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Original article

Intracranial, intraocular and ocular perfusion pressures: differences between morning and afternoon measurements

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Abstract

Purpose: To assess how intracranial pressure (ICP), intraocular pressure (IOP) and ocular perfusion pressure (OPP) differ between the morning and the afternoon in healthy subjects.
Design: Prospective pilot study.
Methods: Ten healthy subjects age 26.5 (1.2) years were included in the prospective pilot study. For each participant, blood pressure, heart rate, IOP, ICP and calculated OPP, translaminar pressure difference (TPD) were assessed two times per day, in the morning (9 ± 1 a.m.) and afternoon (2 ± 1 p.m.) by the same experienced operator. Best-corrected visual acuity and body mass index were also evaluated. TPD was calculated as IOP minus ICP. ICP was measured using a non-invasive two-depth transcranial Doppler device. $P < 0.05$ was considered significant.
Results: Mean ICP was higher during afternoon (10.09 (1.8) mmHg) compared to morning ICP (9.80 (2.2) mmHg), but the difference was not statistically significant ($p = 0.14$). By analyzing ICP according to different refractive errors categories, we found that emmetropic patients had higher ICP (morning 11.94 (3.0), afternoon 11.5 (2.6) mmHg), compared to myopic (accordingly, 9.14 (1.2) and 9.72 (1.3) mmHg) or hypermetropic (accordingly, 8.85 (0.7) and 9.17 (0.8) mmHg) patients, but the difference

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was not statistically significant ($p > 0.05$). We also found that higher OPP in the morning was correlated to lower TPD ($r = -0.65$; $p = 0.04$).
Conclusion: We found no significant variations in ICP, IOP or OPP during morning and afternoon in young healthy subjects. Higher OPP was related to lower TPD in the morning. Further prospective studies are warranted to investigate diurnal ICP variations in glaucoma patients to understand if fluctuations in ICP and TPD may contribute to the disease process.

Key words: Intracranial pressure, intraocular pressure, diurnal variations, healthy subjects, ocular perfusion pressure, translaminar pressure difference

1. Introduction

Intracranial pressure (ICP) is the pressure inside the skull, corresponding brain tissue, and cerebrospinal fluid (CSF). The human body has various mechanisms by which it keeps ICP within certain limits through shifts in production and absorption of CSF.[1] ICP and intraocular pressure (IOP) are interrelated and relatively independent pressure systems, which facilitate a relatively stable state through aqueous and CSF circulations. These two circulating fluids are both produced by carbonic anhydrase-catalyzed reactions, generally represent an ultrafiltrate of blood, and have nearly identical chemical composition, except that CSF has more proteins and less ascorbates.[2-3] Normal ICP varies with age but is generally considered to be 5-15 mmHg in healthy supine adults, 3-7 mmHg in children, and 1.5-6 mmHg in infants.[4-6] The mean IOP in healthy adults is 15-16 mmHg, with a standard deviation of nearly 3 mmHg. The upper limit of normal IOP is statistically defined as two standard deviations above normality.[7-8] Low ICP has recently been implicated in the pathogenesis of glaucoma,[9-14] as optic nerve is exposed not only to IOP in the eye, but also to ICP as it is surrounded by CSF in the subarachnoid space (SAS). Furthermore, CSF pressure represents the true counter-pressure against the IOP across the lamina cribrosa and is one of the two determinants of the translaminar pressure difference (TPD). Studies have shown that higher TPD may lead to abnormal function and damage of the optic nerve due to changes in axonal transportation, deformation of the lamina cribrosa, altered blood flow, or a combination thereof leading to glaucomatous damage.[15-16] However, measuring TPD in glaucoma and healthy subjects has not been historically feasible due to the invasiveness of traditional ICP measurements and the potential risk of intracranial hemorrhages, infection, persistent leak of CSF and/or cerebral herniation.[17] Many different technologies have been explored to overcome the invasive limitation of ICP measurements,[18-20] but all these approaches are based solely on correlation of various anatomical or physiological parameters of the human head and brain with ICP. Therefore, previous attempts to non-invasively measure ICP have not provided absolute ICP values in mmHg greatly

limiting specificity of their measures.

In an attempt to overcome these previous methodological limitations, an innovative method for non-invasive measurement of ICP absolute values was recently developed using transcranial Doppler ultrasound. This methodology measures and compares blood flow pulsatilities in the intracranial and extracranial segments of the ophthalmic artery (OA). The sensitivity, specifity and diagnostic value of this device has been proven in previous prospective studies with healthy subjects and patients with neurological diseases.[21-22] In order to provide insight on these emerging dynamic glaucomatous risk factors, we conducted a pilot study with the aim to assess diurnal variations of ICP, IOP, and ocular perfusion pressure (OPP) in healthy subjects to establish a baseline understanding of their diurnal activity in disease free stasis.

2. Materials and methods

Ten healthy subjects (age 26.5 (1.2)) participated in a prospective pilot clinical study. All study procedures were carried out according to the Declaration of Helsinki, and the study protocol was approved by the Lithuanian University of Health Sciences Review Board. Study objectives and methods were explained to all subjects prior to examination. All participants provided written informed consent. All examinations were performed on one randomly chosen study eye.

Quantities of blood pressure (BP), heart rate, IOP and ICP were measured two times per day, in the morning (9 ± 1 a.m.) and afternoon (2 ± 1 p.m.) by the same experienced operator (L.S.), which allowed us to estimate quantities of OPP and TPD. TPD was calculated as IOP minus ICP. OPP was calculated using the equation OPP = 2/3MAP – IOP, where MAP is mean arterial pressure. Systolic ocular perfusion pressure (SOPP) was determined by subtracting IOP from systolic BP. Diastolic ocular perfusion pressure (DOPP) was determined by subtracting IOP from diastolic BP. An average of two separate measurements with a 15 minutes undisturbed rest period constituted the mean value of parameters. Best-corrected visual acuity and body mass index (BMI) were also evaluated.

Non-invasive absolute ICP values were measured using a two-depth Transcranial Doppler (TCD) device (Vittamed UAB, Kaunas, Lithuania) that does not require individual patient specific calibration. A head frame with fixed ultrasound transducer was placed over the closed eyelid. A small inflatable ring cuff placed over the tissues surrounding the eyeball produced external pressure on the orbit. The TCD transducer and the external pressure device were connected to a computer with specific software allowing it to assess simultaneous an insonation angle independent blood flow pulsation monitoring in the intracranial and extracranial segments of the OA (Fig. 1). External pressure was automatically increased gradually from 0 to 20 mmHg by pressure steps of 4 mmHg. In order to decrease ICP value

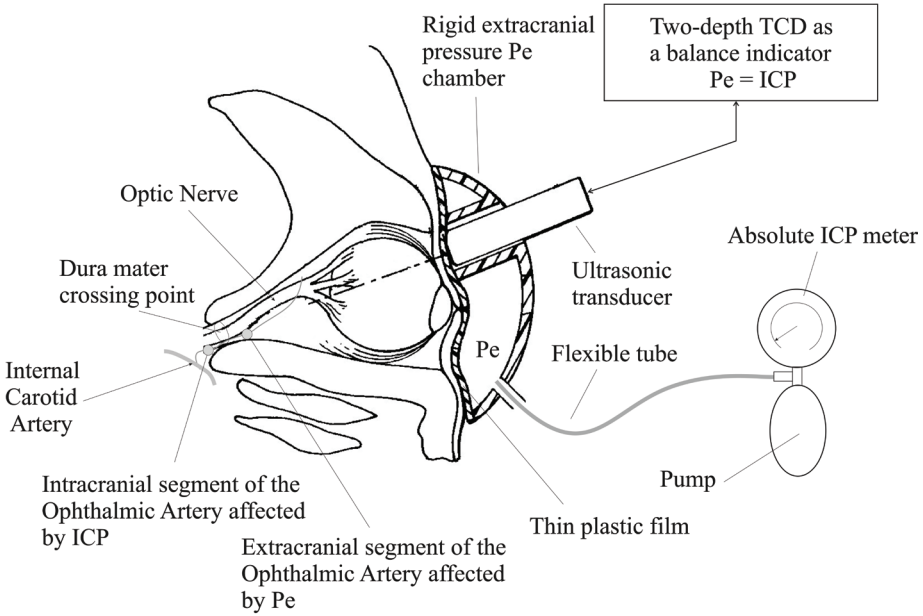

Fig. 1. Non-invasive two-depth TCD device components showing the relevant eye/brain anatomy. The ultrasound transducer of the Doppler subsystem is surrounded by an externally applied pressure chamber with a controlled external pressure (Pe) source and measurement. (Reprinted with permission from Ragauskas *et al.* 2012.)

sampling error, if the first measured absolute ICP value was lower than 10 mmHg, then the measurement was repeated using 2 mmHg pressure steps until external pressure reached 12 mmHg. The value of external pressure, when blood flow signals in both OA segments are equal, was fixed and expressed automatically in absolute units of mmHg. The duration of one ICP measurement was up to 10 minutes.

Non-invasive ICP was measured in the supine position, and therefore IOP was measured in the same position using a Schiotz impression tonometer.

Inclusion criteria consisted of healthy subjects over 18 years of age with no history of glaucoma or other diseases that could disturb the results and willingness to sign informed consent form prior to initiation of the study. Pregnant or nursing women, patients with uncontrolled systemic diseases, patients with a history of allergy to local anesthetics, orbital/ocular trauma, neurological or other diseases that could bias study results were excluded from the study.

The statistical data analysis was performed using computer program SPSS 17.0 for Windows. All variables were defined by methods of descriptive statistics. The analysis of the quantitative variables included calculation of the mean and standard deviation (x (SD)). The Wilcoxon signed-rank test was used when comparing two related samples on a single sample to assess whether their population mean ranks

differ. The hypothesis of equality of means among three groups was analyzed using the Kruskall-Wallis test. Association between categorical variables or abnormally distributed continuous variables was assessed by Spearman's correlation. The level of significance $p < 0.05$ was considered significant.

3. Results

Ten healthy subjects (80% women, 20% men) were included in the prospective pilot study. Patients characteristics are provided in Table 1.

Morning and afternoon parameters are shown in Table 2. There were no statistically significant differences between morning and afternoon IOP, TPD, BP and OPP ($p > 0.05$). ICP was higher during afternoon (10.09 (1.8) mmHg), compared to morning ICP (9.80 (2.2) mmHg), but the difference was not statistically significant ($p = 0.14$) (Fig. 2). By analyzing ICP according to different refractive errors between subjects (Table 3), we found that emmetropic patients had higher ICP compared to myopic or hypermetropic patients, but the difference was not statistically significant ($p > 0.05$). We also found that in the morning higher OPP was correlated to lower TPD ($r = -0.65$; $p = 0.04$).

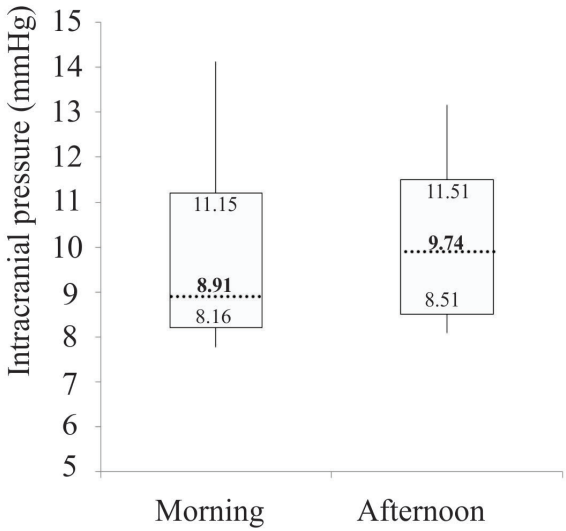

Fig. 2. Morning and afternoon intracranial pressure variations. Box-plot showing distribution of intracranial pressure during morning and afternoon in healthy subjects. Box-plots show the median, interquartile range, minimum and maximum values.

Table 1. Patient characteristics.

	Healthy subjects (N = 10) Mean (SD)
Sex (N (%)): Male Female	 2 (20%) 8 (80%)
Age (years): Range	26.5 (1.2) 25-29
Best corrected visual acuity Height (m) Weight (kg)	1.0 (0.0) 1,71 (0.1) 63.6 (16.6)
Body mass index (kg/m^2)	21.4 (3.1)
Systemic medications	0

SD = standard deviation; N = number.

Table 2. Changes in parameters during morning and afternoon.

	Morning (9 ± 1 a.m.)		**Afternoon** (2 ± 1 p.m.)		**p value**
	Mean (SD)	Median	Mean (SD)	Median	
ICP (mmHg)	9.80 (2.2)	8.91	10.09 (1.8)	9.74	0.14
Range:	7.77-14.13		8.08-13.16		
IOP (mmHg)	13.4 (2.0)	13.1	13.6 (1.8)	13.1	0.58
TPD (mmHg)	3.64 (2.0)	3.71	3.49 (1.8)	3.28	0.95
Systolic BP (mmHg)	115.1 (7.3)	114.0	115.9 (7.1)	114.0	0.28
Diatolic BP (mmHg)	77.3 (7.9)	76.5	75.7 (6.5)	75.0	0.44
OPP (mmHg)	50.1 (4.7)	50.8	50.3 (3.7)	49.5	0.61
SOPP (mmHg)	101.7 (7.3)	101.6	102.3 (6.8)	100.9	0.47
DOPP (mmHg)	63.9 (7.4)	63.6	62.1 (5.6)	60.4	0.44
Heart rate (bpm)	64.4 (4.8)	62.5	64.5 (4.5)	62.5	0.86

*****Wilcoxon signed-rank test. Significance level $p < 0.05$. SD = standard deviation; ICP = intracranial pressure; IOP = intraocular pressure; TPD = translaminar pressure difference; BP = blood pressure; OPP = ocular perfusion pressure; SOPP = systolic ocular perfusion pressure; DOPP = diastolic ocular perfusion pressure.

Table 3. Differences in intracranial pressure between different refractive errors.

	Emmetropia (n = 3) Mean (SD)	**Myopia (n = 4)** Mean (SD)	**Hypermetropia (n = 3)** Mean (SD)	**p value**
Morning ICP (9 ± 1 a.m.) (mmHg)	11.94 (3.0)	9.14 (1.2)	8.53 (0.7)	0.23
Afternoon ICP (2 ± 1 p.m.) (mmHg)	11.50 (2.6)	9.72 (1.3)	9.17 (0.8)	0.40
p value	0.59	0.14	0.11	

***** Wilcoxon signed-rank test. ****** Kruskal Wallis test. Significance level $p < 0.05$. N = number; SD = standard deviation; ICP = intracranial pressure.

4. Discussion

There is a growing body of evidence that indicates ICP and TPD may be involved in the disease process of glaucomatous optic neuropathy. These physiological variables, along with BP and IOP, likely fluctuate during the diurnal cycle, allowing for possible periods of susceptibility and tissue damage. While it is accepted that diurnal IOP fluctuations are greater in eyes with glaucoma,[23] it is currently not established whether that is also true of ICP variations. Several studies concluded that IOP fluctuations were more strongly related to progression of visual field damage than the level of mean IOP.[24-25] Mechanistically this may occur due to previous findings of repeated mechanical stress on neurons being more harmful than steady stress.[26-28]

In this study we reported morning and afternoon ICP measurements in healthy subjects. We found that during first part of the day ICP changed marginally, though ICP was higher at afternoon. Several experimental studies analyzed circadian variations in conscious and partially restrained Sprague-Dawley rats and found nocturnal elevation in ICP[29-30] by 3.9 mmHg.[31] Another study with conscious, freely moving Sprague-Dawley rats showed a relatively constant ICP in the light and dark periods.[32] Although circadian ICP variations were insignificant, endogenous variations in the ICP regulatory factors might be significant. It has been revealed that human CSF production exhibits a circadian pattern – CSF production is two to three-and-a-half times higher in the middle of the night compared to late afternoon.[33-34] However, since healthy subjects have ICP homeostasis, the significant change in CSF production might not lead to a parallel day/night ICP pattern.[35] Furthermore, Kropyvnytskyy *et al.* in their study with severely neurologically affected patients found no detectable 24-hour ICP rhythm in head injury patients.[36]

Given that humans sleep in the supine or prone position but are upright during the day, it is important to note that IOP and ICP are dynamic parameters and vary

according to changes in body position or individual activities.[37] Therefore we assessed these parameters in the standard ICP measuring state – a supine position.[38] Understanding posture and its affects on these dynamic variables is important as prospective studies have found that in healthy subjects CSF pressure was related to the systemic arterial BP and IOP.[41] According to several population-based studies, IOP was also related to the systemic arterial BP so that pressures in all three fluid-filled compartments were related to each other,[42-43] however, the mechanism of such a triangular relationship remains unclear. Samuels *et al.* in an experimental study with rats found that chemical stimulation of the dorsomedial and perifornical hypothalamic neurons evoked substantial increases in IOP, CSF pressure, TPD, heart rate and MAP.[44] In our study we did not find any correlations between ICP, IOP or BP, however, we found a negative correlation between OPP and TPD in the morning. It is important to consider that in this correlation some signs of triangulation can be found, as these parameters are calculated by the following formulas: TPD = IOP – ICP; OPP = 2/3MAP – IOP. There are many variations in all body fluid spaces, cardiac output, peripheral resistance and blood flow to various vascular beds,[45-46] however, all these variations are insignificant to young healthy adults as they have intact homeostasis and ability of a vascular bed to maintain its blood flow despite changes in perfusion pressure. In our study we did not find significant variations from morning to afternoon in IOP, BP, OPP or TPD in healthy individuals. Unlike our participant population, glaucoma patients have been demonstrated to have pathological variations in IOP, BP, OPP[23,47-48] that could result in higher TPD. Higher IOP or lower ICP also result in higher TPD, leading to barotraumatic damage to the optic nerve. In other words, there is a likelihood of misbalance between IOP, ICP and BP in glaucoma patients contributing to their disease process.

In our study we analyzed young healthy adults and found that mean ICP was about 10 mmHg. Several studies that have examined CSF pressure and age failed to find a relationship of significance,[49-50] while Fleischman *et al.* in their retrospective analysis of 33,922 patients who had lumbar puncture revealed that CSF pressure decreases with older age. This study found that CSF pressure was stable for the first 50 years of life (11.5 (2.8) mmHg) after which there was a steady decline by 2.5% at age 50-54 and by 26.9% at age 90-95. However, CSF pressure of the included patients varied from 4.41 to 18.38 mmHg.[51] Other authors analyzing primary open-angle glaucoma (POAG) and healthy subjects found inconsistent ICP values: Ren *et al.* in a prospective study analyzed 71 healthy subjects with a mean age of 45.7 and found mean a ICP of 12.9 mmHg.[41] Similar ICP results were found by Berdahl *et al.* in a retrospective study, however, the mean age of included healthy subjects was 68.2.[52] These studies measured ICP invasively via lumbar puncture (41,52). Siaudvytyte *et al.* evaluated ICP non-invasively and found it to be 10.5 mmHg in 51.9-years-old healthy subjects.[14]

Positive BMI and CSF pressure associations were found by various prospective and retrospective studies.[52-54] Fleischman *et al.* analyzed CSF pressure in five

different age groups and found that BMI was positively correlated with CSF pressure in every age group. Adult patients younger than 42 years of age with BMI between 10.1 to 22.3 kg/m^2 had a mean CSF pressure of 9.92 mmHg.[51] This data corresponds to ours as our results showed a mean ICP of about 10 mmHg with BMI of 21.4(3.1) kg/m^2.

We also found no statistically significant differences in ICP between subjects with different refractive errors. Our included subjects had mild myopia/hypermetropia, therefore higher refractive errors influence on ICP still remains unclear.

There are several limitations in our study. Firstly, it was a small sample pilot study aiming to evaluate physiological fluctuations of IOP, ICP and OPP in healthy young adults with presumably intact autoregulation that likely does not reflect glaucoma populations. Therefore this study establishes a baseline of fluctuations in healthy subjects for comparative purposes and our data should not be considered representative of any disease state. However, it represents an exciting future direction for our pilot analysis to build upon. A larger sample may also allow future analysis to confirm other relationships of IOP, ICP and OPP variations. Secondly, we obtained only morning and midday measurements of these parameters, and therefore it does not present diurnal or circadians variations. Thirdly, due to the requirement of measuring ICP in the supine position and the fact that IOP varies according to posture we measured IOP with Schiotz tonometer, which may not be the same as the current gold standard Goldmann tonometer, besides it has errors related to sclera rigidity and corneal curvature.[55] Fourthly, we used a non-invasive ICP measurement method by using two-depth TCD device, instead of golden standard invasive ICP measurement methods, which may represent sample errors yet to be discovered. Nevertheless, a prospective study with 108 neurological patients showed that diagnostic sensitivity, specificity and the area under the ROC curve of this non-invasive absolute ICP method were 68.0 %, 84.3 % and 0.87, respectively.[56] However, it remains unclear whether ICP is directly related to the CSF pressure in the orbit around the optic nerve. Experimental studies on dogs showed that CSF pressure in optic nerve SAS is equal to CSF pressure in the lateral ventricle of the brain at the level of eye.[15] Of note, the method depends on the optic nerve path at SAS between the orbital and intracranial parts. It is not known what happens when the optic nerve canal is blocked, in such cases as suprasellar meningioma, tuberculous meningitis, intracanalicular OA aneurysm, etc. It is thought that CSF is distributed evenly with a continuous flow through all CSF spaces, including ventricles, cisterns and SAS. The SAS of the optic nerve is bridged by a variety of trabeculae and septa, which number and morphology depend on their location within SAS: the retrobulbar portion of the optic nerve is composed of delicate trabeculae, the midorbital SAS – of broad septae, the canalicular portion – combination of septae and trabeculae.[57] In addition, unlike in other areas, the dura of optic nerve sheath contains atypical meningeal tissue with lymphoid characteristics.[58] Interestingly, Killer and colleagues[59] found that CSF flow between the basal cisterns and the SAS surrounding the optic nerve was

different between patients with NTG and healthy subjects, showing that NTG had decreased CSF flow in this area.

5. Conclusion

We found no significant ICP, IOP and OPP variations during morning and afternoon in young healthy subjects. Higher OPP was related to lower TPD in the morning. Further prospective studies are warranted to investigate diurnal ICP variations in glaucoma patients to understand how fluctuations in ICP and TPD may contribute to the glaucoma process.

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