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Clinical paper

A comparison of non-invasive versus invasive measures of intracranial pressure in hypoxic ischaemic brain injury after cardiac arrest

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Abstract

Aim: Increased intracranial pressure (ICP) in hypoxic ischaemic brain injury (HIBI) can cause secondary ischaemic brain injury and culminate in brain death. Invasive ICP monitoring is limited by associated risks in HIBI patients. We sought to evaluate the agreement between invasive ICP measurements and non-invasive estimators of ICP (nICP) in HIBI patients.

Methods: Eligible consecutive adult (age > 18) cardiac arrest patients with HIBI were included as part of a single centre prospective interventional study. Invasive ICP monitoring and nICP measurements were undertaken using: a) transcranial Doppler ultrasonography (TCD), b) optic nerve sheet diameter ultrasound (ONSD) and c) jugular venous bulb pressure (JVP). Multiple measurements applied in linear mixed-effects models were considered to obtain the correlation coefficient between ICP and nICP as well as their predictive abilities to detect intracranial hypertension (ICP ≥20 mm Hg).

Results: Eleven patients were included (median age of 47 [range 20–71], 8 males and 3 females). There was a linear relationship between ICP and nICP with ONSD (R = 0.53 [$p < 0.0001$]), JVP (R = 0.38 [$p < 0.001$]) and TCD (R = 0.30 [$p < 0.01$]). The ability to predict intracranial hypertension was highest for ONSD and TCD (area under the receiver operating curve (AUC) = 0.96 [95% CI: 0.90–1.00] and AUC = 0.91 [95% CI: 0.83–1.00], respectively). JVP presented the weakest prediction ability (AUC = 0.75 [95% CI: 0.56–0.94]).

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Conclusions: ONSD and TCD methods demonstrated agreement with invasively-monitored ICP, suggesting their potential roles in the detection of intracranial hypertension in HIBI after cardiac arrest.

Keywords: Non-invasive intracranial pressure, Optic nerve sheath diameter ultrasonography, Transcranial doppler ultrasonography, Hypoxic ischaemic brain injury, Cardiac arrest

Introduction

The onset of cerebral oedema in hypoxic ischaemic brain injury (HIBI) following cardiac arrest can cause secondary injury, lead to *trans*-tentorial herniation, and culminate in brain death.[1] Stemming from both vasogenic and cytotoxic-mediated mechanisms, real time assessment of cerebral oedema-induced intracranial hypertension is essential to detect this downward pathophysiologic spiral.[2]

Increased ICP can occur in HIBI, but there appears to be significant between-patient variability[3] and also temporal changes with increased ICP occurring during the re-warming phase after targeted temperature management.[4] These between-patient variances and changes over time highlight the dynamic nature of ICP fluctuations. Hence, broad assumptions of ICP patterns in HIBI do not account for the marked variation, reinforcing the need of ICP monitoring techniques in HIBI.

Invasive ICP monitoring is commonly used in managing patients with severe traumatic brain injury (TBI). However, the use of invasive ICP monitoring in patients following cardiac arrest is obviated because of the frequent need for anticoagulant or anti-platelet therapy, particularly in the case of acute coronary syndrome. As such, non-invasive methods to measure ICP would be highly attractive. Of the available methods, optic nerve sheath diameter (ONSD) ultrasonography and transcranial Doppler (TCD)-based ICP estimation have emerged as viable techniques. Increased ONSD has repeatedly been associated with elevated ICP in TBI.[5,6] A recent systematic review and *meta*-analysis demonstrated a robust prediction ability (area under the receiver operating curve (AUC) of 0.94) of ONSD ultrasonography to detect intracranial hypertension.[6] Similarly, TCD-based calculation of ICP demonstrated reasonable predictive abilities for the detection of intracranial hypertension ($AUC > 0.7$).[7–9] Increased ICP can affect cerebral blood flow velocity by yielding decreased diastolic flow velocity, peaked waveforms, and a higher pulsatility index.[10,11] Non-invasive ICP derivation using these principles has demonstrated agreement with simultaneously measured invasive ICP.[12]

A less explored alternative for nICP assessment focuses on the relationship between ICP and cerebral venous sinus pressure, as studies have demonstrated correlations between increased ICP and elevated cerebral venous blood flow velocity.[13–15] As such, placement of a jugular venous bulb oximetry catheter lends itself ideally to monitoring the relationship between ICP and the jugular bulb venous pressure (JVP).

We sought to investigate the agreement between non-invasively derived ICP with ONSD, TCD, and JVP versus invasively-monitored ICP in hypoxic ischaemic brain injury after cardiac arrest.

Methods

We performed a single centre prospective study in 11 HIBI patients using invasive ICP monitoring with real time measurements of ONSD, TCD, and JVP. This nested cohort study was conducted a priori as part of a prospective neuromonitoring study in HIBI patients which was approved by the University of British Columbia clinical research ethics board (H16-00466).

Study setting

The study was completed between November 2016 and January 2018 with ongoing recruitment at the Vancouver General Hospital Intensive Care Unit (ICU), which is a closed 34-bed mixed medical and surgical unit with board-certified intensivists and is affiliated with the University of British Columbia. Our ICU manages approximately 50 post-cardiac arrest patients annually with targeted temperature management (35–36 °C) for 24–48 h. Patients were treated in accordance with a management protocol encompassing intravenous propofol and fentanyl as first-line sedatives. Intermittent bolus dosing of rocuronium were administered for shivering during targeted temperature management (36 °C) for 24–48 h with surface cooling devices. Haemodynamic targets are set in accordance with international post-cardiac arrest care guidelines.[15]

Study subjects

Patients were included if they met the following criteria: (a) time to return of spontaneous circulation (ROSC) > 10 min, (b) post-ROSC un-confounded Glasgow Coma Score < 9, (c) inclusion within 72 h of cardiac arrest, and (d) at least 20 min of sustained spontaneous circulation following ROSC. We excluded patients under the following circumstances: (a) concurrent coagulopathy (INR > 1.5, prothrombin time > 40 s, platelets $< 100 \times 10^9$/L), (b) anticipated cardiac catheterisation within 7 days, (c) concurrent or anticipated anticoagulant or anti-platelet therapy within the next 7 days, (d) temperature < 35 °C, (e) prior TBI, intracranial haemorrhage, or stroke, (f) anticipated withdrawal of care within 72 h, (g) prior optic nerve or orbital pathology, (h) skull base fracture with a cerebrospinal fluid (CSF) leak, (i) inaccessible temporal TCD window, and (j) clinical or radiological suspicion of vasospasm.

Data collection

Intra-parenchymal ICP (Camino®, Integra Lifesciences, U.S.A.) was placed through a dual lumen cranial bolt in the non-dominant frontal lobe. We transduced the pressure (JVP) from a jugular venous bulb oximetry catheter (Pediasat®, Edwards Lifesciences, U.S.A.) placed in the dominant jugular vein. The transducer was positioned at the ipsilateral mastoid process and catheter positioning was confirmed with X-ray. We also recorded end-tidal CO_2 ($ETCO_2$), core body temperature, mean arterial blood pressure zeroed at the level of the right atrium (MAP), and cerebral perfusion pressure continuously. All aforementioned physiologic variables were displayed on bedside monitors (Carescape®, General Electric, U.S.A.) then incorporated into ICM+® neuromonitoring software at a sampling rate of 300 Hz (Cambridge Enterprise, https://icmplus.neurosurg.cam.ac.uk/) in real time.

We conducted optic nerve sheath diameter (ONSD) ultrasonography bilaterally with a linear 7 MHz probe over both orbits (Sonosite®, U.S.A.). The probe was oriented perpendicularly in the vertical plane and at

approximately 30° in the horizontal plane with subjects positioned at 30°. The widest diameter visible 3 mm behind the retina in both eyes was recorded for both the vertical and horizontal planes. The final ONSD value was calculated by averaging these four consecutive measured values following previously described insonation techniques.[14,16-20]

Transcranial Doppler (Sonosite®, U.S.A.) assessment of the middle cerebral artery was conducted at the bedside using a 2 MHz phased-array probe in the temporal window bilaterally on each subject.[21,22] Middle cerebral artery mean flow velocity (FV_m) and diastolic flow velocity (FV_d) were recorded. The final values of flow velocities were calculated by averaging the two bilaterally-measured values.

ONSD and TCD measurements were conducted by an experienced operator (MSS, with more than 30 ultrasound examinations of experience before the onset of recruitment as previously described[19]) three times per day over a 15-min period while invasive ICP monitoring was in-situ with the operator blinded to the ICP. Data were recorded on a case report form with averaged physiological data pertaining to MAP, ICP, cerebral perfusion pressure (CPP), JVP, $ETCO_2$, and positive end-expiratory pressure (PEEP) extracted from ICM+® over the 15 min during the TCD and ONSD measurements.

Non-invasive ICP estimation

The absolute values of nICP derived from ONSD ($nICP_{ONSD}$) were estimated according to a regression analysis between ICP and ONSD from a previous study by Robba et al.[14]:

$$nICP_{ONSD} = 5 \times ONSD - 13.92mmHg) \quad (1)$$

TCD-based nICP ($nICP_{FVd}$) was calculated in accordance with the method described by Czosnyka et al.[23]

$$nICP_{FVd} = MAP \times 1 - \frac{FV_d}{FV_m}) - 14\text{mm Hg} \quad (2)$$

Statistical analysis

Analyses were conducted with *R* Studio software (*R* version 3.4.1). Mixed-effects models were applied to account for within-subject clustering of repeated measures of the variables of interest. Given the multiple measurements of ONSD in different anatomical views performed by a single operator, we verified the intra-rater reliability of these measurements using the intra-class correlation (ICC) and its 95% confidence interval (*R* function *ICCest*). ICC values less than 0.5 indicate poor reliability, between 0.5 and 0.75 moderate reliability, between 0.75 and 0.9 good reliability, and greater than 0.90 excellent reliability.[24]

The relationships between ICP and the non-invasive measurements were expressed as linear mixed-effects models (*R* package *lme4*[25]). As fixed effects, we entered ICP and the non-invasive estimators into the model. As random effects, we had intercepts and slopes for the repeated measurement points for each patient (N = 78 measurements). Chi-square (χ^2) and p-values for model comparisons were obtained by likelihood ratio tests of the full model with random intercepts and slopes against the null model with random intercepts only. The repeated measures correlations (*R* package *rmcorr*[26]) between ICP and the non-invasive estimators were verified (R, with the level of significance set at 0.05). The relationships between nICP estimators and the potential physiological confounders $ETCO_2$ and PEEP were also tested using repeated measures correlations.

Bland–Altman analysis for repeated measures was used to determine the agreement between invasive ICP and the nICP assessments.[27] The confidence interval represents the method's estimation performance and contemplates the range of values around the bias (absolute difference between mean values of non-invasive ICP and ICP) in which data can be found. The area under the curve (AUC) of the receiver operating characteristic curve (ROC) for repeated measures was performed to determine the ability of the non-invasive methods to detect intracranial hypertension (ICP > 20 mm Hg; N = 78 measurements). Statistical differences between ROC curves were verified using the DeLong's test for two correlated ROC curves (*R* package *pROC*[28]).

Results

Twenty-two patients were screened with 11 eleven included into the final analysis. Patients were excluded for the following reasons: 5–concurrent coagulopathy, 4–anticipated withdrawal care within 72 h, 1–previous traumatic brain injury, 1–concurrent anti-platelet therapy. Demographic characteristics of the cohort are shown in Table 1 and a

Table 1 – Demographics of patient cohort.

Patient	Gender	Age	Initial rhythm	Aetiology	Witnessed	ROSC (min)	Post ROSC GCS	Epi doses	APACHE II	Initial lactate	Co-morbidities
1	M	19	Asystole	Hanging	N	16	7	0	16	1.3	None
2	M	46	PEA	Hanging	N	15	7	1	19	5.7	None
3	M	20	PEA	Haemorrhage	Y	60	3	25	21	19	None
4	F	68	Asystole	Hypoxemia	N	14	3	3	28	12.4	HTN, Dyslipidaemia
5	M	69	Asystole	Anaphylaxis	N	33	3	5	38	9.3	Myelodysplasia, Dyslipidaemia
6	M	37	PEA	Drowning	Y	40	3	0	26	13.4	None
7	F	69	Asystole	Asthma	N	14	3	2	32	7.6	Asthma, HTN, DMII
8	M	47	PEA	Opiate OD	N	34	3	3	25	11.9	None
9	M	54	PEA	Asthma	Y	19	6	3	20	9.2	Smoker
10	M	39	PEA	Cocaine	N	21	3	4	31	16	None
11	F	45	PEA	MVA	Y	12	5	2	28	6.7	None

Abbreviations: DMII, Diabetes mellitus type II; Epi, Epinephrine; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; HTN, Hypertension; MVA, Motor vehicle accident; OD, Overdose; PEA, Pulseless electrical activity; ROSC, Return of spontaneous circulation.

summary of the simultaneous neurophysiologic variables are presented in Table 2. A total of 78 measurements of ONSD and TCD were included in the final analysis over a median of 3 days per patient (range: 1–3 days). The percentage of measurements during episodes of intracranial hypertension (ICP ≥ 20 mm Hg) was 18% (14/78). The intra-rater reliability analysis of the averaged ONSD measurements presented an intra-class correlation of 0.60 (95% CI: 0.37–0.83), indicating moderate reliability.[24]

Agreement of ONSD, TCD, and JVP vs ICP

We found significant linear relationships between invasive ICP and all nICP estimators: ONSD, $nICP_{FVd}$, and JVP ($\chi^2 = 39.73$ [$p < 0.001$]; $\chi^2 = 6.23$ [$p < 0.05$]; $\chi^2 = 6.98$ [$p < 0.05$], respectively representing the full mixed-effects models for every estimator — Fig. 1). ONSD demonstrated the strongest correlation with invasive ICP (R = 0.53 [95% CI: 0.33–0.69] [$p < 0.0001$]), followed by JVP (R = 0.43 [95% CI: 0.21–0.61] [$p < 0.001$]). $nICP_{FVd}$ presented the weakest correlation (R = 0.30 [95% CI: 0.07–0.51] [p = 0.01]). The agreement of these methods obtained by Bland–Altman testing for repeated measures analysis revealed wide 95% CIs for prediction of the ICP absolute value: $nICP_{ONSD}$ yielded a bias of 0.29 ± 20.56 mm Hg; $nICP_{FVd}$, 3.00 ± 18.78 mm Hg; JVP, 5.66 ± 22.55 mm Hg (Fig. 2).

We found significant correlations between both JVP and $nICP_{FVd}$ with $ETCO_2$ (JVP: R = 0.26 [95% CI: 0.02–0.47] [p= 0.03]; $nICP_{FVd}$: R = 0.26 [95% CI: 0.02–0.47] [p = 0.03] but not ONSD (R = 0.22 [95% CI: −0.03–0.44] [p = 0.07]) or ICP (R = 0.003, p = 0.97). There were significant relationships between PEEP and ICP, ONSD, and $nICP_{FVd}$ (R = 0.41 [95% CI: 0.18–0.59] [$p < 0.001$], R = 0.44 [95% CI: 0.22–0.62] [$p < 0.001$], R = 0.32 [95% CI: 0.08–0.52] [$p < 0.01$]), respectively. We did not find a significant relationship between JVP and PEEP (R = 0.12 [95% CI: −0.12–0.35] [p = 0.33]).

Table 2 – Neurophysiological variables during measurements.

Parameter	Median (IQR)
ICP (mm Hg)	12 (8–16)
CPP (mm Hg)	73 (66–80)
MAP (mm Hg)	87 (79–94)
$ETCO_2$ (mm Hg)	4.2 (3.8–4.5)
ONSD (mm)	5.6 (5.5–6.3)
$nICP_{ONSD}$ (mm Hg)	14 (13–16)
FV_d (cm/s)	32 (30–36)
FV_m (cm/s)	46 (44–50)
$nICP_{FVd}$ (mm Hg)	10 (8–15)
JVP (mm Hg)	9 (6–12)

Abbreviations: Cerebral perfusion pressure, CPP; Intracranial pressure, ICP; Mean arterial blood pressure, MAP; ABP; Middle cerebral artery flow velocities (mean (FV_m), and diastolic (FV_d)); end-tidal CO_2 concentration, ETCO2; Jugular venous bulb pressure, JVP; Non-invasive ICP derived from ONSD, $nICP_{ONSD}$; TCD-based non-invasive ICP, $nICP_{FVd}$.

ROC analysis of ONSD, TCD, and JVP vs ICP

ONSD demonstrated the best discriminative ability in identifying intracranial hypertension (AUC = 0.96 [95% CI: 0.90–1.00]), followed by $nICP_{FVd}$ (AUC = 0.91 [95% CI: 0.83–1.00]). The DeLong's test for two correlated ROC curves did not reveal a statistically significant difference between ONSD and $nICP_{FVd}$ (p = 0.052). JVP demonstrated the weakest predictive ability (AUC = 0.75 [95% CI: 0.56–0.94]). The optimal ONSD, $nICP_{ONSD}$, $nICP_{FVd}$, and JVP cut-off values (followed by sensitivity and specificity thresholds) for prediction of intracranial hypertension were 5.95 mm (0.86 and 1.00), 15.66 mm Hg (0.91 and 1.00), 14.80 mm Hg (0.87 and 0.86), and 12.65 mm Hg (0.87 and 0.64), respectively (Fig. 3). The positive and negative predictive

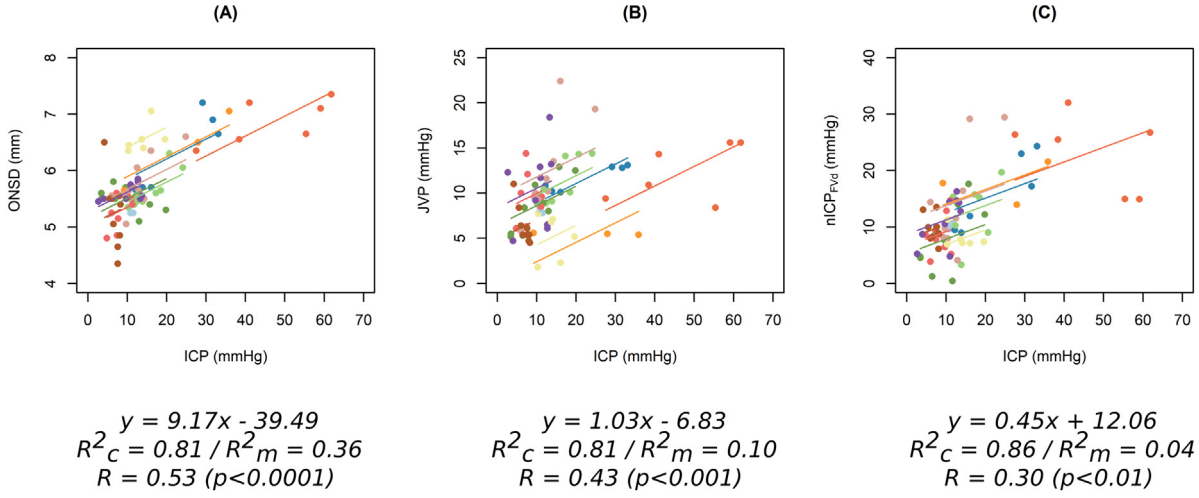

Fig. 1 – Scatterplots of the linear relationship between intracranial pressure (ICP) and different non-invasive ICP estimators. (A) optic nerve sheath diameter (ONSD, R = 0.53 [$p < 0.0001$]); (B) jugular bulb venous pressure (JVP, R = 0.43 [$p < 0.001$]); (C) estimator based on the diastolic cerebral blood flow velocity ($nICP_{FVd}$, R = 0.30 [$p < 0.01$]). Repeated measurements for each patient are plotted in the same colour pattern. Linear regression lines are correspondent to repeated measurements within patients. R^2_c represents the conditional coefficient of determination given by the mixed-effect linear models between ICP and non-invasive estimators, describing the proportion of variance explained by both the fixed and the random factors. R^2_m represents the marginal coefficient of determination given by the fixed-effect linear models between ICP and non-invasive estimators, describing the proportion of variance explained by the fixed factors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

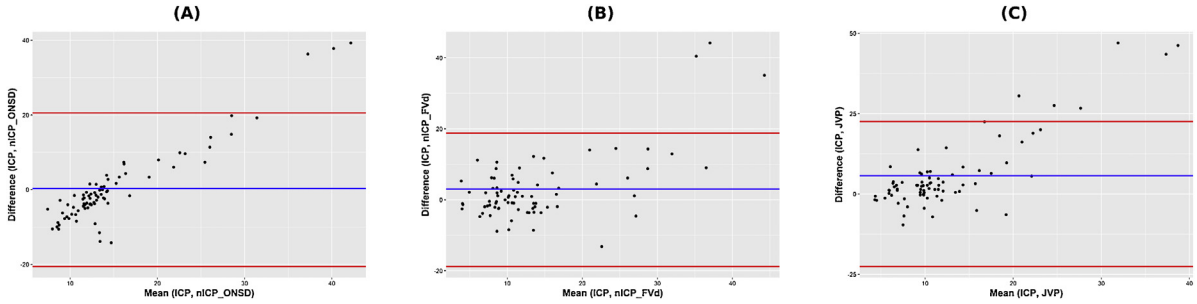

Fig. 2 – Bland-Altman plots showing the bias (solid middle blue line) and 95% CI for prediction of ICP (upper and lower red solid lines) for: (A) estimator based on the optic nerve diameter ($nICP_{ONSD}$, 0.29 ± 19.89 mm Hg); (B) estimator based on the diastolic cerebral blood flow velocity ($nICP_{FVd}$, 3.0 ± 18.38 mm Hg); (C) jugular bulb venous pressure (JVP, 5.66 ± 21.78 mm Hg). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

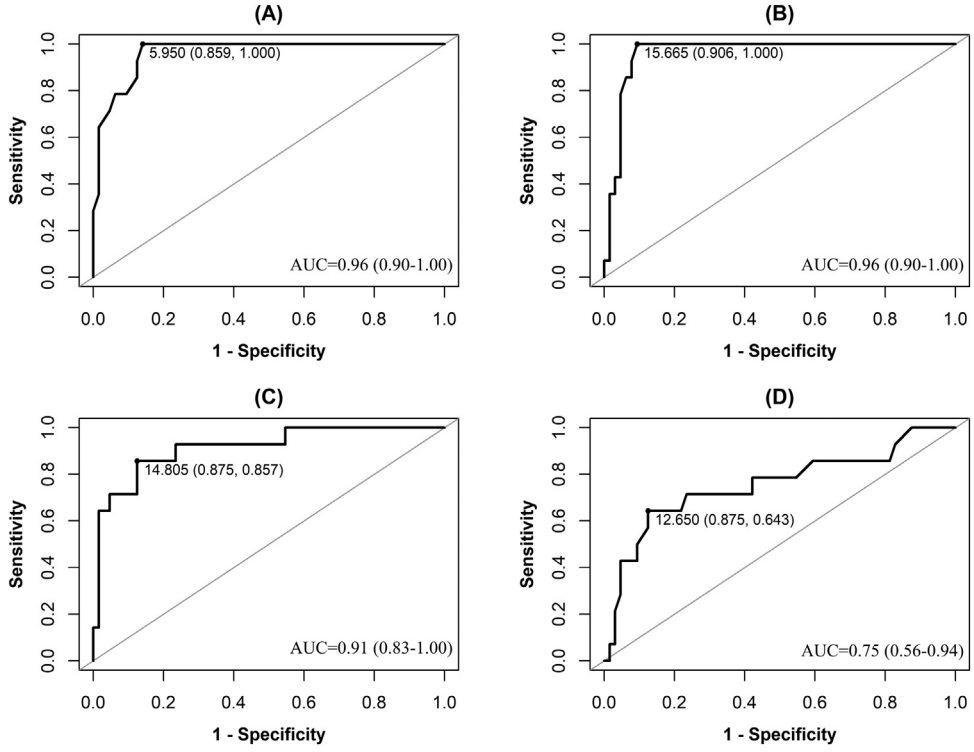

Fig. 3 – Receiver operating characteristic (ROC) analysis of the different non-invasive ICP predictors for a threshold of ICP ≥20 mm Hg. (A) optic nerve sheath diameter method (ONSD); (B) estimator based on the optic nerve diameter ($nICP_{ONSD}$); (C) estimator based on the diastolic cerebral blood flow velocity ($nICP_{FVd}$); (D) jugular bulb venous pressure (JVP). The values shown on the curves in (A), (B), (C), and (D) represent the best thresholds (cut-off values presenting the best sensitivity and specificity [in brackets]) for prediction of intracranial hypertension (ICP ≥ 20 mm Hg). AUC presented on individual plots is followed by the 95% confidence interval.

powers for $nICP_{ONSD}$, $nICP_{FVd}$, and JVP at the threshold of ICP ≥20 mm Hg were 0.88 & 0.75, 0.91 & 0.89, 0.82 & 0.00, respectively. A summary of these results is presented in Table 3.

Discussion

In this study, we examined the correlation, agreement, and performance characteristics comparing three non-invasive estimators of ICP with invasively monitored ICP in a cohort of post-cardiac arrest patients with HIBI. Our results indicate that ONSD and JVP have the strongest correlation with invasively-monitored ICP. ONSD and $nICP_{FVd}$ performed as the best non-invasive tests to detect intracranial hypertension.

In the context of cardiac arrest, the use of non-invasive ultrasound-based techniques has focussed on cerebral autoregulation,[29,30] patterns of cerebral blood flow,[31] prognostication,[32] and identifying the critical closing pressure and determination of optimal MAP.[33] Studies using TCD have demonstrated impairment of cerebral autoregulation in the acute phase of cardiac arrest, different patterns of cerebral blood flow depending on the degree of cerebrovascular resistance after ROSC, and increased critical closing pressure of the

Table 3 – Summary of the receiver operating characteristic curve analysis results.

	AUC	Cut-off ICP ≥ 20 mm Hg	PPV	NPV
ONSD	0.96 (0.90–1.00)	5.95 mm (0.86; 1.00)	–	–
$nICP_{ONSD}$	0.96 (0.90–1.00)	15.66 mm Hg (0.91; 1.00)	0.88	0.75
$nICP_{FVd}$	0.91 (0.83–1.00)	14.80 mm Hg (0.87; 0.86)	0.91	0.89
JVP	0.75 (0.56–0.94)	12.65 mm Hg (0.87; 0.64)	0.82	0

Abbreviations: jugular venous bulb pressure, JVP; non-invasive ICP derived from ONSD, $nICP_{ONSD}$; TCD-based non-invasive ICP, $nICP_{FVd}$.

cerebrovasculature.[34,35] Studies using ONSD ultrasonography after cardiac arrest have focussed on its importance relative to prognostication.[34–41] Finally, jugular venous oximetry after cardiac arrest has mainly been utilised for assessing the balance of cerebral oxygen delivery and utilisation in HIBI patients.[42] As of yet, there is paucity of data investigating the use of these non-invasive techniques in the assessment of nICP after cardiac arrest.

Ultrasound-based techniques have garnered significant attention for nICP assessment in recent years, principally in neurotrauma patients,[9,14,43–45] but also in non-neurotrauma related pathologies.[16,22,46] Specifically, ONSD ultrasonography has demonstrated robust diagnostic accuracy in detecting intracranial hypertension[44] with an optimal ONSD cut-off value to be 5.5–6.0 mm.[6,44,47–49] Our results agree with previous findings in traumatic brain injury and subarachnoid haemorrhage patients, demonstrating a cut-off value of 5.95 mm for detecting intracranial hypertension.

Theoretically, the accuracy of ONSD as a non-invasive surrogate for ICP may require a state of patent cerebrospinal fluid flow dynamics. In TBI, concomitant cerebrospinal fluid leakage and therapeutic interventions such as decompressive craniectomy or external CSF diversion can alter these relationships, potentially limiting the utility of ONSD to serve as a surrogate for ICP. In HIBI, these conditions rarely arise, thereby enhancing the widespread use of ONSD as a screening test for increased ICP post-cardiac arrest. These assumptions are based on the premise that if CSF circulates freely, it cancels possible pressure gradients in the brain, as according to Pascal's law, pressure is uniformly distributed in fluid. For example, following TBI, local or global brain swelling may acutely disturb CSF circulation, which has challenged the concept that the intracranial compartment is a space in which ICP is uniformly distributed.[50–52] Therefore, changes in ONSD, given its physiological mechanism, would directly depend on the patency of CSF circulation. In conditions where this is disturbed, we would consequently expect a less reliable assessment of ICP using ONSD, since possible pressure gradients in the brain would impair the free circulation of CSF from the intracranial space to the optic nerve sheath. In HIBI, the global nature of the onset of cerebral oedema may mitigate the aforementioned limitations of ONSD as a non-invasive estimator of ICP.

Recently, $nICP_{OSND}$ has been proposed as a formula-based estimation for ICP from the absolute OSND measurement value[14]; however, its applicability in scenarios other than TBI still requires further confirmation. In our assessment, this formula yielded a wide and unreliable 95% CI for prediction ($> \pm 19$ mm Hg). Further research is required to determine the utility of $nICP_{ONSD}$ in HIBI patients.

TCD-based $nICP_{FVd}$ has demonstrated variable consistency for nICP assessment. Previous reports have yielded conflicting results with demonstrating moderate[45,53] or non-significant agreements compared to invasive ICP.[54,55] However, multiple studies have demonstrated nICP's strong predictive ability for detecting intracranial hypertension (AUC ≥ 0.70).[45,53] Specifically, Rasulo et al. compared $nICP_{FVd}$ with invasive ICP monitoring and reported an AUC of 0.96 (95% CI 0.898–1.00), with sensitivity and specificity for the estimated optimal threshold (24.8 mm Hg) of 100% and 91.2%, respectively.[9] In our cohort, $nICP_{FVd}$ showed similar results except for an underestimated optimal threshold (14.80 mm Hg) as a cut-off value in detecting intracranial hypertension. Rasulo et al.[9] further demonstrated that the estimation bias and 95% CI for ICP prediction was 6.2 ± 11.8 mm Hg. In our study, we similarly established that $nICP_{FVd}$ yielded a substantial spread of data (3.00 ± 18.38 mm Hg). Importantly, the radial arterial lines yielding ongoing MAP monitoring were zeroed at the level of the right atrium instead of the foramen magnum, as is common practice in many dedicated neurocritical care units. This may have affected the accuracy of $nICP_{FVd}$ as a surrogate of invasively-monitored ICP in our study. Moreover, it has been previously observed that changes in arterial CO_2 tension (from mild hypocapnia to normocapnia) producing a decrease in the measured CPP (and increase in ICP) resulted in a slight increase in $nCPP_{FVd}$ (as a consequence of an increase in the FV_d/FV_m factor due to vasodilation).[23] In such conditions, $nICP_{FVd}$ would underestimate ICP, given that $nICP_{FVd} = ABP - nCPP_{FVd}$. In our study, $ETCO_2$ was moderately correlated with $nICP_{FVd}$, which could have negatively influenced the agreement.

Although moderately correlated with invasive ICP, JVP was the weakest nICP estimator. In comparison to previous studies using venous TCD at the straight sinus, which have shown showed strong correlations with ICP,[14,21] we found JVP to be a marginal estimator of ICP in HIBI (AUC = 0.75). One possible explanation includes a mal-positioned pressure transducer of the catheter. Upon confirmation of adequate placement of the catheter, the distal lumen was attached to a pressure transducer which was then zeroed at the level of the ipsilateral mastoid process with medical tape. Furthermore, ensuring correct positioning of the transducer with interventions of bedside medical care could not be guaranteed. This technique could also be influenced by jugular venous obstruction and increased intra-thoracic pressure. Future studies aimed at investigating the utility of JVP as a non-invasive method of ICP assessment must carefully ensure accurate transducer positioning. An additional plausible explanation for the weak correlation between invasive ICP and JVP accounts for the compensatory mechanism by which venous blood flow preserves intracranial pressure-volume relationships. As stated, as ICP increases, the transmitted pressure enhances blood flow from the bridging veins to the large venous sinuses, which likely increases JVP. In states of extreme limited intracranial compliance and increased ICP, the collapse of the bridging veins may limit any increase in blood volume and pressure seen at the jugular bulb, thereby limiting the relationship between ICP and JVP.

Regardless of the inaccuracy and intrinsic limitations in predicting the ICP value, ultrasound-based non-invasive ICP methods may have potential clinical utility as screening tools for the detection of elevated ICP in HIBI after cardiac arrest, as well as aid in the identification of cases suitable for invasive monitoring. Both $nICP_{OSND}$ and $nICP_{FVd}$ demonstrated strong positive and negative predictive powers (>0.8 and 0.7, respectively), indicating a utility to identify and exclude intracranial hypertension. In this context, a recent case report on the utilisation of ONSD and TCD for nICP assessment applied in a clinical protocol for intracranial hypertension has demonstrated the successful management of a patient with non-TBI related pathology presenting with raised ICP.[46] Similarly to many post-cardiac arrest conditions, the risk of coagulopathy precluded invasive monitoring for this patient. This

demonstrates one of the potential utilities of ultrasound-based non-invasive ICP assessment in the critical care setting, specially ONSD given its higher association with ICP across different clinical conditions. Moreover, studies have demonstrated the ability of ONSD to reflect relative real-time changes in ICP,[56–60] which indicates its feasibility for frequent assessments to evaluate the behaviour of ICP over time or guide protocols to manage intracranial hypertension.

Although this study is unique in evaluating the characteristics of non-invasive estimators of ICP versus invasive ICP, there are important limitations. Firstly, we had a small sample size with limited episodes of intracranial hypertension (ICP $\geq$20 mm Hg) during the study period. Statistically, this may mitigate the agreement assessment between invasive ICP and the non-invasive methods. Nevertheless, well-controlled ICP was a result of the management protocol in place during the study. Further studies with larger sample sizes are necessary to validate the use of various methods of non-invasive ICP estimation in HIBI, specially regarding estimation formulae derived from different clinical conditions. This is the case for $nICP_{ONSD}$ and $nICP_{FVd}$, derived from traumatic and acute brain injuries conditions, and it is unclear why these estimators demonstrated unreliable prediction characteristics. The single centre nature of our study also precludes generalisability and future studies should focus on assessing the agreement across multiple sites. Secondly, we had only one operator conducting ONSD and TCD ultrasonography, thereby limiting the generalisability of our results. Future studies should evaluate the agreement across multiple operators to ensure within-observer agreement of TCD and ONSD measurements. Finally, the patients in our study suffered cardiac arrest from numerous causes (haemorrhage, asphyxia from hanging, hypoxia, ventricular fibrillation, etc.). It is possible that the underlying cause of cardiac arrest, particularly from an obstructive aetiology, may lead to cerebral venous congestion and may yield variable relationships between invasively monitored ICP and nICP estimators.

Conclusions

In our prospective observational study, ONSD and $nICP_{FVd}$ demonstrated the best agreement to assess ICP non-invasively in HIBI patients after cardiac arrest. Our results suggest that ONSD and $nICP_{FVd}$ may help detect and rule out intracranial hypertension.

Conflict of interest

MC and PS have financial interest in licensing ICM+ software (Cambridge Enterprise Ltd). CR is a junior editor for Intensive Care Medicine journal. The remaining authors have disclosed that they have no conflicts of interest.

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