



Hypertensive men with previous mild COVID-19 exhibit increased cardiovascular variability and reduced autonomic complexity

Los hombres hipertensos con antecedentes de COVID-19 leve presentan mayor variabilidad cardiovascular y menor complejidad autonómica

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Abstract

Introduction: The impact of COVID-19 on cardiovascular autonomic regulation in individuals with systemic arterial hypertension (SAH) remains poorly understood. Given that hypertension is itself associated with autonomic cardiovascular alterations, SARS-CoV-2 infection may further affect autonomic regulation in this population.

Objective: To investigate the long-term effects of mild COVID-19 on cardiovascular autonomic parameters in hypertensive men, with a particular focus on heart rate variability (HRV).

Methods: Participants were allocated into two age-matched groups based on anthropometric profile, physical fitness, and pharmacological treatment, being: hypertensive individuals evaluated before the COVID-19 pandemic (SAH group, n=40), and hypertensive individuals assessed at least 12 months after mild COVID-19 (SAH-COV group, n=47). Anthropometric, hemodynamic, and metabolic assessments were performed, along with continuous heart rate and blood pressure recordings obtained by electrocardiography and photoplethysmography.

Results: Compared with the SAH group, the SAH-COV group exhibited higher HRV variance (1995 ± 1634 vs. 1304 ± 829 ms², $p = 0.031$), greater low-frequency power in absolute units (632 ± 572 vs. 376 ± 270 ms², $p = 0.012$), higher 0V% (39.0 ± 14.2 vs. 30.9 ± 12.8 %, $p = 0.007$), and greater SD2 values (40.4 ± 15.3 vs. 32.2 ± 12.4 ms, $p = 0.013$). Additionally, the SAH-COV group presented lower entropy indices and reduced baroreflex effectiveness.

Conclusion: Hypertensive men with a previous history of mild COVID-19 exhibited persistent alterations in cardiovascular autonomic regulation characterized by increased cardiovascular variability, reduced physiological complexity, and lower baroreflex effectiveness. These findings suggest that the long-term effects of SARS-CoV-2 infection may contribute to autonomic cardiovascular dysregulation in hypertensive individuals.

Keywords

Autonomic nervous system; cardiovascular autonomic control; COVID-19; heart rate variability; hypertension.

Resumen

Introducción: El impacto de la COVID-19 sobre la regulación autonómica cardiovascular en individuos con hipertensión arterial sistémica (HAS) sigue siendo poco conocido. Dado que la hipertensión ya se asocia con alteraciones autonómicas cardiovasculares, la infección por SARS-CoV-2 podría agravar estas alteraciones.

Objetivo: Investigar los efectos a largo plazo de la COVID-19 leve sobre la regulación autonómica cardiovascular en hombres hipertensos, con énfasis en la variabilidad de la frecuencia cardíaca (VFC).

Métodos: Los participantes fueron distribuidos en dos grupos emparejados por edad, características antropométricas y aptitud física: hipertensos evaluados antes de la pandemia (grupo HAS, n = 40) e hipertensos evaluados al menos 12 meses después de una COVID-19 leve (grupo HAS-COV, n=47). Se realizaron evaluaciones antropométricas, hemodinámicas y metabólicas, además de registros continuos de frecuencia cardíaca y presión arterial.

Resultados: En comparación con el grupo HAS, el grupo HAS-COV presentó una mayor varianza de la VFC (1995 ± 1634 frente a 1304 ± 829 ms²; $p=0,031$), mayor potencia de baja frecuencia en unidades absolutas (632 ± 572 frente a 376 ± 270 ms²; $p=0,012$), valores más elevados de 0V% ($39,0 \pm 14,2$ frente a $30,9 \pm 12,8$ %; $p=0,007$) y mayores valores de SD2 ($40,4 \pm 15,3$ frente a $32,2 \pm 12,4$ ms; $p=0,013$). Además, mostró menores índices de entropía y menor eficacia barorrefleja.

Conclusión: Los hombres hipertensos con antecedentes de COVID-19 leve presentaron alteraciones persistentes de la regulación autonómica cardiovascular, caracterizadas por una mayor variabilidad cardiovascular, una menor complejidad fisiológica y una menor eficacia barorrefleja. Estos hallazgos sugieren que la infección por SARS-CoV-2 puede contribuir a la desregulación autonómica cardiovascular a largo plazo en esta población.

Palabras clave

Control autonómico cardiovascular; COVID-19; hipertensión arterial; sistema nervioso autónomo; variabilidad de la frecuencia cardíaca.



Introduction

The autonomic nervous system (ANS) comprises complex afferent and efferent pathways that interact with multiple physiological systems to maintain body homeostasis. The ANS elicits a broad range of compensatory responses to adapt to different physiological disturbances, whether acute or chronic (Wehrwein et al., 2016). Within the cardiovascular system, autonomic modulation is continuously adjusted to maintain cardiac output according to the organism's metabolic and hemodynamic demands through changes in sympathetic and vagal tone. Therefore, functional alterations in the ANS may indicate the presence of pathophysiological disturbances even before overt clinical manifestations become apparent (Shaffer & Ginsberg, 2017; Task Force, 1996).

Systemic arterial hypertension (SAH) is the most prevalent noncommunicable disease worldwide, affecting millions of individuals globally (WHO, 2024). It is characterized by persistently elevated blood pressure (BP) levels and has been associated with alterations in autonomic cardiovascular control, particularly in parameters related to autonomic modulation of heart rate variability (HRV), blood pressure variability (BPV), and baroreflex sensitivity (BRS) (De Paula Facioli et al., 2022; Mancía & Grassi, 2014; Philbois et al., 2024). Although the mechanisms underlying these alterations are not yet fully understood, evidence suggests that SAH promotes structural and functional adaptations in central and peripheral mechanisms involved in autonomic cardiovascular regulation (Carthy, 2014; Floras, 2009; Mancía & Grassi, 2002). In addition, hypertensive individuals frequently exhibit sympathetic hyperactivity, endothelial dysfunction, and chronic activation of neurohumoral pathways, conditions that may increase susceptibility to further cardiovascular disturbances.

COVID-19, caused by the SARS-CoV-2 virus, has also been associated with cardiovascular autonomic alterations. The virus uses the angiotensin-converting enzyme II (ACE2) receptor to invade host cells, a receptor highly expressed in the lungs, which characterizes the disease as a predominantly respiratory infection (Gralinski & Menachery, 2020). However, ACE2 receptors are also expressed in neurological, cardiovascular, and endothelial tissues, rendering these systems potentially vulnerable to both the direct and indirect effects of viral infection (Woo et al., 2023; Yachou et al., 2020). Accordingly, significant disturbances in cardiovascular autonomic regulation have been reported both during the acute phase of the disease and in individuals who develop persistent symptoms associated with long COVID. Recent evidence has demonstrated that individuals previously affected by COVID-19 may exhibit long-lasting alterations in HRV autonomic modulation, even months after the initial infection (Marques et al., 2023; Suh et al., 2023). Considering that hypertensive individuals already present autonomic imbalance and preexisting cardiovascular alterations, it is plausible that SARS-CoV-2 infection may further aggravate these alterations in this population.

Given that cardiovascular autonomic imbalance is recognized as an important predictor of morbidity and mortality, investigating whether COVID-19 may exacerbate the autonomic cardiovascular alterations commonly observed in hypertensive individuals is of considerable clinical relevance. Therefore, the aim of the present study was to investigate late cardiovascular autonomic alterations induced by mild COVID-19 in hypertensive men, with particular emphasis on the autonomic modulation of HRV.

Method

Study Design and Ethical Considerations

This is an observational study approved by the Ethics Committee of the Clinical Hospital of the Ribeirão Preto Medical School (HCFMRP/USP), under protocol number 5.651.063/2022 (CAAE: 58843122.0.0000.5440). All volunteers were informed about the study and assured that their safety and anonymity would be preserved, with all provided information kept strictly confidential. They were also informed that they could withdraw from the study at any time without consequences. Those who agreed to participate signed an informed consent form detailing the study's rationale, objectives, procedures, risks, and benefits. Evaluations were conducted at the Ribeirão Preto Medical School (FMRP), University of São Paulo (USP), Brazil.



Sampling

Male volunteers aged 35 to 55 years, classified as sedentary (self-reported physical activity less than 150 minutes per week at moderate intensity or 75 minutes per week at vigorous intensity), diagnosed with SAH for at least five years (self-reported), and classified in stages 1 or 2 (Barroso et al., 2021), were included. Participants were under treatment with renin-angiotensin system inhibitors, with or without diuretics. Exclusion criteria included smoking, the presence of other diseases beyond SAH, and the use of pharmacological treatments that directly or indirectly affect autonomic cardiovascular control.

Participants were divided into two age-matched groups based on anthropometric profile, physical fitness, and pharmacological treatment. The hypertensive group (SAH, N = 40) comprised volunteers assessed in 2019, prior to the COVID-19 pandemic, as part of a clinical trial conducted by the same research group at the same institution and approved by the same Ethics Committee (Protocol No. 2.280.910/2017; RBR-8k2dsc). The hypertensive group post-COVID-19 infection (SAH-COV, N = 47) included individuals who had contracted COVID-19 at least six months before evaluation (2022–2023), with confirmed diagnosis via reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, or rapid antigen testing. All participants in the SAH-COV group had only mild symptoms, such as flu-like syndrome and/or gastrointestinal symptoms, without requiring hospitalization.

To minimize potential confounding factors, smokers, individuals using beta-blockers, and those presenting acute or chronic degenerative conditions, including hypercholesterolemia, arrhythmias, and diabetes mellitus, were excluded from the study. Additionally, participants were not eligible if they had experienced SARS-CoV-2 infection within the previous six months or had required hospitalization during the course of the disease.

Assessment Protocols

All data recordings were conducted in the morning during a single visit to the laboratory at FMRP/USP. The following procedures were performed: anamnesis, anthropometric assessment, continuous heart rate (HR) and BP recordings, followed by a submaximal cardiopulmonary exercise test. The sequence and details of the protocols are described below.

Body Composition Assessment - Anthropometry

Body mass index (BMI) was calculated using weight (kg) divided by height squared (m^2). Body fat percentage was estimated using the Pollock and Jackson protocol, employing a skinfold caliper (Sanny®) to obtain measurements from seven skinfold sites (thoracic, mid-axillary, triceps, subscapular, abdominal, suprailiac, and thigh), followed by the Siri Equation (Pollock & Jackson, 1984; Siri, 1993). The techniques used for anthropometric measurements followed the recommendations of the International Society for the Advancement of Kinanthropometry (ISAK, International Society For The Advancement Of Kinanthropometry, 2001).

Heart Rate and Blood Pressure Records

HR and BP were simultaneously recorded for 40 minutes using an electrocardiograph (ECG; ADInstruments, Bella Vista, Australia) and a digital photoplethysmograph (Finometer Pro, Finapres Medical Systems, Amsterdam, The Netherlands), respectively, both interfaced with a data acquisition system (LabChart 8.0, ADInstruments, Bella Vista, Australia; ML866/P PowerLab). Participants remained at rest in the supine position for 30 minutes, followed by 10 minutes of active orthostatism (tilt test). All recordings were performed in a quiet environment with controlled temperature (22 °C), humidity (50–60 %), and lighting conditions.

Heart Rate Variability and Blood Pressure Variability Analysis

HRV and BPV were assessed using R-R interval (RRi) recordings obtained from the ECG and beat-to-beat systolic blood pressure (SBP) recordings obtained via photoplethysmography. These measurements were collected in both the supine position (30 minutes) and the orthostatic position (10 minutes). For the supine condition, only the final 20 minutes were analyzed to allow an initial adaptation period of 10 minutes.



HRV analysis included both linear and nonlinear approaches and was performed using CardioSeries v2.7 and Kubios HRV Standard software (University of Eastern Finland, Kuopio, Finland). BPV analysis was performed using linear spectral analysis with CardioSeries v2.7 software (Penteado, s.d.).

Time-domain HRV indices obtained through CardioSeries v2.7 included RMSSD (root mean square of successive differences between adjacent normal RR intervals) and SDNN (standard deviation of normal-to-normal RR intervals). Spectral analysis was performed after RRI and SBP series were resampled at 3 Hz using cubic spline interpolation. The data were segmented into sequential series of 512 beats with 50 % overlap. Signal stationarity was visually inspected, and segments containing artifacts or transient signals were excluded. Stationary segments were subsequently analyzed using Fast Fourier Transform (FFT), as previously described (Facioli et al., 2018; Philbois et al., 2021; Veiga et al., 2026).

Power spectral density obtained from RRI and SBP recordings was integrated into very low-frequency (VLF: < 0.04 Hz), low-frequency (LF: 0.04–0.15 Hz), and high-frequency (HF: 0.15–0.40 Hz) bands and expressed as absolute values (ms^2). In addition, RRI spectral components were expressed in normalized units (nu), calculated as the percentage contribution of LF and HF power relative to total spectral power after subtraction of the VLF component (Billman, 2011; van de Borne et al., 1997). This normalization procedure was applied to minimize variations in absolute LF and HF power (Malliani et al., 1991; TASK FORCE 1996). Furthermore, the LF/HF ratio was calculated to assess the sympathovagal balance of cardiac autonomic modulation (Montano et al., 1994).

Nonlinear HRV analysis included symbolic analysis using CardioSeries v2.7 software. RRI values were categorized into six levels (0 to 5) and grouped into sequences of three symbols (triads), classified into four families: 0V%: No variation pattern (three identical symbols), associated with sympathetic modulation; a) 1V%: one variation pattern (two consecutive symbols without variation and one different), not associated with autonomic modulation; b) 2LV%: two equal variations (three symbols forming ascending or descending ramps); c) 2UV%: two different variations (three symbols forming peaks or valleys). The results of 2LV% and 2UV% were combined and presented as 2V%, which is associated with parasympathetic modulation (Guzzetti et al., 2005).

Using Kubios HRV Standard software, the following nonlinear HRV indices were obtained: dispersion of points perpendicular to the identity line in the Poincaré plot (SD1) and dispersion along the identity line (SD2); detrended fluctuation analysis (DFA) indices for short-term (α_1) and long-term (α_2) components; and entropy indices, including approximate entropy (ApEn) and sample entropy (SampEn). RRI artifacts deviating by more than 25 % from the previous RRI were excluded and replaced via conventional spline interpolation, following established methodologies and applying the median filter provided by Kubios HRV Standard (Tarvainen et al., 2014). A prior smoothing approach with a lambda value of 500 was used to remove LF baseline trend components (Shaffer & Ginsberg, 2017).

Spontaneous Baroreflex Sensitivity Analysis

Spontaneous BRS was assessed by evaluating the relationship between changes in RR interval (RRI, ms) as a function of SBP using the sequence method. This approach identifies four or more consecutive pressure pulses in which a progressive increase in SBP (ramp) leads to a progressive increase in RRI (Up gain, ms/mmHg). Similarly, sequences where both SBP and RRI decrease were classified as Down gain (ms/mmHg). Only baroreflex sequences with a correlation coefficient of ≥ 0.8 between SBP and RRI values were considered. Spontaneous BRS was determined by calculating the mean slope of the linear regression between SBP and RRI values for each detected sequence (Parati et al., 1995).

Cardiopulmonary Exercise Test

The submaximal cardiopulmonary exercise test was conducted on an incremental treadmill (Super ATL Millenium®, Inbramed/Inbrasport, Porto Alegre, RS, Brazil) using the Modified Bruce Protocol (Bruce, Robert A, 1971). The submaximal intensity was defined as the HR resulting from the sum of baseline HR and 90 % of HR reserve ($\text{HR}_{\text{max}} - \text{HR}_{\text{baseline}}$). HR was continuously recorded via electrocardiography (ECG) using the CM5 lead configuration (ML866 PowerLab, ADInstruments, Bella Vista, Australia), while BP was monitored using the auscultatory method with a stethoscope and an analog sphygmomanometer. Respiratory parameters, including expired volume (VE), oxygen consumption (VO_2), and carbon dioxide expiration volume (VCO_2), were directly assessed using a metabolic analyzer (PowerLab/8M, ADInstruments, Bella Vista, Australia).



Statistical Analysis

Results are presented as mean $\pm$ standard deviation (SD) for normally distributed data and as median and interquartile range (IQR) for non-normal data. Sample size was calculated as 41 participants per group, using SigmaStat software (version 11), with a 95 % confidence level and 80 % statistical power, considering LF and HF variables in normalized units, with an estimated SD of 19 and a minimum detectable difference of 12 between means.

Comparisons between groups were performed using the unpaired Student's t-test, while paired Student's t-tests were used for within-group analyses, both conducted with Jamovi® software, version 2.3 (available at <https://www.jamovi.org>). Variable normality was assessed using the Shapiro-Wilk test. For non-normally distributed data or cases where variance homogeneity assumptions were not met, non-parametric tests were applied: the Mann-Whitney test for independent group comparisons and the Wilcoxon paired test for within-group comparisons. Statistical significance was set at $p < 0.05$.

Results

Initially, 110 participants were screened. Of these, 40 were evaluated before COVID-19 and included in the SAH group. Among the 70 participants affected by COVID-19, 23 were excluded, leaving 47 in the SAH-COV group (Figure 1).

Figure 1. Study flowchart.

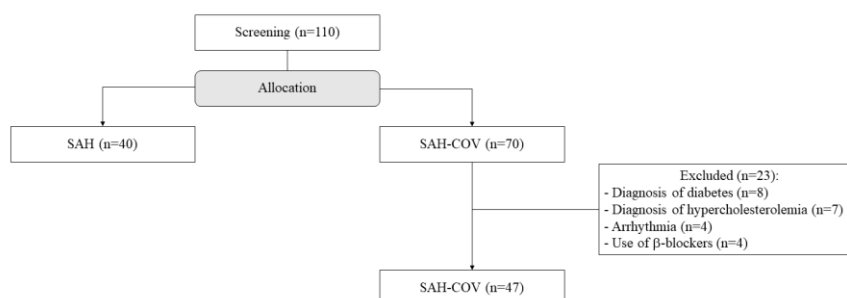


Table 1 presents the anthropometric, metabolic, and hemodynamic parameters of the SAH and SAH-COV groups. No significant differences were observed in anthropometric and metabolic parameters between the groups. However, regarding hemodynamic parameters, the SAH-COV group exhibited higher SBP values.

Table 1. Anthropometric parameters and metabolic and hemodynamic values obtained in control (SAH) and COVID-19 (SAH-COV) groups.

	SAH	SAH-COV	Mean Difference (CI 95 %)	p
Anthropometric Parameters				
Age (years)	44 [40 – 50]	45 [43 – 52]	2.00 (-1.01; 4.34)	0.237
Height (m)	1.75 [1.68 – 1.80]	1.75 [1.70 – 1.81]	0.10 (-0.20; 0.40)	0.373
Body mass (kg)	97 [86 – 112]	97 [91 – 105]	-0.39 (-6.70; 5.90)	0.902
BMI (kg/m ²)	31.8 [29 – 35]	31.4 [29 – 34]	-0.38 (-1.90; 1.20)	0.632
Body fat (%)	29.9 [26 – 35]	30.4 [28 – 34]	0.46 (-1.61; 2.52)	0.663
Metabolic and Hemodynamic Values				
VO _{2peak} (mL.kg ⁻¹ .min ⁻¹)	28 [25 – 31]	26 [23 – 29]	-1.38 (-3.02; 0.26)	0.098
HR (bpm)	68 [62 – 77]	67 [64 – 73]	-1.05 (-4.15; 2.04)	0.501
SBP (mmHg)	120 [110 – 130]	130 [120 – 135]	6.00 (0.77; 11.23)	0.010
DBP (mmHg)	81 [80 – 88]	80 [80 – 90]	2.10 (-0.01; 4.02)	0.236
MBP (mmHg)	96 [92-105]	102 [96 – 106]	4.06 (-0.01; 8.40)	0.057

Values are presented as mean $\pm$ standard deviation (SD) for normally distributed variables, and as median and interquartile range (IQR) for non-normally distributed variables. m, meter; kg/m², kilogram per square meter; %, percent; VO₂, oxygen uptake; mL.kg⁻¹.min⁻¹, milliliters per

kilogram per minute; bpm; beats per minute; mmHg, millimeters of mercury; BMI, body mass index; HR, heart rate;; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure

Table 2 displays the results of time-domain linear HRV analysis in supine and orthostatic positions (active tilt test). When comparing the groups, the SAH-COV group showed higher SDNN values in both positions. In the intragroup comparison (supine vs. orthostatic), both groups exhibited reductions in RRI, RMSSD, and SDNN values due to orthostatism.

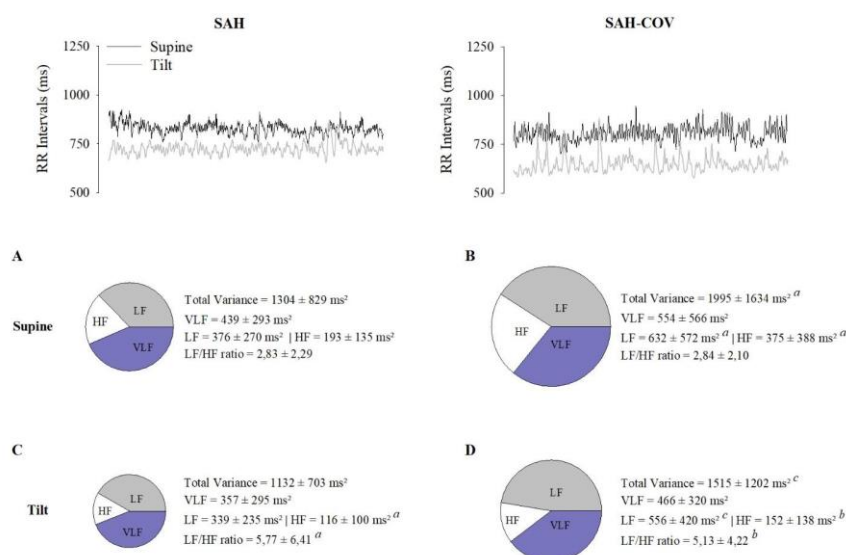
Table 2. Parameters of autonomic modulation of heart rate variability (HRV) obtained in the supine and orthostatic (active tilt test) position through linear analysis in time domain in control (SAH) and COVID-19 (SAH-COV) groups.

	SAH	SAH-COV	Mean Difference (CI 95 %)	p
Time Domain				
Supine				
RRI, ms	859 [790 – 920]	865 [788 – 937]	-4.60 (-47.8; 38.60)	0.833
RMSSD, ms	25.0 [14 – 30]	22.5 [17 – 35]	-6.99 (-13.7; -0.28)	0.041
SDNN, ms	24.8 [18 – 33]	26.7 [23 – 43]	-8.09 (-13.63; -2.55)	0.005
Orthostatic				
RRI, ms	727 [695 – 781] ^a	745 [690 – 807] ^b	-12.52 (-52.6; 27.6)	0.537
RMSSD, ms	15.4 [9 – 23] ^a	15.6 [13 – 20.6] ^b	2.51 (-6.45; 1.42)	0.207
SDNN, ms	23.9 [14 – 28] ^a	26.4 [20 – 34] ^b	-4.89 (-8.95; -0.83)	0.019

Values are presented as mean $\pm$ standard deviation (SD) for normally distributed variables, and as median and interquartile range (IQR) for non-normally distributed variables. RRI, intervals between the R-R waves of the electrocardiogram; ms, milliseconds; RMSSD, square root of the mean square of the differences between adjacent normal RR intervals. SDNN, standard deviation of normal-to-normal R-R-intervals. ^a $p < 0,05$ in the intragroup comparison of the same variable in the SAH group. ^b $p < 0,05$ in the intragroup comparison of the same variable in the SAH-COV group.

The spectral HRV analysis results for the SAH and SAH-COV groups in the supine and orthostatic positions are presented in Figure 2. In the supine position, the SAH-COV group exhibited higher variance and greater absolute LF and HF power than the SAH group. During orthostatism, the SAH-COV group also demonstrated higher variance and greater absolute LF power. Within-group comparisons revealed a reduction in absolute HF power and an increase in the LF/HF ratio during orthostatism relative to the supine position in both groups.

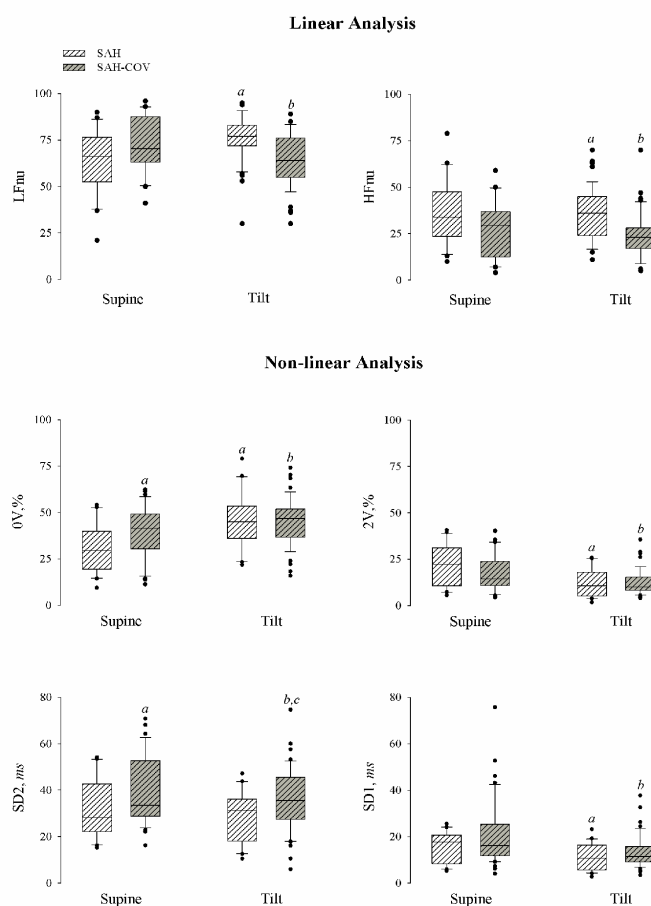
Figure 2. Spectral parameters of heart rate variability



At the top of the figure, representative beat-to-beat RRI series for each studied group are displayed. At the bottom of the figure, the pie charts illustrate the mean values of the HRV parameters: (A) hypertensive group (SAH) in the supine position, (B) hypertensive group post-COVID-19 infection (SAH-COV) in the supine position, (C) SAH group in the orthostatic position, and (D) SAH-COV group in the orthostatic position. VLF: very low-frequency oscillations; LF: low-frequency oscillations; HF: high-frequency oscillations; ms: milliseconds; ms^2 : milliseconds squared; nu, normalized units. ^a $p < 0.05$ vs. SAH group in the supine position; ^b $p < 0.05$ vs. SAH-COV group in the supine position; ^c $p < 0.05$ vs. SAH group in the orthostatic position.

Figure 3 presents the normalized LF and HF components of HRV obtained through spectral analysis, as well as the results of symbolic analysis and Poincaré plot indices in the supine and orthostatic positions. No between-group differences were observed for normalized LF and HF power. However, within-group comparisons revealed an increase in normalized LF power accompanied by a reduction in normalized HF power during orthostatism compared with the supine position. Symbolic analysis demonstrated higher 0V% values in the SAH-COV group than in the SAH group during the supine condition. In both groups, orthostatism elicited an increase in 0V% and a concomitant reduction in 2V%. Poincaré plot analysis revealed higher SD2 values in the SAH-COV group compared with the SAH group in both the supine and orthostatic positions. Moreover, only the SAH-COV group exhibited a significant increase in SD2 during orthostatism. No between-group differences were observed for SD1 in either position; however, both groups showed reduced SD1 values during orthostatism relative to the supine condition.

Figure 3. symbolic and Poincaré analyses.

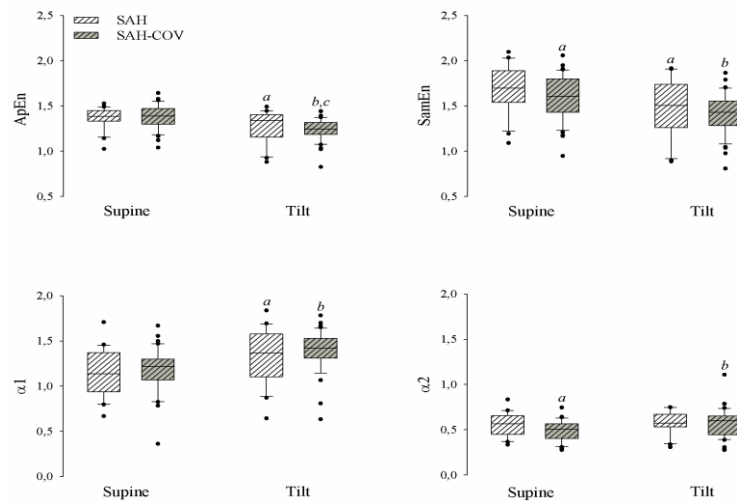


Linear and nonlinear parameters of symbolic and Poincaré analyses of both groups were obtained from recordings performed in the supine and standing positions. LF, low-frequency oscillations (sympathetic autonomic modulation); nu, normalized units; HF, high-frequency oscillations (vagal autonomic modulation); 0V, patterns without variation (sympathetic autonomic modulation); %, percentage; 2V, pattern with two variations (vagal autonomic modulation); SD1, short-course dispersions of the Poincaré plot; ms, milliseconds; SD2, long-course dispersions of the Poincaré plot. ^a $p < 0.05$ vs. SAH group in the supine position; ^b $p < 0.05$ vs. SAH-COV group in the supine position; ^c $p < 0.05$ vs. SAH group in the standing position.

Figure 4 presents entropy and DFA analyses of RRi recordings. The SAH-COV group exhibited lower SampEn values in the supine position and lower ApEn values in the orthostatic position compared with the SAH group. Within-group comparisons revealed reductions in both entropy indices during orthostatism relative to the supine condition. Figure 4 also shows that the SAH-COV group presented lower α_2 values in the supine position than the SAH group. In response to orthostatism, the SAH-COV

group exhibited increases in both α_1 and α_2 , whereas the SAH group demonstrated an increase only in α_1 .

Figure 4. Analyses of entropies and detrended fluctuations (DFA)



Nonlinear parameters of the analyses of entropies and DFA of both groups, were obtained through recordings made in the supine and orthostatic positions. ApEn, approximated entropy; SamEn, sample entropy; DFA, analysis of fluctuations trends; α_1 , short-term components; α_2 , long-term components. ^a $p < 0.05$ vs. SAH group in the supine position; ^b $p < 0.05$ vs. SAH-COV group in the supine position; ^c $p < 0.05$ vs. SAH group in the standing position.

Table 3 presents the BPV and BRS results obtained in the supine and orthostatic positions for both groups. No between-group differences were observed in BPV parameters under supine conditions. However, during orthostatism, the SAH-COV group exhibited higher BPV variance values than the SAH group. Within-group comparisons revealed increases in LF oscillations during orthostatism in both groups.

Regarding BRS, no significant between-group differences were observed for most parameters. Nevertheless, the SAH-COV group presented lower baroreflex effectiveness index (BEI) values than the SAH group in the supine position. In response to orthostatism, both groups exhibited reductions in BRS indices compared with the supine condition.

Table 3. Parameters of autonomic modulation of systolic BPV and BRS obtained in the supine and orthostatic (active tilt test) position in control (SAH) and COVID-19 (SAH-COV) groups.

	SAH	SAH-COV	Mean Difference (CI 95 %)	p
Systolic Blood Pressure Variability				
Supine				
Variance mmHg ²	32.2 [28.5 – 42]	29.5 [24 – 53.1]	3.78 (-9.16; 16.72)	0.563
LF, mmHg ²	9.1 [6.1 – 11.8]	9.9 [7.5 – 13.2]	-0.91 (-2.93; 1.34)	0.520
Orthostatic				
Variance, mmHg ²	36.5 [30.1 – 46.4]	52.1 [37.5 – 72.2] ^b	-15.0 (-25.6; -4.40)	0.006
LF, mmHg ²	16.2 [9.9 – 22.6] ^a	18.4 [14.1 – 28.7] ^b	-4.0 (-9.15; 1.15)	0.127
Baroreflex Sensitivity				
Supine				
BEI	0.51 ± 0.14	0.38 ± 0.11	0.13 (0.07; 0.19)	< 0.001
Ramps, n ^o	81 ± 33	88 ± 25	-6.94 (-19.21; 5.33)	0.264
Up, ms/mmHg	6.4 [4.9 – 7.4]	6.8 [5.5 – 8.2]	-0.57 (-1.60; 0.41)	0.277
Down, ms/mmHg	6.8 [5.4 – 8.1]	7.1 [6.0 – 8.7]	-0.54 (-1.58; 0.50)	0.308
Gain, ms/mmHg	6.62 [5.1 – 7.7]	7.1 [5.8 – 8.4]	-0.59 (-1.57; 0.40)	0.237
Orthostatic				
BEI	0.48 ± 0.21	0.43 ± 0.17 ^b	0.04 (-0.05; 0.13)	0.339
Ramps, n ^o	79 ± 39	71 ± 32 ^b	8.0 (-8.26; 24.30)	0.329
Up, ms/mmHg	4.6 [3.0 – 6.1] ^a	4.2 [3.2 – 5.4] ^b	0.61 (-0.45; 1.69)	0.256
Down, ms/mmHg	4.2 [3.5 – 7.0] ^a	4.5 [3.7 – 5.4] ^b	0.54 (-0.34; 1.41)	0.227
Gain, ms/mmHg	4.1 [3.2 – 6.5] ^a	4.6 [3.7 – 5.1] ^b	0.60 (-0.32; 1.51)	0.202

Values are presented as mean $\pm$ standard deviation (SD) for normally distributed variables, and as median and interquartile range (IQR) for non-normally distributed variables. mmHg², millimeters of mercury squared; LF, low-frequency oscillations band (0.04 – 0.15 Hz); BEI, baroreflex effectiveness index; Down, associated response of reduction in blood pressure accompanied by reflex reduction in RR intervals (RRi); Up, associated response of increased blood pressure accompanied by a reflex increase in RRi; ms, milliseconds; mmHg, millimeters of mercury. ^a $p < 0,05$ in the intragroup comparison of the same variable in the SAH group. ^b $p < 0,05$ in the intragroup comparison of the same variable in the SAH-COV group.

Discussion

The present study demonstrated that hypertensive individuals with a previous history of mild COVID-19 exhibited persistent alterations in cardiovascular autonomic regulation when compared with hypertensive individuals assessed before the pandemic. Although the SAH-COV group showed higher global HRV indices, as evidenced by increased SDNN, variance, and absolute LF and HF power, these findings were accompanied by lower RMSSD, SampEn, and ApEn values, as well as higher SD2 and 0V%. Taken together, these results suggest that the increased overall variability observed in the SAH-COV group was accompanied by reduced physiological complexity and altered autonomic organization rather than enhanced autonomic regulation. Furthermore, individuals with previous COVID-19 presented higher SBP and greater BPV. Collectively, these findings support the presence of persistent cardiovascular autonomic dysregulation following mild COVID-19 in hypertensive men.

The mechanisms through which COVID-19 may contribute to persistent alterations in cardiovascular autonomic regulation in hypertensive individuals are likely multifactorial. During the acute phase of the disease, SARS-CoV-2 infection is associated with autonomic activation and a robust immune response, resulting in increased production of pro-inflammatory cytokines (Marques et al., 2023; Mol et al., 2021). In severe cases, this response may progress to a cytokine storm, leading to widespread systemic inflammation affecting multiple organs and systems, including the cardiovascular and nervous systems (Dani et al., 2021; HU et al., 2020). Although these processes are primarily described during the acute stage of infection, persistent low-grade inflammation, endothelial dysfunction, and neuroimmune alterations have been proposed as potential mechanisms underlying the long-term autonomic disturbances observed after COVID-19. Given that hypertension itself is characterized by chronic inflammatory activation (Leitzke et al., 2020; Solak et al., 2016), it is plausible that SARS-CoV-2 infection may further aggravate pre-existing autonomic and cardiovascular dysregulation. Although inflammatory biomarkers were not assessed in the present study, the potential contribution of persistent inflammatory processes should not be overlooked.

Interestingly, despite the reductions observed in entropy- and vagally-related indices, the SAH-COV group exhibited higher SDNN, variance, SD2, and absolute spectral power. Traditionally, increases in some of these indices have been interpreted as reflecting greater overall variability (Task Force, 1996; Veiga et al., 2026). However, when considered alongside the reductions in entropy and baroreflex effectiveness observed in the present study, these findings may reflect greater cardiovascular oscillatory behavior rather than enhanced autonomic regulation. Thus, increased variability does not necessarily imply better physiological control, particularly when accompanied by reduced complexity and impaired reflex regulation (Ishaque et al., 2021; Mccraty & Shaffer, 2015).

In addition to alterations in HRV, hypertensive individuals with previous COVID-19 exhibited higher SBP values, greater BPV, and lower baroreflex effectiveness. These findings suggest that the autonomic alterations observed after COVID-19 may extend beyond HR regulation and involve broader cardiovascular control mechanisms. Reduced baroreflex effectiveness may contribute to a diminished capacity to buffer spontaneous BP fluctuations, thereby favoring greater systolic variability (Floras et al., 1988; Yousuf et al., 2025).

The literature remains inconclusive regarding the long-term effects of COVID-19 on cardiovascular autonomic regulation. While several studies have reported autonomic disturbances consistent with the findings of the present study, others have found minimal or no alterations following infection (Cunha et al., 2023; Kurtoğlu et al., 2022; Liviero et al., 2023). These discrepancies may be explained by differences in disease severity, follow-up duration, methodological approaches, and the extent to which potential confounding factors, such as age, sex, and comorbidities, were controlled (TASK FORCE, 1996; Catai et al., 2020; Souza et al., 2021). In addition, the autonomic consequences of COVID-19 may vary according to the baseline cardiovascular and inflammatory status of the population studied.



Some orthostatic responses differed between groups. The SAH-COV group exhibited increases in SD2 and $\alpha 2$ during orthostatism, whereas these changes were not observed in the SAH group. Although the physiological interpretation of these indices remains complex, both have been associated with long-term cardiovascular dynamics and regulatory mechanisms (Carrasco et al., 2001; Castiglioni & Faini, 2019). Therefore, these findings may suggest that previous COVID-19 influences the manner in which autonomic and cardiovascular control systems adapt to physiological stressors. Likewise, both groups demonstrated the expected increase in normalized LF power and reduction in normalized HF power during orthostatism, reflecting the autonomic adjustments required during postural transition. The similarity of these responses between groups further supports the preservation of the fundamental autonomic mechanisms involved in orthostatic adaptation.

Taken together, these findings suggest that the long-term effects of mild COVID-19 in hypertensive individuals may be more evident in resting cardiovascular autonomic regulation than in the autonomic adjustments elicited by physiological stress. Further studies are needed to determine whether these subtle differences in orthostatic responses have clinical implications.

Despite the strengths of the present study, some limitations should be acknowledged. First, the cross-sectional design precludes establishing causal relationships between COVID-19 and the autonomic alterations observed. Second, inflammatory biomarkers and direct measures of autonomic activity were not assessed, limiting the ability to explore the physiological mechanisms underlying the findings. Third, although the control group consisted of hypertensive individuals evaluated before the COVID-19 pandemic using identical protocols, equipment, environmental conditions, and research personnel, the use of historical controls may introduce residual sources of bias. Finally, the study included only men with hypertension and a history of mild COVID-19, which may limit the generalizability of the findings to women, normotensive individuals, or patients who experienced more severe forms of the disease.

Conclusions

In conclusion, hypertensive men with a previous history of mild COVID-19 exhibited persistent alterations in cardiovascular autonomic regulation characterized by increased overall cardiovascular variability, reduced physiological complexity, and impaired baroreflex effectiveness. These findings suggest that the long-term effects of SARS-CoV-2 infection may extend beyond the acute phase and contribute to sustained autonomic cardiovascular dysregulation in hypertensive individuals. Further studies are warranted to clarify the mechanisms underlying these alterations and to determine their potential clinical implications.

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