Heart rate variability and cardiac autonomic functions in post-COVID period

Lale Dinc Asarcikli1 · Mert İlker Hayiroglu1 · Altug Osken1 · Kivanc Keskin1 · Zeynep Kolak1 · Tolga Aksu2

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Abstract
Background The heart rate variability (HRV) is a non-invasive, objective and validated method for the assessment of autonomic nervous system. Although acute manifestations of COVID-19 were widely researched, long-term sequela of COVID-19 are still unknown. This study aimed to analyze autonomic function using HRV indices in the post-COVID period that may have a potential to enlighten symptoms of COVID long-haulers.

Methods The 24-h ambulatory electrocardiography (ECG) recordings obtained >12 weeks after the diagnosis of COVID-19 were compared with age–gender-matched healthy controls. Patients who used drugs or had comorbidities that affect HRV and who were hospitalized with severe COVID-19 were excluded from the study.

Results Time domain indices of HRV analysis (standard deviation of normal RR intervals in 24 h (SDNN 24 h) and root mean square of successive RR interval differences (RMSSD)) were significantly higher in post-COVID patients (p < 0.05 for all). Among frequency domain indices, high frequency and low frequency/high frequency ratio was significantly higher in post-COVID patients (p = 0.037 and p = 0.010, respectively). SDNN >60 ms [36 (60.0%) vs. 12 (36.4%), p = 0.028] and RMSSD >40 ms [31 (51.7%) vs. 7 (21.2%), p = 0.003] were more prevalent in post-COVID patients. Logistic regression models were created to evaluate parasympathetic overtone in terms of SDNN >60 ms and RMSSD >40 ms. After covariate adjustment, post-COVID patients were more likely to have SDNN >60 msn (OR: 2.4, 95% CI:1.2–12.8) and RMSSD >40 ms (OR: 2.5, 95% CI: 1.4–9.2).

Conclusion This study revealed parasympathetic overtone and increased HRV in patients with history of COVID-19. This may explain the unresolved orthostatic symptoms occurring in post-COVID period which may be associated with autonomic imbalance.

Keywords COVID-19 · Post-COVID · Heart rate variability · Autonomic dysfunction

1 Introduction

The coronavirus disease 2019 (COVID-19), caused by a new coronavirus (SARS-CoV-2) emerged in Wuhan, China, rapidly evolved into a pandemic that caused morbidity and mortality worldwide. As of 2020 March 11, WHO declared it as a pandemic [1]. COVID-19 leads to a wide spectrum of clinical manifestations ranging from asymptomatic (fever, headache, myalgia, sore throat, cough, anosmia) to symptomatic severe viral pneumonia,
which usually progresses to acute respiratory distress syndrome and multi-organ failure.

COVID-19 has various presentations which is elucidated by SARS-CoV-2 having targets on various tissues such as lung parenchyma, myocardium, hypothalamus, pituitary, adrenal glands and olfactory nerve endings [2, 3]. This virus enters the target cells by binding to angiotensin-converting enzyme 2 (ACE2) [4]. The neurotropism of SARS-CoV-2 has recently been proved by demonstrating the presence of viral particles in brain tissues and cerebrospinal fluid of COVID-19 patients [5]. The hypothalamic pituitary adrenal axis (HPA) was affected by SARS-CoV-2 and could lead to dysautonomia. Acute manifestations of COVID-19 were widely researched and published; however, long-term sequela of COVID-19 are unknown and still investigated. Most patients with COVID-19 recover completely without sequela, while some patients continue to have diverse symptoms including autonomic dysfunction for longer than 12 weeks without an alternative diagnosis, also called “Post-COVID-19 syndrome” [6]. COVID long-haulers have symptoms of inappropriate palpitations, fatigue, orthostatic intolerance, dizziness, brain fog, nausea, anxiety, hyperhidrosis and syncope, and there is a lack of evidence how long these autonomic symptoms will last [7].

Heart rate variability (HRV) is a simple, non-invasive, objective and validated measure for the assessment of the autonomic nervous system function [8]. Time domain indices of HRV describe the amount of variability in duration between consecutive heartbeats. Time domain indices include standard deviation of normal to normal (NN) intervals (SDNN), root mean square of successive RR interval differences (rMSSD) and percentage of successive RR intervals (pNN50) [8]. Frequency domain indices of HRV include low frequency (LF) and high frequency (HF) band in spectral analysis. The HF delineates the parasympathetic activity, whereas LF delineates both sympathetic and parasympathetic activity, and SDNN, rMSSD and pNN50 describe parasympathetic activity [8, 9]. The LF/HF index is thought to represent the sympathetic and parasympathetic balance [8].

Impaired HRV has been associated with poor outcomes in various diseases [10]. There are few studies that analyzed the status of the autonomic nervous system (ANS) by measuring HRV in hospitalized COVID-19 patients and few case reports presented autonomic dysfunction in COVID-19 patients [2, 11–14]. However, there is no investigation in recovered COVID-19 patients examining the autonomic balance using HRV in the post-infectious period. In the present study, we aimed to analyze autonomic imbalance using HRV variables in patients after COVID-19 that may have a potential to enlighten the symptoms of COVID long-haulers.

2 Material and methods

2.1 Study population

In this retrospective study analyzing the HRV parameters, 60 consecutive patients treated COVID-19 between March 2020 and March 2021, and 33 age-matched healthy controls were enrolled. Study group consisted of consecutive post-COVID patients evaluated in the outpatient clinic who had 24-h Holter monitoring for the indication of palpitations, within 12 to 26 weeks following the diagnosis of COVID-19 (post-COVID period). Following COVID, symptoms can persist up to 12 weeks (ongoing symptomatic COVID). To analyze the effect of post-COVID on HRV indices, we enrolled 24-h ambulatory ECG recordings that were performed in post-COVID period. All cases of COVID-19 were confirmed through real-time reverse-transcriptase polymerase chain reaction assays on nasopharyngeal swabs. None of the patients had any of the active COVID-19 disease manifestations during evaluation (no symptoms for at least 1 month). The control group was selected from the non-COVID era database (before December 2019), to avoid unintentional inclusion of individuals who may have had asymptomatic COVID-19. Control group consisted of consecutive subjects with palpitations, no known autonomic imbalance, cardiovascular diseases or risk factors, who had 24-h Holter monitors. For all patients, medical comorbidities, physical examination findings, laboratory findings and standard 12-lead electrocardiograms obtained in the index outpatient clinic visit day were recorded for analysis.

All patients had a transthoracic echocardiogram performed routinely at the outpatient clinic visit by using 2.5–3.5 MHz transducer (S5-1 transducer with Phillips EPIQ 7C System-Philips Healthcare, Andover, MA, USA) [15]. The intraobserver variability of echocardiographic measurements ranged between 4 and 7%, and all examinations were performed by an experienced echocardiographer, who had no knowledge of the patient’s clinical information.

Patients with overt cardiovascular disease including coronary artery disease, arrhythmia, hypertension, left ventricular hypertrophy, moderate or severe valvular heart disease, renal failure, depression, morbid obesity, diabetes and obstructive sleep apnea were excluded. Patients with history of syncope, presyncope or known arrhythmias were excluded. Patients who had severe COVID infection (hospitalized in intensive care unit or requiring of high flow oxygen treatment) were excluded Individuals who use drugs that affect ANS function (beta blockers, inhaled beta-mimetics, atropine, glycosides, selective serotonin reuptake inhibitors, angiotensin-converting enzyme inhibitors, etc.) were also excluded. A diagram summarizing patient selection and allocation into groups is provided in Fig. 1.
This study was conducted in accordance with the 1975 Declaration of Helsinki and its subsequent revision, and the study was approved by institutional ethics committee.

2.2 Assessment of heart rate variability

HRV was analyzed using 24-h ambulatory ECG recordings through a multichannel electronic data recording system which permits to transfer and analysis of ECG data. ECG data were transferred from recording unit (DMS300-4A Holter ECG recorder) to the computer with dedicated software installed (CardioScan Premier 12, USA). The recorded series of RR intervals were processed in terms of frequency and time domain analysis during the 24-h period. Frequency domain indices of HRV that include LF and HF are calculated using spectral analysis during the 24-h period. 24-h Holter data were also evaluated for arrhythmias including atrial fibrillation, atrial flutter, supraventricular tachycardia, frequent premature ventricular contractions (defined as ≥10% premature ventricular contractions on 24-h Holter recording), ventricular tachycardia, ventricular fibrillation and atrioventricular block (second degree or higher).

2.3 Statistical analysis

The distribution of normality was assessed by Kolmogorov–Smirnov test. Continuous variables were given as median and interquartile range, or mean and standard deviation compared using the t-test or the Mann–Whitney U test, as appropriate. Categorical variables were given as numbers and percentages and analyzed by Pearson’s Chi-square test or the Fisher exact test. Logistic regression models were formed in order to elucidate the effect of SDNN>60 and RMSSD>40 by COVID-19 infection. In accordance with the distribution of the SDNN and RMSSD of the study population, SDNN >60 ve RMSSD>40 were determined as the higher parasympathetic tone which were used previously in the literature [2, 9]. The results of regression analysis were given as the odds ratio (OR) with 95% confidence interval (CI). Two models were used in the logistic regression analysis: model I; unadjusted and model II; adjusted. Model II was adjusted to age, gender, creatinine, left ventricle ejection fraction and left atrial anteroposterior diameter with healthy group serving as a reference group. A P value <0.05 was considered significant. Analyses were performed using Statistical Package for Social Sciences software; SPSS 25.0 (IBM Inc., USA).

3 Results

Sixty patients with a history of COVID-19 and thirty-three age-gender matched healthy controls were included in the final analyses. The general characteristics of the patients are shown in Table 1. There was no significant difference for clinical characteristics, hemoglobin and blood cell counts, and echocardiographic parameters between patients and controls.

In the time domain indices of HRV analysis, rMSSD (41 (27-61) vs. 31 (22-37), \( p = 0.002 \)) and PNN50 (14 (11-18) vs. 9(3-16), \( p = 0.032 \)) were significantly higher in the study group. In the frequency domain analysis of HRV, HF was significantly higher in the study group (325 (175-540) vs. 148 (105-544), \( p = 0.037 \)) reflecting the differences in vagal tone (Fig. 2, Table 2). In the frequency domain analysis of HRV, LF values which indicate dominance of sympathetic nervous system were similar between groups (712 (478 – 946) vs. 665 (561 – 1065), \( p = 0.599 \)). However, as an indicator of sympathetic predominance LF/HF ratio was lower in the study group (1.99 (1.29 – 3.80) vs. 3.53 (1.97 – 5.78), \( p = 0.010 \)).

To put forth parasympathetic overtone, RMSSD >40 ms and SDNN >60 ms were compared between groups [9]. In the logistic regression models, the ratio of SDNN >60 ms and RMSSD >40 ms was more prevalent in the study group (36 (60.0%) vs. 12 (36.4%), \( p = 0.028 \)) for SDNN and 31
After covariate adjustment, it was revealed that patients with history of COVID-19 were more likely to have SDNN >60 ms (OR: 2.4, 95% CI: 1.2–12.8) and RMSSD >40 ms (OR: 2.5, 95% CI: 1.4–9.2) (Table 3).

As shown in Supplementary Table 1, no significant differences in HRV indices according to the gender were detected when the effect of gender on HRV indices was investigated in both healthy controls and post-COVID patients.

Overall, atrial fibrillation or flutter was identified in 2 (3.33%) patients in the study group. Frequent premature ventricular contractions were seen in 6 (10.0%) patients. There was no ventricular tachycardia or ventricular fibrillation in any patient. Atrioventricular block (Mobitz type 1) was seen in 4 (6.66%) patients. No arrhythmia was detected in control group.

4 Discussion

The main findings of the current study were as follows: i) patients with confirmed history of COVID-19 demonstrated increased HRV indices suggesting higher parasympathetic
tone than controls, ii) history of COVID-19 has no clear effect on HRV indices reflecting sympathetic activity. HRV alteration and autonomic dysfunction have been previously described in various viral infections [16, 17]. The long-term prognosis of the post-COVID patients in terms of cardiovascular effects and other sequela is still unknown. Recent case reports and studies revealed that many patients developed postural orthostatic tachycardia syndrome (POTS) after COVID-19 [6, 18]. To detect POTS and dysautonomia, multidisciplinary integrated clinical diagnostic care is needed because dysautonomia symptoms cross over into the areas of multiple expertise. These patients require longer visits and need more clinical resources for comprehensive diagnostic evaluation.

HRV, which is affected by autonomic nervous system, is a simple, noninvasive and validated method. Parasympathetic

Table 2  Comparison of 24-h ambulatory rhythm monitoring findings of healthy controls and study group

| Variables                  | Normal ranges* | Healthy controls (n=33) | Study group Post-COVID patients (n=60) | P value |
|----------------------------|----------------|-------------------------|---------------------------------------|---------|
| Total beats                |                | 107.668 (99.307 – 115.451) | 106.022 (99.288 – 117.336) | 0.664   |
| Mean heart rate, bpm       | 78 ± 7         | 79 (72 – 85)            | 77 (71 – 82)                         | 0.424   |
| HRV time domains           |                |                         |                                       |         |
| SDNN 24 h, ms              | 143 ± 32       | 147 (126 – 166)         | 155 (144 – 177)                      | 0.015   |
| SDANN, ms                  | 130 ± 33       | 135 (114 – 154)         | 154 (127 – 166)                      | 0.041   |
| SDNN index                 | 64 ± 15        | 53 (47 – 64)            | 64 (54 – 97)                         | 0.003   |
| SDNN >60 ms                | 12 (36.4%)     | 36 (60.0%)              |                                       | 0.028   |
| RMSSD, ms                  | 35 ± 11        | 31 (22 – 37)            | 41 (27 – 61)                         | 0.002   |
| RMSSD >40 ms               | 7 (21.2%)      | 31 (51.7%)              |                                       | 0.003   |
| PNN50, %                   | 13 ± 9         | 9 (3 – 16)              | 14 (11 – 18)                         | 0.032   |
| HRV frequency domains      |                |                         |                                       |         |
| TP, ms²                    |                | 2.854 (2.212 – 4.195)   | 3.148 (2.348 – 4.408)                | 0.474   |
| LF, ms²                    |                | 665 (561 – 1065)        | 712 (478 – 946)                      | 0.599   |
| HF, ms²                    |                | 148 (105 – 544)         | 325 (175 – 540)                      | 0.037   |
| LF/HF                      |                | 3.53 (1.97 – 5.78)      | 1.99 (1.29 – 3.80)                   | 0.010   |

Table 3  Logistic regression models for SDNN>60 and RMSSD>40 by Post-COVID patients

| Variables                  | Healthy controls (n=33) | Post-COVID patients (n=60) | P value |
|----------------------------|-------------------------|---------------------------|---------|
| SDNN >60, n (%)            | 12 (36.4)               | 36 (60.0)                 |         |
| SDNN >60, OR (95% CI)      |                         |                           |         |
| Model 1: unadjusted        | 1[Reference]            | 2.6 (1.1 – 6.3)           | 0.001   |
| Model 2: adjusted for all covariates* | 1[Reference]        | 2.5 (1.1 – 6.6)           |         |
| RMSSD >40, n (%)           | 7 (21.2)                | 31 (51.7)                 |         |
| RMSSD >40, OR (95% CI)     |                         |                           |         |
| Model 1: unadjusted        | 1[Reference]            | 3.9 (1.4 – 10.5)          |         |
| Model 2: adjusted for all covariates* | 1[Reference]        | 4.6 (1.5 – 13.6)          |         |

*Umetani K, Singer DH, McCratty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. J Am Coll Cardiol. 1998 Mar 1;31(3):593-601

Continuous variables are presented as median (interquartile range)

SDNN, standard deviation of normal-to-normal R-R intervals 24-h; SDANN index, standard deviation of the mean R-R intervals calculated over a 5-min period; SDNN index, mean of the standard deviation of R-R intervals calculated over a 5-min period; rMSSD, square root of the mean squared difference of successive R-R intervals; pNN50, the percentage of the differences between adjacent normal R-R intervals exceeding 50 milliseconds; TP, total power; HF, high frequency; LF, low frequency

CI, confidence interval; OR, odds ratio

Adjusted for; age, gender, hemoglobin, creatinine, left ventricular ejection fraction and left atrial anteroposterior diameter
system increases HRV while decreased vagal activity reduces HRV [8]. Analysis of HRV has been demonstrated to be useful for early detection of acute inflammatory response and prognosis of COVID-19 in hospitalized patients [11, 12]. In acute disease stages, sympathetic activation results in inflammatory cytokine release, and to counterbalance this response, vagal anti-inflammatory reflex results in an anti-inflammatory response. Autonomic balance is essential for appropriate and balanced response to existing infection, and it is crucial for the maintenance of the body’s homeostasis. This strong hyper-immune reaction is in turn balanced by a compensatory anti-inflammatory response modulated by vagal-cholinergic pathway [19]. Parasympathetic and sympathetic tones are well known to influence HRV. Kalyaperumal et al. investigated HRV parameters in hospitalized COVID-19 patients with mild to moderate symptoms [2]. They found that acute COVID-19 infection was associated with parasympathetic dominancy compared to healthy controls [2]. In another study analyzing HRV in critically ill COVID-19 patients, they revealed the presence of autonomic imbalance with predominance of parasympathetic system due to sympathetic tone depletion [12]. Our study correlates with these investigations presenting long-term existence of parasympathetic overtone in post-COVID patients.

In a study from Mayo Clinic, including patients with symptoms concerning for para−/−postinfectious autonomic dysfunctions after COVID-19 found that 17 of 27 (63%) patients had abnormal findings on standardized autonomic function testing (head-up tilt test, sudomotor axon reflex testing, thermoregulatory sweat test, cardiovascular function by analyzing heart rate responses to deep breathing and Valsalva maneuver) [7]. The most common autonomic manifestation post-COVID-19 was orthostatic intolerance and remaining presentations ranging from symptomatic postural orthostatic tachycardia to severe autonomic dysfunctions. Our observation and clinical data suggest that patients with COVID disease have higher heart rates during the acute infection and also continue to have higher heart rates in early days and weeks in the convalescence. Our findings suggest that the patients who are 12-weeks or longer in the convalescence might have a reactive ‘overshoot’ of parasympathetic activity. An autonomic imbalance observed with COVID-19 infection modulating the sympathetic tonus increase in the early period may prevent parasympathetic overshooting.

COVID-19 has known adverse effects on multi-organ system resulting in fatigue, dyspnea, cognitive disturbances, chest pain, arthralgia and decline in the quality of life on long-term follow-up [20]. While most people with COVID-19 recover completely, some patients continue to have chronic and diverse symptoms including autonomic manifestations. Prolonged parasympathetic activity might be responsible for these symptoms. Further follow-up and prospective studies were needed to make interpretation about the effect of parasympathetic dominancy on the prognosis in post-COVID.

5 Limitations

Our study has several limitations. This was a single-center study with small sample size. We only include mild-moderate degree severity of COVID-19 patients admitting to our hospital. Asymptomatic and severe symptomatic patients with COVID-19 were not included. Unfortunately, we do not have data on the HRV indices of post-COVID asymptomatic patients, as these patients were not included in the study. Prolonged hospitalization and steroid use in severe COVID-19 cases may have a confounding effect on HRV. HRV indices, especially HF and LF indices, are influenced by the rate and depth of breathing. Patients’ breathing characteristics were not measured and standardized in this study. We did not measure degree of inflammation at the time of illness with inflammatory markers; instead, we classified the disease severity only with radiological involvement. Only patients, who did undergo holter monitoring, were included in the study population, so the results may not represent whole post-COVID population. Control groups were not selected from the same time period they were recruited from non-COVID era (pre-2019) which could introduce bias.

6 Conclusion

This study revealed parasympathetic overtone and increased HRV in patients with history of COVID-19 in post-COVID period. This may explain the unresolved symptoms especially orthostatic symptoms occurring in post-COVID which may be associated with autonomic imbalance.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10840-022-01138-8.

Declarations

Ethical approval Permission was taken from Haydarpasa Numune Education and Research Hospital Ethics Committee with dated 01.02.2021, and No: HNEAH-KAEK 2021/KK/42.

Patients’ consent Informed consent is not required as it is a retrospective study and patient identity was kept anonymous.

Conflict of interest The authors declare that they have no conflict of interest.

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