Original Article

The Effect of COVID-19 Infection on Heart Rate Variability: A Cross-sectional Study

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Abstract

Introduction and Objectives: Heart rate variability (HRV) measurement is a non-invasive procedure used to evaluate autonomic nervous system (ANS) activity. We aimed to investigate the coronavirus disease 2019 (COVID-2019) infection effects on time-domain and frequency-domain HRV parameters to determine COVID-19 effects on the ANS. **Materials and Methods:** From the registry of the COVID-19 outpatient clinics between July 2020 and October 2021, 6127 patients with polymerase chain reaction (PCR) results positive for COVID-19 in real-time PCR (RT-PCR) test were obtained. Eighty-seven patients with at least 24 h of Holter electrocardiogram (ECG) recording with at least 90% normal–normal interval analysis referred to as the first Holter ECG analysis. Those patients underwent follow-up for the second Holter ECG analysis within 3 months following the first positive RT-PCR tests. The HRV time and frequency domain parameters by means of six standard time domain measures: standard deviation (SD) of all normal sinus RR intervals over 24 h (SDNN), mean of the SDs of all normal sinus RR intervals for all 5-min segments (SDNN index), root-mean-square of successive normal sinus RR interval difference (rMSSD), low-frequency (LF) band, high-frequency (HF) band, and LF/HF ratios were recorded from both the first and second Holter ECG analyses. Moreover, the third Holter ECG analysis was planned for patients if any statistically significant differences were observed among the first and the second Holter ECGs. **Results:** After COVID-19 infection with the second Holter ECG analysis, we found a significant decrease in SDNN, SDNN index, and a significant increase in LF/HF ratio ($P < 0.05$). Moreover, with the third Holter ECG analysis, which was performed in 48 of the 87 patients after 3 months following the second Holter ECG analysis, we have shown that those decreases in SDNN and SDNN index were reversed, and we found a significant increase in LF band and a non-significant decrease in LF/HF ratio ($P = 0.052$). **Conclusion:** The reversal in the changes of HRV parameters that occurred within the first 3 months following COVID-19 diagnosis may be an indicator of acute autonomic dysfunction due to COVID-19 infection.

Keywords: Autonomic nervous system, coronavirus disease 2019 infection, heart rate variability

Introduction

Heart rate variability (HRV) is a physiological phenomenon indicating the variation in the time intervals between consecutive heartbeats referred to as beat-to-beat intervals. HRV measurement is a non-invasive procedure commonly used to evaluate the effects of the autonomic nervous system (ANS) on heart rate (HR).[1] Non-invasive HRV measurement methods are divided into four main categories: time domain, spectral or

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frequency domain, geometric, and non-linear methods. Other methods of HRV measurement are baroreflex sensitivity and HR turbulence. The measurements can be calculated over either a short time as a 5-min electrocardiogram (ECG) recording or as a 24-h long-term ECG recording based on the chosen parameter.[2]

The stability of the selected time domain analysis (such as SDNN, SDNN index, and rMSSD) parameters over time in healthy individuals makes them preferable for the evaluation of ANS function.[3] Increased sympathetic nervous system (SNS) or decreased parasympathetic nervous system (PNS) activity decreases HRV, whereas increased PNS or decreased SNS activity increases HRV.[4]

Moreover, low HRV values have also been used as a risk marker for many cardiac or non-cardiac conditions.[5-8] Aging and psychiatric disorders can lead to reduced HRV, and gender variations have also been shown in HRV.[9,10]

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is the agent virus of coronavirus disease-2019 (COVID-19), has spread worldwide in the past 2 years causing serious morbidity and mortality in millions of patients.[11,12] Two recent clinical trials have suggested that COVID-19 may be associated with autonomic symptoms due to ANS dysfunction.[13,14]

In a recently published case report, reduced HRV was observed in a patient during COVID-19 infection.[15] To the best of our knowledge, no clinical study has yet investigated the effect of COVID-19 on HRV changes. Therefore, this study aimed to determine whether COVID-19 infection decreased HRV acutely due to ANS involvement.

Materials and Methods

This cross-sectional study was conducted in the cardiology department of a high-volume training and research hospital. The study protocol was approved by the local ethics committee of the hospital in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all the study participants.

Patient selection

From the registry of the COVID-19 outpatient clinics between July 2020 and October 2021, 6127 patients with polymerase chain reaction (PCR) results positive for COVID-19 in real-time PCR test of upper respiratory specimens were obtained. All were aged >18 years. Of those patients, 304 had a 24-h Holter ECG recording (Pathfinder, Spacelabs Healthcare, Snoqualmie, WA, USA) at least 6 months before their first positive PCR results were determined from hospital records. The Holter ECG recordings had been ordered due to symptoms of heart palpitation. Exclusion criteria were defined as: a rhythm other than sinus rhythm, diagnosis of sinoatrial atrioventricular conduction defect, use of beta-blockers, diltiazem, digoxin, or other anti-arrhythmic drugs that could cause significant changes in HRV values, any infectious disease diagnosed during Holter ECG recording, use of any medication for a psychiatric disorder, active smoking, a history of thyroid disease, cancer, autoimmune disease, hypertension, diabetes, peripheral neuropathy, metabolic disorders, chronic bronchitis, or asthma (documented or newly diagnosed after referral to internal medicine or neurology outpatient clinics),[16-19] computed tomography (CT) findings of pulmonary involvement in COVID-19, the clinical presentation with at least one symptom (eg, breathlessness, ankle swelling, or fatigue) and/or at least one sign (eg, elevated jugular venous pressure, pulmonary crackles, or peripheral edema) of heart failure.[20] After implementation of the exclusion criteria, 151 patients were eligible for the study.

The 24-h Holter ECG recordings of those 151 patients' data were collected. Only 87 patients with at least 24 h of Holter ECG recording with at least 90% normal–normal interval analysis referred to as the first Holter ECG analysis were accepted as suitable for HRV measurement. Those 87 patients were invited to participate in the study within 3 months following the positive PCR (after completing 14 days in quarantine) and included for analysis [Figure 1].

Time and frequency domain measures of heart rate variability in 24-h Holter electrocardiogram monitoring

The 24-h Holter ECG monitoring of all 87 patients was made using the same recording devices. These 87 ECG recordings, referred to as the second Holter ECG analysis, were found to be sufficient for HRV measurement. The mean HR, three main time-domain standard HRV parameters (standard deviation [SD] of all normal RR [NN] intervals [SDNN], mean of the SDs of all normal sinus RR intervals for all 5-min segments [SDNN index], and the root-mean-square of successive differences between NN intervals [rMSSD]), and three frequency-domain HRV parameters (low-frequency [LF] band, high-frequency [HF] band, and LF/HF ratio) were automatically calculated by the recording devices. All the

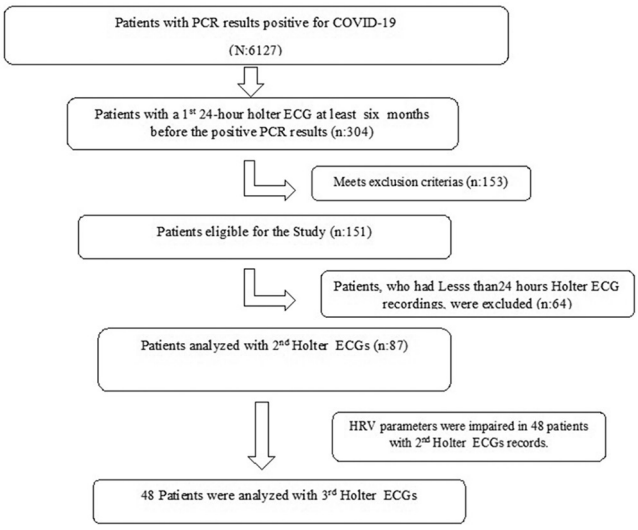

Figure 1: Patient selection criteria for the study

parameters from the first Holter ECG analysis and the second Holter ECG analysis were obtained by a clinician blinded to the characteristics of the patients. A third Holter ECG analysis was planned if any statistically significant differences were observed among the first and the second Holter ECGs.

Each patient's demographic characteristics, clinical characteristics, chronic medications, treatments for COVID-19 (favipiravir, oseltamivir, remdesivir, antibiotics, heparin, and hydroxychloroquine), and laboratory measurements for COVID-19 (creatinine level, white blood cell count, D-dimer level, ferritin level, BNP/proBNP [N-terminal prohormone of brain natriuretic peptide], troponin level, and C-reactive protein level) were collected. In addition, all the patients included in the study were assessed for orthostatic hypotension (OH) using a manual blood pressure cuff. OH was defined as a fall of >20 mmHg systolic and >10 mmHg diastolic after standing for 3 min.[21]

Statistical analysis

All statistical analyses were performed using IBM (SPSS Inc., Chicago, IL, USA) Statistics 25 software. The variables were stated as mean ± SD values when the distribution was normal according to the Kolmogorov–Smirnov test, otherwise as median and minimum–maximum values. Fisher's exact test was used to compare the categorical variables. For comparisons of the repeated measurements (HRV parameters, mean HR, and Holter ECG recording durations), the paired samples *t*-test was applied. $P < 0.05$ was considered statistically significant.

Ethical statement

This study was approved by the University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital Non-Interventional Health Sciences Research Ethics Committee with the decision number 2011-KAEK-25 2021/04-11, dated 28/04/2021.

Results

The patients comprised 26 (29.9%) males and 61 (70.1%) females, with a mean age of 43.39 ± 14.12 years (minimum: 19 and maximum: 73). None of the patients had syncopal episodes, whereas 11 (%12.6) of the patients stated at least an episode of dizziness that occurs after COVID-19 positivity. The demographic characteristics and chronic medications of the patients are shown in Table 1.

The median time interval between the date of the positive PCR test and the date of the second Holter ECG analysis was 36 days (minimum: 15 and maximum: 83). The laboratory measurements and treatments for COVID-19 are shown in Table 2.

The mean edited Holter ECG recording duration was similar in the first Holter ECG analysis and the second Holter ECG analysis (23.45 ± 0.91 h vs. 23.46 ± 0.87 h, $P = 0.17$). The second Holter ECG analysis showed that there was a significant decrease in SDNN and SDNN index, and an increase in LF/HF ratio ($P < 0.05$). The HF band was decreased but not at a significant level ($P = 0.092$) [Table 3].

Table 1: Demographic, clinical characteristics, and medications of the patients (*n*=87)

Variables	Results
Age (years), mean±SD	43.39±14.12
Male, *n* (%)	26 (29.9)
Hyperlipidemia, *n* (%)	4 (4.6)
CAD, *n* (%)	6 (6.9)
Kidney damage*, *n* (%)	3 (3.4)
ASA, *n* (%)	18 (20.7)
Furosemide, *n* (%)	3 (3.4)
Statins, *n* (%)	7 (8.0)
Syncope, *n* (%)	0
Dizziness, *n* (%)	11 (12.6)
OH, *n* (%)	6 (6.9)

*Glomerular filtration rate <60 ml/min/1.73 m^2. SD: Standard deviation, ASA: Acetylsalicylic acid, CAD: Coronary artery disease, OH: Orthostatic hypotension

Table 2: Laboratory measurements and treatments for coronavirus disease 2019

Variables	Results
Favipiravir, *n* (%)	87 (100)
Hydroxychloroquine, *n* (%)	17 (19.5)
Cephalosporin, *n* (%)	6 (6.9)
Macrolide antibiotic, *n* (%)	2 (2.3)
Quinolone antibiotic, *n* (%)	3 (3.4)
Heparin, *n* (%)	9 (10.3)
WBC, $\times 10^9$/L, mean±SD (*n*=45)	6.36±2.47
Neutrophils, $\times 10^9$/L, mean±SD (*n*=45)	3.38±1.43
Lymphocytes, $\times 10^9$/L, mean±SD (*n*=45)	2.48±0.93
D dimer, mg/L, mean±SD (*n*=45)	0.37±0.05
Hs-CRP, mg/L, median (minimum-maximum) (*n*=45)	10.5 (3.11-53.20)
Hs-cTn-T, ng/L, mean±SD (*n*=45)	3.51±0.76
Ferritin, ng/ml, median (minimum-maximum) (*n*=45)	128.90 (12-574)
BUN, mg/dl, mean±SD (*n*=45)	16.77±6.29
Creatinine, mg/dl, mean±SD (*n*=45)	0.86±0.18
Potassium, mmol/L, mean±SD (*n*=45)	4.65±0.47

WBC: White blood cell, BUN: Blood urea nitrogen, Hs-CRP: High-sensitivity C-reactive Protein, Hs-cTn-T: High-sensitive cardiac troponin T, SD: Standard deviation

To determine whether the changes in the HRV parameters recovered with time, 24-h Holter monitoring was repeated 3 months after the second Holter ECG analysis (third Holter ECG analysis). After implementation of the exclusion criteria and manual removal of artifacts and extra beats, 48 of the third Holter ECG analysis were eligible for comparison with the second Holter ECG analysis. In the comparison, a significant increase was observed in SDNN and SDNN index, and a significant decrease in the LF band ($P < 0.005$). The decrease in LF/HF ratio was not found to be statistically significant ($P = 0.052$) [Table 4].

Table 3: Comparisons of heart rate variability parameters in first Holter electrocardiogram analysis and second Holter electrocardiogram analysis

	First Holter ECG analysis (n=87)	Second Holter ECG analysis (n=87)	P
SDNN, ms, mean±SD	138.77±25.28	129.86±33.18	0.006
SDNN index, ms, mean±SD	42.53±9.08	40.68±10.83	0.032
rMSSD, ms, mean±SD	33.32±7.81	33.72±9.65	0.713
LF, ms^2, mean±SD	1168.97±222.65	1199.60±238.79	0.108
HF, ms^2, mean±SD	454.65±72.74	440.55±79.82	0.092
LF/HF, mean±SD	2.39±0.46	2.56±0.13	0.021
HR bpm, mean±SD	79.68±9.80	78.90±8.78	0.405

SD: Standard deviation, HF: High frequency, HR: Heart rate, LF: Low frequency, rMSSD: Root-mean-square of successive differences between NN intervals, SDNN: SD of all normal RR (NN) intervals, ECG: Electrocardiogram

Table 4: Comparisons of heart rate variability parameters between second Holter electrocardiogram analysis and third Holter electrocardiogram analysis in time interval <3-month group

	Second Holter ECG analysis (n=25)	Third Holter ECG analysis (n=25)	P
Holter ECG duration hours, mean±SD	23.64±0.80	23.30±0.69	0.102
SDNN, ms, mean±SD	130.60±37.97	145.71±38.64	0.013
SDNN index, ms, mean±SD	41.55±11.15	45.85±11.73	0.006
rMSSD, ms, mean±SD	35.89±10.92	37.54±14.71	0.356
LF, ms^2, mean±SD	1141.83±238.31	1073.00±196.18	0.018
HF, ms^2, mean±SD	445.04±81.30	476.93±129.20	0.070
LF/HF, mean±SD	2.56±0.12	2.34±0.50	0.052
HR bpm, mean±SD	79.64±9.32	78.07±10.25	0.209

SD: Standard deviation, HF: High frequency, HR: Heart rate, LF: Low frequency, rMSSD: Root-mean-square of successive differences between NN intervals, SDNN: SD of all normal RR (NN) intervals, ECG: Electrocardiogram

Discussion

The study revealed that a significant decrease was determined in the mean SDNN and SDNN index, a significant increase in LF/HF ratio, and a non-significant decrease in HF band in the patients who had a positive PCR result for COVID-19 within the past 3 months. The third Holter ECG analysis showed that the decrease in SDNN and SDNN index and the increase in LF/HF ratio were reversed 6 months after the second Holter ECG analysis. Moreover, a significant decrease in the LF band was observed.

SDNN, which is the SD of all normal RR (NN) intervals, is the most widely used time-domain HRV parameter. When calculated over 24 h, it indicates all the cyclic components which contribute to HRV.[22-24] A reduced SDNN value mostly refers to sympathetic overactivity or reduced vagal tonus or both.[25] LF band refers to oscillations of HR in the 0.04–0.15 Hz frequency range. It denotes both parasympathetic and sympathetic activities. The LF/HF ratio is another parameter indicating the sympathovagal balance.[26] It expresses the ratio of LF band to HF band which includes 0.16–0.4 Hz oscillations of HR. An increased LF/HF ratio indicates depressed vagal activity.[27,28] The current study findings that the decrease in SDNN and SDNN index and the increase in LF/HF ratio were reversible and may be associated with ANS dysfunction in COVID-19 favoring sympathetic overactivity or reduced vagal tonus for a short period. Similarly, Mittal *et al*.[29] showed that all the HRV parameters were decreased in the early stages of human immunodeficiency virus infection, in which autonomic dysfunction is relatively common.[30] In another clinical trial, the onset of autonomic symptoms occurred within a short interval after COVID-19 symptoms (median: 7 days).[14] In parallel with the results of the third Holter ECG analysis in this study, Asarcikli *et al*.[31] reported that post-COVID patients were more likely to have SDNN >60 msn, RMSSD >40 msn, and low LF/HF ratio compared to healthy individuals, indicating parasympathetic overtones in the post-COVID period.

Previous reports have shown that COVID-19 may cause Guillain–Barré syndrome or other types of peripheral neuropathy.[32,33] Neurological symptoms have been mostly observed in cases with severe COVID-19 infection. Direct viral invasion of the peripheral nervous system by the SARS-Cov-2 virus and/or immune-mediated damage to peripheral nerves have been considered two possible mechanisms of peripheral neuropathy in patients with COVID-19.[34]

The release of cytokines, which are tiny circulating peptides that act as mediators of the inflammatory response, is the primary host reaction in sepsis.[35] The pathophysiology of the systemic inflammatory response syndrome is thought to be an imbalance between the pro- and anti-inflammatory effects of cytokines.[36] Cytokines have wide-ranging impacts on signal transduction mechanisms and can hamper the sympathetic and PNSs on the regulation of HR.[35] For instance, the cytokines of tumor necrosis factor-alpha, interleukin (IL)-1b, and IL-6

increase HR. However, they can also blunt HR responses to beta-adrenergic agonists.[35]

IL-6 levels in the blood have been found to significantly associate with measures of reduced HRV in a variety of clinical situations, according to epidemiological research.[36] The indices of reduced HRV in systemic inflammation showed the highest connection with IL-6 among the cytokines. Gholami *et al*.[36] showed that on BALB/c mice, IL-6 receptor (gp130) is expressed in mouse atria, and incubation of isolated atria with recombinant IL-6 impaired the negative chronotropic response to cholinergic stimulation. Because cytokines could potentially blunt beta-adrenergic signaling, it has been proposed that cytokine overexpression and subsequent loss of beta-adrenergic responsiveness may contribute to the decrease in HRV during inflammation.[37] As a result, there is insufficient evidence to support the hypothesis that impaired responsiveness to the beta-adrenergic system contributes to changes in HRV indexes during systemic inflammation.[38] We did not measure plasma concentrations of catecholamines and cytokines in the study population. Further, studies are needed to elucidate whether COVID-19 affects the ANS in the same way as it affects the peripheral nervous system.

Study limitations

This study had several limitations, primarily that it was conducted in a single center, it was retrospective in design, and the female predominance may have affected the results. Second, anxiety disorders due to COVID-19 disease were not evaluated in the study and these may have contributed to the decrease in HRV values by increasing SNS activity. Third, we did not measure plasma concentrations of cytokines in the study population. Finally, coincident infectious diseases may have affected the results, so it is not possible to state definitively that the findings were specific to COVID-19.

Conclusion

The reversal in the changes of HRV parameters that occurred within the first 3 months following COVID-19 diagnosis may be an indicator of acute autonomic dysfunction due to COVID-19 infection.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Sassi R, Cerutti S, Lombardi F, Malik M, Huikuri HV, Peng CK, *et al.* Advances in heart rate variability signal analysis: Joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society. Europace 2015;17:1341-53.
2. Kleiger RE, Stein PK, Bigger JT Jr. Heart rate variability: Measurement and clinical utility. Ann Noninvasive Electrocardiol 2005;10:88-101.
3. Kleiger RE, Bigger JT, Bosner MS, Chung MK, Cook JR, Rolnitzky LM, *et al.* Stability over time of variables measuring heart rate variability in normal subjects. Am J Cardiol 1991;68:626-30.
4. Stein PK, Bosner MS, Kleiger RE, Conger BM. Heart rate variability: A measure of cardiac autonomic tone. Am Heart J 1994;127:1376-81.
5. Bigger JT Jr., Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Correlations among time and frequency domain measures of heart period variability two weeks after acute myocardial infarction. Am J Cardiol 1992;69:891-8.
6. Casolo G, Balli E, Taddei T, Amuhasi J, Gori C. Decreased spontaneous heart rate variability in congestive heart failure. Am J Cardiol 1989;64:1162-7.
7. Niklasson U, Olofsson BO, Bjerle P. Autonomic neuropathy in familial amyloidotic polyneuropathy. A clinical study based on heart rate variability. Acta Neurol Scand 1989;79:182-7.
8. Guzzetti S, Josa D, Pecis M, Bonura L, Prosdocimi M, Malliani A. Effects of sympathetic activation on heart rate variability in Chagas' patients. J Auton Nerv Syst 1990;30 Suppl:S79-81.
9. Friedman BH, Thayer JF. Autonomic balance revisited: Panic anxiety and heart rate variability. J Psychosom Res 1998;44:133-51.
10. Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. Biol Psychiatry 1996;39:255-66.
11. Huyut MA, Alisha G, Cetintulum Huyut B, Aliyeva A. Metoprolol's potential beneficial effects on covid-19 patients. Harran Univ Tip Fakultesi Derg 2022;19:22-9.
12. Huyut MA. Novel coronavirus pneumonia and cardiomyopathy: A case report. Arq Bras Cardiol 2020;114:843-5.
13. Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, *et al.* Autonomic dysfunction in 'long COVID': Rationale, physiology and management strategies. Clin Med (Lond) 2021;21:e63-7.
14. Shouman K, Vanichkachorn G, Cheshire WP, Suarez MD, Shelly S, Lamotte GJ, *et al.* Autonomic dysfunction following COVID-19 infection: An early experience. Clin Auton Res 2021;31:385-94.
15. Buchhorn R, Baumann C, Willaschek C. Heart rate variability in a patient with coronavirus disease 2019. Int Cardiovasc Forum J 2020;20:34-6.
16. Kaufman ES, Bosner MS, Bigger JT Jr., Stein PK, Kleiger RE, Rolnitzky LM, *et al.* Effects of digoxin and enalapril on heart period variability and response to head-up tilt in normal subjects. Am J Cardiol 1993;72:95-9.
17. Cook JR, Bigger JT, Kleiger RE, Fleiss JL, Steinman RC, Rolnitzky LM. Effect of atenolol and diltiazem on heart period variability in normal persons. J Am Coll Cardiol 1991;17:480-4. doi:10.1016/s0735-1097(10)80119-6.
18. Yeragani VK, Pohl R, Balon R, Ramesh C, Glitz D, Weinberg P, *et al.* Effect of imipramine treatment on heart rate variability measures. Neuropsychobiology 1992;26:27-32.
19. Zuanetti G, Latini R, Neilson JM, Schwartz PJ, Ewing DJ. Heart rate variability in patients with ventricular arrhythmias: Effect of antiarrhythmic drugs. Antiarrhythmic Drug Evaluation Group (ADEG). J Am Coll Cardiol 1991;17:604-12.
20. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.
21. Lahrmann H, Cortelli P, Hilz M, Mathias CJ, Struhal W, Tassinari M. EFNS guidelines on the diagnosis and management of orthostatic hypotension. Eur J Neurol 2006;13:930-6.
22. Kuusela T. Methodological aspects of heart rate variability analysis. In: Kamath MV, Watanabe MA, Upton AR, editors. Heart Rate

Variability (HRV) Signal Analysis. Boca Raton, FL: CRC Press; 2013. p. 9-42.
23. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93:1043-65.
24. Laborde S, Mosley E, Thayer JF. Heart rate variability and cardiac vagal tone in psychophysiological research – Recommendations for experiment planning, data analysis, and data reporting. Front Psychol 2017;8:213.
25. Salles GF, Ribeiro FM, Guimarães GM, Muxfeldt ES, Cardoso CR. A reduced heart rate variability is independently associated with a blunted nocturnal blood pressure fall in patients with resistant hypertension. J Hypertens 2014;32:644-51.
26. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: An integrative review of the heart's anatomy and heart rate variability. Front Psychol 2014;5:1040.
27. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;17:354-81.
28. Berntson GG, Bigger JT Jr., Eckberg DL, Grossman P, Kaufmann PG, Malik M, *et al.* Heart rate variability: Origins, methods, and interpretive caveats. Psychophysiology 1997;34:623-48.
29. Mittal CM, Wig N, Mishra S, Deepak KK. Heart rate variability in human immunodeficiency virus-positive individuals. Int J Cardiol 2004;94:1-6.
30. Carod-Artal FJ. Infectious diseases causing autonomic dysfunction. Clin Auton Res 2018;28:67-81.
31. Asarcikli LD, Hayiroglu Mİ, Osken A, Keskin K, Kolak Z, Aksu T. Heart rate variability and cardiac autonomic functions in post-COVID period. J Interv Card Electrophysiol 2022;63:715-21.
32. Finsterer J, Scorza FA. Guillain-Barre syndrome in 220 patients with COVID-19. Egypt J Neurol Psychiatr Neurosurg 2021;57:55.
33. Bureau BL, Obeidat A, Dhariwal MS, Jha P. Peripheral neuropathy as a complication of SARS-Cov-2. Cureus 2020;12:e11452.
34. Ftiha F, Shalom M, Jradeh H. Neurological symptoms due to coronavirus disease 2019. Neurol Int 2020;12:8639.
35. Griffin MP, Moorman JR. Toward the early diagnosis of neonatal sepsis and sepsis-like illness using novel heart rate analysis. Pediatrics 2001;107:97-104.
36. Gholami M, Mazaheri P, Mohamadi A, Dehpour T, Safari F, Hajizadeh S, *et al.* Endotoxemia is associated with partial uncoupling of cardiac pacemaker from cholinergic neural control in rats. Shock 2012;37:219-27.
37. Malave HA, Taylor AA, Nattama J, Deswal A, Mann DL. Circulating levels of tumor necrosis factor correlate with indexes of depressed heart rate variability: A study in patients with mild-to-moderate heart failure. Chest 2003;123:716-24.
38. Hajiasgharzadeh K, Mirnajafi-Zadeh J, Mani AR. Interleukin-6 impairs chronotropic responsiveness to cholinergic stimulation and decreases heart rate variability in mice. Eur J Pharmacol 2011;673:70-7.