Assessing Autonomic Nervous System Imbalance in Post-COVID-19 Patients through Heart Rate Variability during Tilt Testing

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Abstract

This study investigated heart rate variability (HRV) in post-COVID-19 patients during a tilt test to assess potential dysfunctions of the autonomic nervous system. Nine (9) healthy volunteers (Control Group) and ten (10) individuals with a confirmed history of COVID-19 (Study Group) were included. The results revealed significant differences in HRV parameters between the groups, suggesting possible autonomic dysfunctions in post-COVID-19 patients. This study highlights the importance of the LF/HF ratio as an indicator of cardiovascular health and autonomic nervous system balance, with elevated values being associated with an excessive sympathetic nervous system response. However, caution is needed in interpreting the results due to the sample size. Nevertheless our data shows the importance of HRV parameters to improve our understanding of the impact of COVID-19 on heart rate regulation and the autonomic nervous system.

1. Introduction

The COVID-19 pandemic has infected more than 250 million people worldwide. While knowledge about COVID-19 has been expanding, we still know little about the alteration of the sympathetic/parasympathetic system and its influence on heart rate regulation caused by SARS-CoV-2. After the World Health Organization declaration of the end of the COVID-19 pandemic, new symptom patterns and syndromes, such as "Long COVID," started to emerge [1]. These patterns may be explained by autonomic nervous system (ANS) instability due to pre-existing conditions, or because of the virus itself. These syndromes represent a significant proportion of primary and secondary care consultations. Rapid detection and accurate diagnosis of these symptoms are essential for the individual's prompt recovery[2].

One approach to detect these instabilities is the tilt test, where the individual is placed on a bed and tilted to a 75-degree position relative to the horizontal while the heart and blood pressure are measured. Due to the positional change there is a shift of blood volume from the upper to the lower body, which can lead to a decrease in blood pressure and result in a compensatory increase in heart rate [3,4]. These changes are mediated by the parasympathetic and sympathetic systems that, with their complementary effects, try to achieve an optimal regulation of the cardiovascular system [3,5,6].

1.1. Hypothesis

SARS-CoV-2 could produce deleterious effects on the neurological system that jeopardize the normal response to postural changes. These alterations could be visualized and quantified using the tilt test.

1.2. Objective

To evaluate the changes in the heart rate variability and blood pressure during the tilt test in individuals that suffered from COVID-19 compared to healthy volunteers.

These changes can point up to alterations in the autonomic nervous systems and help to design strategies to ameliorate the symptoms of Long COVID-19

2. Methodology

2.1. Data acquisition

A heart rate was measured by an ECG System (ECG model PC1000 by Tecnologia Electronica Brasileira TEB™) followed by the calculation of HRV in the time and frequency domain. Blood pressure (BP) was measured on the left arm by an automatic digital sphygmomanometer (Hem-7320-Br by ONROM™). ECG sampling frequency was 1.5 kHz. BP was checked every 1 minute.

The tilt test used the following protocol [7]:

i. The participant lay horizontal on a bed where electrodes were connected for monitoring heart rate (Leads II) and BP. This phase lasted for 15 minutes.
ii. The bed with the participant was tilted to 75 degrees for 15 minutes while monitoring HR and BP.
iii. The patient was returned to a horizontal position for 20 minutes.
iv. The test was concluded when HR and BP measurements returned to their original values.

2.2. Population

A total of 19 volunteers of both sexes, ages between 20, and 55 years old (36.2 ± 12.4), enrolled in the Brazilian public health system (SUS) participated in the study. (Table 1) Research Location: Polyclinic Hospital / University of Mogi das Cruzes (UMC), Dom Antônio Cândido de Alvarenga Street, 170 - Centro, Mogi das Cruzes, SP, Brazil. The protocol was approved by the Ethics Committee of the UMC (process # 5.770.826, CAAE register 64561022.7.0000.5497). All participants were informed and signed the consent form, which described the study in detail in accordance with the Helsinki Declaration.

Table 1. Clinical Profile. DBP: Diastolic blood pressure. SBP: Systolic blood pressure. (*) $p<0.05$. (‡) borderline, $p= 0.06$.

	Study Group (mean ± SD)	**Control Group** (mean ± SD)	*p*
Participants n (%)	10 (55%)	9 (45%)	
Sex F (%)	5(26.31%)	2(10.52%)	
Age, [Year]	42.40 ± 9.34	29.22 ± 10.87	0.01*
Weight, [kg]	80.91 ± 14.97	79.10 ± 16.21	0.59
Height, [m]	1.67 ± 0.08	1.74 ± 0.07	0.08
BMI, [kg/m^2]	28.91 ± 5.36	26.01 ± 4.74	0.17
DBP rest [mmHg]	78.7 ± 9.1	68.9 ± 3.9	0.32
SBP rest, [mmHg]	125.2 ± 17.8	116.7 ± 9.4	0.01*
HRrest, [bpm]	71.60 ± 10.4	61.89 ± 7.3	0.06‡

2.3. Inclusion / Exclusion criteria

Inclusion criteria:

i. History of COVID-19 infection, SARS-CoV-2, documented by real-time PCR technique and/or genomic sequencing.
ii. Negative PCR at the beginning of the study.
iii. Age between 18 and 75 years.
iv. Normal cardiovascular, respiratory, and neurological examinations, blood tests, and lung images.
v. Women of childbearing age with a negative pregnancy test.
vi. Presented symptoms associated with post-COVID-19 such as fatigue, ageusia, anosmia, headache, dyspnea, joint and muscle pain, palpitations, fainting.

Exclusion criteria:

i. Patients with a history of stroke and/or neurological pathology, pneumonia, myocarditis, vertigo, seizures, and sleep disorders.
ii. Shortness of breath, chest pain.
iii. Presence of at least one clinically relevant symptom, spirometry or radiological lung abnormality.
iv. Patients taking duloxetine, amitriptyline, nortriptyline, fludrocortisone, midodrine, clonidine, methyldopa, propranolol, verapamil, amiodarone.
v. Pregnant or breastfeeding.
vi. Patients with mobility restrictions, recent surgeries, or acute illnesses.

2.4. Statistics

Data normality was evaluated using the Shapiro - Wilk goodness-of-fit test. Our null hypothesis was that there is no difference among groups. The Mann-Whitney test was used to assess differences between group followed by the Bonferroni post-hoc test, p values < 0.05 were considered statistically significant.

3. Results

3.1. Tilt test response

Figure 1 shows the tilt test response for both: (a) control and (b) study group participants. Upper panel: SBP and DBP, lower panel: HR. The resting phase takes place between 0 to 15 min, tilting from 15 to 30 min and returning to initial state from 30 to 50 min. Morphological and quantitative differences are observed. The CG participant exhibited an increase in HR and a decrease in the difference between SBP and DBP (ΔBP) when the bed changes an inclined position (70 degree). Upon returning

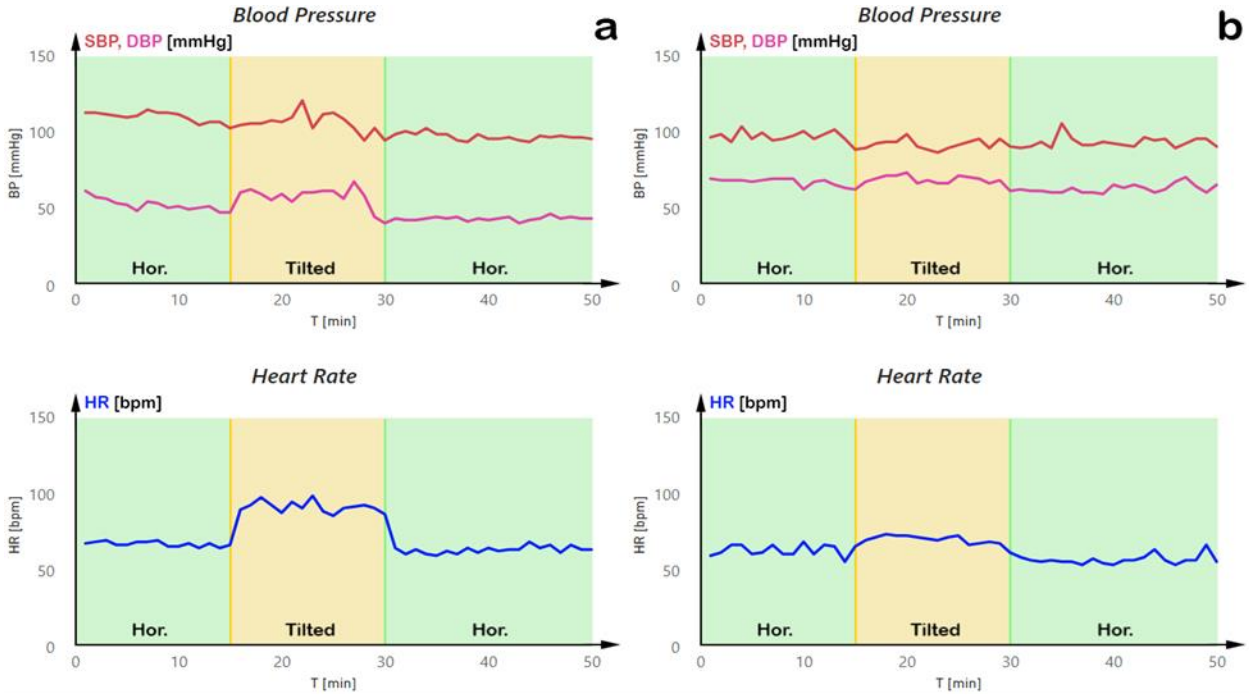

Figure 1. Tilt Test Recordings. a) Control Group participant, upper panel: blood pressure, $\overline{SBP}$ = (104.0 ± 7.0) mmHg, $\overline{DBP}$ = (50.9 ± 7.4) mmHg, lower panel: heart rate $\overline{HR}$ = (73.2 ± 12.4) bpm; b) Study group participant, upper panel: blood pressure $\overline{SBP}$ = (94.5 ± 4.0) mmHg, $\overline{DBP}$ = (66.5 ± 3.7) mmHg; lower panel: heart rate $\overline{HR}$ = (63.1 ± 6.3) bpm. Different color areas indicate resting, tilting and returning phases.

to the original position, HR and BP stabilized at their initial values (Figure 1a). The SG participant did not exhibit increase in HR nor decrease in ΔBP (Figure 1b). Of note: During the rest phase both participants displayed a normal HR range.

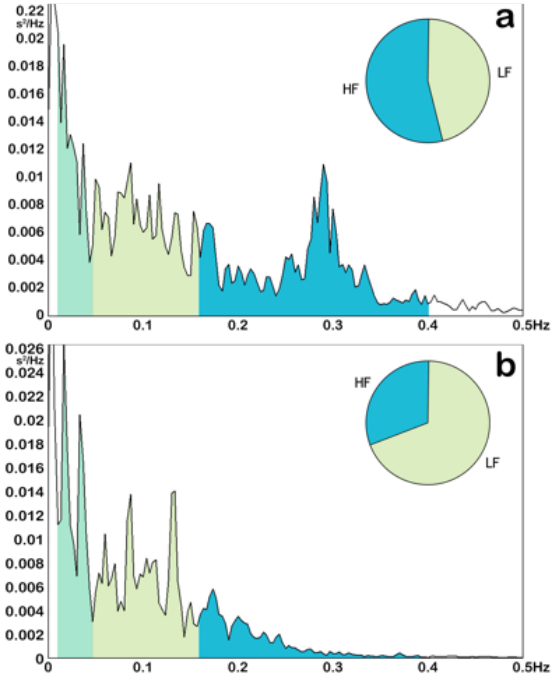

Figure 2. Spectral Density: a) CG participant. b) SG participant. High component in the 0.04 to 0.4 Hz range (HF band).

3.3. HRV analysis

We analyzed the HR spectral density in three different bands: 1) Very Low Frequency (VLF) [0.0033, 0.04] Hz, it is related to hormonal regulation, thermoregulation, respiration, and other bodily functions; 2) Low Frequency (LF) [0.04, 0.15] Hz, it is primarily associated with sympathetic nervous system activity, although it can also be influenced by the parasympathetic nervous system; and 3) High Frequency (HF) [0.15, 0.4] Hz, primarily associated with parasympathetic nervous system activity, although it can also be influenced by the sympathetic nervous system. Figure 2 shows a representative HR spectral density for a Control group (a) and Study group (b) participants. It can be observed in the later a significant reduction in spectral density specifically in the HF band. This reduction may reflect the effects of viral infection on the autonomic nervous system[8]. The ratio LF/HF, which indicates the sympathetic vs parasympathetic relationship, differs significantly (2.2 ± 1.4 for SG vs 1.1 ± 0.7 for CG, $p<0.05$), the HR variance (HR var) offers a significant index to identify members of each group: 61.64 ± 25.37 for study group, and 175.03 ± 113.50 for control group ($p<0.001$). Conversely the activity in the VLF and LF bands do not

show significant change. In the time domain SDNN, NN50, pNN50 and RMSSD parameters differ significantly between the groups, suggesting that individuals who were affected by SARS-CoV-2 respond to the postural changes with a narrow range of heart frequencies (see Table 2).

Table 2. HRV statistical analysis. (*) $p < 0.05$. (‡) $p<0.001$.

	Study Group	**Control Group**	***p***
	mean ± SD	mean ± SD	
Time domain			
HR mean [bpm]	73.0 ± 8.8	70.9 ± 6.2	0.62
NN mean [ms]	838.6 ± 93.5	877.8 ± 76.7	0.54
SDNN [ms]	94.7 ± 26.62	160.9 ± 42.0	0.0007*
NN50	305.4 ± 257.6	791.5 ± 404.5	0.01*
pNN50 [%]	10.7 ± 9.3	23.3 ± 12.2	0.03*
RMSSD	32.6 ± 19.1	77.36 ± 34.27	0.003*
Triang. index	20.3 ± 5.9	25.05 ± 8.18	0.20
Frequency domain			
VLF [s^2]	1148.3 ± 2051.6	1704.2 ± 2169,4	0.11
LF [s^2]	2099.1 ± 5081.8	3123,2 ± 4723.1	0.04*
HF [s^2]	1011.3 ± 2188.9	2200.2 ± 1658.2	0.008*
LF/HF ratio	2.2 ± 1.4	1.1 ± 0.7	0.04*
Variance			
HR var	61.64 ± 25.37	175.03 ± 113.50	0.001‡
SBP var	29.66 ± 14.40	28.47 ± 19.71	0.65
DBP var	33.07 ± 18.26	38.94 ± 14.41	0.40

4. Discussion

The Tilt Test combined with HRV study proposed in this research successfully assessed the cardiovascular response to postural changes and may be recommended to study the effects of diseases on the nervous system. Particularly mean value of 1 for LF/HF ratio is indicative of good cardiovascular health and autonomic nervous system balance (Control Group =1.1 ± 0.7). Conversely a mean value of 2.2 ± 1.4 in the Study Group can be indicative of an excessive sympathetic nervous system response. Also, HR var is significantly higher in healthy participants, being the optimal index to separate both groups. Interestingly, blood pressure changes do not parallel the heart frequency changes indicating a possible miscommunication in the baroreflex system[9].

It's important to emphasize that HRV parameters can vary depending on the individual's conditions, including age, gender, health status, etc… adding to the fact the low n of this sample Therefore, prudence should be taken to state any clinical consequences at this time. These limitations will improve as more data is collected.

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