A Noninvasive Technique for Cerebral Compliance Monitoring in Neurocritical Care

Sérgio Brasil (sbrasil@alumni.usp.br)
Universidade de Sao Paulo https://orcid.org/0000-0003-2397-9947
Davi Jorge Fontoura Solla
Ricardo de Carvalho Nogueira
Manoel Jacobsen Teixeira
Luiz Marcelo Sá Malbouisson
Wellingson Silva Paiva

Research Article

Keywords: Intracranial compliance, intracranial pressure, intracranial hypertension, acute brain injury

Posted Date: July 12th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-325217/v1

Abstract

Background In neurocritical care, studies have shown that adequate intracranial pressure (ICP) control reduces mortality and increases functionality. Unfortunately, the monitoring ICP through an intracranial catheter as the gold standard currently adopted, is invasive technique and often not available for all patients in need of ICP monitoring. Recently, a device has been developed (B4C), able to obtain recordings of cranial dilatation at each heartbeat and disclose ICP pulses waveforms, as the intracranial compliance (IC) status. However, despite promising results reported in animal and small sample studies, the correlation between this new technique with invasive ICP measurement in particular clinical situations was lacking. The present study aimed to evaluate the use of this noninvasive IC monitoring system in a set of neurocritical care patients, correlating its data with invasive ICP monitoring. Methods: Neurocritical patients under ICP monitoring were consecutively included for the evaluation with B4C sensor concomitantly. ICP values, ICP waveforms, B4C IC waveforms, were correlated. Results: We present results of 22 patients. Traumatic brain injury, subarachnoid hemorrhage, and stroke were among the main causes for ICP monitoring. Pearson's correlation for B4C parameters such as P2/P1 ratio and time-to-peak disclosed moderate correlation with mean ICP values (0.63 and 0.66 respectively). No reports of adverse events were obtained. Conclusion The novel intracranial compliance monitoring technique demonstrated to be safe and correlated with invasive ICP. This discovery may widen the comprehension, coverage and applications of intracranial compliance in critical care.

Introduction

It is well-established that continuous intracranial pressure (ICP) monitoring is crucial for surveillance and intracranial hypertension (ICH) management in the intensive care setting [1,20]. Conventional ICP monitoring methods include trepanation and insertion of a catheter through the skull for measurement. This catheter produces quantitative measure in mmHg [8,32,21,25], and qualitative recordings, presenting waves that are attributed to intracranial compliance (IC) [19]. IC expresses the relationship between intracranial components (brain, cerebrospinal fluid and blood) and may indicate loss of hemostasis between them when increases in ICP are substantial [30].

However, this procedure exposes the patient to risks of intracranial hematoma precipitation, worsening of cerebral edema, parenchymal lesions, intracerebral hemorrhage and intracranial infection, being the last, the most common complication, reported in up to 8% of monitored patients with intraparenchymal and subarachnoid sensors and 26.6% in intraventricular monitoring [4,6,28]. Moreover, ICP monitoring in many places around the world is not available for all patients in need.

Considering all the mentioned disadvantages, the need to monitor ICP with a less invasive method is extremely important [20,7,5,16]. To date, no other method has been shown to be accurate enough to replace invasive methods for measuring ICP [18]. However, a mechanical sensor (B4C) that detects cranial elastance has been recently developed, which is placed outside the scalp. The *in vivo* analyzes

obtained a good correlation when compared with the invasively obtained ICP values, indicating that this method obtains a noninvasive record of IC [32,21,9,8,3,25].

However, application of this method in clinical field is still ongoing. Validation of such technique would be of value for screening patients prior to suffer the consequences of persistent ICH. Therefore, the primary endpoint was the comparison of ICP curve morphology obtained with ICP invasive monitoring and B4C sensor, with focus on the characteristics of the ICP pulse waveform in a set of neurocritical patients.

Methods

A single center, observational and prospective study in 6 intensive care units (ICUs) of Hospital das Clínicas, São Paulo University, Brazil, have received ethics committee approval, and is ongoing since 2017. Consecutive patients are being recruited, although due to COVID-19 pandemic, patient recruitment has been temporarily interrupted. This clinical trial (CT) study protocol was approved by the local Ethics Committee, in April/2017 and registered under number NCT03144219 (available at clinicaltrials.gov). All methods were performed in accordance with the relevant guidelines and regulations, informed consent was obtained from all legally authorized representatives (LAR)/next of kin instead of the patients because of illness severity.

Study Design

All patients included in the study have suffered acute brain injury with need of ventilatory support and submitted to invasive ICP monitoring according to the neurosurgical guidelines adopted by our institution. Data collection consisted in a single 10-minutes session for patient, with simultaneous record of invasive arterial blood pressure, ICP, B4C, ECG and oxygen saturation in spontaneous variations. These short-length sessions were performed to avoid the occurrence of substantial changes in these parameters during recording. As these variables were continuously recorded during the procedure, a minimum of 600 pulses to be analyzed were obtained from each patient. No intervention was performed during recording. In case of ICH prior or during data collection, the Brain Trauma Foundation (BTF) guidelines for its management were applied. The study protocol was according to the Standards for Reporting of Diagnostic Accuracy Studies (STARD) statement (Supplemental Table).

Participants

Inclusion criteria consisted in neurocritical patients of any cause, sex or age, whose underwent ICP monitoring displaying both ICP numeric values and curves, until the fiftieth day of catheter insertion. Data obtained by the B4C sensor was not used for clinical management. We excluded patients presenting fixed mydriatic or mean pupils for more than 2 hours after ventilatory and hemodynamic stabilization (systolic BP> 100 mmHg; PaO_2> 100 mmHg; $PaCO_2$ < 30 or > 42 mmHg). Presence of coagulopathies, severe systemic diseases or severe multisystem trauma.

Clinical variables

The clinical variables collected were age in years (continuous variable), diagnostic, Marshall tomographic score in the case of TBI, Fisher tomographic score in case of SAH, arterial blood pressure, axillar temperature, heart and respiratory rates, oxygen saturation and sedatives administrated.

Invasive ICP Monitoring (Gold Standard)

The intraventricular measurement system will be used as the standard method. The ICP Neurovent monitoring system (Raumedic®, Munchberg, Germany) consists of a pressure probe for ventricular use. This system can be attached to any monitor using a small zero-point specific simulator for the patient monitor type. Changes in the monitor during measurement do not result in loss of calibration. The tip of the Neurovent system has a diameter of about 1.6 mm. The function is based on an electronic chip at its end. The chip is made of silicon and its central portion is flattened, which results in a thin membrane. This membrane protrudes from the degree of pressure to which it is exposed. Pressure is measured by determining membrane deformity using the piezoelectric system. The required measurement accuracy and independence of inlet pressure variations are ensured by an integrated measuring bridge on the chip. The Neurovent probe has a sensitivity of 5 μV / V / mmHg L 1%. Linearity errors taken in isolation may be present but of small value as they are given as a combined value. The maximum of this combined error is 0.5% (data provided by the manufacturer). The American standard for blood pressure systems allows an individual deviation of up to 2% for each of the parameters.

Noninvasive Intracranial compliance monitoring (B4C)

IC was evaluated non-invasively by assessing cranial deformation using a specific device (B4C; Brain4care Corp., São Carlos, Brazil). The B4C sensor consists of a support for a sensor bar that detects local cranial bone deformations using specific sensors. The detection of these deformations is obtained by a cantilever bar modeled through finite element calculations. Voltage meters are attached to this bar for deformation detection. Non-invasive contact with the skull is obtained by adequate pressure directly into the scalp by means of a pin. The system is positioned in the frontotemporal region, around 3 centimeters over the first third of the orbitomeatal line; consequently, avoiding temporal superficial artery main branches and temporal muscle, providing contact of the sensor with an area of thin skin and skull, whereas slight pressure is applied to the adjustable band until optimal signal is detected.

Variations in ICP cause deformations in the cranial bone, which are detected by the sensor bar. The device filters, amplifies and scans the sensor signal and sends the data to a mobile device. The method is completely non-invasive and painless. In addition, it does not interfere with any routine monitoring. The waveform obtained is equivalent to ICP waveform obtained using invasive techniques, such intraparenchymal probes or external ventricular derivation [3], and the relation between its different components provides information on ICC [27]. In particular, each cardiac beat corresponds to an ICP waveform composed of three peaks: arterial pulsation (P1); cerebral venous flow, which is secondary to

cyclic fluctuations of arterial blood volume, reflecting intracranial compliance (P2); the aortic valve closure (P3; Figure 1) [26].

Figure 1

The B4C analytics system verified all data collected by the sensor, i.e., ICP pulse waves morphology parameters such as the P2/P1 ratio, the time-to-peak (TTP) interval and pulses amplitudes. For this study, all calculations were performed using the mean pulse of the ICP, calculated by identifying and extracting all ICP pulses, excluding possible artifacts. The mean pulse was used to calculate the amplitudes of the P1 and P2 peaks, which were obtained by detecting the highest point of these peaks and subtracting the base value of the ICP pulse. The P2/P1 ratio was calculated by dividing the amplitude of these two points. In case of P2>P1, ICC was defined as “abnormal”. Furthermore, the automated system calculated the time interval where P2 should be depicted on the waveform and TTP according to the cardiac cycle, instead of where it may be disclosed in the spectrum [15]. For B4C system, this value is considered abnormal when higher than .22 ms (figure 2).

Figure 2

Sample

For neurocritical patients, the presence of intracranial hypertension, depending on the type of injury, may occur in 10 to 70% of patients. An *in vitro* study comparing minimally invasive ICP measurements with invasive ICP values identified correlation is greater than 80% (4). The sample desired was of 20 consecutive subjects, for this pilot description of findings of this new unharmful technique [24], although data collection is still ongoing because of high prevalence of ICH among neurocritical patients.

Statistical analysis

Statistical analysis consisted of an adjustment of a Deming Regression for the variables P2/P1 and TTP to verify the equivalence between invasive and non-invasive methods and Pearson's correlation was calculated with 95% confidence intervals obtained via bootstrap. The Bland-Altman graph was depicted for both variables, which gives us an idea of the difference between the two methods and whether there is any type of trend.

Results

Sample features

The presented results were with reference to 22 consecutive patients admitted in our institution between November 2019 and May 2020 who underwent ICP monitoring. Overall groups features are described in table 1.

Table 1

ICP x B4C correlation

The data were pooled from one 10-minute session (figure 3) from 22 patients, resulting in a total sample size of 13.435 cardiac pulses. The first part of the analysis was adjusting a Deming Regression to show how B4C and ICP are related. The adjusted regression line was Y= 0.5 [0.41, 0.59] + 0.62 [0.55, 0.7] X for the variable P2/P1, with Y corresponding to the variable ICP and X corresponding to B4C, as shown in figure 4, in which the 95% confidence intervals were obtained using the bootstrap procedure. For both methods to be considered equivalent, the confidence band of the adjusted line would have to contain the dashed line, which has the equation Y= 0 + 1 X Y=X, but this did not happen, so we cannot say that both methods are equivalent. As for the variable TTP, the estimated line of Y= 0.02 [0.0, 0.05] + 0.96 [0.85, 1.09] X in figure 4 is closer to the dashed line, showing a better equivalence. Pearson's correlation between PIC and B4C for the variable P2/P1 is equal to 0.63 [0.38, 0.8] and for TTP it is equal to 0.66 [0.39, 0.85], both with a median correlation.

Figure 4

In the second part an agreement analysis was performed using the Bland-Altman graph. Figure 5 shows the graph for the variable P2/P1, which the average difference between B4C and PIC of -0.061 [-0.09, -0.032] shows that the PIC values tend to be slightly higher than the B4C values. It is expected that approximately 95% of the observations will have a difference between -0.343 [-0.384, 303] and 0.221 [0.190, 0.254] and no type of trend is observed along the horizontal axis (average between the two measurements), meaning that the behavior of the difference between B4C and PIC remains the same across the range of P2/P1.

For the TTP variable, figure 5 shows a Bland-Altman graph that has a behavior very similar to the variable P2/P1. The average difference of -0.015 [-0.023, -0.006] shows slightly higher ICP values, which approximately 95% of these differences are between -0.093 [-0.106, -0.080] and 0.064 [0.055, 0.073] and none are observed trend type along the horizontal axis.

Figure 5

Discussion

Main findings

ICP and ICC are linked, despite being different concepts. The possibility of ICC impairment coexisting with ICP under normal range and vice versa have been described, being the strict leash of ICP to its mean values criticized [17]. Monitoring ICP should provide means to detect its trends and patterns, in order of yielding decision making effective and preventive.

Results of this study demonstrated a statistically significant correlation in the ICP signal and waveform parameters between the gold standard invasive ICP monitoring and the B4C system, although the latter is exclusively a system for observation of the hemostasis of the intracranial components, there is,

intracranial compliance, in real-time resolution. While the study had a limited sample size, and further data may be necessary to develop a mapping between the B4C and invasive ICP parameters, the study outcomes demonstrate comparable effectiveness between the B4C device and commonly used invasive ICP devices for use in monitoring and assessing variations in ICP waveform parameters over time. The joint distributions between ICP and B4C parameters presented a nonlinear shape correlation with a statistical dependence between them, that indicates that a more complete model might lead to a map between B4C and ICP parameters. Considering that the physical properties of the sensors and measurements locations differ – the invasive one is placed into the ventricle and the B4C outside the skull/scalp – a strong agreement between B4C and ICP waveform parameters would not be expected. However, they indeed obtained a relatively large region of agreement between the parameters, with significant average bias, confirmed by statistical tests.

Clinical observation of multiple parameters

Spontaneous cardiac-derived pulsatile signals overlapped in time domain with the respiratory cycle (about 4–8 waves per minute), as Lundberg C waves [23] were observed during the study. As the study was designed in order to avoid adding multiple confounding factors, short monitoring sessions were performed. Otherwise, continuous long-term monitoring may allow to verify different wave-morphologies that could reflect the residual compensatory capacity of the brain, since changes in the ICP wave shape are informative on an incoming or established alteration of the intracranial system. Therefore, A (vasogenic) or B waves are of high importance being differentiated, because Lundberg A waves are clearly severe and with elevated risk of poor prognosis, whereas the clinical implication of the B waves is a research question that remains to be determined, since they are non-specific indicators of diminished compliance and can also be present in patients with normal ICP [22,26].

Not accounted for data analysis presented here, posteriorly to study period, and with no invasive ICP monitoring, the assessment of patient 7 displayed slow waves of almost 4 minutes length, with elevated P2/P1 ratio, suggesting pathological waves with risk for clinical deterioration (figure 6). Otherwise, stable TTP and P2/P1 ratio (although the latter was elevated), were indicative of no imminent compromising. TCD performed concomitantly with monitoring revealed no suppression of cerebral blood flow during plateaus, which was compatible with clinical improvement in the following days.

Figure 6

Enlargement of cardiac pulses amplitudes and time interval between ICP peaks when ICH is present have been also described previously thru data obtained with invasive systems [2,23,31]. The changing dynamics of cerebrovascular system, through the vasodilation and contraction stimulation, regulate CBF. This change in pulse-waveform shape may be related to the aforementioned change in intracranial compliance. As the craniospinal compliance decreases during vasodilation, the change in capacitance may alter the attenuation range or phase shift of these frequencies. However, to our knowledge, literature on the effect of intracranial compliance and the frequency spectrum of the CBF volume pulse-waveform is still poor [14].

Limitations of the study

This study was designed to perform direct observation and correlation between both techniques' parameters in a single short session, hence, no outcome analysis for included patients was suitable.

B4C system limitations

The main limitation of the system is the need of patient's cooperation for those awake, since in cases of agitation the sensor will not maintain ideal contact with cranial skin. In cases of decompressive craniectomy, the system can be used since there is enough rigid structure to comprehend the band, being the sensor placed in the integrate side of the skull.

Other limitations for consideration; for preterm neonates (cranial vault lesser than 47 cm), the system is not yet suitable. As the system keep contact with the skin, it should be relocated hourly to avoid scalp erythema. Finally, while the B4C system presents analytical capabilities to provide additional ICC waveform information to the clinician, clinicians should always use their professional judgment to determine additional interventions necessary in the management of their patients.

B4C system attributes

Utilization of this noninvasive system offers no additional risks for patients. The reports produced may be tracked anywhere, permitting the physician to monitor a particular, or several patients remotely. The application and data collection may be performed by a trained technician. The system is not a surrogate for its predicate, otherwise may aid screening for ICP invasive monitoring.

Considerations for the future

Although strong recommendations, class I evidence for each modality of monitoring in neuro ICU is still lacking [13,10,18], unless for ICP monitoring in cases of imminence for brain herniation [18]. Hindrances to reach high evidence levels are more related to the difficulties for designing randomized controlled trials in the field than the techniques particularities *per se*. Especially in the case of ICP, randomizing patients for whether monitoring or not exclusively for study purposes is quite debatable [11]. As this new system for ICC monitoring do not portray additional risks, it represents an option for the development of trials in critical care, since ICC impairment may be present not exclusively for CNS primary diseases, but also in situations of severe acute respiratory syndrome, cardiac, hepatic [29] or kidney failures [33], anesthetics, extracorporeal membrane oxygenation [12] and many more.

Conclusions

Our study demonstrated that micrometric beat-by-beat cranial pulses are reliable markers of intracranial compliance and correlated with intracranial pressure. The discovery may widen applicability and understanding of ICP in clinical fields yet not explored.

Declarations

Declaration of interest

Dr. Sérgio Brasil joined brain4care scientific committee, although no conflict of interest that could be perceived as prejudicing the impartiality of the research is reported.

Funding:

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Author contribution

SB designed research, collected data of the study and wrote the manuscript. DJFS statistical analysis. MJT, RCN, WSP and LMSM critically revised the manuscript.

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Table 1

Table 1. Sample characteristics

Variable	Total (22)
Age	39.8 ± 24.8 (1; 74)
Male sex	11 (50%)
Pathology	
Traumatic brain injury	11 (50%)
Marshall II	2 (18%)
Marshall III	3 (27%)
Marshall V	6 (55%)
Subarachnoid hemorrhage	6 (27%)
Fisher IV	6 (100%)
Stroke	4 (18%)
Tumor	1 (5%)
Mean arterial pressure	133.9 ± 22.1 (94; 176)
Sedated regimen	
No sedation	6 (27%)
Fentanyl	1 (5%)
Propofol / Fentanyl	10 (45%)
Propofol / Midazolam / Fentanyl	3 (14%)
Thiopental / Fentanyl	2 (9%)
Intracranial hypertension	6 (27%)

Continuous variables presented as mean ± standard deviation (min; max). Categorical variables presented as n (%).

Supplemental Table

A Supplemental Table is not available with this version.

Figures

Figure 1

Intracranial pressure waves morphology in accordance with cerebral compliance.

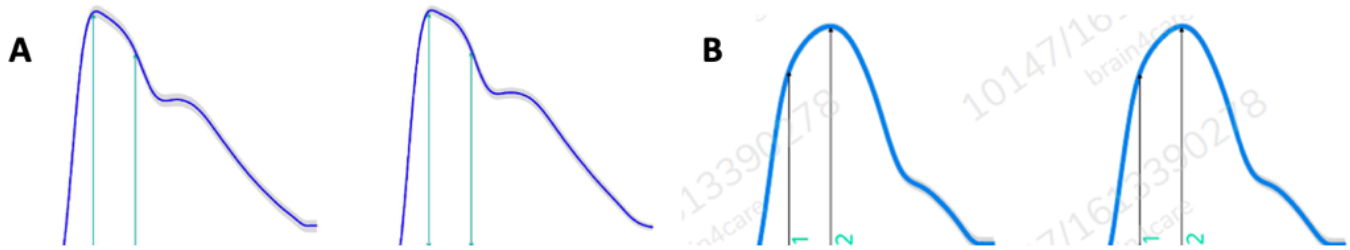

Figure 2

P2/P1 ratio and time-to-peak under standards (A) and altered (B).

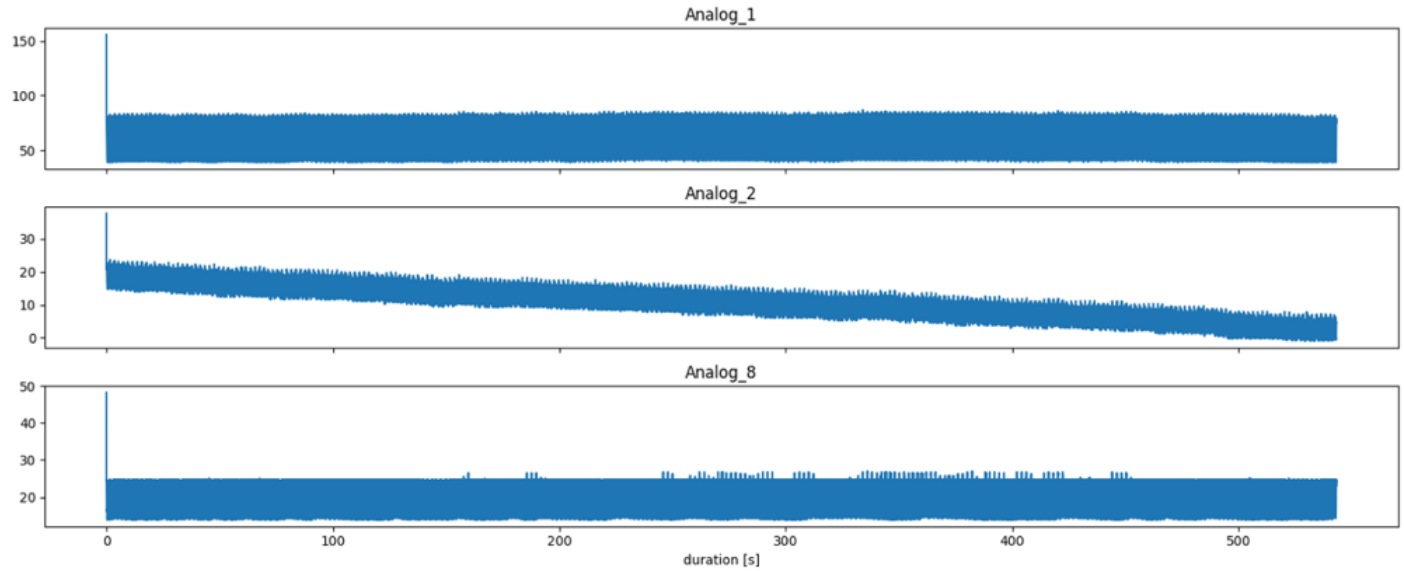

Figure 3

Patient 5 record disclosed in the upper image: arterial blood pressure (ABP, analog 1), B4C sensor (analog 2) and ICP (analog 8), the decrease in the B4C register is normally produced by sensor adjustment with the skull, whereas this do not compromise beat by beat pulses analyses and correlations seen in middle three spectral lines. At the lower image, an average pulse with confidence interval (because of

spontaneous fluctuations) of each variable is depicted, with P2/P1 ratio range from 1.09 to 1.23 whereas mean ICP ranged from 19 to 25 mmHg.

Figure 4

(A) Deming regression for variable P2/P1, with the line adjusted to the form Y= 0.5 [0.41, 0.59] + 0.62 [0.55, 0.7] X. **(B)** Deming regression for variable TTP, with the line adjusted to the form Y= 0.02 [0.0, 0.05] + 0.96 [0.85, 1.09] X.

Figure 5

(A) Bland-Altman graph for the variable P2/P1, **(B)** Bland-Altman graph for the TTP variable.

Figure 6

Interpretation of multiple waveforms parameters. A patient displaying slow waves of almost 4 minutes length, raising possibility for whether A or B Lundberg slow waves (A and B). The stable P2/P1 ratio and time-to-peak indicated B waves (C and D). Transcranial Doppler evaluation revealed no influence of these waves on cerebrovascular resistance and mean blood flow velocities.