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Effects of Acute Intracranial Pressure Changes on Optic Nerve Head Morphology in Humnans and Pig Model

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EFFECTS OF ACUTE INTRACRANIAL PRESSURE CHANGES ON OPTIC NERVE HEAD MORPHOLOGY IN HUMANS AND PIG MODEL

by

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The optic nerve head (ONH) is located at the interface of intracranial and intraocular compartments. It is comprised of lamina cribrosa (LC), a fenestrated connective tissue tethered to the posterior sclera across the scleral canal. Since LC is exposed to intraocular pressure (IOP) anteriorly and intracranial pressure (ICP) posteriorly, it is an ideal site for noninvasively detecting intracranial pressure (ICP) fluctuation. We hypothesized that the pressure differential between IOP and ICP across LC, will determine LC position and meridional diameter of scleral canal (also called Bruch's membrane opening- BMOD). We tested our hypothesis in 19 human subjects undergoing medically necessary lumbar puncture (LP) to lower ICP and 6 anesthetized pigs, whose ICP were increased in 5mm Hg increments using lumbar drain. We imaged the ONH using Optical Coherence Tomography (OCT) and measured IOP and ICP at baseline and after each intervention. We measured the following ONH morphological parameters: BMOD, anterior LC depth (ALCD) and retinal thickness from the OCT images. We modeled the effects of acute ICP changes on ONH morphological parameters using AVOVA for human study and generalized linear model with fixed intercepts for the pig study. We found that there was no significant effect of acute ICP changes on ONH morphological parameters in both humans and pigs. We conclude that the LC is resistant to displacement across large changes of ICP. Proposed mechanisms include compensatory change in IOP, and non-linear or non-monotonic effects of IOP and ICP across the LC.

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ICP: Intracranial pressure

ONH: Optic nerve head morphology

ONS: Optic nerve sheath

LP: Lumbar puncture

LC: Lamina cribrosa

OCT: Optical Coherence Tomography

EDI: Enhanced depth imaging

IOP: Intraocular pressure

CSF: Cerebrospinal fluid

OP: Opening pressure

CP: Closing pressure

BMOD: Bruch's membrane opening diameter

ACLD: Anterior lamina cribrosa depth

pBM: peri-papillary Bruch's Membrane

Chapter 1: Introduction

Intracranial pressure (ICP) measurement is important in management of catastrophic neurological conditions (traumatic brain injury and intracranial hemorrhage) as well as chronic diseases such as idiopathic intracranial hypertension and normal pressure hydrocephalus. Current methods for ICP measurement, such as external ventricular drainage, parenchymal monitoring or lumbar puncture are invasive. These methods provide accurate ICP measurements, but may cause serious complications, such as chronic pain, infections and neurological deficits. Moreover, these methods can only be performed in clinical settings by personnel who have expertise in performing these procedures. Thus, there is a great need to develop non-invasive methods for ICP estimation. The anatomic and physiologic relationship between the intracranial and orbital compartment as described below, make the optic nerve head (ONH) an ideal site for non-invasive biomarkers for acute ICP changes.

The ONH is comprised of a fenestrated band of connective tissue called lamina cribrosa (LC) tethered to the sclera at its posterior opening called scleral canal or Bruch's membrane opening (BMO). The neurovascular structures of the globe-axons, central retinal artery and vein transit through this opening into the retrobulbar optic nerve (Figure 1).

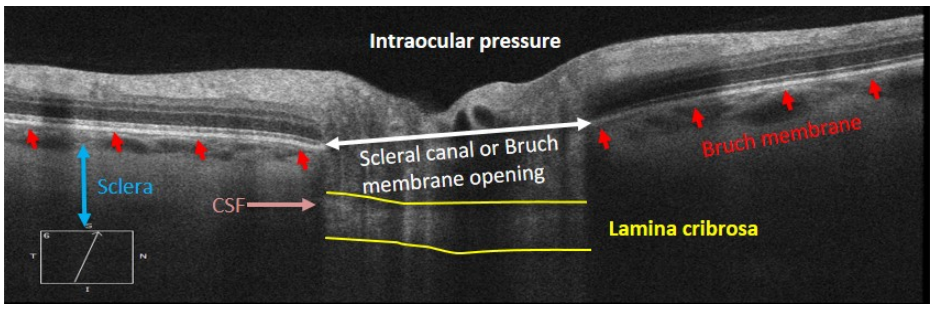

Figure 1: Anatomy of the optic nerve head as seen on optical coherence tomography imaging

The optic nerve is enclosed by a CSF filled meningeal tissue called the optic nerve sheath (ONS), which maintains hydrostatic continuity with the intracranial subarachnoid space. The ONS inserts into the posterior sclera and transmits the ICP to the ONH (Hayreh, 1984). Since the LC is exposed to the intraocular pressure (IOP) anteriorly and the ICP posteriorly, a pressure gradient called translaminar gradient (TLPG), defined as the difference between IOP and ICP, is created across the LC, (Morgan *et al.*, 1998) (Figure 2).

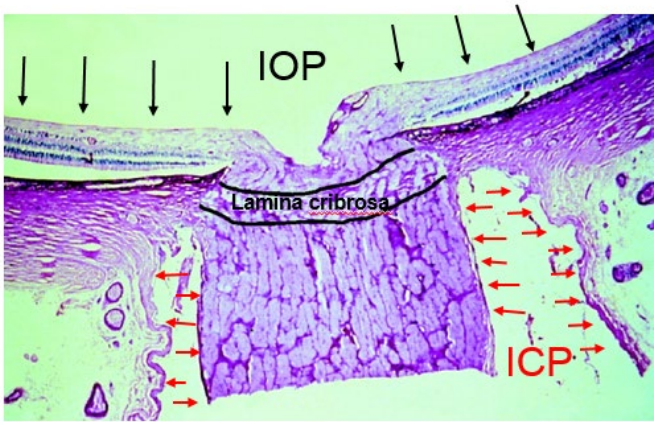

Figure 2: Translaminar pressure gradient (Modified from Jost B. et. al. Invest. Ophthalmol. 2003)

The impact of these two pressure loads on the ONH are not similar. Biomechanical models of the ONH show that the IOP produces a pressure load perpendicular to the inner surface of eye wall, generating an in-wall circumferential stress known as the hoop stress which pulls the lamina cribrosa taut across the scleral canal, similar to a trampoline pulled taut across the steel frame (Downs *et al.*, 2008). Mathematical models show that reduced IOP produces anterior LC displacement and scleral canal narrowing through reduced hoop stress, while increased ICP, will produce anterior LC displacement and increased diameter of scleral canal through its effect on the posterior globe (Tong *et al.*, 2019).

The biomechanical effects of chronic ICP elevation on the ONH are well known to clinicians. Papilledema or ONH swelling occurs due to increased optic nerve tissue pressure resulting in axoplasmic stasis and intraneuronal edema (Hayreh, 1977). Since this process occurs over days to weeks, papilledema is not a reliable indicator of acute ICP increase (Selhorst *et al.*, 1985; Steffen *et al.*, 1996).

There is paucity in literature for studies evaluating the effects of acute ICP changes on ONH morphology. In 35 rhesus monkeys, Hayreh produced acute ICP elevation at the rate of 5 mm Hg every 5 minutes to 40-50 mm Hg by injecting normal saline into the cerebello-medullary cistern. He did not observe acute changes of the ONH using ophthalmoscopy such as edema or hemorrhage (Hayreh, 1968; Hayreh, 2016). In a subsequent study, Hayreh studied ONH morphology using stereoscopic color fundus photo images in rhesus monkey whose ICP was elevated using intracranial balloons. He found early ONH changes such as mild optic disc edema in 30% of animals within 24 hours and 50% within 48 hours (Hayreh, 1977; Hayreh, 2016). Clinically visible changes on ophthalmoscopy (optic disc hyperemia, striation of the peripapillary nerve fibers) were not visible till 3-7 days following ICP elevation (HAYREH, 1964). In a more recent study, Morgan et al. showed that acute ICP elevation in dogs caused immediate anterior displacement of the optic disc surface using confocal scanning laser tomography (Morgan *et al.*, 2002). With further advances in ocular imaging such as Optical Coherence Tomography (OCT), there is now renewed interest in quantifying ONH morphological changes following acute ICP changes.

The OCT uses a technique called low coherence interferometry to non-invasively image and quantify tissue parameters of the retina and optic nerve with an axial resolution of 3-5 microns. Using OCT imaging, patients with papilledema secondary to chronic ICP elevation, were noted to have an asymmetric anterior deformation of peripapillary retina (Bruch's membrane layer) (Kupersmith *et al.*, 2011). After ICP was lowered through surgical or medical intervention, this anterior ONH deformation resolved with return of the natural "V-shape" (Sibony *et al.*, 2014). Similar effects of ICP changes were not seen in patients with non-edematous optic discs. In a study of 16 eyes of 8 non-glaucomatous subjects undergoing lumbar puncture (LP) to lower CSF pressure, there was no change in the ONH morphology on OCT imaging at 5, 60 and 360 minutes

after LP. Notably, in this study, CSF closing pressure was not measured and a maximum of 2.5 cc of CSF volume was removed, producing very small ICP changes (Poli *et al.*, 2017). In another study, 5 subjects with idiopathic intracranial hypertension, a chronic condition with high ICP in young, obese, otherwise healthy patients, had ONH imaged by OCT before and after LP. All eyes showed small but statistically insignificant changes of retinal nerve fiber layer thickness, scleral canal opening and papillary height and a significant change of the Bruch's membrane angle using OCT imaging. This study had small sample size and methodological limitations that prevent generalization (Anand *et al.*, 2016).

Although sparse, the available literature supports our hypothesis that acute ICP changes will alter the TLPG, resulting in measurable changes in the ONH morphology defined by the position of LC and diameter of scleral canal or BMO (BMOD) (Figure 3). Increased ICP should reduce TLPG resulting in an anterior shift of LC and reduction of the BMOD through reduced circumferential scleral canal hoop stress. ICP reduction should produce a posterior shift of LC through increased TLPG and increased BMOD through increased scleral canal hoop stress. We tested this hypothesis in a cohort of patients undergoing lumbar puncture (ICP reduction) and in an animal model of elevated ICP.

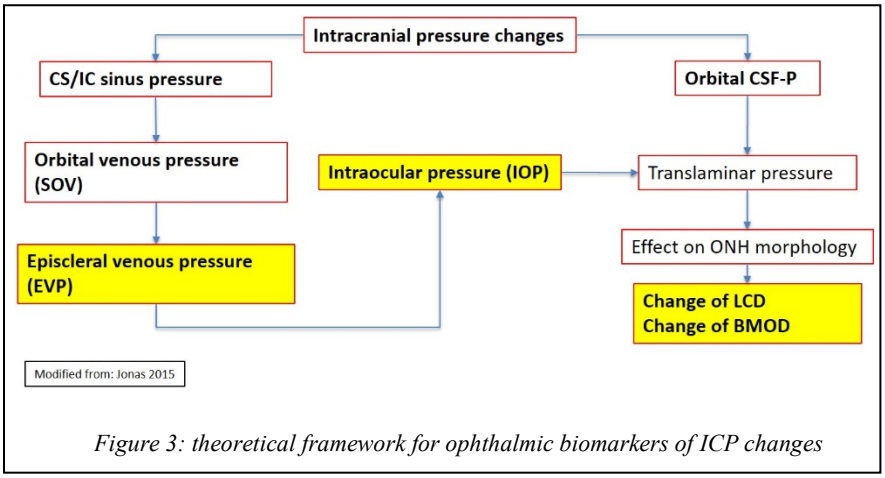

Figure 3: theoretical framework for ophthalmic biomarkers of ICP changes

Chapter 2: Methods

Two different interventional studies were conducted to assess the effects of acute ICP changes on the ONH. The University of Nebraska Medical Center's Institution Review Board and Institutional Animal Care and Use Committee reviewed and approved the human and animal study protocols respectively.

Lumbar puncture study: Nineteen consecutive human subjects scheduled for a medically necessary lumbar puncture (LP) were enrolled after a signed written consent was obtained. These subjects were being evaluated for multiple sclerosis (8), idiopathic intracranial hypertension (5), dementia (4), neuropathy (1) and headache (1). All LP procedures were performed by a single expert neurologist in the left lateral decubitus position using standard clinical methods. The head, neck and extremities were relaxed for CSF opening and closing pressure measurements, obtained using a column manometer. CSF pressure was defined as the height of the CSF column in the manometer as it oscillates about a mean. The following parameters were assessed before and 30 minutes after LP:

Intraocular pressure: IOP was measured using iCare rebound tonometer in the sitting position by a single experienced ophthalmologist. IOP was defined as the average of 2 measurements which were within 2mm Hg of each other. If there was a difference of greater than 2 mm Hg between measurements, a third reading was obtained. The median value was used as IOP value.

Ophthalmoscopic examination by 2 masked experienced ophthalmologists to characterize disc margins, presence of papilledema and spontaneous venous pulsation.

Optic disc imaging: Using spectral domain optical coherence tomography (SD-OCT; Cirrus HD-OCT (Carl Zeiss Meditec Inc.)), twelve radial scans with enhanced depth imaging (EDI)

centered on the ONH were obtained. Each B-scan was acquired at 938× 625 pixel and an aspect ratio of 0.5 (Fig.1B). Optic disc cube (6 mm by 6mm; 200 x 200 scan) was used to obtain optic disc morphological parameters and the peri-papillary retinal nerve fiber layer thickness (RNFL) using the proprietary software provided by Carl-Zeiss Meditec Inc. The pre LP images were used as reference for the post LP images for all subjects.

Pig model study: We used a well-established pig model of acute ICP elevation due to comparable intra-cranial, intra-orbital and ocular anatomy as well as surgeon experience with lumbar and intracranial CSF access in this species (Twedt, 2017). Seven female domestic pig (*Sus domesticus*) weighing between 65-75 kg were used to study the effect of acute ICP changes on the ONH. A lumbar drain and an intraparenchymal ICP transducer (Camino, Integra LifeSciences Corporation, Plainsboro, NJ, USA) was placed in all pigs by an experienced neurosurgeon. The lumbar drain was connected to a fluid bag with an adjustable flow using a 3-way stopcock, while the ICP was monitored through the intraparenchymal pressure transducer placed in the frontal lobe through a burr hole in the skull (Figure 3). We excluded 1 pig due to difficulty in placing the lumbar drain and the intra-parenchymal pressure transducer resulting in inaccurate waveforms. Femoral lines were inserted to monitor blood pressure. After baseline measurements, ICP was slowly elevated in increments of 5-10 m Hg to a maximum of 40 mm Hg, by adjusting the fluid flow. ICP was allowed to stabilize (±2 mm Hg) for 10 minutes before the following measurements were obtained:

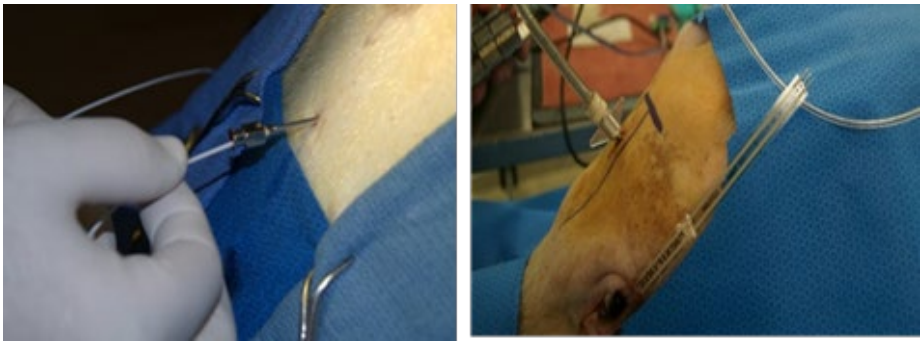

Figure 4: Lumbar drain (left) and parenchymal pressure monitor (right) being inserted in an anesthetized pig

Intraocular pressure: IOP was measured in the right eye using pneumatonometry (Model 30, Reichert USA), by experienced glaucoma researchers (Eisenberg *et al.*, 1998). Two measurements were obtained at each ICP level. If there was a difference of greater than 2 mm Hg between the 2 measurements, a third reading was obtained. The median value was used as the measurement for that ICP level.

Optic disc images: The left optic disc was imaged using a SD-OCT (Spectralis, Heidelberg, Germany). We obtained 12 radial enhanced depth images (EDI) centered on the optic disc) at baseline, which was used as the reference image for all subsequent OCT imaging at each ICP level.

Image analysis: All 12 radial scans from both eyes of the human subjects and the left eye of the pig model were eligible for analysis if image signal quality was 7 or greater. The images were downloaded as TIFF images, assigned a code and randomized prior to analysis using ImageJ 1.50i

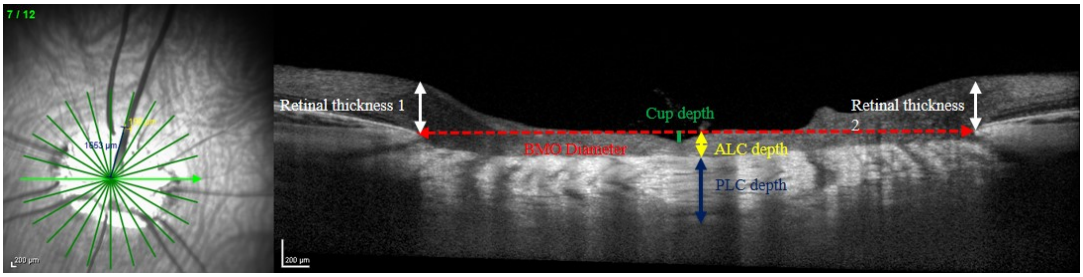

Figure 5: Optic nerve morphological parameters measured on OCT images

(National Institutes of Health, USA). Two trained, masked graders independently performed segmentation of ONH structures, identified the opening of the Bruch's membrane, anterior lamina cribrosa surface and measured the diameter of Bruch's membrane opening (BMOD) and anterior lamina cribrosa depth (ALCD). Additional parameters such as posterior lamina cribrosa depth, cup depth and retinal thickness (defined as the thickness to the internal limiting membrane at either edge of the BMO) was also measured in the pig images.

If discrepancy between the 2 graders was greater than 10% of parameter average, a third expert grader independently analyzed the images. If the discrepancy between any 2 graders was within 10% of parameter average, an average between the 2 graders was used as the parameter value; else the image parameter was classified as ungradable. Intra-grader reliability was tested by having each grader grade the same image 5 times at 2 hours' interval.

Statistical methods: The ONH parameters (ALCD, BMOD and retinal thickness) were the primary outcome measures, while cup volume/depth, spontaneous venous pulsations were secondary outcome measures. Sample size for the LP study was calculated using data from a proof of concept (unpublished) study by our group. In 20 normal volunteers performing Valsalva, we found that subjects had a change in anterior lamina cribrosa depth of approximately 20 µm with a standard deviation of 14 µm. A sample size of 28 eyes would achieve 80% power to detect a difference of 15 µm difference in the ALCD with an estimated standard deviation of 20 µm at a significance level (alpha) of 0.05 using two-sided one-sample t-test. Since the pig study was exploratory, a sample size was not calculated.

Inter-and intra-grader reliability was assessed by measuring accuracy, precision and intra-class correlation (ICC). Summary statistics are provided for the parameters using mean, standard deviation and range for continuous variables and percentages for nominal variables. The influence of ICP on ONH parameters was determined as follows: For the lumbar puncture study, repeated measures ANOVA was used to evaluate differences in ONH parameters over time (Pre vs. Post procedures) in both the right and left eyes. Covariates to explain linear sources of variation include gender, age, body mass index, and changes in ICP and IOP. For the pig model, change in optic nerve parameters was modeled with a fixed effect model for longitudinal data. Slopes were evaluated to determine if changes in ICP were associated with changes in

outcomes. The effect of blood pressure and IOP at each ICP level was controlled in the model. SAS statistical software (SAS USA) was used for analysis.

Chapter 3: Results

Image analysis: 1224 OCT images (864 human eye and 360 pig eye images) were analyzed by the graders. Images of poor quality (signal quality <7) and those with discrepancy > 10% between graders were excluded from analysis (Table 1).

Table 1: Imaging characteristics

	Variables	Excluded values N (%)	Inter-grader reliability	Intra-grader ICC
Humans (864 images)	BMOD	108 (12.5%)	ICC: 0.97 Precision coefficient: 0.97 Accuracy coefficient: 0.99	0.99
	LCD	209 (24%)	ICC: 0.80 Precision coefficient: 0.81 Accuracy coefficient: 0.98	0.98
Pig model (360 images)	BMOD	64 (17%)	ICC: 0.78 Precision coefficient: 0.81 Accuracy coefficient: 0.97	0.99
	Cup depth	78 (21%)	ICC: 0.83 Precision coefficient: 0.83 Accuracy coefficient: 0.99	0.98
	ALCD	88 (24%)	ICC: 0.78 Precision coefficient: 0.79 Accuracy coefficient: 0.98	0.99
	PLCD	133 (37%)	ICC: 0.56 Precision coefficient: 0.65 Accuracy coefficient: 0.87	0.77
	RT1	62 (17%)	ICC: 0.80 Precision coefficient:0.81 Accuracy coefficient: 0.99	NA
	RT2	83 (23%)	ICC: 0.73 Precision coefficient:0.78 Accuracy coefficient: 0.94	NA

Lumbar puncture study: Table 2 describes the baseline characteristics for the human cohort. There were no significant baseline inter-ocular differences for IOP, RNFL, cup volume, disc area or rim area. Four subjects (8 eyes) had papilledema at baseline. The CSF opening pressure showed a significant correlation with age (Pearson correlation coefficient -0.64 (p=0.001)) and BMI (Pearson correlation coefficient 0.72 (p=0.003)).

Table 2: Baseline data for the cohort of patients undergoing lumbar puncture

Variable	Mean (standard deviation)	Range
Age	44.4 (15) years	19-71 years
BMI	31 (9)	15.8- 51.3
CSF opening pressure	15.7 mm Hg	3.7- 31 mm Hg
CSF closing pressure	8.2 (5.2) mm Hg	1.1-14.3 mm Hg
CSF-pressure change	7.5 (5) mmHg	2.5-19.3 mm Hg
IOP (Right eye)	13.8 (3.8) mm Hg	9.5-25 mm Hg
IOP (Left eye)	13.6 (3.3) mm Hg	9.5-23 mmHg

Following ICP reduction after lumbar puncture, there were no significant changes for any of the optic nerve head morphological parameters (Table 3). There was slight reduction of the IOP in both eyes, with greater reduction in IOP being noted for patients a diagnosis of IIH.

Table 3: The effect on ophthalmic parameters of acute ICP lowering following lumbar puncture.

Variable	Right eye	Left eye
Intraocular pressure	-0.737 (2.4) mm Hg	-0.474 (2) mm Hg
Retinal nerve fiber layer thickness	0.5 (2.2)	2.1 (14)
Rim area	0.04 (0.13)	0.15 (0.43)
Disc area	0.04 (0.16)	0.15 (0.46)
Cup volume	-0.009 (0.03)	0.00 (0.06)
Spontaneous venous pulsation	Pre LP: 10 eyes (52.6%) Post LP: 12 eyes (63%)	Pre LP: 12 eyes (63%) Post LP: 12 eyes (63%)

Using, repeated measures ANOVA, we did not find significant effects of ICP reduction on differences in ONH parameters over time (Pre vs. Post LP) in both the right and left eyes after controlling for gender, age, body mass index, and changes in ICP and IOP.

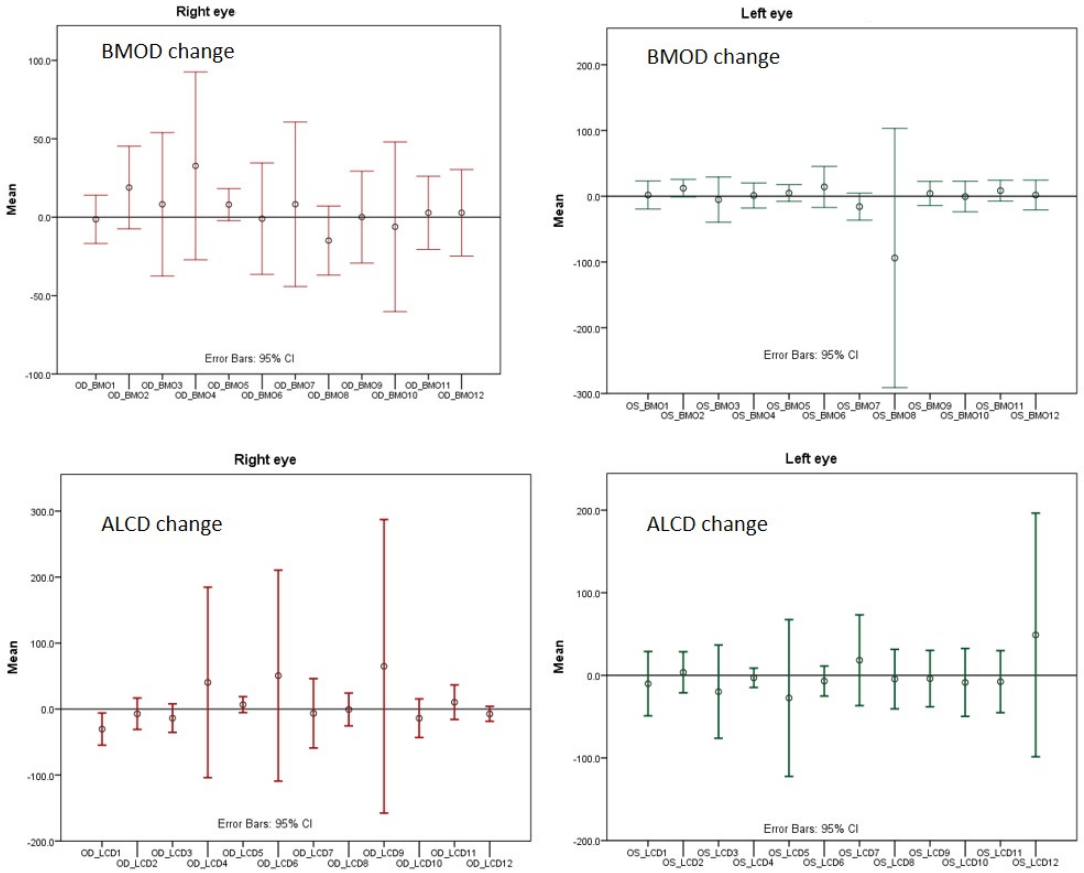

Figure 6: Whisker plot demonstrating the mean and 95% confidence interval for changes in Bruch's membrane opening diameter (BMOD) and Anterior Lamina Cribrosa Depth (ALCD) in each of the 12 meridian in the right and left eyes.

Pig Model study: Results are reported for 6 pigs (one pig was excluded due to technical difficulty as described above). At baseline, average ICP was 5.4 ± 2.7 mm Hg and IOP was 12.6± 2.1 mmHg (mean ± standard deviation). ICP was successfully increased in 6 pigs in 5-10 mm Hg increments using normal saline infusion through the lumbar drain. Maximum stable ICP achieved ranged from 18-40 mmHg. Fixed effects model demonstrated significant changes in systolic blood pressure (β=1.383, p=0.02), diastolic blood pressure (β=0.566, p=0.008) and IOP (β=0.38, p<0.01) with acute ICP changes. There were no significant effects of ICP change on optic nerve morphology.

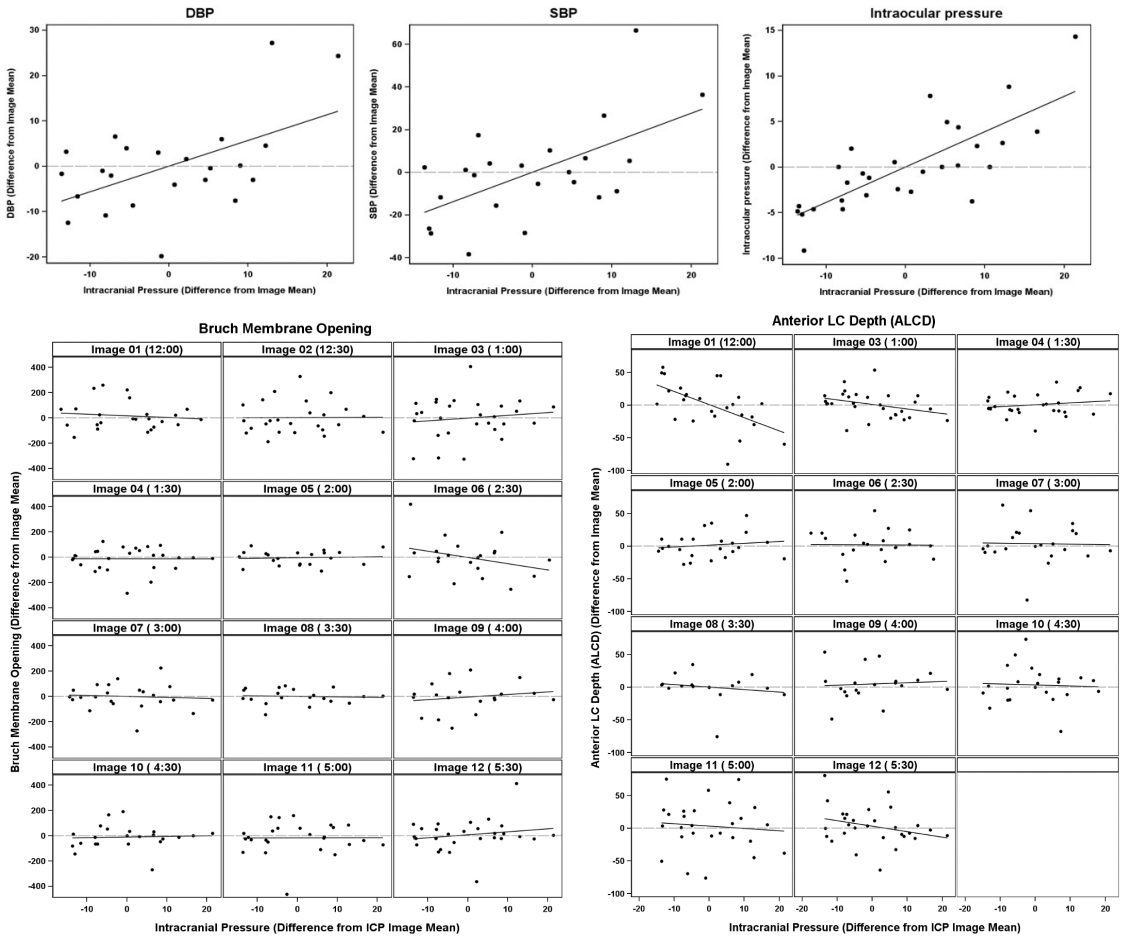

Figure 7: Slopes generated using linear effects model demonstrate a linear relationship between changes in ICP and changes in Diastolic Blood Pressure (DBP), Systolic Blood Pressure (SBP) and intraocular blood pressure (top panel). The effects on optic nerve head morphology were not significant (lower panel).

Chapter 4: Discussion

Acute changes in ICP did not result in consistent or significant changes of ONH morphology in both humans and animal models. We propose the following factors might mitigate the effects of acute ICP on ONH in order to prevent damage to the ONH.

First, IOP and ICP appear to be tightly coupled such that any change in ICP would result in a compensatory change in IOP such that the translaminar pressure gradient remains unchanged. In our animal model, we found a significant linear association between ICP and IOP, where the IOP increased by 37% for each unit of ICP increase. This coupling of IOP and ICP has previously been demonstrated in both humans and in animal models (Sheeran *et al.*, 2000; Lashutka *et al.*, 2004; Spentzas *et al.*, 2010; Ghate *et al.*, 2017). In a dog model, continuous ICP reduction using intraventricular CSF drainage, was accompanied by a linear reduction in IOP (Hou *et al.*, 2016). In the LP study, we found a small, statistically insignificant IOP decrease of 0.6 mm Hg following lumbar puncture. Although our study was not designed to test the influence of ICP on IOP, other investigators have found a statistically significant linear decrease in IOP following lumbar puncture (Gonzalez-Camarena *et al.*, 2017). We believe this coupling is mediated by the influence of acute ICP changes on the orbital venous system, which drain into the intracranial cavernous sinus.

Second, the lamina cribrosa might not be the site of maximum impact from changes in ICP. Finite element mathematical models of the ONH show that acute elevations of ICP maximally impacts strain distributions within the retrolaminar nerve tissue rather than lamina cribrosa (Feola *et al.*, 2016; Hua *et al.*, 2017). Using an anatomically accurate, mathematical model of the ONH incorporating 24 anatomical and mechanical factors, Hua et al simulated acute effects of IOP, ICP and blood pressure (Hua *et al.*, 2018). They found that IOP and ICP affect different

aspects of ONH and do not balance each other out. Intraocular pressure exerts a posterior force on the lamina cribrosa and the peripapillary sclera resulting in increased scleral canal opening size and a “hoop” stress on the LC pulling it taut. ICP, on the other hand, compresses the retrolaminar neural tissue, distends the dural sheath and deforms the posterior globe surface by exerting an anterior force on the peripapillary sclera.

Third, the magnitude of the effects of pressure changes on ONH morphology varies with specific tissue anatomy and mechanical properties (Hua *et al.*, 2018). Tran et. al. performed in-vivo OCT imaging of the ONH in eye of a rhesus monkey, while acutely changing IOP and ICP. By comparing the images at different pressure points using a novel image correlation technique, they found the effects of pressure changes on LC were localized, nonlinear and non-monotonic (Tran *et al.*, 2017). This is consistent with our observations that changes in BMOD and LCD with ICP changes varied meridionally within the same eye of an individual and between eyes of different individuals.

Fourth, anatomic variations of the optic nerve sheath may affect the transmission of acute ICP changes to the ONH. The principle of hydrostatic continuity suggests that pressure is transmitted equally through all contiguous CSF compartments. This was shown to be true in an experimental model where the CSF pressure was varied in 4 dogs and a significant linear relationship between optic nerve sheath pressure and CSF pressure within the lateral ventricle was observed (Morgan *et al.*, 1995) . There is no published study which establishes the relationship between ICP and optic nerve sheath pressure in humans. In 16 patients who were undergoing removal of a blind eye, researchers, measured the optic nerve subarachnoid pressure to be 4-14 mm Hg, which falls within the known physiologic ICP range. In 5 patients who were placed in Trendelenburg position, the optic nerve pressure was found to increase by 1-2 mm Hg, which suggests that ICP increase due to gravity was transmitted to the optic nerve

(Liu and Michon, 1995). Lack of simultaneously measured ICP was a major limitation in this study. In an unpublished study, investigators simultaneously catheterized the optic nerve sheath and lumbar cistern subarachnoid spaces in 7 eyes of 6 patients, who were undergoing orbital procedure for different disease conditions (personal communication Gregory Kosmorski D.O.). The CSF pressure was varied using a lumbar drain. They found that the initial pressure was equal in both compartments in 4 of 7 eyes while optic nerve sheath pressure was higher in 3 of 7 eyes. The response of optic nerve sheath pressure to ICP changes, however, was highly variable with significant differences in the rates of rise and fall of optic nerve sheath pressure within the same eye as well as between eyes, which suggests that communication between the intracranial and optic nerve sheath subarachnoid space might be inconsistent.

We acknowledge the limitations of our study. We had small sample size in both parts of our study and we might have missed a small effect size. However, variability of the morphological parameters within the same eye, between eyes and across different experimental time points suggests a lack of effect rather than a small true effect. We did not measure the peripapillary Bruch's Membrane (pBM) shape changes, which was recently proposed as a useful biomarker for acute ICP changes (Malhotra *et al.*, 2018). In the next phase of our collaborative work, we will analyze pBM shape changes using the technique of geometric morphometry. Lastly, in the LP study, we measured CSF pressure in the lateral decubitus position and IOP in the sitting position, which might have influenced the results of this study. In the sitting or upright position, gravity causes a caudal shift of the CSF towards the lumbar cisterns, resulting in differential CSF pressure along the neuraxis (Magnaes, 1976). In this scenario, CSF opening pressure obtained in the lateral decubitus position may not accurately reflect pressure within the optic nerve sheath in a sitting position. This, however, was not the case in the animal model where both pressures

were obtained simultaneously in the prone position, which suggests that the effect of gravity on ONH morphology is minimal.

In conclusion, we were unable to detect significant alteration of ONH morphology secondary to acute ICP increase in the pig model or acute ICP decrease in patients undergoing LP. These results further our understanding of the homeostatic mechanisms which preserve the integrity of ONH morphology during states of acute ICP fluctuation.

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