Original Article

Evaluation of Different Pharmacological Strategies and Intracranial Compliance in Hypertensive Patients

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Abstract

Background: **Intracranial compliance (IC) refers to the brain's ability to accommodate variations in intracranial volume without substantial increases in pressure. Alterations in compliance are associated with cardiovascular (CV) conditions such as hypertension. Understanding the relationship between blood pressure (BP) control, pharmacological treatment strategies, and IC may aid in managing cerebrovascular risk.**

Objective: **To evaluate the association between IC parameters, BP control, and different antihypertensive therapeutic strategies in patients with systemic arterial hypertension (AH).**

Methods: **This cross-sectional study included 140 hypertensive patients followed in a specialized outpatient clinic between November 2022 and August 2023. Clinical data, CV risk factors, antihypertensive drug classes, central and peripheral BP, and IC parameters obtained using the Brain4Care (B4C) system were collected. Patients were classified into Group A (vasodilators), Group B (non-vasodilators), and Group C (mixed therapy). Continuous variables were presented as mean and standard deviation and compared using Student's t-test. Categorical variables were compared using Pearson's chi-square or Fisher's exact tests. Correlations were assessed using Pearson's correlation coefficient. A significance level of 5% was adopted.**

Results: **A total of 140 patients were included; 77.9% were women, with a mean age of 67.9 ± 11.1 years. All patients were using antihypertensive medication, predominantly combination therapy (62.1%), especially mixed therapy (65%). Uncontrolled peripheral BP was associated with higher P2/P1 values. Among those with P2/P1 > 1.4, 85.7% had uncontrolled BP (p = 0.002). There was no association between type of therapy and changes in IC parameters.**

Conclusion: **In this sample of hypertensive patients followed in a specialized outpatient clinic, no statistically significant differences in IC parameters were observed across the therapeutic groups evaluated. Peripheral BP control was the factor most strongly associated with more favorable IC values. Prospective studies with more balanced groups are needed to confirm these findings.**

Keywords: **Hypertension; Cerebrovascular Circulation; Intracranial Pressure.**

Introduction

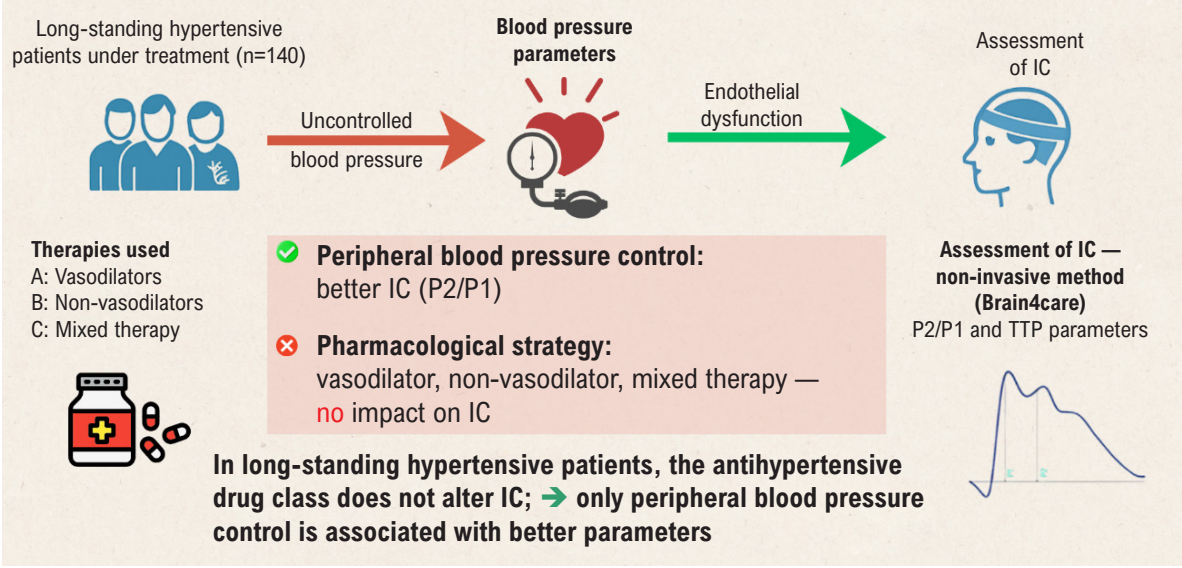
Population aging has been accompanied by a marked increase in the prevalence of cardiovascular (CV) and cerebrovascular diseases.[1] Among these conditions, arterial hypertension (AH) stands out as one of the main risk factors for stroke and cognitive decline, compromising quality of life, increasing disability rates, reducing autonomy, diminishing work capacity, and overburdening public and private healthcare systems.[2-4] In Brazil, the 2013 National Health Survey reported that 32.3% of adults were hypertensive, with prevalence reaching 71.7% among individuals over 70 years of age.[5] Despite this scenario, few studies address blood pressure (BP) control and treatment strategies in the context of cerebral hemodynamics.[6]

Elevated BP can cause endothelial injury, partly due to reduced nitric oxide (NO) bioavailability.[7,8] Endothelin, a potent vasoconstrictor peptide derived from the endothelium, contributes to vascular inflammation and the progression of CV diseases.[9,10] Vasodilator drugs act by stimulating NO release, which antagonizes the effects of endothelin, activates guanylate cyclase in vascular smooth muscle cells, increases cyclic guanosine monophosphate

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Central Illustration: Evaluation of Different Pharmacological Strategies and Intracranial Compliance in Hypertensive Patients



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IC: intracranial compliance

levels, and promotes muscle relaxation. In contrast, non-vasodilator drugs, such as beta-blockers, reduce heart rate and myocardial contractility, decreasing cardiac oxygen demand but without direct vasodilatory action.[11-13]

The relationship between BP parameters and intracranial compliance (IC) remains poorly explored.[14] IC corresponds to the ability of the intracranial system to adapt to variations in brain, blood, and cerebrospinal fluid volumes within the cranial vault.[15,16] In adults, cranial rigidity – after closure of the fontanelles – requires that any increase in one of these components be compensated by a proportional reduction in the others.[17,18] Although the classical Monro-Kellie doctrine considered the cranial vault to be absolutely rigid, recent evidence shows that it can undergo small, measurable deformations in response to changes in intracranial pressure (ICP), reinforcing the role of IC in adapting to oscillations in cerebral blood volume throughout the cardiac cycle.[19] Currently, IC can be assessed using non-invasive methods such as the Brain4Care (B4C) system.[20]

Given that chronic AH may impair endothelial function, alter cerebral hemodynamics, and influence IC, the potential associations between different antihypertensive therapeutic strategies and ICP waveform morphology remain uncertain. Therefore, the present study aimed to evaluate the association between IC parameters, BP control, and different therapeutic strategies in hypertensive patients followed in a specialized outpatient clinic.

Methods

Patient Selection

This cross-sectional study was conducted between November 2022 and August 2023 in a Brazilian public healthcare service specialized in the treatment of AH. The research is part of a cross-sectional analysis approved by the Research Ethics Committee (CAAE: 70448823.1.0000.5078), aimed at evaluating IC through the analysis of ICP waveform morphology obtained non-invasively in hypertensive patients.

Adult individuals with a previous diagnosis of AH undergoing pharmacological treatment were included. Exclusion criteria comprised pregnant or postpartum women, patients with a prior diagnosis of intracranial hypertension (ICH), and those with hydrocephalus.

Data collection was performed on a single day, following this sequence: medical interview, physical examination, and recording of clinical variables. The following data were obtained: age, sex, body mass index (BMI, Kg/m^2), peripheral systolic and diastolic BP (pSBP and pDBP, mmHg), central systolic and diastolic BP (cSBP and cDBP, mmHg), pulse wave velocity (PWV, m/s), augmentation index (AIx) corrected to a heart rate of 75 bpm (%), history of CV risk factors, and presence of previous CV disease, including myocardial infarction (MI), stroke, type 2 diabetes mellitus (T2DM), and dyslipidemia, as well as the number and class of antihypertensive medications in use. Individuals

aged ≥ 65 years were classified as older adults.[21]

On the same day, non-invasive measurement of ICP waveform morphology was performed. Antihypertensive therapy was classified into:

Group A (vasodilators): angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers, and direct vasodilators.

Group B (non-vasodilators): beta-blockers and/or diuretics.

Group C (mixed therapy): combination of drugs from Groups A and B.

All data were recorded and organized using the REDCap (Research Electronic Data Capture) platform.

Assessment of Peripheral and Central BP

Measurements of pSBP, pDBP, cSBP, cDBP, PWV, and AIx were performed using the oscillometric Mobil-O-Graph® device (IEM, Stolberg, Germany), following the methodology recommended by the 2024 Brazilian Guidelines for Blood Pressure Measurement.[22]

PWV measurements were obtained in triplicate, using C1 calibration (diastolic average), and processed with the ARCSolver® algorithm (Austrian Institute of Technology, Vienna, Austria). All assessments were performed on the left arm, with the participant seated, feet flat on the floor, legs uncrossed, and the arm supported at heart level on a table.

Before measurement, individuals rested for 10 minutes and were instructed to avoid alcohol consumption in the 10 hours preceding the exam and to abstain from caffeine, smoking, and physical activity for the 3 hours prior. Three consecutive BP measurements were taken, and the arithmetic mean was used for analysis.

Peripheral BP was classified as uncontrolled when pSBP ≥ 140 mmHg and/or pDBP ≥ 90 mmHg.[23]

ICP assessment

Non-invasive ICP monitoring was performed with patients in the supine position for a total period of seven minutes. For analysis, recordings from the first and last minute were excluded to minimize interference from initial adjustments or final movements.

The brain4care® (B4C) sensor, previously validated,[24,25] was placed on the parietotemporal region of each participant's head (Figure 1). The device detects nanometric deformations of the cranial vault throughout each cardiac cycle, allowing indirect estimation of IC and identification of patterns compatible with elevated ICP.

Invasive monitoring defines ICH as sustained ICP > 20 mmHg for more than five minutes.[26] In the non-invasive B4C method, the P2/P1 ratio corresponds to the relationship between the amplitude of the first peak (P1), associated with pulse pressure transmitted by systolic cerebral blood flow, and the second peak (P2), related to the ability of the intracranial compartment to accommodate increases in ICP. Time to peak (TTP) represents the interval (in seconds) between the beginning of the waveform and the P1 peak. For

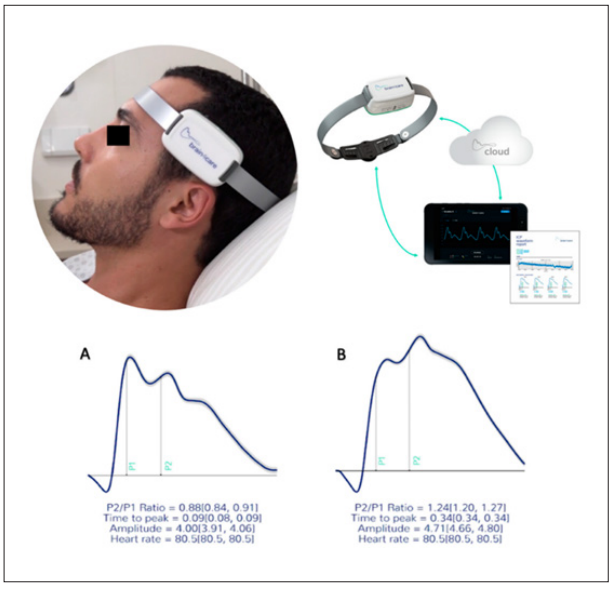


Figure 1 – *Real-time monitoring of ICP waveform morphology. A: normal pattern with P2/P1 and TTP within the physiological range. B: alterations compatible with ICH; source: Moraes et al., 2022*[25]

ICH risk analysis, patients were classified as follows: very low risk: P2/P1 = 0.6-0.8; low risk: P2/P1 = 0.8-1.2; potential risk: P2/P1 = 1.2-1.4; high risk: P2/P1 > 1.4.

In our study, high-risk ICH values were defined as TTP ≥ 0.3 seconds, whereas values < 0.3 seconds were considered low risk.[15,27,28]

Statistical analysis

Data were entered into the REDCap platform and exported to IBM SPSS software (version 26) for analysis.

Independent variables included demographic characteristics (age, sex, BMI), peripheral and central hemodynamic parameters (pSBP, pDBP, cSBP, cDBP, PWV, AIx), CV risk factors (history of MI, stroke, T2DM, and dyslipidemia), and antihypertensive therapeutic strategy (vasodilator, non-vasodilator, or mixed therapy). Dependent variables were the P2/P1 ratio and TTP, obtained from non-invasive ICP monitoring.

Continuous variables were described as mean and standard deviation. Comparisons between independent groups were performed using Student's t-test. Categorical variables were expressed as absolute and relative frequencies and compared using Pearson's chi-square test or Fisher's exact test when appropriate. Correlations between continuous variables were assessed using Pearson's correlation coefficient. A significance level of 5% ($p < 0.05$) was adopted.

Results

A total of 140 hypertensive patients undergoing pharmacological treatment participated in the study (Table 1), with a mean age of 67.9 ± 11.1 years. The mean BMI was 29.3 ± 5.5 kg/m². This study represents a

Table 1 – Characteristics of the sample

Variable	n (%)
Sex	
Female	109 (77.9)
Male	31 (22.1)
BMI	
Normal	30 (21.4)
Overweight	48 (34.3)
Obese	53 (37.9)
Unknown	9 (6.4)
Age range	
Older adults (≥ 65 years old)	92 (65.7)
Non-older adults	48 (34.3)
Diabetes Mellitus	
Yes	71 (50.7)
No	69 (49.3)
Dyslipidemia	
Yes	127 (90.7)
No	13 (9.3)
AMI	
Yes	20 (14.3)
No	120 (85.7)
Stroke	
Yes	17 (12.1)
No	123 (87.9)

BMI: body mass index.

sub-analysis of a larger sample in which patients had been diagnosed with AH for more than 20 years.[29]

The PWV, RVT, and P2/P1 ratio were similar between sexes. Among the variables analyzed, the AIx showed the most robust difference, with women presenting significantly higher values compared with men (Table 2). This finding is consistent with the literature, which demonstrates greater arterial stiffness and a stronger influence of the reflected wave in women, possibly related to anatomical differences (shorter stature and smaller arterial diameter) and hormonal factors.[30]

TTP was slightly higher in women compared with men (Table 2). This finding may indicate subtle changes in IC dynamics, suggesting that the timing of ICP responses may vary according to sex.

There were no differences between men and women regarding the distribution of pharmacological groups used or the number of prescribed medications.

The pharmacological groups A (vasodilators), B (non-vasodilators), and C (mixed therapy) did not differ regarding the presence of high ICH risk based on TTP or low risk (Table 4).

We evaluated whether BP control (peripheral and central) influenced IC assessed by TTP, using Fisher's exact test. There was no difference between patients with controlled or uncontrolled peripheral or central BP. Most individuals had uncontrolled peripheral and central BP in both groups. BP control was not associated with the risk of altered IC according to TTP.

There was no difference between the type of medication and IC assessed by the P2/P1 ratio. Regarding peripheral BP, individuals with controlled values were mostly classified as low risk for ICH. In contrast, among patients with uncontrolled BP, potential-risk and high-risk levels were more frequent. Peripheral BP control was associated with a more favorable IC profile. Central BP levels were not related to ICH risk (Table 5).

In our study population, the type and number of antihypertensive drugs showed no association with BP control, whether peripheral or central.

Discussion

This study evaluated the relationship between different antihypertensive pharmacological strategies, peripheral and central BP control, and IC parameters in long-standing hypertensive patients followed at a Brazilian public health unit specialized in hypertension management. The analysis sought to understand how clinical and therapeutic variables influence cerebral hemodynamics, particularly through the TTP and P2/P1 indices derived from non-invasive ICP monitoring.

Although no statistically significant differences were observed among the therapeutic groups evaluated, this result should be interpreted with caution. The distribution of participants was not homogeneous across treatment groups, with a predominance of patients receiving combination therapy. Additionally, a higher proportion of women and individuals with uncontrolled BP was observed. Therefore, the present study does not allow us to assert equivalence among the different pharmacological strategies, but only that no statistically significant differences were identified in this sample.

Sex-stratified analysis showed that men and women did not differ in ICH risk according to TTP and P2/P1 metrics (Table 3). There were no differences between men and women regarding the pharmacological group used (A, B, or C) or the number of medications prescribed. The pharmacological group and the number of drugs used were not associated with the risk of altered IC, whether assessed by TTP or P2/P1.

There was no association between BP control (peripheral or central) and ICH risk according to TTP. However, peripheral BP control showed a significant association with IC assessed by the P2/P1 metric, such that patients with uncontrolled BP more frequently exhibited potential or high ICH risk (central figure). In contrast, central BP control was not related to changes in IC. These findings reinforce the

Table 2 – Analysis of clinical variables according to mean values and standard deviation

	Sex			
	Male	Female	Total	
BP	Mean (±SD)	Mean (±SD)	Mean (±SD)	P value*
cSBP	117.8 (16.6)	119.7 (16.9)	119.3 (16.8)	0.578
cDBP	83.7 (13.8)	80.4 (11.9)	81.1 (12.3)	0.191
pSBP	126.5 (17.2)	129.7 (17.7)	129.0 (17.6)	0.379
pDBP	82.3 (13.6)	79.0 (11.7)	79.7 (12.2)	0.187
PWV	10.1 (2.0)	9.9 (1.9)	9.9 (1.9)	0.678
AIx	17.2 (11.4)	24.7 (9.1)	23.1 (10.1)	<0.001
Return time	1.4 (0.2)	1.4 (0.2)	1.4 (0.2)	0.531
P2/P1 ratio	1.3 (0.3)	1.4 (0.3)	1.4 (0.3)	0.324
TTP	0.228 (0.047)	0.250 (0.050)	0.245 (0.051)	0.035

cSBP: central systolic blood pressure; cDBP: central diastolic blood pressure; pSBP: peripheral systolic blood pressure; pDBP: peripheral diastolic blood pressure Independent samples Student's t-test; BP: blood pressure; PWV: pulse wave velocity; AIx: augmentation index; TTP: Time to peak.

Table 3 – Distribution of variables related to IC according to sex

	Sex			
	Male	Female	Total	
Variables	n (%)	n (%)	n (%)	p-value*
TTP				0.055**
High risk	1 (3.2)	17 (15.6)	18 (12.9)	
Low risk	30 (96.8)	92 (84.4)	122 (87.1)	
P2/P1				0.197
Very low risk of ICH	---	1 (0.9)	1 (0.7)	
Low risk of ICH	9 (29.0)	24 (22.0)	33 (23.6)	
Potential risk of ICH	13 (41.9)	30 (21.4)	43 (30.7)	
High risk of ICH	9 (29.0)	54 (49.5)	63 (45.0)	

*ICH: intracranial hypertension; TTP: Time to peak. *chi-square test p-value; **Fisher's exact test; high risk (≥ 0.3); low risk (TTP < 0.3); P2/P1: very low risk (P2/P1 = 0.6–0.8); low risk (P2/P1 = 0.8–1.2); potential risk (P2/P1 = 1.2–1.4); high risk (P2/P1 > 1.4)*

hypothesis that effective BP control may influence IC and, consequently, ICP dynamics.[29,31]

In an experimental model of renovascular hypertension, early elevation of the P2/P1 ratio was observed, favoring the development of ICH.[32] In the same study, treatment with losartan improved IC, highlighting the role of adequate BP management in preserving intracranial function, especially in the early stages of hypertension.

Similarly, a study[29] evaluating 401 individuals with long-standing hypertension found that 45.6% had P2/P1 > 1.2, indicating potential or high risk of ICH. The authors suggested that loss of cerebral autoregulation and blood–brain barrier dysfunction are plausible explanations for these findings, likely occurring before clinical manifestations of neurodegeneration.

These observations are consistent with those of another study,[33] which demonstrated a progressive reduction in blood-brain barrier (BBB) integrity as BP increases, regardless of the presence of a formal hypertension diagnosis. In addition, it was shown that patients with controlled hypertension exhibited lower BBB permeability, suggesting a protective effect of BP control on cerebral integrity.

The exact mechanism by which hypertension compromises IC is still only partially understood. It is believed that vascular damage resulting from hypertension may reduce cerebral autoregulatory capacity and impair the BBB even in the early stages of the disease.[34] Considering that the population in the present study consisted of

Table 4 – Distribution of variables related to pharmacological treatment and BP control according to TTP

	TTP			
	High risk	Low risk	Total	
	n (%)	n (%)	n (%)	P value
Pharmacological group				0.553*
A	3 (16.7)	31 (25.4)	34 (24.3)	
B	3 (16.7)	12 (9.8)	15 (10.7)	
C	12 (66.7)	79 (64.8)	91 (65.0)	
Number of drugs				0.798*
Monotherapy	5 (27.8)	26 (21.3)	31 (22.1)	
Two to three (combinations)	10 (55.6)	77 (63.1)	87 (62.1)	
Four or more	3 (16.7)	19 (15.6)	22 (15.7)	
Peripheral pressure				
Controlled	4 (22.2)	29 (23.8)	33 (23.6)	0.576**
Uncontrolled	14 (77.8)	93 (76.2)	107 (76.4)	
Central pressure				
Controlled	7 (38.9)	51 (41.8)	58 (41.4)	
Uncontrolled	11 (61.1)	71 (58.2)	82 (58.6)	0.513**

*p-value for the chi-square test; ** p-value for Fisher's exact test; TTP: high risk (≥ 0.3), low risk (TTP < 0.3); group A (vasodilators); group B (non-vasodilators); group C (mixed therapy)*

Table 5 – Distribution of variables related to pharmacological treatment and BP control according to IC (P2/P1) and the risk of ICH

	IC (P2/P1)					
	Very low risk	Low risk	Potential risk	High risk	Total	
	n (%)	n (%)	n (%)	n (%)	n (%)	P value*
Pharmacological group						0.815
A	--	7 (21.2)	13 (30.2)	14 (22.2)	34 (24.3)	
B	--	2 (6.1)	5 (11.6)	8 (12.7)	15 (10.7)	
C	1 (100.0)	24 (72.7)	25 (58.1)	41 (65.1)	91 (65.0)	
Number of drugs						0.692
Monotherapy	--	6 (18.2)	12 (27.9)	13 (20.6)	31 (22.1)	
Two to three (combinations)	1 (100.0)	22 (66.7)	27 (62.8)	37 (58.7)	87 (62.1)	
Four or more	---	5 (15.2)	4 (9.3)	13 (20.6)	22 (15.7)	
Peripheral pressure						0.002
Controlled	---	16 (48.5)	8 (18.6)	9 (14.3)	33 (23.6)	
Uncontrolled	1 (100.0)	17 (51.5)	35 (81.4)	54 (85.7)	107 (76.4)	
Central pressure						
Controlled	---	18 (54.5)	18 (41.9)	22 (34.9)	58 (41.4)	0.246
Uncontrolled	1 (100.0)		25 (58.1)	41 (65.1)	82 (58.6)	

** p-value for the chi-square test. Group A (vasodilators); Group B (non-vasodilators); Group C (mixed therapy); P2/P1: Very low risk (P2/P1 = 0.6–0.8); Low risk (P2/P1 = 0.8–1.2); Potential risk (P2/P1 = 1.2–1.4); High risk (P2/P1 > 1.4). IC: intracranial compliance*

individuals with long-standing hypertension, it is possible that irreversible structural changes were already established, limiting the potential for reversing IC dysfunction through different pharmacological strategies.

Indeed, our results did not show significant differences in P2/P1 and TTP parameters among patients treated with vasodilator drugs, non-vasodilators, or combination therapies. This absence of differential effects may indicate that, in advanced stages of hypertension, the protective impact of certain antihypertensive classes on cerebral function is reduced. This raises an important question: at what point in the natural history of hypertension do cerebral protective mechanisms begin to fail, and what would be the most appropriate stage to initiate antihypertensive treatment to preserve IC? Longitudinal studies, particularly those involving individuals in the early phases of hypertension, may clarify whether the type of antihypertensive strategy influences the preservation of IC over time.

This study presents limitations that should be considered. In addition to its cross-sectional design, which prevents causal inferences, the non-homogeneous distribution of participants across therapeutic groups, sexes, and BP control strata represents an important limitation. This characteristic may have reduced the statistical power to detect differences among the pharmacological strategies evaluated.

Conclusion

In this sample of hypertensive patients followed in a specialized outpatient clinic, no statistically significant differences were observed in IC parameters among the different therapeutic groups evaluated. Peripheral BP control was associated with more favorable IC parameters. Considering the limitations inherent to the cross-sectional design and the unequal distribution of participants across therapeutic groups, prospective studies with more balanced samples are needed to confirm these findings.

Author Contributions

Conception and design of the research: Costa TO, Vitorino PVO, Sousa ALL, Barroso WKS; acquisition of data: Costa TO, Correia MC, Costa MM; analysis and interpretation of the data: Costa TO, Inuzuka S, Costa MM, Vitorino PVO, Sousa ALL, Barroso WKS; statistical analysis: Vitorino PVO, Sousa ALL, Barroso WKS; obtaining financing: Frigieri G, Barroso WKS; writing of the manuscript: Costa TO, Inuzuka S; critical revision of the manuscript for intellectual content: Costa TO, Inuzuka S, Vitorino PVO.

Potential Conflict of Interest

Gustavo Frigieri is Scientific Director of Brain4care, the company that provided the equipment used for non-invasive intracranial pressure waveform monitoring in this study. The remaining authors declare no conflict of interest relevant to this article.

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Study Association

This article is part of the master's thesis of Thiago Oliveira Costa at the Universidade Federal de Goiás (UFG).

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee of the Universidade Federal de Goiás (CEP/UFG) under the protocol number CAAE 70448823.1.0000.5078. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

During the preparation of this work, the author(s) used ChatGPT (OpenAI) for assistance with language editing, improvement of readability and clarity, and refinement of the scientific writing of the manuscript. The author(s) reviewed and edited the content as necessary and take full responsibility for the content of the published article.

Availability of Research Data

The data supporting the findings of this study are not publicly available due to ethical and privacy considerations involving human participants. De-identified data may be made available by the corresponding author upon reasonable request, subject to applicable ethical and institutional requirements.

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