Autonomic Dysfunction in Long COVID: Correlations Between Blood Pressure and Heart Rate Variability in Tilt Testing

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Abstract

This study characterized autonomic dysfunction in Long COVID using head-up tilt testing with integrated blood pressure and heart rate variability analysis in 39 patients and 22 controls. Patients demonstrated significant autonomic abnormalities across all test phases: reduced mean RR intervals indicating general autonomic impairment, sympathetic deficiency during tilt (LF power 68.9±7.8 vs 79.1±6.5 n.u., $p<0.05$; LF/HF ratio 3.81±0.7 vs 5.91±0.9, $p<0.05$), paradoxical vagal predominance (HF power 31.1±7.8 vs 20.9±6.5 n.u., $p<0.05$), and impaired hemodynamic recovery (ΔBP 43.6±4.9 vs 47.5±5.3 mmHg, $p<0.05$). These findings define a distinct autonomic phenotype featuring orthostatic sympathetic failure with maladaptive vagal compensation. Strong correlations between BP variability and HRV parameters ($r=0.98$, $p<0.01$) suggest combined baroreflex and central autonomic dysfunction. Combined BP-HRV analysis during tilt testing provides valuable diagnostic information for post-COVID dysautonomia.

1. Introduction

Post-COVID-19 condition, commonly referred to as Long COVID, presents a major challenge to global healthcare systems, affecting a substantial proportion of individuals following the acute phase of SARS-CoV-2 infection [1]. Among its diverse clinical manifestations, autonomic dysfunction is a frequent and often debilitating complication. Patients frequently report symptoms of orthostatic intolerance, postural tachycardia, persistent fatigue, and blood pressure instability, which align with the spectrum of postural orthostatic tachycardia syndrome (POTS) and other forms of dysautonomia [2]. The underlying pathophysiology may involve direct or indirect effects of the virus on the autonomic nervous system, potentially mediated by autoimmune mechanisms, persistent inflammation, endothelial injury, or neuroinflammation [3]. The head-up tilt test (HUTT) is the gold standard for assessing cardiovascular autonomic regulation, providing a controlled provocation of orthostatic stress [4]. While heart rate variability (HRV) analysis is traditionally used to infer sympathovagal balance, an integrated approach that combines HRV with continuous, dynamic blood pressure (BP) analysis throughout all HUTT phases may offer a more comprehensive assessment of baroreflex integrity and central autonomic network function in chronic conditions [5]. Although recent research has started to describe autonomic abnormalities in Long COVID, a detailed characterization of the specific autonomic phenotype—evaluated through combined BP and HRV parameters across a complete HUTT protocol—remains inadequately defined. Elucidating these correlations is fundamental for understanding the pathophysiology, establishing objective diagnostic biomarkers, and guiding effective therapeutic strategies. This study was designed to address this gap by performing a combined, time-resolved analysis of BP and HRV during HUTT in a cohort of Long COVID patients.

2. Hypothesis and Objectives

We hypothesize that individuals with Long COVID syndrome exhibit a distinct pattern of cardiovascular autonomic dysregulation, characterized by basal parasympathetic withdrawal at rest, an attenuated sympathetic response to orthostatic stress, a paradoxical vagal predominance during tilt, and persistently impaired hemodynamic and autonomic recovery. We propose that these abnormalities are quantifiable through the integrated analysis of blood pressure variability and heart rate variability parameters during a standardized tilt-table test and that they reflect underlying baroreflex and central autonomic network dysfunction [6], [7].

The primary aim of this study is to compare blood pressure variability and heart rate variability parameters across the supine, tilt, and recovery phases of HUTT between Long COVID patients and matched healthy controls. Furthermore, we aim to correlate the magnitude

of blood pressure variability abnormalities with HRV indices to assess baroreflex impairment and to define the specific autonomic phenotype of Long COVID to inform future diagnostic and therapeutic approaches.

3. Material and Methods

3.1. Participants

This cross-sectional study was conducted at the Polyclinic Hospital of the University of Mogi das Cruzes, São Paulo, Brazil. The sample comprised 61 participants: 39 in the study group (SG) with Long COVID and 22 in the control group (CG). The groups were balanced in terms of clinical and demographic characteristics, as detailed in Table 1. All participants provided written informed consent. The study protocol was approved by the institutional ethics committee (CAAE: 64561022.7.0000.5497) and is part of the FAPESP project "On-line non-invasive detection of postural orthostatic tachycardia syndrome in post-COVID-19 patients."

Table 1. Clinical and Demographic Characteristics. Data presented as mean (95% confidence interval).

	CG	SG
Sex (F/M)	7 / 15	22 / 17
Age (years)	33.1 (26.6 – 39.5)	39.4 (34.7 – 44.1)
Weight (kg)	78.6 (71.2 – 86.1)	76.8 (71.5 – 82.2)
Height (cm)	171 (167 – 175)	167 (164 – 170)
BMI (kg/m^2)	31.6 (24.8 – 38.3)	27.5 (25.8 – 29.2)
Basal HR (bpm)	72.9 (68.7 – 77.0)	69.9 (66.6 – 73.2)
DBP (mmHg)	73.4 (69.6 – 77.2)	76.1 (73.2 – 78.9)
SBP (mmHg)	116 (111 - 121)	117 (113 – 122)

Inclusion criteria required participants to be aged 18-75 years. Exclusion criteria comprised acute COVID-19 infection, pregnancy, and use of medications known to affect autonomic nervous system responses.

3.2. Data Collection Protocol

Following consent procedures, participants underwent clinical anamnesis documenting vaccination history, pre-existing conditions, current medications, and COVID-19 infection details. Anthropometric measurements (weight and height) were collected for BMI calculation.

For the tilt test, participants were positioned supine on an inclined stretcher. Electrocardiogram (ECG) signals were acquired at 1.5 kHz using standard Lead II configuration. Simultaneously, automated blood pressure measurements were obtained from the left arm at one-minute intervals throughout the protocol.

3.3. Tilt Test Protocol

The head-up tilt test followed a standardized three-phase protocol: Phase 1 (Baseline): 15 minutes in supine position; Phase 2 (Tilt): 15 minutes at 75° inclination, and Phase 3 (Recovery): 20 minutes returning to supine position[4], [6].

The pulse pressure (ΔBP) was calculated as the difference between systolic (SBP) and diastolic blood pressure (DBP) for each phase. Figure 1 shows the heart rate and blood pressure response of a participant in the control group during the Tilt Test.

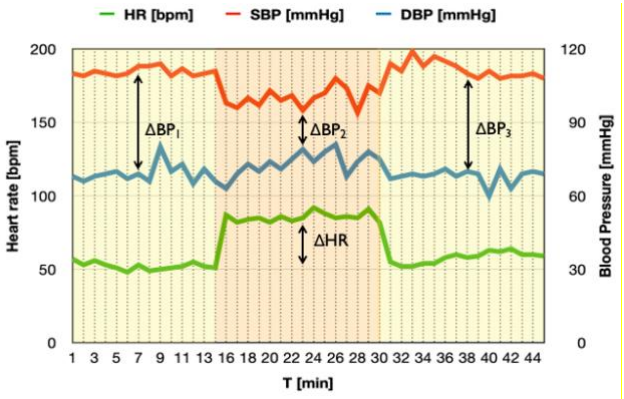

Figure 1. SBP, DBP and HR of CG participant during Tilt Test. ΔBP = SBP – DBP define to phase 1 (yellow), 2 (light orange), 3 (yellow).

3.4. Data Processing and Analysis

The acquired signals underwent a comprehensive processing pipeline to extract relevant cardiovascular parameters. Continuous ECG recordings were processed using PyBioS software, which implemented digital filtering to remove baseline wander and powerline interference[8]. R-wave peaks were automatically detected and manually verified to ensure accuracy. From these identified beats, time-domain HRV parameters were calculated, including the mean RR interval.

Concurrently, blood pressure waveforms were analyzed to extract systolic (SBP) and diastolic (DBP) values for each cardiac cycle. Pulse pressure (ΔBP) was computed as the difference between SBP and DBP (ΔBP = SBP - DBP) on a beat-to-beat basis. Frequency-domain HRV analysis was performed using Fast Fourier

Transform (FFT) with a Hanning window, decomposing the heart rate signal into its spectral components. The power in the low-frequency (LF: 0.04-0.15 Hz) and high-frequency (HF: 0.15-0.4 Hz) bands was calculated and expressed in normalized units (nu), with the LF/HF ratio computed as an indicator of sympathovagal balance[5].

Baroreflex sensitivity (BRS) was quantified using the sequence method, identifying sequences of three or more consecutive heartbeats where SBP and RR intervals progressively increased (up-up sequences) or decreased (down-down sequences) in concordance. Only sequences with correlation coefficients >0.85 were included in the analysis, with BRS expressed as the slope of the regression line between SBP and RR interval changes (ms/mmHg). Statistical analysis employed the Mann-Whitney test for between-group comparisons of all parameters across the three tilt-test phases.

Spearman's correlation analysis was performed to assess relationships between HRV indices and ΔBP values. The significance level was set at $p < 0.05$.

4. Results

Cardiovascular autonomic parameters derived from the *HUTT* for both the SG with Long COVID and the CG are summarized in Table 2. The results demonstrate significant dysregulation in the SG across all phases of the test.

Table 2. Cardiovascular Parameters. (*) Data presented as mean ± standard deviation. $p < 0.05$ SG vs. CG in the same phase. BRS: Baroreflex Sensitivity.

Parameter	Group	Phase 1 (Supine)	Phase 2 (Tilt)	Phase 3 (Recovery)
Mean RR (ms)	CG	915.5 ± 115.2	700.5 ± 98.7	942.1 ± 121.5
	SG	932.9 ± 108.4	782.5 ± 105.3*	966.5 ± 118.9
LF (nu)	CG	52.9 ± 8.1	79.1 ± 6.5	54.7 ± 7.9
	SG	56.4 ± 7.5	68.9 ± 7.8*	55.5 ± 8.2
HF (nu)	CG	47.1 ± 8.1	20.9 ± 6.5	44.6 ± 7.9
	SG	43.6 ± 7.5	31.1 ± 7.8*	44.6 ± 8.2
LF/HF Ratio	CG	1.51 ± 0.4	5.91 ± 0.9	1.45 ± 0.3
	SG	1.55 ± 0.3	3.81 ± 0.7*	1.85 ± 0.4*
ΔBP (mmHg)	CG	46.9 ± 5.1	35.7 ± 4.8	47.5 ± 5.3
	SG	44.2 ± 4.8	35.5 ± 5.0	43.6 ± 4.9*
BRS (ms/mmHg)	CG	12.4 ± 2.1	6.8 ± 1.5	11.9 ± 2.3
	SG	9.1 ± 1.8*	4.3 ± 1.2*	8.7 ± 1.9*

Spearman correlation analysis revealed significant relationships between autonomic indices and hemodynamic parameters. In the control group, strong negative correlations were observed between ΔBP and both LF power ($r = -0.99$, $p < 0.01$) and LF/HF ratio ($r = -1.00$, $p < 0.01$) across test phases, while a strong positive correlation was found with HF power ($r = 0.99$, $p < 0.01$).

The Long COVID group showed similarly strong correlations between ΔBP and spectral HRV parameters (LF: $r = -0.99$; HF: $r = 0.99$; LF/HF: $r = -1.00$; all $p < 0.01$). Notably, baroreflex sensitivity demonstrated significant positive correlations with time-domain HRV parameters in both groups. In the SG, BRS showed strong correlation with Mean RR ($r = 0.97$, $p < 0.01$) across test phases, while in the CG this correlation was even stronger ($r = 1.00$, $p < 0.01$). These correlation patterns suggest preserved neurovascular coupling mechanisms in Long COVID patients, despite the overall impairment in autonomic function.

During the supine rest (Phase 1), the SG presented a significant reduction in baroreflex sensitivity (BRS) compared to the CG (9.1 ± 1.8 ms/mmHg vs. 12.4 ± 2.1 ms/mmHg, $p < 0.05$), indicating initial autonomic impairment. No other parameters showed significant differences at baseline.

The response to orthostatic stress (Phase 2) revealed a blunted sympathetic activation in the SG. This was evidenced by a significantly lower increase in the LF/HF ratio (3.81 ± 0.7 vs. 5.91 ± 0.9, $p < 0.05$), driven by both a reduced rise in LF power (68.9 ± 7.8 nu vs. 79.1 ± 6.5 nu, $p < 0.05$) and an insufficient withdrawal of HF power (31.1 ± 7.8 nu vs. 20.9 ± 6.5 nu, $p < 0.05$). The BRS remained significantly more depressed in the SG during this phase (4.3 ± 1.2 ms/mmHg vs. 6.8 ± 1.5 ms/mmHg, $p < 0.05$). In the recovery phase (Phase 3), the SG demonstrated sustained autonomic and hemodynamic dysregulation.

The LF/HF ratio failed to normalize completely, remaining elevated compared to the CG (1.85 ± 0.4 vs. 1.45 ± 0.3, $p < 0.05$). Concurrently, the pulse pressure (ΔBP) was significantly lower in the SG (43.6 ± 4.9 mmHg vs. 47.5 ± 5.3 mmHg, $p < 0.05$), and BRS values continued to be impaired (8.7 ± 1.9 ms/mmHg vs. 11.9 ± 2.3 ms/mmHg, $p < 0.05$).

5. Discussion

This study identifies a distinct autonomic phenotype in Long COVID characterized by parasympathetic insufficiency, impaired sympathetic response, and baroreflex failure. The observed parasympathetic withdrawal at rest aligns with evidence of SARS-CoV-2 neurotropism affecting brainstem autonomic centers [9].

The blunted sympathetic activation during tilt (reduced LF/HF ratio) demonstrates compromised cardiovascular adaptation to orthostatic stress. The paradoxical vagal predominance represents a maladaptive pattern not seen in

normal physiology. Strong correlations between ΔBP and HRV parameters ($|r| > 0.97$) confirm preserved neurovascular coupling, though operating at suboptimal levels in Long COVID patients.

The baroreflex sensitivity impairment across all test phases provides mechanistic insight into Long COVID dysautonomia. Significantly reduced BRS values indicate defective baroreceptor function or central integration, explaining inadequate cardiovascular compensation during postural changes [10].

The sustained dysregulation during recovery, with incomplete LF/HF normalization and reduced pulse pressure, suggests chronic autonomic impairment rather than transient dysfunction. This pattern may involve persistent inflammation or autoimmune-mediated neuropathy unique to SARS-CoV-2 [11].

Clinical implications are substantial. Combined BP-HRV analysis during HUTT provides an objective diagnostic tool for post-COVID dysautonomia. Therapeutic strategies should target the specific autonomic impairment pattern, including pharmacological approaches and graded orthostatic training.

While limited by sample size and cross-sectional design, these findings provide a physiological basis for persistent Long COVID symptoms. Future longitudinal studies should examine autonomic evolution and treatment responses.

In conclusion, our results characterize a specific autonomic signature in Long COVID featuring baseline parasympathetic insufficiency, orthostatic sympathetic failure, and global baroreflex impairment. These alterations persist during recovery and demonstrate strong correlation with hemodynamic parameters, suggesting combined central and peripheral autonomic network dysfunction. These findings provide a physiological basis for understanding persistent symptoms in Long COVID patients and highlight potential targets for therapeutic intervention.

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