant decrease in RGC number when compared to normal (OD: 36.8 ± 22.8%, OS: 28.3 ± 19.1% reduction, p<0.05) or sham control (OD: 33.2 ± 15.8% reduction, p<0.05) or sham control (OD: 36.8 ± 22.8%, OS: 28.3 ± 19.1% reduction, p<0.05). This reduction was also reflected in a lowered axonal density compared to normal (OD: 24.5 ± 11.7%, OS: 26.8 ± 10.0% reduction) or sham control (OD: 33.2 ± 3.0%, OS: 14.2 ± 14.4% reduction). In rats where ICP was lowered, fibrotic and compressed axons were observed in the optic nerve.

**Conclusions:** Sustained ICP reduction caused a decrease in RGCs and optic nerve axons in the rat IVC model. The rat IVC model can be an effective tool to investigate and establish the role of ICP as an important contributory factor in the pathophysiology of glaucoma.

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**Presentation Time:** 8:30 AM–10:15 AM

Dynein, Kinesin and Morphological Changes in Optic Nerve Axons in a Rat Model with Cerebrospinal Fluid Pressure Reduction
Qian Liu, Zheng Zhang, Ningli Wang. Beijing Institute of Ophthalmology, Beijing Tongren Hospital, Beijing, China.

**Purpose:** To examine the influence of experimentally reduced cerebrospinal fluid pressure (CSFP) as compared to elevated intraocular pressure (IOP) on axonal morphology and motor proteins in retinal ganglion cells (RGCs).

**Methods:** The experimental study included 30 rats which underwent cerebrospinal fluid drainage for 6 hours, 30 rats which unilaterally underwent IOP elevation for 6 hours, and 30 rats in a control group with changes neither in IOP nor CSFP. Six hours after baseline, the animals were sacrificed and the eyes were histologically and immunohistochemically examined.

**Results:** Both, in the high-IOP group and in the low-CSFP group as compared to the control group, RGC axons became abnormally dilated and accumulating vesicles. The high-IOP group and the low-CSFP group as compared to the control group showed immunohistochemically an accumulation of dynemin IC at the optic nerve.
nerve head and retina, a reduction in kinesin HC immunoreactivity in the optic nerve fiber axons. As a corollary, Western blot analysis showed an elevation of dynein IC protein levels in the optic nerve head and retina, and a Decrease in kinesin HC protein levels in the optic nerve.

Conclusions: The results suggest that experimental models with an acute IOP rise or with an acute CSFP reduction showed similar morphologic changes in the retinal ganglion cell axons and similar immunohistochemical changes in the levels of the axonal motor proteins kinesin HC and dynein IC. It supports the hypothesis that disrupted axonal transport in RGC may be involved in the pathogenesis of optic neuropathy in normal-pressure glaucoma.

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Axonal Transport in the Rat Optic Nerve Following Short-Term Reduction in Cerebrospinal Fluid Pressure or Elevation in Intraocular Pressure
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Purpose: To examine the influence of short-term reduction in cerebrospinal fluid pressure (CSFP) as compared to short-term elevation in intraocular pressure (IOP) on axonal transport.

Methods: The study included 111 adult Sprague-Dawley rats. For six hours, IOP was elevated to 40mmHg (IOP40-study-group) (n=27,right eyes), IOP was increased to a value of 25mmHg below the mean blood pressure (“PP25-study-group”) (n=27,right eyes), or cerebrospinal fluid pressure was reduced by continuous aspiration of cerebrospinal fluid (“Low-CSFP-study-group”) (n=27). A “sham control group” (with a trocar in cisterna magna without cerebrospinal fluid release) included 24 rats. The left eyes of the IOP40-study-group and PP25-study-group served as additional “control group”. The orthograde axonal transport was examined by intravitreally injected rhodamine-ß-isothiocyanate, the retrograde axoplasmic flow was assessed by fluorogold injected into the superior colliculi.

Results: At 24hours after baseline, the intensity of RITC staining of the optic nerve was significantly (P<0.05) lower in the IOP40-study-group, PP25-study-group and Low-CSFP-study-group than in the control groups. At six hours after the fluorogold injection, fluorogold fluorescence was significantly lower in the IOP40-study-group, the PP25-study-group and the Low-CSFP-study-group than in the control groups. At 5 days after baseline, fluorogold fluorescence no longer differed significantly between the IOP40-study-group or the Low-CSFP-study-group and the control groups.

Conclusions: Both, short-term lowering of CSFP and short-term rise in IOP, were associated with a disturbance of both the orthograde and retrograde axonal transport. The finding supports the notion of an association between abnormally low CSFP and optic nerve damage.

Staining of Retinal Ganglion Cells by Fluorogold on Retinal Flat Mounts after Injection of Fluorogold in Both Superior Colliculi in Rats of the Control Group (A), in Rats with a Short-Term (6 Hours) Elevation of Intraocular Pressure to 40 mmHg (B), in Rats with a Short-Term (6 Hours) Reduction of the Ocular Perfusion Pressure to 25mmHg (C), in Rats of a Sham Control Group (D), and in Rats with an Experimental Short-Term (6 Hours) Reduction in Cerebrospinal Fluid Pressure (E), Imaged at Six Hours after Baseline; F: Quantitative Analysis of the Retrograde Axonal Transport Assay.

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