

Effect of Body Position on Intraocular Pressure (IOP), Intracranial Pressure (ICP), and Translaminar Pressure (TLP) Via Continuous Wireless Telemetry in Nonhuman Primates (NHPs)

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PURPOSE. Recent retrospective clinical studies and animal experiments have suggested that cerebrospinal fluid pressure (CSFP) is important in glaucoma, acting through the translaminar pressure ($TLP = IOP - CSFP$), which directly affects the optic nerve head. In this study, IOP and intracranial pressure (ICP; a surrogate of CSFP) were measured at various body positions to quantify the determinants of TLP.

METHODS. We have developed an implantable wireless pressure telemetry system based on a small piezoelectric sensor with low temporal drift. Telemetry transducers were placed in the anterior chamber to measure IOP and in the brain parenchyma at eye height to measure ICP. IOP was calibrated against anterior cannulation manometry, and ICP/CSFP was calibrated against an intraparenchymal Codman ICP Express microsensors. We measured IOP, ICP, and $TLP = IOP - ICP$ continuously at 200 Hz in three male nonhuman primates (NHPs) in three trials; pressures were then averaged for 30 seconds per body position. Relative change of IOP, ICP, and TLP from the supine (baseline) position to the seated, standing, and inverted positions were quantified.

RESULTS. TLP changed significantly and instantaneously from the supine to seated (+14 mm Hg), supine to standing (+13 mm Hg) and supine to inverted (−12 mm Hg) positions ($P < 0.05$). There was no significant TLP change for supine to prone. ICP showed greater relative change than IOP.

CONCLUSIONS. TLP change due to body position change is driven more by ICP/CSFP than IOP. IOP, ICP, and TLP variability, coupled with telemetry, should allow us to test the hypotheses that IOP, ICP, or TLP fluctuations contribute independently to glaucoma onset or progression.

Keywords: intraocular pressure, intracranial pressure, translaminar pressure, nonhuman primate

Intraocular pressure (IOP) is a primary risk factor for both glaucoma onset and progression.^{1–4} In addition, recent retrospective clinical studies and animal experiments have suggested that cerebrospinal fluid pressure (CSFP) is also important in glaucoma pathogenesis and progression.^{5,6} Damage to the visual pathways is generally thought to occur in the lamina region of the optic nerve head (ONH).^{7,8} Hence, it has been hypothesized that the translaminar pressure ($TLP = IOP - CSFP$), which directly affects the biomechanics of the optic nerve head and contained lamina cribrosa, is important in glaucoma pathophysiology. Unfortunately, the lack of methods to accurately and continuously monitor IOP and CSFP have impeded research into the role of TLP in glaucoma.

Previous work has studied the glaucoma prevalence related to IOP changes with body position, such as degrees of tilt, the supine sleeping position and the lateral decubitus position.^{9–24} Several of these reports suggest that positional changes that increase IOP also increase glaucoma risk.^{10,15,17,21,24} Reports on CSFP variation with body position used sensors placed remotely and calculated the hydrostatic pressure difference from the eyes and retrobulbar optic nerve to quantify TLP, rather than placing sensors close to the eye itself.^{25–28} Eklund and colleagues¹¹ measured CSFP via lumbar puncture and IOP via applanation tonometry to estimate TLP in human patients in the seated, supine and 9° head-down tilt positions, and adjusted the measurements for hydrostatic height differences using magnetic resonance

TABLE 1. Animal Demographics

NHP	Age (Years)	Sex	Number of Days of IOP and ICP Telemetry Monitoring	Number of Body Position Trials
150069	4.5	M	69	3
12.38	6.5	M	88	3*
150110	4.5	M	281	3
150172	4.5	M	0	0†

* NHP 12.38 was only used for body position testing.

† NHP 150172 was only used for hydrostatic indifference point testing.

imaging. Results from this human study reported TLP of 12.3 and 19.8 mm Hg in the supine and sitting positions, respectively. Values for the standing and inverted positions were not reported. Hand-held tonometers used in the aforementioned studies also have inherent measurement error, further necessitating the need for accurate measures.^{29,30}

Previous studies have reported changes in IOP, CSFP (or intracranial pressure [ICP]) and TLP with body position using snapshot measurements.^{9,11,14–17,19,21,22,31,32} These studies used single timepoint measurements and did not describe the time course of change in IOP, CSFP/ICP, and TLP.^{11,31} Given that IOP changes on a second-to-second timescale, continuous IOP measurement is necessary to fully characterize IOP change over time.^{33–35} In addition, results indicate that CSFP/ICP changes are greater than IOP with positional change, and therefore TLP is likely more affected by positional changes in CSFP/ICP than IOP. Pressure measurements have not been measured continuously for IOP and CSFP/ICP to quantify TLP, so the time course of pressure changes have not been reported. Turner et al.³³ reported continuous IOP changes with body position in nonhuman primates (NHPs) equipped with wireless telemetry, with results showing the greatest increase in IOP in the inverted position and greatest decrease in IOP in the seated and standing positions.

The purpose of this study was to characterize the time course and magnitude on IOP, ICP, and quantified TLP (IOP – ICP) with body position change in three male NHPs instrumented with wireless IOP and ICP telemetry systems. The relative change of IOP, ICP, and TLP from the supine (baseline) position to the seated, standing, and inverted positions were quantified in three trials. A second purpose of this study was to characterize the hydrostatic indifference point of CSFP in NHPs, which is the location in the spinal column where CSFP is the same in the upright and supine positions. We used intraparenchymal measurements of ICP at the height of the eyes as a surrogate for CSFP in the retrobulbar optic nerve; previous studies have indicated these are equivalent.³⁶ The use of continuous wireless telemetry allows for accurate quantification of both mean pressures and the time course of pressure change with body position.

METHODS

Animals

All animals were treated in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research under an approved Institutional Animal Care and Use Committee protocol monitored by the University of Alabama at Birmingham. Four male rhesus macaques, aged 4.5 to 6.5 years old (Table 1), with no ocular abnormalities were used in this study, but only three of the four were

available for body position testing, and three were used for hydrostatic indifference point testing. All animals were kept on a 06:00/18:00 light-dark cycle and fed daily at approximately 06:00 and 14:00, with water available ad libitum through a continuous feed. Food and water intake were not monitored.

TSE-Systems Stellar IOP, ICP and Arterial BP Telemetry System

We have developed and validated an implantable pressure telemetry system (Fig. 1) based on a small piezoelectric transducer with low temporal drift that accurately measures IOP in the anterior chamber, ICP (as a surrogate for CSFP) in the parenchyma of the brain, and arterial blood pressure (BP) in the lumen of a major artery (BP data are not presented in this study).³⁷ An in-depth description of the surgical procedure and placement of both the wireless telemetry implant and pressure transducers was described in a recent study.³⁷ In brief, the IOP transducer was placed in the right eye and the ICP transducer was placed in the right frontal lobe, ~2.5 cm from the midline of the brain at the same height as the IOP transducer when the animal is upright (Fig. 1).³⁷ The telemetry system wirelessly records 200 measurements of each physiologic pressure per second.

IOP and ICP Calibration

Anesthesia was induced with an intramuscular injection of ketamine (3 mg/kg) with dexmedetomidine (50 µg/kg) and then maintained using inhaled isoflurane (1%–3%) for all procedures. NHPs were kept warm with a warming blanket and systemically monitored for heart rate, SpO₂, end tidal CO₂ volume, electrocardiography, and core body temperature, with documentation every 15 minutes during all procedures.

As previously described, the IOP telemetry transducer was calibrated every two weeks via anterior chamber cannulation manometry with a 27-gauge needle placed through the cornea at the limbus under slit-lamp biomicroscopy.³⁷ Proparacaine hydrochloride (0.5% ophthalmic solution) was applied to anesthetize the cornea before anterior chamber cannulation. To assess the error in the IOP transducer reading, absolute manometric IOP is elevated from 5 to 30 mm Hg in 5 mm Hg steps, with the 15 mm Hg IOP level used for error calculation. All IOP data are corrected for signal drift between calibrations and transducer drift is approximately 2 mm Hg/month.

The ICP telemetry transducer was calibrated once a month in the same session as the biweekly IOP telemetry transducer calibration. For the purpose of this study, ICP and IOP calibrations were performed immediately after the positional testing in the same session. As previously described,

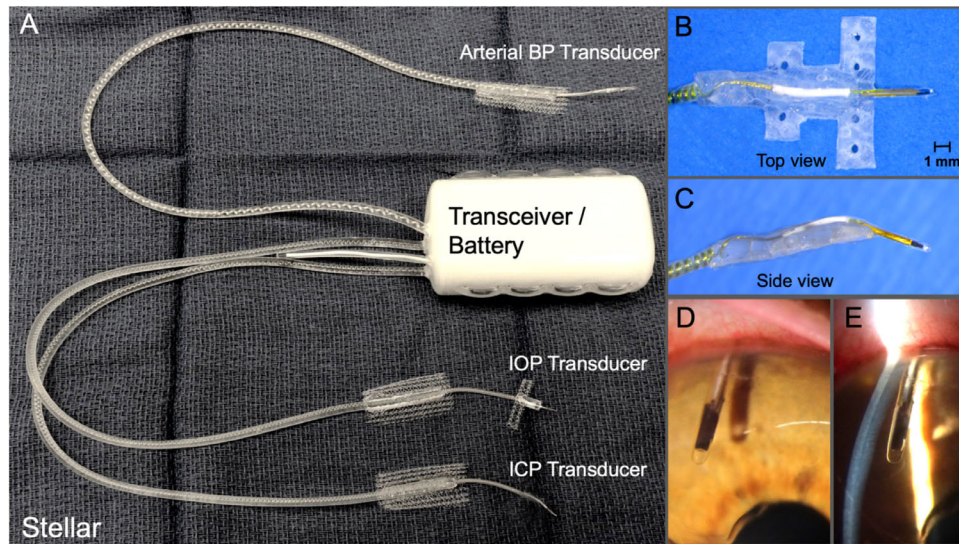


FIGURE 1. (A) TSE-Systems Stellar IOP/ICP/BP total implant system. (B) Top view of the IOP transducer and integrated scleral baseplate for affixing the transducer to the sclera under Tenon's capsule and conjunctiva. (C) Side view of the IOP transducer and integrated scleral baseplate. (D) En face photograph of the piezoelectric IOP transducer in the anterior chamber. (E) Slit lamp photograph of the intraocular placement of the piezoelectric IOP transducer in the anterior chamber relative to the cornea and iris. Reprinted from Jasien et al.³⁷ with permission.

the clinical gold-standard Codman ICP Express microsensors (DePuy Synthes, Raynham, MA, USA) was inserted through an indwelling custom titanium port in the cranium that allows access to the left brain parenchyma (Fig. 2).³⁷ ICP was then measured by both the indwelling Stellar telemetry transducer and the adjacent Codman microsensors simultaneously at various body positions.³⁷ The prone position was used as the reference for all ICP calibration sessions (Fig. 3).³⁷ ICP transducer drift was similar to IOP transducer drift at approximately 2 mm Hg/month and calibrated TLP was continuously quantified as IOP-ICP. All IOP and ICP data are recorded with NOTOCORD-hem data acquisition software (Instem, Stone, Staffordshire, UK) and all pressure data are drift-corrected continuously between calibration procedures via software post-processing assuming linear drift between calibrations.

Body Position Testing

Before IOP and/or ICP calibration during the same session, the NHPs were anesthetized as described above and then moved manually from the baseline supine position, to the prone, seated, standing, and inverted positions in turn (Fig. 4). NHPs were returned to the baseline supine position between each body position change, and each position was held for 30 seconds after IOP, ICP, and TLP had stabilized. The order of these positions was performed three times within one session to obtain an average measurement for each position for each NHP. One observer (JVJ) performed all body position movements during waking hours to maintain consistency between positions across trials and animals.

Statistical Analysis

Mean relative changes in IOP, ICP, and TLP = $IOP - ICP$ were calculated across the three body position trials for each NHP for each body position with supine as the baseline position. Means for all NHPs were also calculated from all

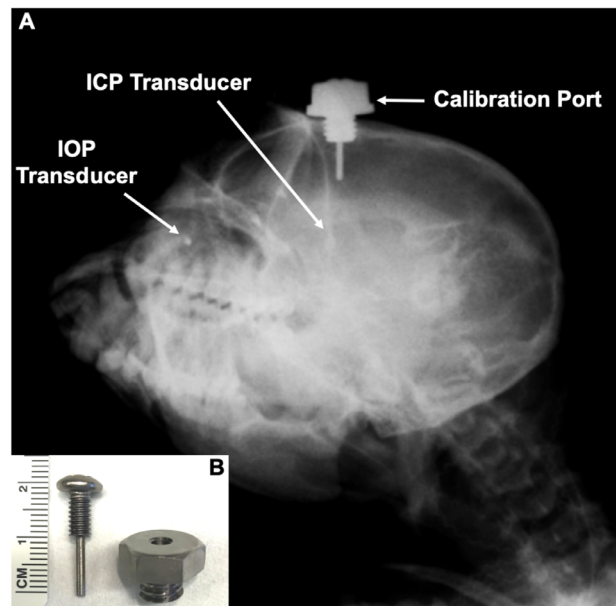


FIGURE 2. (A) Oblique X-ray of an NHP with the stellar implant (IOP and ICP transducers) and custom indwelling titanium ICP calibration port installed. The IOP transducer is in the right eye and the ICP transducer is in the right lobe of the brain, whereas the calibration port is in the left lobe. The IOP and ICP transducers and bottom of the screw post within the calibration port are all at the same height when the animal is in the upright position. (B) Photograph of the custom indwelling titanium ICP calibration port, showing the bolt with central screw. Note that the screw is sealed to the bolt with a sterile medical-grade silicone washer when installed. Reprinted from Jasien et al.³⁷ with permission.

sessions. A paired *t*-test was used to determine whether IOP, ICP, and TLP change relative to the supine position were different across body positions.

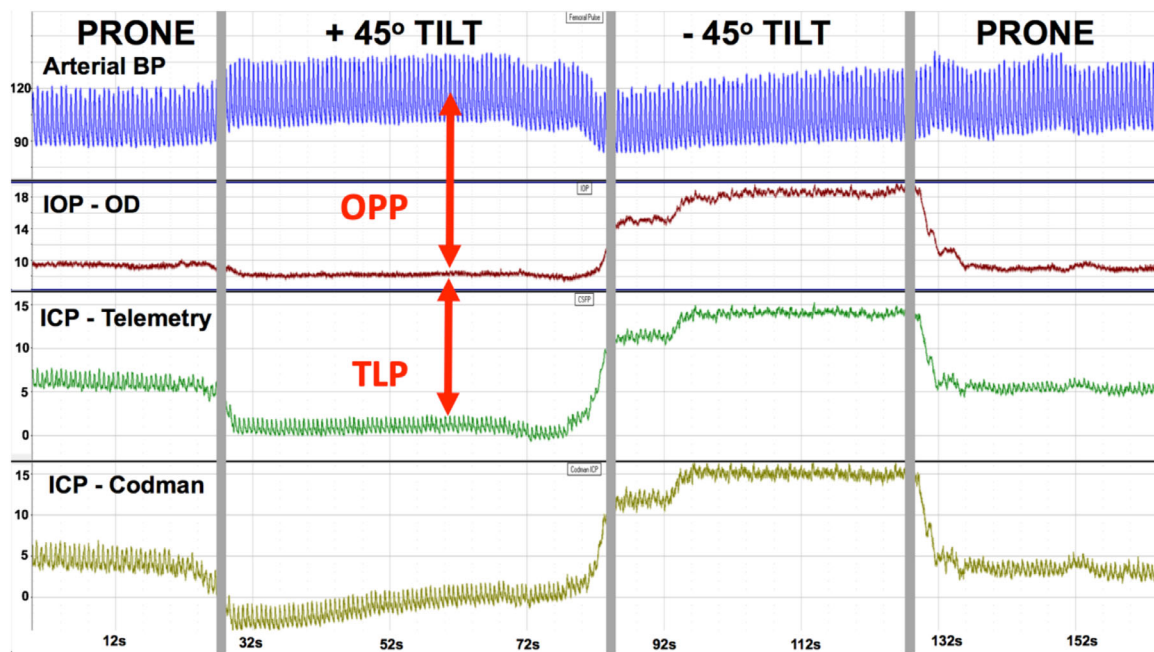


FIGURE 3. Screenshot of the pressure telemetry signals acquired during a typical ICP transducer calibration procedure wherein the NHP is moved from the prone position to positive 45° incline (head up tilt) to negative 45° decline (head down tilt) and back to prone. Arterial BP (blue), IOP in the right eye (red), ICP from Stellar Telemetry (green), and ICP from the Codman microsensors (gold) are recorded at 200 Hz during the calibration procedure; Y-axis scale is mm Hg for all signals. Note that all pressures responded nearly instantaneously to change in body position. OPP, ocular perfusion pressure. Reprinted from Jasien et al.³⁷ with permission.

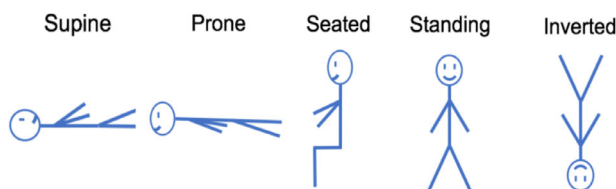


FIGURE 4. Order of body positions changes, with the supine position as baseline. Positions were held for 30 seconds after all pressures had stabilized, and the NHP was returned to the supine baseline position prior to moving to the next position. Adapted from Turner et al.³⁵ with permission.

RESULTS

Body Position Testing

TLP changed significantly from the supine to seated (+14 mm Hg), supine to standing (+13 mm Hg) and supine to inverted (−12 mm Hg) positions ($P < 0.05$) (Fig. 5 and Table 2). There was no significant TLP change for supine to prone. ICP showed greater relative change than IOP in all positions (Fig. 6). IOP did not show a significant relative change among any of the body positions tested herein.

Individual and mean relative change IOP, ICP and TLP values for the three sessions for each animal and total mean across all sessions are presented in Table 2. All pressures change immediately with change in body position. Specifically, the mean time required for ICP to change from the supine baseline position to the seated, standing and inverted positions was 2.4 ± 0.5 , 2.7 ± 0.1 and 2.3 ± 0.4 seconds, respectively, averaged across three trials in all NHPs. The time course of IOP changes were similar at 2.3 ± 0.8 ,

2.4 ± 0.4 and 3.5 ± 0.1 seconds, respectively, although the pressure changes were not statistically different from the supine baseline position. It took similar amounts of time to manually change the NHP's body position, so the pressure changes occurred simultaneous to positional change.

Intracranial Pressure Hydrostatic Indifference Point Testing

The ICP hydrostatic indifference point (HIP) was calculated in all NHPs, which is defined as the point in the spinal column where CSFP is the same when the NHP is in either the lateral decubitus or sitting position. This is valuable herein to understand the NHP ICP HIP relationship to human CSFP HIP measurements with positional change. The Codman ICP Express microsensors (DePuy Synthes) was used for all HIP-related measurements in the same manner as used during ICP calibrations described above.³⁷ Anesthetized animals were secured on a custom tilt table in the supine position with integrated shoulder and pelvic supports. The table was manually tilted to +45° (head-up tilt) in 15° increments, returned back to the supine position, tilted to −45° (head-down tilt) in 15° increments, and again returned to the supine position (Fig. 7). ICP measurements were recorded continuously at 200 Hz during the tilt testing, with stable ICP obtained for at least 30 seconds at each position. Additional measurements were obtained in the seated position in the same session to allow for HIP calculation per Magnaes' published method.^{25,26} ICP measurements at each position were averaged over the 30-second stable period, then converted to centimeters (cm) of water. To calculate the CSFP in the lateral decubitus position, the CSFP measured in the supine position was adjusted to be equivalent to

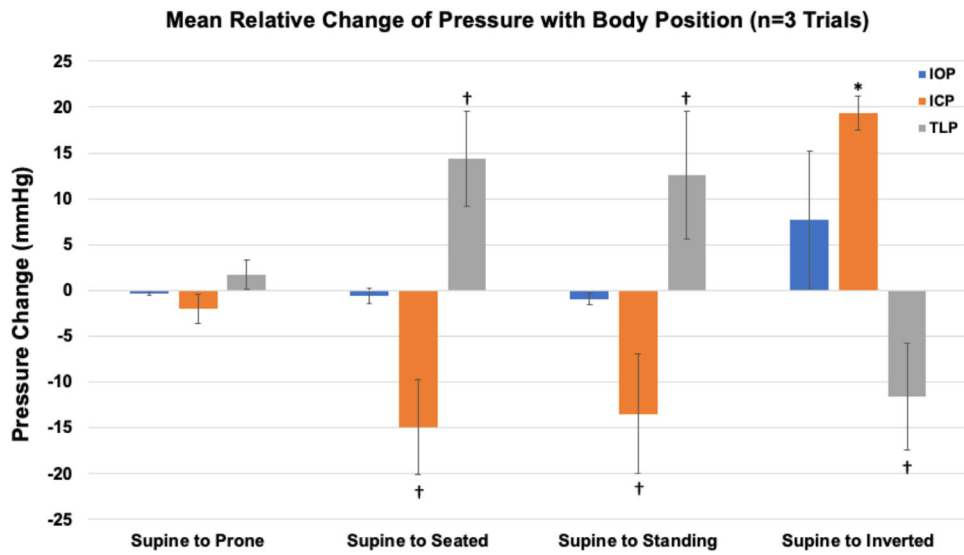


FIGURE 5. Mean relative change of IOP, ICP and TLP (mm Hg) of three NHPs by change of body position with standard deviation and P value (*P < 0.01 and †P < 0.05).

TABLE 2. Relative Change of IOP, ICP, and TLP of Each NHP and Mean of All NHPs With Standard Deviation and P Value

NHP	Supine to Prone	Supine to Seated	Supine to Standing	Supine to Inverted
Relative Change in IOP				
150069	-0.3	0.1	-0.9	8.1
150110	-0.5	-1.5	-1.7	15
12.38	-0.2	-0.3	-0.4	0.1
Mean	-0.3 ± 0.2	-0.6 ± 0.8	-1 ± 0.7	7.7 ± 7.5
Relative Change in ICP				
150069	-0.3	-10.8	-8.4	20.4
150110	-2.6	-13.3	-11.3	20.5
12.38	-3.3	-20.7	-20.8	17.4
Mean	-2 ± 1.6	-15 ± 5.1 [†]	-13.5 ± 6.5 [†]	19.4 ± 1.8*
Relative Change in TLP (IOP - ICP)				
150069	-0.1	10.9	7.5	-12.3
150110	2.1	11.8	9.7	-5.5
12.38	3.1	20.4	20.5	-17.2
Mean	1.7 ± 1.6	14.4 ± 5.2 [†]	12.6 ± 7 [†]	-11.7 ± 5.9 [†]

* P < 0.01.

† P < 0.05.

the lateral decubitus position using the hydrostatic column height of the intraparenchymal ICP transducer from the central spinal plane, such that it was functionally equivalent to CSFP measured via lumbar puncture as in prior human studies. The point in the spinal column at which CSFP is zero in the sitting position, relative to the height position of the pressure transducer, is simply the negative of the intraparenchymal ICP measurement (cm of water) in the sitting position. Hence, the ICP (cm of water) in the sitting position is simply added to the transducer position to identify the zero-pressure location in the spinal column. The HIP was calculated as the location in the spinal column where CSFP is the same in the lateral decubitus and sitting positions, expressed as the vertical height (cm) from the ICP transducer position in the frontal lobe (level with the centerline of the eye; Table 3).

DISCUSSION

Results show that ICP changes much more than IOP with body position, and thus ICP change drives TLP change to a greater degree than IOP. Hence, TLP changes much more than IOP with body position, and these changes occur very rapidly with body position change. The rapid changes in IOP and ICP with body position were about 2.7 and 2.5 seconds, respectively, for each body position. The HIP was located in the lower cervical/upper thoracic spine, 9.2 to 14.7 cm from the eyes toward the tail, consistent with prior human studies.²⁵

IOP is a primary risk factor for glaucoma and damage to the retinal ganglion cell axons is thought to occur at the ONH. ONH biomechanics have been hypothesized to play an important role in glaucoma pathophysiology, and

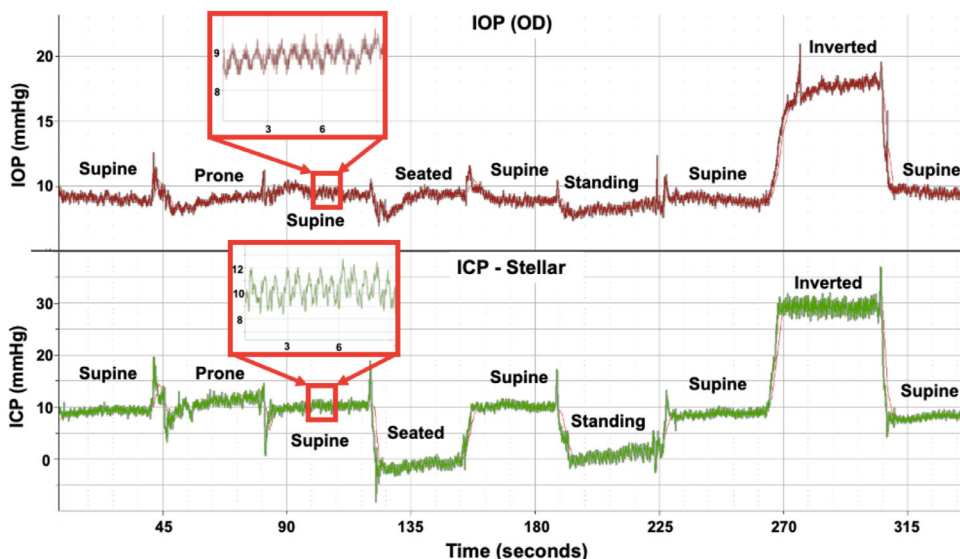


FIGURE 6. A single body position trial in one NHP showing IOP (OD) (top, red trace) and ICP (bottom, green trace) change with body position change from the supine baseline position. The insets show IOP (top, red trace) with the ocular pulse amplitude and ICP (bottom, green trace) with the vascular pulse amplitude in ICP.

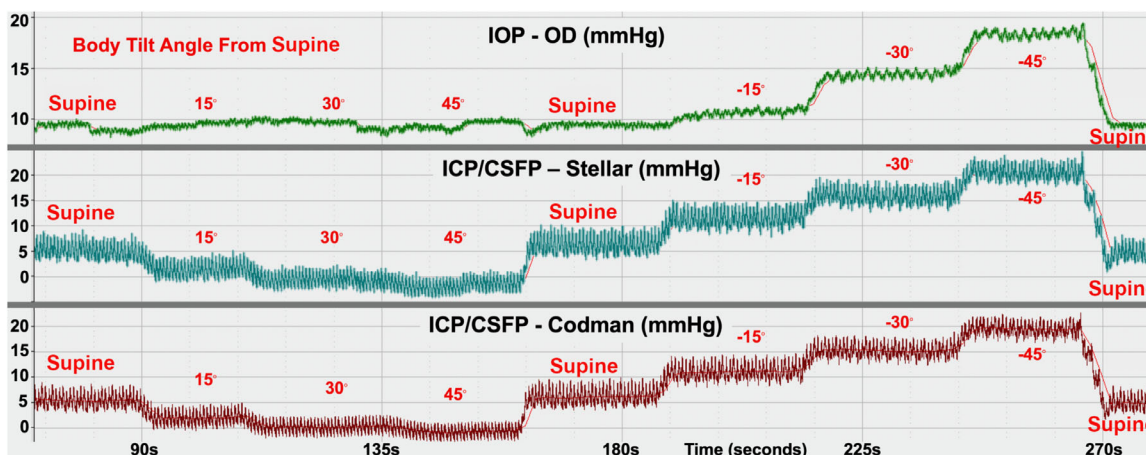


FIGURE 7. Continuous IOP and ICP during body tilt from the supine baseline to +45° and then to -45° in 15° increments, acquired during HIP testing. (Top, green trace) IOP in the right eye (OD) measured in the anterior chamber with the indwelling Stellar telemetry transducer; (Middle, cyan trace) ICP/CSFP measured intraparenchymally with the indwelling Stellar telemetry transducer; (Bottom, maroon trace) ICP/CSFP measured intraparenchymally with the adjacent Codman ICP Express microsensor.

yet IOP is not the only mechanical pressure affecting this region.^{38–42} Cerebrospinal fluid pressure surrounding the retrobulbar optic nerve counteracts IOP, but only at the ONH, although both experimental studies and numerical simulations indicate this interplay is complex.^{43–48} IOP acts

on the entire corneoscleral shell and therefore IOP fluctuations can expand or contract the scleral canal, directly affecting the levels of in-plane mechanical stretch in the lamina cribrosa. CSFP however, only acts on the retrolaminar optic nerve and where the subarachnoid space abuts the peripap-

TABLE 3. Calculated CSFP HIP Measurements Expressed As Vertical Height From The Indwelling Intraparenchymal ICP Transducer

NHP	Spinal CSFP in Lateral Decubitus Position (cm of water)	Intraparenchymal CSFP at the Level of the Eyes in the Sitting Position (cm of water)	Zero CSFP in Sitting Position: Vertical Distance from ICP Transducer toward the Tail (cm)	CSFP Hydrostatic Indifference Point: Vertical Distance from ICP Transducer toward the Tail (cm)
150069	10.1	-4.6	4.6	14.7
150110	7.2	-2.0	2.0	9.2
150172*	9.2	-4.1	4.1	13.3

* NHP 150172 was used only for HIP testing, and not body position.

illary sclera.^{39,43,45,47,49–51} Although IOP has been shown to be important in glaucoma, TLP may be the more relevant factor when considering biomechanical risk for the disease.

Eklund et al.'s¹¹ results on positional changes in humans showed that the largest calculated TLP change was observed when moving from the supine to the seated position. Similarly, Linden et al.³¹ studied the changes of IOP and ICP in human patients with positional change and reported larger changes in ICP than IOP measurements. Both these studies showed that the calculated retrobulbar CSFP changed much more than IOP with body position change which agree with the results reported herein. The similarity in the direction and relative magnitudes of IOP, ICP, and TLP changes seen in this study and previous studies show that the NHP is an appropriate model for positional testing and changes in systemic pressure measurements.

The relative changes in IOP with body position are largely consistent with our previously published work, with one exception.³³ IOP changes in NHP 12.38 were not consistent with the other two animals, especially for the supine to inverted position (Table 3), thus resulting in a large standard deviation of the mean across the three animals. It is possible that IOP measurements in this animal are erroneous and the error is related to implant failure that occurred shortly after these measurements were taken. That said, the IOP data from fellow eyes are consistent across all three body position trials and IOP calibration data from the sessions before and after the body position testing reported herein indicated proper IOP transducer function in this NHP. Hence, we elected to include the IOP measurements from this animal in the analysis despite the inconsistencies with the other NHPs and data from prior studies. There is no obvious explanation for these results.

It should also be noted that ICP is the best surrogate measure for both optic nerve subarachnoid space pressure and retrolaminar tissue pressure. However, it has been previously shown that ICP is likely affected by orbital tissue pressure and pia mater tension when ICP decreases below ~3 mm Hg.⁴⁹ Therefore it can be assumed that the interaction between ICP and the orbital tissue pressure thus also affects the true TLP when ICP levels are very low in the sitting and standing positions. Due to this effect, it is reasonable to conclude that the relative change in ICP and TLP from the supine to the seated and standing positions we report ignore the interaction of with orbital tissue pressure, leading to an overstatement of true TLP change. That said, ICP tracks subarachnoid space pressure very well for ICP >3 mm Hg, so this effect would be limited to approximately 20% of the 15 and 13.5 mm Hg ICP changes we report for body position change from supine baseline to seated and standing positions, respectively. Also, it is unlikely that this previously reported phenomenon⁴⁹ would alter the reported increases in ICP and TLP in the inverted position.

The study is limited by the following considerations. First, the study was limited to a small sample size of three NHPs due to the preliminary nature of the investigation. Hence, the reported results may not translate to the larger population of Rhesus macaques, although the results showed significant differences between body positions and ICP and TLP, showing that the results were consistent between trials and across animals such that we had adequate statistical power to detect effects. Also, these results may not translate to the human population because of differences in eye and body size, although similar changes in IOP, ICP/CSFP and TLP with body position, and similar variability between

subjects, have been reported in patients.^{11,31} Similarly, the hydrostatic indifference point calculation was also limited in sample size, although the results are consistent with those of humans in terms of the location of the HIP between the lower cervical spine and the upper thoracic spine in both NHPs and humans.²⁵ Second, the adolescent age of the NHPs is a limiting factor, in that the reported results may not directly translate to older NHPs or humans in whom glaucoma would be prevalent. However, the magnitude of TLP change due to body position is much more likely to be driven by physics (cephalad fluid shifts) than any age-related physiological phenomenon. However, we report the time course and magnitude of TLP change with body position in adolescent NHPs, as well as the location of the HIP, and future positional studies should be performed in older NHPs. Third, the tilt table is unable to position animals in the upright (seated/standing) or inverted positions, so positional testing was done manually. However, the tilt table was used to accurately assess and measure the HIP of three animals, two of which were included in this body position study. A future study using precisely controlled angular tilt in a larger number of animals will be performed. Finally, the third NHP (NHP 150172) used for the HIP testing was not included in the body position analyses because he did not have a working IOP transducer. Similarly, NHP 12.38 was not used for HIP testing because his telemetry implant failed shortly after the body position testing was performed. There is no reason to suspect that this biased the reported results in any way.

Body position testing in NHPs showed that TLP change due to body position change is driven more by ICP/CSFP than IOP, suggesting that ICP/CSFP variability is an important driver of ONH and laminar biomechanics. Natural IOP, ICP, and TLP variability, coupled with telemetry, should allow us to test the hypotheses that IOP, ICP, or TLP fluctuations contribute independently to glaucoma onset or progression.

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