NORMAL AGE- AND SEX-RELATED VALUES OF THE OPTIC NERVE SHEATH DIAMETER AND ITS DEPENDENCY ON POSITION AND POSITIVE END-EXPIRATORY PRESSURE

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INTRODUCTION

Elevated intracranial pressure (ICP) is a serious neurologic condition with high morbidity and mortality, and the non-invasive detection method of choice for neurologists before the advent of computed tomography was fundoscopy for the presence or absence of papilledema caused by the connection of the ventricular system to the optic nerve head *via* the optic canal (Ropper et al. 2005). From the late 1990s, the development and continuous improvement of transorbital high-resolution B-mode sonography (TOS) enabled the detection of papilledema and optic nerve sheath diameter (ONSD) changes to estimate changes in cerebrospinal fluid (CSF) pressure and led to a variety of studies related to pathologic CSF conditions (Hansen and Helmke 1997). These included idiopathic intracranial hypertension (IIH) (Bauerle and Nedelmann 2011), craniocerebral trauma (Houze-Cerfon et al. 2019), malignant middle cerebral artery stroke, spontaneous intracranial hypotension (SIH) (Fichtner et al. 2016) and hypoxic ischemic encephalopathy (Ertl et al. 2018), among others.

A recent systemic review and meta-analysis calculated an area under the receiver operating characteristic curve of 0.94 (0.91−0.96) for the detection of ICP levels >20 cm H_2O, yet transorbital ONSD sonography is still regarded to be in the preliminary stage as different thresholds are used in the analyzed studies (Fernando et al. 2019). Reasons for skepticism toward TOS also include the ultrasound inherent investigator variability, the small magnitude of ONSD changes in relation to the spatial resolution of the ultrasound frequencies used (Ertl et al. 2014), anatomic variations especially with respect to

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pressure conduction through the optic canal (Killer et al. 2007) and the ICP expansion, which can be unilateral (*i.e.,* in intracerebral basal ganglia hemorrhage). Although studies often used normal control groups and addressed the reliability and reproducibility of the technique (Bauerle et al. 2012, 2013) there remains a lack of widely accepted normal ONSD reference values.

Recently, Schroeder et al. (2020) published a meta-analysis of studies on optic nerve diameter and ONSD illustrating a large variety of the latter with normal values from 4.09 to 6.9 mm. They discuss ultrasound machine and ultrasound frequency differences, ethnic/racial variabilities and different methods for measuring these differences, yet exclude significant correlation between ONSD and age, sex or geographic origin.

In the study described here, we established normal ONSD values in three different age groups for our neurosonography laboratory. We observed sex-specific differences upon positional and mild ICP changes derived from positive end-expiratory pressure (PEEP) ventilation important, for example, in positional headache in SIH or IIH.

METHODS

The study protocol was approved by the ethics committee of the University of Regensburg in accordance with the guidelines of the Declaration of Helsinki (No. 14-101-0076). All probands provided written informed consent before enrollment.

Study population

Within a 13-mo period, 187 patients without central nervous system (CNS) diseases were enrolled in this prospective observational study. Volunteers were recruited from the outpatient clinic (patients with peripheral nervous system diseases) and also comprised acquaintances and relatives. In addition to absent CNS disease and especially previous or known elevated ICP, clinical suspicion of raised ICP (*i.e.,* headache, reduced level of consciousness, abducens nerve palsy) and any previous history of ocular pathology (*i.e.,* cataract surgery, ablation, glaucoma) were contraindications to participation in the study. The following volunteer-specific data were registered: age and sex, heart rate, blood pressure, size, weight, relevant diseases such as hypertension and diabetes and current medication if applicable.

Transorbital ONSD sonography and transcranial sonography

The examination was performed as previously described (Ertl et al. 2014). Two medical students performed all examinations but the initial 30 patients were examined together with two experienced ultrasound examiners (F.S. and M.E.) accredited by the German Ultrasound Society (DEGUM). The accuracy of all measurements was checked by a board-certified neurosonologist (F.S.) using an electronic ultrasound image archive (ClinWinData, Erlangen, Germany). A high-frequency linear transducer (12 MHz) was used in combination with a high-end ultrasound machine (Xario XG, PLT-1204 BT transducer [for TOS], PSB-30 BT [for transcranial sonography], Toshiba, Tokyo, Japan). A pre-specified ocular pre-set was used to comply with the required safety parameters (Ertl et al. 2014).

A layer of acoustic gel was applied to the closed eyelids, after which the transducer was placed on the upper lid with the examiner's hand resting on the patient's orbital margin. The ONSD was measured 3 mm behind the optic disc; the diameter was determined by measuring the distance between the outer hyper-echogenic borders of the optic nerve sheath (ONS; Fig. 1). Each ONSD measurement is the average of three individual measurements, in which the investigator repositioned the ultrasound probe and scrolled the image memory containing around 20 images per second to a frame with satisfactory delineation of the subarachnoid space/dura mater border. This allows for compensation of the lateral and axial resolution (at 10 MHz: ~300 μm and ~150 μm, respectively [Maissan et al. 2015]), with good inter- and intrarater reproducibility as previously described (Bauerle et al. 2012, 2013).

The first set of measurements were taken with the volunteer in a supine position. In addition, the width of the third ventricle was also assessed by using transtemporal ultrasound with a phased array with a transmit frequency of 2 MHz from both sides and calculating the average. Thereafter a second set of ONSD measurements were made in upright position within 1 min ("standing"). The

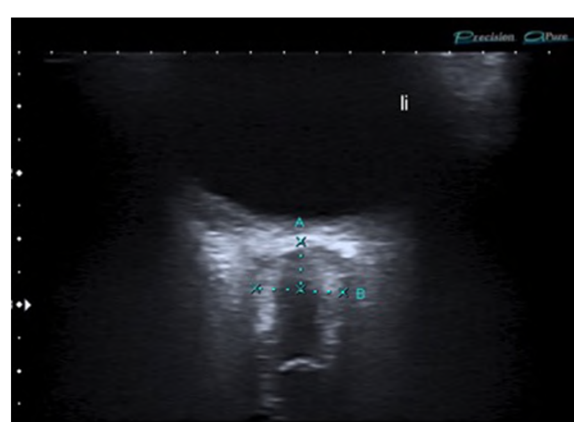

Fig. 1. Example figure of measurement of optic nerve sheath diameter with marker placement on the outermost borders of the hyper-echogenic optic nerve sheath. The ultrasound probe is in the mediolateral position to obtain the optic nerve in line with the ultrasonic beam.

third set of measurements were then acquired after 5 min, again with the volunteer in an upright posture ("sustained standing"). After completion of this set of examinations, the volunteer was asked to lie down again for PEEP measurements as follows. The volunteers were asked to constantly exhale against a special valve maintaining a PEEP of 20 mm Hg (Fig. 2). This value was chosen in the setup tests performed by the authors and was the maximum tolerable level that could be sustained for 3–5 min. Meanwhile, ONSDs were once again measured three times, and mean values were calculated. The difference in ONSD values measured without and without PEEP for volunteers in the supine position was termed ΔONSD/PEEP, with an increase in ONSD after application of PEEP leading to a negative ΔONSD/PEEP.

Statistical analysis

For data acquisition and storage, Microsoft Excel 2013 was used. Mean and median ONSDs with standard deviations and 95% confidence intervals (CIs) were calculated for all ONSD measurements. ONSD measurements were compared across all age groups using analysis of variance. Linear regression modeling was used to compare the relationship between mean ONSD and the other aforementioned characteristics such as sex and weight. Statistical analysis was performed using SPSS Statistics Version 22.0 (IBM, Armonk, NY, USA).

RESULTS

Study population

In total, 187 healthy volunteers between the ages of 20 and 85 were enrolled and analyzed. Of these, 94 (50.3%) were women. To further differentiate ONSDs by age, three groups in the age ranges 20–39 (group A), 40–59 (group B) and >60 (group C) were established. Baseline characteristics of each group are outlined in Table 1.

For analysis, values for both eyes were analyzed together, as data from the literature (Bauerle et al. 2012) indicated no significant differences between eyes in the same patient.

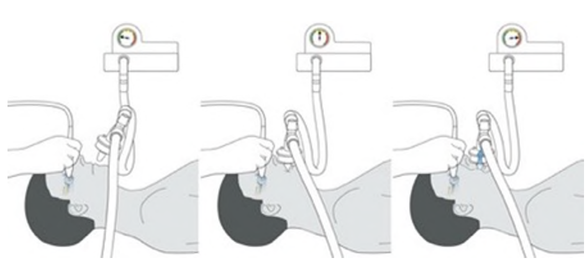

Fig. 2. Process of transorbital sonography and increase in positive end-expiratory pressure (PEEP) Probands were asked to exhale against a maximum PEEP of 20 mm Hg. Different levels of PEEP are illustrated on the manometer (top of figure). (©Copyright Anja Giger, Inselspital Bern, with the kind permission of Professor Jürgen Beck.)

Because of handling difficulties, PEEP measurements were feasible in only 106 probands. The third ventricle could be visualized in 157 probands, mainly because of a lacking or insufficient temporal bone window.

Values of third ventricle and correlation with ONSD

As depicted in Figure 3, ONSD ($R = 0.33$) and the third ventricle ($R = 0.60$) were linearly correlated with progressive age. With increasing age, we obtained higher absolute values and also higher standard deviations of the third ventricle (group A: $\Delta = 3.94$ mm, group B: $\Delta = 6.15$ mm, group C: $\Delta = 10.75$ mm). There was a statistically significant difference between the mean values for third ventricle diameter in all age groups ($p = 0.000$; Table 2). When age and sex are taken into account, there was no difference between groups A and B, but there was a significant difference between men and women from the age of 60 ($p = 0.003$).

ONSD in supine position

Dependence on age and sex. Mean values depending on sex and age are outlined in Table 2. Similar to the diameter of the third ventricle, the range (difference between highest and lowest value) of ONSD values also increased with age (group A: 1.69 mm, group B: 2.61 mm, group C: 3.48 mm). ONSD mean values also increased with age, an effect that was mainly by the male group (difference in mean values between groups: A/B = 0.25 mm, $p = 0.013$; A/C = 0.34 mm, $p < 0.001$; Fig. 4). In group B (average difference: 0.41 mm, $p = 0.001$, C (average difference 0.51 mm, $p = 0.002$) there was a significant difference between ONSD values of men and women; group A also exhibited a strong tendency toward that significant difference (Fig. 4). In men, ONSD was significantly larger in groups B and C than in group A.

Influence of hypertension, weight and diabetes

Only marginal differences in ONSD could be detected between volunteers with and those without the aforementioned factors (data not shown).

Dependence of ONSD variability on body position and PEEP. No significant differences between the supine and upright position shortly after standing up and after sustained standing could be delineated in all age groups with no relevant influence of sex. However, under PEEP, ONSD values measured in the supine position increased significantly in female probands. This effect was more pronounced in younger patients and diminished with age. The most significant difference was seen between groups A and

Table 1. Baseline characteristics of all probands

Characteristic	Age group		
	A	B	C
Median age (y)	24	51	70
No. of volunteers	70	57	60
No. (%) of women	43 (61.4%)	26 (45.6%)	25 (41.7%)
Average body mass index (range)	23.47(17.25–57.16)	25.86(17.37–32.87)	28.57(20.06–40.12)
Known diabetes mellitus type II	0	1	7
Known arterial hypertension	0	12	19

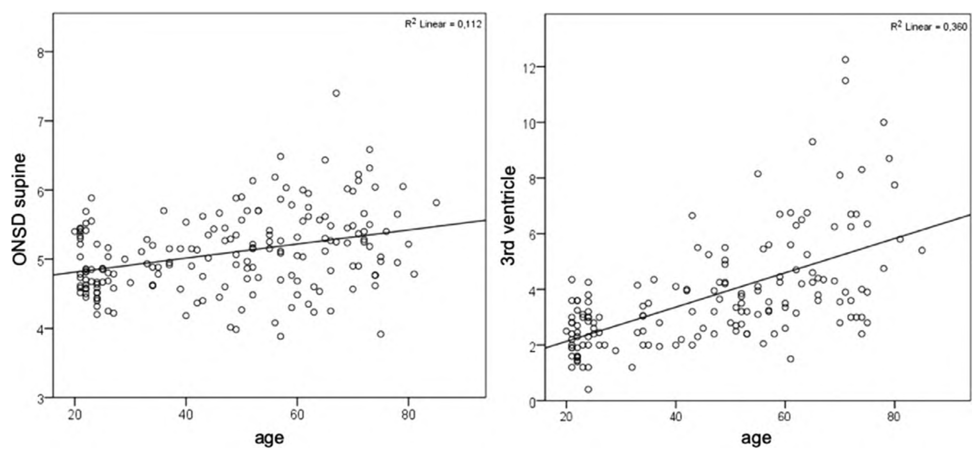

Fig. 3. Scatterplot with regression analysis of optic nerve sheath diameter (ONSD) (a) and third ventricle diameter (b) values depending on age. Each ONSD value is the mean of three independent measurements to compensate for error caused by the axial and lateral resolution. Each third ventricle value is the mean of bitemporal measurements.

Table 2. Dependence of ONSD and third ventricle measurements on sex and age in volunteers measured in supine position

	Age group						Significance (concerning sex)
	Men			Women			
	A	B	C	A	B	C	
ONSD	93			94			
No. of volunteers	27	31	35	43	26	25	
Diameter (mm)	5.3 ± 0.6 mm			4.9 ± 0.5 mm			$p < 0.001$
	5.0 ± 0.4	5.3† ± 0.5	5.5‡ ± 0.6	4.8 ± 0.3	4.8 ± 0.6	5.0 ± 0.6	
Third ventricle	76			81			
No. of volunteers	22	26	28	39	22	20	
Diameter	4.3 ± 2.3 mm			3.2 ± 1.4 mm			$p < 0.001$
	2.6 ± 0.8	3.8 ± 1.2	6.1 ± 2.6	2.5 ± 0.9	3.8 ± 1.5	4.1 ± 1.5	

ONSD = optic nerve sheath diameter.
*Values for diameter are expressed as the mean and mean ± standard deviation.
† Significant difference between groups A and B in men ($p = 0.022$).
‡ Significant difference between groups A and C in men ($p = 0.003$).

C (ΔONSD/PEEP A = −0.21 mm vs. ΔONSD/PEEP C = −0.04, $p = 0.008$; Fig. 5).

DISCUSSION

This study represents a large comparative study in Caucasian volunteers without CNS diseases analyzing the influence of age, sex and basic vascular risk factors on ONSD including positional and pressure challenge using TOS. We observed an increase in ONSD after the third decade of life, which was significant in male probands with a strong trend in women; a smaller ONSD in women; and a diminishing increase in ONSD under PEEP challenge only in women with age.

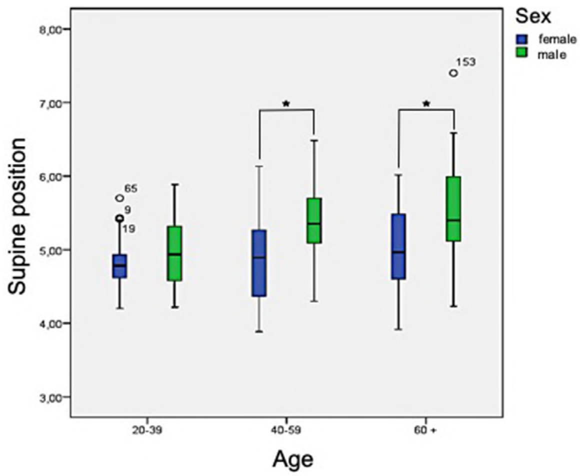

Fig. 4. Boxplot of sex-dependent differences in optic nerve sheath diameter. *Significant differences between groups.

Increased ICP is an important complication of a variety of brain injuries, but even though TOS has been reported to be a reliable and non-invasive method for identification of elevated ICP in a semiquantitative manner and was recently found to be linearly correlated with invasively measured ICP (Cardim et al. 2019), the method has still not gained widespread acceptance in clinical practice.

Recently, Schroeder et al. (2020) reported a large variety of normal values in the published literature. The average age of the normal values used in the meta-analysis was 36.1 y—an age after which we observed the only significant increase in male probands, as well as a trend in women. In addition, our values match best with the European values analyzed in Schroeder et al. (2020) (5.1 mm vs. 4.9−5.3 mm in the present study), but in contrast we observed significantly smaller ONSDs in women than in men. The reason may be the quality of the data used in the meta-analysis, but in conjunction with the increased response to PEEP challenge, this observation possibly reflects important sex-related differences.

Another publication on the relationship between ICP, body mass index, age, sex and ONSD found no differences between men and women with respect to ICP; the relationship between sex and ONSD was not investigated. The normal values based on patients with normal ICP but with an indication for lumbar puncture were similar to the values published in our study, but no age or gender differentiation was made (Liu et al. 2017).

Idiopathic intracranial hypertension seems to be a hallmark disease with a sex-specific response to changes in ICP. A recent meta-analysis on the epidemiology of IIH revealed a female predominance (87%), an average age of 29.8 y and a high prevalence of obesity (McCluskey et al. 2018). In a landmark article by Bauerle and Nedelmann (2011), the IIH population was 80% female with an average age of 26.2 y, while the reference population was predominantly male and older (44% female, average age: 45.8 y). Using a sex- and age-matched population would have led either to a lower cutoff value for detection of IIH or to a higher sensitivity and specificity than published (5.8 mm, sensitivity 90%, specificity 84%). Our study also indicates an explanation for the sex difference in IIH, with the greater response to pressure changes (PEEP > positional challenge) in women perhaps caused by the more elastic connective tissue within the dura mater. The opposite disease, spontaneous intracranial hypotension, has also a strong preference for young women, and the pathophysiology, a dural spinal leak, may be enhanced by differences in connective tissue (Schievink 2006). In SIH, Fichtner et al. (2016) found a greater decrease in ONSD upon upright

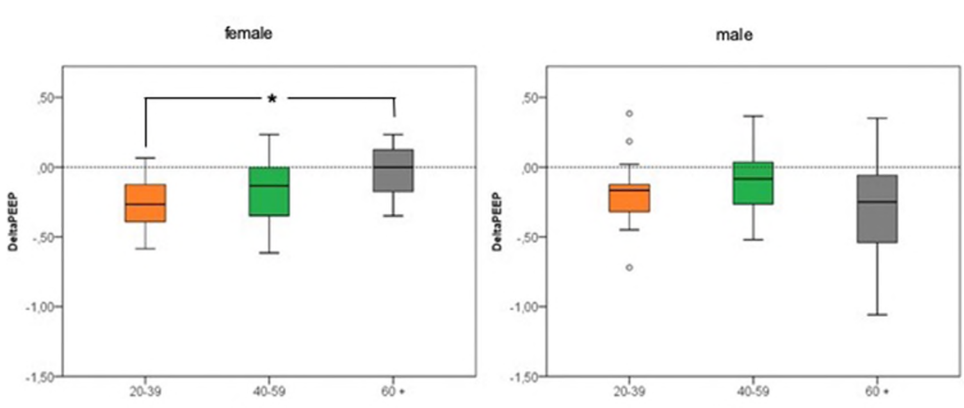

Fig. 5. Boxplot depicting changes in positive end-expiratory pressure depending on age group. *Significant difference between groups.

positioning, but only in patients with a respective clinical affection, mainly positional headache. In aging, the opposite phenomenon—a reduced elasticity of ONSD—could, for example, already be detected in a subgroup of patients with normal-pressure hydrocephalus (Ertl et al. 2017).

Reliable normal values for ONSD are still scarce in the Caucasian population and are concentrated in children or adolescents (Steinborn et al. 2015; Haratz et al. 2019). The only study having systematically analyzed normal values in that population was Goeres et al. (2016), who did find a significant difference between men and women but not with age, while our study revealed an enlargement of the ONSD and the third ventricle with increasing age. Higher ONSD values with age, especially in the male population, could therefore be a correlate of atrophic processes. The upper age limit investigated in that study was 65 (mean age: 29.3), while in our study 23% of all volunteers were ≥60 y. However, the main difference was the reported mean ONSD of 3.68 mm (95% CI: 2.85−4.40), a value so low that it ranges around the optic nerve diameter itself according to Schroeder et al. (2020). Interestingly, Goeres et al. (2016) also found higher ONSDs in men (3.78 mm, 95% CI: 3.23−4.48) than in women (3.60 mm, 95% CI: 2.83−4.11).

Limitations

Although the numbers of patients in all age groups were well balanced, there were some difficulties in the upright measurements in the older population. PEEP measurements were also limited in this subgroup because of handling problems.

CONCLUSION

Our study revealed age, sex and pressure dependencies for ONSD investigated by TOS. Thus, the interpretation of ONSD values depends largely on the reference population—which should be elaborated in each neurosonography laboratory before application in specific brain diseases— and the specific disease. Values for patients with IIH, who are predominantly young and female, must be interpreted differently, as should those for patients with malignant middle cerebral artery stroke, who constitute a predominantly older and male population. In clinical practice, ONSD ultrasound can therefore be employed to observe pathologic changes over time within the same patient or using defined cutoff values from age, sex and position-dependent normal values. The dynamic and mobile nature of TOS allows for pathophysiologic considerations in ICP-related diseases.

Conflict of interest disclosure—All authors declare that there are no conflicts of interest.

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