Full title: Prospective study on non-invasive assessment of ICP in head injured patients: comparison of four methods

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Abstract

Elevation of intracranial pressure (ICP) may occur in many diseases and therefore the ability to measure it non-invasively would be useful. Flow velocity signals from Transcranial Doppler (TCD) have been used to estimate ICP, however the relative accuracy of these methods is unclear. This study aimed to compare 4 previously described TCD-based methods with directly measured ICP in a prospective cohort of head injured patients. Non-invasive ICP (nICP) was obtained using the following methods: I) a mathematical "black-box" model based on interaction between TCD and ABP (*nICP_BB*); II) based on diastolic FV (*nICP_FVd*); III) based on critical closing pressure (*nICP_CrCP*) and IV) based on TCD-derived pulsatility index (*nICP_PI*).

In time domain, for recordings including spontaneous changes in ICP greater than 7 mmHg, *nICP_PI* showed the best correlation with measured ICP (R=0.61). Considering every TCD recording as an independent event, *nICP_BB* generally showed to be the best estimator of measured ICP (R=0.39, $p<0.05$; 95% CI=9.94 mmHg; AUC= 0.66, $p<0.05$). For *nICP_FVd*, although it presented similar correlation coefficient to n*ICP_BB* and marginally better AUC (0.70, $p<0.05$), it demonstrated a greater 95% CI for prediction of ICP (14.62 mmHg). *nICP_CrCP* presented a moderate correlation coefficient (R=0.35, $p<0.05$) and similar 95% CI to *nICP_BB* (9.19 mmHg), but failed to distinguish between normal and raised ICP (AUC=0.64, $p>0.05$). *nICP_PI* was not related to measured ICP using any of the above

statistical indicators. We also introduced a new estimator (*nICP_Av*) based on the average of 3 methods (*nICP_BB, nICP_FVd* and *nICP_CrCP*), which overall presented improved statistical indicators (R=0.47, p<0.05; 95% CI=9.17 mmHg; AUC= 0.73, p<0.05).

nICP_PI appeared to reflect changes in ICP in time most accurately. *nICP_BB* was the best estimator for ICP 'as a number'. *nICP_Av* demonstrated to improve the accuracy of measured ICP estimation.

Keywords

Non-invasive ICP monitoring; Transcranial Doppler; Traumatic Brain Injury.

Introduction

Intracranial Pressure (ICP) has at least four components, driven by different physiological mechanisms[1]. The first component is associated with arterial blood inflow and volume of arterial blood. Most common phenomenon associated with this component is plateau wave of ICP. Second component of ICP is associated with venous blood outflow. Every obstruction to the outflow of blood leads to elevation of ICP (like venous compression due to wrong head position, but also venous thrombosis). Third component is related to problems with cerebrospinal fluid (CSF) circulation, like commonly seen in 'acute hydrocephalus' after brain injury or subarachnoid haemorrhage. In neurocritical care this component is commonly eradicated by extraventricular drainage. Finally, the fourth component is related to increase in brain volume (oedema) or volume of contusion (like haematoma). Osmotherapy or surgical decompression is commonly used to eradicate this component. In clinical practice, it is important not only to monitor absolute value of ICP, but also to recognize which component is responsible for observed intracranial hypertension, as clearly different measures are appropriate for controlling different components.

Direct intracranial pressure measurement requires invasive insertion of a pressure transducer within the cerebrospinal fluid compartment or the brain tissue. However, because of the risk of infection or bleeding, direct measurement of ICP is not often considered. To provide alternatives for patients who might benefit from ICP monitoring,

some attempts have been made to develop methods to assess it non-invasively and continuously.

Several methods for non-invasive assessment of ICP (nICP) have been described so far: Transcranial Doppler Ultrasonography (TCD) to measure cerebral blood flow velocity indices[2]; skull vibrations[3]; brain tissue resonance[4], or transcranial time of flight[5]; venous ophthalmodynamometry[6]; optic nerve sheath diameter assessment (ONSD)[7]; sensing tympanic membrane displacement (TMD)[8,9]; otoacoustic emissions[10]; magnetic resonance imaging to estimate intracranial compliance[11]; ultrasound guided eyeball compression[12] and recordings of visual evoked potentials[13]. These methods are better suited for one-point assessment of instant value of ICP rather than continuous monitoring. Reported absolute accuracies (95% confidence interval for prediction of ICP) are described for transcranial time of flight as 20 mmHg and 9 mmHg; 3-5 mmHg for ophthalmodynamometry; 5-10 mmHg for ONSD, 15-20 mmHg for TMD and otoacoustic emissions[14] and 9-16 mmHg for methods based on TCD waveforms.

TCD waveform analysis, due to its sensitivity to detect changes in cerebral blood flow, has been investigated as a non-invasive ICP estimator[15–29]. In these methods, the insonated compliant middle cerebral artery (MCA) is interpreted as a 'biological' pressure transducer, whose walls can be deflected by transmural pressure (equivalent to cerebral perfusion pressure (CPP)), modulating accordingly the pulsatile waveform of cerebral blood flow velocity (FV). Transmission of this 'transducer', its linearity, stability in time and calibration coefficients are unknown - and these factors mainly contribute to limited accuracy of TCD-based methods. The absolute error may be compensated for by the ability to monitor

dynamics of changes in measured ICP and also because monitoring can easily be repeated bedside without any risk for the patient.

Existing non-invasive ICP methods based on TCD waveform analysis present with different confidence intervals for prediction of ICP in traumatic brain injury (TBI) patients. Schmidt et al., applying a mathematical "black-box" model (i.e., based not on physiological structure, but rather on a set of formal mathematical expressions) to estimate ICP from cerebral blood flow velocity (FV) and arterial blood pressure (ABP), found a maximum 95% confidence interval (CI) for ICP prediction of 12.8 mmHg[15]; Heldt et al., also using a model based on FV and ABP found 15 mmHg[27] ; and Bellner et al., investigating the relationship between ICP and TCD-derived pulsatility index (PI) reported a 95% CI for prediction of 4.2 mmHg[17]. Such an optimistic accuracy was not confirmed by other authors: with paediatric patients the absolute value of TCD-derived pulsatility index (PI) was found to be an unreliable non-invasive estimator for ICP in TBI[18]. Correlation with ICP in this case was 0.36 ($p=0.04$), much weaker than the correlation found by Bellner et al. in adults ($R=0.938$, $p<0.0001$)[17].

Other TCD approaches for non-invasive ICP monitoring were originally intended for estimating the non-invasive cerebral perfusion pressure (nCPP). However, non-invasive ICP can be calculated based on the assumption that **nICP = ABP - nCPP**[30,31].

Because of the variability in the reported degree of agreement between TCD-based nICP methods and measured ICP, this study aimed to systematically compare 4 TCD-based nICP methods with measured ICP in a single prospective cohort of TBI patients.

Materials and methods

Patient population

This study included prospectively collected data from 40 traumatic brain injury patients (32 males (80%), 8 females (20%), population mean age 35±15 years), hospitalized in the Neurocritical Care Unit of Addenbrooke's Hospital between 2013 and 2015. Patients were sedated, ventilated, and managed in the Neurocritical Care Unit with a therapeutic protocol aiming for an ICP <25 mmHg and CPP around 60‑70 mmHg. The median pre-intubation Glasgow Coma Scale (GCS) score of the patients was 6 (range 3–14). The data included daily recordings of ABP, ICP, and TCD, in a total of 66 recordings. Informed consent was obtained from all patients (or their next of kin) for the use of collected data for research purposes. The study was approved by the research ethics committee (29 REC 97/291).

Data collection and calculations

For ABP recordings, a pressure monitoring kit (Baxter Healthcare Health Care Corp. Cardio Vascular Group, Irvine, CA, USA) at the radial artery was used, zeroed at the level of the

heart. ICP monitoring was performed via an intraparenchymal probe (Codman ICP MicroSensor, Codman & Shurtleff, Raynham, MA, USA). Cerebral blood FV was obtained from the MCA, bilaterally when possible, with a 2-MHz probe and monitored with the Doppler Box (DWL Compumedics Ltd, Germany). The TCD recordings were performed for periods ranging from 10 minutes up to 1 hour, starting from the day of initiation of invasive ICP monitoring. An analog–digital converter was used to digitize the raw data signals at a sampling frequency of 50 Hz, which were then recorded using ICM+ software (Cambridge Enterprise, http://www.neurosurg.cam.ac.uk/icmplus/). All calculations, including mean values of ABP, ICP and FV were performed over a moving average window of 10 seconds. For FV, the right MCA was chosen because the intraparenchymal ICP probe was inserted on the right side, but in recordings which right FV was of poor quality and left side was better, left side was taken instead.

Non-Invasive ICP methods

The four methods used for nICP estimation in this study were:

1) Schmidt et al. "black-box" (BB) model[20] (***nICP_BB***): in this model, the intracranial compartment was considered a black-box system. This mathematical model is based on results from systems analysis, which provides a method to describe systems, in particular physiological systems, with input and output signals. The outgoing signals are considered the system's responses to its stimulation by incoming signals. In this case, the intracranial compartment was indirectly described by a transfer function approach[32,33] which connected the assumed input signal ABP with the output signal

ICP (nICP). The transformation rules between ABP and ICP were controlled and continuously adjusted by selected hemodynamic parameters (TCD-characteristics), characterising patterns of FV as well as the ABP-FV relationship. The output data provides full waveform of nICP (in mmHg). Constant relationship between FV-ABP and ABP-nICP transformations was derived from analysis of database including 140 TBI patients. Non-invasive ICP estimation using this method was performed using a plugin developed for ICM+ software. An illustrative representation of this model is presented in Figure 1.

2) Czosnyka et al.[30] (***nICP_FVd***): Transcranial Doppler ultrasonography offers non-quantitative measurements of cerebral blood flow (CBF). Global changes in CBF can be monitored continuously and non-invasively using blood flow velocity[34]. Over this concept, some studies have demonstrated that specific patterns of TCD waveform reflect inadequate cerebral perfusion caused by a decrease in CPP[30,35]. In such cases, there is a drop in diastolic flow velocity, whereas the systolic component remains relatively unchanged (as illustrated in Figure 2). These characteristics observed in the CBF velocity waveform pattern can be used as indicators of perfusion derangements and have been applied as variables for nCPP estimation. For this method, based on waveform analysis of blood flow velocity measured in the middle cerebral artery (MCA), the diastolic flow velocity was used for the estimation of nCPP. nICP, on the other hand, was calculated as the difference between ABP and nCPP (nICP = ABP - nCPP). The equation for nCPP estimation was:

$$nCPP = ABP \times \frac{FVd}{FVm} + 14\ mmHg \quad \textbf{(Equation 1)}$$

FVd and *FVm* (cm/s) represent diastolic and mean flow velocity, respectively.

3) Varsos et al.[31] (***nICP_CrCP***): similarly, this method calculates nICP based on nCPP, in this case specifically using the concept of Critical Closing Pressure (CrCP). According to Burton's model, CrCP is equal to the sum of ICP and vascular wall tension (WT)[36,37]: CrCP = ICP + WT. By definition, critical closing pressure denotes a threshold of ABP, below which the brain microvascular blood pressure is inadequate to prevent the collapse and cessation of blood flow[36]. Given the association of CrCP with the vasomotor tone of small blood vessels (i.e., wall tension), this concept may be able to provide information regarding the state of cerebral haemodynamics in several neurological conditions[36,38–41], and for this method was applied as a variable for nCPP estimation. Figure 3 illustrates the concept of critical closing pressure, showing its interaction with ICP and WT in a situation of intracranial hypertension. The equation for nCPP estimation is:

$$nCPP = ABP \times \left[0.734 - \frac{0.266}{\sqrt{(CVR \times Ca \times HR \times 2\pi)^2 + 1}}\right] - 7.026 \quad \textbf{(Equation 2)}$$

CVR (mmHg/(cm/sec) represents cerebral vascular resistance, *Ca* (cm/mmHg) denotes compliance of the cerebral arterial bed and *HR* expresses heart rate (beats/sec), with ABP and FV as the required measurements. Finally, nICP can be obtained as the difference

between ABP and nCPP (nICP = ABP - nCPP). Constant coefficients (0.734, 0.266, 7.026 mmHg) are derived from analysis of database of 232 retrospective cases[31].

4) ***nICP_PI***: Pulsatility index describes quantitatively and qualitatively changes in the morphology of the TCD waveform resulting from CVR changes. It is a relationship between the difference of Fvs (systolic flow velocity) and FVd divided by FVm (Figure 4 and Equation 4). PI-based methods rely on the observation that during rise in ICP, pulsatility index increases. However, there are several situations in which PI may increase independently of an increase in ICP. This may occur, for example, during lowering in CPP (which may involve either a rise in ICP or a decrease in ABP), and also during hypocapnia or increase in pulsatility of ABP waveform. nICP estimation based on TCD-derived PI was based on the linear regression among known values of ICP and PI from a population cohort of 292 TBI patients. The regression equation was based on data analysed by Budohoski et al.[42] and given by:

$$nICP = 4.47 \times PI + 12.68\ mmHg \quad \textbf{(Equation 3)}$$

$$PI = \frac{FVs - FVd}{FVm} \quad \textbf{(Equation 4)}$$

Statistical analysis

Statistical analysis of the data was conducted with OriginPro statistical software (version 8, OriginLab Corporation). The analysis included correlations between non-invasive ICP estimators and measured ICP in terms of mean values, with R representing the Pearson

correlation coefficient, with the level of significance set at 0.05. Results were presented as mean±SD. The Bland-Altman method was used to determine the agreement between invasive ICP and the different nICP methods, with their respective 95% CI for prediction and bias. The confidence interval represents the method's estimation performance and contemplates the range of values around the bias (absolute difference between mean values of nICP and ICP) in which data can be found with a significance level of 0.05. The area under the curve (AUC) of the receiver operating characteristic curve (ROC) was applied to determine the ability of the non-invasive methods to predict raised ICP (using a threshold of 17 mmHg). This threshold was chosen due to its proximity to values which would commonly prompt treatment in the clinical setting (normally above 20-25 mmHg[1]). The predicting ability is considered reasonable when the AUC is higher than 0.7 and strong when the AUC exceeds 0.8[43]. For recordings which mean ICP changes were greater than 7 mmHg, averaged correlation between ICP and nICP methods was calculated in time domain, as well as correlation between ΔICP and ΔnICP. In this case, "Δ" is the difference between maximum and minimum mean value in each recording during ICP changes.

Results

Table 1 presents basic demographic characterization of the prospective cohort.

Out of the 66 recordings, 8 presented a considerable spontaneous variation of ICP (ΔICP) ≥7 mmHg in time domain. An example of nICP recording with the four investigated methods is presented in Figure 5. Averaged correlation coefficients between real trend of ICP and nICP were summarized in Table 2. In the same table, correlations between ΔICP and ΔnICP were compared.

Statistical comparisons among non-invasive methods adopted in this work are presented in Table 3. It takes into consideration all 66 TCD recordings as separate events and includes Pearson correlations, Bland-Altman analysis (95% CI for predictions and bias) and area under the curves obtained from ROC analysis for an ICP threshold of 17 mmHg. As observed in Table 1, the cohort presented low range of mean ICP values, which made necessary the use of a threshold close to, but bellow critical values for intracranial hypertension treatment, in order to obtain a consistent ROC analysis.

nICP_BB, *nICP_FVd* and *nICP_CrCP* demonstrated moderate but significant correlations ($p<0.05$) with measured ICP; while *nICP_PI* had poor correlation with measured ICP ($p>0.05$)

(figure 6). In regards to Bland-Altman analysis, *nICP_BB* and *nICP_PI* showed biases close to zero, and along with *nICP_CrCP,* presented similar 95% CI (around 10 mmHg). FVd-based method showed greater bias and 95% CI (figure 7). In Figure 7, each plot was complemented by the corresponding error histogram, on which the plot of a Gaussian (normal) distribution of the same bias and 95% CI is superimposed for visual comparison. The Gaussian distribution and 95% CI represent the interval in which data are not randomly distributed.

The best AUC value was presented by *nICP_FVd* (AUC=0.70). In addition, table 3 also presents results from the arithmetic average of only the best non-invasive ICP estimators (*nICP_Av*), i.e., n*ICP_BB*, *nICP_FVd* and *nICP_CrCP,* which generally showed slightly improved statistics, with AUC=0.73 (figure 8).

Discussion

In this comparison of TCD-based nICP estimators, we found a significant, albeit not very strong relationship between nICP and measured ICP. Of the 4 studied estimators, *nICP_BB* appeared to have the strongest relationship with measured ICP understood 'as a number'- i.e. averaged value of nICP assessed during single TCD session. For replicating trace of measured ICP in time in individual patient, *nICP_PI* proved to provide best accuracy. Potential explanations and comparison with previous studies are discussed below.

Monitoring of ICP dynamics can be done most efficiently with *nICP_PI* method, which showed the strongest mean correlation coefficient across 8 patients (R=0.61), followed by *nICP_BB* (R=0.48). However none of the methods presented satisfactory correlation of ΔnICP with ΔICP, *nICP_BB* was the best considering variations of ICP ≥7 mmHg (R=0.68, p=0.06). Considering "Δ" as the difference between maximum and minimum values, it represents the ability of the nICP methods to detect differences in the magnitude of a change in measured ICP recorded in time.

Certain events, as critically reduced CPP in the setting of intracranial hypertension in TBI, as well as episodic rises in ICP caused by hyperaemia, can be identified by marked reductions

in TCD flow velocity[44]. As ICP increases and CPP correspondingly decreases, a characteristic highly pulsatile flow velocity pattern is observed. Continuing increases in ICP result first in a reduction and then loss of diastolic flow, progressing to an isolated systolic spike of flow in the TCD waveform, and eventually to an oscillating flow pattern which signifies the onset of intracranial circulatory arrest[45,46]. Even though accuracy for mean ICP changes presented in this work did not demonstrate a strong correlation with measured ICP, cerebral circulation dynamics can be observed with the TCD-based methods as nICP changes in time domain, and tracked in real-time in the clinical setting. This form of monitoring is one of the advantages of Transcranial Doppler Ultrasonography and may become particularly useful as a primary assessment tool in centres where ICP measurements are not routinely applied, or in patients in whom ICP monitoring is unavailable or may not be clearly indicated (mild closed head injury, for example).

Treating each monitoring session as an independent event and calculating averaged nICP, the comparison of four methods indicates *nICP_BB* to be the best statistically-wise, as it presented the most consistent indicators for prediction of ICP. In regards to bias, for instance, a non-significant difference between non-invasive and invasive methods is desirable, which means that both methods are not different in rendering mean ICP values. For *nICP_BB*, bias was not significantly different from zero and 95% CI for prediction was even smaller as previously reported by Schmidt et al. (12.8 mmHg)[15] or Heldt et al. (15 mmHg), in their model also based on TCD and ABP[27]. In addition, AUCs for *nICP_BB* were close to reasonable values (0.7) and asymptotic probabilities for ROC analysis were also significant, denoting the method's ability to detect differences between high and normal ICP values.

In contrast, *nICP_FVd* and *nICP_CrCP* both presented biases significantly different from zero. However, for *nICP_FVd*, moderate correlation coefficients and reasonable AUC were observed. n*ICP_CrCP*, conversely, did not present significant asymptotic probabilities for AUC according to ROC analysis. Considering 95% CI, *nICP_FVd* had the greatest prediction error and *nICP_CrCP* the smallest.

nICP_PI, despite the best ability to detect changes in ICP across time, did not show any consistent statistical parameter for estimating ICP as to correlation with mean values, CI and AUC, and thus can be considered the weakest estimator. This assumption contradicts results published by Bellner et al. in their previous study for the assessment of the relationship between PI and ICP, that PI would strongly correlate with ICP[17]. On the other hand, it is in agreement with results from Figaji et al., whose work shows that PI is not a reliable non-invasive estimator of ICP in children with severe TBI[18].

Averaging estimation methods is a useful computational technique, capable of approximating the different features of each estimator considered. In our case, in an attempt to find a more reliable method using this approach, we averaged those which presented the best estimation for ICP 'as a number', i.e., *nICP_BB, nICP_FVd* and *nICP_CrCP*. The inclusion of *nICP_PI* in the average did not yield any improvement in estimation. Named *nICP_Av*, it proved to approximate the most consistent characteristics of its three components, in comparison to single methods. In comparison to *nICP_BB*, for instance, which was the best estimator out of the three considered, *nICP_Av* only presented inferior values as to bias, which was significantly different from zero. Thus, this new estimator might represent a more reliable way to predict ICP non-invasively, possibly because it takes advantage of a broader set of inputs (ABP, FV, FVd and CrCP).

Regarding inputs, the different nICP accuracies observed may be explained by what each method is fundamentally based on. *nICP_BB*, for instance, reflects ABP waveform being constantly modified by TCD characteristics, and then is mostly susceptible to changes of vascular components (such as cerebrovascular resistance, arterial compliance) and consequently cerebral blood flow. *nICP_FVd*, which is derived from a non-invasive estimation of CPP (Equation 1), is mostly modulated by the factor FVd/FVm, which is evident during hyperventilation, when FVd/FVm decreases due to vasodilation[30]. It also replicates changes in ICP provoked by rapid changes in ABP, as mean ABP is a multiplier in the formula. *nICP_CrCP*, according to Equation 2, is also modulated by changes in CVR and Ca. For *nICP_PI*, it is known that decreasing CPP produces (like during plateau waves of ICP) specific changes in FV with stable systolic and falling diastolic values[45,47]. These changes may be observed in the pulsatility index, which has been reported to be inversely proportional to CPP[45,47]. Although all methods essentially reflect changes in cerebrovascular parameters, which lead to variations of cerebral blood flow velocity acquired via TCD ultrasonography, each one is modulated by different factors.

Provided that the confidence intervals for prediction of ICP for all nICP methods were determined, a question that can be raised out of this is regarding the degree of accuracy expected or required for a non-invasive monitor to be considered a clinically useful tool in estimating ICP. According to the Association for Advancement of Medical Instrumentation (AAMI), all sorts of ICP monitoring devices should have continuous output in the 0-100 mmHg range with an accuracy of ±2 mmHg in the 0-20 mmHg range, and maximum prediction error of 10% for ICP above 20 mmHg, the specifications supported by the Brain Trauma Foundation guidelines[14,48]. In the case of this study, the estimation performance

represented by the 95% CI for prediction of ICP ranged around 10 mmHg, with all methods above these specified limits.

Another aspect that should be taken into consideration when assessing new non-invasive modalities is to examine the accuracy of current invasive methods and their mutual agreement. In the clinical practice, ventricular and parenchymal pressure methods remain as the primary approaches to ICP monitoring. However, epidural probes are also often used. Simultaneous measurement of ICP by a parenchymal probe and ventriculostomy showed a bias of −1.2 and a 95% CI of 6.8 mmHg (SDE of 3.4 mmHg)[49]. In another study, simultaneous measurements of ICP using a parenchymal probe and an epidural probe presented a bias of 4.3 mmHg, with 95% CI of 17 mmHg (SDE of 8.5 mmHg)[50].

Although it would be ideal that TCD-based nICP methods presented similar measures of accuracy to the invasive ones, it is important to highlight that these techniques are subjected to certain interferences (signal attenuation and movement artefacts, for instance) which certainly influence their degree of accuracy. Nevertheless, considering the performance characteristics reported for invasive methods, the nICP methods applied in this study, showing biases ranging from -0.5 to 7.34 mmHg and 95% CI from 9.19 to 14.68 mmHg (Table 3), in general performed better than the invasive epidural method still used in the clinical management of patients.

As mentioned previously, TCD-based nICP methods, despite their intrinsic limitations to predict absolute mean ICP values, may have a potential clinical utility as a primary assessment tool in diagnosing intracranial hypertension in TBI and other conditions especially in the early stages of management, due to its ability to detect cerebrovascular derangements originated from ICP changes.

In this context, out of the four methods compared, *nICP_BB* proved to be the best estimator for ICP in this cohort of TBI patients. Methods based on diastolic FV and CrCP showed intermediate accuracy. Pulsatility index method presented good correlation in time domain during variations of ICP. We suggested a new method based on averaging *nICP_BB*, *nICP_FVd* and *nICP_CrCP*, which overall demonstrated stronger statistical indicators for ICP prediction.

Limitations

During the process of data analysis, we found that poor quality of TCD recordings has profound effects on the accuracy of the methods assessed. Aspects such as depleted signal resolution and noise (example in figure 9) may act as limitations to the study and must be prevented for meaningful nICP estimation. Good quality of TCD and ABP recordings are essential requirements for ICP estimation using TCD-based methods, and then must be met accordingly in future investigations. TCD quality depends, among other parameters, on the experience of the operator for accurately insonating the targeted artery (MCA). Additionally, unlike ABP measurements, TCD monitoring was not continuous but instead it consisted of short recordings for every patient, therefore preventing a continuous nICP assessment. Shortcomings for continuous monitoring were mainly related to the routine of the neurointensive care environment, where treatment of patients requires changes of body position and transfers for imaging procedures, which hindered the possibility of continuous or longer TCD recordings with existing probe holders.

The use of radial artery ABP zeroed at the level of the heart instead of actual blood pressure in the brain could also be considered a limitation to the study. This condition might non-accurately approximate peripheral ABP to intracranial ABP, which can specifically change the accuracy of methods that rely on ABP waveform analysis, such as *nICP_BB*. Moreover, heart-level calibration leads to an overestimation of CPP[51], yielding a difference that might affect the calculation of nCPP (i.e. for *nICP_CrCP* and *nICP_FVd* methods) that derives information from ABP measurements[31].

Changes in cerebrovascular resistance, such as that produced by variations in $PaCO_2$, may disturb CPP estimation (nCPP), and could also act as a limitation or confounding factor to the study. As observed by Czosnyka et al.[30], although an increase in arterial CO_2 tension (from mild hypocapnia to normocapnia) decreased the measured CPP (due to associated decrease in ABP), it resulted in a slight increase in nCPP (mainly because of an increase in the FVd/FVm factor due to vasodilation). In such conditions, for example, *nICP_FVd* method would render an underestimation of nICP.

Low range of ICP values found in the patient's cohort as observed in Table 1 may also consist of a limitation, as it prevented a more extensive analysis on how nICP methods behave in conditions of elevated intracranial pressure. This characteristic may be attributed to the therapeutic protocol patients were submitted.

Finally, the fifth possible method based on TCD, as described by Heldt et al.[19,27], was not compared, as a replication of very complex algorithm on a basis of description given in literature was not possible, mainly due to phase shift between ABP and FV time series (MB – personal communication).

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Author Disclosure Statement

ICM+ software is licensed by the University of Cambridge, Cambridge Enterprise Ltd. MC and PS have a financial interest in a part of its licensing fee. Non-invasive ICP plugin is protected by patent DE 19600983. BS and MC have a financial interest in part of its licensing fee. No competing financial interests exist for the corresponding author and the rest of the co-authors.

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