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Intracranial compliance in patients with COVID-19: a multicenter observational study

Complacência intracraniana em pacientes com COVID-19: um estudo observacional multicêntrico

Ana Flávia Silveira[1] Marcella Barreto Santos[2] Nelci Zanon Collange[2,3] Cintya Yukie Hayashi[4] Gustavo Henrique Frigieri Vilela[5] Samantha Longhi Simões de Almeida[6] João Brainer Clares de Andrade[2,7] Salómon Rojas[8] Fabiano Moulin de Moraes[2] Viviane Cordeiro Veiga[8] Uri Adrian Prync Flato[9] Thiago Luiz Russo[1] Gisele Sampaio Silva[2,10]

[1] Universidade Federal de São Carlos, Departamento de Fisioterapia, São Carlos SP, Brazil.
[2] Universidade Federal de São Paulo, Departamento de Neurologia e Neurocirurgia, São Paulo SP, Brazil.
[3] Centro de Neurocirurgia Pediátrica (CENEPE), São Paulo SP, Brazil.
[4] Universidade de São Paulo, Departamento de Neurologia, São Paulo SP, Brazil.
[5] Braincare Desenvolvimento e Inovação Tecnológica S.A., Departamento Cientifico, São Paulo SP, Brazil.
[6] Hospital Samaritano Higienopolis, Unidades Terapia Intensiva, São Paulo SP, Brazil.
[7] Centro Universitário São Camilo, São Paulo SP, Brazil.
[8] Beneficência Portuguesa Hospital, Divisão da Unidade de Terapia Intensiva Neurológica, São Paulo SP, Brazil.
[9] Hospital Samaritano, Américas Serviços Médicos, Unidade de Terapia Intensiva Geral, São Paulo SP, Brazil.
[10] Hospital Israelita Albert Einstein, Departamento de Neurologia, São Paulo SP, Brazil.

Address for correspondence Gisele Sampaio Silva (email: giselesampaio@hotmail.com).

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Abstract

Background Patients with severe coronavirus disease-19 (COVID-19) may require the use of invasive mechanical ventilation (MV) for prolonged periods. Aggressive MV parameters have been associated with changes in intracranial pressure (ICP) in patients with acute intracranial disorders. Significant ICP elevation could compromise intracranial compliance (ICC) and cerebrovascular hemodynamics (CVH). However, the effects of these parameters in individuals without neurological disorders have not yet been evaluated.

Objective To evaluate ICC in patients on MV with COVID-19 infection compared to other diagnoses, to better characterize the effects of MV and COVID-19 upon ICC. We also compared between the ICC in patients with COVID-19 who did not require MV and healthy volunteers, to assess the isolated effect of COVID-19 upon ICC.

Methods This was an exploratory, observational study with a convenience sample. The ICC was evaluated with a noninvasive ICP monitoring device. The P2/P1 ratio was calculated by dividing the amplitude of these two points, being defined as "abnormal" when P2 > P1. The statistical analysis was performed using a mixed linear model with random effects to compare the P2/P1 ratio in all four groups on the first monitoring day.

Results A convenience sample of 78 subjects (15 MV-COVID-19, 15 MV non-COVID-19, 24 non-MV-COVID-19, and 24 healthy participants) was prospectively enrolled. There was no difference in P2/P1 ratios between MV patients with and without COVID-19, nor between

Keywords
- COVID-19
- Intracranial Pressure
- Hemodynamic Brain Response
- Neurophysiological Monitoring

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non-MV patients with COVID-19 and healthy volunteers. However, the P2/P1 ratio was higher in COVID-19 patients with MV use than in those without it.
Conclusion This exploratory analysis suggests that COVID-19 does not impair ICC.

Resumo

Antecedentes Pacientes com doença grave por coronavírus-19 (COVID-19) podem necessitar do uso de ventilação mecânica (VM) invasiva por um período prolongado. Parâmetros agressivos de VM têm sido associados a alterações na pressão intracraniana (PIC) em pacientes com doenças intracranianas agudas. Elevações significativas da PIC podem comprometer a complacência intracraniana (CIC) e a hemodinâmica cerebrovascular (HVC). No entanto, os efeitos desses parâmetros em indivíduos sem doenças neurológicas ainda não foram sistematicamente avaliados.
Objetivo Avaliar a CIC em pacientes em VM com COVID-19 comparados com outros diagnósticos, para melhor caracterizar os efeitos da VM e COVID-19 sobre a CIC. Também foi feita a comparação entre a CIC em pacientes com COVID-19 sem VM e voluntários saudáveis, para avaliar o efeito isolado da COVID-19 sobre a ICC.
Métodos Trata-se de um estudo exploratório, observacional com amostra por conveniência. A CIC foi avaliada com um dispositivo não invasivo de monitoramento da PIC. A relação P2/P1 foi calculada dividindo-se a amplitude desses dois pontos, sendo definida como "anormal" quando P2 > P1. A análise estatística foi realizada usando um modelo linear misto com efeitos aleatórios para comparar a relação P2/P1 nos quatro grupos no primeiro dia de monitoramento.
Resultados Uma amostra de conveniência com 78 voluntários (15 COVID-19 em VM, 15 sem COVID-19 em VM, 24 com COVID em respiração espontânea e 24 saudáveis) foram prospectivamente incluídos. Não houve diferença nas razões P2/P1 entre pacientes em VM com e sem COVID-19, nem entre pacientes sem VM com COVID-19 ou saudáveis. No entanto, a relação P2/P1 foi maior em pacientes com COVID-19 com uso de VM do que naqueles sem.
Conclusão Os dados dessa análise exploratória sugerem que a COVID-19 não prejudica a CIC.

Palavras-chave
- COVID-19
- Pressão Intracraniana
- Acoplamento Neurovascular
- Monitorização Neurofisiológica

INTRODUCTION

The incidence of neurological symptoms, including headache, dizziness, myalgia, hypogeusia/dysgeusia, and hyposmia/anosmia, in individuals with the coronavirus disease-19 (COVID-19) is substantial, accounting for approximately 36% of reported symptoms.[1,2] However, the pathophysiology underlying the neurological manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection remains incompletely understood.[3–9]

Neuropathological changes resulting from the coronavirus infection are believed to arise from direct virus invasion or molecular alterations, secondary to a systemic inflammatory response. The virus may access the central nervous system through hematogenous or retrograde routes, such as the olfactory nerve.[8–14] Viral ribonucleic acid (RNAs) have been detected in the cerebrospinal fluid and brain tissue during postmortem examinations of selected patients affected by the disease.[15]

These neuropathological changes can lead to alterations in vascular permeability, a crucial factor in maintaining the integrity of the blood–brain barrier, regulating gas exchange, and governing cerebral blood flow (CBF). Several factors influence CBF, including arterial pressure, intracranial pressure (ICP), and cerebrovascular resistance. Any factor that affects these determinants can lead to changes in cerebrovascular hemodynamics. Additionally, mechanical ventilation (MV) may induce cardiac overload in patients, as evidenced by increased jugular and central venous pressures, diminished cerebral venous return, and consequent elevation of ICP levels.[16–24]

Even small positive end-expiratory pressure (PEEP) values were associated with increased ICP in patients with brain injury. While the PEEP's impact on ICP varies among patients with different neurological injuries, its overall effect is minor.[23–28] Patients with severe SARS-CoV-2 infection usually require prolonged MV with extreme parameters. Nonetheless, the influence of ventilator settings on ICP and compliance in patients lacking brain injury still needs to be more adequately explored. Multimodal brain monitoring offers a means to assess cerebrovascular hemodynamics (CVH) and evaluate the effect of protective lung ventilation, particularly the arterial partial pressure of carbon dioxide

(PaCO2) and PEEP, on cerebral blood flow (CBF) and intracranial compliance (ICC).[29]

The objective of this study was to evaluate the ICC in patients with COVID-19 infection on MV, compared to patients with other diagnoses, to better characterize its effects. We also compared the ICC in patients with COVID-19 infection not requiring mechanical ventilation and healthy volunteers, to assess the isolated effects of this disease.

METHODS

Study design and setting

This prospective, observational, exploratory, multicenter study was conducted in four tertiary care centers and one university (Federal University of São Carlos) registered on Clinical Trials.gov (registration number 31589920.7.1001.5505). Our study followed the consolidated standards of reporting trials (CONSORT) recommendation for observational studies.[30,31]

Our convenience sample was recruited and followed for 15 days after study inclusion. All patients or legal representatives signed an informed consent form. The present study followed the declaration of Helsinki, and it was approved by the Ethics Committee of the Federal University of São Paulo (UNIFESP) and São Carlos (UFSCar) under the protocols 31589920.7.1001.5505 and 32338920.5.0000.5504, respectively.

Selection of participants

All COVID-19 participants tested positive on the reverse transcription polymerase chain reaction (RT-PCR), and symptoms onset was < 15 days from study inclusion. For MV patients, the time between hospital admission and study inclusion was $\leq$ 72 hours. The MV non-COVID-19 group was composed of patients in MV due to alternative diagnoses. The healthy volunteer group comprised healthy subjects with no acute respiratory symptoms during evaluation. We excluded patients presenting with acute central nervous system disorders.

Data collection and outcomes

Data obtained from electronic medical records included demographics, anthropometric measurements (weight and height), clinical characteristics, the timing of symptoms, and results of diagnostic tests, including chest imaging and arterial blood gas analysis. Physiological data (heart and respiratory rates, oxygen saturation, and blood pressure) and the utilization of ventilatory support were systematically collected during ICC monitoring. Patients were monitored for 20 to 60 minutes, while healthy controls were evaluated for 90 minutes in a room with appropriate climatization and temperature after 15 minutes of rest.

A certified evaluator applied the modified Rankin scale (mRS) on day 15 of the study participation, either in person or by telephone, to discharge patients. A poor outcome was defined as mRS > 2. A missed outcome was the impossibility of contacting the patient after discharge.

Intracranial compliance measurements

We evaluated ICC with a noninvasive ICP waveform monitoring device developed by Brain4Care Inc. (Johns Creek, GA, USA). The Braincare sensor was placed on the patient's scalp without shaving, surgical incision, or drilling, as previously described by Moraes et al.[32] (►**Figure 1A**). Minimal changes in the skull caused by changes in ICC were captured by the sensor and provided the ICP waveform, as a proxy.[32–34]

Each cardiac beat generated an ICP waveform with three peaks: P1, associated with systolic arterial pressure transferred from the choroid plexus to the cerebrospinal fluid; P2, associated with the reflection (rebound) of the blood pressure wave in the brain tissue; and P3, related to the closure of the aortic valve. These waveforms closely resembled those obtained through invasive ICP measurements, and the relationship between their components provided insights into the ICC (►**Figure 1B**).[32–34]

The B4C (Brain4Care Inc.) analytics system validated all sensor-collected data, including the P2/P1 ratio, a parameter indicating the morphology of the ICP pulse wave. The software automatically determined P1 and P2, which were visually confirmed by inspecting the waveforms. The amplitudes of the peaks were measured by subtracting the baseline value of the ICP waveform. The P2/P1 ratio was calculated by dividing the amplitude at these two-time points. The mean pulse and its corresponding 95% confidence interval (CI) were computed using all valid alignment pulses through a nonparametric

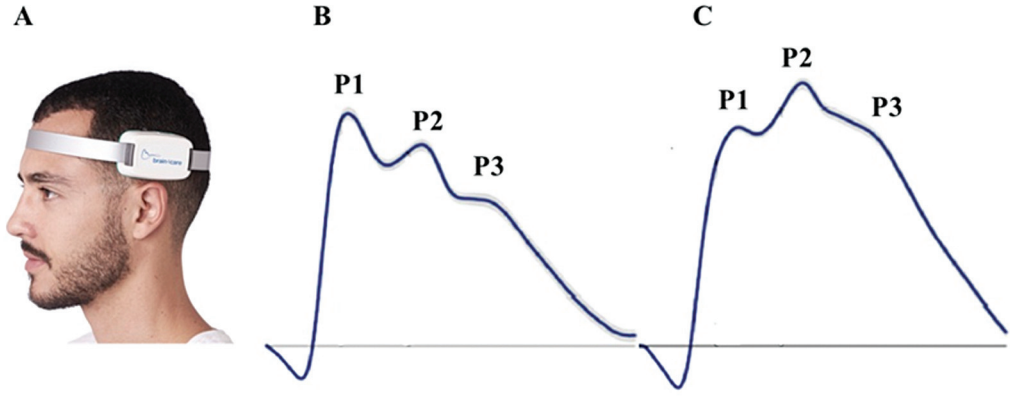

Figure 1 The Brain4Care device in use.

bootstrap procedure with 1,000 replications. When P2 > P1, the ICC was categorized as "abnormal" (►**Figure 1C**). The minute-by-minute analysis compared the defined indices with previously reported values.[34]

Statistical analysis

Qualitative variables were summarized in absolute (n) and relative (%) frequencies. Continuous variable distributions were assessed for normality by skewness, kurtosis, and graphical methods. Those with normal distribution were presented as mean and standard deviations and compared with the independent samples Student t-test. Otherwise, they were presented as medians and interquartile ranges and compared with the Mann-Whitney nonparametric test. Categorical variables were analyzed using the Chi-Square test.[35–38]

The P2/P1 ratios were analyzed using a mixed linear model with random effects in four groups: MV patients (COVID-19 and non-COVID-19), nonmechanically ventilated COVID-19 patients, and healthy volunteers.[39–41] The P2/P1 ratio was obtained from the average of all valid pulses each minute; all results outside 0.5 to 1.8 were considered artifactual and excluded.

For all analyses, statistical significance was set at p-value < 0.05. The R (R Foundation for Statistical Computing, Vienna, Austria) software, version 4.0.5, was used for all analyses.

RESULTS

Between June 2020 and September 2021, 192 participants were recruited for this research. However, only 78 participants were included to the final sample, among whom 15 were mechanically ventilated COVID-19 patients (MV-COVID-19), 15 mechanically ventilated participants without COVID-19 (MV non-COVID-19), 24 were nonmechanically ventilated COVID-19 patients (non-MV-COVID-19), and a control group with 24 healthy individuals (►**Figure 2**). In all four groups, the majority were men (60% MV COVID-19, 60% MV non-COVID-19, 67% non-MV-COVID-19, and 67% healthy volunteers) (►**Figure 2**).

Mechanically ventilated patients (COVID and non-COVID) were similar in age, sex, and body mass index (BMI). There was no difference in P2/P1 ratios in mechanically ventilated patients (COVID-19 vs. non-COVID-19), $p = 0.65$ (►**Figure 3**). The MV COVID-19 patients had a higher frequency of systemic arterial hypertension and type II diabetes ($p = 0.03$) (►**Table 1**).

The non-MV patients (both COVID-19 and healthy volunteers) were also similar in age and sex. Non-MV-COVID-19 patients had a higher BMI ($p < 0.01$) and a higher frequency of comorbidities than healthy volunteers (►**Table 2**). There was no difference in P2/P1 ratios in non-MV patients (COVID-19 and healthy volunteers, $p = 0.70$) (►**Figure 3**).

The MV COVID-19 patients were older than non-MV-COVID-19 patients (median age 66 [53–72] vs. 52 [45–65], $p = 0.04$). Other demographic and clinical characteristics were similar between the two groups. The P2/P1 ratio was higher in the MV COVID-19 patients than in the non-MVCOVID-19 (1.13 ± 0.27 vs. 1.07 ± 0.58, $p < 0.01$), as shown in ►**Figure 3**.

At the follow-up, 15 days after study inclusion, 40% of the MV-COVID-19 patients were still on MV, while 75% of the non-MV-COVID-19 patients had been discharged. A poor functional outcome (mRS 3–6) at 15 days was observed in 87% of the MV-COVID-19 and 80% of MV-non-COVID-19

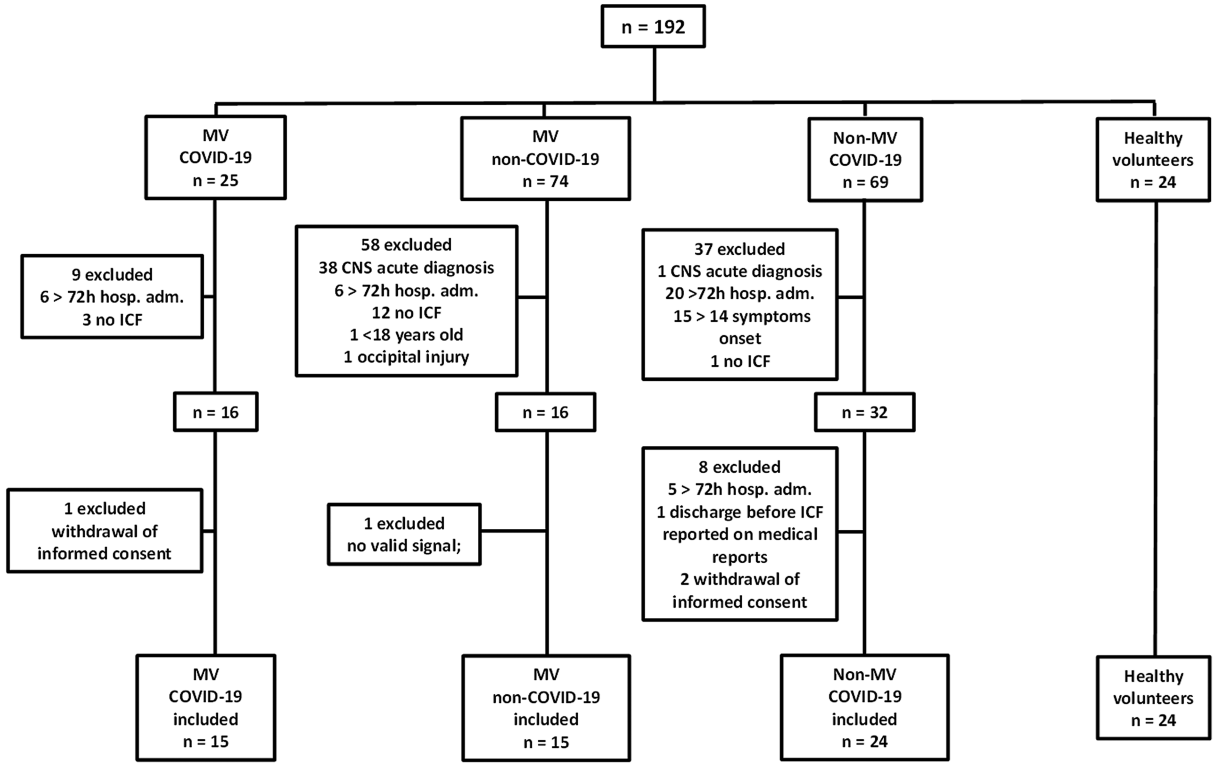

Figure 2 Flow diagram of the study.

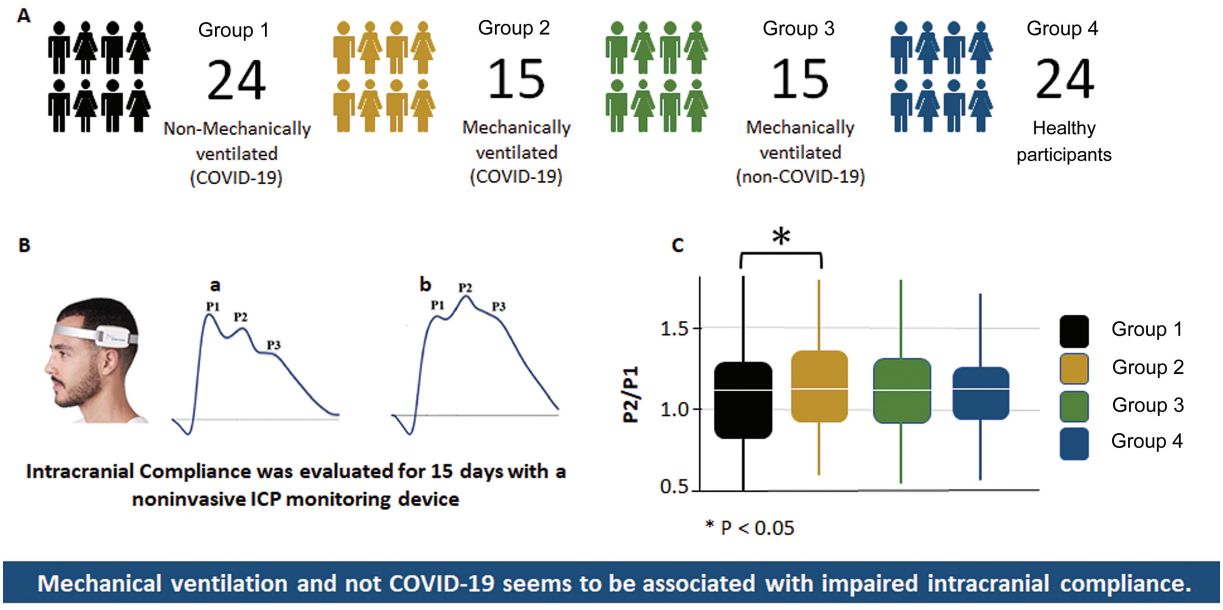

Figure 3 Summary of all research.

Table 1 Mechanical ventilation sample characterization

		MV COVID-19 (n = 15)	MV non-COVID-19 (n = 15)	*p*-value
Male sex (%)		60	60	1.00
Age, years – median (IQR)		66 (53–72)	55 (42-70)	0.22
BMI – median (IQR)		26 (24–28)	25 (23-27)	0.17
Comorbidities (%)	SAH	60	20	0.03*
	DM2	60	20	0.03*
	Current smoker	27	40	0.44
	Obesity	21	0	0.07
	CKD	20	13	0.62
	Other	60	41	0.46

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease-19; CKD, chronic kidney disease; DM2, diabetes mellitus type 2; IQR, interquartile range; MV, mechanical ventilation; SAH, systemic arterial hypertension. Note: *Statistically significant *p*-value.

Table 2 Non-mechanically ventilated participants

		Non-MV COVID-19 (n = 24)	Healthy volunteers (n = 24)	*p*-value
Male sex (%)		67	67	1.00
Age, years – median (IQR)		52 [45-65]	45 [43-55]	0.09
BMI – median (IQR)		31 [27-32]*	24 [22-26]	<0.01*
Comorbidities (%)	SAH	42	0	<0.01*
	DM2	33	0	<0.01*
	Current smoker	17	0	0.04*
	Obesity	54	29	0.07
	CKD	21	0	0.02*
	Other	28	0	<0.01*

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease-19; CKD, chronic kidney disease; DM2, diabetes mellitus type 2; IQR, interquartile range; MV, mechanical ventilation; SAH, systemic arterial hypertension. Note: *Statistically significant *p*-value.

patients. A good functional outcome (mRS 0–2) was observed in 50% of the non-MV COVID-19.

DISCUSSION

Our exploratory study showed no difference in P2/P1 ratios in mechanically ventilated patients (COVID vs. non-COVID). The P2/P1 ratio was higher in MV COVID-19 patients than in non-MVCOVID-19 patients. This finding is suggestive that changes in ICC previously described in COVID-19 patients might have been an effect of MV itself.

There were two studies that evaluated COVID-19 patients under MV within 72 hours of intubation using the B4C and other hemodynamic cerebral parameters.[29,42] Patients who were obese and nonobese were compared, and an ICC/CVH score was altered in obese patients.[42] The authors suggested an association between ICC impairment and obesity, which may have led to unfavorable prognosis in patients with severe COVID-19. In another series, the P2/P1 ratio was abnormal in 66% of subjects, with the P2/P1 ratio between 1.01 and 1.2 in 48%.[29] However, as showed by the authors, neither of these studies used a control group or aimed to evaluate the effect of COVID-19 on ICC, making it impossible to disentangle the impact of COVID-19 from that of MV alone.

A systematic review[22] regarding brain-injured patients and MV concluded that PEEP could reduce CBF. However, there are still many questions regarding the impact of airway pressure on ICP, especially in nonneurological patients.[29,42–44] The influence of MV parameters on cerebral blood flow and ICC must be further evaluated. Permissive hypercapnia leading to vasodilation, which is frequently seen in MV-COVID-19 patients, might play a role in derangements of CBF associated with MV.[23,45] Therefore, as used in our series, noninvasive neurological monitoring might be important in preventing cerebral complications in MV patients.

Our exploratory study has several limitations. First, we utilized a convenience sample. Second, we obtained data from the initial monitoring day, thus providing a single instance of P2/P1 behavior during the intensive care unit stay. Third, we conducted our study in the opening year of the COVID-19 pandemic, when higher mortality rates were witnessed internationally due to lack of familiarity with the disease and understaffed hospitals. Finally, due to the short follow-up period, we did not have enough time to assess our population's functional outcome in the long term.

In conclusion, our data suggest that COVID-19 does not impair ICC, as measured by a noninvasive ICP waveform monitor. However, these results must be interpreted carefully since this study is exploratory. Further studies, with a more elaborate design correlating ventilatory parameters, sedation, and long-term cognitive parameters at follow-up, are of utmost importance to understanding the real impact of MV and COVID-19 upon ICC.

Authors' Contributions

AFS: conceptualization, data curation, formal analysis, investigation, methodology, resources, writing – original draft; MBS: data curation, investigation, methodology, writing – original draft; NZC: project administration, resources, supervision, writing – original draft; CYH: formal analysis, funding acquisition, software; GHF: funding acquisition, resources, software; SLSA: resources; supervision; JBCA: project administration, writing – original draft; SR: project administration; resources; FM: investigation, supervision, writing – review and editing; VCV: project administration, supervision; UAPF: resources; TLR: conceptualization, formal analysis; methodology, supervision, visualization, writing – review & editing; GSS: formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – review & editing.

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Trial Registration

This study was registered in the Clinical Trials platform at 31589920.7.1001.5505 on April 27, 2021 (https://clinicaltrials.gov/ct2/show/NCT04861402).

Conflict of Interest

AFS: has a scholarship financial support from FAPESP (São Paulo Research Foundation) grant 2023/00506-3. GF: is an employee at Brain4care Development and Innovation Technological S.A. and received financial support in form of salary during this study. MBS, NZC, CYH, SLSA, JBCA, SR, FMM, VCV, UAPF, TLR, GSS: have no conflicts of interest to declare.

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