


ORIGINAL WORK



Assessment of Cerebral Autoregulation Using Invasive and Noninvasive Methods of Intracranial Pressure Monitoring

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Abstract

Background: Pulse amplitude index (Pax), a descriptor of cerebrovascular reactivity, correlates the changes of the pulse amplitude of the intracranial pressure (ICP) waveform (AMP) with changes in mean arterial pressure (MAP). AMP relies on cerebrovascular compliance, which is modulated by the state of the cerebrovascular reactivity. Pax can aid in prognostication after acute brain injuries as a tool for the assessment of cerebral autoregulation and could potentially tailor individual management; however, invasive measurements are required for its calculation. Our aim was to evaluate the relationship between noninvasive Pax (nPax) derived from a novel noninvasive device for ICP monitoring and Pax derived from gold standard invasive methods.

Methods: We retrospectively analyzed invasive ICP (external ventricular drain) and non-invasive ICP (nICP), via mechanical extensometer (Brain4Care Corp.). Invasive and non-invasive ICP waveform morphology data was collected in adult patients with brain injury with arterial blood pressure monitoring. The time series from all signals were first treated to remove movement artifacts. Pax and nPax were calculated as the moving correlation coefficients of 10-s averages of AMP or non-invasive AMP (nAMP) and MAP. AMP/nAMP was determined by calculating the fundamental frequency amplitude of the ICP/nICP signal over a 10-s window, updated every 10-s. We then evaluated the relationship between invasive Pax and noninvasive nPax using the methods of repeated-measures analysis to generate an estimate of the correlation coefficient and its 95% confidence interval (CI). The agreement between the two methods was assessed using the Bland–Altman test.

Results: Twenty-four patients were identified. The median age was 53.5 years (interquartile range 40–70), and intracranial hemorrhage (84%) was the most common etiology. Twenty-one (87.5%) patients underwent mechanical ventilation, and 60% were sedated with a median Glasgow Coma Scale score of 8 (7–15). Mean Pax was 0.0296 ± 0.331 , and nPax was 0.0171 ± 0.332 . The correlation between Pax and nPax was strong ($R = 0.70$, $p < 0.0005$, 95% CI 0.687–0.717). Bland–Altman analysis showed excellent agreement, with a bias of -0.018 (95% CI -0.026 to -0.01) and a localized regression trend line that did not deviate from 0.

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Conclusions: P_{Ax} can be calculated by conventional and noninvasive ICP monitoring in a statistically significant evaluation with strong agreement. Further study of the applications of this clinical tool is warranted, with the goal of early therapeutic intervention to improve neurologic outcomes following acute brain injuries.

Keywords: Intracranial pressure monitoring, Noninvasive cerebral monitoring, Cerebral autoregulation

Introduction

Cerebral autoregulation (CA) refers to the central nervous system's ability to maintain cerebral blood flow relatively constant within a certain range of slow changes in mean arterial pressure (MAP) [1, 2]. Impaired CA has been correlated with worse outcomes in patients with acute brain injuries [3–7]. Ongoing trials of CA-guided blood pressure management hold the promise of individualized patient management strategies with improved patient outcomes [8].

Today's bedside monitoring technology used to assess CA and cerebrovascular reactivity in the clinical setting includes transcranial Doppler, which measures cerebral blood flow velocity; near-infrared spectroscopy, which

measures regional cerebral oxygen saturation; and invasive brain oxygen monitors, which measure tissue oxygen partial pressure [9]. Although these methodologies for the assessment of CA have been described, the best validated methods require the placement of invasive intracranial pressure (ICP) probes, which limits their widespread use [10–12]. Furthermore, current noninvasive techniques of CA assessment have well-known limitations, including surface insonation windows and extracerebral vasculature contamination, and provide only moderate agreement with invasive standards [9, 13–15]. The validation of a CA index based on the ICP waveform obtained noninvasively would represent a novel development that could have implications in the

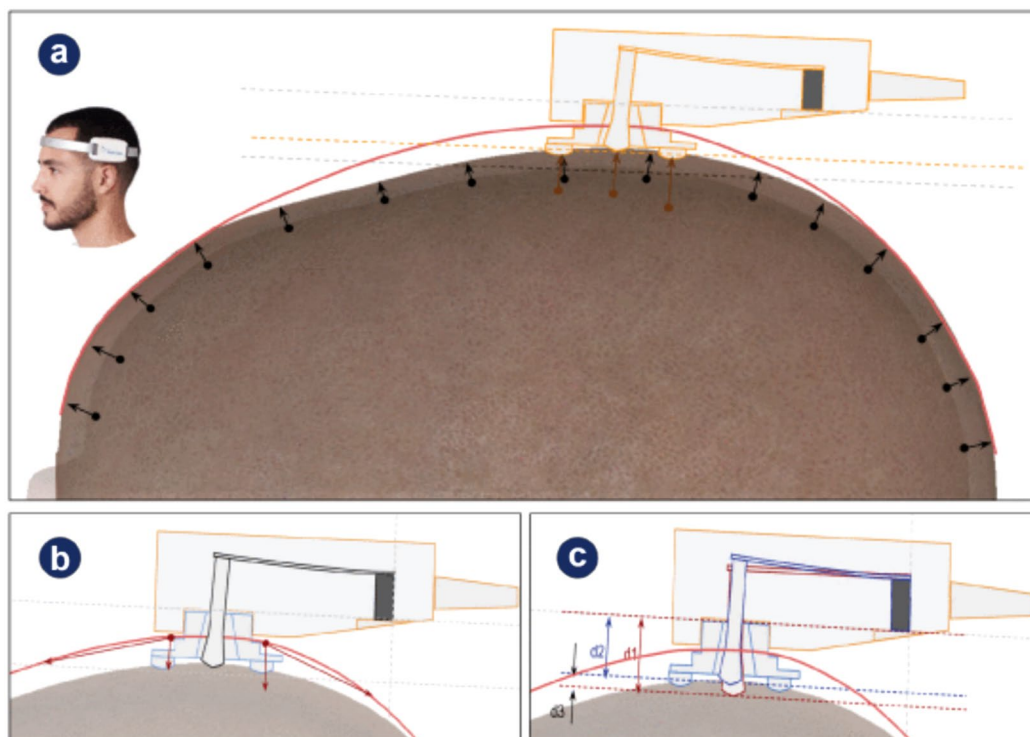


Fig. 1 An illustration of the mechanical extensometer. As arterial blood pressure drives blood into the intracranial space, producing pulsatile expansions of the cerebral arteries walls, the skull then experiences small deformations owing to these volume and pressure variations (as depicted in an amplified manner) (a). By adjusting the sensor's headband (red line) (b) to a certain tension extent, the pin of the sensor touches the head and keeps the device in place on the frontotemporal region of the head above the ears. The skull deformations can then be detected by the sensor as displacements of the pin that bends the sensor's cantilever beam c. The displacement detected by the sensor, in which the resulting displacement (d_3) is the difference between the initial (d_1) and final (d_2) positions ($d_3 = d_1 - d_2$), having the support bar of the sensor as a reference. Extracted and modified from Andrade et al. [23]

monitoring and management of patients with acute brain injuries.

The use of a novel noninvasive mechanical extensometer has been recently validated [16–18]. This technology is designed to detect small skull expansions originating from pulsatile beat-to-beat ICP variations, which subsequently generates a surrogate ICP waveform (Fig. 1). As extensively reported in the literature, an ICP waveform analysis carries significant clinical and pathophysiologic information, including associated parameters relating to intracranial dynamics and compliance [19–22].

The pulse amplitude index (P_{Ax}), a descriptor of cerebrovascular reactivity, is a validated index of cerebrovascular reactivity that correlates the changes of pulse amplitude of ICP (AMP) with changes in MAP [22]. The pulsatile component of ICP reflects the beat-to-beat changes in cerebral blood volume [20–22, 24]. Cardiac pulsations in arterial blood pressure produce pulsatile expansions of the cerebral arteries walls and consequently pulsations in cerebral blood volume, which in turn are transmitted to the surrounding brain parenchyma and cerebrospinal fluid. This transmission depends on the compliance of the cerebrovascular bed, which is a function of the vasomotor tone; therefore, AMP is modulated by the state of the cerebrovascular reactivity. AMP is calculated as the frequency amplitude of the first (fundamental) spectral harmonic component of the ICP waveform [4, 24, 25]. In previous studies, AMP monitored over time appeared to present better stability than mean ICP values because AMP is not subject to drifts and shifts of the absolute values of ICP because it is obtained in the frequency domain [26, 27].

Although P_{Ax} can aid in prognostication and potentially management after acute brain injuries as a tool for the assessment of CA, invasive ICP methods are required for its calculation [5]. A non-invasive P_{Ax} (nP_{Ax}) surrogate could provide cerebrovascular reactivity monitoring in patients without an ICP monitor who remain at high risk for neurologic deterioration. Our aim was to evaluate the agreement between nP_{Ax}, derived from a novel device for ICP waveform monitoring (nICP), and P_{Ax} obtained from gold standard invasive methods.

Methods

Study Design

This is a single-center retrospective study of adult patients admitted to Cleveland Clinic's neurointensive care unit between January 2021 and December 2021 with acute brain injury who underwent nICP monitoring with a US Food and Drug Administration–approved novel mechanical extensometer device (Brain4Care Corp.). To be included in the present study, patients also must

have undergone ventriculostomy insertion and arterial catheter placement as part of standard medical care as determined by the neurosurgical and neurointensive care teams.

All methods were performed in accordance with the relevant guidelines and regulations. An investigational review board exempt protocol was obtained for the creation of a multimodal monitoring database in which relevant clinical data are stored in a Health Insurance Portability and Accountability Act–compliant, password-protected server in place at our institution since 2019. To ascertain high-quality reporting of this observational study, the Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed [28].

Monitoring Protocol

Monitoring data from patients with acute brain injuries, who, at the discretion of the managing team and as part of standard clinical care, undergo invasive ICP monitoring, invasive cerebral oximetry, transcranial Doppler ultrasonography, nICP monitoring, and/or near-infrared cerebral oximetry, are stored in the multimodal monitoring database for subsequent offline review. In the present investigation, we selected patients who had nICP monitoring as well as concomitant continuous arterial blood pressure and invasive ICP monitoring in place.

The nICP sensor consists of a support for a sensor bar for the detection of local skull bone deformations, adapted with mechanical extensometers (Brain4care Corp.) (Fig. 1). Detection of these deformations is obtained by a cantilever bar modeled by finite elements calculations. To this bar, strain gauges are attached for strain detection. Noninvasive contact with the skull is obtained by adequate pressure directly on the scalp by a pin. Changes in ICP cause deformations in the skull bone detected by the sensor bar. Variations in ICP lead to deformations in the bar, which are captured by the strain sensors. The equipment filters, amplifies, and digitalizes the signal from the sensor and sends the data to the bedside patient monitor.

The sensor pin is placed about two inches above the level of the external auditory meatus, far away from any palpable arterial pulses, and held in place by a headband. Because of the known artifactual mechanical drift that is present soon after placement of the nICP sensor, data recording does not typically start until 20 min after placement. Although the duration of the monitoring session varies, it usually ranges from 20 to 40 min to obtain sufficient data for agreement analysis.

Data Retrieval and Processing

Once patients who met all inclusion criteria were identified, monitoring data for ICP, nICP, and MAP were

retrieved with the ICM+ software platform (Cambridge Enterprise, Cambridge, UK) with a sampling frequency of 300 Hz. MAP was monitored invasively through the radial artery using a standard pressure monitoring kit. ICP was monitored using an external ventricular drain, which was closed during the monitoring time frame. The time series from all signals were first treated to remove movement artifacts identified by visual inspection.

PAX and nPAX were calculated as moving Pearson correlation coefficients between changes in 30 consecutive 10-s averages of the MAP signal and corresponding pulse amplitudes of ICP and nICP (with 50% overlap of data), as previously described. The AMPs of ICP and nICP were obtained using a fast Fourier transform to convert the time-series signals into the frequency domain and to extract the fundamental first harmonic amplitude using tools implemented on ICM+ software.

Statistical Analysis

Patient descriptive characteristics and categorical data were presented as absolute frequencies and percentages. Quantitative data were presented as median values with their interquartile range (IQR) or mean \pm standard deviation based on Shapiro–Wilk's normality tests. Repeated-measures correlation was used to evaluate the relationship between the invasive PAX and nPAX to ensure that the relationship was not curvilinear. Bland–Altman analysis was used to test the agreement between invasive PAX and nPAX. All statistical analyses were performed using RStudio software (version 4.0.3) and SAS v 9.4. A *p* value < 0.05 was considered statistically significant.

Results

The monitored cohort included 24 patients with acute brain injury. There were 9 female patients, and the median age was 53.5 years (IQR 40–70). The admission neurologic evaluation depicted a median Glasgow Coma Scale (GCS) score of 8 (IQR 7–15). The majority of patients were admitted with an intracerebral hemorrhage (46%) or aneurysmal subarachnoid hemorrhage (37.5%) diagnosis. Summary statistics for baseline demographics and comorbidities are shown in Table 1.

Intensive Care Management on Day of Monitoring

On the day of monitoring, 21 patients (87.5%) required mechanical ventilation (Table 1). During the monitoring session, the majority (67%) received sedative agents by either continuous administration, bolus therapy, or a combination of both. Fentanyl (54%) was the most common sedative agent used, followed by propofol (21%). A Richmond Agitation Sedation Scale score of less than –2 was common. Four patients (17%) were

Table 1 Baseline demographics, comorbidities, and admission demographics

	Non-invasive ICP-monitored patients (N = 24)
Baseline demographics	
Age, median (IQR)	53.5 (40–70)
Height (cm), median (IQR)	174 (165–181)
Weight (kg), median (IQR)	86 (72–99)
BMI, median (IQR)	27 (25–34)
Female sex, <i>n</i> (%)	9 (37.5%)
Ethnicity, <i>n</i> (%)	
African American	19 (80%)
Caucasian	3 (12.5%)
Hispanic	1 (4%)
Other Listed	1 (4%)
Comorbidities, <i>n</i> (%)	
Hypertension	16 (67%)
Hyperlipidemia	13 (54%)
Diabetes	10 (42%)
Coronary artery disease	7 (29%)
Chronic kidney disease	5 (21%)
Asthma	6 (25%)
Active malignancy	0
History of ischemic stroke	3 (12.5%)
History of hemorrhagic stroke	0
Smoking history	13 (54%)
Alcohol abuse history	2 (8%)
Mood disorder	6 (25%)
Admission demographics	
Glasgow Coma Scale (GCS), median (IQR)	8 (7–15)
Mechanical ventilation, <i>n</i> (%)	14 (58%)
Admission diagnosis, <i>n</i> (%)	
Intracerebral hemorrhage	11 (46%)
Aneurysmal subarachnoid hemorrhage	9 (37.5%)
Ischemic stroke	2 (8%)
Intraventricular hemorrhage	2 (8%)
Intensive care management on day of monitoring	
GCS on day of monitoring, median (IQR)	8 (6–10)
Mechanical ventilation, <i>n</i> (%)	21 (87.5%)
Sedation/analgesia, <i>n</i> (%)	
Bolus	3 (12.5%)
Continuous	10 (42%)
Both	3 (12.5%)
None	
Sedation/analgesia agent, <i>n</i> (%)	
Propofol	5 (21%)
Fentanyl	13 (54%)
Midazolam	1 (4%)
Dexmedetomidine	0
Richmond Agitation–Sedation Scale, <i>n</i> (%)	

Table 1 (continued)

	Non-invasive ICP-monitored patients (N = 24)
0 to -1	6 (25%)
-2 to -3	10 (42%)
-4 to -5	8 (33%)
Vasopressor, n (%)	4 (17%)
ICP optimization, n (%)	
Hypertonic Saline	7 (29%)
Mannitol	0
Sedation	2 (8%)
Paralytics	1 (4%)
Continuous renal replacement therapy, n (%)	0

BMI, body mass index; GCS, Glasgow Coma Scale; ICP, intracranial pressure; IQR, interquartile range

monitored while on vasopressor therapy. No patients underwent renal replacement therapy on the day of monitoring.

Monitoring and Outcome Data

A single monitoring session was completed for each patient, and the median time for the total monitored period was 40 min (IQR 36–42.5). Continuous physiologic data yielded a median MAP of 88 mm Hg (IQR 77–94 mm Hg) and invasive ICP of 9.3 mm Hg (IQR 5.4–12.9 mm Hg). Ten patients underwent active cerebral edema management, with the majority requiring hypertonic saline (29%) decided by the clinical team. For the cohort, 83% (20 of 24 patients) survived, with a median discharge GCS score of 13 (IQR 9.75–15) and a median modified Rankin scale score of 4 (IQR 3–5). Table 2 summarizes discharge location for the survivors.

Correlation Between PAX and nPAX

The mean PAX calculated by invasive ICP measurements was 0.0296 ± 0.331 . The mean nPAX calculated by non-invasive ICP measurements was 0.0171 ± 0.332 . Figure 2 illustrates the linear relationship between the two measures PAX and nPAX ($R = 0.70$, $p < 0.0005$, 95% confidence interval [CI] 0.687–0.717).

Test of Method Agreement

Agreement between PAX and nPAX methods was analyzed using the Bland–Altman test (Fig. 3). The bias between the two measurement systems was -0.018 (95% CI -0.026 to -0.01). The pattern of the locally weighted scatterplot smoothing line remained close to the mean of the differences, there were no excursions outside the 95%

Table 2 Monitored data and clinical outcomes at discharge

	Value
Monitoring data	
Total monitored time (minutes), median (IQR)	40 (36–42.5)
Mean arterial blood pressure (mm Hg), median (IQR)	88 (77–94)
Intracranial pressure (mm Hg), median (IQR)	9.3 (5.4–12.9)
PAX, mean \pm (SD)	0.0296 ± 0.331
nPAX, mean \pm (SD)	0.0171 ± 0.332
Clinical outcomes at discharge	
Survivors, n (%)	20 (83%)
GCS on discharge, median (IQR)	13 (9.75–15)
Modified Rankin score on discharge, median (IQR)	4 (3–5)
Discharge location, n (%)	
Home	3 (12.5%)
Acute rehab	5 (21%)
Skilled nursing facility	4 (17%)
Long-term care facility	8 (33%)
Hospital mortality	4 (17%)

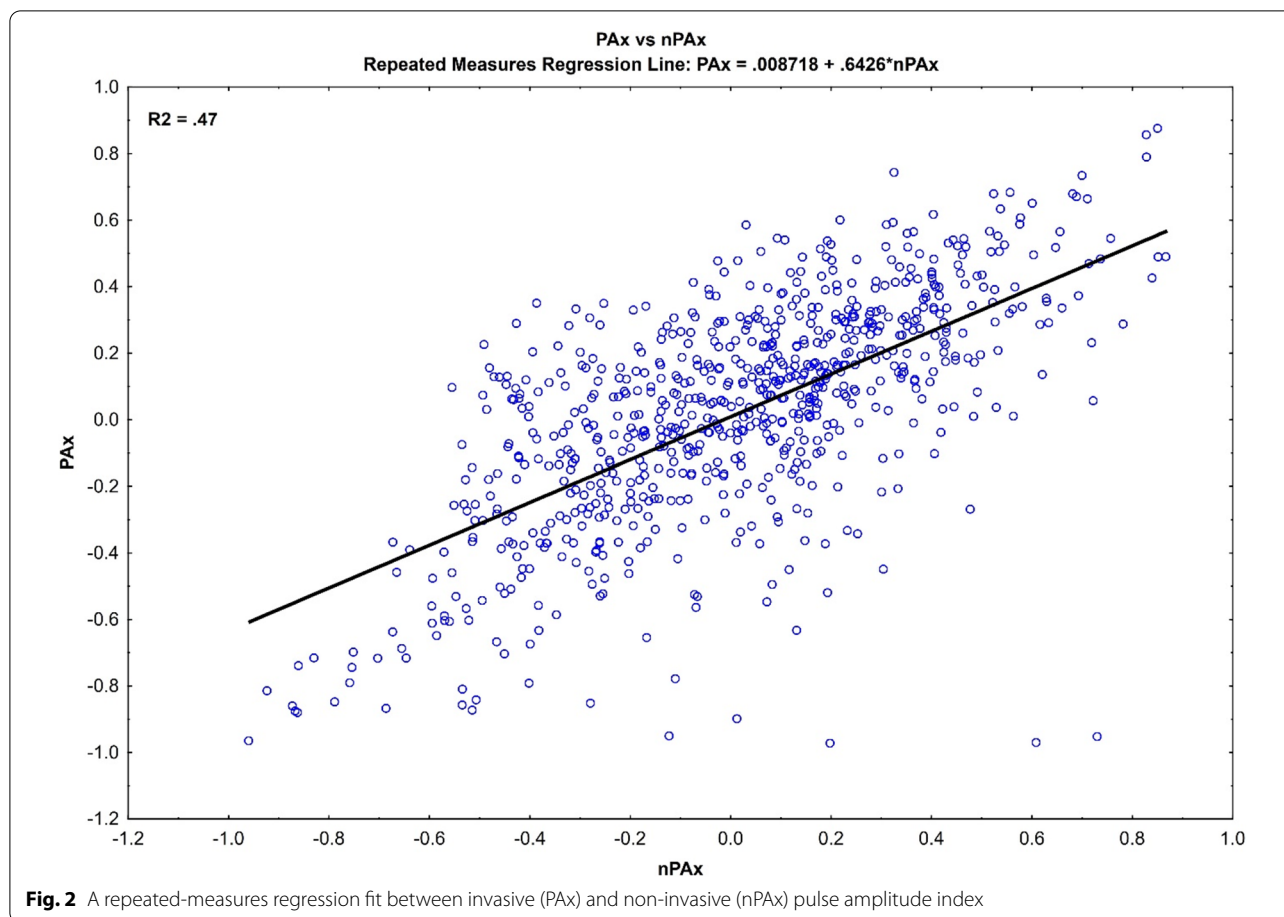
GCS, Glasgow Coma Scale; IQR, interquartile range; nPAX, non-invasive pulse amplitude index; PAX, invasive pulse amplitude index

CI, the differences were normally distributed, and there were no patterns in the data. The plot and the fit confirm the two methods are in agreement.

Discussion

We aimed to compare the agreement of an index of CA (PAX) obtained with conventional and noninvasive methods for ICP waveform monitoring. The mechanical extensometer demonstrated comparable performance to the invasive standard to generate a surrogate ICP waveform, which can then be analyzed to monitor cerebrovascular reactivity (Fig. 4). Individual Bland–Altman plots do indicate patient-to-patient changes in the bias of the measurements. Given the difference in patients, as well as differing locations of placement of the noninvasive device, these differences are not unexpected. Overall, our results demonstrate that PAX can be calculated by a non-invasive ICP monitoring method in patients with acute neurologic injury. To our knowledge, no previous studies have sought to evaluate noninvasive surrogates of ICP waveform for a CA index.

The strong agreement between the conventional and noninvasive ICP monitoring of PAX supports other recent studies that have validated the use of mechanical extensometer [16–19]. A small prospective study reported that the noninvasive ICP waveform monitor depicted agreement with the standard invasive method with an acceptable discriminatory power to detect intracranial hypertension via waveform morphology parameters (P2/



P1 ratio) [19]. Although our study did not evaluate the detection of intracranial hypertension and rather focused on cerebrovascular reactivity, the findings presented here support the use of the mechanical extensometer to obtain secondary CA indices from surrogate noninvasive ICP waveform analysis.

Total intracranial compliance is a complex, nonlinear relationship among the different compartmental compliances of the intracranial system (i.e., cerebrospinal fluid, arterial and venous circulations). The pulse amplitude of the ICP waveform (AMP) can approximate the compliance of the cerebral arterial bed (relating to the arterial circulation compliance), which is modulated by cerebrovascular reactivity [20–22, 24]. The clinical utility of this novel tool to obtain a noninvasive CA index will rely on future prospective trials with targeted, CA-directed therapy showing significant clinical benefits and improved patient outcomes. Such clinical trials of autoregulation-guided hemodynamic management are ongoing and have shown early promise in patients with traumatic brain injuries and patients with acute ischemic stroke undergoing large vessel recanalization [29, 30]. Whether nPAX could be used to guide

therapeutic interventions in these or other patient populations remains to be further defined.

Invasive devices remain the gold standard for ICP monitoring; however, they can be associated with significant complications [9]. Given the evidence from our data that the ICP waveform morphology can be recorded noninvasively to obtain a cerebrovascular reactivity index, this has the potential to increase our pathophysiologic understanding of intracranial complications of several diseases. Furthermore, our findings suggest that nPAX can be estimated in a vast majority of patients who traditionally are not considered good candidates for invasive ICP probe placement, which potentially may help expand its clinical use.

This study has several limitations. This is a small retrospective single-center study. Different monitoring periods as well as different treatment protocols (such as presence/mode of ventilation, sedative medications, and cerebral edema optimization) were used during monitoring sessions. Therefore, we cannot rule out the impact of treatment on cerebral dynamics. Another limitation is the presence of a heterogeneous

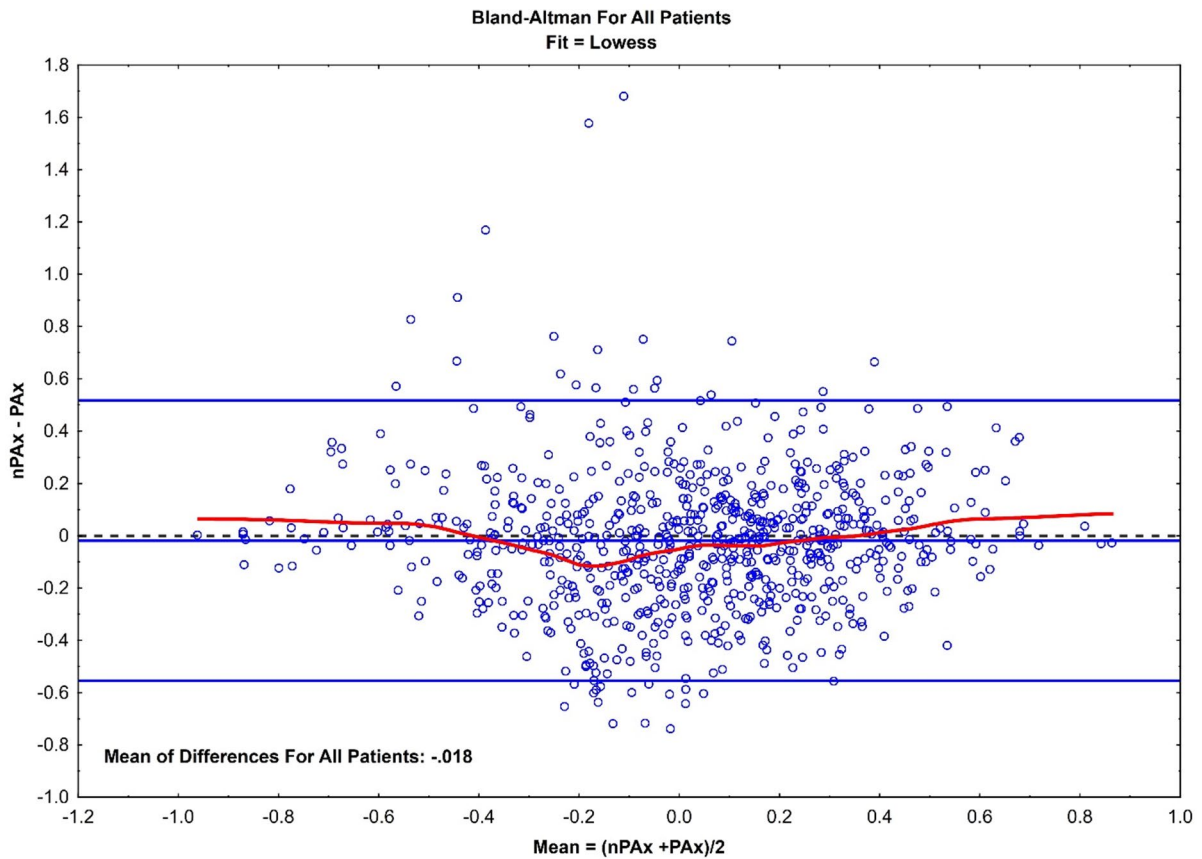


Fig. 3 Bland–Altman plot depicting the agreement between invasive (PAX) and non-invasive (nPAX) pulse amplitude index with superimposed locally weighted scatterplot smoothing fit. The mean bias within the measurement systems was -0.018 (95% confidence interval -0.026 to -0.01)

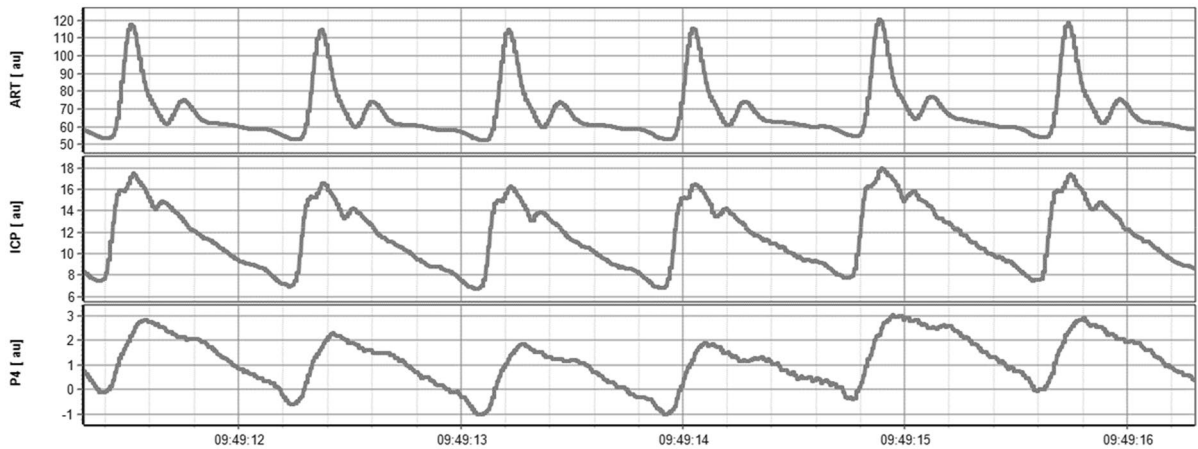


Fig. 4 Real-time waveform data over 5-s from a selected representative patient. The top panel represents arterial blood pressure (ART), the middle panel represents invasive intracranial pressure (ICP) from external ventricular drain, and the lower panel represents noninvasive ICP from mechanical extensometer (P4) waveforms

population with brain injury. It is unknown if the presence of intracranial hematoma, cerebral edema, or subarachnoid blood affects the ability to obtain a non-invasive ICP waveform. The heterogeneous group of patients and monitoring conditions support the non-invasive device's adaptability and performance in various settings. The mechanical extensometer's sensor pin cannot allow for prolonged monitoring periods without consequence of skin breakdown. Unlike its invasive counterpart, this sensor has a limited role in continuous monitoring; however, serial daily monitoring can still detect changes in cerebral dynamics, and an improved design of the sensor may eventually allow for safe continuous monitoring.

Obtaining the noninvasive ICP waveform using the mechanical extensometer device was easily prone to artifactual noise (such as a strong respiratory pattern) that could eliminate the waveform, as well as the need currently for manual artifact removal, which can be time consuming. Although artifact removal is currently performed manually, it is feasible that computer algorithms could be developed to aid in this task. The presence of these factors and other sources of special cause variation undoubtedly contributed to large confidence intervals in the Bland–Altman analysis. An examination and elimination of their effect will reduce the observed differences between the methods that are clinically acceptable. Despite these limitations, the main aim of this investigation was to test agreement between invasive and noninvasive methods for P_{Ax} calculation, which was found to be comparable.

Conclusions

P_{Ax} can be calculated by conventional and noninvasive ICP monitoring in a statistically significant evaluation with strong agreement. Further study of the applications of this clinical tool is warranted, with the goal of intervening early to improve neurologic outcomes following acute brain injuries.

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Author contributions

CEH: conceptualization, data curation, investigation, methodology, writing of the original draft, and review and editing. SPU: data curation. RB: formal analysis. NZM: review and editing. DC: conceptualization, data curation, formal analysis, and review and editing. JAG: conceptualization, data curation, investigation, methodology, writing of the original draft, and review and editing.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Ethical approval/informed consent

The article adheres to ethical guidelines and was approved by Cleveland Clinic's Institutional Research Board for retrospective study.

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