# Heart Rate Regulation in Long-Covid-19 Patients According to the Year of Infection

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## Abstract

*This study explores the lasting effects of COVID-19 on the cardiovascular system by examining heart rate variability (HRV) in long-COVID-19 patients using the Tilt Test, a tool that assesses the sympathetic and parasympathetic system (SPS). The study involved 30 long-COVID-19 patients, categorized based on the year of infection (2020, 2021, and 2022), and compared their HRV parameters in time and frequency domains to a control group (CG) of 14 individuals. Significant variations ($p<0.05$) in heart rate (HR) were observed across the different groups, with the 2022 infection group showing the most significant discrepancies from the CG, suggesting potential SPS disturbances. The 2020 group's HR variance was closer to the CG, while the 2021 group exhibited HR variance nearer to the CG than the 2022 group. These variations were further supported by the LF/HF ratio results, which mirrored the HR variance patterns ($p<0.05$). The findings highlight the importance of considering the year of infection and emphasize the need for prolonged monitoring to understand the long-term cardiac impact of COVID-19 on patients. However, the study also points out the need for further research, given the limited sample size and data availability, to thoroughly understand the virus's impact on the autonomic nervous system and cardiovascular health.*

## 1. Introduction

The COVID-19 pandemic has triggered intense scientific scrutiny in pursuit of a comprehensive understanding of the multifaceted effects of this virus. Among the numerous facets explored, the physiological response of the cardiovascular system in infected patients has become one of the crucial pillars of contemporary medical research [1.2].

Some of the approaches used to assess sympathetic and parasympathetic activity in patients with long-standing COVID-19 are being discussed. It is important to note that research is ongoing, and new methods may have been developed or applied since then for a more complete understanding of the effects of long COVID on the autonomic nervous system. These studies have utilized various techniques to assess this activity, including Biomarkers and Laboratory Tests: In addition to direct autonomic function tests, analyses of specific biomarkers have also been performed to detect possible changes in hormone levels and other indicators that may reflect imbalances in the autonomic nervous system1 .Functional Imaging and Imaging Studies: Some studies have used imaging methods, such as functional magnetic resonance imaging (fMRI), to investigate brain activity associated with autonomic regulation[2]. Autonomic Response Tests: Some studies have used tests such as the Tilt Test, mentioned earlier, to assess the response of the autonomic nervous system to postural challenges. Other tests, such as Valsalva and breathing maneuvers, were also used to assess autonomic functioning[3]. Heart Rate Variability (HRV) Analysis: HRV is a valuable tool for assessing autonomic nervous system activity. Studies have investigated HRV in patients with long-standing COVID-19 to identify imbalances in the heart's autonomic modulation[3,4].

Therefore, while these approaches are valuable for understanding autonomic nervous system activity in patients with long COVID, it is important to recognize their limitations and consider an integrated approach, combining different techniques and exploring new methodologies to gain a more comprehensive and accurate understanding of autonomic disorders associated with long COVID [4,5].

In this context, the Tilt Test emerges as a crucial diagnostic tool, allowing a thorough evaluation of the



Computing in Cardiology 2024; Vol 51 Page 1 ISSN: 2325-887X DOI: 10.22489/CinC.2024.420

regulation of the autonomic system, especially the interaction between the parasympathetic and sympathetic systems. This test, by inducing a controlled postural change, challenges the body to maintain blood pressure and heart rate in challenging conditions, thereby revealing distinct patterns in the physiological response of individuals.

The ability of the Tilt Test to investigate cardiovascular autonomic regulation is critical, as it unravels nuances in the function of the parasympathetic and sympathetic systems, allowing for a deeper understanding of the mechanisms underlying heart rate variations. This approach offers valuable insights into the adaptive capacity of the cardiovascular system in the face of challenging stimuli, such as those induced by the Tilt Test.

Thus, the application of this tool in the context of the current study not only allowed the assessment of the heart rate response in COVID-19 infected patients but also offered a more comprehensive understanding of the dynamics of autonomic regulation in these individuals. This detailed approach makes the Tilt Test a valuable ally in the characterization of cardiovascular responses, providing a window into understanding the effects of COVID-19 on the autonomic nervous system and its implications for patients' cardiovascular health.

## 1.1. Objective

This study aimed to investigate, in a thorough and longitudinal manner, the variation in heart rate (HR) during the Tilt Test in individuals who contracted the virus in different periods, between the years 2020 and 2022, establishing precise comparisons with a control group.

## 2. Material and Methods

## 2.1 Equipment and Software

Heart rate was measured by an ECG system (ECG model PC1000 of the Brazilian Electronic Technology TEB™), followed by the calculation of HRV in the time and frequency domain. Blood pressure (BP) was measured in the left arm by an automatic digital sphygmomanometer (ONROM'™ s Hem-7320-Br). The ECG sampling frequency was 1.5 kHz. BP was checked every 1 minute.

## 2.2 Inclusion and exclusion criteria

**Inclusion criteria:**

i. History of COVID-19, SARS-CoV-2 infection, documented by real-time PCR and/or genomic sequencing technique; ii. Negative PCR test at baseline; iii. Age between 18 and 75 years; iv. Normal cardiovascular, respiratory, and neurological examinations, blood tests, and normal lung imaging; v. Women of childbearing potential with a negative pregnancy test. Saw. Presentation of 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, a history of syncope, pneumonia, myocarditis, vertigo, seizures, and sleep disturbances; ii. Shortness of breath, chest pain; iii. Presence of at least one clinically relevant symptom, lung abnormality on spirometry or x-ray; iv. Patients taking duloxetine, amitriptyline, nortriptyline, fludrocortisone, midodrin, clonidine, methyldopa, propranolol, verapamil, amiodarone; v. Pregnant or nursing. Saw. Patients with mobility restrictions, recent surgeries, or acute illnesses.

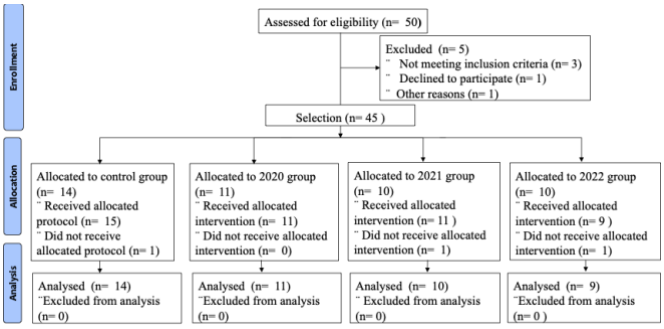


Figure 1. Consort Flow. Experimental sample.

## 2.3 Population

In total, 44 volunteers of both sexes, aged between 20 and 55 years (36.2 ± 12.4), enrolled in the Brazilian Public health system (SUS), participated in the study, (Table 1). Research location: Hospital Policlinica / UMC, Rua Dom Antônio Cândido de Alvarenga, 170 - Centro, Mogi das Cruzes, SP, Brazil (EC No. 5.770.826, CAAE registration 64561022.7.0000.5497).

| | **Study Group** | **Control Group** | *p* |
|---|---|---|---|
| Participants n (%) | 30 (70.73%) | 14 (29.27%) | |
| Sex F (%) | 15(83.34%) | 4(16.66%) | 0.1 |
| Age, [Year] | 44.4 ± 12.0 | 32.8 ± 13.7 | 0.01* |
| Weight, [kg] | 81.4 ± 15.0 | 77.7 ± 15.6 | 0.4 |
| Height, [m] | 167.0 ± 5.95 | 144.0 ± 19.30 | 0.5 |
| BMI, [kg/m$^2$] | 28.7 ± 4.35 | 26.3 ± 5.67 | 0.5 |
| DBP rest [mmHg] | 77.1 ± 7.3 | 68.9 ± 3.8 | 0.003* |
| SBP rest, [mmHg] | 121.0 ± 14.4 | 116.7 ± 9.4 | 0.5 |
| HRrest, [bpm] | 66,63 ± 9,33 | 61.88 ± 7.24 | 0.8 |

Table 1. Clinical profile n=44. BPD: Diastolic blood pressure. SBP: Systolic blood pressure. (*) p<0.05.

All participants were informed and signed a consent form, which described the study in detail in accordance with the Declaration of Helsinki.

**Experimental protocol**

The tilt test followed the following protocol [7]:

i. The participant lay horizontally on a bed where electrodes were connected to monitor heart rate (Lead II) and blood pressure. This phase lasted 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 the horizontal position for 20 minutes.

Iv. The test was completed when HR and BP measurements returned to their original values.

**Data analysis**

Data normality was assessed using the Shapiro-Wilk adherence test. Our null hypothesis was that there is no difference between the groups. The Mann-Whitney and Dwass-Steel-Critchlow-Fligner tests were used to evaluate differences between groups, followed by the Bonferroni post-hoc test; Values of $p < 0.05$ were considered statistically significant.

## 3. Findings

### 3.1 Tilt-test by years infection

The unpredictability and complexity of the effects of the virus on the human body have raised crucial questions about the impact of COVID-19 on the cardiovascular system and, particularly, on heart rate dynamics. Figure 2, presented in this study, shows a revealing picture of HR variations between the groups of infected patients and the control group.

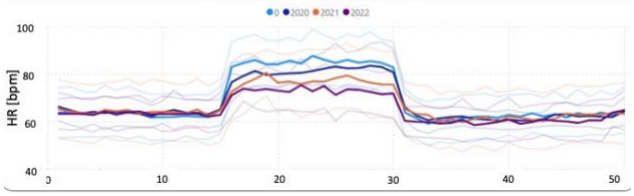


Figure 2. Tilt test of participants infected in 2020, 2021 and 2022 compared to the Control Group (0)

Notably, the largest discrepancy from control was observed in the infected group in 2022, while those infected in 2020 demonstrated a relative proximity to the control group. This temporal evolution in the HR response raises essential questions about the progression of the disease and its cardiac implications.

### 3.2 Variance by years infection

Figure 3 enriches our understanding by detailing the HR variance in the different years of infection and in the control group. The results reveal a complex dynamic: while the 2021 group demonstrates a convergence with the control group in terms of variance HR, the disparity is more pronounced in those infected in 2022. This diversity in physiological response between groups over the years of infection underscores the need for a thorough and comprehensive look at the cardiovascular implications of the virus.

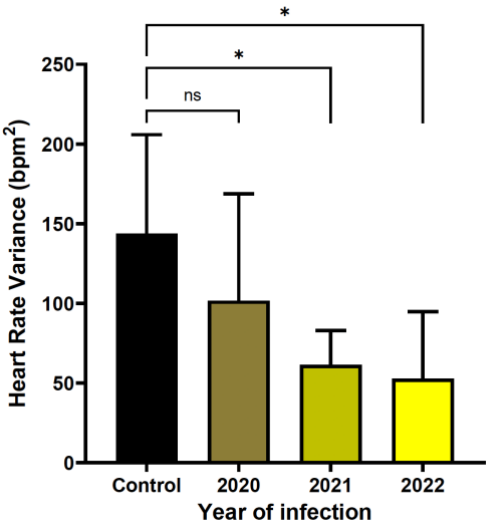


Figure 3. Evolution of the infected participant in 2020, 2021, 2022 in relation to the control group (0). a) Heart rate variance in the different years of infection and in the control group. LF/HF ratio over different years of COVID-19 infection and the control group ($p<0.05$).

Figure 3 show that the participants of the study group infected in 2021 in the amount of frequency variability demonstrate a greater proximity to the control group. Figure 2 shows a progression of the LF/HF ratio over the years between from 15 to 30min, with the greatest disparity in relation to the control group evident in those infected in 2022. On the other hand, the group infected in 2020 shows greater proximity to the control group.

### 3.3. Heart Rate Regulation

In addition, the detailed statistical analysis shows a consistent trend of reduction in HR variation over the years of infection. The wide dispersion of the data underscores the complexity and heterogeneity of the values observed, highlighting significant differences in 2021 and 2022 compared to the control group. These thought-provoking results offer a nuanced perspective on the evolution of the cardiovascular response in COVID-19-infected patients

over different periods since the onset of the pandemic. Table 2 shows the evolution of the infected participant in 2020, 2021, 2022.

| Table Analyzed | HR Variance |
|---|---|
| ***Brown-Forsythe ANOVA test*** | |
| F* (DFn, DFd) | 7.278 (3.000, 23.80) |
| P value | 0.0012 |
| P value summary | ** |
| Significant diff. among means (P < 0.05)? | Yes |
| ***Welch's ANOVA test*** | |
| W (DFn, DFd) | 4.690 (3.000, 17.82) |
| P value | 0.0138 |
| P value summary | * |
| Significant diff. among means (P < 0.05)? | Yes |
| Data summary | |
| Number of treatments (columns) | 4 |
| Number of values (total) | 44 |

Table 2. Evolution of the infected participant in 2020, 2021, 2022 in relation to the control group (0). a) Heart rate variance in the different years of infection and in the control group. b) Multiple comparison of heart rate variance.

Significant differences were observed in the segmented heart rate response signal during the tilt test, specifically in the tilted interval for the LF/HF variable ($p<0.05$) when analyzed by year of infection. his study aimed to contribute to a deeper understanding of the virus's impact on the cardiovascular system.

## 4. Discussion

The long-term implications of COVID-19 infection on the autonomic nervous system are still being fully understood. This research examines the heart rate response during the Tilt Test in infected patients at various stages of the pandemic, providing important yet evolving insights into the complexities of the virus's impact on the cardiovascular system [4].

Considering the variability of the results across different years of infection is essential (Figure 2). The temporal evolution of physiological responses in participants infected in 2020, 2021, and 2022 underscores the potential for varied trajectories of recovery or persistence of effects on the cardiovascular system over time (Table 2). These discrepancies indicate the necessity for long-term follow-up of these patients to comprehensively understand the cardiac outcomes of COVID-19 (Table 2, $p <0.05$) [4,5].

The study's findings suggest a potential reduction in heart rate variability over the years of infection, while also revealing significant heterogeneity in the observed patterns [5]. Further analysis is required to understand these heterogeneous patterns, considering potential confounding factors such as individual variations in recovery, the presence of prior comorbidities, and the influence of different virus variants.

While this study significantly advances our understanding of COVID-19's effects on the autonomic nervous system, it has limitations. The analysis of heart rate during the Tilt Test in COVID-19 patients offers valuable initial insights into cardiovascular dynamics. However, more longitudinal and comprehensive studies are needed to fully understand the long-term impact of the virus on the autonomic nervous system and cardiovascular health.

## Acknowledgments

DGG and WTW acknowledge the financial support from FAPESP - São Paulo Research Foundation, Brazil (Grant# 2021/14231-0 & Grant# 22/12866-1). ALGdS has a scholarship PIBIC / CAPES.

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