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ORIGINAL RESEARCH

# Comparison of Noninvasive Measurements of Intracranial with Tap Test Results in Patients with Idiopathic Normal Pressure Hydrocephalus

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**Background:** Normal pressure hydrocephalus is a disease directly related to the change in intracranial compliance and consequent repercussions in the brain parenchyma. Invasive monitoring of such parameters proves to be reliable especially for prognosis in neurocritical patients; however, it is not applicable in an outpatient service setting. The present study describes the comparison between the tap test results and the parameters obtained with a non-invasive sensor for monitoring intracranial compliance in patients with suspected NPH.

**Methods:** Twenty-eight patients were evaluated before and after lumbar puncture of 50mL of CSF (the tap test), comprising clinical assessment, magnetic resonance imaging, physical therapy assessment using the Timed Up and Go test, Dynamic Gait Index, BERG test, neuropsychological assessment, and recording of non-invasive intracranial compliance data using the Brain4care® device in three different positions (lying, sitting, and standing) for 5 min each. The tap test results were compared to the Time to Peak and P2/P1 ratio parameters obtained by the device.

**Results:** The group that had a positive Tap test result presented a median P2/P1 ratio greater than 1.0, suggesting a change in intracranial compliance. In addition, there was also a significant difference between patients with positive, negative, and inconclusive results, especially in the lying position.

**Conclusion:** A non-invasive intracranial compliance device when used with the patient lying down and standing up obtained parameters that suggest correspondence with the result of the tap test.

**Keywords:** normal pressure hydrocephalus, intracranial pressure, biomedical technology, cerebrospinal fluid pressure

## Introduction

Normal pressure hydrocephalus (NPH) is a clinical condition characterized by ventriculomegaly associated with gait changes, cognitive disturbances, and urinary incontinence. The disease was first described by Salomon Hakim in 1964 and can be classified as to its etiology as idiopathic or secondary, which can have no identified cause, or can be secondary to a previous factor causing the disorders, such as meningitis, head trauma, or subarachnoid hemorrhage.[1–6]

NPH is diagnosed by characteristic clinical signs (gait disorders, urinary incontinence, and dementia), neuroimaging exams (magnetic resonance imaging [MRI], computed tomography [CT]), functional cerebrospinal fluid (CSF) tests—such as tap test and normal initial CSF manometry.[7–9]

The disease can be classified as possible, probable, and definite NPH. This classification even considers the response to fluid shunt procedure and ventriculoperitoneal shunt (VPS) surgery besides the classic triad symptoms, imaging exams, manometry, disease history, and tap test results.[10–17]

Many theories have been proposed for the pathophysiology of NPH. The main ones refer to disturbances in cerebral hydrodynamics, where there is an imbalance between secretion and reabsorption of CSF, there are also



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changes in the brain parenchyma caused by decreased cerebral and venous compliance, resulting in metabolic changes, neuroinflammation, gliosis, and impairment of the blood–brain barrier and glymphatic system.[18,19]

Studies evaluating intracranial pressure in NPH are rare, but useful for determining diagnosis and indications for VPS placement, especially if baseline CSF pressure, CSF pulse pressure waves, and B-wave frequency are increased. Interventional studies suggest increased amplitude and decreased latency after VPS placement in responding patients, so the correlation between amplitude and pressure is high.[13,20,21]

Despite being greatly important in clinical evaluation, intracranial compliance (ICC), intracranial pressure (ICP), and central perfusion pressure (CPP) are not commonly measured outside the context of neurocritical care or in non-specialized centers. This is due to the need for invasive standard methods for ICP monitoring (intraparenchymal, intraventricular, epidural, and subdural) and their inherent risks for the patient, such as infection, brain tissue injury, hemorrhage, and other vascular complications.[22–24]

The ICP waveform has a tracing similar to the arterial pulse wave, with three characteristic peaks: the percussion wave (P1), the tidal wave (P2), and the dicrotic wave (P3). P1 is the most constant in amplitude and derives from the pulsation of the great cerebral arteries to the choroid plexus, the P2 wave comes from cerebral elastance consisting of the direct reflection of the impact of P1 on the brain and cranium. Wave P3 is separated from P2 by the dicrotic notch, which corresponds to the closure of the cardiac aortic valve during diastole 130–132. In normal PIC situations, the amplitude of these three peaks is related as follows: P1> P2> P3. However, in some pathological conditions, wave morphology changes, especially P2, denoting a decrease in brain tissue compliance and consequently an increase in ICP.[25,26]

Considering that there is evidence suggesting a correlation between altered ICC and NPH, the use of a non-invasive device seems to be interesting in the outpatient service context.

The present study proposed to associate the noninvasive ICC measurement with the tap test by comparing the result with the variables available in the noninvasive device (Figures 1 and 2) and to verify the device's ability to detect true positives and true negatives after being submitted to the tap test. It is known that the tap test has a sensitivity of 58% and a specificity of 75%,[23] so it is suggested that the non-invasive device for measuring intracranial compliance can be a differential in the diagnosis among these patients.

## Objective

Therefore, the objective of this study was to analyze whether the ICC parameters obtained with the Brain4care® (B4C) noninvasive sensor in patients with suspected NPH were reliable compared to tap test results.

**Figure 1** Headband used on patients' heads for the Brain4care non-invasive ICP measuring device.

**Figure 2** Band connected to Brain4care's non-invasive ICP measuring device.

# Method

## Type of Study

This is an observational, prospective, cohort study conducted at the outpatient clinic of a tertiary referral university hospital in the city of São Paulo, Brazil.

## Population

Twenty-eight consecutive patients with a diagnostic hypothesis of NPH and medical indication for a tap test were selected at the outpatient clinic of the HC-FMUSP Brain Hydrodynamics Group of the Psychiatry Institute and invited to participate in the study by signing the informed consent form.

## Inclusion Criteria

- Age >60 years;
- Diagnosis of "possible NPH" (more than one of the classic triad symptoms as gait disturbance, urinary incontinence, cognitive impairment not fully explained by another neurological or non-neurological disorder other than any previous disease that can cause hydrocephalus including subarachnoid hemorrhage, meningitis, traumatic brain injury, congenital hydrocephalus, and aqueductal stenosis.) according to the guidelines for management of idiopathic normal pressure hydrocephalus: third edition.[27]
- The following neuroimaging criteria were considered: ventriculomegaly, disproportionate enlargement of the sylvian fissures, deletion of the sulci and subarachnoid spaces in high convexity and focally dilated sulci without adjacent atrophy, ventricular dilatation disproportionate to the degree of cerebral atrophy (Evans index >0.3), associated with rounding of the frontal horns; diffuse periventricular hypersignal on T2 and FLAIR; elevation of the corpus callosum, with an angle of the corpus callosum between 40 and 90 degrees (measurable in the coronal plane, at the level of the posterior commissure) and dilatation of the temporal horns not explained by hippocampal atrophy.

## Exclusion Criteria

- Contraindication for lumbar puncture and/or tap test;
- Absence of an imaging exam of the brain (MRI or CT);
- Malignancy;
- Visual and/or hearing deficits;
- Acute or chronic-degenerative diseases in advanced stage and/or associated problems in the acute stage;
- Motor disease or sequelae making testing impossible;
- Previous craniotomy and/or craniectomy.

## Evaluation

The research was conducted for 24 months and evaluated a group of 28 consecutive patients using the ICC noninvasive measurement device for 5 min in the following positions: dorsal decubitus, sitting with back support, and standing.

These tests were associated with all the tests already performed during disease investigation:

- Imaging tests (Magnetic Resonance Image or Computed Tomography);
- Clinical evaluation of gait 7 days before and 3 h after CSF puncture (Timed up and Go, Dynamic Gait Index, Functional Independence Measure, Japanese NPH Scale, and BERG Balance Test)[28–31]
- Neuropsychological evaluation 7 days before and 3 h after CSF puncture (Addenbrooke's Cognitive Examination, Digits, Corsi Cubes, Stroop Color, Hayling Test, Trail Making Test, Part A and B, Rey Auditory Verbal Learning Test, and FAS Phonemic Verbal Fluency Test).[32–38]

The tap test was considered positive when there was a 20% improvement in any of the tests evaluated or an improvement greater than 10% in three or more tests in each patient; inconclusive when there was improvement greater than 10% in less than three tests; and negative when it was not possible to detect any quantitative improvement in the tests.

ICC was noninvasively evaluated using the B4C device, which consists of a mechanical strain gauge fixed to a mechanical device that comes into direct contact with the surface of the scalp in the fronto-parietal-temporal region of the skull. This device can detect small skull oscillations due to ICC changes without invasive or surgical procedures.[39,40] The strain gauge is attached to a band that adjusts to the subject's head circumference and is wired to a monitor that shows the patient's ICP curve pattern and is manually adjusted using a zoom, which helps verify if the device is properly attached. The B4C device is FDA cleared (#K182073) and ANVISA (Brazil - #81157910002) cleared. It showed sensitivity of 80% and specificity of 100% with an accuracy of 98.21% for predicting episodes of increased ICP in previous hydrocephalus study.[40]

The band was placed around the head so that the mechanical device that measures skull oscillations was positioned above the left ear of all patients.

The patients underwent ICC recording with B4C before and after a lumbar puncture in the dorsal decubitus, sitting with back support, and standing positions for 5 min in each.

After the recording, the data were transmitted to the device's platform (www.analyticsbraincare.com), where it was analyzed by its own algorithm.

The parameters evaluated were the P2/P1 ratio and Time To Peak (TTP). The ICP pulse is formed by three subcomponents: P1, cardiac systole; P2, tidal wave—the form intracranial fluids are distributed; and P3, cardiac diastole. The normal arrangement of these subcomponents is P1>P2>P3. Changed arrangements represent a reduced ICC.[40,41] The P2/P1 ratio corresponds to the division of the P2 amplitude by P1 amplitude and quantifies an increased P2 component in relation to P1. In this case, a ratio greater than 1.0 indicates ICC changes. TTP refers to the time taken by the ICC curve to reach the highest peak, so that a shorter time indicates a higher probability of an ICC curve with normal morphology.

## Statistical Analysis

Bootstrap[42] is a resampling technique widely used in statistics. The technique allows calculating various accuracy measures such as bias, variance, and confidence intervals of sample estimates. In addition, it also allows one to calculate the sampling distribution of most statistics. Informally, the technique produces different samples from the original sample with replacement and calculates the statistic of interest.

The Wilcoxon test[43] (Wilcoxon, 1992) (or Wilcoxon-Mann-Whitney test or Wilcoxon rank sum test) is used when we want to compare two independent samples (or two groups). More generally, the test checks whether both groups have the same location. The test assumptions are as follows: 1. Dependent variable is measured on an ordinal scale (Likert scale) or continuous scale (weight, age); 2. Independent variable has only two levels (man and woman or before and after); 3. Independence of observations within each group and between groups; 4. Both samples have the same distribution. The first three assumptions, in general, can be justified by the design of the experiment itself. However, the last assumption

can be violated. That is, we are assuming that the behavior of the dependent variable (P2/P1 and TTP in this case) is the same for both groups. Therefore, it can be said that the hypotheses are as follows: H0: the median of the two groups is the same vs H1: the median of the two groups is different. If this assumption is violated, the test is used to compare the distribution of the two groups.

# Results

## Population

The study included 28 consecutive patients (20 men and eight women) with a mean age of 72 years. Of the 28 tap tests performed, eighteen were considered positive, seven negative, and three inconclusive (Table 1).

A comparative analysis was made between the moment before and after the CSF puncture separating the subjects by position and tap test result.

## Inconclusive Tap Test (P2/P1 Ratio)

Table 2 shows the result of descriptive statistics of the groups and Table 3 shows the statistical analysis of the P2/P1 ratios for patients with inconclusive TT. Figure 3 shows a trend towards equality of position in the sitting position, while

**Table 1** Clinical Background of Patients

| | | Positive (n=18) | Negative (n=07) | Inconclusive (n=03) |
|---|---|---|---|---|
| **Age (Mean±SD)** | | 73,2 ± 6,8 | 75,7 ± 6,7 | 70,7± 1,2 |
| **Gender female** | | 4 | 3 | 1 |
| **Gender Male** | | 14 | 4 | 2 |
| **Duration of symptoms (Months)** | | 18,3±3,1 | 22,1±4,2 | 19,3±3,3 |
| **FIM (mean score)** | | 85,7±29,5 | 54,1±37,4 | 63±34,4 |
| **iNPH Grading Scales, Mean / SD scores** | | | | |
| **TUG (sec)** | **Pre-tt** | 34,8±38,3 | 50±69,2 | 91,3±129,9 |
| | **Post-tt** | 29,2±28 | 45±33,2 | 140±242,5 |
| **DGI** | **Pre-tt** | 7,7±7,5 | 2,2±5,2 | 0±0 |
| | **Post-tt** | 8,2±7,9 | 2,5±7,6 | 0±0 |
| **BBT** | **Pre-tt** | 30±17,7 | 16,1±15,9 | 3,7±0 |
| | **Post-tt** | 34±17,8 | 19,2±19,5 | 0±0 |
| **JNS** | **Pre-tt** | 6,2±3,7 | 6,2±4,5 | 8,7±2,3 |
| | **Post-tt** | 4,7±3,8 | 4,7±4,9 | 5,7±5,5 |

**Abbreviations**: FIM, Functional Independence measure; TUG, Timed up and Go; DGI, Dynamic Gait Index; BBT, Berg Balance Test; JNS, Japanese NPH Scale; tt, tap test.

**Table 2** P-value of the Variable P2/P1 in the Inconclusive Tap Test in Each Position

| Group | P-value for the Wilcoxon Test |
|---|---|
| **Dorsal decubitus** | 0.124 |
| **Standing** | < 0.001 |
| **Sitting** | < 0.001 |

**Table 3** Statistics of the Variable P2/P1 in the Inconclusive Tap Test for Each Moment According to Position

| Inconclusive Tap Test | Position | | | | | |
|---|---|---|---|---|---|---|
| | Dorsal Decubitus | | Standing | | Sitting | |
| **Moment** | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** |
| **Average** | 1.131 [1.087; 1.175] | 1.116 [1.018; 1.228] | 0.965 [0.922; 1.002] | 1.587 [1.527; 1.650] | 1.145 [1.120; 1.171] | 1.608 [1.586; 1.633] |
| **Median** | 1.069 [1.043; 1.108] | 0.943 [0.910; 1.148] | 0.933 [0.899; 1.011] | 1.560 [1.536; 1.619] | 1.127 [1.105; 1.159] | 1.606 [1.572; 1.635] |
| **Standard Deviation** | 0.230 [0.191; 0.265] | 0.313 [0.221; 0.386] | 0.179 [0.130; 0.237] | 0.140 [0.068; 0.200] | 0.143 [0.114; 0.169] | 0.065 [0.050; 0.077] |
| **n** | 100 | 33 | 73 | 21 | 125 | 30 |

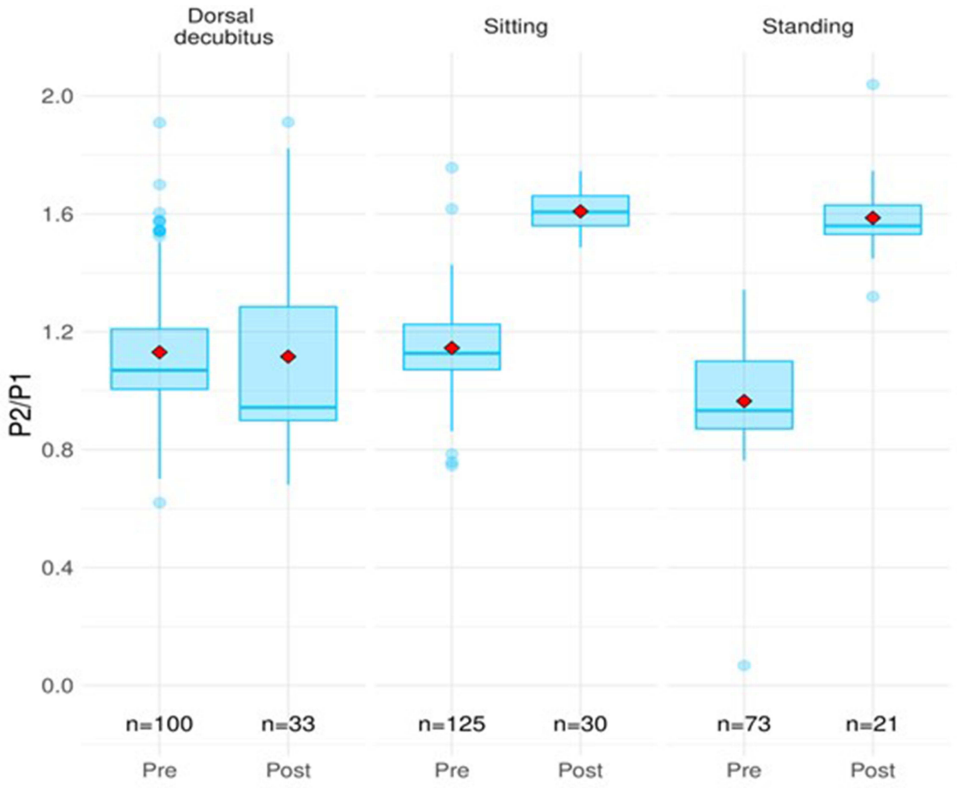


**Figure 3** Comparison of the P2/P1 variable in relation to the inconclusive tap test before and after the puncture.

in the other two positions the groups show different positions. Table 3 confirms the trend shown in Figure 3, where patients sitting (p=<0.001) and standing (p=<0.001) show differences before and after lumbar tapping for this variable.

## Inconclusive Tap Test (TTP)

The same analyses were performed as for the previous variable (Figure 4), and the result proved to be different because in this analysis, the lying down group also showed a difference between the pre- and post-puncture moments in the TTs considered inconclusive (Table 4 and Table 5).

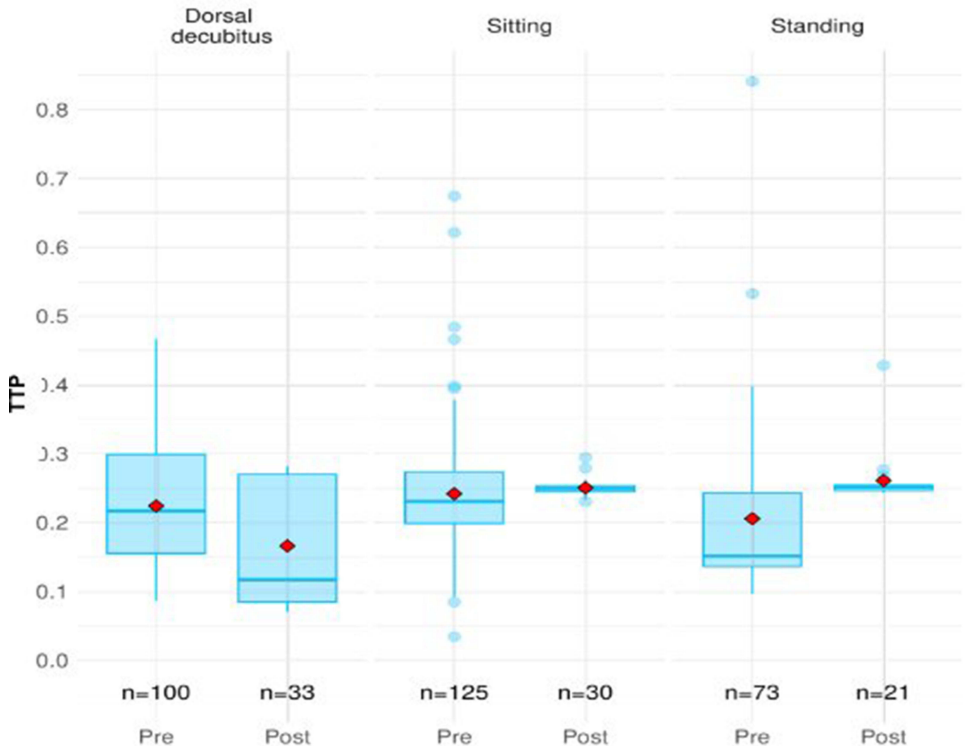


**Figure 4** Comparison of the TTP variable in relation to the inconclusive tap test before and after the puncture.

**Table 4** P-value of the TTP Variable in the Inconclusive Tap Test in Each Position

| Group | P-value for the Wilcoxon Test |
|---|---|
| **Dorsal decubitus** | < 0.001 |
| **Standing** | < 0.001 |
| **Sitting** | 0.014 |

**Table 5** Statistics of the TTP Variable in the Inconclusive Tap Test for Each Moment According to Position

| Inconclusive Tap Test | Position | | | | | |
|---|---|---|---|---|---|---|
| | Dorsal Decubitus | | Standing | | Sitting | |
| **Moment** | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** |
| **Average** | 0.224 [0.209; 0.240] | 0.166 [0.140; 0.197] | 0.206 [0.183; 0.233] | 0.261 [0.250; 0.280] | 0.242 [0.228; 0.258] | 0.251 [0.247; 0.256] |
| **Median** | 0.217 [0.170; 0.243] | 0.117 [0.087; 0.264] | 0.151 [0.141; 0.204] | 0.251 [0.247; 0.254] | 0.231 [0.221; 0.240] | 0.250 [0.247; 0.253] |
| **Standard Deviation** | 0.083 [0.074; 0.092] | 0.088 [0.078; 0.093] | 0.112 [0.068; 0.157] | 0.039 [0.006; 0.069] | 0.084 [0.061; 0.106] | 0.012 [0.006; 0.017] |
| **n** | 100 | 33 | 73 | 21 | 125 | 30 |

## Negative Tap Test (P2/P1)

When comparing the results of the variable P2/P1 (Figure 5) between the groups with patients with tap tests considered negative, there were differences in all positions, where the sitting position showed lower values before the puncture and higher values after, while for the lying down and standing positions, the opposite effect happened (Table 6 and Table 7).

## Negative Tap Test (TTP)

The evaluation of the TTP variable for the group with Tap test considered negative shows the same trend of results as the P2/P1 variable (Figure 6), where the evaluations done in dorsal decubitus and orthostatism have lower values before the puncture with a tendency to increase after the removal of CSF (Table 8 and Table 9).

## Positive Tap Test (P2/P1 Ratio)

In patients with a tap test considered positive, there were differences in the lying down position and in orthostatism, while in the sitting position there was no difference between the pre and post-puncture moment (Figure 7). The P2/P1 variable showed higher values before the puncture, with a tendency to increase after CSF removal in the lying and standing positions (Table 10 and Table 11).

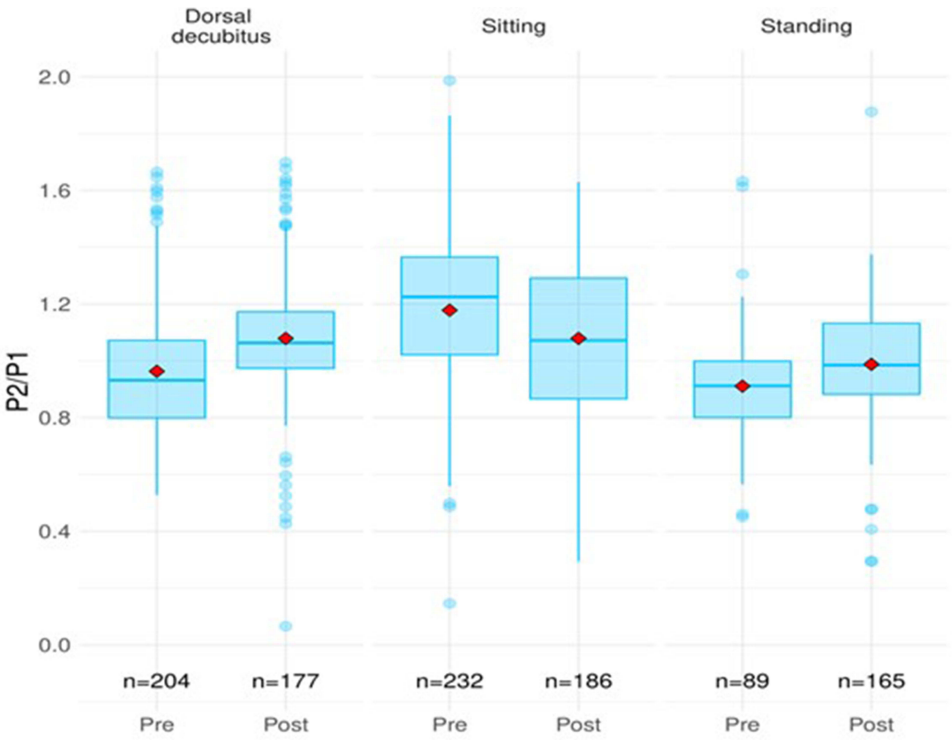


**Figure 5** Comparison of the P2/P1 variable in relation to the negative tap test before and after the puncture.

**Table 6** P-value of the Variable P2/P1 in the Negative Tap Test in Each Position

| Group | P-value for the Wilcoxon Test |
|---|---|
| **Dorsal decubitus** | < 0.001 |
| **Standing** | < 0.001 |
| **Sitting** | < 0.001 |

**Table 7** Statistics of the P2/P1 Variable in the Negative Tap Test for Each Moment According to Position

| Negative Tap Test | Position | | | | | |
|---|---|---|---|---|---|---|
| | Dorsal Decubitus | | Standing | | Sitting | |
| **Moment** | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** |
| **Average** | 0.963 [0.933; 0.998] | 1.079 [1.048; 1.113] | 0.911 [0.872; 0.952] | 0.988 [0.957; 1.021] | 1.178 [1.145; 1.213] | 1.079 [1.038; 1.118] |
| **Median** | 0.932 [0.904; 0.954] | 1.063 [1.045; 1.091] | 0.912 [0.876; 0.942] | 0.985 [0.955; 1.032] | 1.226 [1.160; 1.281] | 1.072 [1.006; 1.127] |
| **Standard Deviation** | 0.237 [0.212; 0.260] | 0.232 [0.195; 0.265] | 0.197 [0.152; 0.238] | 0.207 [0.172; 0.239] | 0.268 [0.242; 0.295] | 0.274 [0.251; 0.296] |
| **n** | 204 | 177 | 89 | 165 | 232 | 186 |

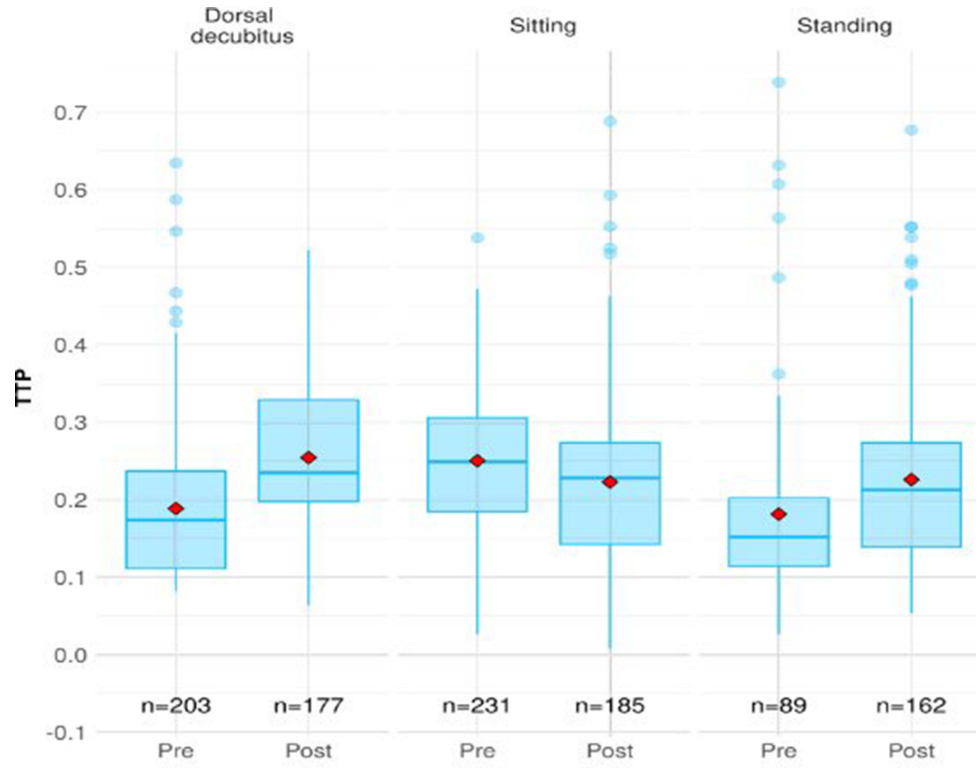


**Figure 6** Comparison of the TTP variable in relation to the negative tap test before and after the puncture.

**Table 8** P-value of the TTP Variable in the Negative Tap Test in Each Position

| Group | P-value for the Wilcoxon Test |
|---|---|
| **Dorsal decubitus** | < 0.001 |
| **Standing** | < 0.001 |
| **Sitting** | < 0.001 |

**Table 9** Statistics of the TTP Variable in the Negative Tap Test for Each Moment According to Position

| Negative Tap Test | Position | | | | | |
|---|---|---|---|---|---|---|
| | Dorsal Decubitus | | Standing | | Sitting | |
| **Moment** | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** |
| **Average** | 0.189 [0.177; 0.201] | 0.255 [0.241; 0.268] | 0.182 [0.158; 0.206] | 0.226 [0.210; 0.244] | 0.251 [0.239; 0.261] | 0.223 [0.210; 0.237] |
| **Median** | 0.174 [0.166; 0.181] | 0.235 [0.225; 0.264] | 0.152 [0.133; 0.164] | 0.213 [0.198; 0.220] | 0.249 [0.234; 0.266] | 0.228 [0.207; 0.246] |
| **Standard Deviation** | 0.091 [0.074; 0.106] | 0.090 [0.080; 0.099] | 0.124 [0.084; 0.160] | 0.110 [0.092; 0.126] | 0.088 [0.080; 0.096] | 0.097 [0.080; 0.113] |
| **n** | 203 | 177 | 89 | 162 | 231 | 185 |

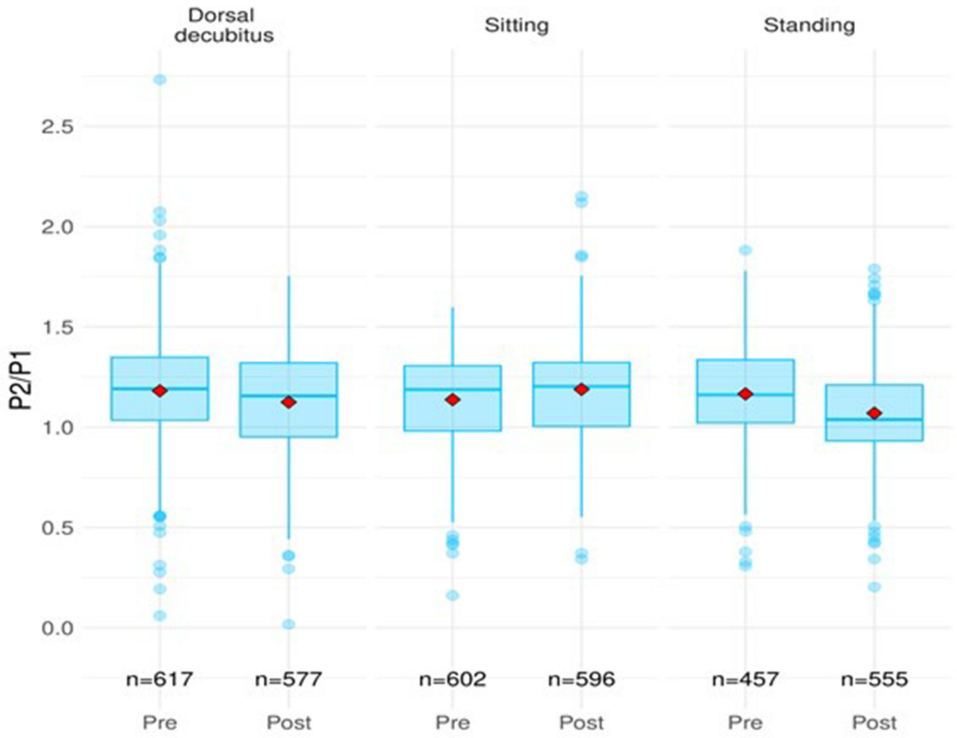


**Figure 7** Comparison of the P2/P1 variable in relation to the positive tap test before and after the puncture.

**Table 10** P-value of the Variable P2/P1 in the Tap Test Positive in Each Position

| Group | P-value for the Wilcoxon Test |
|---|---|
| **Dorsal decubitus** | < 0.001 |
| **Standing** | < 0.001 |
| **Sitting** | 0.008 |

**Table 11** Statistics of the P2/P1 Variable in the Positive Tap Test for Each Moment According to Position

| Positive Tap Test | Position | | | | | |
|---|---|---|---|---|---|---|
| | Dorsal decubitus | | Standing | | Sitting | |
| **Moment** | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** |
| **Average** | 1.181 [1.159; 1.202] | 1.125 [1.106; 1.143] | 1.166 [1.142; 1.190] | 1.070 [1.052; 1.088] | 1.137 [1.119; 1.156] | 1.189 [1.169; 1.207] |
| **Median** | 1.191 [1.178; 1.213] | 1.156 [1.122; 1.184] | 1.161 [1.133; 1.188] | 1.038 [1.022; 1.057] | 1.188 [1.167; 1.209] | 1.204 [1.182; 1.231] |
| **Standard Deviation** | 0.271 [0.247; 0.293] | 0.243 [0.228; 0.259] | 0.249 [0.232; 0.266] | 0.215 [0.200; 0.231] | 0.231 [0.216; 0.244] | 0.231 [0.216; 0.246] |
| **n** | 617 | 577 | 457 | 555 | 602 | 596 |

## Positive Tap Test (TTP)

As in the previous analysis, there were differences between the moments before and after puncture in lying down and standing positions, with higher values before and higher values after CSF removal (Figure 8, Table 12 and Table 13).

# Discussion

Invasive ICP and ICC monitoring is reliable in terms of prognosis, being used in several centers and studies, especially in neurocritical patients, while noninvasive measurements are not yet established in clinical practice, although there are

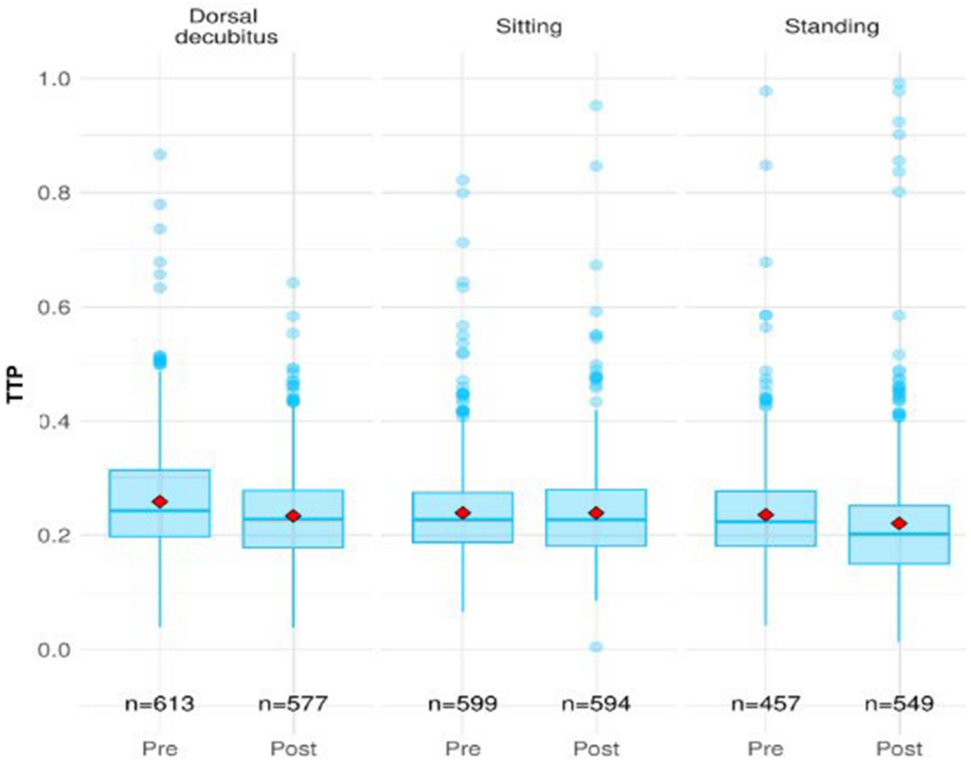


**Figure 8** Comparison of the TTP variable in relation to the positive tap test before and after the puncture.

**Table 12** P-value of the Variable P2/P1 in the PositiveTap Test in Each Position

| Group | P-value for the Wilcoxon Test |
|---|---|
| **Dorsal decubitus** | < 0.001 |
| **Standing** | < 0.001 |
| **Sitting** | 0.968 |

**Table 13** Statistics of the TTP Variable in the Positive Tap Test for Each Moment According to Position

| Positive Tap Test | Position | | | | | |
|---|---|---|---|---|---|---|
| | Dorsal decubitus | | Standing | | Sitting | |
| **Moment** | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** |
| **Average** | 0.259 [0.251; 0.267] | 0.234 [0.227; 0.242] | 0.236 [0.228; 0.245] | 0.221 [0.212; 0. 230] | 0.239 [0.232; 0.247] | 0.239 [0.232; 0.246] |
| **Median** | 0.243 [0.238; 0.250] | 0.228 [0.223; 0.232] | 0.224 [0.217; 0.229] | 0.202 [0.193; 0.210] | 0.228 [0.223; 0.235] | 0.227 [0.222; 0.235] |
| **Standard Deviation** | 0.102 [0.092; 0.112] | 0.088 [0.082; 0.094] | 0.093 [0.077; 0.110] | 0.114 [0.093; 0.134] | 0.089 [0.079; 0.100] | 0.089 [0.077; 0.102] |
| **n** | 613 | 577 | 457 | 549 | 599 | 594 |

indications of correspondence between both methods, as shown by the study by Mase,[44] which measured and demonstrate ICC changes in patients with NPH using MRI.

Some studies suggest that as ICC decreases, intracranial volume variations increasingly correlate with mean ICP changes, so that the intracranial pulse has a direct effect on brain hydrodynamic changes, which in turn lead to a CSF redistribution that may imply pathological changes in the brain parenchyma, such as NPH.[45–48]

Based on this principle, the understanding of intracranial fluids becomes fundamental and, considering ICP measurements within the normal range in this pathology, ICC becomes necessary in the diagnosis of the disease, as shown in the study by Mascarenhas et al[36] which showed small cranial volume variations due to CSF pressure.

NPH is a neurological entity of difficult diagnosis that depends on imaging and clinical tests to be diagnosed. Therefore, the process of NPH identification requires simplification and greater accuracy considering the importance of an early and accurate diagnosis. In this context, the tap test is the most used in clinical practice due to its lower complexity and low cost; however, despite being simple, the test is invasive due to the need for lumbar puncture for CSF collection.[11–16,45,46]

Cerebral vascular compliance refers to the degree of change in the volume of all blood vessels located between the skull base arteries and venous sinuses that result from pressure fluctuations during the cardiac cycle. Several studies have been performed using MRI and invasive measurements of intracranial compliance, and the findings converge on an association between low intracranial compliance and NPH. Thus, the purpose of this study is to determine whether non-invasive measurement of intracranial compliance can produce results similar to current tests used to diagnose Normal Pressure Hydrocephalus.[44,46–49]

A comparative analysis between P2/P1 and TTP, before and after puncture, based on the Tap-test results, indicates that the test results are in line with the variables analyzed by the device. When tests produce inconclusive results, a large heterogeneity in P2/P1 values is observed, possibly influenced by the small number of patients with this result, although it may also indicate the presence of other conditions affecting the response to the test.

When evaluating the comparisons of the variables in patients with negative Tap-test, both the measurements in the sitting position and in orthostatism show an increase of P2/P1 (mean of 0.93 before the puncture) and TTP (mean of 0.18 before the puncture) after the puncture (1.07 and 0.25, respectively), although in the sitting position this relationship is inverted, with larger measurements before the puncture. These results indicate that the variables analyzed tend to approach normality standards in cases without alterations in brain compliance, that is, in cases without NPH. The increased values may be explained by the hyperdrainage caused by the test, while the different pattern in the sitting position may have been influenced by the increased intra-abdominal pressure characteristic of this position, as shown in a study by Bunevicius,[50] who points out the influence of intra-abdominal pressure on increased intracranial pressure.

This data is of great importance, since there is an urgent need to implement a sensor evaluation protocol in order to save time and optimize the evaluation. Considering the age of the population studied, it is possible that the dorsal decubitus position is also less uncomfortable for the patient, facilitating the maintenance of the proper position and thus improving the effectiveness of the test.

When comparing the variables in relation to the Tap test-positive patients, the results were similar. The three moments differed from each other, and in the lying down and standing positions, it was observed that the P2/P1 and TTP data were higher before the puncture and lower after the removal of the cerebrospinal fluid, which corroborates the test results.

The results obtained confirm the thesis that intracranial hypertension is directly related to disturbances in cerebral hydrodynamics and decreased cerebral compliance. Therefore, the Tap test can significantly alter these parameters and, consequently, the compliance curve in patients with intracranial hypertension, either with a trend towards normalization (in the case of a positive Tap test) or worsening of morphology (in the case of a negative or inconclusive Tap test).

It is a consensus in the literature that intracranial hypertension is a multifactorial disease, as evidenced by several studies on its pathophysiology. Altered brain compliance is one of the most common factors in investigations, making the evaluation of this variable very useful for determining therapeutic strategies and evaluating the effects of treatments in many neurological entities, including intracranial hypertension.[20,51–53]

Previous studies conducted by infusion testing have demonstrated a positive correlation between increased pressure transit time (PTP) and better outcomes after ventriculoperitoneal shunting (VPS), as well as the P2/P1 ratio has been indicated as a compensatory reserve signal in patients with decreased pressure volume. Thus, these parameters are considered valuable in the follow-up of patients with NPH.[44,47]

A retrospective study of 39 patients undergoing VPS showed that those with increased amplitude of the intracranial pressure curve respond better to VPS, with a high correlation between amplitude and pressure. Another prospective study of 30 patients undergoing VPS revealed an increase in amplitude and a decrease in pulse pressure latency in patients with NPH, being inversely proportional due to low brain compliance in these patients. These results corroborate the findings of the present study.[54]

The tap-test demonstrates a high specificity of 75% (33–100%), along with a positive predictive value of 92% (73–100%). However, it has a sensitivity of 58% (26–87%) and a negative predictive value of 37% (18–50%), resulting in an accuracy of 62%. On the other hand, DESH has a positive predictive value of 77% and a negative predictive value of 25%. This suggests the possibility of false-negative results in many tests, making them inaccurate in detecting patients with signs and symptoms that mask the diagnosis.[27]

Like the Tap test, DESH also has a high positive predictive value and low negative predictive value, which emphasizes the difficulty of diagnosing patients who do not have the characteristics described in the imaging exam for the diagnosis of NPH.[27]

This limitation in testing may lead to a repeat procedure to try to get a diagnosis, or in some cases, the patient may undergo a surgical procedure even with a negative result.

Noninvasive assessment of intracranial compliance can provide greater accuracy and identify parameters that differentiate patients who are not really candidates for a Ventriculoperitoneal Bypass.

Although the results suggest similarity between the Tap test and the non-invasive evaluation of the intracranial compliance curve, it is important to take into consideration the limitation of the Tap test, which does not have a high negative predictive value.

Therefore, it is still not possible to scientifically determine whether the ICC evaluation is a superior method to the tap-test, but a viable alternative. Moreover, it is important to emphasize that the methodology used evaluated only patients diagnosed with "probable PNH", being necessary a postoperative follow-up to confirm the findings in patients with "definite NPH".

The results obtained in this study provide evidence that changes in brain compliance may be detectable by means of a noninvasive method, allowing the detection of findings that were previously undetectable in outpatient settings. This represents a new perspective and sophistication in the evaluation of possible carriers of the disease, accelerating and facilitating the diagnosis and treatment of these individuals, besides offering less invasiveness, without pain or discomfort to the patient, which enables its use in outpatient settings without the need for CSF puncture.

## Limitations

The present study obtained a lower number of subjects than expected due to the Covid-19 pandemic, which interrupted the research for approximately 18 months as the population studied was one of the groups at risk for the coronavirus. No analysis was performed on a possibly significant difference regarding the clinical context of the patients, since these data serve as parameters for clinical assessment of symptom progression, but would have no relation to the proposed endpoints. Patients were not followed up after VPS surgery. In addition, studies with larger populations are needed to determine the accuracy of the test in order to assist critical decisions such as shunting in patients with an inconclusive tap test.

## Conclusion

We conclude that the parameters evaluated using the non-invasive intracranial compliance measurement device correspond to the results of the touch test, as it was capable of differentiating the results between the positive, negative, and inconclusive groups, in addition to detecting improvement in the intracranial compliance curve after the removal of CSF in patients with a positive touch test. In addition, the results of measurements with the patient in the supine or standing position were more consistent, so that in these positions there is no influence of intra-abdominal pressure that can cause discomfort in the measurement of the ICC. Therefore, there is evidence that this device can be useful in the context of outpatient services as a complementary exam for patients with suspected NPH, but studies with a larger sample are needed, as well as follow-up of patients after VPS.

## Abbreviations

CPP, central perfusion pressure; CT, computed tomography; CSF, cerebrospinal fluid; ICC, intracranial compliance; ICP, intracranial pressure; MRI, magnetic resonance imaging; NPH, normal pressure hydrocephalus; TTP, time to peak; VPS, ventriculoperitoneal shunt.

## Data Sharing Statement

Upon request to corresponding author.

## Ethics Approval and Consent to Participate

This study was approved by the Local Ethics Committee (CAPPESQ-HCFMUSP / protocol CAAE 09309119.5.0000.0068) and was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from each participant or their legal representatives.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

CYH declares personal fees as employee (Research Nurse) from Braincare Desenvolvimento e Inovação Tecnológica S. A., Brazil, during the conduct of the study. GF declares personal fees as employee (Research Director) from Braincare Desenvolvimento e Inovação Tecnológica S.A., Brazil, during the conduct of the study; In addition, GF has a patent US9826934B2 issued, and a patent US9993170B1 issued. LK declares personal fees as employee (Data Analyst) from Braincare Desenvolvimento e Inovação Tecnológica S.A., Brazil, during the conduct of the study. The authors report no other conflicts of interest in this work.

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