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Normal-Tension Glaucoma Has Normal Intracranial Pressure

A Prospective Study of Intracranial Pressure and Intraocular Pressure in Different Body Positions

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Purpose: To test the hypothesis that normal-tension glaucoma (NTG) is caused by an increased pressure difference across the lamina cribrosa (LC) related to a low intracranial pressure (ICP).

Design: Prospective case-control study.

Participants: Thirteen NTG patients (9 women; median 71 [range: 56–83] years) were recruited for investigation with the same protocol as 11 healthy volunteers (8 women; 47 [30–59] years). A larger control group (n = 51; 30 women; 68 [30–81] years) was used only for ICP comparison in supine position.

Methods: ICP and intraocular pressure (IOP) were simultaneously measured in supine, sitting, and 9° head-down tilt (HDT) positions. Trans-lamina cribrosa pressure difference (TLCPD) was calculated using ICP and IOP together with geometric distances estimated from magnetic resonance imaging to adjust for hydrostatic effects.

Main Outcome Measures: ICP, IOP, and TLCPD in different body positions.

Results: Between NTG patients and healthy volunteers, there were no differences in ICP, IOP, or TLCPD in supine, sitting, or HDT (P ≥ 0.11), except for IOP in HDT (P = 0.04). There was no correlation between visual field defect and TLCPD, IOP, or ICP and in any body position (P ≥ 0.39). Mean ICP in supine was 10.3 mmHg (SD = 2.7) in the NTG group (n = 13) and 11.3 (2.2) mmHg in the larger control group (n = 51) (P = 0.24).

Conclusions: There was no evidence of reduced ICP in NTG patients as compared with healthy controls, either in supine or in upright position. Consequently, the hypothesis that NTG is caused by an elevated TLCPD from low ICP was not supported. Ophthalmology 2018;125:361-368 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Investigations of this hypothesis in humans are at present limited to performing ICP measurements and assuming a CSF communication along the optic nerve to the retrobulbar region. With a lumped comparison between IOP and ICP it is not possible to investigate the local mechanical strains in the LC and optic nerve head. The lumped comparison will, however, give information on the maximum potential pressure difference across the LC—retrobulbar region and thereby test the physiological plausibility of the theory of a reduced ICP as a component in NTG.

In previous studies of TLCPD, posture has not been accounted for. Measurement of IOP is traditionally performed in a sitting position, whereas lumbar puncture is performed in a lateral decubitus position, which is also the situation in the above-mentioned studies investigating TLCPD in glaucoma. We recently showed that the reduction in ICP when moving from supine to sitting is large compared to the small reduction in IOP, corresponding to a higher TLCPD in sitting than in supine position. These findings imply that (1) in scientific evaluation of the TLCPD importance in glaucoma, assessment of IOP and ICP must be performed with the patient in the same posture; and (2) TLCPD in upright position is unknown in glaucoma and has potential to give new understanding of the pathophysiology. Consequently, the aim of this study was to determine if patients with NTG have a reduced ICP and an increased TLCPD compared with healthy subjects.

Methods

Our objective was to measure both ICP and IOP simultaneously in a single experimental procedure, which includes both upright and supine posture, to investigate if ICP and/or TLCPD in patients with NTG are different, compared with healthy subjects. We also compared ICP in supine position to reference data from a previously published cohort of healthy subjects.

Patients

Charts of all patients diagnosed with NTG at the 3 hospitals within the County Council of Västerbotten were reviewed. Patients who met the inclusion criteria were invited to participate in this prospective study. All study procedures were undertaken at Umeå University Hospital between February and May 2016. The study was registered at ClinicalTrials.gov (ID: NCT02776449). The study protocol followed the tenets of the Declaration of Helsinki and was reviewed and approved by the Regional Ethical Review Board at Umeå University. All patients and healthy volunteers signed a written informed consent after oral and written explanation of the study.

Patients had unilateral or bilateral NTG, defined as untreated and treated IOP readings in the patient history of maximum 21 mmHg with an occasional measurement up to 24 mmHg, optic disc damage, and corresponding visual field defects of glaucomatous origin. Patients with neurologic diseases, medications known to affect ICP (e.g., carbonic anhydrase inhibitors), previous brain surgery, or previous lumbar puncture were excluded, as were patients with previous glaucoma surgery. All included eyes were on antiglaucoma eye drops, but all IOP-lowering medication was terminated 28 days before the IOP-ICP study day.

Seventeen patients with NTG entered the study. One patient was excluded after the magnetic resonance imaging (MRI), owing to a cyst affecting the spinal cord, and 1 patient withdrew at the time of lumbar puncture. Two subjects were excluded owing to mean IOP values >21 mmHg registered at the IOP-ICP study day. Thus, the NTG group consisted of 13 patients, 11 of whom had bilateral disease. Characteristics of the NTG subjects are presented in Table 1.

Healthy Controls

Eleven healthy volunteers (3 men/8 women) with a median age of 47 (range, 30–59) years were included and investigated with the same protocol as the NTG patients. Original data were collected to investigate TLCPD and its body position dependence and is provided in the report of Eklund et al. The control subjects had no past or present neurologic or ophthalmologic disease. To confirm their health they had undergone an ophthalmologic and neurologic examination.

Specifically for ICP comparison in supine position, previously published reference material of 40 healthy subjects was added to the group of 11 healthy volunteers. In this group of 40 subjects no IOP measurements were performed and the ICP was only measured in supine position, but with the same lumbar puncture and data acquisition method as the one used in the present study. The 2 reference materials were merged to form the supine ICP control population, resulting in a group of 51 healthy subjects (21 men/30 women) with a median age of 68 (range, 30–81) years. The age of the NTG group was not significantly different from the age of the supine ICP control group (n = 51) (P = 0.26).

Baseline Examinations

To assess baseline ocular status and to verify patient eligibility, all patients underwent a comprehensive baseline ophthalmologic examination including medical history, weight, height, slit-lamp examination of the anterior segment, and biomicroscopy of the fundus. Visual acuity was assessed with Early Treatment Diabetic Retinopathy Study (ETDRS) charts and measurement of central corneal thickness was performed with IOLMaster 700 R (Carl Zeiss Meditec AG, Jena, Germany). IOP was measured with both Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland) and the Applanation resonance tonometer (ART) (BioResonant Good Eye, Umeå, Sweden). Visual field was evaluated with Humphrey Field Analyzer 3, HT24-2 SITA Fast program (Carl Zeiss Meditec AG, Jena, Germany). The visual field index (VFI) in that program expresses the visual field as a percentage of a normal age-adjusted visual field and was used to assess disease severity.

A neurologic examination was obtained from all participants and an

| Table 1. Characteristics of Normal-Tension Glaucoma Patients |
|------------------------|------------------|
| Age (years) | 71 (56–83) |
| Gender (F/M) | 9/4 |
| NTG diagnosis (years) | 10 (4–16) |
| Height (m) | 1.65 (1.56–1.93) |
| Weight (kg) | 77 (60–100) |
| Body mass index | 24.7 (21.1–35.7) |
| Blood pressure, systolic | 138 (110–162) |
| Blood pressure, diastolic | 85 (62–90) |
| Central corneal thickness (µm) | 534 (493–626) |
| Best-corrected visual acuity (logMAR) | 0.04 (–0.08 to 1.30) |
| Visual field index (%) | 61 (7–90) |

NTG = normal-tension glaucoma.

All values except gender are presented as median (range).
MRI investigation including standard anatomic sequences was performed; both had to be normal for inclusion.

Investigational Protocol for the Intraocular Pressure—Intracranial Pressure Study Day

Measurements of ICP and IOP were performed simultaneously in supine, sitting, and head-down tilt (HDT) positions. To control the body positions, ranging from supine to sitting, the tilt function of the backrest of the investigational bed was used (the legs were kept horizontal in all positions). The body position was altered according to the following procedure: (1) 15 minutes in supine (0° tilt angle); (2) 25 minutes when the patient was brought from the supine toward the sitting position in 5 steps at tilt angles 8°, 16°, 24°, 32°, and 40°, each of 5-minute duration; (3) 7 minutes sitting (69° tilt angle); (4) back to supine position for 7 minutes; (5) 7 minutes in the HDT position (−9° tilt angle). ICP was continuously recorded at all tilt angles, whereas IOP was measured at phases 1, 3, 4, and 5 (Fig 1). The second supine position was added because repeated IOP applanation measurements have been shown to reduce IOP22,23 and therefore a new supine baseline was acquired before HDT measurements. A lower IOP is thus to be expected in second supine position compared with first, whereas the approximately 30 minutes between first supine IOP and sitting position should make the sitting IOP unaffected by the first supine IOP assessment.

A lumbar puncture (18-gauge needle) was performed in sitting position and the needle connected to a standardized pressure transducer (Likvor CELDA system, Likvor AB, Umeå, Sweden), whereafter the patient was placed in supine position and the study protocol started. Using this standardized high-precision method to measure lumbar CSF pressure, it has previously been shown that lumbar CSF pressure agrees with the ICP.21 In all postures the zero-pressure reference level for ICP was placed at the auditory meatus (Fig 1). For ICP we used the auditory meatus as the reference point because the measured lumbar CSF pressure was already hydrostatically adjusted with respect to the auditory meatus to estimate the ICP. The vertical distances contributing to hydrostatic pressure effects were estimated based on distances determined from anatomic MRI sequences (Fig 2). Patients were examined by MRI of the brain with a T2-weighted sequence using a 3 Tesla GE scanner with a 32-channel head coil (GE Discovery MRT750, General Electric Healthcare, Waukesha, WI). For each subject the images were analyzed to determine the distance between the relevant locations, as measured in the superior-inferior (ICP) and anterior-posterior (ICP and IOP) directions. The resulting vertical distances in supine, sitting, and HDT positions were then calculated using these distances and the angle of the backrest of the bed (0°, 69°, and −9°). The TLCPD was defined as the difference between IOP_{LC} and ICP_{LC}.

Statistical Analyses

The study had a sample size resulting in a power of 0.8 to detect an ICP difference between NTG and healthy subjects of 2 mmHg or higher, assuming within-group standard deviations of 1.75 mmHg. Statistical analysis was performed using SPSS (PASW Statistics 18, SPSS, Chicago, IL). The Student paired t test was used for statistical comparisons within the NTG group. For comparisons with the control groups independent t tests were used (no assumption of equal variance). Correlation between VFI and pressure variables was determined with Pearson linear correlation coefficients; additionally, a mixed-model analysis was performed so as to be able to assess these relationships based on the IOP values from both eyes of all subjects with bi-ocular glaucomatous injury and in all body positions. Data are presented as mean values ± standard deviation (SD) when not stated otherwise. A P value < 0.05 was considered statistically significant.

Results

ICP and IOP in the various positions are presented in Table 2. There was no difference in IOP or ICP between NTG and healthy subjects, except in the HDT position, where IOP was significantly lower in NTG than in healthy subjects. For the larger cohort of healthy elderly subjects (n = 51), ICP in supine position was 11.3 ± 2.2 mmHg. This was different neither from the (first) supine value for the NTG subjects of 10.3 ± 2.7 mmHg (P = 0.24) nor from the second supine value of 11.2 ± 2.4 mmHg (P = 1.00). The ICP values for NTG and healthy subjects (n = 11) in all body positions investigated in the present protocol (including intermediate tilt angles between supine and sitting where no IOP measurements were performed; Fig 1) are shown in Figure 3. ICP did not differ between the 2 groups in any body position (P = 0.39–0.97).

Values for Pressures at the Level of the Lamina Cribrosa

IOP_{LC}, ICP_{LC}, and TLCPD in supine and sitting position are presented in Table 3. There were no significant differences between NTG patients and healthy controls in these parameters in any body position (including the second supine measurement and HDT) (P > 0.05). There was no correlation between visual field defect (i.e., VFI) and TLCPD, IOP, or ICP in any body position (Fig 1). The data did not reveal any significant relationship between VFI and IOP, TLCPD, or ICP (P > 0.10), either using a full factorial model (i.e., including interaction effect between variables) or using a model limited to main effects.
ICP showed a larger change than IOP with respect to posture (Table 2). Between supine and sitting position, both ICP and IOP decreased significantly (mean change in NTG patients, ICP: $-10.8 \pm 4.1$ mmHg; IOP: $-3.8 \pm 2.8$ mmHg, $P < 0.01$) (Table 2), whereas TLCPD increased (mean change: $7.0 \pm 4.6$ mmHg, $P < 0.01$) (Table 3).

Between the second supine measurement and the HDT position, ICP increased significantly (mean change: $3.7 \pm 3.0$ mmHg, $P < 0.01$), whereas IOP showed no significant change (mean change: $0.0 \pm 1.2$ mmHg, $P = 0.98$) and TLCPD decreased significantly (mean change: $-4.0 \pm 1.9$ mmHg, $P < 0.01$).

Discussion

The hypothesis that glaucoma is caused by an increased TLCPD has led to the assumption that NTG may be caused by a low ICP, which would create a similar pressure relationship between the ICP and IOP as an elevated IOP. The present study is the first to prospectively evaluate ICP and IOP simultaneously in both supine and upright positions in patients with a well-established diagnosis of NTG and healthy controls. No evidence of reduced ICP in NTG patients was found and consequently the current hypothesis could not be supported by our findings.

The literature on the hypothesis of an increased TLCPD has a common limitation in that it is based on assessments of IOP in upright posture and ICP in horizontal posture. Because both pressures vary with posture, the pressure difference over LC has not been evaluated per se. These studies have primarily investigated if patients with glaucoma have a reduced ICP when they are lying down. We spend 16 hours per day upright, and because ICP is...
decreased substantially in upright posture (compared with horizontal), very little is known of the true LC gradient. Accounting for the effect of postural dependency had the potential to give new insights into glaucoma. We addressed this knowledge gap in this study by (1) measuring ICP and IOP in both supine and upright positions, (2) assessing the intraposture differences in these pressures at the level of the LC, and (3) comparing NTG patients with a group of healthy volunteers investigated with the same protocol. We found no significant differences between NTG and healthy subjects, for ICP or TLCPD, regardless of body position. These findings indicate both that the craniospinal CSF dynamics are not disturbed in NTG and that the main postural control mechanism for ICP, the collapse of the internal jugular veins,26,27 is intact in NTG patients and probably not a part of the pathophysiology of glaucoma. This was further supported by the finding of no correlation between visual field defect and TLCPD, IOP, or ICP in any body position.

Regarding the mean ICP in the horizontal posture, our results are in contradiction to most previous reports and reviews on ICP in glaucoma patients. Much of the literature on this subject is in the form of reviews4,6,7,10,28 or based on indirect measurements of ICP,9,29–32 which is still not

<table>
<thead>
<tr>
<th>Posture</th>
<th>ICP</th>
<th>IOP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NTG (N = 13)</td>
<td>Healthy (N = 11)</td>
</tr>
<tr>
<td>Supine (first)</td>
<td>10.3 (2.7)</td>
<td>10.5 (1.5)</td>
</tr>
<tr>
<td>Sitting</td>
<td>11.3 (2.4)</td>
<td>11.5 (0.8)</td>
</tr>
<tr>
<td>HDT</td>
<td>15.0 (2.6)</td>
<td>15.8 (1.2)</td>
</tr>
</tbody>
</table>

HDT = head-down tilt; ICP = intracranial pressure; IOP = intraocular pressure; NTG = normal-tension glaucoma.

All values presented as mean (SD) in mmHg.

*Statistically significant difference between NTG and healthy subjects.

1N = 8 healthy controls; exclusions of values in these body positions were made because of suspected unreliable ICP estimation owing to reduced cerebrospinal fluid contact (as indicated by very low ICP pulsations).

2N = 7 healthy controls; exclusions of values in these body positions were made because of suspected unreliable ICP estimation owing to reduced cerebrospinal fluid contact (as indicated by very low ICP pulsations).

Figure 3. Intracranial pressure (ICP) at all evaluated body positions for the normal-tension glaucoma subjects (white circles, n = 13) and the healthy controls (black diamonds, n = 11). The x-axis shows the tilt angle of backrest of the investigational bed, where 0° corresponds to supine position, 70° to sitting position, and −9° to head-down tilt position. The bars represent ±1 SD.

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Table 2. Intracranial Pressure and Intraocular Pressure in Different Body Positions
considered reliable enough for clinical use. We have only identified 3 studies in which direct measurements of ICP were performed (Table 4). In a retrospective analysis Berdahl et al. found a statistically significant lower ICP in NTG patients as compared with patients with high-tension glaucoma or age-matched non-glaucoma controls from a primarily white dataset. That result was later supported in a prospective study of a Chinese cohort. The control group in the first study consisted of people with refractive errors or cataract who had undergone lumbar puncture for neurologic indication unrelated to ophthalmic findings. The control group in the second study contained patients with various neurologic diseases. In a recently published retrospective analysis of NTG patients undergoing lumbar puncture during computer-assisted cisternography, Pircher et al. were not able to confirm either a reduced ICP or an increased TLCPD. Because no control group was investigated, they compared the results with those of previous studies. In the present study the control materials consisted of prospectively collected data from healthy volunteers with no medical indication to perform lumbar puncture.

The similar ICP in NTG and healthy subjects was surprising to us, but it is noteworthy that our findings had dissimilarities to the studies by Ren et al.  and Berdahl et al. regarding ICP primarily for the control group (Table 4). A statistical comparison between the ICP in the NTG subjects in the studies of Ren et al. and Berdahl et al. and the present study reveals no significant difference (analysis of variance, $P = 0.62$), whereas if we compare the ICP of the corresponding control material there was a statistically significant difference (analysis of variance, $P < 0.01$). Thus, the main difference, compared with previous studies, is a lower ICP in the control group. We have used a standardized technique and specialized equipment for ICP recording, used for 40 years for diagnostic purposes in idiopathic intracranial hypertension and in hydrocephalus. The protocol includes careful avoidance of leakage when placing the needle, setting the zero level very precisely to the auditory meatus with a horizontal laser beam, and then recording the CSF pressure for 15 minutes with the patient in a restful supine position in a silent room. Average pressure during the last 2-5 minutes is used as ICP in supine position. Both control subjects and NTG patients were investigated with the same protocol. We are therefore confident that the ICP assessment in the present study is reliable. The controls (n = 68) from Berdahl et al. with a mean ICP of 12.7 mmHg and mean age of 68 years, were extracted from a larger cohort (n = 1218) that was later published in a study of ICP vs. age. The later study showed a mean value for the age span 60–80 years of 10.3 mmHg (n = 4284), which is close to the ICP in the NTG group of Berdahl et al. and lower than the ICP in the control group (n = 51) of the present study. The control population in the study by Ren et al. revealed a high ICP compared with known normal data. In summary, this study does not support a difference in ICP between NTG and healthy subjects for the horizontal posture.

A pertinent question is what magnitude of pressure difference would be clinically relevant. There is some evidence that a 30% reduction of IOP significantly reduces the progression of NTG. Assuming an average IOP in NTG patients of 16 mmHg, a therapeutic effect may be detected if the IOP is reduced by 5 mmHg. One could argue that a corresponding ICP reduction would be required in NTG. The present study was designed to detect a pressure difference in ICP of 2 mmHg. Thus, based on the negative findings in this study there is no indication of a clinically relevant pressure difference responsible for glaucomatous damage.

Our estimates of TLCPD assumes a free communication between the intracranial CSF space and the LC in all body positions. It has been suggested and indicated in an animal study that in normal physiology the ONS occludes around the optic nerve when ICP is reduced below the surrounding

### Table 3. Adjusted Intracranial Pressure, Adjusted Intraocular Pressure, and Trans-Lamina Cribrosa Pressure Difference in Supine and Sitting Positions

<table>
<thead>
<tr>
<th>Posture</th>
<th>ICP&lt;sub&gt;LC&lt;/sub&gt;</th>
<th>IOP&lt;sub&gt;LC&lt;/sub&gt;</th>
<th>TLCPD = IOP&lt;sub&gt;LC&lt;/sub&gt; − ICP&lt;sub&gt;LC&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NTG</td>
<td>Healthy</td>
<td>NTG</td>
</tr>
<tr>
<td>Supine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTG</td>
<td>7.0 (2.9)</td>
<td>6.6 (1.4)</td>
<td>20.7 (3.2)</td>
</tr>
<tr>
<td>Healthy</td>
<td>6.6 (1.4)</td>
<td>6.6 (1.4)</td>
<td>18.9 (1.8)</td>
</tr>
<tr>
<td>Sitting</td>
<td>−4.9 (2.7)</td>
<td>−4.7 (3.8)</td>
<td>15.8 (3.2)</td>
</tr>
<tr>
<td>NTG</td>
<td>15.8 (3.2)</td>
<td>15.1 (2.3)</td>
<td>13.7 (3.8)</td>
</tr>
<tr>
<td>Healthy</td>
<td>15.1 (2.3)</td>
<td>12.3 (2.2)</td>
<td>20.7 (3.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19.8 (4.6)</td>
</tr>
</tbody>
</table>

ICP<sub>LC</sub> = intracranial pressure adjusted for hydrostatic gradients between the auditory meatus (ICP measurement reference point) and the lamina cribrosa; IOP<sub>LC</sub> = intraocular pressure adjusted for hydrostatic gradients between the cornea (IOP measurement reference point) and the lamina cribrosa; NTG = normal-tension glaucoma; TLCPD = trans–lamina cribrosa pressure difference.

All values presented as mean (SD) in mmHg.

NTG: $n = 13$; healthy: $n = 11$.

### Table 4. Summary of Results from Studies Comparing Intracranial Pressure in Normal-Tension Glaucoma and Controls

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Design</th>
<th>NTG</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N ICP</td>
<td>N ICP</td>
<td>P</td>
</tr>
<tr>
<td>Berdahl et al. (2008)</td>
<td>Retrospective</td>
<td>11 9.3 (3.2)</td>
<td>68 12.7 (3.9)</td>
</tr>
<tr>
<td>Pircher et al. (2016)</td>
<td>Retrospective</td>
<td>38 11.6 (3.7)</td>
<td>na na na na</td>
</tr>
<tr>
<td>Ren et al. (2010)</td>
<td>Prospective</td>
<td>14 9.5 (2.2)</td>
<td>71 12.9 (1.9)</td>
</tr>
<tr>
<td>Present study</td>
<td>Prospective</td>
<td>13 10.3 (2.7)</td>
<td>51 11.3 (2.2)</td>
</tr>
</tbody>
</table>

ICP = intracranial pressure; na = not available; ns = not significant; NTG = normal-tension glaucoma.
intraorbital pressure.\textsuperscript{45} \(\text{ICP}_{\text{LC}}\) would then be constrained to a minimum level corresponding to the intraorbital pressure, producing a safety mechanism against high TLCPD in upright position. This occlusion effect would give a TLCPD in sitting position of about 12.5 mmHg,\textsuperscript{47} which is close to the value we found in supine posture and much lower than the value of about 20 mmHg that is predicted by a fully communicating CSF system (Table 3). A pathologic stiffening of the ONS could lead to incomplete occlusion and full fluid contact, and thereby maintained hydrostatic coupling and pressure transfer between the LC and the intracranial CSF space in upright position. The \(\text{ICP}_{\text{LC}}\) would then correspond to ICP rather than to the intraorbital pressure, resulting in a TLCPD of 20 mmHg (as determined in this study) rather than the 12.5 mmHg that could be expected with an ONS that occludes from intraorbital pressure. This indicates that a stiff ONS could result in abnormal TLCPD in upright position, giving a potential pathophysiological component in NTG, even with a normal upright ICP. However, it has been demonstrated that the CSF turnover in the optic nerve subarachnoid space is reduced in papilledema and in NTG,\textsuperscript{15} and that the optic canal cross-sectional area is smaller.\textsuperscript{46} Both these findings indicate that there is occlusion and an inhibited fluid communication between the intracranial CSF space and optic nerve subarachnoid space in NTG, rather than failure of the ONS occlusion mechanism.

In conclusion, we assessed ICP and IOP simultaneously in both supine and upright positions in NTG patients and healthy controls and found no evidence of reduced ICP or increased TLCPD in NTG patients, indicating that the ICP regulatory system or disturbed CSF dynamics are not the major components of the NTG pathophysiology.

References


**Footnotes and Financial Disclosures**

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Analysis and interpretation: Lindén, Qvarlander, Jóhannesson, Eklund
Obtained funding: Not applicable
Overall responsibility: Lindén, Qvarlander, Jóhannesson, Johansson, Östlund, Malm, Eklund

Abbreviations and Acronyms:
ART = applanation resonance tonometer; CSF = cerebrospinal fluid; HDT = head-down tilt; ICP = intracranial pressure; IOP = intraocular pressure; LC = lamina cribrosa; MRI = magnetic resonance imaging; NTG = normal-tension glaucoma; ONS = optic nerve sheath; TLCPD = trans–lamina cribrosa pressure difference; VFI = visual field index.

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