



Does COVID-19 impact cardiac autonomic modulation and vascular endothelial function in patients with systemic arterial hypertension?

A COVID-19 impacta a modulação autonômica cardíaca e a função endotelial vascular em pacientes com hipertensão arterial sistêmica?

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Abstract

Background: Systemic arterial hypertension (SAH) is associated with a higher risk of complications in patients with COVID-19. However, it remains unclear whether mild COVID-19 infection affects cardiac autonomic modulation and vascular endothelial function (VEF) in hypertensive individuals. **Aim:** To evaluate cardiac autonomic modulation and VEF in hypertensive patients with and without a diagnosis of COVID-19. **Methods:** This was a cross-sectional study including 33 hypertensive patients, divided into two groups: G1 (with prior COVID-19 diagnosis confirmed by RT-PCR) and G2 (without diagnosis). All participants underwent electrocardiography and VEF assessment using the flow-mediated dilation (FMD) technique in the brachial artery. Heart rate variability (HRV) was analyzed using linear (time and frequency domains) and nonlinear methods (symbolic analysis and entropy). The Shapiro-Wilk test was used to assess normality, and Student's t test or Mann-Whitney test was applied according to data distribution, with a significance level of 5%. **Results:** No statistically significant differences were observed between groups for HRV or VEF parameters ($p > 0.05$). **Conclusion:** In hypertensive patients with mild symptoms of COVID-19, no significant changes in cardiac autonomic modulation or vascular endothelial function were identified. These findings suggest that mild infection may not negatively impact these physiological systems in individuals with well-controlled hypertension. Future longitudinal studies with larger sample sizes are needed to better understand the long-term cardiovascular effects of COVID-19 in this population.

Keywords: SARS-CoV-2; Autonomic Nervous System; Cardiovascular Risk.

Resumo

Introdução: A hipertensão arterial sistêmica (HAS) está associada a maior risco de complicações em pacientes com COVID-19. No entanto, ainda não está claro se a infecção leve por COVID-19 influencia a modulação autonômica cardíaca e a função endotelial vascular (FEV) em indivíduos hipertensos. **Objetivo:** Avaliar a modulação autonômica cardíaca e a FEV em pacientes hipertensos com e sem diagnóstico de COVID-19. **Métodos:** Estudo transversal com 33 pacientes hipertensos, divididos em dois grupos: G1 (com diagnóstico prévio de COVID-19 confirmado por RT-PCR) e G2 (sem diagnóstico). Foram realizados eletrocardiograma e avaliação da FEV pela técnica de dilatação mediada por fluxo (DMF) na artéria braquial. A variabilidade da frequência cardíaca (VFC) foi analisada por métodos lineares (tempo e frequência) e não lineares (análise simbólica e entropia). A normalidade dos dados foi verificada pelo teste de Shapiro-Wilk, e os testes t de Student ou Mann-Whitney foram aplicados conforme a distribuição das variáveis, com nível de significância de 5%. **Resultados:** Não foram observadas diferenças estatisticamente significativas entre os grupos para os parâmetros de VFC e FEV ($p > 0,05$). **Conclusão:** Em pacientes hipertensos com sintomas leves de COVID-19, não foram detectadas alterações significativas na modulação autonômica cardíaca ou na função endotelial vascular. Esses achados sugerem que a

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infecção leve pode não impactar negativamente esses sistemas fisiológicos em indivíduos com HAS controlada. Estudos futuros com delineamento longitudinal e maior amostragem são necessários para aprofundar essa compreensão.

Palavras-chave: SARS-CoV-2; Sistema Nervoso Autônomo; Risco Cardiovascular.

INTRODUCTION

The COVID-19 pandemic has affected more than 774 million people worldwide, causing acute and chronic systemic effects, even weeks after the original infection¹. A significant number of people continue to have symptoms for more than 12 weeks after diagnosis, even in the absence of alternative explanations. Terms such as post-COVID-19 syndrome, long COVID, and chronic COVID-19 have been suggested to describe this clinical condition².

Systemic arterial hypertension (SAH) is one of the most common comorbidities among infected individuals and has been associated with worse clinical outcomes³. Given the high clinical and economic impact of the pandemic, it is crucial to understand how COVID-19 can affect hypertensive patients, even those suffering from mild cases of the disease. In this perspective, it is worth highlighting the importance of investigating physiological parameters that predict complications, such as cardiac autonomic modulation and vascular endothelial function (VEF)^{3,4}.

Heart rate variability (HRV) and flow-mediated dilation (FMD) are noninvasive methods that allow the assessment of cardiac autonomic regulation and endothelial function, respectively. Although studies have demonstrated significant changes in these parameters in patients hospitalized for COVID-19, data on hypertensive patients with only mild symptoms, especially after recovery, are lacking^{4,5}.

Therefore, this study aimed to assess whether COVID-19 infection impacts cardiac autonomic modulation and vascular endothelial function in patients with systemic arterial hypertension with a history of mild symptoms of the disease.

METHODS

Study design and population

This is a cross-sectional observational study, following the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines⁶. The participants for this study were selected based on medical records of patients diagnosed with COVID-19 who did not require hospitalization, as reported by the Municipal Health Secretariat (SESAU), in the city of Petrolina, Brazil. In addition, the study was publicized on radio, television, and digital media platforms.

This observational study was conducted from July 2021 to September 2022 at the University of Pernambuco (UPE) in the city of Petrolina, Brazil. The assessments

were performed at the Cardiorespiratory Physiotherapy Laboratory (LAFIC) at UPE, and the assessors were blinded to the participants' groups.

Participants

We assessed 113 people, both men and women, aged between 31 and 80, who had been diagnosed with hypertension at least a year earlier and had been taking antihypertensive drugs continuously for at least three months, regardless of whether they had contracted COVID-19 or not. Participants were allocated into the following two groups: Group 1 (G1; n = 17), patients with hypertension diagnosed with COVID-19 and confirmed by Reverse Transcription – Polymerase Chain Reaction (RT-PCR) test within six months of confirmation, presenting mild symptoms; and Group 2 (G2; n = 16), consisting of individuals with SAH, without clinical diagnosis of COVID-19, and with negative results also confirmed by RT-PCR.

The study was approved (CAAE – 48683521.8.0000.5191) by the Research Ethics Committee of the Amaury de Medeiros Integrated Health Center (protocol 4848824), according to the Declaration of Helsinki for medical research involving humans. All participants provided a written informed consent form.

Patients were not included in the study if the cardiologist previously confirmed some of the following: Pregnant women and patients with a previous diagnosis of neurological diseases, chronic obstructive pulmonary disease, SBP above 180/100 mmHg, severe aortic stenosis, atrial fibrillation, malignant ventricular arrhythmia, severe coronary artery disease (>50%), supraventricular tachycardia, complex ventricular ectopic beats, severe ventricular failure, use of pacemakers, type 2 and 3 atrioventricular block, as well as any physical or mental limitation at the time of evaluation or any significant clinical condition that would impact the performance of the tests by a , . In addition, we excluded patients who were unable to perform the tests and/or evaluation protocols, as well as patients with type 2 diabetes mellitus diagnosed with cardiovascular neuropathy according to Ewing et al.⁷.

Sample size

A non-probabilistic sample and sample size calculation were based on means and standard deviations from a previous study⁸ that evaluated endothelial function in hospitalized patients with COVID-19. The sample size calculation was based on the DMF variable, resulting in a total of 34 individuals, 17 in each group. Calculation was



performed by G-Power software (study power of 0.80%, α error of 0.05, effect size of 0.80).

Assessments

Patients underwent anamnesis interviews to collect data such as age, sex, body mass, height, presence of comorbidities (cardiac, hepatic, neoplastic, pulmonary, metabolic, renal, cerebral, and vascular diseases), habits (smoking and alcohol consumption), and physical examination to record vital signs (blood pressure, heart rate, respiratory rate – RR, and peripheral oxygen saturation). In addition, patients underwent a medical evaluation accompanied by a cardiologist to detect possible pathologies that met the exclusion criteria for the study.

Cardiac Autonomic Modulation

This assessment was conducted at LAFIC at UPE, Petrolina Campus. Before the assessment, patients were instructed not to consume alcoholic beverages for 24 hours and stimulants (coffee, tea, chocolate, soft drinks, and energy drinks) for 12 hours before the exam, to get a good night's sleep, and to avoid moderate and/or intense physical exercise on the day before and the day of the assessment.

For HRV collection, patients were instructed to remain at rest in the supine position for 10 minutes. Throughout the period, patients were instructed not to speak unnecessarily and to breathe spontaneously. BP was measured at the beginning and end of HRV recording for monitoring purposes. RR was assessed continuously by visual inspection of respiratory cycles. In addition, a minimum flow of people was maintained in the assessment area, while the room temperature was controlled⁴.

The RR intervals were recorded for HRV analysis using a 12-lead electrocardiogram (Wincardio, MICROMED Biotecnologia Ltda, Brasília/DF, Brazil) placed on specific points on the participant's chest. The recordings were stored on a computer for later analysis. Subsequently, stable segments of 256 data points were selected for each participant. The chosen segment was used to process the linear (time and frequency domain) and nonlinear (symbolic analysis and entropies) analyses of HRV.

Time domain analysis was performed by calculating the mean and variance of RR intervals. Frequency domain analysis was performed using an autoregressive model. Two spectral components in absolute and normalized units were considered: low frequency (LF – from 0.04 to 0.15 Hz) and high frequency (HF – from 0.15 to 0.50 Hz), together with the LF/HF ratio⁹.

For symbolic analysis, RR intervals were transformed into a sequence of numbers ranging from 0 to 5. Subsequently, patterns of a sequence of three beats were built. These patterns were grouped into four families: (a) patterns without variation (0V); (b) patterns with one

variation (1V: 2 consecutive identical symbols and one different symbol); (c) patterns with two similar variations (2LV); and (d) patterns with two different variations (2UV: 3 symbols forming a peak or a valley). The occurrence rate of each pattern is defined as 0V%, 1V%, 2LV%, and 2UV%, where 0V% and 2LV% can be considered markers of sympathetic and vagal modulation, respectively¹⁰. The distribution of patterns was calculated by Shannon entropy (ES)¹¹.

Conditional entropy (CE) was assessed through the complexity index (CI); in addition, the normalized CI (NCI) was calculated. The higher the CI and NCI, the greater the complexity and the lower the regularity of the time series¹¹.

Vascular Endothelial Function (VEF)

VEF was assessed using the noninvasive FMD technique with an ultrasound system (LOGIQe model, by GE).

Measurements were performed using the duplex ultrasound technique, with a linear transducer (L9-3 RS probe, GE LOGIQe (R7), California, USA) at an insonation angle of 60°, with the participant lying supine, the non-dominant upper limb abducted at 90° and supported by a cuff. The patient remained still and silent throughout the data collection process¹².

Subsequently, a cuff was placed on the forearm of the same arm (just below the cubital fossa), inflated, and maintained at a pressure of 220 mmHg, inducing arterial occlusion for five minutes. Then, for one minute, images were recorded to obtain blood flow velocity and artery diameter in Doppler mode, which were determined by automatic software (FMD Studio, Quipu srl, Pisa, Italy). Afterwards, the cuff was deflated, and images to obtain blood flow velocity and artery diameter were recorded for three minutes after hyperemia¹².

Endothelial function was assessed by FMD and calculated by the percentage increase in artery diameter after occlusion compared to baseline values¹².

Statistical analysis

Data normality was assessed by the Shapiro-Wilk test. The t-test was used for parametric variables, while the Mann-Whitney test was used for nonparametric variables to compare groups. The results were presented as mean $\pm$ standard deviation or median, minimum value, and maximum value. All statistical analyses were performed on SAS® Studio software, with $p \leq 0.05$ considered statistically significant.

RESULTS

Participants in both groups were similar in age, with close averages between G1 (55.5 years; 95% CI: 49.0–61.9) and G2 (55.1 years; 95% CI: 48.2–62.0), with no statistically significant difference ($p = 0.94$). Regarding gender, most



participants in G1 were male (58.8%), while in G2 the proportion of men was 50%. Figure 1 summarizes the flowchart of participants. Tables 1 and 2 describe the characteristics of the patients. There were no statistical differences in terms of body mass, height, body mass index (BMI), or resting diastolic blood pressure (DBP). Only the variable resting systolic blood pressure (SBP) differed, with G1 showing higher values.

No statistical differences were found between the groups for the indices evaluated in the FMD (Table 3). There were no statistical differences between the groups for the HRV indices in the supine position (Table 4). All participants

showed RR within the high-frequency band range (0.15 to 0.50 Hz), i.e., more than nine breaths per minute.

DISCUSSION

This study aimed to assess FEV and cardiac autonomic modulation in hypertensive patients diagnosed with or without COVID-19. Our results suggest that COVID-19 did not alter cardiac autonomic modulation or FEV in hypertensive patients.

The presence of endothelial dysfunction in patients hospitalized with COVID-19 has been associated with an

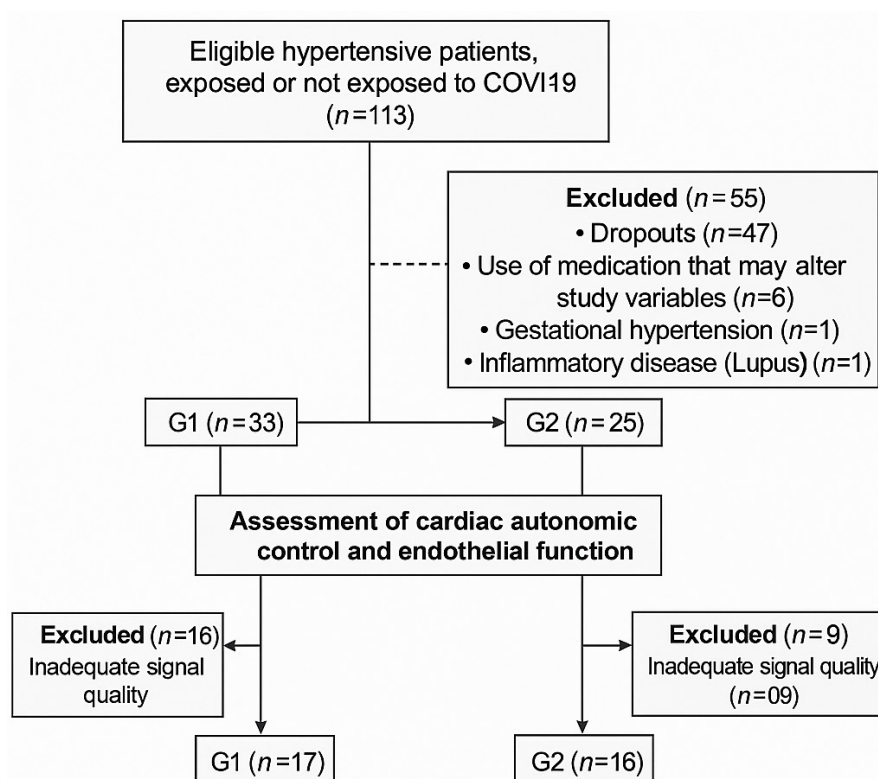


Figure 1. Flowchart.

Source: Author.

Table 1. Characteristics of hypertensive patients infected or not infected with COVID-19.

Variable	G1 (n=17)	G2 (n=16)	SD	p
Age (years)	55.5 (49.0 – 61.9)	55.1 (48.2 – 62.0)	12.6	0.94
Weight (kg)	83.1 (71.9 – 94.3)	82.2 (75.8 – 88.6)	17.5	0.89
Height (m)	1.6 (1.6 – 1.7)	1.7 (1.6 – 1.7)	0.1	0.53
BMI (kg/m ²)	30.9 (27.1 – 34.7)	31.7 (26.6 – 36.9)	8.0	0.77
SBP (mmHg)	136.2 (128.3 – 144.1)	125.2 (119.0 – 131.5)	14.6	0.03
DBP (mmHg)	93.3 (87.0 – 99.6)	85.6 (78.1 – 93.1)	13.5	0.10
6MWD (m)	469.3 (443.9 – 194.8)	515.1 (463.9 – 566.3)	75.2	0.10

6MWD: distance walked in six minutes; BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation; G1: hypertensive patients not infected with COVID-19; G2: hypertensive patients infected with COVID-19. The significance level of the Student's t-test was set at 5%. Data presented as mean (95% CI).

Source: Author.

**Table 2.** Use of medications by hypertensive patients infected and not infected with COVID-19.

Medication	G1 (n=17)	G2 (n=16)	p
Antihypertensive drugs			
Angiotensin II Blockers	8 (47.06%)	9 (56.25%)	0.73
Angiotensin II Receptor Antagonists	4 (23.52%)	1 (6.25%)	0.33
Statins			
Simvastatin	3 (17.64%)	2 (12.50%)	0.34
Rosuvastatin	0 (0.00%)	3 (18.75%)	0.10
Diuretics			
Hydrochlorothiazide	5 (29.41%)	0 (0.00%)	0,04

G1: hypertensive patients not infected with COVID-19; G2: hypertensive patients infected with COVID-19. The significance level for the chi-square test was set at 5%. Data presented as N (%).

Source: Author.

Table 3. Vascular responses of hypertensive patients infected and not infected with COVID-19.

Variable	G1 (n=17)	G2 (n=16)	SD	p
FMDmax (%)	4.3 (2.6 – 6.0)	4.2 (2.9 – 5.6)	2.9	0.65
Corrected FMD	0.9 (0.5 – 1.2)	1.0 (0.6 – 1.4)	0.7	0.37
Basal shear rate (S ⁻¹)	404.1 (249.4 – 558.7)	364.8 (188.2 – 541.5)	311.7	0.61
Maximum shear rate (S ⁻¹)	712.0 (476.1 – 947.9)	706.1 (520.5 – 891.6)	402.6	0.96
Basal diameter (mm)	5.1 (4.8 – 5.5)	4.8 (4.2 – 5.5)	0.9	0.40
Maximum diameter (mm)	5.4 (5.0 – 5.7)	5.1 (4.4 – 5.7)	0.9	0.41

FMD: flow-mediated dilation; G1: hypertensive patients not infected with COVID-19; G2: hypertensive patients infected with COVID-19; SD: standard deviation. The significance level of the Student's t-test was set at 5%. Data are presented as mean (95% CI).

Source: Author.

increased risk of mortality, especially in severe cases¹³. Gao et al.¹⁴ reported a reduction in endothelial function in patients hospitalized with moderate or severe symptoms, compared to controls matched for sex, age, and risk factors such as hypertension. These findings indicate that dysfunction may be related to the intense inflammatory process observed in patients with greater clinical severity.

Similarly, Heubel et al.¹⁵ reported a mean DMF of 0.24 mm (<0%) in patients with SAH and COVID-19, assessed up to 72 hours after admission for moderate symptoms. This value reflects a reduction in the contraction and relaxation response of the vascular wall in response to variations in blood flow, possibly influenced by lower availability of nitric oxide (NO).

Meanwhile, Bianconi et al.¹⁶ found a median DMF $\geq 4.4\%$ in 408 hospitalized patients with moderate to severe symptoms. The authors pointed out that endothelial dysfunction was more common in people with severe COVID-19 and long hospital stays. These results were reinforced by Oikonomou et al.¹⁷, who identified a significant reduction in endothelial function in patients admitted to the ICU, compared to healthy uninfected controls ($1.65 \pm 2.31\%$ vs. $6.51 \pm 2.91\%$).

In contrast, other authors have found that COVID-19 can act like a chronic subclinical inflammatory condition, even after clinical recovery. Gao et al.¹⁴ observed that inflammatory markers, such as TNF- α , remained elevated up to a year after infection, suggesting persistent inflammation in individuals with moderate or severe forms of the disease.

Nevertheless, Riou et al.⁸ found no differences in DMF between patients with mild to moderate cases and those with severe forms of the disease. Thus, the authors suggest that endothelial dysfunction may not be directly linked to the severity of COVID-19.

In our study, infected patients showed only mild symptoms and were assessed three months after infection, without progressing to severe conditions. This may explain the absence of changes in endothelial function observed by DMF.

Furthermore, no significant changes in cardiac autonomic modulation were detected, as assessed by HRV through linear and nonlinear methods. This stability may be associated with the lower intensity of the inflammatory process triggered in mild cases.

Prior studies have highlighted the association between SAH and greater severity of COVID-19^{18,19}. However, even

Table 4. Heart rate variability responses in hypertensive patients infected and not infected with COVID-19.

Linear analysis				
Variable	G1 (n=17)	G2 (n=16)	SD	p
Mean	849.8 (782.8 – 916.8)	870.7 (768.0 – 973.3)	161.3	0.83
Variance (ms ²)	1051.2 (78.6 – 2023.7)	804.1 (428.2 – 1180.0)	1427.6	0.98
LFabs (ms ²)	276.9 (108.3 – 445.5)	190.5 (109.6 – 271.4)	257.8	0.34
LFnu (%)	44.99 (35.7 – 54.3)	40.73 (27.4 – 54.0)	21.4	0.58
HFabs (ms ²)	187.3 (80.4 – 294.2)	293.1 (10.14 – 576.0)	395.8	0.71
HFnu (%)	46.8 (36.7 – 56.9)	42.3 (30.7 – 54.0)	20.5	0.54
Non-linear analysis				
Variable	G1 (n=17)	G2 (n=16)	SD	p
Shannon entropy	3.5 (3.4 – 3.7)	3.6 (3.3 – 3.8)	0.4	0.95
0V (%)	19.9 (13.7 – 26.0)	21.3 (14.1 – 28.6)	12.6	0.74
1V (%)	47.4 (44.3 – 50.5)	44.0 (41.4 – 46.6)	5.7	0.09
2LV (%)	13.3 (9.5 – 17.1)	12.3 (8.7 – 16.0)	7.1	0.74
2UV (%)	19.4 (15.5 – 23.4)	22.3 (14.8 – 29.8)	11.1	0.48
NCI	0.8 (0.7 – 0.8)	0.7 (0.7 – 0.8)	0.1	0.25
CI	1.1 (1.0 – 1.1)	1.1 (1.0 – 1.2)	0.2	0.86

0V: indicates patterns with no variation; 1V: patterns with 1 variation; 2LV: patterns with 2 similar variations; 2UV: patterns with 2 different variations; G1: hypertensive patients not infected with COVID-19; G2: hypertensive patients infected with COVID-19; HFabs: high frequency band expressed in absolute values; CI: complexity index; NCI: normalized complexity index; LFabs: low frequency band expressed in absolute values. LFnu: normalized low frequency band; SD: standard deviation. The significance level for the Student's t-test was set at 5%. Data are presented as mean (95% CI).

Source: Author.

among individuals with mild symptoms, some authors have described autonomic changes. For example, a study involving 63 patients matched by sex and age reported increased sympathetic modulation in infected individuals with mild symptoms compared to healthy controls²⁰.

In contrast, hospitalized patients with severe disease showed an overall reduction in cardiac autonomic modulation²¹. This dysfunction appears to be related to the systemic inflammatory process typical of severe forms of COVID-19. In the context of our study, the lower intensity of the inflammatory response may explain the preservation of autonomic modulation observed.

It is worth noting that all infected patients were undergoing antihypertensive treatment and had controlled blood pressure. The entry of SARS-CoV-2 into human cells depends on the angiotensin-converting enzyme 2 (ACE-2), which acts as a receptor for the viral spike protein²². Studies suggest that antihypertensive drugs may increase ACE-2 expression²³, which initially raised concerns about the risk of greater severity in these patients²⁴.

However, in vitro studies have shown that the use of antihypertensive drugs may be associated with less severe COVID-19 in hypertensive patients²⁵. This finding reinforces the hypothesis that pharmacological control of SAH may play a protective role against cardiovascular complications associated with infection.

In addition, a randomized clinical trial identified improved endothelial function in hypertensive patients treated with hydrochlorothiazide, with a significant increase in FMD (from 2.97 ± 1.56 to $3.95 \pm 1.86\%$, $p < 0.05$)²⁶. The fact that some patients in our sample were taking this medication may have influenced the results, contributing to preserving endothelial function.

The absence of significant changes in cardiac autonomic modulation and vascular endothelial function found here might be explained by physiological mechanisms linked to both high blood pressure and the autonomic response to viral infections. Hypertension is characterized by chronic endothelial dysfunction and increased sympathetic activity, which, over time, leads to the cardiovascular system adapting to altered levels of autonomic and vascular control. In patients with well-controlled SAH undergoing drug treatment, these systems may show relative stability in the face of additional stressors, such as a mild viral infection²⁷.

In addition, viral infections such as COVID-19 induce an acute inflammatory response that, in mild cases, may be limited to mild and short-lived clinical manifestations. This reduces the impact on the hypothalamic-pituitary-adrenal axis and the autonomic nervous system, minimizing measurable changes in HRV and MFF. In particular, activation of the sympathoadrenal axis and systemic oxidative stress tend to be more pronounced in severe



infections, which does not apply to the patients evaluated in this study²⁸.

Despite the relevant findings, this study has some methodological limitations that should be considered when interpreting the results. The small sample size may limit the statistical power to detect subtle differences between groups, especially in physiological parameters with wide interindividual variability. In addition, the cross-sectional design hinders the analysis of changes over time, thus limiting conclusions about autonomic and endothelial evolution after COVID-19 infection. Another relevant aspect is the possibility of a heterogeneous response to viral infection among different subgroups of hypertensive patients, considering factors such as sex, age, presence of other comorbidities, and type of antihypertensive treatment, which may modulate autonomic and endothelial responses²⁹.

Moreover, this study has important strengths that provide our findings with robustness. The use of advanced methods for analyzing heart rate variability, including nonlinear metrics such as entropy and symbolic analysis, allows for a more comprehensive assessment of autonomic modulation, overcoming the limitations of traditional approaches based solely on the time and frequency domains³⁰. In addition, strict inclusion and exclusion criteria were adopted, with detailed clinical evaluation and excluding conditions that could interfere with physiological measurements, ensuring greater homogeneity and internal validity of the sample evaluated.

CONCLUSION

Our results show that people with high blood pressure who had a mild COVID-19 infection showed no major changes in their autonomic heart modulation or vascular endothelial function compared to uninfected patients with high blood pressure. These findings suggest that mild SARS-CoV-2 infection may not significantly compromise autonomic or endothelial mechanisms in individuals with controlled hypertension.

From a clinical standpoint, this evidence contributes to reducing concerns about potential subclinical cardiovascular sequelae in hypertensive patients with mild manifestations of COVID-19. Furthermore, it reinforces the importance of rigorous blood pressure control and continued antihypertensive treatment, which may have influenced the stability of the physiological parameters found.

Future studies featuring larger samples, a longitudinal approach, and analysis of pharmacological variables could shed light on the mechanisms of cardiovascular adaptation to COVID-19 in hypertensive patients. Moreover, investigations that consider the impact of recurrent infections and different viral variants on the cardiovascular system could broaden knowledge of the long-term effects of the disease in this population.

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CONFLICT OF INTEREST

There is no conflict of interest to be declared.

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RESEARCH DATA AVAILABILITY

Os dados serão disponibilizados mediante a solicitação aos autores.

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