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INTRACRANIAL COMPLIANCE ASSESSED BY INTRACRANIAL PRESSURE PULSE WAVEFORM

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ABSTRACT

Background: Morphological alterations in intracranial pressure pulse waveform (ICPPW) secondary to intracranial hypertension (ICP >20 mmHg) and reduction in intracranial compliance (ICC) are well known indicators of neurological severity. To date, no studies have documented the ICPPW modifications after intracranial hypertension resolution with decompressive craniectomy (DC). The present study aimed to assess the morphological alterations in ICPPW among neurocritical care patients with and without DC, by comparing the variations of ICPPW features according to elevations in mean ICP values.

Methods: Patients requiring ICP monitoring because of severe traumatic or spontaneous conditions were included. Mean ICP values were compared with ICPPW features (P2/P1 ratio, TTP and pulse amplitude). Elevation in ICP was produced by means of ultrasound-guided manual internal jugular veins compression. Results were distributed for three groups: intact skull (exclusive burr hole for ICP monitoring), craniotomy/large fractures (group 2) or DC (group 3).

Results: 57 patients were analyzed. 21 (36%) presented no skull defects, whereas 15 (26%) had DC. ICP was not significantly different between groups: ±13.59 for intact and ±17.66 mmHg for DC, with ICP induced elevation also similar between groups (p= 0.56). Significant elevation was observed for P2/P1 ratio for groups 1 and 2, whereas reduction was observed in group 3 (elevation of ±0.09 for groups 1 and 2, whereas reduction of 0.03 for group 3, p=0.01).

Conclusion: In the present study, intracranial pressure pulse waveform analysis indicated that intracranial compliance was significantly more impaired among decompressive craniectomy patients, although ICPPW indicated DC to be protective for further influences of ICP elevations over the brain. Analysis of ICPPW seems to be an alternative to real time ICC assessment.

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INTRODUCTION

The skull content - the cerebrospinal fluid (CSF), the brain, and the blood volumes - is a major component and determinant of intracranial pressure (ICP). The capacity to accommodate the different intracranial compartments is named intracranial compliance (ICC). ICC is a property of dynamic volumes inside a cavity whose expansion is very limited, indicating the hemostasis amongst them [1]. In addition, ICC may reflect the compensatory changes of vessels (mainly the great intracranial venous sinuses) and the CSF spaces (cisterns, ventricles and subarachnoid), according to ICP elevations [2-4].

Recently, the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care made a list of recommendations that included ICP monitorization[5]. The consensus strongly recommends ICP monitoring to guide medical and surgical interventions, and to detect life-threatening imminent herniation. Nevertheless, the ICP threshold value for intervention is still uncertain. The continuous assessment and monitoring of ICP, including waveform quality, is also strongly recommended [6]. In addition, the committee indicated that further research into the relationship between ICP and clinical outcomes will benefit from automated, high-resolution monitoring and alternate forms of analysis [5].

Likewise, in recent years the knowledge on the ICP pulse waveform (ICPPW) has advanced, as well as its clinical application. ICPPW is an early marker of ICC impairment [3,7-9] and is mainly represented by three distinct peaks, P1 (percussion wave), P2 (tidal wave) and P3 (dicrotic wave)[10]. Under physiologic conditions, P1 produced by arterial contraction is the highest peak observed, with P2 reflecting both vascular and ventricular repercussion of pressure pulse spread. As cerebrovascular resistance is normally lower[11] in comparison with other systems and organs, the tidal wave assumes an amplitude lower than P1. When the buffering mechanisms described above are exhausted and intracranial hypertension (ICH) is present there is [12] deformation of ICPPW, with P2 assuming an

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amplitude higher than P1, and the ICPPW becomes progressively pyramidal[13], with the enlargement of time interval between P1 and P2[7] (figure 1).

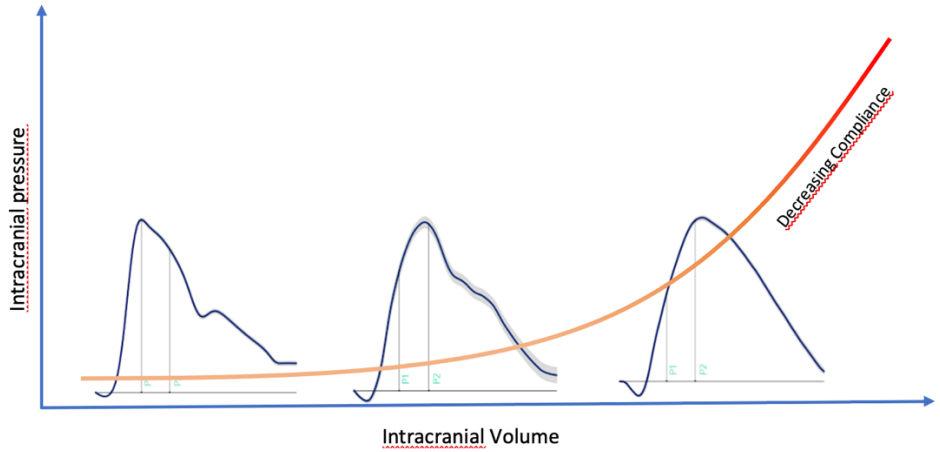

Figure 1. Langfitt's pressure/volume wave superimposed with ICP waveforms disclosing as intracranial compliance is reducing, a more pyramidal shape is assumed (progressive P2/P1 ratio).

All the findings described above have been investigated in animal models or clinical observational studies; however, the ICPPW changes after ICH treatment surgery has never been assessed. Surgery for mass lesion removal or decompressive craniectomy (DC) changes brain architecture and dynamics[14]; what makes ICP thresholds also change. In this environment, multimodal monitoring becomes essential to guide therapeutic interventions[15,16]. Although neurosurgical procedures are effective for ICP control, morbidity remains high, which might be explained by the persistence of low ICC (despite ICP in the "normal" range). The primary objective of the present study was to evaluate the ICPPW changes after surgery procedures and correlate it with ICC.

METHODS

This is a single center, uncontrolled, clinical trial in the neurological intensive care unit of Hospital das Clínicas, São Paulo University, Brazil. This clinical trial (CT) study

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protocol was approved by the local Ethics Committee, in May/23/2017 (REB register 66721217.0.0000.0068) 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 suffered an acute brain injury with the need for ventilatory support and invasive ICP monitoring in accordance with guidelines adopted by our institution. Data collection consisted in a 10-minutes session of simultaneous recording of spontaneous fluctuations of invasive arterial blood pressure, ICP, heart rate and oxygen. At minute 7, an ultrasound-guided manual internal jugular veins compression (IJVC) was performed for 60 seconds (figure 2).

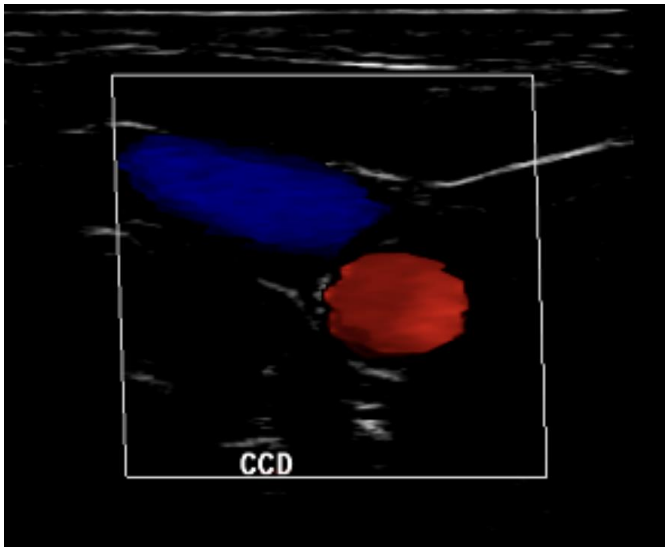

Figure 2: A manual internal jugular veins (blue) compression was performed for 60 seconds to elevate ICP with the aid of ultrasound to avoid compressing common carotid artery (red).

Participants

Inclusion criteria consisted of any neurocritical patients who underwent ICP invasive monitoring up to the fifth day of catheter insertion. We excluded those presenting with fixed

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mydriatic or middle-sized pupils for more than 2 hours after ventilatory and hemodynamic stabilization.

Clinical and intracranial variables

Demography, clinical, imaging presentation and severity scores were recorded. The clinical variables collected were age in years (continuous variable), diagnostic, Marshall tomographic score in the case of TBI, modified Fisher tomographic score in case of SAH, arterial blood pressure, axillar temperature, heart and respiratory rates, oxygen saturation and sedatives administrated. ICP was monitored with the Neurovent monitoring system (Raumedic®, Munchberg, Germany), which 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.

Data acquisition and analysis

The automated analytics system verified all data collected i.e., ICP pulse waves morphology parameters such as the P2/P1 ratio (P2 amplitude divided for P1 amplitude), the time-to-peak (TTP- time interval from the beginning of each pulse until P2) interval and pulses amplitudes (mean amplitudes of each pulse) [17]. For this study, all calculations were performed using the mean pulse of the ICP, excluding possible artifacts. The mean pulse was obtained by calculating the amplitudes of the P1 and P2 peaks and subtracting to the base value of the ICP pulse. The automated system calculated the time interval where P2 should be depicted on the waveform and TTP according to the cardiac cycle (figure 3).

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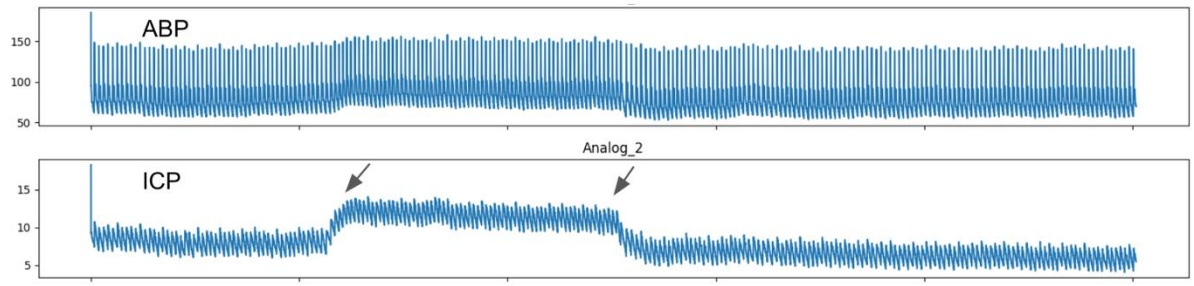

Figure 3. Mean ICP, P2/P1, TTP and pulse amplitude were calculated and correlated between basal and 60 seconds IJV compression (plateau arrows) intervals.

Sample size

The study sample size had 80% power to detect interactions between the three skull groups (intact, craniotomy/fracture and craniectomy) and the two moments (before and during jugular vein compression) with an effect size (η^2) of at least 0.06 (moderate), assuming alpha error probability 0.05 and correlation among repeated measures 0.5.

Statistical analysis

For descriptive purposes, categorical variables were presented through relative and absolute frequencies and compared using the chi-squared or Fisher exact test, as appropriate. Continuous variables distributions were deemed normal as assessed by skewness, kurtosis and graphical methods. There was no missing data for the intracranial monitoring parameters.

Repeated measures ANOVA analyses were employed to compare the intracranial monitoring parameters behavior between the groups along the experiment. The effect size was standardized by the eta squared (η^2). As a sensitivity analysis, a multivariable linear regression was modeled to verify the effect of the skull defect in the intracranial parameter variation (during compression – baseline) after adjustment for age and the baseline parameter.

All tests were 2-sided and final p values under 0.05 were considered statistically significant. All analyzes were conducted with the SPSS software (IBM Corp. SPSS Statistics para Windows, version 24.0. Armonk, NY).

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RESULTS

Sample features

A total of 98 eligible, consecutive patients admitted between August 2017 and May 2020 were included. Due to poor quality of ICPPW data, 41 patients were excluded from this analysis. A final sample of 57 patients was analyzed. Table 1 depicts the sample characteristics according to skull defect groups. Age, sex, hemoglobin and general clinical severity (SAPS3) were similar between groups. Regarding the pathology, stroke was more frequent among those with craniectomy (adjusted residual 3.4, p=0.028).

Table 1. Sample characteristics according to skull defect (n=57)

Variable	Skull			p value
	Intact (21)	Craniotomy or Fracture (21)	Craniectomy (15)	
Age	35.2 ± 22.8	40.2 ± 20.3	39.3 ± 22.1	0.741
Male sex	15 (71.4)	10 (47.6)	12 (80.0)	0.098
Pathology				0.028
Traumatic brain injury	17 (81.0)	14 (66.7)	9 (60.0)	
Subarachnoid hemorrhage	4 (19.0)	5 (23.8)	1 (6.7)	
Stroke	0 (0.0)	1 (4.8)	5 (33.3)	
Tumor	0 (0.0)	1 (4.8)	0 (0.0)	
Hemoglobin	10.3 ± 1.6	10.0 ± 1.5	10.3 ± 1.8	0.854
<10mg/dL	8 (38.1)	9 (42.9)	6 (40.0)	0.951
<9mg/dL	5 (23.8)	4 (19.0)	4 (26.7)	0.857
<8mg/dL	2 (9.5)	1 (4.8)	0 (0.0)	0.447
SAPS3	53.5 ± 12.1	62.2 ± 12.6	63.2 ± 14.3	0.082

Categorical variables are presented as n (%). Continuous variables are presented as mean ± standard deviation.

Table 2 presents the intracranial monitoring parameters according to skull defect and adjusted for age. All groups had an ICP increased during IJVC, but no interaction was disclosed between group

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and period (baseline/compression) (p=0.565) (Figure 4). P2 / P1 ratio also increased during IJVC for the intact and craniotomy/fracture groups but didn't change for the craniectomy group (p value for interaction 0.010 and partial η^2 0.161, a large effect size). Time to peak and amplitude didn't change significantly during IJVC nor presented interaction between group and period (baseline/compression). These results are the same after adjustment for hemoglobin and SAPS3.

Table 2. Intracranial monitoring parameters according to skull defect (n=57)

Parameter	Skull	Baseline	Jugular vein compression	Difference (95% CI)	p value	Partial η^2
Intracranial pressure	Intact	15.11 ± 8.10	19.45 ± 7.65	4.54 (3.22 – 5.87)	0.565	0.021
	Craniotomy or Fracture	15.33 ± 6.53	19.62 ± 7.44	3.90 (2.90 – 4.91)		
	Craniectomy	20.81 ± 10.22	23.93 ± 9.46	2.44 (1.64 – 3.24)		
P2 / P1 ratio	Intact	1.01 ± 0.24	1.11 ± 0.22	0.09 (0.04 – 0.15)	0.010	0.161
	Craniotomy or Fracture	1.14 ± 0.30	1.21 ± 0.28	0.07 (0.02 – 0.11)		
	Craniectomy	1.21 ± 0.32	1.18 ± 0.26	-0.03 (-0.8 – 0.03)		
Time to peak	Intact	0.20 ± 0.08	0.21 ± 0.08	0.01 (-0.01 – 0.03)	0.693	0.014
	Craniotomy or Fracture	0.23 ± 0.09	0.25 ± 0.08	0.02 (-0.01 – 0.05)		
	Craniectomy	0.22 ± 0.10	0.23 ± 0.10	0.01 (-0.01 – 0.03)		
Amplitude	Intact	10.87 ± 7.80	11.35 ± 7.79	0.48 (-0.06 – 1.03)	0.739	0.011
	Craniotomy or Fracture	5.58 ± 3.32	6.06 ± 3.92	0.48 (0.07 – 0.90)		
	Craniectomy	4.31 ± 3.09	4.56 ± 3.32	0.25 (-0.17 – 0.67)		

Data presented as mean ± standard deviation. The p values refer to the interaction between

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skull defect and time. Adjusted for age. CI: Confidence interval.

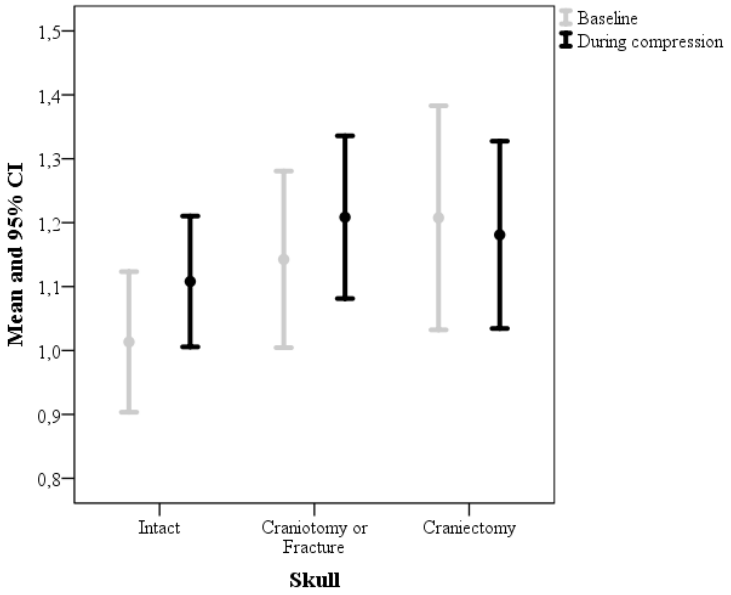

Figure 4. P2 / P1 ratio according to skull defect

Since baseline ICP and P2/P1 ratio tended to be higher in the craniectomy group, sensitivity analyses were conducted to verify the independent association between this skull defect and the P2/P1 ratio behavior during IJVC. Figure 5 presents a stratified analysis of the P2 / P1 ratio behavior during IJVC according to baseline P2/P1 status (normal or altered). Those with altered baseline P2/P1 ratio and intact skull (n=6 [28%]) or craniotomy/fracture (n=10 [47%]) presented an increase in the P2/P1 ratio during IJVC (mean difference 0.05, 95% IC 0.01 - 0.09, p = 0.033), but not those with craniectomy (n=9 [60%]); mean difference -0.07, 95% IC -0.15 - 0.02, p = 0.103; p value for interaction 0.026). Thus, the results presented in Table 2 and Figure 4 can't be attributed to a ceiling effect. Similarly, those with normal baseline P2/P1 ratio and intact skull (n=15) or craniotomy/fracture (n=11) presented an increase in the P2/P1 ratio during IJVC (mean difference 0.10, 95% IC 0.05 - 0.16, p = 0.001), but not those with craniectomy (n=6; mean difference 0.03, 95% IC -0.02 - 0.08, p = 0.134), although the interaction didn't reach statistical significance (p = 0.425).

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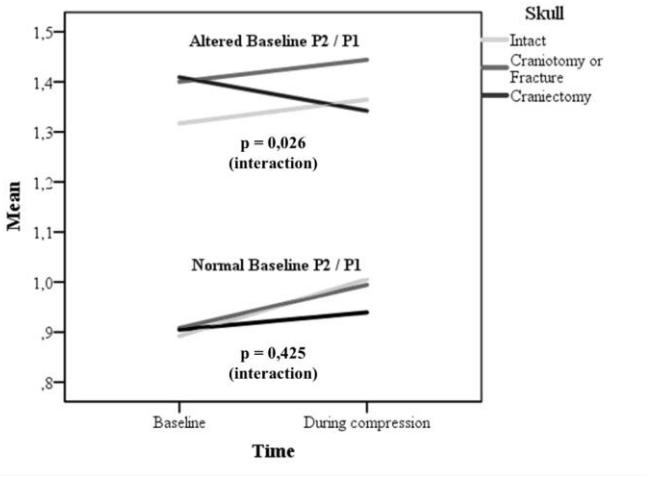

Figure 5. P2 / P1 according to skull defect and baseline P2 / P1 status

Aiming another sensitivity analysis, a multivariable linear regression was modeled to verify the effect of the skull defect in the P2/P1 ratio variation (during compression – baseline) after adjustment for age and the baseline parameter (Table 3). Compared to the intact or craniotomy/fracture groups, the craniectomy was independently associated with less P2/P1 ratio variation (-0.09, 95% IC -0.15 - -0.02, p=0.009), regardless of the baseline status.

Table 3. Multivariable linear regression for P2 / P1 variation (after compression-baseline)

Variable	Coefficient (95% CI)	SE	Standardized coefficient	t value	p value
Craniectomy (compared to intact or craniotomy/fracture)	-0.09 (-0.15 - -0.02)	0.03	-0.33	-2.72	0.009
Altered baseline P2/P1 ratio	-0.07 (-0.13 – -0.01)	0.03	-0.30	-2.49	0.016
Age	-0.001 (-0.002 – 0.001)	0.001	-0.20	-1.74	0.088

CI: Confidence interval; SE: Standard error.

No adverse events were reported during this study's intervention and monitoring.

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DISCUSSION

Previous studies have focused either on the extraction of indexes or ICP areas under curves calculations to obtain measures of ICC [10]. To our knowledge, this is the first study on the relations of ICP peaks observing the P2/P1 ratio, time-to-peak and amplitudes variations among neurocritical patients with a slight provoked ICP elevation. The main finding was the observation of an opposite behavior regarding the P2/P1 ratio among subjects with acute closed skull brain damage and even after craniotomy, in comparison with the craniectomized patients. Although not statistically significant, DC patients disclosed higher baseline mean ICP levels and P2/P1 ratio, with a significant decrease in the latter when ICP elevation was induced. Thus, the study demonstrated that P2/P1 ratio may bring additional information for neuromonitoring [3,18] and the effect of DC that not just ameliorated ICP but also increased the intracranial compliance, protecting for further elevations in ICP. This agrees with previous studies using different methodologies [19-21].

Patients submitted to DC have more severe neurological condition and that's the reason why the ICP was higher and the P2/P1 ratio remained higher after DC in comparison to other groups. Interestingly, despite the higher ICP values our study demonstrated greater ICC in this group as observed with P2/P1 ratio after induced raise of ICP [22] [23]. This phenomenon has never been demonstrated before and should be further explored as an indicator of successful DC.

DC is an effective procedure to alleviate extremely high ICP although the evidence of efficacy amongst different neurological pathologies is variable [24] [25]. For most diseases, an ICP threshold of 19 mm Hg has been associated with good outcome, nevertheless, lower ICP values may improve survivance[26]. Notwithstanding, mortality decrease has not been proven, especially because of difficulties for studies elaboration with this subject[15].

The improvement of cerebral perfusion after DC is associated with favorable outcomes [19,20] and with the prevention of metabolic crisis[27,28]. This association was evaluated by Jin et al. in 60 DC patients suggesting thresholds for predicting good prognosis in DC according to ICP values (ICP <19 mmHg in the first 24 h) and transcranial Doppler (TCD) derived parameters (mean blood flow velocity >56.33 cm/s, end-diastolic blood flow velocity >40.28 cm/s, and resistance index

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<0.57)[29]. Moreover, Lubillo et al. assessed 42 DC patients and observed that "changes in brain oximetry before and after DC, measured with probes in non-injured brain have independent prognostic value for the 6-month outcome in TBI patients"[30].

Applicability of ICP waveform derived information to date is mostly restricted because of the need for specialized hardwares and softwares, making these observations and findings less present in daily practice. Timofeev et al.[31] using dedicated software (ICM+, University of Cambridge, UK) studied ICP waveform amplitude in correlation with mean ICP values, the RAP index, and the correlation between arterial blood pressure and ICP, the PRx. Likewise, Asgari et al.[32] with another dedicated software (MOCAIP, University of California at Los Angeles, USA) performed automated ICP peaks analysis in elapse of cerebrovascular changes. However, the opportunity of a non-invasive bedside observation of ICC has been recently developed (B4C, São Carlos, Brazil) and was validated in children with hydrocephalus[33] and severe COVID-19 cases[34]. This system provides the ICPPW in real time, with automated P2/P1 ratio calculation. Further investigations may validate the use of this technology as a screening tool for patients with progressive ICC deterioration whose should undergo decompressive craniectomy.

In neurocritical care, multimodality for acquisition of brain metabolism, electrical activity, oxygenation, cerebral perfusion and ICP probably cover all patients' needs, with real hindrances relying on the limitations and reliability of each technique itself. Altogether, with reference to ICP, these advice showed the importance to consider not only the mean values of ICP in mmHg, but also the characteristics of the ICPPW, which combines markers of both cerebral hemodynamics and cerebrospinal pressure-volume compensation that encodes information about the biophysical characteristics of the intracranial space[35-37].

Limitations

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Although IJVs compression is a maneuver able to be performed at the bedside, thus, reproducible in clinical sets, this is not an ICP controlled measure, being considerable variation observed among patients. The results observed in the present study were with reference mostly to slight variations in ICP, because stimulating higher elevations would be considered unethical. Thus, it is not possible to predict ICPPW behavior with reference to substantial elevations in ICP.

CONCLUSIONS

Intracranial pressure pulse waveform is a reliable marker of intracranial compliance and may play a role besides intracranial pressure mean values for the neurocritical patient. After decompressive craniectomy, further elevations in ICP did not lead to additional deterioration on intracranial compliance.

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