



# Analysis of intracranial pressure waveform using a non-invasive method in individuals with craniosynostosis

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## Abstract

**Purpose** Craniosynostosis can lead to symptoms resulting from cranial compliance (CC) changes and intracranial hypertension (ICH), which may cause cognitive and visual impairment. Non-invasive methods have emerged, including a new device that captures and processes the intracranial pressure waveform (ICPw) by the skull's oscillation. The present study evaluates ICPw obtained non-invasively (NIICPw) in patients with craniosynostosis.

**Methods** This prospective, cross-sectional, and descriptive study was conducted at a single center. Patients diagnosed with craniosynostosis and who provided informed consent were included. A US Food and Drug Administration–approved mechanical extensometer device (Brain4Care Corp.) was used to obtain a NIICPw. An ophthalmologist did a point-of-care retinography to check the optic nerve papilla. The P2/P1 ratio and the morphology of the NIICPw were analyzed, as well as the retinography.

**Results** Thirty-five patients were evaluated, and 42 registers were obtained because seven were assessed before and after the surgery. The two patients who presented papilledema had low CC (NIICPw shape Class 3 or 4). There was a significant association between NIICPw and papilledema.

**Conclusion** The ratio P2/P1 and the NIICPw morphology provided by a non-invasive monitor are related to CC changes before papilledema occurs. This is especially useful in patients with craniosynostosis because invasive ICP monitoring is not always feasible. Further studies are warranted to establish the clinical utility of NIICPw in patients with craniosynostosis.

**Keywords** Intracranial hypertension · Craniosynostosis · Intracranial pressure · Papilledema

## Introduction

Patients with craniosynostosis may present symptoms and signs resulting from changes in cranial compliance (CC). Compliance is a physical concept that relates to the container

and its contents. Therefore, CC is the relationship between intracranial volume and the pressure exerted by intracranial components: blood volume (arterial and venous), brain tissue, and cerebrospinal fluid. Low CC occurs when the intracranial volume (ICV) is decreased, the pressure inside the skull is elevated, or both. Analyzing individuals with craniosynostosis, it is known that ICV may be altered but not necessarily decreased. Eventually, ICV is average or above the normal in syndromic and isolated craniosynostosis [1–3].

Regarding intracranial pressure (ICP) measured by invasive [3–7] or non-invasive monitoring [6, 8–11], studies demonstrate a high frequency of intracranial hypertension (ICH) in individuals with craniosynostosis, which is related to several factors, such as increased venous pressure, changes in the base of the skull, hypercapnia secondary to airway obstruction, and hydrocephalus (associated with the presence of Chiari 1 and cerebral venous hypertension) [12–15]. The consequences of ICH in children are visual impairment

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[16] and a decrease in cortical thickness and neuronal rarefaction, which is related to cognitive impairment [12, 17, 18]. So, children with craniosynostosis have multiple reasons to have lower CC, either due to alteration of ICV or increased ICP. At this point, it is essential to remember that there are ways to compensate for low CC through cerebral autoregulatory mechanisms; however, when autoregulatory mechanisms are exhausted, signs and symptoms of elevated ICP will appear [19]. Invasive intracranial monitoring is the gold standard method to evaluate ICP because, besides providing the value, it shows the ICP's waveform, which includes information on autoregulatory mechanisms and CC [20]. Several non-invasive methods have been used to determine ICH, including fundoscopy, imaging exams, measurement of the optic nerve sheath, optical coherence tomography, near-infrared spectroscopy, evoked potentials, transcranial Doppler, and pupillometry [21]. A new device assesses the intracranial pressure wave (ICPw) generated by the skull's oscillation caused by a systolic pulse [22]. It captures and amplifies the skull oscillations, generating a non-invasive intracranial pressure wave pulse (NIICPw), and has been used to monitor patients in the intensive care unit [23]. Despite the Monro-Kellie doctrine [24] stating that the skull is inelastic, several authors have demonstrated that the arterial pulse disperses through the cranial bones, generating oscillations [25–28]. Since patients with craniosynostosis may present ICH and considering the emergence of non-invasive equipment that records the ICPw, we conducted this study to correlate the ICPw obtained non-invasively in patients with craniosynostosis with their retinography.

## Methods

### Study design

This study was carried out at a single center in a prospective, cross-sectional, and descriptive manner. The patients are followed up at the Hospital of Rehabilitation of Craniofacial Anomalies of the University of São Paulo. The inclusion criteria for the study were as follows: a diagnosis of craniosynostosis validated by the geneticist of the craniofacial surgery team and a signature of the informed consent form. The records were done between October 2020 and February 2023. Patients came to the hospital for routine evaluation and underwent NIICPw monitoring by a neurosurgeon and retinography by an ophthalmologist. NIICPw monitoring was done using a US Food and Drug Administration–approved mechanical extensometer device (Brain4Care Corp.) Following the NIICPw procedure, the ophthalmologist registered the optic nerve papilla using a portable fundus camera (Phelcom Eyer Corp). The evaluation was done in individuals submitted to a surgical procedure as in patients non-operated.

Due to the lack of collaboration, some individuals did the NIICPw monitoring under general anesthesia. There was no direct public or private funding in this study, except for the availability of the device and the technical support given by Brain4care (B4c) Inc. The local ethics committee approved this clinical trial study protocol on February 1, 2019 (register: 03843118.0.0000.5505).

### Patient cohort

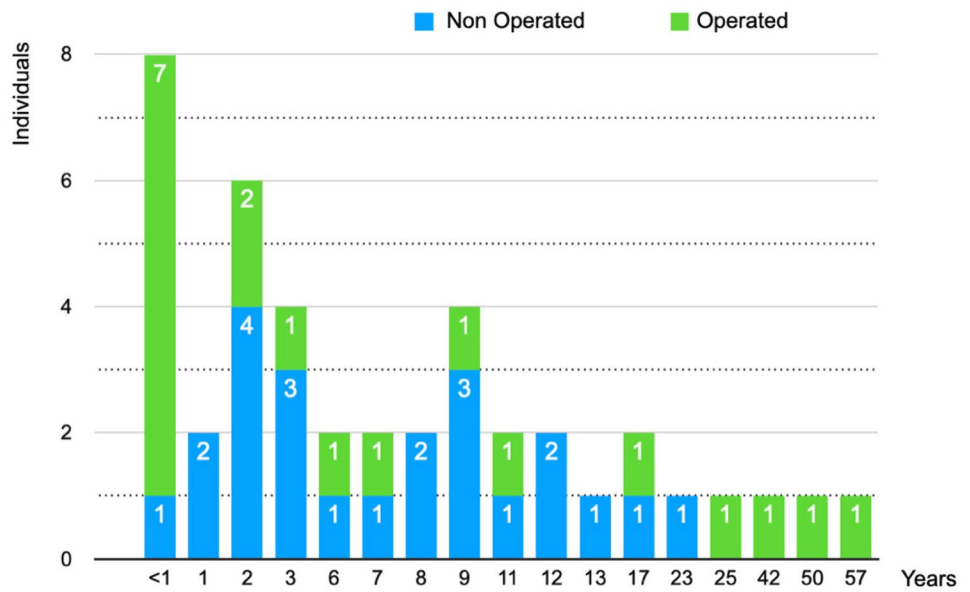
Thirty-five patients, eighteen individuals were females, and 17 were males, aged from < 1 to 57 years, were evaluated (Fig. 1). The older patients, specifically the three oldest ones, were parents of syndromic patients and were already adults when they received the diagnosis. The diagnosis was non-syndromic craniosynostosis (scaphocephaly, plagiocephaly, brachycephaly, and trigonocephaly) and syndromic: Apert, Crouzon, and Pfeiffer syndromes.

The patients were sequentially selected and were divided into two groups as they attended the hospital for their appointments. The non-operated group of patients was evaluated in two different ways: for the older and cooperative patients, the evaluation occurred in the outpatient clinic after their regular consultation. For the infants, the evaluation was performed in the operating room under general anesthesia before the surgical procedure, following a specific anesthetic protocol. This group included those who did not receive a surgical recommendation because they started their follow-up as adults and did not have any complaints or desire to undergo a procedure. The operated group consisted of individuals who underwent cranial surgery regardless of the timing. The surgeries the patients underwent were frontal advancement, monobloc advancement, posterior decompression with distractors, or cranial remodeling. For older and cooperative patients, with or without specific complaints, the evaluation occurred in the outpatient clinic after their regular consultation. In the case of infants, they were monitored under general anesthesia during surgical procedures (as distractors removal) or due to some symptoms related to ICH. In this circumstance, the parents were informed about the importance of undergoing retinography and how the evaluation of the intracranial pressure curve could contribute to the assessment of suspected ICH. The evaluation was conducted after providing explanations and obtaining the parents' consent.

### Non-invasive intracranial pressure wave monitoring (NIICPw) protocol

For the NIICPw registration, the brain4care (B4C) sensor was used. It captured the deformation of the skull caused by arterial blood pressure using an extensometer [22]. The method is painless, but proper acquisition requires patient

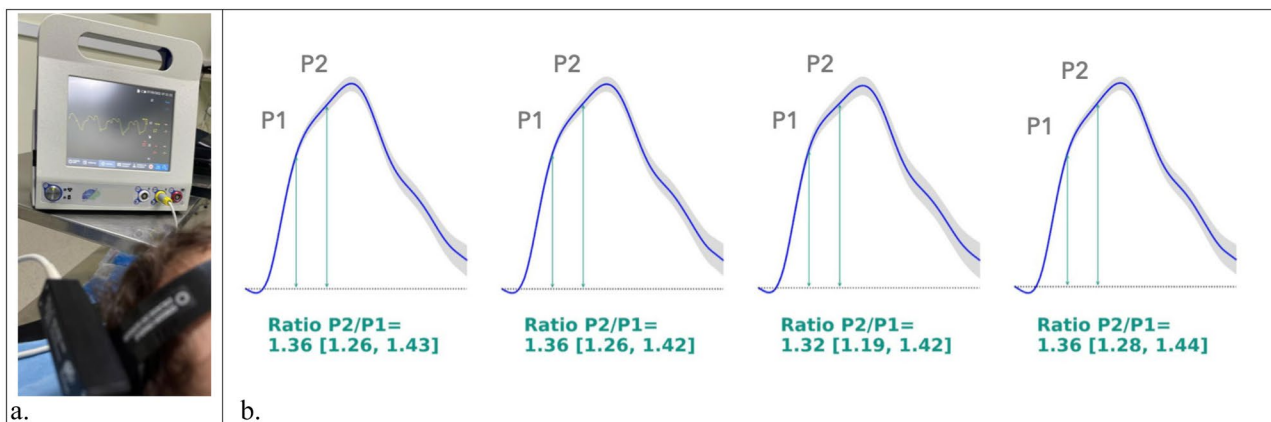
**Fig. 1** Distribution by age and by group



cooperation with minimal movements. As collaboration was not possible in all cases, especially in children under 3 years or patients with behavioral issues, some patients underwent the examination under anesthesia. The NIICPw registration was performed with patients in the supine position and the head of the bed at zero degrees, with the sensor adjusted on the right or left frontotemporal region. The monitoring lasted up to 30 min, and although painless, patients were warned they might feel a slight pressure on the head. The software processed the ICPw captured by the sensor, which provided a report with the NIICPw shape and the P2/P1 ratio (Fig. 2).

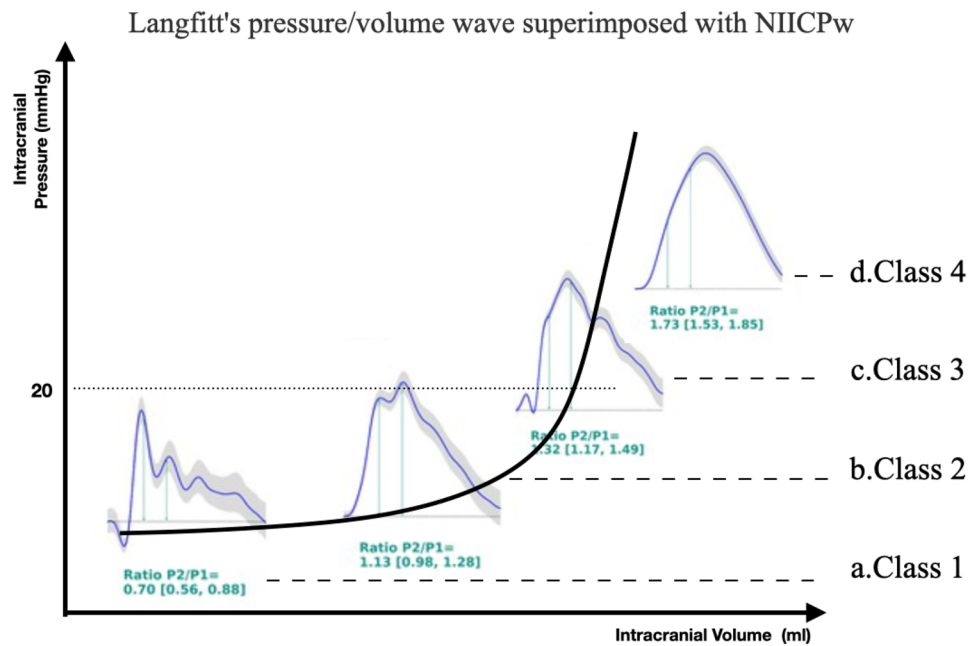
The shape of the ICPw is determined by arterial blood flow within the skull, venous outflow from the head, and cerebrospinal fluid mechanical properties, resulting in a pulse with three characteristic peaks: P1 (percussion

wave), P2 (tidal wave), and P3 (dirotic wave) [19, 29]. A typical curve shows P1 higher than P2 and P3. But in situations that decrease CC, as mentioned earlier, P2 becomes higher than P1, making the P2/P1 index greater than 1. In a previous study that compared the NIICPw with invasive ICP in intensive care patients, there was a correlation of P2/P1 ratio > 1.2 with an ICP value above 20 mmHg [23]. When the CC is low, the shape of the NIICPw changes. The ICP pulse loses its peaks and becomes triangular or rounded according to Nucci's classification [30]: Class 1: normal, Class 2: potentially pathological, Class 3: likely pathological, and Class 4: pathological. We classified the NIICPw obtained according to the P2/P1 ratio and Nucci's classification. So, a P2/P1 ratio > 1.2 or NIICPw class 2, 3, or 4 were signs of low CC related to raised ICP [20, 31, 32] (Fig. 3).



**Fig. 2** a Monitor B4C and NIICPw registration. b NIICPw curve and P2/P1 ratio

**Fig. 3** The correlation between Langfitt volume  $\times$  pressure curve and NIICPw morphological classification. **a.** Class 1: normal, **b.** Class 2: potentially pathological, **c.** Class 3: likely pathological, **d.** Class 4: pathological



## Retinography

Retinography was done to detect optic nerve edema or pallor, defined as any grade of blurring of the optical disk. The examination lasted a few minutes and was performed by an ophthalmologist. The study was documented using a portable fundus camera (PHELCON-EYER®), using the retina mode focused on the optic nerve (Fig. 4). The photos and the ophthalmological report were stored on an eye cloud, including Frisien's classification [33].

## Anesthesia protocol

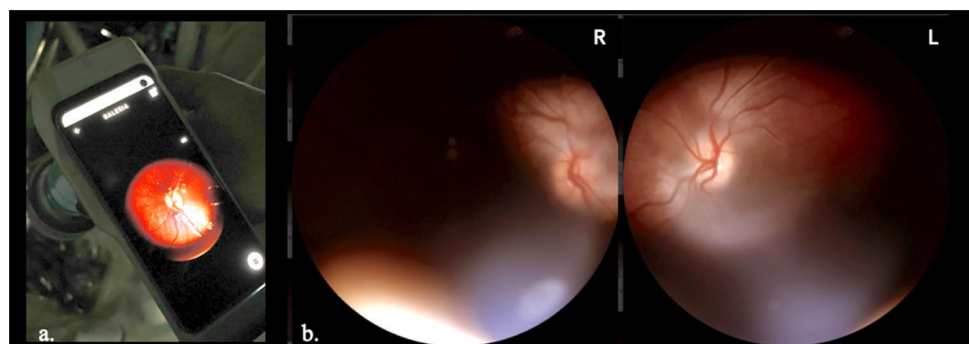
No pre-anesthetic medication was administered before the procedure. The individuals were positioned in the horizontal dorsal decubitus and monitored with electrocardiography (ECG), pulse oximetry, and non-invasive blood pressure measurement. Then a face mask was administered with 40% oxygen, 60% nitrous oxide, and 5% Sevoflurane. Shortly after, an appropriate level of consciousness was

obtained, a peripheral intravenous line was installed, and a laryngeal mask was introduced, maintaining spontaneous ventilation. Sevoflurane was then reduced to 0.9% or 50% minimum alveolar concentration (MAC), nitrous oxide was discontinued, and the diluent mixture of air and oxygen was held at 50%. The Dräger® Vamos® gas analyzer was used for expired gas concentration measurement. The patient remained positioned in the horizontal dorsal decubitus, and the B4C sensor was installed around the patient's head. Only after the Sevoflurane respiratory end-tidal level was less than 0.9% did the B4C monitor start recording the ICPw variation curves for about 25 min. When B4C was on, there was no N<sub>2</sub>O detected at the gas analyzer. All hemodynamics and end-tidal CO<sub>2</sub> ranges were at normal values. The same anesthesiologist did all the cases.

## Statistical analysis

The numerical or ordinal, demographic, and clinical data were descriptively analyzed. The Fisher exact test assessed

**Fig. 4** **a** Point-of-care retinography. **b** Fundoscopy with papilledema



the correlation between these two variables. A *p*-value less than 0.05 was statistically significant. All analyses were performed in Jamovi software.

### Results

Thirty-five patients were assessed to record their NIICPw and funduscopy findings. There were 19 evaluations in the non-operated group and 23 in the operated group, resulting in 42 evaluations due to seven patients being assessed twice. In the non-operated group, fourteen patients had NIICPw classes 2, 3, or 4. Two patients exhibited papilledema: one with a class 3 waveform and another with a class 4 waveform, both associated with CS syndrome (Fig. 5). In the operated group, no patients had papilledema, but we identified one patient with a class 3 waveform (frontonasal dysplasia plus plagiocephaly) and one patient with a class 4 waveform (Apert syndrome) (Fig. 6). Five patients were evaluated under anesthesia during surgery, and one patient underwent two assessments: one during the cranial advancement procedure and another when the distractor was removed. Twelve patients were evaluated in the outpatient clinic, and five patients required anesthesia for evaluation due to specific complaints, including behavioral changes (Class 2 waveform), speech delay (Class 1, 1, 2, and 2 waveforms), and confirmation of autism in one patient with a Class 1 waveform.

Among the 42 evaluations, two patients presented with papilledema; sixteen had Class 1 NIICPw, fifteen had Class 2, nine had Class 3, and three had Class 4. When applying Fisher’s exact test in all 42 evaluations, a statistically significant association between NIICPw and papilledema was found with a *p*-value of 0.022. The table also shows papilledema in patients with low CC (Classes 3 and 4) (Table 1).

The morphological classification into classes is based on the relationship between the peaks of the ICP curve, particularly an elevated P2, which leads the ICP curve to lose its peaks and become rounded or triangular. In the same way, the elevations of P2 affect the P2/P1 ratio. As cited earlier, a previous study has established a correlation between a P2/P1 ratio above 1.20 and invasive ICP values exceeding 20 mmHg [23]. Therefore, we described each patient’s average P2/P1 ratio and NIICPw class (Table 2).

### Discussion

Given the potential manifestation of raised intracranial pressure (ICP) symptoms in patients with craniosynostosis [1, 3, 34] attributed to altered cranial compliance (CC), as well as the associated risks and limitations of invasive ICP monitoring, we conducted a study to assess ICP using a non-invasive method based on skull oscillations [35, 36] and to correlate the findings with papilledema. This study included 35 patients and 42 evaluations because seven patients were monitored twice. The study included 35 patients, resulting in 42

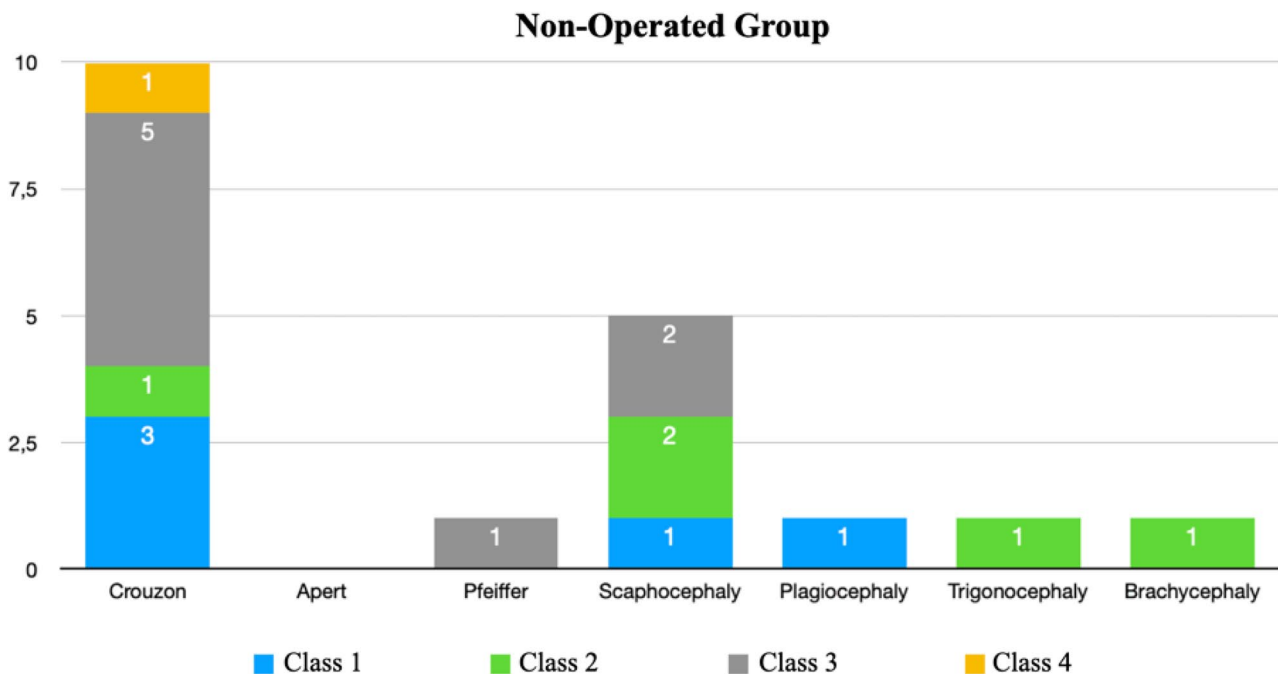
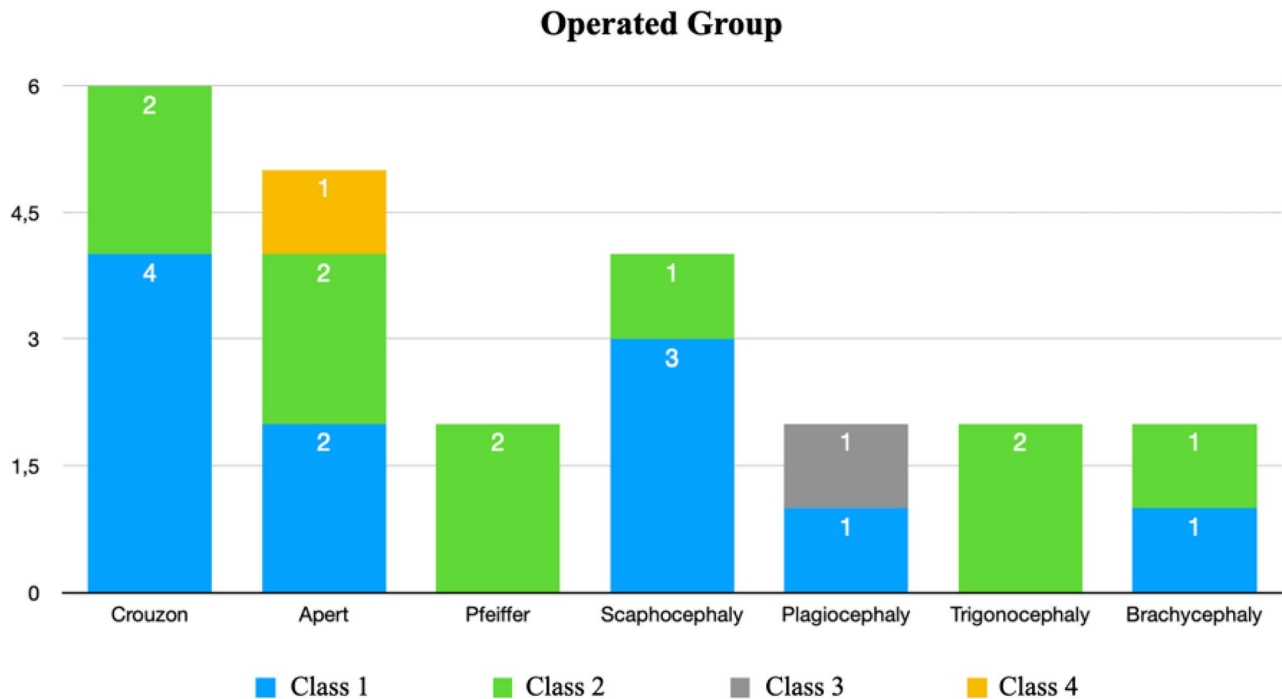


Fig. 5 Distribution of NIICPw classes by diagnosis in the non-operated group (19 evaluations)



**Fig. 6** Distribution of NIICPw classes by diagnosis in the operated group (23 evaluations)

evaluations due to repeat monitoring in seven patients. Two parameters were employed to evaluate ICP changes: morphological analysis of the ICP waveform using Nucci’s classification [30] and the P2/P1 ratio [37, 38]. Even though these parameters do not directly provide ICP values, they offer insights into CC, which is typically reduced in patients with intracranial hypertension (ICH), specifically with Class 3 or 4 curves, along with a P2/P1 ratio above 1.2. Papilledema, assessed through retinography by an ophthalmologist, also demonstrated increased ICP and was conducted as part of the routine assessment for all patients with craniosynostosis.

Among the 42 patients, two presented with papilledema, sixteen had Class 1 NIICPw, fifteen had Class 2, nine had

Class 3, and two had Class 4. Fisher’s exact test revealed a statistically significant association between papilledema and increasing NIICPw class. Although only two patients presented with papilledema, out of the 42 evaluations conducted, we observed that eleven patients had Class 3 and 4 waveforms, and thirteen exhibited a P2/P1 ratio above 1.2 (two had Class 2 NIICPw). A previous study correlated a P2/P1 ratio > 1.2 with invasive ICP above 20 mmHg in intensive care patients [37]. However, even when ICP values are still normal, P2/P1 ratio is higher than 1.0, and Class 3 or 4 waves are potentially threatening [31, 39]. Class 4 waveforms were related to the increased mortality rate in patients with head trauma with normal ICP [40]. We noticed 11 evaluations with waveforms classified as 3 or 4, and 10 evaluations showed a P2/P1 index above 1.2. Seven of these patients underwent primary surgery, while one with Apert syndrome had previously undergone cranial decompression. This patient had a Class 4 curve (and P2/P2 ratio of 1.3) at the time of monobloc advancement, and when he returned to remove the internal distractor, the curve was Class 2 and P2/P1 ratio of 1.18. One adult patient chose not to have surgery, one lost follow-up during the study period, and another was already scheduling surgery at the time of study closure.

Monitoring ICP in patients with craniosynostosis is crucial for evaluating its effects and determining appropriate treatment approaches. Even though decompressive surgeries or cranial advancements in patients with craniosynostosis do not directly impact intracranial components, an

**Table 1** Correlation between classes and papilledema considering all 42 evaluations

| Class               | Papilledema  |          | N  |
|---------------------|--------------|----------|----|
|                     | With         | Without  |    |
| I                   | 0            | 16       | 16 |
| II                  | 0            | 15       | 15 |
| III                 | 1            | 8        | 9  |
| IV                  | 1            | 1        | 2  |
| Total               | 2            | 40       | 42 |
| $\chi^2$ tests      | <b>Value</b> | <b>p</b> |    |
| Fisher’s exact test |              | 0.022    |    |
| N                   | 42           |          |    |

**Table 2** The NIICPw morphology and P2/P1 ratio

| P2/P1 ratio |     |  |             |   |       |  |
|-------------|-----|--|-------------|---|-------|--|
| Class       | ≤ 1 |  | > 1.0 ≤ 1.2 |   | > 1.2 |  |
|             | N   | Ratio  | N           | Ratio   | N     | Ratio  |
| 1           | 15  | 0.59/ 0.71/ 0.76/ 0.63/ 0.77/ 0.78/ 0.83/ 0.83/<br>0.84/ 0.87/ 0.9/ 0.95/ 0.96/ 0.97/ 0.98 | 1           | 1.15  | 0     |  |
| 2           | 3   | 0.86/ 0.95/ 0.98   | 9           | 1.01/ 1.01/ 1.02/ 1.07/ 1.12/<br>1.14/ 1.15/ 1.18/ 1.18 | 3     | 1.21/ 1.22/ 1.27                                   |
| 3           | 0   |  | 1           | 1.16  | 8     | 1.24/ 1.28/ 1.29/ 1.3/<br>1.34/ 1.37/ 1.38/<br>1.5 |
| 4           | 0   |  | 0           |   | 2     | 1.3/ 1.68  |
| Total       | 18  |  | 11          |   | 13    |  |

increase in ICV reduces CC, compensating for the effects of ICH. This underscores the importance of monitoring signs of decreased CC in patients with craniosynostosis not just before the surgical procedures but also after the surgeries when the bones are fused. In the operated group of patients, 10 had class 2, two had class 3 or 4 NIICPw, and none had papilledema. This data highlights the need to repeatedly monitor signs of low CC in patients with craniosynostosis, which is unreasonable using invasive IPC monitoring. NIICPw technology provides a non-invasive way to obtain information about CC in patients with craniosynostosis, analyzing the P2/P1 ratio and ICPw waveform [30, 32, 38]. The primary result demonstrated a significant correlation between NIICPw and papilledema, suggesting that this novel device may be valuable in patients with craniosynostosis. Limitations of the study include a small sample size, a wide age range, and the need for longitudinal follow-up. It is necessary to mention that despite the sensor being non-invasive, the lack of cooperation required monitoring under general anesthesia, which introduces a new variable in the data analysis, which is also a limitation of the study. Since this new technology has no prior studies in patients with craniosynostosis, further studies are warranted.

**Author contributions** Michele Brandao is the lead researcher and this study is part of her doctoral degree. She evaluated all patients. Cristiano Tonello is the craniofacial surgeon who operated on the patients. Aldo Igr is the co-advisor of this research. Isabella Parizotto is the ophthalmologist who performed retinography on all patients and provided the optic nerve classification. Luciano Brandao is the anesthesiologist who administered anesthesia to the patients in this study and developed the anesthesia protocol. Nivaldo Alonso is the senior professor, department chair, and the study's advisor.

## Declarations

**Conflict of interest** The authors have no competing interests to declare relevant to this article's content.

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