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TAKE NOTICE TECHNOLOGY

Optic Nerve Ultrasound for the Detection of Raised Intracranial Pressure

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Abstract
Background Optic nerve ultrasonography (ONUS) may help identify raised intracranial pressure (ICP). The optimal optic nerve sheath diameter (ONSD) cut-off for the identification of intracranial hypertension has not been established, with some clinical studies suggesting a higher cut-off than may be expected on the basis of prior laboratory investigation.
Objective To validate ONUS performed by neurointensivists as a technique for the detection of intracranial hypertension and identify the optimal ONSD criterion for the detection of ICP $>$ 20 mmHg.
Methods Prospective blinded observational study. Patients in the ICU with either external ventricular drains or intraparenchymal ICP monitors at risk for intracranial hypertension were enrolled. The ONSD was measured by neurointensivists at the bedside with simultaneous invasive ICP measurement. An ROC curve was constructed to determine the optimal ONSD for the detection of ICP $>$ 20 mmHg.
Measurements and Results A total of 536 ONSD measurements were performed on 65 patients. Diagnoses included subarachnoid hemorrhage, traumatic brain injury, intracerebral hemorrhage, ischemic stroke and brain tumor. ROC curve analysis revealed area under the curve (AUC) = 0.98 (95% CI 0.96–0.99; $P < 0.0001$ for AUC = 0.5). Optimal ONSD for detection of ICP $>$ 20 mmHg was $\geq$0.48 cm sensitivity 96% (95% CI 91–99%); specificity 94% (92–96%). Sensitivity of the higher cutoff of $\geq$0.52 cm proposed by some authors was only 67% (58–75%), with specificity 98% (97–99%).
Conclusions Bedside ONSD measurement, performed by neurointensivists, is an accurate, non-invasive method to identify ICP $>$ 20 mmHg in a heterogeneous group of patients with acute brain injury. ONSD $\geq$0.48 cm has the greatest accuracy, however, internal validation of ONSD criteria may be required.

Keywords Optic nerve · Intracranial hypertension · Ultrasonography · Intracranial pressure · Papilledema · Brain injuries

This study was performed at the University of Michigan.

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Introduction

Raised intracranial pressure (ICP) is a common problem in the neurointensive care unit and published guidelines recommend ICP monitoring with a goal ICP $<$20–25 mmHg in the setting of TBI as well as other forms of acute brain injury [1, 2]. Standard techniques of invasive ICP monitoring, with either an intraparenchymal probe or an intraventricular catheter, carry the risk of hemorrhage as

well as infection [3, 4]. In the absence of invasive monitoring, the presence of CT and MR signs suggestive of raised ICP (such as effacement of basal cisterns, diffuse sulcal effacement and the presence of significant midline shift) are often used to make decisions on the management of intracranial hypertension, although it is not clear that these are accurate predictors. An accurate and reliable non-invasive tool to identify the presence of intracranial hypertension would be of significant value in situations where there is clinical suspicion for intracranial hypertension but invasive monitoring is unavailable or risky to perform, and might also potentially be used to select high-risk candidates for invasive monitoring. To be most useful and cost-effective, such a technique should not require specialized equipment and should be easily performed by clinicians at the bedside using point-of-care equipment.

The sheath around the optic nerve is in fact a continuation of the dura, and the subarachnoid space extends along the optic nerve within the sheath. A rise in ICP is therefore transmitted to the optic nerve head, eventually resulting in swelling of the optic disc and papilledema [5]. While the development of papilledema can take hours to many days, early human studies have shown that an increase in ICP results in distension of the retrobulbar optic nerve sheath within seconds [6, 7]. Ultrasonographic measurement of the optic nerve sheath diameter (ONSD) a fixed distance from the retina has been evaluated as a non-invasive way to identify the presence of ICP, primarily in patients with Traumatic Brain Injury (TBI) and Intracranial Hemorrhage (ICH) [8–13]. It is not clear, however, whether institutions that want to use this technique as a clinical tool in a more heterogeneous group of patients at risk for intracranial hypertension can safely adopt criteria from previously published material. This is particularly important because some of the suggested sonographic ONSD criteria for the detection of raised ICP in the published literature are significantly higher than might be expected on the basis of experimental studies of optic nerve sheath distension [6–9, 13, 14].

The primary objectives of our study were to validate our bedside technique of optic nerve ultrasonography (ON-US) for the detection of intracranial hypertension, using a point-of-care ultrasound machine in a heterogeneous group of patients in the neuro-ICU, and to identify the optimal ONSD cutoff for the identification of ICP.

Methods

Study Design and Setting

Prospective blinded observational study. Approval was obtained from the institutional review board of the University of Michigan and informed consent obtained either from the patient or the next-of-kin.

Inclusion and Exclusion Criteria

Patients admitted to the neurointensive care unit between November 2008 and May 2011 who had an external ventricular drain (EVD) or intraparenchymal ICP monitor in place and were judged by the treating clinician to be at risk for the development of ICP were enrolled in the study. Exclusion criteria were age <18 years, known orbital injury and pre-existing optic nerve pathology. Enrollment was based on investigator availability.

ONSD and Invasive ICP Measurement Protocol

Blinded ONSD measurements paired with simultaneous measurement of intracranial pressure via invasive monitoring were performed at enrollment and intermittently during the course of the patients' stay in the ICU. Enrollment and subsequent measurements were on the basis of investigator availability. Most ONSD measurements were performed by a single investigator with 3 years experience performing ONUS in a clinical setting (VR). Some were performed by a second investigator with 2 months' experience performing ONUS. The sonographer was blinded to the simultaneous invasive ICP measurement. The bedside monitor was turned away from the sonographer and toward the bedside nurse who recorded the invasive ICP while the ONSD measurement was being performed. The sonographer was, however, not blinded to the patient's diagnosis or clinical history. All EVDs were transduced to the monitor for the duration of the ONSD measurements. The mean of the minimum and maximum ICP observed on the monitor during each individual ONSD measurement was recorded as the corresponding invasive ICP measurement by the bedside nurse. During each measurement cluster at least three ONSD measurements were attempted on each side for a total of at least 6 attempted measurements per measurement cluster.

All ONUS scans were performed using a general-purpose, point-of-care Sonosite™ M-Turbo (SonoSite Inc., Bothell, WA, USA) ultrasound machine with a 13–6 MHz linear-array probe with orbital imaging settings and a high resolution optimization setting. The probe was placed on the superior and lateral aspect of the orbit against the upper eyelid with the eye closed and angled slightly caudally and medially (Fig. 1) until the optic nerve was visualized as a linear hypoechoic structure with clearly defined margins posterior to the globe (Fig. 2). While no complications have been reported to our knowledge from the use of ocular ultrasound for the detection of intracranial hypertension, certain basic precautions were observed, and adverse

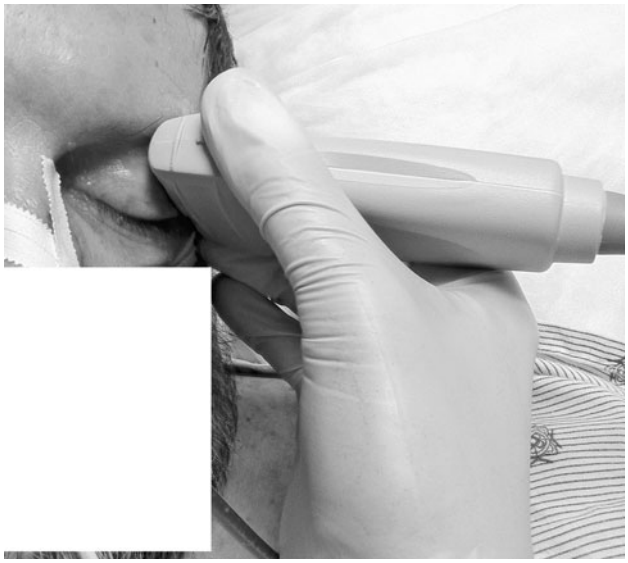

Fig. 1 Technique of optic nerve ultrasound. The probe is placed on the superior and lateral margin of the orbit directed slightly inferiorly and medially with the eyes closed

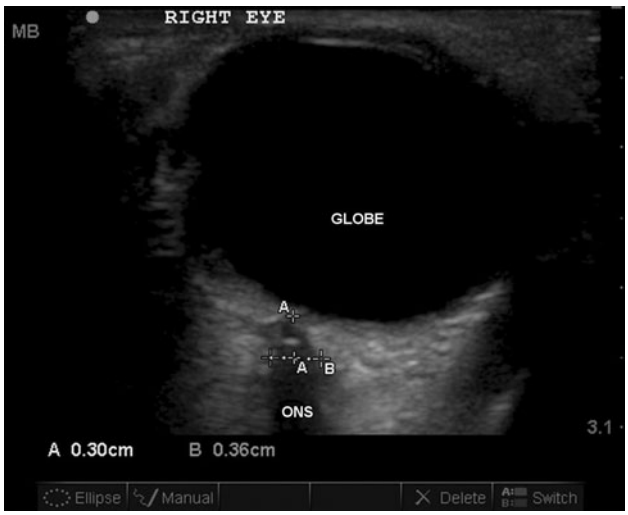

Fig. 2 Greyscale image of orbit. optic nerve sheath (ONS) and the globe are marked. The ONS is a linear hypoechoic structure posterior to the globe. Caliper *A* identifies the site of ONSD measurement 0.3 cm behind the retina. Caliper *B* measures the ONSD (0.36 cm in this case)

effects, if any, recorded. The probe was always placed gently on the closed eyelid and never in direct contact with the cornea or sclera, to avoid corneal abrasions. Contact with the eye was gentle at all times and pressure never directly applied on the globe with the probe, as this can theoretically result in nausea/vomiting and a vagal response. Probes and settings specifically approved by the FDA for ocular imaging are recommended, as excess acoustic power can theoretically result in damage to the retina. All images were obtained in a transverse/axial plane for uniformity. Magnification was not routinely performed. The ONSD was measured 3 mm behind the retina (Fig. 2). In our experience, a major source of error during ONSD measurement is the linear hypoechoic artifact frequently seen posterior to the globe that might be confused with, or partially overlapping, the actual optic nerve sheath. Emphasis was placed on using careful angulation of the transducer during real-time imaging to clearly demarcate the margins of the optic nerve sheath distinct from linear hypoechoic artifact. Images were reviewed off-line while still blinded and the image discarded if the margins of the optic nerve sheath were not sharply defined, there was suspicion of overlap with hypoechoic artifact, or the calipers were found to be incorrectly placed. Correlation was made primarily between each ONSD measurement and the corresponding ICP measurement, rather than, as previous studies have done, comparing the mean of a group of ONSD measurements (including some on the left and some on the right) with the mean of the corresponding invasive ICP measurements. This was done because we frequently observed, prior to this study, the invasive ICP demonstrating enormous variation in the period of time it took to carefully obtain six ONSD measurements, often ranging from intracranial hypertension to normal ICP. A mean of these measurements would thereby decrease the number of true episodes of intracranial hypertension being evaluated with ON-US and potentially detract from the assessment of the accuracy of this technique, particularly its ability to detect a transient, but potentially clinically relevant, elevation in ICP. We also, however, then compared the mean ONSD and mean ICP measurements for the group of 6 measurements, as was done in previous studies, to identify any major difference in identified ONSD criteria that may result from these two different ways of analyzing the data.

All EVDs were Bactiseal™ (Codman & Shurtleff Inc., Raynham, MA, USA) antimicrobial coated external ventricular drainage catheters. All intraparenchymal probes were Codman™ MicroSensor (Codman & Shurtleff Inc., Raynham, MA, USA) intraparenchymal probes that could transduce pressures but not drain cerebrospinal fluid.

Comparison to CT and MR Signs of Raised ICP

All CT and MR scans of the brain performed within a 24 h period of each cluster of ONSD/invasive ICP measurements were reviewed by two investigators (MV and VR) for the presence of previously designated signs of ICP (Table 1), while blinded to invasive ICP measurements. These radiological signs were chosen in view of the heterogeneous nature of the patient population. Previously described CT imaging scores, such as those used specifically for patients with traumatic brain injury, would likely not be applicable to this population. The value of the presence of at least one of

Table 1 Previously designated signs of raised intracranial pressure on CT and MR imaging

Imaging sign	*N* (%)
Diffuse sulcal effacement	36 (63%)
In one cerebral hemisphere	11 (19%)
In both cerebral hemispheres	25 (44%)
Effacement of the basal cisterns	29 (51%)
On one side	14 (25%)
On both sides	15 (26%)
Hydrocephalus, defined as	28 (49%)
Both temporal horns $>$ 2 mm	
Evan ratio (largest width of the frontal horns to maximal biparietal diameter) $>$ 0.3	
Midline shift $>$ 5 mm	22 (39%)
Imaging evidence of uncal or transtentorial herniation	6 (10%)
Any sign of increased intracranial pressure	44 (77%)

these signs on CT or MR in predicting the presence of mean invasive ICP $>$ 20 mmHg for that cluster of measurements was calculated.

Statistical Analysis

The distribution of all variables analyzed such as age, ONSD, time taken to perform measurement and ICP was subjected to the D'Agostino-Pearson test of Normal distribution. Mean and standard deviation with range was calculated for variables with normal distribution. For variables without normal distribution the median with interquartile range (IQR) was used. To test whether there was a univariate association between categorical patient variables and the presence of intracranial hypertension on invasive monitoring (defined as invasive ICP $>$ 20 mmHg in at least one group/cluster of measurements), χ^2 or Fisher's exact test was used. Univariate associations of continuous patient variables with a normal distribution were assessed with the independent sample two-tail Student's *t* test and continuous variables with non-normal distributions were assessed with the Mann–Whitney *U* test. Variables with $P < 0.1$ on univariate analysis were included in a multivariate logistic regression model to identify the independent variables associated with the presence of intracranial hypertension on invasive monitoring. $P < 0.05$ was used as the threshold for statistical significance. The mean of left eye ONSD measurements and the mean of right eye ONSD measurements in each measurement cluster were calculated. The degree of side to side variability between ONSD in the left and right eyes was assessed by calculating the median difference between the average of ONSD measurements in the left and right eyes in each measurement cluster as well as the intraclass correlation coefficient with 95% confidence interval for absolute agreement of single measures between left and right ONSD measurements. A scatter diagram of ONSD versus invasive ICP measurement was produced and the correlation coefficient between these two continuous variables with the corresponding *P* value calculated. For non-normal distributions, Spearman's coefficient of rank correlation (ρ) was calculated. A receiver operating characteristic (ROC) curve was then constructed to determine the optimal ONSD cut-off to detect ICP $>$ 20 mmHg. We then calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of this cut-off with 95% confidence intervals for the detection of ICP $>$ 20 mmHg by invasive monitoring. Separate ROC curves were constructed for subgroups of patients on and off mechanical ventilation. An ROC curve was also constructed to determine the optimal ONSD for the detection of invasive ICP $>$ 25 mmHg. Mann–Whitney, Spearman's correlation and ROC curve analysis were first performed using individual ONSD measurements and the corresponding invasive ICP measurement and repeated using the mean ONSD measurement for each group/cluster of measurements versus the mean invasive ICP measurement for each group of measurements. The proportion of patients with and without ICP $>$ 20 mmHg with at least one sign of raised ICP on imaging was calculated and tested for a statistically significant difference ($P < 0.05$) using Fisher's exact test. The sensitivity, specificity, NPV and positive predictive value (PPV) with confidence intervals of at least one sign of raised ICP on imaging in the prediction of ICP $>$20 mmHg were determined. Statistical analyses were performed using MedCalc for Windows, version 11.6.0.0 (MedCalc software, Mariakerke, Belgium).

Results

Sixty-five patients underwent ON-US for ONSD measurement with simultaneous invasive measurement of ICP. Overall there were 39 women and 26 men. The mean age was 53 years (standard deviation 16, range 18–90). Diagnoses were subarachnoid hemorrhage ($n = 30$), traumatic brain injury ($n = 11$), intracerebral hemorrhage ($n = 11$), brain tumor ($n = 5$), Ventriculo-peritoneal shunt malfunction ($n = 5$), ischemic stroke ($n = 1$), cerebral venous sinus thrombosis ($n = 1$), and acute liver failure ($n = 1$). No corneal abrasions or other adverse effects (nausea, vomiting, vagal response) were observed following performance of ocular ultrasound in any patient.

The characteristics of patients with and without intracranial hypertension on invasive monitoring (defined as the presence of at least one cluster of measurements with mean

Table 2 Characteristics of patients with and without intracranial hypertension on invasive monitoring

Variable	Patients with intracranial hypertension on invasive monitoring ($n = 26$)	Patients without intracranial hypertension on invasive monitoring ($n = 39$)	P value (univariate)
Age in years, mean ± std deviation	51 ± 16	55 ± 16	0.32
Sex—female	14 (54%)	25 (64%)	0.57
Body mass index (kg/m^2), median	25 (IQR 24–31)	36 (IQR 22–31)	0.65
Mechanical ventilation	12 (46%)	15 (38%)	0.72
Type of invasive monitor = intraparenchymal (vs. EVD)	9 (35%)	5 (13%)	0.07
Craniotomy performed	7 (27%)	9 (23%)	0.95
Osmotherapy (3% NaCl infusion or around-the-clock dosing of mannitol) in use at time of measurement	12 (46%)	9 (23%)	0.09
Largest measured ONSD (cm), median	0.45 (IQR 0.39–0.52)	0.39 (IQR 0.34–0.41)	0.0008*
Diagnosis			0.17
Subarachnoid hemorrhage	10 (38%)	20 (51%)	
Traumatic brain injury	7 (27%)	4 (10%)	
Intracerebral hemorrhage	6 (23%)	5 (13%)	
Brain tumor	2 (8%)	3 (8%)	
Ventriculoperitoneal shunt malfunction	0 (0%)	5 (13%)	
Ischemic stroke	0 (0%)	1 (3%)	
Cerebral venous sinus thrombosis	1 (4%)	0 (0%)	
Acute liver failure	0 (0%)	1 (3%)	

Intracranial hypertension on invasive monitoring was defined as the presence of at least one cluster of measurements with mean invasive ICP $>$ 20 mmHg. All P values are on univariate analysis, $P < 0.05$ was considered statistically significant. *Variables that were statistically significant independent associations following multivariate logistic regression analysis
IQR interquartile range

invasive ICP $>$ 20 mmHg) is shown in Table 2. In univariate analysis, only highest measured ONSD and the use of intraparenchymal monitor (vs. EVD) achieved $P < 0.1$. On multivariate logistic regression analysis, the only factor independently associated with intracranial hypertension on invasive monitoring was the patient's highest measured ONSD ($P = 0.002$).

ONSD and Invasive ICP Measurements

A total of 576 ONSD measurements, over a total of 97 groups (clusters) of measurements, were made with simultaneous measurement of invasive ICP. Forty (7%) of these measurements were discarded following off-line review of the quality of the measurement while still blinded to the corresponding invasive ICP value. A total of 536 correlations were therefore made between measured ONSD and the corresponding invasive ICP measurement. Of the invasive measurements, 414 (77%) were from EVDs and 122 (23%) from intraparenchymal probes. VR performed 518 (96%) measurements while JF performed 18 (4%). The median time taken to perform an ONSD measurement was 1.83 min (IQR 1.33–2.33 min). ONSD and ICP values failed tests of normal distribution. The median ONSD measurement was 0.42 cm (IQR 0.37–0.48 cm). The median invasive ICP measurement was 12 mmHg (IQR 9–19 mmHg). There were 125 (23%) invasive ICP measurements $>$20 mmHg and 49 (9%) $>$25 mmHg. During each cluster of ONSD measurements (at least three attempted from each eye per cluster) the median range of recorded invasive ICP measurement (difference between the highest and lowest invasive ICP among the six measurements) was 4 mmHg (IQR 2–8 mmHg, minimum 0 mmHg, maximum 21 mmHg). Of note, 20 of 97 (21%) measurement clusters included invasive ICPs both above and below 20 mmHg and 9 of 97 (9%) clusters included ICPs both below 20 mmHg and above 25 mmHg, illustrating the importance of studying the correlation between individual ONSD measurements and the corresponding invasive ICP in addition to correlating the means of ONSD and invasive measurements in each group of measurements.

The median ONSD for measurements corresponding to invasive ICP $>$ 20 mmHg was 0.53 cm (IQR 0.51–0.57 cm) while the median ONSD with invasive ICP $\leq$20 mmHg was 0.40 cm (IQR 0.36–0.43 cm). The difference was statistically significant (Mann–Whitney $U = 1043$, two-tailed probability

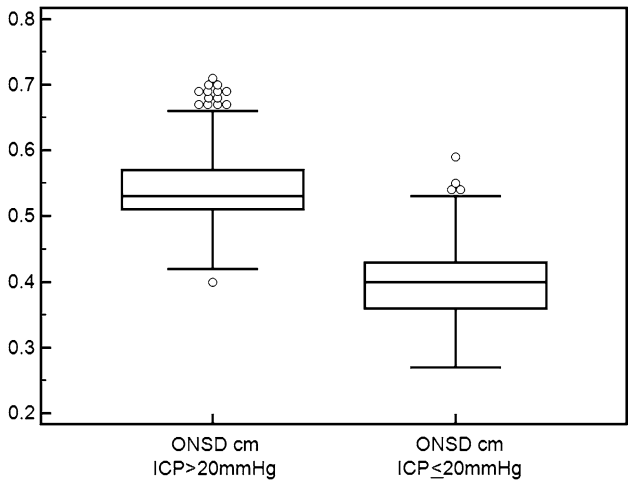

Fig. 3 Box and whisker plot of ONSD in patients with and without ICP > 20 mmHg on invasive monitoring. In the *box-and-whisker plot*, the *central box* represents the values from the lower to upper quartile (25–75 percentile). The middle line represents the median. The *horizontal line* extends from the minimum to the maximum value, excluding outside and far out values, which are displayed as separate points

$P < 0.0001$, Fig. 3). When the mean ONSD and invasive ICP measurements for each group (cluster) of measurements was used instead of individual measurements, the difference was once again statistically significant (median ONSD with invasive ICP > 20 mmHg = 0.52 cm, median ONSD with ICP ≤ 20 mmHg = 0.40 cm, Mann–Whitney U test = 6, two-tailed probability $P < 0.0001$). Spearman's coefficient of rank correlation (ρ) between individual ONSD and invasive ICP measurements was 0.73 (95% CI 0.66–0.80, $P < 0.0001$, Fig. 4). Rank correlation remained strong between mean ONSD and invasive ICP measurements for each group (cluster) of measurements $\rho = 0.76$ (95% CI 0.66–0.83, $P < 0.0001$).

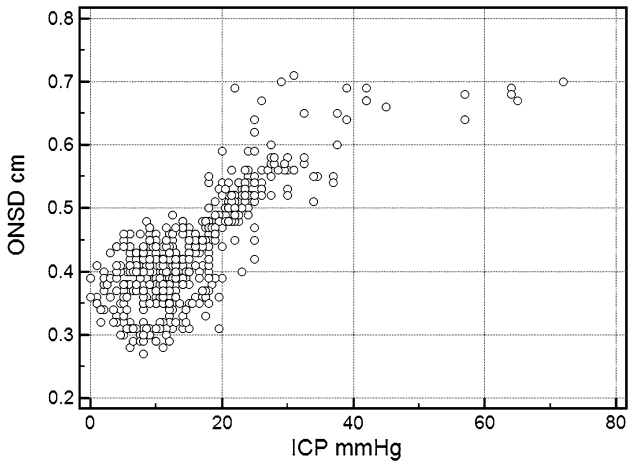

Fig. 4 Scatter diagram of ONSD versus invasive ICP measurements

Left Versus Right Eye ONSD Measurements

The distribution of the difference between the average left eye ONSD and the average right eye ONSD in each measurement cluster failed normal distribution. The median difference between left eye mean ONSD and right eye mean ONSD was only 0.01 cm (IQR 0.01–0.03 cm). The intraclass correlation coefficient for absolute agreement between left and right eye ONSD measurements was high (0.92, 95% CI 0.87–0.96), suggesting the presence of only minimal side-to-side variation in the ONSD.

ROC Curve

The ROC curve of ONSD for the detection of invasive ICP > 20 mmHg is shown in Fig. 5a. The area under the curve (AUC) was 0.98 (95% CI 0.96–0.99, P was <0.0001 for AUC = 0.5). Optimal ONSD cutoff for the detection of invasive ICP > 20 mmHg was ≥ 0.48 cm. The sensitivity of this cutoff was 96% (95% CI 91–99%), specificity 94% (95% CI 92–96%), positive predictive value 84% (95% CI 77–89%) and NPV 99% (95% CI 97–100%). Accuracy of different ONSD cutoffs for the detection of invasive ICP > 20 mmHg and invasive ICP > 25 mmHg is shown in Table 3. Of note, the sensitivity of a ≥0.52 cm cutoff, suggested by some authors, was only 67% (95% CI 58–75%) for the detection of ICP > 20 mmHg in our study. When the ROC curve was constructed for the detection of ICP > 25 mmHg (Fig. 5b), the area under the curve (AUC) was 0.98 (95% CI 0.97–0.99, p for AUC = 0.5 was <0.0001). Optimal ONSD cutoff for the detection of invasive ICP > 25 mmHg was ≥0.52 cm sensitivity 98% (95% CI 89–100%), specificity 91% (95% CI 88–94%), PPV 53% (95% CI 42–64%) and NPV 100% (95% CI 99–100%). An ROC curve was also constructed using the means of ONSD and invasive ICP measurements in each cluster of measurements. The area under the curve (AUC) was 0.99 (95% CI 0.95–1.00, P for AUC = 0.5 was <0.0001). Optimal mean ONSD cutoff for the detection of mean invasive ICP > 20 mmHg was ≥0.47 cm sensitivity 100% (95% CI 85–100%), specificity 92% (83–97%), PPV 80% (95% CI 61–92%), NPV 100% (95–100%).

Mechanical Ventilation

The ONSD retained high accuracy for the detection of ICP > 20 mmHg for patients on and off mechanical ventilation, with a small difference in the optimal ONSD cutoff between the two groups. The ROC analysis for patients on mechanical ventilation (216 measurements in 27 patients) revealed AUC = 0.97 (95% CI 0.94–0.99, $P < 0.0001$) and optimal ONSD cutoff ≥0.50 cm with sensitivity 90% (95% CI 79–97%), specificity 98%

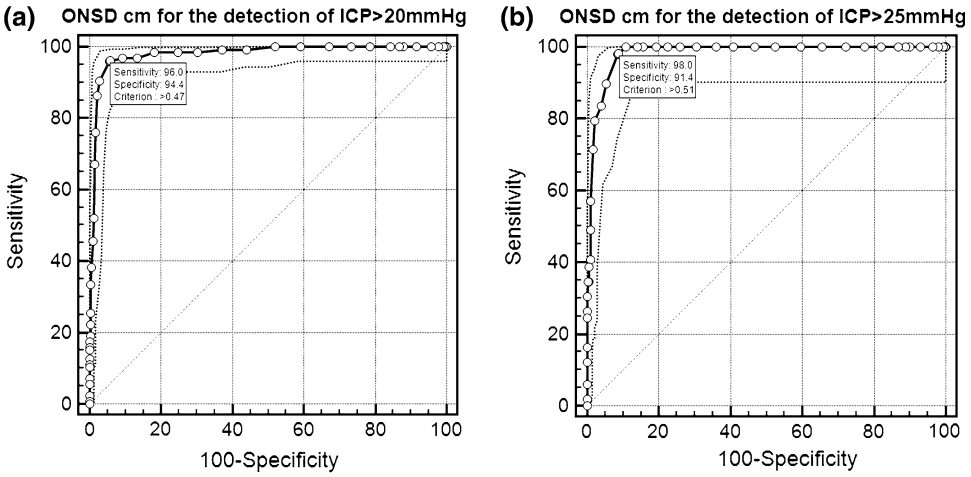

Fig. 5 ROC curves of ONSD for the detection of invasive ICP > 20 mmHg (**a**) and invasive ICP > 25 mmHg (**b**). *Dotted tracing* represents 95% confidence bounds

Table 3 Accuracy of different ONSD criteria for the detection of intracranial hypertension

High ICP criterion (mmHg)	ONSD criterion (cm)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
>20	≥0.48	96% (91–99%)	94% (92–96%)	84% (77–89%)	99% (97–100%)
>20	≥0.50	86% (79–92%)	98% (96–99%)	92% (86–96%)	96% (94–98%)
>20	≥0.52	67% (58–75%)	98% (97–99%)	93% (86–97%)	91% (88–93%)
>20	≥0.59	19% (13–27%)	100% (99–100%)	96% (80–100%)	80% (76–84%)
>25	≥0.52	98% (89–100%)	91% (88–94%)	53% (42–64%)	100% (99–100%)

(94–99%), PPV 92% (95% CI 81–98%), NPV 97% (93–99%). For patients not on mechanical ventilation (320 measurements in 38 patients), ROC analysis revealed AUC = 0.97 (95% CI 0.94–0.99, $P < 0.0001$) and optimal ONSD cutoff ≥0.48 cm with sensitivity 99% (95% CI 93–100%), specificity 95% (91–97%), PPV 85% (95% CI 76–92%), NPV 100% (98–100%).

CT/MR Versus Invasive ICP

Fifty seven of ninety seven (59%) measurement clusters were performed in the same 24 h period as a CT or MR scan (54 CT scans and 3 MR scans). The scans were performed a mean of 7 h from ONSD measurement (SD 7 h, range 15 min to 18 h). Overall, 44 of 57 (77%) scans demonstrated at least one of the previously designated signs (Table 1) of elevated intracranial pressure. Thirteen of sixteen (81%) scans performed within the same 24 h period of a measurement cluster with mean invasive ICP > 20 mmHg versus 31 of 41 (76%) scans performed within the same 24 h period of measurement clusters with mean invasive ICP recording ≤ 20 mmHg demonstrated at least one radiological sign of raised ICP (Fisher Exact 2-tail probability $P = 0.74$). Sensitivity was 77% (95% CI 46–95%), specificity 29% (17–45%), PPV 24% (95% CI 12–40%) and NPV 81% (95% CI 54–96%) for the detection of invasive ICP > 20 mmHg.

Discussion

A reliable non-invasive means to detect intracranial hypertension is an important unmet need in the field of neuro-intensive care. While papilledema is a long-recognized clinical sign of intracranial hypertension, it can take many hours-to-weeks to develop and cannot be relied upon in the critical care setting for the detection of acutely elevated ICP [5]. While our study was not specifically designed to analyze the predictive value of CT and MR imaging for ICP, the analysis of CT and MR images performed within 24 h of measurement revealed no correlation between signs of raised ICP on imaging and the presence of invasive ICP > 20 mmHg in this mixed group of neuro-ICU patients. Other studies, in patients with TBI, have also shown that CT imaging cannot always be relied upon to identify ICP [14, 15]. Several other non-invasive techniques of ICP measurement have been evaluated, including transcranial doppler sonography, ophthalmic doppler flow measurement and near-infrared spectroscopy among others [16]. Most of these techniques have had mixed results or are not easily available to the clinician at the bedside.

Our study demonstrates that ON-US with measurement of ONSD—when performed by an experienced operator—is a highly accurate non-invasive technique for the detection of intracranial hypertension (whether defined as

invasive ICP > 20 mmHg or >25 mmHg). We have also demonstrated that this technique can be performed by neurointensivists at the bedside, using point-of-care ultrasound machines that are already widely available and in routine use in many intensive care units and emergency rooms for applications such as vascular access, bedside echocardiography and the focused assessment with sonography in trauma (FAST). Where a point-of-care ultrasound machine is already available, this is a study that can be performed for no additional expense. Each measurement can be performed quickly (the median time per measurement was <2 min), which is important during neurological emergencies. These features may be particularly valuable in prehospital care, military settings, and in the developing world, where the availability and utilization of invasive monitoring is limited [17]. Although the underlying mechanism of optic nerve sheath distension is probably similar to that underlying the development of papilledema (transmission of raised ICP through the subarachnoid space to the optic nerve sheath and disk), optic nerve sheath distension occurs within seconds of an ICP elevation, making ONUS potentially useful even for the detection of acute, and possibly hyperacute, ICP elevations. The high NPV of ONUS may be particularly useful for exclusion of intracranial hypertension in complicated patients in the ICU with multiple neurological and medical comorbidities and acutely altered mental status of uncertain etiology, where imaging is equivocal/unreliable and the placement of an invasive monitor may not be immediately indicated. This includes, potentially, patients with liver failure, intracranial hemorrhage, intracranial mass lesions, VP shunts, and trauma.

Other studies have demonstrated good correlation between sonographically measured ONSD and the presence of intracranial hypertension [8–13]. Our study, which also demonstrates very good correlation, is important for several reasons. Our study included the largest number of individual test subjects with acute brain injury ($n = 65$) as well as the largest number of individual correlations ($n = 536$) between measured ONSD and simultaneous invasive ICP monitoring currently in the literature. Studies that have included a small number of patients or correlations may be of questionable validity [18, 19]. Most published studies of ONSD measurement that have included at least 30 direct correlations have demonstrated good correlation between ONSD and invasive ICP measurements [8–13]. It is very likely that, similar to other point-of-care ultrasound applications [20], more measurements reflect greater operator experience. Operator inexperience and error may confound the ability to assess the intrinsic value of the technique itself. This is particularly true of ONSD measurement because optic nerve sheath dimensions are very small and the presence of retrobulbar linear hypoechoic artifact can greatly confound measurements. In contrast to previous studies, which mostly included patients with a single type of intracranial injury (traumatic brain injury or intracranial hemorrhage), our series demonstrates the accuracy of ONUS in a heterogeneous group of patients with acute brain injury, including subarachnoid hemorrhage, trauma, intracerebral hemorrhage, brain tumors and malfunctioning ventriculoperitoneal shunts. The ONSD was found to be the only factor independently predicting intracranial hypertension, regardless of diagnosis, suggesting also that the predictive value was not related to the performance of multiple observations in individual patients.

Another important finding in our study was that the optimal ONSD criterion for the detection of ICP > 20 mmHg (≥0.48 cm in our study) may be significantly lower than previously suggested. The optimal ONSD cut-off in our study is closest to the 0.5 cm cutoff described in a study of 15 patients (38 measurements) from the Massachusetts General Hospital [9]. The ONSD cut-off of 0.52 cm identified by Moretti et al. [12], at our institution, would miss a third of invasive ICP measurements > 20 mmHg and was more appropriate, in our study, for the detection of invasive ICP > 25 mmHg (Table 3). The 0.59 cm cutoff identified by Geeraerts et al. [11] would miss 81% of invasive ICP measurements >20 mmHg. While, for reasons described below, we consider our ONSD criteria to be more accurate, we also believe that this finding highlights the importance of internal, institutional validation of sonographic ONSD criteria prior to the routine clinical use of this modality. This is analogous to internal validation of Carotid Doppler criteria for carotid stenosis, when feasible [21]. Differences in equipment and operator technique can result in systematic differences in measurements. ONSD measured in the axial plane (as performed in our study), for example, has been found to be consistently larger than ONSD measured in the sagittal plane [13].

We believe, however, that the ≥0.48 cm sonographic cut-off is likely to be a more acute criterion for the detection of an acutely distended optic nerve sheath in the setting of intracranial hypertension. A post-mortem study of adult optic nerve specimens distended with gelatin found the diameter of most distended nerve sheaths to be between 4 and 5 mm, while the diameter of most non-distended nerve sheaths was between 3 and 4 mm [7]. Another study, in which ONSD measurements as well as directly transduced cerebrospinal fluid pressure measurements were performed during intrathecal infusions of saline, describes the presence of ICP > 30 mmHg concurrent with an ONSD of 0.48 cm [6]. It is possible that a lower ONSD threshold is required to identify a hyper-acute elevation in ICP, compared to a more established ICP elevation. A recent experimental study suggested that the reversibility

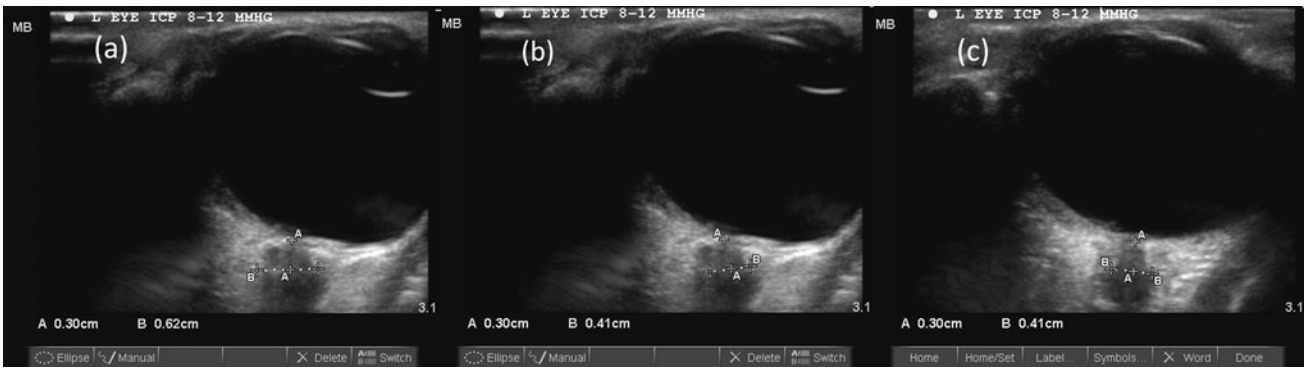

Fig. 6 Retrobulbar linear hypoechoic artifact and ONSD. Caliper *A* identifies the site of ONSD measurement 0.3 cm behind the retina and Caliper *B* measures the ONSD. Invasive ICP is 8–12 mmHg during acquisition of all three images. In **a** there is superimposition of artifact on the optic nerve, resulting in an inaccurately large ONSD reading of 0.62 cm. The actual margins of the optic nerve sheath, depicted by Caliper *B* in **b** are hard to differentiate from the superimposed artifact. In **c**, slight angulation of the probe has mostly eliminated hypoechoic artifact and the ONSD can be accurately measured at 0.41 cm

of optic nerve sheath distension may be reduced following prolonged intracranial hypertension [22]. It is possible that our series included more hyper-acute elevations than other studies—21% of measurement clusters in our study included measurements both above and below 20 mmHg. Of note, the higher ONSD cutoffs in the Geeraerts (>0.58 cm) and Moretti (>0.51 cm) studies did demonstrate high sensitivity (95 and 93%, respectively) but had significantly lower specificity (74 and 79%, respectively) than the ≥ 0.48 cm cutoff in our study (sensitivity 96% and specificity 94%). It is possible that the higher specificity in our study reflects the emphasis we placed on obtaining sharp boundaries to the optic nerve sheath, during real-time imaging as well as off-line review, in order to avoid contamination with linear hypo-echoic artifact posterior to the globe. This previously described artifact is very common and can make the ONSD appear larger than it is [23]. This linear hypoechoic artifact is always central in relation to the globe and is always aligned perpendicular to the surface of the probe (Fig. 6), suggesting that it is an acoustic shadow of an ocular structure. In contrast, the actual optic nerve sheath may be visualized at a variety of angles in relation to the globe, depending on probe and eye position, as the nerve courses medially from the globe to exit the orbit. While the exact origin of this linear artifact has not been clearly defined, it has been suggested that it is an acoustic shadow of the lamina cribrosa [23]. Figure 6 illustrates the large error that can be introduced by the super-imposition of artifact over the actual optic nerve sheath. 8% of all completed and recorded ONSD measurements in our study were discarded based on off-line review of the definition of the margins of the optic nerve sheath, while still blinded to invasive ICP. It is possible that cut-offs that are larger but have lower specificity may have been established as a result of inadvertent contamination with hypoechoic linear artifact in a significant number of measurements.

The principal weakness of our study is the fact that the vast majority of scans were performed by a single experienced operator. The accuracy of this technique when performed by operators with more varied experience—such as physicians in training or nursing staff—was not assessed. This is significant because, in view of the small dimensions being measured and the frequent occurrence of artifact, ONSD measurement may yield inconsistent results when performed by inexperienced and untrained operators. A minimum number of supervised measurements of both normal and distended optic nerve sheaths are likely essential before an operator can independently perform ONSD measurements, similar to the requirements for other point-of-care ultrasound applications such as the focused assessment with sonography in trauma. Since the issue of interobserver variability may be a key factor limiting the widespread adoption of this technique, we are currently enrolling patients in a prospective trial assessing the inter-observer variability of ONUS when performed by less experienced operators. Another weakness of our study is that while the sonographer was blinded to the concurrent invasive ICP, he could not be blinded to the overall clinical condition of the patient or the diagnosis because the clinician-sonographer often had primary responsibility for clinical management. While ONUS is a potentially valuable tool in the arsenal of the neurointensivist, the requirement for adequate experience and training with the technique, the small dimensions that discriminate normal from ICP (i.e., 0.47 cm being "normal" vs. 0.50 cm suggesting elevated ICP) and the presence of confounding artifact are all factors that may limit the widespread adoption of this technology at its current stage. There are other limitations inherent to ONUS, even when it is performed with high accuracy. First,

it is a qualitative rather than quantitative assessment of ICP (high vs. not high) and cannot assess the degree of intracranial hypertension. Also, measurement of ONSD is a point-in-time/snapshot assessment for intracranial hypertension only, rather than a continuous assessment, and will likely need to be repeated at regular intervals for the patient at risk for the development of intracranial hypertension who does not have invasive monitoring. For these reasons, it is clear that ONUS, even when accurate, can only complement, rather than replace, the use of standard-of-care invasive monitoring.

In conclusion, measurement of ONSD using ocular sonography is an accurate, non-invasive technique for the detection of intracranial hypertension when performed by an experienced operator. Internal institutional validation of optimal ONSD criteria for the detection of intracranial hypertension may be required.

Conflicts of interest None of the authors have any conflicts of interests or disclosures.

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