Original Article

Post-COVID-19 Syndrome and the Autonomic Repercussions on Cardiovascular Variables

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Abstract

Background: **The SARS-CoV-2 virus is responsible for the COVID-19 pandemic. Several adverse effects on the cardiovascular system were observed in patients hospitalized for COVID-19. SARS-CoV-2 infection added another possible arrhythmia-causing agent due to increased cytokines. It is believed that patients who have had COVID-19 are more prone to develop cardiovascular disease after infection. Heart rate variability (HRV) is an important marker of heart health, with lower values indicating a decrease in vagal heart rate control.**

Objectives: **To analyze the autonomic modulation of the heart rate of patients with Post-COVID-19 Syndrome.**

Methods: **Our study assessed 50 patients, of both sexes, with at least six months of recovery from COVID-19 and who were attended to in a cardiology outpatient clinic. The recording of RR intervals was performed with a portable heart rate monitor.**

Results: **The values of the Root Mean Square of the Successive Differences (RMSSD) (36.3±35.7 ms, p=0.0363) and high frequency (HF) (446.3±632.2 ms², p=0.0394) were higher in the post-COVID group when compared to the control group. In addition, TINN values (228.0±120.9 ms, p=0.009), LF/HF (3.8±3.8 a.u., p=0.1020), SD2 (40.1±19.3 a.u., p=0.005), and SD1/SD2 (2.2±1.0 a.u., p<0.0001) were lower in the post-COVID group.**

Conclusion: **The present study showed an increase in parameters related to parasympathetic autonomic activity and its modulation. In addition, lower heart rate variability was observed in patients during a post-recovery period of COVID-19 when compared to a group that had not contracted the disease.**

Keywords: **Coronavirus; Post-Acute COVID-19 Syndrome; Cardiovascular System; Autonomic Nervous System.**

Introduction

COVID-19, caused by the Severe Acute Respiratory Syndrome Virus (Sars-CoV-2), is a respiratory disease that received its current name in February 2020, but it was first reported in Wuhan,[1,2] capital of the Chinese province of Hubei, on December 31, 2019. Angiotensin-converting enzyme 2 (ACE2) has been established as the functional host cell receptor for Sars-CoV-2, enabling its viral infection. ACE2 is a membrane protein which plays a pivotal role in blood pressure regulation and vasculature through the renin-angiotensin-aldosterone system,[3,4] which is expressed more specifically in type II pneumocytes, but it is also expressed in the heart, intestine, kidneys, oral mucosal cells, and tongue. Studies show that the main cardiovascular complications of the disease are: hypertension, myocardial injury and heart failure, myocarditis, and myocardial arrhythmia.[5]

The most probable causes of arrhythmia, based on data obtained from SARS-CoV cases in 2002, include: a) hypoxia generated by lung injury caused by infection, leading to an electrical instability (atrial fibrillation); b) SARS-CoV-2 direct injury in myocardial tissue and/or in the cardiac electrical conduction system; c) aggravated SARS-CoV2 due to pre-existing cardiac and/or conduction disturbances; d) anxiety, leading to increased endogenous catecholamine release. In SARS-CoV-2 infection, another possible arrhythmia-causing event was added: a cytokine storm triggered by an imbalanced response of type 1 and type 2 T-CD4 cells, an intense interferon-mediated event that damages the myocardial wall.[6]

The cardiovascular damage has not yet been well described in the literature, a limitation due to the reduced time for conclusive results regarding long-term sequelae; however, some assumptions are possible, in accordance with pathophysiological analyses of similar diseases. Among the sequelae not yet known, many may be subclinical, such as type 2 myocardial infarction caused by the difference between supply and demand. Analyzing patients with fibrosis and/or myocarditis due to inflammatory

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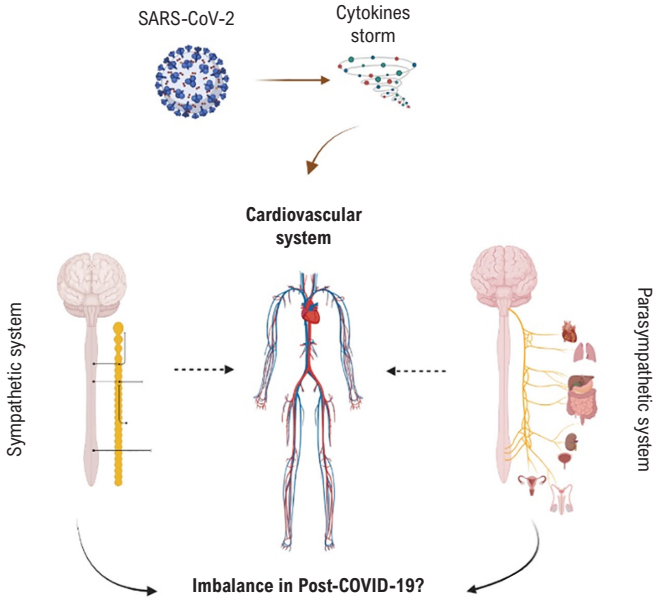
Central Illustration: Post-COVID-19 Syndrome and the Autonomic Repercussions on Cardiovascular Variables



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processes caused by viral infections similar to SARS-CoV-2, an increase in the prevalence of cardiac arrest,[7] ventricular and/or atrial arrhythmias, and fibrillations and heart failure[8] were observed in these patients. Studies also indicate a possible reduction in ventricular ejection fraction.[9] We hypothesized that there is an imbalance of cardiac autonomic modulation in patients with post-COVID-19 Syndrome when compared with uninfected individuals. Therefore, the present study aimed to analyze the autonomic modulation of heart rate among patients with post-COVID-19 Syndrome and compare it with a population that did not contract the infection.

Methods

This was a cross-sectional study, following the STROBE guidelines, conducted from February 2021 to October 2021 with patients from the Hospital Estadual Mário Covas [*Mário Covas State Hospital*] and the Specialties Outpatient Clinic of the Centro Universitário da Faculdade de Medicina do ABC [*University Center of ABC's Medical School*] (Brazil). All participants signed the Informed Consent Form (ICF) to confirm that they agreed to enroll in the study. This study was approved by the Research Ethics Committee of the Centro Universitário FMABC (# 4,875,433) in accordance with resolution 466/12.

Participants

Our study included individuals of both sexes, aged over 18 years and under 80 years, who consented to participate in the research after signing the ICF. The present study was conducted in accordance with the relevant guidelines and regulations/ethical principles of the Declaration of Helsinki.

One hundred patients were included in this analysis. The patients were divided into two groups: the inclusion criteria for the COVID-19 group (SG— 50 patients) were: having tested positive for COVID-19, having recovered from the disease for more than 6 months, and not having been vaccinated during the period of infection. The inclusion criteria for the control group (CG— 50 patients, all healthy individuals) was: being over 18 years and under 80 years and not presenting any cardiovascular or metabolic dysfunction. All patients were assessed by a pediatric cardiologist. Patients with neurological diseases, smokers, and alcoholics were not included in the control group. The control group consisted of individuals who had no known comorbidities, were non-smokers, abstained from alcohol consumption, engaged in regular physical activity, and had no previous documented cases of cardiovascular diseases. These individuals were recruited from a fitness center that they regularly attended, and none of them had a history of COVID-19 infection before the data collection period.

Participants with autoimmune diseases, HIV, hepatitis B and C, and cancer patients were excluded from the study.

Assessment of Heart Rate Variability

The recording of RR intervals was performed with a portable heart rate monitor RS800CX (Polar Electro,

Finland), a validated equipment for portable use, along with a sampling rate of 1kHz. The data were analyzed by the Polar Precision Performance SW software itself, and only series with heart rates of more than 95% were included. The collected data is transferred to the Kubios plotting software and interpreted. Data collection was performed in a room with a temperature between 21°C and 25°C and humidity between 50% and 60%. Volunteers were instructed not to drink alcoholic beverages and caffeine in the 24 hours prior to the assessment. The collection was performed individually, from 6am to 9am in order to standardize the interference of the circadian rhythm. For the collection of HRV data, the volunteers remained seated, at rest, for 10 minutes.

Variables

HRV was captured beat-by-beat during the period of highest signal stability. In the time domain (TD), the statistical indices Root Mean Square of the Successive Differences (RMSSD), Percent of successive RR intervals differing by more than 50 milliseconds (pNN50), as well as the Standard Deviation of NN intervals (SDNN) to predict morbidity and mortality in patients undergoing surgical myocardial revascularization,[10,11] were used for analysis of heart rate variability. The RMSSD index is defined as the root mean of the square of the differences between adjacent normal RR intervals in a time interval predominantly reflecting the vagal tone. The pNN50 index indicates the activity of the parasympathetic autonomic nervous system, defined as the percentage of successive differences of the RR interval, whose absolute value exceeds 50ms. The SDNN, which reflects the participation of both branches of the ANS, represents the standard deviation of the mean of all normal RR intervals, expressed in milliseconds.[12,13]

The triangular index (RRtri) was calculated from the construction of a density histogram of the normal RR intervals, which shows, on the horizontal axis (x axis), the length of the RR intervals and, on the vertical axis (y axis), the frequency with which each of them occurred. The junction of the points of the histogram columns forms a triangle-shaped figure, while the width of the base of the triangle expresses the variability of RR intervals. The TINN consists of the baseline width of the distribution measured as the base of a triangle, approximating the distribution of all RR intervals, and the minimum square difference was used to determine the triangle.

The Poincaré plot allows each RR interval to be represented as a function of the previous interval. For quantitative analysis of the graph, the following indices were calculated: SD1 standard deviation of instantaneous beat-to-beat variability), SD2 (long-term standard deviation of continuous RR intervals), and the SD1/SD2 ratio. For HRV analysis in the frequency domain –low frequency (LF) and high frequency (HF) spectral components in milliseconds squared (ms2) – were used, and the ratio between these components (LF/HF), which represents the relative value of each spectral component in relation to the total power, minus the extremely low frequency (VLF) components. For this analysis, the frequency ranges used were: LF between 0.04 to 0.15 Hz and HF ranging from 0.15 to 0.4 Hz. Spectral analysis was calculated using the fast Fourier transform algorithm.[14]

Sample size

The sample size was selected based on a pilot test, in which the online software provided by the website www.lee.dante.br was used. Based on an alpha risk of 5% and beta risk of 80%, the defined sample size was of at least 40 individuals per group.

Statistical analysis

The Excel software was used to prepare the database and the GraphPad Prism®, version 9.4.0 software was used for statistical analysis. Descriptive statistics were made by measures of central tendency and dispersion. The Shapiro-Wilk test was used to test the normality of the data. The the Mann-Whitney test was used to compare the groups. Differences in these tests were considered statistically significant when the "p" value was less than 0.05

Results

This study assessed 45 CTL participants, 27 men (60%), with a mean age of 44±11 years, and 18 women (40%), with a mean age of 47±11 years. From the post-COVID-19 group, 50 participants were evaluated, 33 women (66%), with a mean age of 45±14 years, and 17 men (34%), with a mean age of 47±11 years (Table 1). The data on the characterization of the groups and on the hospitalization of participants infected with SARS-CoV-2 are described in Tables 1 and 2.

From the data obtained by the HR variability analysis method, it was found that the mean RR of the participants in the post-COVID-19 group showed a decrease when compared to the CTL participants (CTL: 840.2±118.8 ms vs post-COVID-19: 743.0 ±124.7* ms, p=0.001). The mean HR showed that there was an increase in this parameter among post-COVID-19 participants in relation to CTLs (73.2±10.8 bpm vs 82.9±13.8* bpm, p=0.0002). Similarly, there was an increase in RMSSD in post-COVID-19 (36.3±35.7* ms, p=0.0363) when compared to CTLs (24.6±20.4 ms). An increase in TINN was identified in the participants who had the infection, as compared to the uninfected (CTL: 156.6± 74.9 ms vs Post-Covid-19: 228.0±120.9* ms). There was no statistical difference between the groups for the variables pNN50 (CTL: 6.2±9.0% vs Post-Covid-19: 10.4±14.9%) and RR triangular index (CTL: 8.7±4.3 sec vs post-COVID-19: 8.2±3.8 sec) (Figure 1).

Among the data obtained regarding high and low frequency (HF and LF), the following values were obtained: LF (CTL: 404.4±594.1 ms^2 vs Post-Covid-19 664.6± 741.0 ms^2*, *p=0.0005); HF (CTL: 253.2± 429.9 ms^2 vs Post-Covid-19 447.3±632.2 ms^2*, *p=0.0394) and LF/HF ratio (CTL: 2.6± 2.2 a.u. vs post-COVID-19 3.8±3.8 a.u., p= 0.1020) (Figure 2).

From the data obtained from the evaluation of standard deviations (SD1, SD2, and SD1/SD2 ratio) between the studied groups, the following data were found: SD1 (CTL: 18.2±14.1 a.u. vs post-COVID-19: 25.7±25.3 a.u. p=0.782), SD2 (CTL:

Table 1 – Description of the characterization of the studied groups (CTL and post-COVID-19)

	CTL (n=45)	post-COVID-19 (n=50)
Age (mean±SD); years	44±11	47±11
Men (n, %)	27 (60)	17 (34)
Women (n, %)	18 (40)	33 (66)
Self-identified race/ethnicity		
White (n, %)	27 (60)	34 (68)
Brown (n, %)	18 (40)	12 (24)
Black (n, %)	0	4 (8)
Pre-existing comorbidities		
	Without known comorbidities	Without known comorbidities

Data expressed in absolute values (n) and relative (%).

Table 2 – Descriptive data on hospitalization information for participants infected with SARS-CoV-2

COVID-19 hospitalization data	
Without hospitalization (n, %)	31 (62)
Hospitalized (n, %)	19 (38)
Field hospital (n, %)	1 (3,3)
Private hospital (n, %)	2 (8.3)
Municipal hospital (n, %)	5 (25)
Field hospital and Municipal hospital (n, %)	1 (3.3)
Severity of infection	
Mild	30 (60)
Moderate	9 (18)
Severe	11 (22)

Data expressed in absolute values (n) and relative (%).

61.6±35.0 a.u. vs post-COVID-19: 40.1±19.3* a.u., *p=0.0005) and SD1/SD2 ratio (CTL: 4.9±4.2 a.u. vs post-COVID-19: 2.2±1.0 a.u., p<0.0001) (Figure 3).

Discussion

This study analyzed the autonomic modulation of the heart rate of patients with post-COVID-19 Syndrome. The RMSSD and HF values were higher in the post-COVID group when compared to the control group, showing a higher parasympathetic autonomic modulation activity in post-COVID patients. In addition, TINN, LF/HF, SD2, and SD1/SD2 values were lower in the post-COVID group, showing a lower heart rate variability in these patients. A study conducted by Mol et al. showed that the greater the heart rate variability (HRV), the greater the chances of survival; this protective role was observed only in elderly patients.[15]

Bourdillon et al. (2020) showed improvement in parasympathetic activity (RMSSD, HF) during the lockdown period, the authors associated this improvement with

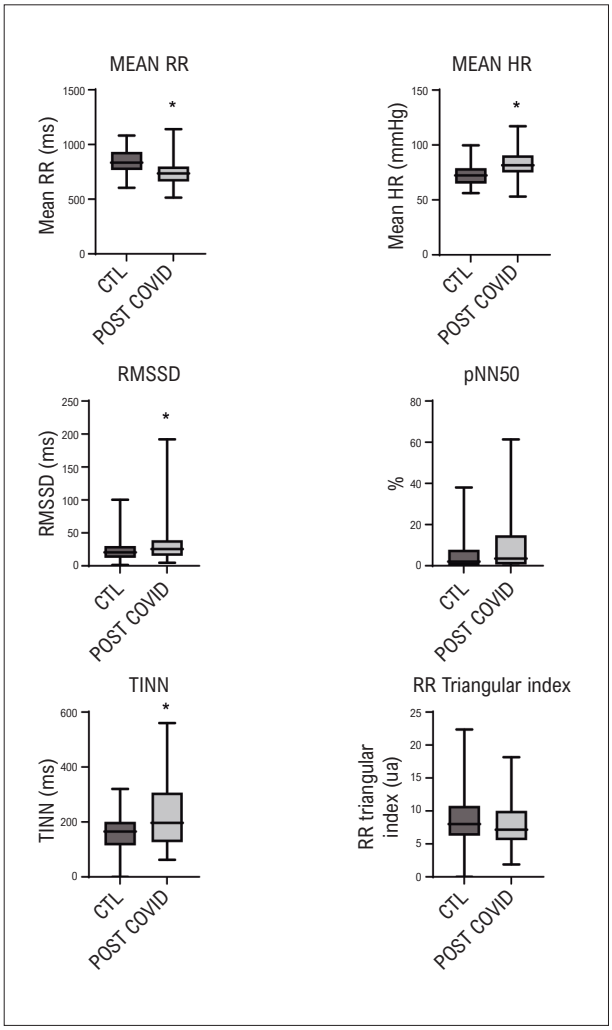

Figure 1 – *Comparison of heart rate variability parameters in the time domain between the control group and the post-COVID-19 group. (A) Mean of RR interval (Mean RR), (B) Mean of heart rate (Mean HR), (C) root mean square of successive differences between normal cycles (RMSSD), (D) percentage of successive cycles with duration difference with more than 50ms (pNN50), (E) triangular interpolation of RR intervals (TINN), and (F) triangular index (RR triangular index). Mann-Whitney test, *p<0.05 vs CTL).*

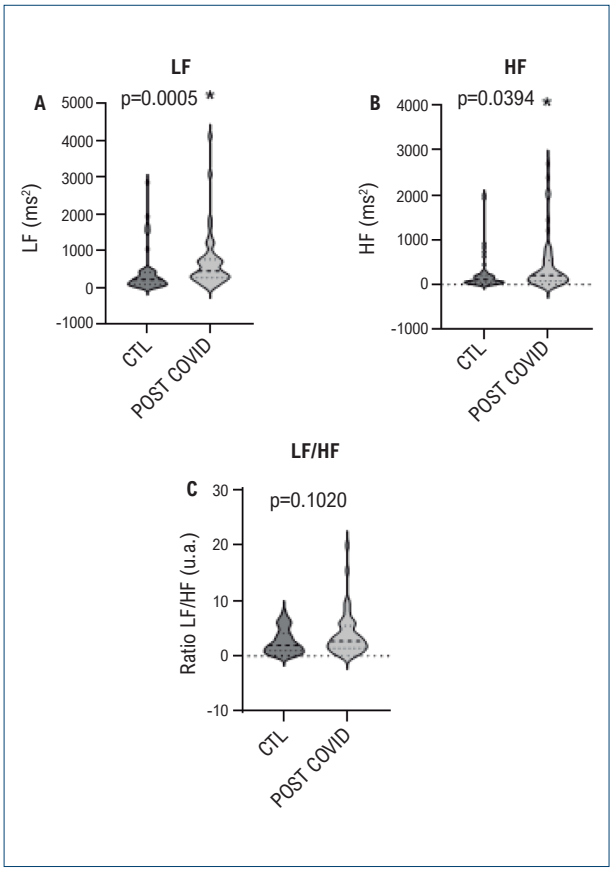

Figure 2 – *Comparison of Low Frequency (LF), High Frequency (HF) and LF/HF Ratio values between CTLs and post-COVID-19 participants. Mann-Whitney test, *p<0.05 vs CTL).*

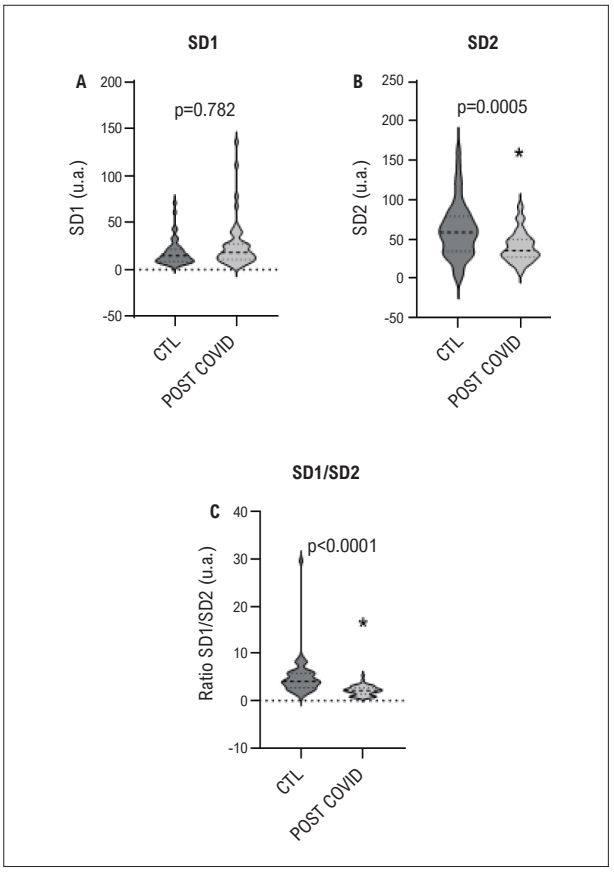

Figure 3 – *Comparison of SD1, SD2, and SD1/SD2 Ratio values between CTLs and post-COVID-19 participants. Mann-Whitney test, *p<0.05 vs CTL).*

subjective well-being responses.[16] However, the data collected in this study aim to analyze possible changes in heart variability that may be related to the disease in a post-recovery moment, and not to the lockdown period and its implications.

Solinski et al. (2022) assessed young male patients during a recovery period, from 4 to 6 weeks after having been cured from the disease, and also found an increase in parasympathetic activity, associating it with a risk of asystole. Their study also describes an increase in the mean respiratory rhythm, hypothesizing the cause as being the increase in pulmonary peripheral vascular resistance, which leads to an impairment in the coupling between respiratory and cardiac frequencies, important in metabolic homeostasis.[17]

Dani et al. (2020) reviewed the possible relationships between dysfunctions of the autonomic nervous system and COVID-19. It seems that the release of pro-inflammatory cytokines results in sympathetic activation. By contrast, vagal stimulation was also observed, resulting in anti-inflammatory responses. This is in accordance with our results, as shown by the values of RMSSD, HF, and SD2, but it is still speculated that there is an autoimmune component in infected individuals.[18] Shouman et al. (2021) showed abnormalities in the autonomic tests, such as orthostatic intolerance, but without hemodynamic alterations.[19]

Nonspecific systemic conditions, physical deconditioning, hypoxia, and heart disease may be causes of autonomic dysfunctions in post-COVID patients.[20]

The main limitation of this study was the small number of patients analyzed. This limitation is due to the difficulty in recruiting patients during the period of restrictions imposed by the pandemic.

Conclusions

In conclusion this study shows that there was an increase in parameters related to the control of the parasympathetic autonomic nervous system and its modulation for the cardiovascular system. In addition, lower heart rate variability was also observed in patients during post-recovery from the COVID-19 period when compared to a group that had not contracted the disease.

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Author Contributions

Conception and design of the research: Murad N, Veiga GL, Fonseca FLA; Acquisition of data: Murad N, Veiga GL, Davanço GY, Torres M, Reis PHA, Barbosa JV, Raimundo RD, Fonseca FLA; Analysis and interpretation of the data: Veiga GL, Davanço GY, Torres M, Barbosa JV, Raimundo RD; Statistical analysis: Veiga GL; Obtaining financing: Davanço GY, Torres M, Fonseca FLA; Writing of the manuscript: Veiga GL, Davanço GY, Torres M, Alves B, Gascón TM, Raimundo RD, Fonseca FLA; Critical revision of the manuscript for important intellectual content: Veiga GL, Davanço GY, Torres M, Reis PHA, Alves B, Gascón TM, Fonseca FLA.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

Sources of funding

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Study association

This article is part of the scientific research submitted by Giulia Yuni Davanço e Matheus Torres, from Centro Universitário Faculdade de Medicina do ABC.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Centro Universitário Faculdade de Medicina do ABC under the protocol number 4.875.433. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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