Optic Nerve Subarachnoid Space Posture Dependency – An MRI Study in Subjects With Normal Tension Glaucoma and Healthy Controls

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Received: June 22, 2023
Accepted: October 29, 2023
Published: December 15, 2023

Citation: Kristiansen M, Holmlund P, Lindén C, Eklund A, Jóhannesson G. Optic nerve subarachnoid space posture dependency – An MRI study in subjects with normal tension glaucoma and healthy controls. *Invest Ophthalmol Vis Sci.* 2023;64(15):20.
https://doi.org/10.1167/iovs.64.15.20

Purpose. The purpose of this study was to examine the differences of optic nerve subarachnoid space (ONSAS) volume in patients with normal tension glaucoma (NTG) and healthy controls in different body positions.

Methods. Eight patients with NTG and seven healthy controls underwent magnetic resonance imaging (MRI) examinations in head up tilt (HUT) +11 degrees and head down tilt (HDT) -5 degrees positions according to a randomized protocol determining the starting position. The ONSAS volume in both body positions was measured and compared between the two groups. The results were analyzed using a generalized linear model.

Results. Between HDT and HUT, the postural ONSAS volume change was dependent on starting position ($P < 0.001$) and group ($P = 0.003$, NTG versus healthy). A subgroup analysis of those that were randomized to HUT examination first, coming directly from an upright position, showed that the patients with NTG had significantly larger positional ONSAS volume changes compared to the healthy controls; 121 ± 22 µL vs. 65 ± 37 µL ($P = 0.049$). Analysis of the ONSAS volume distribution showed different profiles for patients with NTG and healthy controls.

Conclusions. There was a significant difference in ONSAS volume change between patients with NTG and healthy subjects when subjected to posture changes, specifically when going from upright to head-down posture. This indicates that patients with NTG had been exposed to a lower ONSAS pressure when they came from the upright posture, which suggests an increased translaminar pressure difference in upright position. This may support the theory that NTG has a dysfunction in an occlusion mechanism of the optic nerve sheath that could cause abnormally negative ONSAS pressures in upright posture.

Keywords: optic nerve subarachnoid space (ONSAS), glaucoma

Elevated intraocular pressure (IOP) is the most important risk factor for developing glaucoma[1] and we know from landmark studies[2,3] that reducing IOP is beneficial in glaucoma irrespective of IOP level. However, the pathophysiology is still largely unknown, specifically for normal tension glaucoma (NTG) where the IOP is at a level not associated with an increased risk for glaucoma. Multiple theories have been suggested including mechanical[4] and vascular[5] causes. The mechanical theory is focused on stretching and compression of the tissues of the eye damaging the retinal ganglion cells (RGCs) with a special focus placed on disturbed axoplasmic flow seen in glaucomatous optic neuropathy.[6] The translaminar pressure difference (TLCPD) hypothesis states that glaucoma may be caused by mechanical stress on the axons from either increased IOP or decreased intracranial pressure (ICP) or both. In accordance with the TLCPD hypothesis, a disturbed balance between IOP anterior of the lamina cribrosa (LC) and ICP in the optic nerve subarachnoid space (ONSAS) posterior of the LC, would produce both axial and radial forces and deformations[7,8] on the LC, regardless of IOP being high or ICP being low. Thus, the TLCPD hypothesis opens up for a unified pressure-related description for glaucoma that also include patients with NTG.[9–12] However, this requires that the pressure (ICP) that is transferred to the ONSAS behind the eye is reduced in NTG.

Furthermore, the effect of posture must be considered. Changes in body position affect the ICP (from 11 mm Hg to −1 mm Hg when going from supine to sitting) more than the IOP (17 to 15 mm Hg), which leads to postural

differences in TLCPD.[13] This was confirmed in a recent study measuring IOP and ICP in various body positions, but importantly we found no significant difference in IOP-ICP between patients with NTG and control subjects.[14] However, it has been hypothesized that in upright postures, an occlusion (compartmentalization) mechanism of the optic nerve sheath may maintain a higher ONSAS pressure, compared to ICP, immediately behind the LC to protect this balance.[15]

In a study on healthy subjects, we have confirmed that the volume of the ONSAS depends on body posture and we also suggest a model predicting a possible collapse of the ONSAS in the midorbital section of the optic nerve.[16] Such a collapse may thus act as a buffer for the pressure differences associated with changes in body posture, preserving pressure and volume in the ONSAS, and protecting the axons from the hypothesized variations in TLCPD suggested by strict calculations of IOP-ICP. A dysfunction in this occlusion mechanism, potentially due to stiffness differences in the midorbital part of the ONSAS sheath, could result in decreased ONSAS volume and lower ONSAS pressure and a higher TLCPD, increasing the vulnerability of retinal ganglion cells and thus may explain NTG.[15] If there is a collapse in healthy subjects, but not in subjects with glaucoma, this difference in ONSAS volume should be detectable with magnetic resonance imaging (MRI) in alternating body positions. An MRI also grants a further advantage in that it is possible to visualize the entire intraorbital part of the optic nerve and the surrounding ONSAS, allowing for precise measurements. Thus, the aim of this MRI study was to investigate if NTG has an increased change in the ONSAS volume, between head up tilt (HUT) and head down tilt (HDT), as a sign of reduced ONSAS pressure around the optic nerve in upright postures.

Materials and Methods

This prospective single-center study designed to measure changes in the ONSAS volume depending on body position was carried out at the Umeå University Hospital, Sweden. The study was approved by the Swedish Ethical Review Authority. It was performed in accordance with the Declaration of Helsinki. Oral and written consent was acquired before participation in the study.

Subjects from a previous study investigating TLCPD in patients with NTG[14] were offered to participate. All 13 patients with NTG were invited and 8 accepted. The reasons for nonparticipation were deceased ($n = 1$), unable to attend within the study's timeframe ($n = 2$), declined ($n = 1$), and no response ($n = 1$). All patients had bilateral NTG which was defined as untreated and treated IOP readings in the patient's history of a maximum of 21 with the occasional measurement of up to 24 mm Hg coupled with optic disc damage and corresponding glaucomatous visual field defects. All subjects had IOP below 21 mm Hg with no higher recorded pressures at the time of diagnosis. Sixteen healthy controls that had previously been recruited[17] were invited to participate and seven of them accepted. The respective reasons for nonparticipation in this group were; deceased ($n = 2$), unable to attend within the study's timeframe ($n = 2$), declined ($n = 2$), suspected glaucoma ($n = 1$), and no response ($n = 2$). To ensure that no control subjects displayed any signs of glaucomatous disease, they underwent an ophthalmological examination including visual acuity, slit lamp microscopy, Goldmann Applanation Tonometry (GAT), and visual field examination measured as Visual Field Index (VFI) using Humphrey Field Analyzer HT 24-2 (Carl Zeiss Meditec AG, Jena, Germany).

Both groups underwent MRI with a 3-tesla scanner (GE Discovery MR750; General Electric Healthcare, Waukesha, WI, USA) using a 32-channel head coil. The volume of interest was placed perpendicular to the optic nerve intraorbitally to achieve cross-sectional images of the ONSAS and a T2-weighted fast recovery fast spin echo sequence with fat suppression was utilized to clearly depict the ONSAS. The field of view was 160 × 160 mm (matrix 512 × 512) with 25 slices of slice thickness 2 mm (slice gap 0), resulting in a spatial resolution of 0.31 × 0.31 × 2 mm. The repetition time/echo time was 6000/196 ms; number of excitations 3; flip angle 111 degrees; echo-train length 24; and pixel bandwidth 195.312 Hz/pixel. The scanning time per sequence was roughly 2.5 minutes.

Scans were acquired in two body positions, HUT equaling +11 degrees and HDT measuring −5 degrees. We aimed to achieve the maximum tilt angle possible for each subject. Each eye was scanned twice in each body position and the scan with the best signal to noise ratio was chosen for analysis. The starting position was randomized within each group; half of the subjects starting in HUT ($Start_{HUT}$) and the other in HDT ($Start_{HDT}$). A total time in the MRI for each position was approximately 10 minutes (Fig. 1). The two body positions were achieved using a wedge to tilt the upper body of the subjects, as well as the head coil for HUT. Estimates of the ONSAS pressure difference (ΔP) between the two postures was obtained by measuring the change in height to the LC while using the heart as reference. The main outcome variable was the ONSAS volumetric *change* between HUT and HDT, as this approach should not be sensitive to possible differences in ON volume between the groups.

Segmentation

The ONSAS was segmented from the LC to the optic canal directly from the images (across 13 slices) generating a fixed length of 26 mm from the LC for all subjects. The data were anonymized and a masked experienced researcher (author P.H.) performed the measurements for all subjects. The area for each cross-section of the ONSAS was calculated and multiplied by the length of each slice to acquire the volume. The compliance of the ONSAS is defined as the change in volume resulting from a change in pressure, and was calculated as follows:

$$Compliance = \frac{\Delta V}{\Delta P} = \frac{V_{HDT} - V_{HUT}}{P_{HDT} - P_{HUT}}$$

The compliance reflects the malleability of the optic nerve sheath. We manually segmented ON and ONSAS on each slice (see Fig. 2) and integrated ON and ONSAS volumes. The measurements were deemed to have a high reproducibility considering the method and application was evaluated in a previous study in our group.[16]

Statistical Analysis

All calculations were done in SPSS. In both the NTG and control groups, the mean ONSAS volume of both

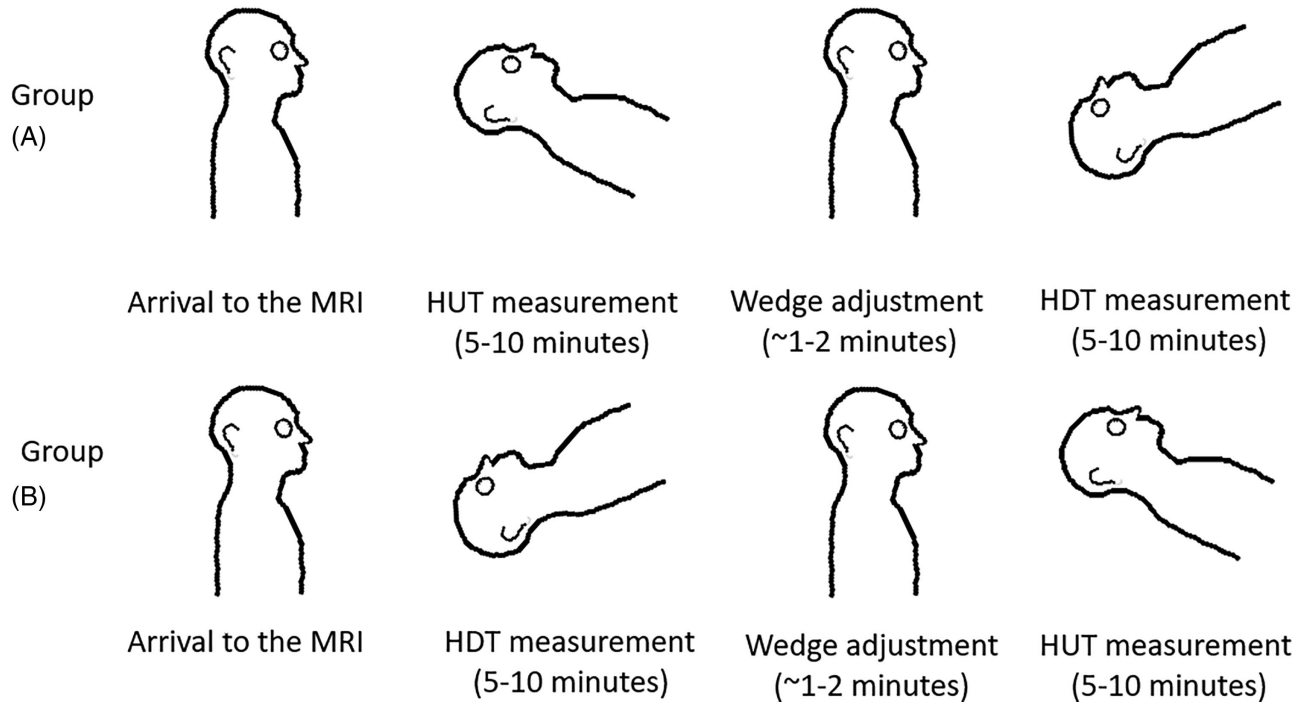

Figure 1. Measurement procedure according to randomization. After being positioned in the starting position, the subjects kept that position for roughly 5 to 10 minutes before the scan was started, which always started with the right eye. Then, the subjects stood up for 1 to 2 minutes and then laid down in the second position for another 5 to 10 minutes before scanning resumed.

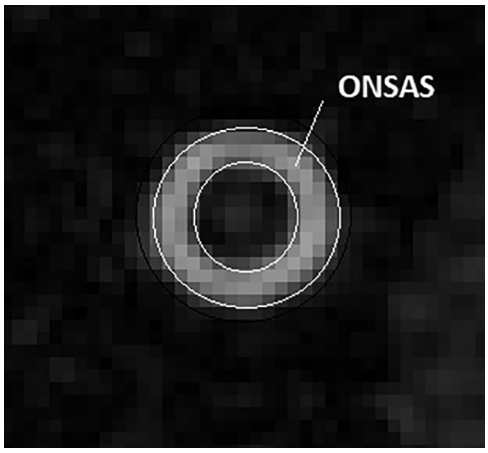

Figure 2. ONSAS fluid area during measurement.

eyes was used for calculation. As two sets of scans were taken for each eye and body posture for every subject, the best image in terms of signal to noise ratio was selected for data analysis. We performed a generalized linear model analysis with disease (yes/no) and randomization ($Start_{HUT}$/$Start_{HDT}$) as predictors of the postural volume change. Results are presented as mean ± standard deviation (SD) unless otherwise specified. For additional clarity, changes to volume were also calculated as percentage based using the $Start_{HUT}$ measurements as baseline. Tests of normality were performed using Shapiro-Wilk test. Student's paired samples *t*-test was used for comparison within the same group and Student's *t*-test with independent groups for comparisons between the groups.

Results

Descriptive statistics and ONSAS volumes are presented in Tables 1 and 2, respectively. Table 3 and 4 present the results of the generalized linear model showing a significant difference in ONSAS volume change between the patients with NTG and the healthy group ($P = 0.009$). Interestingly, it also showed that the randomization ($P < 0.001$) had a significant impact on the results as well as an interaction between the two terms ($P = 0.043$). The results of the generalized linear model resulted in additional analysis being carried out on the subgroups. The difference between HDT and HUT was statistically significant in both the glaucoma group ($P = 0.03$) and the control group ($P = 0.02$). As expected, the ON volume was statistically smaller in the NTG group (see Table 2). Figures 3 and 4 display volume distribution along the optic nerve sheath within the orbital cavity for HUT and HDT, respectively.

Table 1. Descriptive Statistics of the Participants

Descriptives	NTG	Controls	*P* Value
Age, y	74 ± 10	74 ± 9	0.96
Females	8/8	5/7	0.17
VA, logMAR	0.45 ± 0.82	0.1 ± 0.07	0.26
IOP, mm Hg	13.1 ± 2.6	15.3 ± 1.0	0.06
VFI, %	44.8 ± 23.6	97.1 ± 2.1	<0.001
IOP treatment*	1.6 ± 1.1	0	0.003

* Number of IOP-lowering substances.

Table 2. Volume Measurements in Both Positions for Patients With NTG and Healthy Controls

Results	NTG	Control	*P* Value
ONSAS vol HDT, µL	224 ± 52	209 ± 79	0.68
ONSAS vol HUT, µL	150 ± 68	163 ± 84	0.74
ONSAS vol diff, µL	74 ± 56	45 ± 36	0.25
ONSAS vol diff, %	72 ± 72	35 ± 11	0.22
Pressure difference (Δ*P*)[†] mm Hg	7.75 ± 1.92	10.31 ± 1.61	0.015[*]
ON volume HDT, µL	88 ± 15	127 ± 14	0.0002
ON volume HUT, µL	79 ± 9	122 ± 10	<0.0001

[*] This difference is due to slightly larger tilt-angles achieved for the control group.
[†] Estimates of ONSAS pressure difference between the two postures (Δ*P*).

Table 3. Generalized Linear Model of Randomization and Group

Source	Wald Chi-Square	*P* Value
Randomization	32.876	0.000
NTG	6.877	0.009
Interaction between the two factors	4.107	0.043

Table 4. Estimates for the Generalized Linear Model Describing the ONSAS Volume Change Between HDT and HUT

Group	Randomization	Mean Volume Change, µL	Std. Error
NTG	$Start_{HDT}$	27.0	11.7
	$Start_{HUT}$	121.2	11.7
Control	$Start_{HDT}$	19.8	13.5
	$Start_{HUT}$	64.8	11.7

Subgroup Analysis

During data analysis the generalized linear model highlighted that the randomization had a significant impact on the results and further investigation of the data showed that the NTG subjects in the $Start_{HUT}$ group exhibited significantly higher degree of volume change compared to $Start_{HDT}$ (121 ± 22 vs. 27 ± 29 µL, $P = 0.003$). The corresponding number for the healthy control group was not significant (65 ± 37 vs. 20 ± 6 µL, $P = 0.09$).

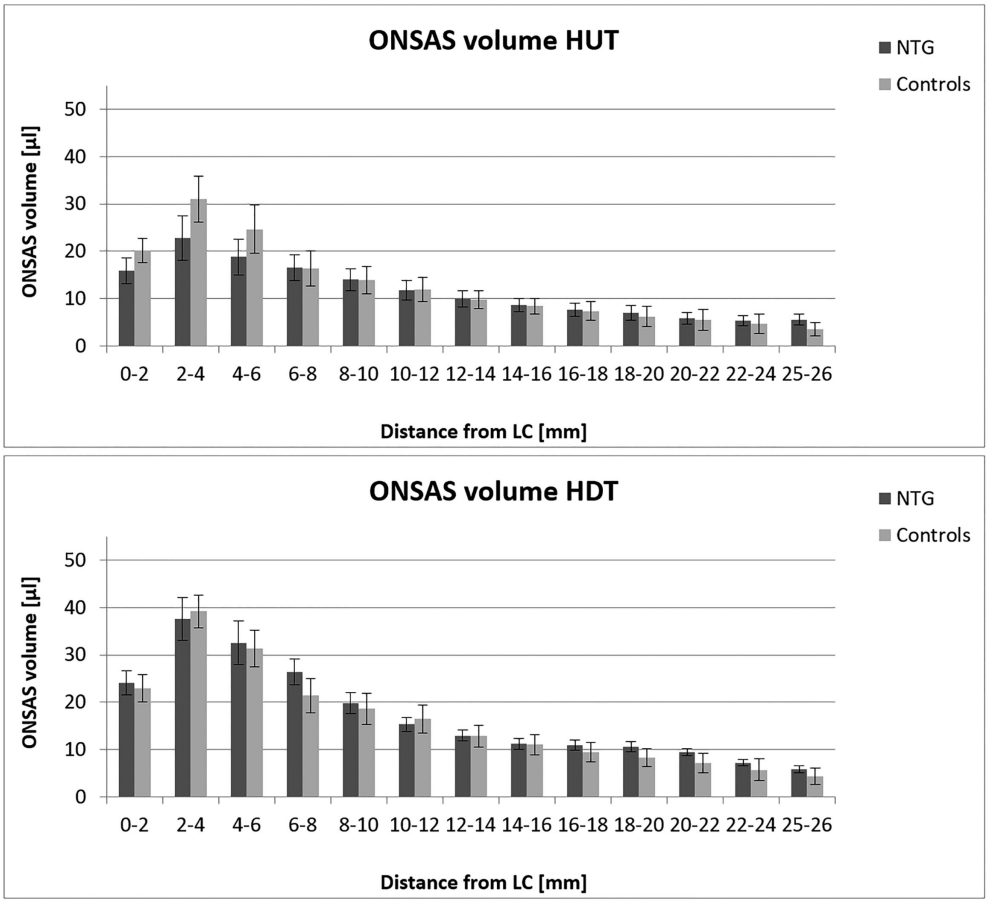

Figure 3. ONSAS volume in HUT and HDT for patients with NTG and healthy subjects. Error bars represent standard error of mean.

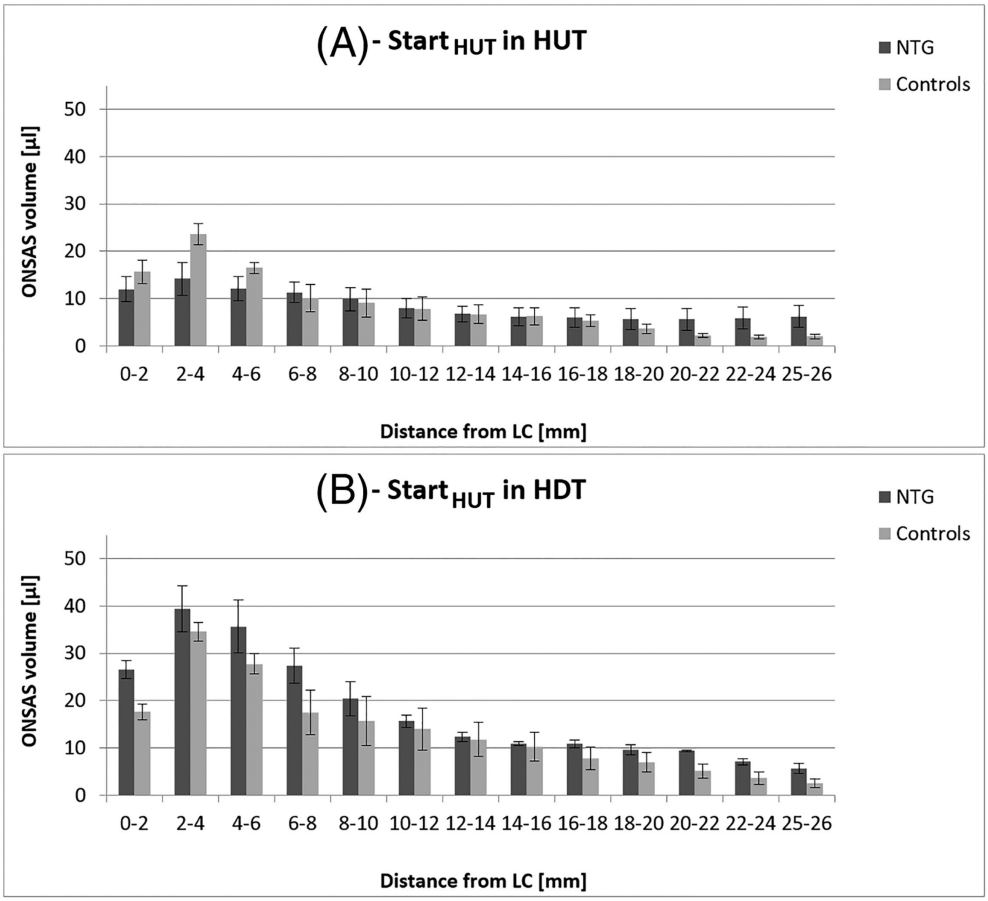

Figure 4. Volumes for $Start_{HUT}$ groups of patients with NTG and healthy controls. (**A**) ONSAS volume of subgroup $Start_{HUT}$ in HUT position of patients with NTG ($n = 4$) and healthy controls ($n = 4$). Note the difference in ONSAS volume between the bulbar and distal orbital segments with respect to patients with NTG and healthy controls. (**B**) ONSAS volume of subgroup $Start_{HUT}$ in the HDT position for patients with NTG ($n = 4$) and healthy subjects ($n = 4$). Error bars represent standard error of mean.

Table 5. Subgroup Analysis Based on Starting Position; $Start_{HUT}$ or $Start_{HDT}$

Subgroup $Start_{HUT}$	NTG $Start_{HUT}$	Controls $Start_{HUT}$	*P* Value
ONSAS vol HDT, µL	231 ± 35	175 ± 63	0.19
ONSAS vol HUT, µL	110 ± 52	111 ± 26	0.98
ONSAS vol diff, µL	121 ± 22	65 ± 37	0.049*
ONSAS vol diff, %	130 ± 55	55 ± 23	0.067
Pressure difference (Δ*P*) mm Hg	7.51 ± 2.12	10.14 ± 2.18	0.13
Subgroup $Start_{HDT}$	**NTG $Start_{HDT}$**	**Controls $Start_{HDT}$**	***P* Value**
ONSAS vol HDT, µL	217 ± 71	253 ± 88	0.59
ONSAS vol HUT, µL	190 ± 61	234 ± 85	0.50
ONSAS vol diff, µL	27 ± 29	20 ± 6	0.66
ONSAS vol diff, %	15 ± 17	9 ± 4	0.57
Pressure difference (Δ*P*) mm Hg	8.00 ± 1.98	10.53 ± 0.68	0.078

* $P < 0.05$.

We therefore performed an extended analysis focusing on the $Start_{HUT}$ group. Data are presented in Table 5. Within the $Start_{HUT}$, the patients with NTG displayed a larger mean change (121 ± 22 µL) compared with the control group (65 ± 37 µL, $P = 0.049$; see Table 5). The difference between groups was most pronounced in the anterior ONSAS section including the bulbar segment, that is, the ONSAS segment closest to the eye (see Fig. 4 for HUT and HDT volumes). For the $Start_{HDT}$ group, there was no significant difference between patients with NTG and the healthy subjects ($P = 0.66$; see Table 5).

Discussion

In this study, we examined the change in ONSAS volume between different body positions in patients with NTG and

healthy subjects. Our hypothesis was that patients with NTG do not exhibit a collapse of the midorbital section of the ONSAS[15] as we predicted would exist in healthy subjects. Dysfunction of such a mechanism could partly explain NTG pathophysiology in accordance with the TLCPD theory, which states that a high TLCPD may be detrimental to the optic nerve and a contributing factor of NTG pathophysiology. A dysfunctional collapse would predict a low ONSAS pressure with corresponding small (drained) ONSAS volume in the upright position in patients with NTG. Hence, we hypothesized that the patients with NTG would display a larger volume difference between the HUT and HDT tests compared to the healthy controls as a result of a possibly disrupted ONSAS collapse.

Our results showed that the volume of the ONSAS varied with body position in both patients with NTG and healthy controls. The results based on all subjects showed a statistical difference both in terms of (a) patients with NTG or healthy controls, (b) the randomization order, as well as (c) a mixed effect of these two factors. Thus, the randomization introduced differences in the ONSAS behavior, revealing a larger change in those that started in HUT compared to those that started in HDT. The mixed term revealed that the dependency of randomization was more prominent in patients with NTG compared to the healthy controls, indicating that when coming from an upright posture, the ONSAS volume was more affected in patients with NTG.

As seen in our subgroup analysis for $Start_{HUT}$, the change in ONSAS volume between HUT and HDT (Δvol) was significantly different between patients with NTG and healthy controls, with patients with NTG displaying a larger change in volume. This difference was particularly seen in the bulbar segment (see Fig. 4). Another fact of interest is the distribution of liquid in the ONSAS along the ON. Whereas the bulbar segment showed a more variable amount of liquid in patients with NTG, the ONSAS of the healthy controls maintained more stable volume. Interestingly, the profile of the distal part of the ONSAS (see Fig. 4) showed different behavior between patients with NTG and healthy controls, with smaller volumes in healthy controls and larger in patients with NTG suggesting a closure of the ONSAS in healthy subjects. These differences may support the theory that there is a dysfunction in the potential collapse mechanism in patients with NTG,[15] which could potentially be related to altered properties of the microstructures of the ONSAS[18,19] or ON atrophy due to glaucoma degeneration. A fully "open" ONSAS would suggest a lower pressure within the bulbar ONSAS segment during an upright position due to a direct transfer of a negative ICP to the ONSAS,[13] that is, no collapse of the ONSAS.

To explain the difference between the two start position groups, we would like to consider the fundamental differences between the two starting positions. In the $Start_{HUT}$ group, subjects come from an extended period of upright posture prior to the examination, whereas subjects randomized to $Start_{HDT}$ have been in the HDT position before the HUT measurements. The approximately 1 to 2 minutes that were spent in an upright position between the measurements of the $Start_{HDT}$ group coupled with the approximately 5 to 10 minutes in the HDT position before measurement did, in this context, not satisfy the normal physiological conditions that an upright position throughout the day entails. Thus, it seems that coming directly from an extended time in the upright position affect the patients with NTG more than the healthy controls. This indicates that patients with NTG have different fluid dynamics compared to healthy subjects and that the fluid dynamics are more strongly dependent on time.

Comparison with similar studies is difficult due to the relatively new interest in dynamic fluid measurements within the ONSAS in different body positions. Previous studies on patients with NTG in supine position performed with ultrasound 3 to 7 mm behind the lamina cribrosa detected a smaller ONSAS area compared to healthy adults indicating a lower ONSAS pressure,[20,21] although contradictory results exist,[22] Pircher et al.[11] have shown that patients with NTG had enlarged optic nerve sheath diameters compared to healthy subjects while maintaining similar levels of ICP in lumbar measurements suggesting an altered communication. The interpretation of our results with a non-collapsing distal orbital section (see Fig. 4) would support a low pressure in patients with NTG but primarily for the upright posture. Consequently, head-to-head comparison is difficult because dynamic posture has not been included in previous study designs.[11,20,21,23] ONSAS diameter and volume has been suggested as a noninvasive surrogate for ICP measurements.[24,25] Although most feasible in vivo, the measurement of ONSAS diameter or volume is an indirect estimate of ICP, and given the results of this study, they are highly dependent on the patient's posture history. Thus, using ONSAS as surrogate for ICP would at least require a standardized protocol with respect to posture and should be evaluated with care.

The field of fluid dynamics within the ONSAS region is only partially understood. Whereas our mechanistic description of pathophysiology is focused on the pressure balance over the LC, there are other theories related to constriction or compartmentalization of the ONSAS.[11,26] Other studies focusing on cerebrospinal fluid (CSF) exchange[18,27] in the ONSAS among patients with NTG revealed a lower exchange within this region indicating compartmentalization of the fluids and suggesting a gradually decreasing CSF flow along the ONSAS on its way to the bulbar segment. This is in contrast with our findings that show an ONSAS difference between patients with NTG and healthy controls in $Start_{HUT}$, that could possibly indicate a larger fluid exchange in patients with NTG. Furthermore, our results suggest that if subjects in the previous studies had been in an upright position for a prolonged time and not exposed to an HDT position, this may account for the difference seen in the respective studies. There are several strengths in this study. First, MRI is a reliable and safe method to quantify the fluid within the ONSAS and on the contrary to ultrasound, MRI offers the possibility of covering the entire length of the optic nerve. Second, the randomization of the order of starting positions proved to be valuable, as without this randomization we would not have discovered the time aspect of the ONSAS volume changes seen in the subgroup analysis. Finally, we used the same protocol for measurements that have been used in previous studies.[16] However, the study also has identifiable weaknesses. The volume of the ONSAS is an indirect indicator of a drainage effect of the ONSAS in an upright posture. It is a small initial study, which increases the chance of a type 2 error considering the small number of participants. Furthermore, although the method has been previously evaluated,[16] the manual delineation introduces a source of error. Finally, due to the fact that the subjects were elderly and some suffered from back and neck problems, the maximum tilt was not achieved in all subjects, which resulted in a slight difference in tilt

angle between the groups. However, the tilt was larger in the control group which would have a diminishing effect on the results and if anything should lessen the observed difference between the groups. Learning from our experience, a structured approach to the time spent in each position and an easily reproducible angle of the subjects' body positions would increase the precision of the experiment. Ideally, a larger study performed with an MRI designed to tilt the board of the MRI, or an upright MRI would enable further and more drastic changes in body position and consequently ICP and the direct assessment of ONSAS volumes in upright posture.

In conclusion, there was a significant difference in ONSAS volume change between patients with NTG and healthy subjects when subjected to posture changes, specifically when going from upright to head-down posture. This may indicate that patients with NTG had been exposed to a lower ONSAS pressure in the upright posture, which suggests an increased TLCPD in upright position. This supports further investigation of a potential dysfunction of an occlusion mechanism along the ONSAS, through an optic nerve sheath collapse around the optic nerve, as a part of NTG pathophysiology.

Acknowledgments

Disclosure: **M. Kristiansen**, None; **P. Holmlund**, None; **C. Lindén**, None; **A. Eklund**, None; **G. Jóhannesson**, None

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