Article

Cardiac Autonomic Function in Long COVID-19 Using Heart Rate Variability: An Observational Cross-Sectional Study

Menezes Jr, Antonio da Silva[1, 2*], Schröder, Aline Andressa [2],Botelho, Silvia Marçal[1,2] and Resende, Aline Lazara[1]

[1] Affiliation 1; Federal University of Goiás and Pontifical Catholic University of Goiás; junior_antonio@ufg.br
[2] Affiliation 2; Pontifical Catholic University of Goiás.
* Correspondence: a.menezes.junior@uol.com.br; Tel.: +5562982711177

Abstract: *Background*: Heart rate variability is a non-invasive, measurable, and established autonomic nervous system test. Long-term COVID-19 sequelae are unclear; however, acute symptoms have been studied. *Objectives*: To determine autonomic cardiac differences between long COVID-19 patients and heathy controls and evaluate associations among symptoms, comorbidities, and laboratory findings. Methods: This single-center study included long COVID-19 patients and healthy controls. The heart rate variability (HRV), a quantitative marker of autonomic activity, was monitored for 24 h using an ambulatory electrocardiogram system. HRV indices were compared between case and control groups. Symptom frequency and inflammatory markers were evaluated. The significance level of 5% (*p*-value 0.05) was adopted. *Results*: A total of 47 long COVID-19 patients were compared to 42 healthy controls. Patients averaged 43.8 (SD14.8) years old, and 60.3% were female. In total, 52.5% of patients had moderate illness. Post-exercise dyspnea was most common (71.6%), and 53.2% lacked comorbidities. COVID-19 patients had 4 times more dyslipidemia. CNP, D-dimer, and CRP levels were elevated (*p*-values of 0.0098, 0.0023, and 0.0015, respectively). The control group had greater SDNN24 and SDANNI (OR = 0.98 (0.97 to 0.99; $p = 0.01$)). Increased low-frequency (LF) indices in COVID-19 patients (OR = 1.002 (1.0001 to 1.004; $p = 0.030$)) and high-frequency (HF) indices in the control group (OR = 0.987 (0.98 to 0.995; $p = 0.001$)) were also associated. *Conclusions*: Patients with long COVID-19 had lower HF values than healthy individuals. These variations are associated with increased parasympathetic activity, which may be related to long COVID-19 symptoms and inflammatory laboratory findings.

Keywords: Heart Rate Variability; Inflammatory markers; Long-term Covid-19; Autonomic nervous system.

1. Introduction

The severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) virus is the source of the pandemic known as coronavirus disease 2019 (COVID-19). This pandemic has been responsible for a significant amount of illness, as well as mortality and disruption. Now, the primary focuses of healthcare practitioners are on the prevention of new instances and the development of rehabilitation regimens. Persistent symptoms at 3 weeks following COVID-19 infection are "post-acute COVID," whereas symptoms lasting for >1 year are "chronic COVID" [1,2], also known as long COVID-19 syndrome, when somatic, physiological, and cognitive symptoms continue following remission. This disease may cause pulmonary, cardiac, and vascular fibrosis, plus fatigue.[1] Scientific, medical, and social institutions recognize this disorder, which affects COVID-19 survivors across various ages and illnesses, including young people and those not hospitalized.[1,2] However, this condition is still poorly understood [2–10].

Dysautonomia is characterized by a change in the activity of the autonomic nervous system (ANS), manifesting in various ways, including fatigue, labile blood pressure, orthostatic hypotension, and heart rate variability (HRV) dysfunction. It is related to several conditions, including metabolic syndrome, diabetes, and neurological disorders, and may

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 November 2022 doi:10.20944/preprints202211.0361.v1

manifest as acute or chronic dystonia, with progressive, reversible symptoms [3–6]. Viral illnesses are a source of dysautonomia [7]. In COVID-19 patients, dysautonomia relates to significant fatigue [7–10].

Owing to inadequate immune response control, HRV dysregulation likely occurs as SARS-CoV-2 infections affect the ANS [11], as the vagus nerve is an inflammation neuro-immuno-modulator. However, the link is complicated: the well-documented cytokine response storm of COVID-19 [12] is caused by sympathetic activity, leading to proinflammatory cytokine release [13,14]. In contrast, vagal stimulation creates an anti-inflammatory response [12], indicating the ANS as a potential therapeutic target.

Inflammatory reactions are encouraged by the sympathetic nervous system, which is responsible for the production of catecholamines and the activation of the beta-adrenergic system. On the other hand, the parasympathetic nervous system is responsible for encouraging anti-inflammatory effects [11]. COVID-19 and long COVID-19 may be systemic disorders linked with inflammation and a procoagulant condition, and they can induce parasympathetic and sympathetic imbalances, with acute and convalescent signs and symptoms. Despite the significant number of individuals who suffer from post-covid syndrome, only a small amount of research has been conducted on this topic thus far.

We aimed to noninvasively measure HRV dysregulation in long COVID-19 patients, reflected by low-frequency (LF) and high-frequency (HF) indices determining sympathetic/parasympathetic equilibrium failure. We hypothesize that the symptoms in late COVID-19 are directly connected to a virus or ANS dysregulation associated with the immune system, resulting in acute or long-term dysautonomia. Dysautonomia assessment may help to monitor the severity of long COVID syndrome.

2. Patients and Methods

2.1. Study Design and Setting

The study was an observational, cross-sectional study on long COVID-19 patients examined at the Medical Education and Clinical Research Center in Brazil between August 2020 and June 2021.

2.2. Participants

2.2.1. Inclusion Criteria

Patients with severe COVID-19 (those who required oxygen support and/or intensive care) were included in the study. In order to prevent possible sources of bias in the analysis of HRV, healthy patients with a negative reverse transcription–polymerase chain reaction (RT-PCR) test result and no symptoms were included in the study as a control group.

The COVID-19 status of all inpatients was determined via RT-PCR testing employing a nasopharyngeal and oropharyngeal swab and a polymerase chain reaction (PCR) kit. An appropriate selection approach was utilized to select eligible male and female inpatients (test group) aged 18–70 years for the sample.

2.2.2. Exclusion Criteria

Patients who were using beta-blockers, beta-mimetics (inhaled or oral), theophylline, or any other medication that had potential chronotropic effects were excluded from the analysis.

2.2.3. Procedures

For cases, we performed the following: comprehensive clinical evaluation (symptoms questionnaire); a 24 h ambulatory electrocardiogram; computed tomography (CT) of the chest; biochemical tests for markers of inflammatory processes, such as ultrasensitive C-reactive protein (CRP) dosage, procalcitonin, calcitonin, D-dimer, interleukin 6, and serum ferritin. For control patients, a 24 h ambulatory electrocardiogram was performed.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 November 2022 doi:10.20944/preprints202211.0361.v1

Moderate cases were defined as those who had clinical signs of pneumonia, but did not have signs of complications, such as SPO2 90% in room air. Severe cases were defined as those who had clinical signs of pneumonia and signs of complications, such as acute respiratory distress syndrome, sepsis, thromboembolic events, and pulmonary involvement. Mild cases of COVID-19 were defined as those who were symptomatic but did not have evidence of major viral pneumonia or hypoxia.

2.3. Heart Rate Variability Assessment

Both groups were instructed to refrain from smoking, caffeine intake, and alcohol intake for 36 h prior to the investigation. HRV, a quantitative index of autonomic activity, was recorded for 24 h using an ambulatory ECG system (DMS equipment NIVIQURE, Bangalore, India). In the temporal domain, measures of SDNN, rMSSD, and the proportion of successive RR periods were considered (pNN50). While measuring power in the frequency domain, it was possible to estimate the distribution of absolute or relative power into separate frequency bands, as well as LF and HF domain measurements.

The parasympathetic component was represented by the HF component, whereas the sympathetic component was represented by the LF component. Furthermore, the parasympathetic activity was quantified into SDNN, rMSSD, and pNN50 components [11,15-18].

2.4. Statistical Analysis

The GPower® 3.1 software was used to estimate the sample size. The dataset was submitted for descriptive and inferential statistics. For categorical variables, absolute and relative percentage frequencies were calculated, as well as mean (central trend measure) and standard deviation (dispersion measure) for continuous variables. In the inferential statistics, the chi-square and G tests were applied to compare the case and control groups for the categorical variables. Additionally, a D'Agostino–Pearson normality test was applied to verify the distribution of the data. The means were compared with the Student's t-tests for two independent samples (for dichotomous variables) and one-way ANOVA (for polytomic variables). BioEstat 5.3 software was used for this. Multivariate logistic regression was used to analyze comorbidities vs. COVID and the effect was estimated with the calculation of an odds ratio (OR) with a 95% confidence interval, using Stata® 16.0. The significance level of 5% (p-value 0.05) was adopted.

2.5. Ethical Approval

This study was conducted in accordance with the principles embodied in the Declaration of Helsinki. Following CNS Resolution 466/2012, the Research Ethics Committee approved the study (approval no. CAAE 47544021.9.0000.0037). All study participants provided written informed consent, which was verified by the research ethics committee.

3. Results

The study included 47 COVID-19-positive (previous RT-PCR positive) patients who completed a questionnaire about their symptoms and relationships and supplemental tests (test group). In total, 42 people who tested negative for COVID-19 (RT-PCR) (control group) had 24 h ambulatory ECGs (Table 1), as seen in the central figure.

Table 1. Demographic characteristics of the case and control groups.

Variable	Case Group (n = 47)		Control Group (n = 42)		p-Value
	n	%	n	%	
Comorbidities					
Arterial hypertension	8	17.0	10	23.8	
Dyslipidemia	7	14.9	3	7.1	
Obesity	4	8.5	5	11.9	

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 November 2022 doi:10.20944/preprints202211.0361.v1

Diabetes mellitus	2	4.3	2	4.8	
Chagas	1	2.1	1	2.4	
None	25	53.2	21	50.0	0.8426
Sex					
Female	28	59.6	30	71.4	
Male	19	40.4	12	28.6	0.2413

The average age of patients was 43.8 years (SD ± 14.8 years), and females accounted for 60.3%. Patients aged >40 years formed the majority of those interviewed (53.2%). A modest COVID-19 profile was seen in most patients (52.5%), and the majority (97.9%) received diagnostic confirmation via a detectable RT-PCR test. An average of 3.6 months (2.6 months) passed between infection and consultation. The treatment was largely performed at home (73%), and >25% of pulmonary involvement was detected in 34% of patients, with a mean degree of impairment of 34.4% (29%) in the most severe cases.

The case group had few comorbidities (53.2%). There was no statistically significant difference between the case patients and the controls (Table 1).

The mild, moderate, and severe profiles of COVID-19 had considerably greater (p 0.0001) pulmonary involvement on chest tomography, with a mean impairment of 4.3%, 14.2%, and 25.8%, correspondingly. BNP, D-dimer, and CRP also showed statistical significance, with p-values of 0.0098, 0.0023, and 0.0015, respectively (Table 2).

Table 2. Descriptive statistics of the case group by disease severity.

Variables (n = 47)	Mild (n = 20)		Moderate (n = 19)		Severe (n = 6)		p-Value
	Mean	SD	Mean	SD	Mean	SD	
Age	41.2	10.3	46.3	11.7	47.5	17.0	0.3132
Time (months)	4.2	2.3	5.2	2.2	4.7	1.9	0.5787
Chest CT (%)	4.3	6.3	14.2	9.3	25.8	10.2	<0.0001
Echocardiography (%)	63.2	5.0	58.7	6.4	58.0	8.9	0.0481
BNP	15.2	12.4	35.0	43.2	44.8	20.9	0.0098
Calcitonin	2.7	1.0	3.2	1.8	3.9	2.3	0.3642
D-dimer	180.8	121.2	312.9	221.0	454.4	179.5	0.0023
Ferritin	209.4	164.6	302.4	232.5	365.8	274.9	0.2102
CRP	3.4	2.8	3.7	2.9	8.9	4.5	0.0015
Procalcitonin	0.4	0.7	1.3	1.9	0.4	0.3	0.1976
Fibrinogen	358.5	163.5	368.4	179.3	454.2	183.6	0.5100
IL-6	3.4	1.4	4.1	1.5	4.0	1.8	0.5921

CT, computed tomography; BNP, brain natriuretic peptide; CRP, C-reactive protein; IL-6: interleukin-6.

SDNN-24 and SDANNi correlated positively (r = 0.9852). rMSSD and pNN50 were strongly correlated (r = 0.9986). Case and control groups had different mean and lowest heart rates. SDNN-24, SDANNi, rMSSD, pNN50, Max QTc, and Max QT showed statistically significant changes from SDANNi. Another significant difference was heart rate (p = 0.0297). Due to the reduced heart rate, the long COVID-19 group had a significant incidence of dysregulated parasympathetic activity (Table 3).

Table 3. Comparisons between the case and control groups.

Variable	Case (n = 47)		Control (n = 44)		p-Value
	Mean	SD	Mean	SD	
Age	44.4	12.2	39.6	12.9	0.0709
HR	82.3	9.2	75.8	10.0	0.0018
Min HR	52.4	11.5	48.1	9.3	0.0253

 doi:10.20944/preprints202211.0361.v1

Max HR	130.9	18.9	125.6	19.2	0.1862
VE	267.7	1533.6	126.6	494.3	0.7060
SVE	90.6	419.1	12.3	36.5	0.9335
SDNN-24	111.6	38.7	133.4	37.8	0.0078
SDANNi	99.7	38.5	122.3	39.9	0.0072
rMSSD	41.8	86.3	34.3	12.2	0.0310
pNN50	18.3	66.7	11.8	8.6	0.0442
Max QTc	544.6	101.8	518.9	44.0	0.0389
Max QT	503.9	77.2	467.5	40.5	0.0086
VLF	2225.7	1631.9	2342.1	1183.8	0.2398
LF	780.4	513.1	828.5	417.7	0.6262
HF	233.6	172.2	307.3	196.1	0.0297

SVE: supraventricular extrasystoles; VE: ventricular extrasystoles SDNN: standard deviation of normal sinus beat interbeat intervals (IBI); SDANNi: standard deviation of the average normal-to-normal (NN) intervals for each 5 min segment; rMSSD: root mean square of consecutive normal heartbeat disparities, determined by first calculating each subsequent time difference in ms; pNN50: proportion of neighboring NN intervals that vary by 50 ms, also required 2 min. The VLF band (0.0033–0.04 Hz) needs a recording time of at least 5 min, but may be best monitored over 24 h; the LF band (0.04–0.15 Hz) is usually recorded for 2 min.

Long COVID-19 was strongly associated with dyslipidemia (OR = 3.9 (1.2 to 12.57; p = 0.02)), which was 4 times more common in COVID-19 carriers than in controls (Table 4).

Table 4. Associations among sociodemographic data, comorbidities, and cardiac data among people with long COVID-19.

Variables	OR	SE	z	*p*-Value	95% CI
Age	1.03	0.02	1.75	0.07	0.99–1.07
Female	2.71	1.4	1.94	0.053	0.98–7.48
Male	1	-	-	-	-
Diabetes	0.47	0.23	−1.5	0.134	0.17–1.25
Systemic arterial hypertension	1.15	0.68	0.24	0.813	0.35–3.71
Obesity	1.18	0.67	0.29	0.772	0.38–3.62
Chagas disease	1.29	0.9	0.37	0.712	0.32–5.06
Dyslipidemia	3.94	2.33	2.32	0.02*	1.23–12.57
Kidney failure	0.69	0.54	−0.46	0.648	0.14–3.26
Smoking	0.26	0.18	−1.92	0.054	0.06–1.02
Sedentary lifestyle	1.87	1.09	1.08	0.281	0.59–5.89
Average heart rate	1.07	0.02	2.89	0.004 *	1.02–1.13
Minimum heart rate	1.04	0.02	1.9	0.057	0.99–1.08
Maximum heart rate	1.01	0.01	1.32	0.18	0.99–1.03
SDNN 24	0.98	0.005	−2.56	0.01 *	0.97–0.99
SDANNI	0.98	0.005	−2.58	0.01 *	0.97–0.99
RMSSD	1	0.004	0.54	0.58	0.99–1.01
PNN50	1	0.005	0.59	0.55	0.99–1.01
QTCMAX	1	0.003	1.46	0.14	0.99–1.01
QTMAX	1	0.003	1.36	0.17	0.99–1.01
P	1.42	0.69	0.73	0.464	0.54–3.71
S	1.67	0.82	1.06	0.29	0.64–4.38
VLF	1	0	0.59	0.55	0.99–1.01
LF	1.002	0.001	2.1	0.03 *	1.0001–1.004
HF	0.987	0.003	−3.26	0.001*	0.98–0.995

 doi:10.20944/preprints202211.0361.v1

* Statistically significant. OR: Probability; SDNN: standard deviation of normal sinus IBI in ms; SDANNi: standard deviation of 5 min normal-to-normal (NN) intervals; rMSSD: root mean square of consecutive heartbeat disparities in ms; pNN50: proportion of neighboring NN intervals that vary by more than 50 ms (needs 2 min); VLF: extremely low frequency, the VLF band (0.0033–0.04 Hz) needs a 5 min recording time but may be monitored for 24 h; LF band (0.04–0.15 Hz) is usually recorded for 2 min. The HF band represents parasympathetic activity and is dubbed the respiratory band because it correlates to HR fluctuations throughout the breathing cycle. P = parasympathetic (%) and S: sympathetic (%).

Long COVID-19 periods were associated with higher mean heart rates (OR = 1.07 (1.02 to 1.13), $p = 0.04$). Higher numbers of SDNN-24 and SDANNi were found in the control group (OR = 0.98 (0.97 to 0.99; $p = 0.01$) for each). Table 4 shows a link between elevated LF in COVID-19 patients (OR = 1.002 (1.0001 to 1.004), $p = 0.03$) and HF in the control group (OR = 0.987 (0.98 to 0.995), $p = 0.001$.

4. Discussion

Cardiorespiratory symptoms were the most common long COVID-19 symptoms in our investigation, indicating that these organs may be involved even beyond the acute phase of the illness [4,19]. CT showed that lung involvement was statistically significant compared to symptom severity, suggesting that CT is effective in evaluating pulmonary injury. BNP, D-dimer, and CRP detect inflammation in various disorders [14]. These inflammatory indicators are crucial for evaluating and monitoring patients with acute and long-term COVID-19, notably CRP, which had lower *p*-values. Multiple lines of evidence show the prognostic utility of this biomarker, which has been the focus of many COVID-19 case publications. Clinical investigations of CRP demonstrate a positive connection between sickness severity and baseline CRP levels [20].

Knowing that CRP is a prognostic marker of inflammation, one research correlated a rise in CRP levels and the disease's inflammatory levels with HRV in these individuals. In long-COVID patients, a 40% drop in HRV followed a 50% rise in CRP [21]. In our research, the case group had lower HRV, contributing to the idea that they had more inflammation.

COVID-19 may be responsible for the perpetuation of arrhythmias due to an increased catecholaminergic state caused by cytokines such as IL-6, IL-1, and tumor necrosis factor-alpha. This increased catecholaminergic state may prolong ventricular action potentials by altering the expression of cardiomyocyte ion channels [22-25]. Atrial fibrillations might be caused by COVID-19 (AF). During a viral infection, adrenergic modulation contributes to the development of postural orthostatic tachycardia syndrome as well as irregular sinus rhythm. Our study found a connection between the features of the heart rate and dysautonomia [26-30].

Heart rate variability (HRV) is a marker of cardiac dysautonomia. In order to provide evidence in favor of the dysautonomia hypothesis, we investigated heart rate variability (HRV) in both the time and frequency domains by performing a non-invasive study of sympathetic and parasympathetic activity in long COVID-19 patients. HRV [31–35] is a legitimate dysautonomia diagnosis. It is possible that HRV may be a useful tool for examining the neuroimmune systems and inflammatory processes of long COVID-19 patients. The high-frequency (HF) component of spectrum analysis and the LF/HF ratio, both of which are indications of vagal dysfunction, have been related with long COVID-19 syndrome. In individuals with long COVID-19, dysautonomia may have a variety of causes, including neurotropism, procoagulation, and inflammation. It is not known whether the protracted COVID-19 dysautonomia is caused by immune-mediated mechanisms after infection or by the autonomic–virus pathway. For the SARS-CoV-2 virus to enter cells during the acute phase of an infection, ACE2 is required. The fact that there was less heart failure in the case group compared to the control group is suggestive of an increase in parasympathetic activity in the extended COVID group [.

 doi:10.20944/preprints202211.0361.v1

In our study, SSDNN-24, SDANNi, rMSSD, pNN50, Max QTc, and Max QT showed substantial differences. When comparing data in the time domain and HRV frequency domain, a high positive association (r = 0.9986) was seen between SDNN-24 and SDANNi. Employing HRV measures in the time domains rMSSD and SDNN better indicated the increase in parasympathetic activity in individuals with COVID-19 and autonomic dysfunction [25]. Another study found that HRV, as measured by the NOL index, was substantially different between patients with extended COVID-19 and tiredness and the control group (without a diagnosis of COVID-19 and fatigue) [4].

Aragn-Benedi et al. [26] found a prevalence of parasympathetic tone and a concomitant withdrawal of sympathetic activity, along with a decline in HRV, in COVID-19-complicated patients, with the latter finding more prominent in those with a poorer outcome. According to the author, this finding is due to the pathogenic, cholinergic, anti-inflammatory response that results from sympathetic overactivity, causing immunological anergy and a poorer prognosis. Pan et al. [27] observed an increase in sympathetic activity during the initial phase of infection. They found a drop in HRV in critically sick patients in terms of SDNN and SDANN, as well as an increase in LF/HF, which coincided with elevations in humoral biomarkers such NT-proBNP and D-dimer.

Hasty et al. [21] found a drop in HRV characteristics in moderate COVID-19 individuals, which predicted a 72-h increase in CRP. In severe phases of the disease, sympathetic activity may explain the disparities between the two studies. After SIRS is diagnosed, the sympathetic–vagal balance may shift towards parasympathetic dominance to minimize systemic inflammation.

Infection with COVID-19 causes a "cytokine storm" with increased CRP and IL-6 [25], and these predict disease severity and poorer outcomes. The ANS regulates inflammation. Increased vagal responses boost HRV and decrease inflammation through the cholinergic anti-inflammatory pathway [26]. Pro-inflammatory sympathetic hyperactivity decreases HRV and has detrimental effects. Low HRV and dysautonomia have been linked to HIV, CAP, and Dengue [27–29]. Short- and long-term HRV recordings are inversely related to inflammatory markers [30,31]. In this study, a protracted COVID duration was linked to a higher mean heart rate. Higher numbers of SDNN 24 and SDANNI in control patients (OR = 0.98 (0.97 to 0.99; $p = 0.01$)) were associated.

Higher LF in COVID-19 patients (OR = 1.002 (1.0001 to 1.004), $p = 0.03$) was associated with increased HF in the control group (OR = 0.987 (0.98 to 0.995), $p = 0.001$). Dysautonomia may explain long COVID-19 patients' symptoms, according to an HRV power spectrum study. Vagal dysfunction is caused by procoagulation and cardiac strain. Long COVID-19 fiber loss may suggest vagal dysfunction [30]. Long COVID-19 autonomic innervation in vivo suggests clinical relevance. Appropriate medication may improve long-term prognoses for COVID-19 patients, who must be examined for diminished vagal activity, protracted NT-ProBNP elevations, and prothrombotic circumstances [31].

5. Limitations

Our study's limitations include the following: small sample size, all the limitations and risk of bias inherent to cross-sectional study designs, the inability to generalize the findings to different populations, and the potential for selection bias due to the single-center design.

6. Conclusions

Prolonged COVID-19 is associated with a preponderance of parasympathetic activity in autonomic heart rhythm control. This is the first study to assess HRV in long COVID-19 patients utilizing frequency and spectrum analysis. Dysautonomia may explain long COVID-19 sufferers' symptoms. Vagal dysfunction in these people may be caused by procoagulation and heart strain.

The impairment to cholinergic nerve fibers in individuals with long COVID-19 may indicate that the vagus nerve is dysfunctional. In our laboratory, we are determining

whether or not individuals with prolonged COVID-19 have autonomic innervation. Our research may have applications in the medical field. Treatment that is appropriate has the potential to improve both the clinical presentation and prognosis of long COVID-19 patients. Patients on the long COVID-19 protocol need to be carefully watched for signs of decreased vagal activity, prolonged elevations in NT-ProBNP, and a prothrombotic condition.

Author Contributions: Conceptualization, ASMJr. and AAS.; methodology, ASMjr.; software, ASMJr and ALR.; validation, ASMJr. and SMB.; formal analysis, ASMjr.; investigation, SMB.; resources, ASMJr and SMB.; data curation, ALR and AAS; writing—original draft preparation, ASMJr.; writing—review and editing, SMB.; visualization, SMB.; supervision, ASMjr.; project administration, ASMJR.All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Pontifical Catholic University of Goiás, (approval no. CAAE 47544021.9.0000.0037). for studies involving humans

Data Availability Statement: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Acknowledgments: The authors thank Editage (www.editage.com) for English language editing.

Conflicts of Interest: The authors declare that they have no conflict of interest.

References

1. Oronsky, B.; Larson, C.; Hammond, T.C.; Oronsky, A.; Kesari, S.; Lybeck, M.; Reid, T.R. A review of persistent post-COVID syndrome (PPCS). *Clin. Rev. Allergy Immunol.* **2021**, 1–9, *epub ahead of print*. https://doi.org/10.1007/s12016-021-08848-3.
2. Augustin, M.; Schommers, P.; Stecher, M.; Dewald, F.; Gieselmann, L.; Gruell, H.; Horn, C.; Vanshylla, K.; Di Cristanziano, V.; Osebold, L.; et al. Post-COVID syndrome in non-hospitalised patients with COVID-19: A longitudinal prospective cohort study. *Lancet Reg. Health Eur.* **2021**, *6*, 100122. https://doi.org/10.1016/j.lanepe.2021.100122.
3. Grubb, B.P. Autonomic Dysfunction as a Consequence of COVID-19 Infection. *J. Am. Coll. Cardiol.* **2022**, *79*, 2331–2332. https://doi.org/10.1016/j.jacc.2022.04.007.
4. Barizien, N.; Le Guen, M.; Russel, S.; Touche, P.; Huang, F.; Vallée, A. Clinical characterization of dysautonomia in long COVID-19 patients. *Sci. Rep.* **2021**, *11*, 14042. https://doi.org/10.1038/s41598-021-93546-5.
5. Sarfraz, Z.; Sarfraz, A.; Barrios, A.; Garimella, R.; Dominari, A.; Kc, M.; Pandav, K.; Pantoja, J.C.; Retnakumar, V.; Cherrez-Ojeda, I. Cardio-pulmonary sequelae in recovered COVID-19 Patients: Considerations for primary care. *J. Prim. Care Community Health* **2021**, *12*, 21501327211023726. https://doi.org/10.1177/21501327211023726.
6. Romero-Duarte, .; Rivera-Izquierdo, M.; de Alba, I.G.-F.; Pérez-Contreras, M.; Fernández-Martínez, N.F.; Ruiz-Montero, R.; Serrano-Ortiz, .; González-Serna, R.O.; Salcedo-Leal, I.; Jiménez-Mejías, E.; et al. Sequelae, persistent symptomatology and outcomes after COVID-19 hospitalization: The ANCOHVID multicentre 6-month follow-up study. *BMC Med.* **2021**, *19*, 129. https://doi.org/10.1186/s12916-021-02003-7.
7. Eshak, N.; Abdelnabi, M.; Ball, S.; Elgwairi, E.; Creed, K.; Test, V.; Nugent, K. Dysautonomia: An overlooked neurological manifestation in a critically ill COVID-19 patient. *Am. J. Med. Sci.* **2020**, *360*, 427–429. https://doi.org/10.1016/j.amjms.2020.07.022.
8. Dani, M.; Dirksen, A.; Taraborrelli, P.; Torocastro, M.; Panagopoulos, D.; Sutton, R.; Lim, P.B. Autonomic dysfunction in 'long COVID': Rationale, physiology and management strategies. *Clin. Med.* **2021**, *21*, e63–e67. https://doi.org/10.7861/clinmed.2020-0896.
9. Stella, A.B.; Furlanis, G.; Frezza, N.A.; Valentinotti, R.; Ajcevic, M.; Manganotti, P. Autonomic dysfunction in post-COVID patients with and witfhout neurological symptoms: A prospective multidomain observational study. *J. Neurol.* **2022**, *269*, 587–596. https://doi.org/10.1007/s00415-021-10735-y.
10. Kanjwal, K.; Jamal, S.; Kichloo, A.; Grubb, B.P. New-onset postural orthostatic tachycardia syndrome following coronavirus disease 2019 infection. *J. Innov. Card. Rhythm Manag.* **2020**, *11*, 4302–4304. https://doi.org/10.19102/icrm.2020.111102.
11. Nunan, D.; Sandercock, G.R.H.; Brodie, D.A. A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. *Pacing Clin. Electrophysiol.* **2010**, *33*, 1407–1417. https://doi.org/10.1111/j.1540-8159.2010.02841.x.
12. Jouven, X.; Empana, J.-P.; Schwartz, P.J.; Desnos, M.; Courbon, D.; Ducimetière, P. Heart-rate profile during exercise as a predictor of sudden death. *New Engl. J. Med.* **2005**, *352*, 1951–1958. https://doi.org/10.1056/nejmoa043012.
13. Ladlow, P.; O'Sullivan, O.; Houston, A.; Barker-Davies, R.; May, S.; Mills, D.; Dewson, D.; Chamley, R.; Naylor, J.; Mulae, J.; et al. Dysautonomia following COVID-19 is not associated with subjective limitations or symptoms but is associated with objective functional limitations. *Heart Rhythm* **2022**, *19*, 613–620. https://doi.org/10.1016/j.hrthm.2021.12.005.

14. Bivona, G.; Agnello, L.; Ciaccio, A.M. Biomarkers for prognosis and treatment response in COVID-19 patients. *Ann. Lab. Med.* **2021**, *41*, 540–548. https://doi.org/10.3343/alm.2021.41.6.540.
15. Laborde, S.; Mosley, E.; Thayer, J.F. Heart rate variability and cardiac vagal tone in psychophysiological research—Recommendations for experiment planning, data analysis, and data reporting. *Front. Psychol.* **2017**, *8*, 213. https://doi.org/10.3389/fpsyg.2017.00213.
16. Shinu, P.; Morsy, M.A.; Deb, P.K.; Nair, A.B.; Goyal, M.; Shah, J.; Kotta, S. SARS CoV-2 organotropism associated pathogenic relationship of gut-brain axis and illness. *Front. Mol. Biosci.* **2020**, *7*, 606779. https://doi.org/10.3389/fmolb.2020.606779.
17. Swai, J.; Hu, Z.; Zhao, X.; Rugambwa, T.; Ming, G. Heart rate and heart rate variability comparison between postural orthostatic tachycardia syndrome versus healthy participants; a systematic review and meta-analysis. *BMC Cardiovasc. Disord.* **2019**, *19*, 320. https://doi.org/10.1186/s12872-019-01298-y.
18. Shaffer, F.; Ginsberg, J.P. An overview of heart rate variability metrics and norms. *Front. Public Health* **2017**, *5*, 258. https://doi.org/10.3389/fpubh.2017.00258.
19. A Taylor, J.; A Lipsitz, L. Heart rate variability standards. *Circulation* **1997**, *95*, 280–281.
20. Tan, C.; Huang, Y.; Shi, F.; Tan, K.; Ma, Q.; Chen, Y.; Jiang, X.; Li, X. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J. Med. Virol.* **2020**, *92*, 856–862. https://doi.org/10.1002/jmv.25871.
21. Hasty, F.; García, G.; Dávila, C.H.; Wittels, S.H.; Hendricks, S.; Chong, S. Heart rate variability as a possible predictive marker for acute inflammatory response in COVID-19 patients. *Mil. Med.* **2020**, *186*, e34–e38. https://doi.org/10.1093/milmed/usaa405.
22. Lazzerini, P.E.; Laghi-Pasini, F.; Boutjdir, M.; Capecchi, P.L. Cardioimmunology of arrhythmias: The role of autoimmune and inflammatory cardiac channelopathies. *Nat. Rev. Immunol.* **2019**, *19*, 63–64. https://doi.org/10.1038/s41577-018-0098-z.
23. Agarwal, A.K.; Garg, R.; Ritch, A.; Sarkar, P. Postural orthostatic tachycardia syndrome. *Postgrad. Med. J.* **2007**, *83*, 478–480. https://doi.org/10.1136/pgmj.2006.055046.
24. Lau, S.-T.; Yu, W.-C.; Mok, N.-S.; Tsui, P.-T.; Tong, W.-L.; Stella, W.C. Tachycardia amongst subjects recovering from severe acute respiratory syndrome (SARS). *Int. J. Cardiol.* **2005**, *100*, 167–169. https://doi.org/10.1016/j.ijcard.2004.06.022.
25. Kaliyaperumal, D.; Rk, K.; Alagesan, M.; Ramalingam, S. Characterization of cardiac autonomic function in COVID-19 using heart rate variability: A hospital based preliminary observational study. *J. Basic Clin. Physiol. Pharmacol.* **2021**, *32*, 247–253. https://doi.org/10.1515/jbcpp-2020-0378.
26. Aragón-Benedí, C.; Oliver-Forniés, P.; Galluccio, F.; Altinpulluk, E.Y.; Ergonenc, T.; Allam, A.E.S.; Salazar, C.; Fajardo-Pérez, M. Is the heart rate variability monitoring using the analgesia nociception index a predictor of illness severity and mortality in critically ill patients with COVID-19? A pilot study. *PLoS ONE* **2021**, *16*, e0249128. https://doi.org/10.1371/journal.pone.0249128.
27. Pan, Y.; Yu, Z.; Yuan, Y.; Han, J.; Wang, Z.; Chen, H.; Wang, S.; Wang, Z.; Hu, H.; Zhou, L.; et al. Alteration of autonomic nervous system is associated with severity and outcomes in patients with COVID-19. *Front. Physiol.* **2021**, *12*, 630038. https://doi.org/10.3389/fphys.2021.630038.
28. Desforges, M.; Le Coupanec, A.; Stodola, J.K.; Meessen-Pinard, M.; Talbot, P.J. Human coronaviruses: Viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. *Virus Res.* **2014**, *194*, 145–158. https://doi.org/10.1016/j.virusres.2014.09.011.
29. Yu, H.; Sun, T.; Feng, J. Complications and Pathophysiology of COVID-19 in the Nervous System. *Front. Neurol.* **2020**, *11*, 573421. https://doi.org/10.3389/fneur.2020.573421.
30. Acanfora, C.; Casucci, G. Neprilysin inhibitor-angiotensin II receptor blocker combination (sacubitril/valsartan): Rationale for adoption in SARS-CoV-2 patients. *Eur. Heart J. Cardiovasc. Pharmacother.* **2020**, *6*, 135–136.
31. Shah, B.; Kunal, S.; Bansal, A.; Jain, J.; Poundrik, S.; Shetty, M.K.; Batra, V.; Chaturvedi, V.; Yusuf, J.; Mukhopadhyay, S.; et al. Heart rate variability as a marker of cardiovascular dysautonomia in post-COVID-19 syndrome using artificial intelligence. *Indian Pacing Electrophysiol. J.* **2022**, *22*, 70–76. https://doi.org/10.1016/j.ipej.2022.01.004.
32. Acanfora, D.; Nolano, M.; Acanfora, C.; Colella, C.; Provitera, V.; Caporaso, G.; Rodolico, G.R.; Bortone, A.S.; Galasso, G.; Casucci, G. Impaired Vagal Activity in Long-COVID-19 Patients. *Viruses* **2022**, *14*, 1035. https://doi.org/10.3390/v14051035.
33. Soliński, M.; Pawlak, A.; Petelczyc, M.; Buchner, T.; Aftyka, J.; Gil, R.; Król, Z.J.; Żebrowski, J.J. Heart rate variability comparison between young males after 4–6 weeks from the end of SARS-CoV-2 infection and controls. *Sci. Rep.* **2022**, *12*, 1–8. https://doi.org/10.1038/s41598-022-12844-8.
34. Marques, K.C.; Silva, C.C.; Trindade, S.D.S.; Santos, M.C.D.S.; Rocha, R.S.B.; Vasconcelos, P.F.D.C.; Quaresma, J.A.S.; Falcão, L.F.M. Reduction of Cardiac Autonomic Modulation and Increased Sympathetic Activity by Heart Rate Variability in Patients with Long COVID. *Front. Cardiovasc. Med.* **2022**, *9*, 862001. https://doi.org/10.3389/fcvm.2022.862001.
35. Asarcikli, L.D.; Hayiroglu, M.I.; Osken, A.; Keskin, K.; Kolak, Z.; Aksu, T. Heart rate variability and cardiac autonomic functions in post-COVID period. *J. Interv. Card. Electrophysiol.* **2022**, *63*, 715–721. https://doi.org/10.1007/s10840-022-01138-8.