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Non-invasive Evaluation of Cerebrospinal Fluid Pressure in Ocular Hypertension: The Beijing Intracranial and Intraocular Pressure Study

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Abstract

Objective: To compare the orbital CSFP and trans-lamina cribrosa pressure difference (TLCPD) determined non-invasively in Ocular Hypertension (OH) and controls, and study its association with the estimated risk of conversion to glaucoma.

Design: Cross-sectional observational study.

Participants: 19 subjects with OH recruited from the Tongren Eye Center and 23 controls enrolled in the Beijing Intracranial and Intraocular Pressure Study between June 2010 to December 2013.

Methods: Magnetic resonance imaging was used to measure orbital subarachnoid space width (OSASW) at 3, 9 and 15 mm posterior to the globe. The CSFP (mmHg) was estimated from a published formula as 17.54 × MRI derived OSASW at 15 mm behind the globe +0.47 × body mass index +0.13 × mean arterial blood pressure -21.52. Estimated TLCPD was calculated as IOP- CSFP. The values of CSFP and TLCPD were compared between OH and controls. The estimated risk of progression to glaucoma in OH was calculated and its correlation with CSFP determined.

Main outcome measures: Orbital subarachnoid space width; MRI derived CSFP value; TLCPD value. Association of risk of progression with CSFP.

Results: The orbital subarachnoid space width was significantly wider (P=0.01) in the OH group than in the control groups at all three measurement locations. The MRI derived CSFP value in OH (14.9 ± 2.9 mmHg) was significantly higher than in the normal group (12.0 ± 2.8 mmHg; P<0.01). The estimated TLCPD value in OH (9.0 ± 4.2 mmHg) was significantly higher than in controls (3.6 ± 3.0 mmHg; P<0.01). The estimated risk of conversion to glaucoma in OH (15.2 ± 8.7%) was negatively correlated with the MRI derived CSFP value (r=-0.51, r2=-0.26, P<0.01).

Conclusions: The wider OSASW and higher estimated CSFP in OH subjects suggest a higher orbital CSFP. Despite a higher orbital CSFP that could be protective, the higher TLCPD in OH may play a significant role in the risk of developing glaucoma.

Keywords: Ocular hypertension; Orbital subarachnoid space width; Cerebral spinal fluid pressure; Trans-lamina cribrosa pressure difference; Magnetic resonance imaging

Introduction

Ocular Hypertension (OH) refers to an intra-ocular pressure (IOP) that is higher than normal, usually considered as ≥ 22 mmHg or higher than two standard deviations above the mean IOP in the population on 2 or more occasions with open angles, normal optics discs and

visual fields [1]. OH is a risk factor for (POAG), and may or may not require treatment.

Recent experimental and clinical investigations have provided evidence that an abnormally low orbital Cerebral Spinal Fluid Pressure (CSFP) may result in elevated Trans-Laminar Cribrosa Pressure Difference (TLCPD) that could be associated with the pathogenesis of POAG, especially normal tension glaucoma [2-9]. OH is often considered the opposite end of the glaucoma spectrum to normal tension glaucoma. This led us to hypothesize that there could be a higher orbital CSFP in OH. If so, it would tend to balance the increased IOP and result in a Trans-Lamina Cribrosa Pressure Difference (TLCPD) within the normal range possibly negating the effect of TLCPD in causing optic nerve damage. This interaction could be one factor that plays a role in whether damage occurs or not. It is also possible that measurement of CSFP if and when it becomes available may have the potential value for detection and monitoring of OH and POAG.

The assessment of the CSFP and TLCPD in therefore mentioned clinical studies was based on a single lumbar CSFP measurement, not the more relevant (and more difficult) measurement of the orbital CSFP [4-7]. While direct measurement of orbital CSFP is invasive and currently impossible in clinical practice, high-resolution MRI has been reported to be a reliable measure of optic nerve, optic nerve sheath and peripheral cerebrospinal fluid with good inter-and intra-observer agreement [10-14]. Several publications have used MRI to evaluate CSFP by measuring the size of the optic nerve sheath or the optic nerve subarachnoid space [15-17]. We have previously reported the non-invasive estimation of CSFP using orbital magnetic resonance imaging (MRI) [18]. A recent study in dogs reported an algorithmic relationship between measured lumbar CSFP and orbital CSFP; while this study was in a different species and the relationship maintained only up to a breakpoint, it supports the use of estimated lumbar CSFP as a surrogate for orbital CSFP [19].

We report the measurements of CSFP and TLCPD in OH and controls as well as the association of estimated CSFP with the risk of conversion to glaucoma.

Materials and Methods

The ethics committee of the Beijing Tongren Hospital approved the study protocol and all participants signed an informed consent. The study was registered in the Chinese Clinical Trial Registry (registration site: ChiCTR-OCC-11001271).

Consecutive subjects with OH seen at Tongren Eye Center, Beijing, China, between June 2010 and December 2013 were enrolled. The control group included subjects with normal IOP and normal optic discs recruited from the local community by advertising the project and were age matched with the OH group. The inclusion and exclusion criteria of OH group were based on the European Glaucoma Prevention Study [20]. And diabetics with any sign of retinopathy were excluded. Those with contraindications to MRI examination as well as those with any factors or disorders that could influence intracranial pressure such as pseudotumor cerebri, intracranial tumors, use of drugs such as carbonic anhydrase inhibitors, previous cranial surgery, traumatic brain injury or previous lumbar puncture were also excluded. The sample size was calculated using a web based statistical software available at http://www.stat.ubc.ca/~rollin/stats/ssize/n2.html. With an α error of 5% and β error of 20%, mean CSFP in OH of 16 mmHg and 12.9 mmHg in controls and standard deviation of 2.5 mmHg, the minimum required sample size was calculated as 11 in each group [4,21].

All subjects including controls underwent a complete ophthalmic and neurologic examination followed by a cranial and orbital MRI. Three glaucoma specialists (XX, NW and HW) examined examination results in a masked manner. All three specialists adjudicated disagreements and if any of the examiners disagreed with the diagnosis, the participant was excluded.

The ophthalmic examination included visual acuity, refraction, slit-lamp biomicroscopy, applanation tonometry, central corneal thickness, gonioscopy, dilated fundus examination, optical coherence tomography and visual field. IOP was measured at 10 am, 2 pm, 6 pm, 10 pm, 2 am, 5 am and 7 am using a calibrated Goldmann applanation tonometer to obtain a "24-hour" IOP profile on all OH subjects. As controls did not agree to be admitted for a 24 h profile, they underwent three IOP measurements on a single occasion and the average of the three readings was recorded. Central corneal thickness (CCT) was measured using an ultrasonic pachymeter (SP-3000; Tomey Co. Nagoya, Japan) and IOP measurements were corrected for CCT as detailed by Kohlhaas and Pillunat [22]. The diagnosis of OH required at least three consecutive CCT corrected IOP measurements higher than 22 mmHg in both eyes. All subjects underwent a minimum of two standard automated perimetry examinations (central 30-2 full threshold program; Humphrey Field Analyzer; Zeiss Meditec AG, Jena, Germany) within a 6-month period. Baseline tests had to meet reliability criteria of <33% false positives, <33% false negatives, and <33% fixation losses. A reliable visual field was defined as abnormal if the Glaucoma Hemifield Test (GHT) was outside normal limits and/or the Corrected Pattern Standard Deviation (CPSD) was P<5%. Fundus photographs (Fundus camera EOS D60; Canon Co., Utsunomiyashi, Tochigiken, Japan) and peripapillary retinal nerve fiber layer thickness measurement by spectral domain optical coherence tomography (RTVue-100; software version 4.0; Optovue, Inc., Fremont, CA, USA) were obtained.

The MRI examination included cranial and orbital MRI performed in the supine position with a 3.0 TESLA whole body scanner (Signa HDx; General Electric Medical Systems, Milwaukee, WI) using an 8-channel, phased-array head coil. To avoid artifacts due to motion of the eye, all subjects were instructed to fixate on a target attached directly to the gantry of the MRI scanner. Both eyes of the patients were examined in the same manner. If a motion artifact was detected during the study, the sequence was repeated.

For the measurement of the optic nerve/sheath complex, a fast recovery fast spin echo sequence (FRFSE) was applied. Scout images in the transverse and oblique sagittal planes were used to ensure optimal head positioning; oblique coronal images were used for quantification. Two basic FRFSE sequences were used [8,18]:

-A T2-weighted fast recovery fast spin echo sequence (T2WI-FRFSE) provided good soft tissue contrast and morphologic data for planning (TR=2760 milliseconds; TE=120 milliseconds; number of excitations=2; echo train length=18; bandwidth=41.67 Hz/pixel; field of view=16 cm × 16 cm; matrix=512 × 256; slice thickness=3 mm; slice gap=0.3 mm; leading to a nominal spatial resolution of 0.2 mm × 0.2 mm). The sequence was applied twice with 12 contiguous slices in transversal and sagittal orientation. The acquisition time was 1′30″ (transversal) and 1′29″ (sagittal), respectively (Figure 1).

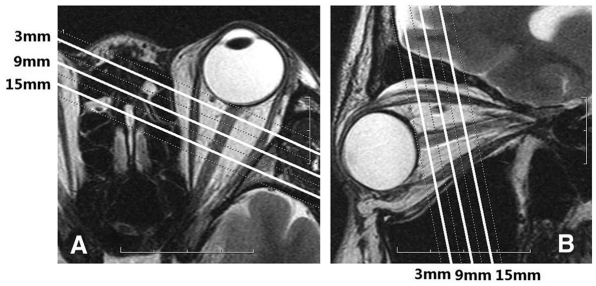

Figure 1: Example of magnetic Magnetic resonance imaging (MRI) scan of the retrobulbar optic nerve (A) transversal section, and (B) oblique sagittal section) T2WI-FRFSE of the retrobulbar optic nerve (digital field of view=8, window width=2000, window level=1000). These images were used to plan the position of 3 slices at 3, 9, and 15 mm behind the globe of T2WI-FRFSE fat-suppressed sequences to measure the optic nerve diameter, optic nerve sheath diameter, and width of the orbital subarachnoid space at 3, 9, and 15 mm behind the globe.

-A T2-weighted fast recovery fast spin echo sequence with fat suppression was optimized for quantification of the morphology (TR=6000 milliseconds; TE=245 milliseconds; number of excitations=2; echo train length=60; bandwidth=20.83 Hz/pixel; field of view=16 cm × 16 cm; Matrix=320 × 320; nominal spatial resolution=0.5 mm × 0.5 mm; slice thickness=3 mm; slice gap=0). The T2WI-FRFSE images were interpolated to a higher matrix size of 1024 × 1024, leading to a pixel size of 0.16 mm × 0.16 mm for better visualization. Seven oblique coronal MR images were continuously acquired perpendicular to the optic nerve orientation with placement of the first slice directly posterior to the globe. The images were acquired for both eyes separately (Figure 1). The optic nerve acquisition time was 1′18″. The acquisition time was 11 seconds per slice. In these oblique coronal images, the cerebrospinal fluid showed a high, white signal and the optic nerve parenchyma a low, dark signal (Figure 2). Three oblique coronal slices perpendicular to the optic nerve at 3, 9, and 15 mm behind the globe were evaluated. Two observers (WC and ZL) evaluated the images independently in a masked manner using ImageJ 1.46r (National Institutes of Health, USA; available at: http://imagej.nih.gov/ij). The oblique coronal image was zoomed to 300X. The horizontal and vertical diameters of the optic nerve and the optic nerve sheath (optic nerve including the meninges) were measured using an electronic caliper. The average diameter of the optic nerve and of the optic nerve sheath was calculated as the mean of the measured horizontal and vertical diameters. The orbital subarachnoid space width (OSASW) was determined by subtraction of the mean optic nerve measurement from the mean optic nerve sheath measurement divided by 2. The inter- and intra-observer repeatability was tested on all 42 participants. For the assessment of the intra-observer repeatability, observer 1 repeated the analysis after three months. All measurements made by both observers were used to calculate inter-observer repeatability.

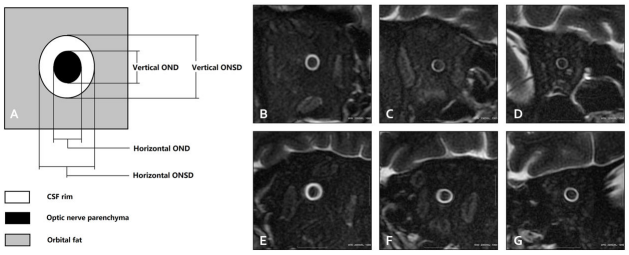

Figure 2: (A) Diagram of optic nerve sheath complex and MRI images at 3 mm, 9 mm, and 15 mm behind the globe. Schematic drawing of the optic nerve sheath complex. The black area represents optic nerve and is surrounded by the white cerebrospinal fluid space. The optic nerve sheath is the black line between the cerebrospinal fluid space and orbital fat. OND: optic nerve diameter. ONSD: optic nerve sheath diameter. Images B-G demonstrate oblique coronal MRI images the optic nerve/sheath complex at 3 mm (B, E), 9 mm (C, F) and 15 mm (D, G) behind the globe. (digital field of view=4, window width=2000, window level=1000) B-D: 57-year-old healthy male. The optic nerve diameter and orbital subarachnoid space width decrease with increasing distance from the globe. E-G: 58-year-old female with ocular hypertension. The orbital subarachnoid space is relatively wide and bright.

The estimated CSFP (mmHg) value was calculated as 17.54 × MRI derived OSASW at 15 mm behind the globe +0.47 × body mass index +0.13 × mean arterial blood pressure-21.52 [18]. Compared to a lumbar spinal CSFP measurement, the mean estimated bias ± standard deviation (and the 95% limits of agreement) by the above formula was 0.08 ± 2.55 (-4.90-5.10) mmHg [18]. Estimated TLCPD was calculated as the difference of mean IOP and estimated CSFP value. Body weight and height were measured for all subjects. Body mass index (BMI) was calculated as measured weight in kilograms divided by the square of measured height in meters. Systolic and diastolic blood pressure was measured in the supine position. Mean arterial blood pressure (MAP) was calculated as 1/3 × systolic blood pressure +2/3 × diastolic blood pressure.

To estimate 5-year risk of developing POAG, the age, IOP, CCT, stereo photograph-based vertical cup-to-disc ratio, and pattern standard deviation of the OH group were imported into the online calculator available at http://ohts.wustl.edu/risk [23-26]. The need for treatment was determined by entering age, pattern standard deviation, CCT, vertical cup-disc ratio, and risk of conversion to glaucoma in 5 years were entered in the "threshold to treat" calculator, available at http://oil.wilmer.jhu.edu/threshold/ [27].

Statistical analysis

Statistical analysis was performed using SPSS (SPSS for Windows, v. 16.0, IBM-SPSS, Chicago, IL). Parameters with a normal distribution were presented as mean ± standard deviation. Parameters that did not follow a normal distribution were presented as median and quartiles. The normal distribution of data was examined using the Shapiro-Wilk's W test, while homogeneity of variance was examined using Levene's test. As they did not follow a normal distribution, the Mann-Whitney test was used for BMI, systolic, diastolic and MAP and vertical cup-to-disc ratio. A two-tailed Student's t-test was used for other

demographic, clinical data, MRI optic nerve/sheath measurements, non-invasive CSFP and TLCPD. A paired sample t-test was used to compare MRI data between the right and the left optic nerves in both groups. The MRI optic nerve/sheath measurements obtained at different measurement locations were analyzed using 2-way repeated-measures ANOVA with group (control group and OH group) as between-subjects factor and location as within-subjects factor. Greenhouse-Geisser correction was applied whenever the sphericity assumption was violated. Multivariate analysis of variance process and Bonferroni correction for multiple comparisons were used to detect significant differences between groups and different measurement locations of each group. P<0.05 was considered statistically significant.

The MedCalc program (v. 11.5.1.0 for Windows; available at: www.medcalc.be; accessed April 20, 2011) was used to calculate the Intra-class correlation coefficient (ICC) and Bland-Altman plot for intra and inter-observer reproducibility of the optic nerve/sheath measurements using at the different measurement locations.

Results

The study included 19 OH subjects and 23 normal controls. The two groups did not differ in age, gender, height, or systolic arterial pressure. However, BMI, weight, MAP and diastolic arterial pressure were higher in OH group (Table 1). The mean CCT was thicker and mean IOP and IOP corrected for CCT significantly higher in the OH group. Retinal nerve fiber layer thickness in the two groups was similar (Table 2).

	Ocular Hypertensive Group	Control Group	t	χ^2	P-Value
No. of patients	19	23			
Age (year)	44.6 ± 14.6	41.33 ± 11.7	0.82		0.42
Gender (Male/Female)	12/7	16/7		0	0.66
Height (cm)	167.5 ± 8.6	166.60 ± 8.2	0.20		0.84
Weight (kg)	73.6 ± 12.6	65.6 ± 11.2	-2.16		0.04*
Body mass index (kg/m²): median; quartiles	25.8 (23.8,27.9)	23.7 (20.8,25.6)		133.00	0.02*
Arterial pressure (mmHg)					
Systolic: median quartiles: median; quartiles	130 (120,140.0)	120 (120,130)		193.50	0.17
Diastolic: median quartiles: median; quartiles	90 (80,90.0)	80 (70,80)		144.50	0.02*
Mean arterial pressure	100 (93.3,108.3)	90 (86.7,98.3)		148.25	0.02*

Two-tailed Student's t-test was used for weight, height, body mass index. Mann–Whitney test was use for systolic, diastolic and mean arterial pressure as they did not satisfy with the Test of normal distribution. Pearson Chi-square was used for gender analysis.

P value: statistical significance of the difference between the two groups.

*. Statistical significance is significant at the 0.05 level (2-tailed).

Table 1: Demographic characteristics of the study population (Mean ± Standard Deviation).

	Ocular Hypertensive Study Group	Control Group	t	χ^2	P-Value
No. of patients	19	23			
Central corneal thickness (μm)	570.8 ± 31.5	534.3 ± 35.5	-3.44		0.001**
Mean IOP (mmHg)	24.0 ± 3.4	15.3 ± 3.0	-9.76		<0.001**
Mean IOP corrected for CCT (mmHg)	23.4 ± 3.3	15.6 ± 2.2	-8.54		<0.001**
Highest recorded IOP (mmHg)	29.9 ± 5.0	N.A.			
Highest recorded IOP corrected for CCT (mmHg)	29.3 ± 4.9	N.A.			
Retinal nerve fiber layer thickness (μm)	107.6 ± 11.3	102.2 ± 8.1	-0.60		0.55
Mean deviation (dB)	-0.98 ± 1.92	-0.74 ± 1.04	-0.70		0.45

CCT: Central Corneal Thickness; IOP: Intraocular Pressure; N.A. : Not Available. Two-tailed Student's t-test was used for central corneal thickness, mean IOP, mean IOP Corrected for central corneal thickness in both eyes, except for mean IOP Corrected for central corneal thickness in left eye as they did not satisfy with the test of normal distribution. P-Value: Statistical significance of difference between the two groups.

**. Statistical significance is significant at the 0.01 level (2-tailed).

Table 2: Ophthalmologic characteristics of the study population (Mean ± Standard Deviation).

The optic nerve diameter measured at 3, 9 and 15 mm behind the globe did not vary significantly between the control group and the OH group (P=0.46, P=0.60, P=0.99, respectively). The optic nerve sheath diameter determined at all the three measurement sites behind the globe was wider in the OH group than control group, but the difference did not reach statistical significance (P=0.14, P=0.09, P=0.24, respectively). The orbital subarachnoid space width was significantly wider (P=0.01) in the OH group than in the control group at all three measurement locations: 0.99 ± 0.22 mm in OH *versus* 0.90 ± 0.11 mm in controls at 3 mm (P=0.08), 0.74 ± 0.11 *versus* 0.67 ± 0.07 mm at 9 mm (P=0.03) and 0.67 ± 0.10 *versus* 0.59 ± 0.07 mm at 15 mm (P=0.02) posterior to the globe (Table 3 and Figure 2). The intra-observer agreement was superior to the inter-observer agreement and for both intra-and inter-observer agreements, the ICCs were better for the measurements taken closer to the globe (Table 4).

	3 mm behind Globe	9 mm behind Globe	15 mm behind Globe	P-Value
Optic nerve diameter (mm)				
Ocular hypertensive group	3.55 ± 0.34	3.09 ± 0.34	2.92 ± 0.32	0.00†
Control group	3.45 ± 0.33	3.05 ± 0.24	2.91 ± 0.17	0.00†
Sum				0.55#
P	0.46*	0.60*	0.99*	0.32‡
Optic nerve sheath diameter (mm)				
Ocular hypertensive group	5.52 ± 0.65	4.59 ± 0.46	4.26 ± 0.47	0.00†
Control group	5.23 ± 0.35	4.38 ± 0.27	4.12 ± 0.23	0.00†
Sum				0.07#
P	0.14*	0.09*	0.24*	0.42‡
Orbital subarachnoid space width (mm)				
Ocular hypertensive group	0.99 ± 0.22	0.74 ± 0.11	0.67 ± 0.10	0.00†
Control group	0.90 ± 0.11	0.67 ± 0.07	0.60 ± 0.07	0.00†
Sum				0.01#
P	0.08*	0.03*	0.02*	0.53‡

#P value: statistical significance of the difference between control and ocular hypertensive study groups at all 3 measurement locations, 3 mm, 9 mm and 15 mm behind globe, overall.

*P value: statistical significance of the difference between control and ocular hypertensive study groups at the same measurement location.

†P value: statistical significance of the difference among 3, 9, and 15 mm locations within the same group.

‡P value: statistical significance of the Interaction effect among 2 study groups and 3 measurement locations.

Table 3: Average size of the optic nerve and optic nerve sheath and orbital subarachnoid space width of the optic nerve/sheath complex (Mean ± Standard Deviation).

Measurement	Intra-observer†		Inter-observer*	
	Difference (95% LoA) (mm)	ICC (95% CI)	Difference (95% LoA) (mm)	ICC (95% CI)
Optic nerve sheath diameter				
at 3 mm behind the globe	-0.01 (-0.62-0.60)	0.91 (0.83-0.98)	-0.04 (-0.43-0.35)	0.89 (0.79-0.99)
at 9 mm behind the globe	-0.08 (-0.52-0.36)	0.87 (0.79-0.95)	-0.01 (-0.38-0.36)	0.86 (0.75-0.98)
at 15 mm behind the globe	-0.05 (-0.58-0.47)	0.84 (0.75-0.92)	-0.08 (-0.37-0.20)	0.82 (0.74-0.90)

Optic nerve diameter				
at 3 mm behind the globe	0.04 (-0.39-0.46)	0.87 (0.76-0.97)	-0.15 (-0.42-0.12)	0.86 (0.74-0.98)
at 9 mm behind the globe	-0.07 (-0.44-0.31)	0.85 (0.74-0.93)	-0.18 (-0.46-0.11)	0.85 (0.72-0.97)
at 15 mm behind the globe	-0.05 (-0.52-0.41)	0.82 (0.74-0.87)	-0.17 (-0.40-0.10)	0.79 (0.69-0.88)

The intraclass correlation coefficient (ICC) was calculated to determine the degree of interobserver and intraobserver reliability. The intraobserver and interobserver variabilities were determined by Bland–Altman analysis.

LoA=limits of agreement. CI=confidence intervals.
*Based on the 1st measurements of the 1st observer and measurements of 2nd observer. †Based on the 1st and 2nd measurements of the 1st observer.

Table 4: Inter-observer and intra-observer repeatability of the optic nerve/sheath complex measurements by MRI.

As shown in Figure 3 the estimated CSFP value in the OH group (14.9 ± 2.9 mmHg) was significantly higher than that in control group (12.0 ± 2.8 mmHg P<0.01). The estimated CSFP values of 4 subjects (33%) in control group and 12 (63%) in OH group were higher than the 15 mmHg considered the upper limit of normal [28].

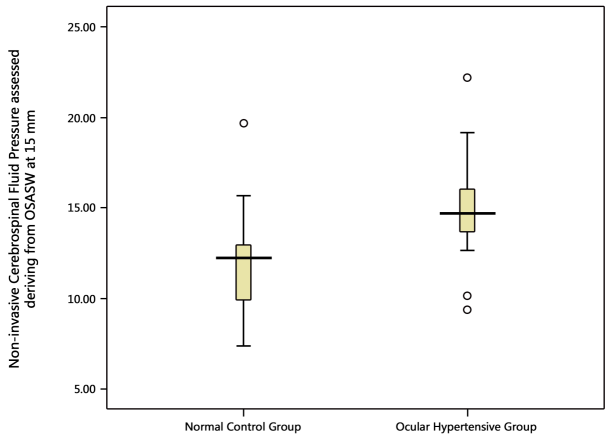

Figure 3: Boxplots showing the distribution of the estimated cerebrospinal fluid pressure in ocular hypertensive and normal subjects. The estimated cerebrospinal fluid pressure value in ocular hypertensive group (14.9 ± 2.9 mmHg) was significantly (P<0.01) higher than in the control group (12.0 ± 2.8 mmHg).

Figure 4 shows that despite the higher CSFP, the estimated TLCPD was still significantly higher in the OH group (9.0 ± 4.2 mmHg *versus* 3.6 ± 3.0 mmHg P<0.01). Of the 19 ocular hypertensive subjects, the estimated TLCPD values in 7 (36.8%) were within the range (2.3 to 6.6 mmHg) found in the control group. The values in the others were higher than in controls: in 6 (31.6%) they ranged from 6.7 to 10 mmHg, and were between 10.5 to 15.4 mmHg in 6 (31.6%).

The mean estimated risk of conversion to glaucoma at 5 years was 15.2 ± 8.7 % in OH group. Figure 5 shows that this risk was negatively correlated with the estimated CSFP value (r=-0.51, r2=-0.26, P<0.01). The correlation between the risk of conversion to glaucoma and mean or highest IOP corrected for CCT was not statistically significant (P=0.8).

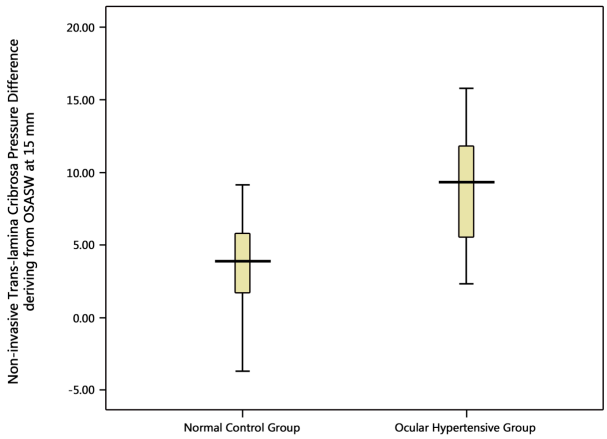

Figure 4: Boxplots showing the distribution of the estimated trans-lamina cribrosa pressure difference in ocular hypertensive group and the control group. The non-invasive trans-lamina cribrosa pressure difference in the ocular hypertensive group (9.0 ± 4.2 mmHg) was significantly (P<0.01) higher, than in control group (3.6 ± 3.0 mmHg).

According to the "threshold to treat" calculator, 9 (47.4%) OH subjects would require treatment. The mean IOP, highest IOP, assessed CSFP and TLCPD in these 9 OH subjects did not differ from the other 10 subjects who did not cross the threshold to treat (all P>0.05).

Discussion

The wider OSASW and the higher estimated CSFP values in OH as compared to controls imply that OH subjects have a higher orbital CSFP. Furthermore, the negative correlation between the estimated risk of conversion to glaucoma and the estimated CSFP value (r=-0.53, r2=-0.26, P<0.01) suggests that elevated CSFP may play a protective role against damage from elevated IOP in OH. Our findings agreed with several previous hospital-based and population-based studies that generated the theory that elevated CSFP may provide a protective effect for the optic nerve [5,21,29].

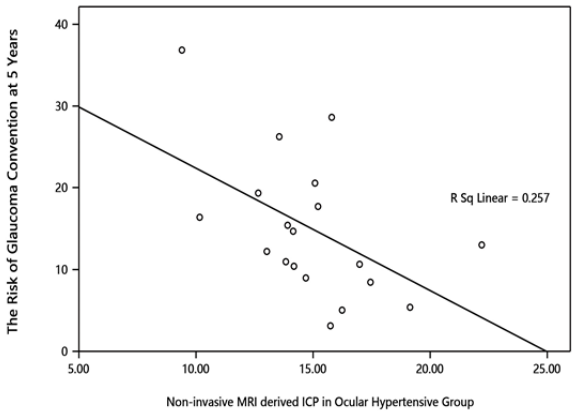

Figure 5: Scatterplot showing distribution of the risk of conversion to glaucoma at 5 years *versus* estimated cerebrospinal fluid pressure measurements in ocular hypertensive subjects. The estimate risk was negatively correlated with estimated cerebrospinal fluid pressure value (r=-0.51, r2=-0.26, P<0.0).

As far as the mechanisms of increased orbital CSFP are concerned, the association with BMI, is a possible explanation. BMI is positively and independently associated with CSFP [22]. A high BMI may increase intra-abdominal pressure leading to increase in venous pressure and consequently CSFP [23,24]. It has been reported that a lower BMI is a possible risk factor for glaucoma and that a higher BMI may be protective [25,26]. In the present study, the BMI and weight were significantly higher in the OH group, and we assume that the higher BMI contributed to the elevated CSP in OH group. However, the role of a higher BMI, its contribution to a higher CSFP and its interplay with other factors that determine progression to glaucoma remain speculative. Another reason for the higher orbital CSFP could be more rapid production of cerebrospinal fluid; brisk cerebrospinal fluid production could lead to increased cerebrospinal fluid turnover with enhanced removal of potentially neurotoxic waste products that accumulate in the optic nerve [27]. The latter theory remains unproven.

It could be argued that the slightly (11%) wider subarachnoid space size in OH could be due to some degree of optic nerve atrophy in subjects who actually had very early glaucoma. However, the optic nerve, OCT and visual fields did not show any evidence of damage. We have previously reported that decreased subarachnoid space width was only present in the normal-pressure glaucoma group and was related to lower orbital CSFP [8]. In the present study, the optic nerve diameter values were similar in the OH and control groups but the OSASW in OH group was significantly wider than that in control group. We conclude therefore that the subarachnoid space was determined by the CSFP, not by optic nerve atrophy.

Despite the higher CSFP, the TLCPD was still higher than in controls in 12 of the 19 OH; in 6 the measurements ranged from 10.5 to 15.4 mmHg; in the other 6 (31.6%) they were 6.7 to 10 mmHg. The population-based Beijing Eye Study reported similar findings using a formula that estimated TLCPD but without the use of MRI measurements. The results of our study were also in accordance with a previous hospital-based study [21].

The wider orbital subarachnoid space and higher estimated CSFP values in OH as compared to controls suggest that OH may have a higher orbital CSFP. Despite this higher orbital CSFP that is potentially protective, the ocular hypertension group did have a higher TLCPD as well. That along with the interplay with other known and unknown factors likely plays a role in some sufficient component causal models for progression of OH to glaucoma.

According to the "threshold to treat" calculator, 9 (47.4%) OH subjects needed treatment. We had hypothesized that the elevated TLCPD might be a risk for the onset of glaucomatous optic nerve damage. However, TLCPD in these 9 OH subjects who needed treatment did not differ from the others who did not cross the threshold to treat (P=0.23). One reason for a non-significant difference is the small sample size as the study was only powered to determine a difference in estimated CSFP. Another possible reason is that cross sectional nature of the study precluded exclusion of those who might convert to glaucoma. A prospective cohort study with an appropriate sample would be required to prove or disprove this.

The study has several limitations. The lack of a 24 h IOP profile in controls would be considered a limitation. While ideal, it was not possible as none of the controls were willing to be admitted for the same. The IOP's in this group were however clearly well within the normal range and do not suggest that we may have inadvertently included some OH in this group. Another limitation is that the cross-sectional nature of the study does not allow us to separate patients who will convert to glaucoma on follow up from those who do not; a prospective study would provide more robust data. Next, a hospital-based study such as this is subject to some biases including possible selection bias. Furthermore, the sample size was small. However, the fact that the difference between the study groups reached statistical significance suggests that the differences are real. We also accept that the CSFP and TLCPD were calculated using a formula that, while reported to be reliable, has not been fully validated and may not stand the test of time [18]. Direct measurement of the orbital CSFP is however currently impossible and till better methods become available this is all we have. We accept that better and more accurate methods may change the results and interpretation. Furthermore, although it is in clinical use, the accuracy of the online calculator to determine conversion to glaucoma can be questioned and is certainly no substitute for a prospective determination. Finally, a major limitation is that only ocular hypertensive cases were compared to controls. The planned follow up of this study is a comparison between ocular hypertensive, low tension and open angle glaucoma.

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Conflict of Interest

None

Trial Registration

Clinical trial registered with the Chinese Clinical Trial Registry: ChiCTR-OCC-11001271

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