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Evaluation of the long-term autonomic dysfunction after the recovery of COVID-19 disease

Ajar Koçak[1], Sezen Bağlan Uzunget[2], Kader Eliz Şahin[3]

[1]*Department of Cardiology, Faculty of Medicine, Ufuk University, Ankara, Turkiye*

[2]*Department of Cardiology, Liv Hospital Ankara, Ankara, Turkiye*

[3]*Department of Cardiology, Kocaeli City Hospital, Kocaeli, Turkiye*

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ABSTRACT

Aims: Beyond the acute phase of the COVID-19 disease, many patients experience persistent symptoms, collectively termed "post-COVID syndrome," which includes autonomic dysfunction. Heart rate variability (HRV) is a well-established method to assess autonomic nervous system (ANS) function. This study aimed to investigate the long-term impact of COVID-19 on autonomic function through evaluating the changes in HRV.

Methods: This retrospective study included 225 participants divided into two groups: 117 post-COVID patients and 108 age and gender matched controls. HRV was assessed using 24-hour Holter monitoring. Time-domain and frequency-domain indices were analyzed, including standard deviation of normal-to-normal intervals (SDNN), root mean square of successive RR interval differences (RMSSD), and low frequency (LF)/high frequency (HF) ratio. Statistical comparisons were performed using independent t-tests, Mann-Whitney U tests, and correlation analyses.

Results: Post-COVID patients exhibited significantly lower HRV indices compared to controls. Time-domain metrics such as SDNN (135.7±39.5 ms vs 149.1±34.2 ms, p=0.007) and RMSSD (32.7±13.7 ms vs 37.5±14.7 ms, p=0.012) were reduced in the COVID-19 group. Frequency-domain indices, including total power (TP) and HF power, were also diminished. Correlation analysis revealed no significant association between the duration of time post-COVID (one-year follow-up) and most HRV parameters.

Conclusion: Post-COVID patients experience significant autonomic dysfunction, marked by reduced parasympathetic activity and increased cardiovascular risks, with some evidence of partial recovery during sleep. Routine HRV monitoring and targeted interventions, alongside further research with larger cohorts, are crucial for better understanding of the long-term effects and improving patient outcomes.

Keywords: Post-COVID syndrome, autonomic dysfunction, heart rate variability

INTRODUCTION

The novel coronavirus SARS-CoV-2, responsible for the 2019 coronavirus disease (COVID-19) global pandemic[1], resulted in significant morbidity and mortality.[2] This disease presents a wide spectrum of clinical manifestations, ranging from asymptomatic or mild symptoms, such as fever, headache, myalgia, sore throat, and anosmia, to severe viral pneumonia, which can progress to acute respiratory distress syndrome and multi-organ failure.[3]

While the acute manifestations of COVID-19 have been extensively studied, there is a growing concern about the long-term effects of the virus, often referred to as "long COVID" or "post-COVID syndrome".[4] This syndrome encompasses a variety of symptoms, including fatigue, cognitive disturbances, chest pain, and autonomic dysfunction, which persist for weeks or months after the initial infection has resolved.[5] The autonomic nervous system (ANS), which regulates involuntary physiological functions, appears to be particularly affected in these patients. Recent studies have demonstrated the neurotropism of SARS-CoV-2, with viral particles being detected in brain tissues and cerebrospinal fluid of COVID-19 patients. This neurotropism suggests a possible mechanism for the autonomic dysfunction observed in many patients during and after the acute phase of the disease.[6]

Heart rate variability (HRV) is a well-established, non-invasive method for assessing the ANS's function.[7] HRV reflects the heart's ability to respond to various physiological and environmental stimuli, and its indices can provide insight into the balance between sympathetic and parasympathetic activity.[8] Time-domain indices of HRV, such as the standard

Corresponding Author: Ajar Koçak, kocakajar@gmail.com

deviation of normal-to-normal intervals (SDNN) and the root mean square of successive RR interval differences (RMSSD), reflect parasympathetic activity.[9] Frequency-domain indices, including low frequency (LF) and high frequency (HF) bands, represent the contributions of sympathetic and parasympathetic nervous systems.[10] Abnormalities of these parameters indicates impaired HRV which is associated with poor cardiovascular prognosis.[11]

Limited research has been conducted on ANS status in recovered COVID-19 patients using HRV indices in the long term of the post-infection period. This study aimed to compare HRV indices in patients recovered from the COVID-19 disease (post-COVID) with individuals who have never contracted the virus. The study seeks to understand the long-term effects of COVID-19 on the ANS in order to obtain valuable insights into the persistent symptoms experienced by those patients and contribute to the development of therapeutic interventions to improve their quality of life.

METHODS

Ethics

The study was conducted following the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from Adıyaman University Non-interventional Clinical Researches Ethics Committee (Date: 21.06.2022, Decision No: 2022/6-4).

Study Population

This retrospective study evaluated 225 participants in two groups: 117 patients in the COVID-19 group and 108 control subjects. The patient group consisted of individuals diagnosed with COVID-19 disease but did not experience severe symptoms requiring hospitalization, this group was evaluated within 12 month after the recovery of the disease. The control group, matched by age and gender to the patient group, was selected from the non-COVID era database to prevent the unintentional inclusion of asymptomatic COVID-19 cases.

The exclusion criteria included the presence of any comorbidities known to influence autonomic function, such as cardiovascular diseases, obesity, diabetes, chronic renal disease, obstructive sleep apnea and depression. Those using medications that could affect HRV (like beta blockers, inhaled beta-mimetics, atropine, glycosides, selective serotonin reuptake inhibitors, angiotensin-converting enzyme inhibitors, etc.) were also excluded.

HRV Assessment

HRV was assessed using 24-hour ambulatory electrocardiography (ECG) recordings. The ECG data were collected using a DMS300-4A Holter ECG recorder and analyzed with CardioScan Premier 12 software. Time-domain indices of HRV including SDNN (standard deviation of all normal RR intervals in a 24-hour period), Standard deviation of the average normal-to-normal intervals (SDANN), SDNNi (the index of SDNN), RMSSD and pNN50 (percentage of successive RR intervals that differ by more than 50 ms) were calculated. Furthermore frequency-domain indices of HRV including LF (low frequency, representing both sympathetic and parasympathetic activity), HF (high frequency, representing parasympathetic activity) and LF/HF ratio (indicating the balance between sympathetic and parasympathetic activity) were also calculated.

Statistical Analysis

Statistical analysis was conducted using SPSS (Statistical Package for Social Sciences) version 20. Normality of the data was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics were presented as mean and standard deviation for numerical variables, and as counts and percentages for categorical variables. Comparative analyses between the study and control groups were performed using independent t-tests for normally distributed numerical data and the Mann-Whitney U test for non-normally distributed data. Categorical variables were compared using the Chi-square test. Pearson correlation analysis was used for variables that met normal distribution criteria, while Spearman correlation was used for non-normally distributed variables. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the study group was 38.7±6.7 years, while the control group had a mean age of 41.3±13.7 years. The gender distribution was comparable between the groups, with 68.5% females in the study group and 58.1% females in the control group.

The HRV metrics for both groups, summarized in **Table**, reveal significant differences. In the time-domain indices, the control group had higher SDNN over 24 hours values than the study group (149.1±34.2 ms vs 135.7±39.5 ms, p=0.007). Similarly, SDANN over 24 hours was higher in the control group compared to the study group (134.7±34.1 ms vs 123.4±41.7 ms, p=0.027). SDNNi over 24 hours was also greater in the control group than the study group (64.2±17.1 ms vs 56.7±16.2 ms, p<0.001). RMSSD was higher in the control group than in the study group (37.5±14.7 ms vs 32.7±13.7 ms, p=0.012), and pNN50 was significantly higher in the control group compared to the study group (14.7±10.5 vs 10.8±9, p=0.003).

In the frequency-domain indices, total power (TP) was significantly higher in the control group compared to the study group (4.254±2.208 ms^2 vs 3.378±1.908 ms^2, p=0.002). LF power was also higher in the control group compared to the study group (992.2±421.6 ms^2 vs 736.5±412.1 ms^2, p<0.001). HF power was elevated in the control group compared to the study group (413.9±272.5 ms^2 vs 305.7±251.5 ms^2, p=0.023). However, the LF/HF ratio did not differ significantly between the two groups (3.05±1.6 vs 3.17±1.8, p=0.597). Similar results were observed during both sleep and waking periods, with the control group consistently showing higher values across most HRV metrics compared to the study group.

Regarding the relationship between the length of the post-COVID period and HRV metrics. Most HRV indices did not show significant correlation with the duration of post-COVID symptoms with 12 months of follow up, except for the LF/HF ratio during sleep, which had a negative correlation (r=-0.23, p=0.02).

Table 1. Descriptive statistics of study variables and comparison between groups

Variable	Control group (n=117)	Study group (n=108)	p
Age (years)	38.7±6.7	41.3±13.7	0.068
Gender n(%)			
Female	68 (58.1%)	74 (68.5%)	0.106
Male	49 (41.9%)	34 (31.5%)	0.107
Post-COVID duration (months)	-	5.8±3.9	-
HRmin	46.7±6.8	49.1±8.6	0.021*
HRmax	145.7±17.9	139.3±28.2	0.041*
HRaverage	79.1±9.2	78.5±9.3	0.627
SDNN ms (24 hours)	149.1±34.2	135.7±39.5	0.007*
SDANN (24 hours)	134.7±34.1	123.4±41.7	0.027*
SDNNi (24 hours)	64.2±17.1	56.7±16.2	<0.001*
RMSSD (24 hours)	37.5±14.7	32.7±13.7	0.012*
pNN50 (24 hours)	14.7±10.5	10.8±9.1	0.003*
TP (24 hours)	4.254±2.208	3.378±1.908	0.002*
LF (24 hours)	992.2±421.6	736.5±412.1	<0.001*
HF (24 hours)	413.9±272.5	305.7±251.5	0.023*
LF/HF ratio (24 hours)	3.05±1.6	3.17±1.8	0.597
Awake SDNN	128.8±29.9	117.3±32.8	0.006*
Awake RMSSD	33.2±14.1	31.4±21.6	0.461
Awake pNN50	11.5±9.6	10.4±9.7	0.393
Awake TP	4.012±2.191	3.118±1.846	0.001*
Awake LF	962.1±415.3	707.6±434.7	<0.001*
Awake HF	360.5±375.9	241.4±193.1	0.004*
Awake LF/HF ratio	3.7±2.1	3.8±2.3	0.734
Sleep SDNN	120.4±35.2	108.4±38.3	0.015*
Sleep RMSSD	46.3±19.3	38.5±18.9	0.003*
Sleep pNN50	22.8±15.1	16.1±15.2	0.001*
Sleep TP	4.695±2.489	3.798±2.487	0.007*
Sleep LF	1046.3±484.1	720.4±450.9	<0.001*
Sleep HF	566.4±378.4	420.6±422.9	0.007*
Sleep LF/HF ratio	2.46±1.5	2.81±1.7	0.102

Abbreviations: HR: Heart rate, SDNN: Standard deviation of normal-to-normal intervals, SDANN: Standard deviation of the average normal-to-normal intervals, SDNNi: Index of the standard deviation of normal-to-normal intervals , RMSSD: Root mean square of successive RR interval differences, pNN50: Percentage of successive RR intervals that differ by more than 50 ms, TP: Total power , LF: Low frequency bands, HF: High frequency bands

DISCUSSION

The findings of this study provide significant insights into the autonomic dysfunction and HRV alterations in post-COVID-19 patients on the long term. This autonomic impairment, reflected in diminished HRV indices, suggests a persistent dysregulation of the ANS following SARS-CoV-2 infection.

The pathophysiological mechanisms underlying the autonomic dysfunction in post-COVID patients remain an area of active research.[12] The observed alterations in HRV among post-COVID-19 patients is likely multifactorial in origin.[13] SARS-CoV-2 is known to invade the central nervous system (CNS) via the olfactory nerve, with subsequent involvement of the hypothalamic-pituitary-adrenal (HPA) axis which is critical for autonomic regulation.[14] This neuroinvasion, combined with a systemic inflammatory response characterized by elevated levels of pro-inflammatory cytokines (e.g., IL-6, TNF-α), likely contributes to autonomic imbalance.[15] Furthermore, the cytokine storm associated with severe COVID-19 exacerbates oxidative stress and endothelial dysfunction, which are critical in mediating autonomic dysregulation leading to chronic dysautonomia.[16]

In comparison with the control group, the post-COVID-19 patients in our study exhibited significant reductions in key HRV parameters, such as the SDNN and the root mean square of successive differences (RMSSD). These reductions suggest a shift towards sympathetic dominance, a condition often associated with poor cardiovascular outcomes. The reduction in parasympathetic tone leads to an increased risk for cardiovascular morbidity, including arrhythmias and myocardial ischemia.[17,18] Furthermore, the persistence of autonomic dysfunction post-COVID-19 raises significant concerns regarding long-term cardiovascular health. These findings underscore the necessity for ongoing cardiovascular monitoring and proactive management strategies in this population.

Recent studies that have reported similar patterns of autonomic dysfunction in COVID-19 survivors.[19] A study conducted using 24-hour Holter monitoring, obtained 12 weeks after the diagnosis of the disease, revealed significant reductions in HRV among post-COVID-19 patients compared to healthy controls. Notably, time-domain indices like SDNN and rMSSD were substantially lower in the COVID-19 group, indicating diminished parasympathetic activity. This finding supports the hypothesis that SARS-CoV-2 infection leads to prolonged autonomic imbalance, which could predispose patients to future cardiovascular complications.[20] Another research tracking HRV in patients up to six months post-COVID-19 hospitalization demonstrated that autonomic dysfunction persists long after the acute phase of the infection.[21]

We evaluated HRV within 12 months after the recovery of the disease and our findings reinforce the concept of autonomic impairment as a sequela of COVID-19, highlighting its persistence over an extended follow-up periods. In addition, we explored the correlation between the duration since recovering from COVID-19 and the degree of autonomic dysfunction. Our results indicated that there is no statistically significant correlation between post-COVID duration and most markers of autonomic function (such as SDNN, RMSSD, and TP) in both awake and sleep states. These results suggest that the duration of time following the recovery of COVID-19 infection does not seem to be associated with a decrease in

autonomic dysfunction. However, one notable exception is the LF/HF ratio during sleep, which showed a statistically significant negative correlation. This suggests that as time passes, there may be a trend toward improved autonomic balance during sleep, characterized by a reduction in the LF/HF ratio, potentially reflecting a shift toward parasympathetic dominance during this period. Therefore, while there is some evidence that autonomic dysfunction may improve over time during sleep, it cannot be generalized across all autonomic parameters. From a clinical perspective, the incorporation of HRV monitoring into routine follow-up for post-COVID-19 patients could serve as a valuable tool for early detection of autonomic dysregulation and impending cardiovascular complications. Moreover, therapeutic interventions aimed at modulating autonomic function, such as exercise-based rehabilitation, biofeedback, and pharmacologic agents (e.g., beta-blockers, ACE inhibitors), can be considered as part of a comprehensive care strategy.

Limitations

This study has some limitations that need to be addressed in future research. The cross-sectional design and the relatively small sample size of the study may limit the generalizability of the findings. Furthermore, the exclusion of severe COVID-19 cases might result in an incomplete representation of the entire spectrum of post-COVID autonomic dysfunction. Future research should consist of longitudinal studies with larger cohorts and diverse populations to explain the course of autonomic recovery and identify potential predictors of persistent dysfunction. Additionally, exploring the impact of various therapeutic interventions on HRV recovery could inform clinical practice and improve patient outcomes.

CONCLUSION

This study provides insights into the autonomic dysfunction elicited by the decreased HRV indices observed in post-COVID patients, highlighting the need for continued research and targeted interventions to address the long-term cardiovascular effects of COVID-19. Understanding and managing these autonomic imbalances will be critical for improving the health and well-being of individuals recovering from COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was obtained from Adıyaman University Non-interventional Clinical Researches Ethics Committee (Date: 21.06.2022, Decision No: 2022/6-4).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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