Autonomic Nervous System Affection Due to Post-Covid Syndrome

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Abstract

The persistence of symptoms for 12 weeks or longer in individuals with Covid-19 and the wide range of symptoms suggested that the autonomic nervous system (ANS) may be affected. The aim of this study is to reveal the possible relationship between Post Covid syndrome (PCS) and ANS disorders by measuring Heart Rate Variability. A total of 60 participants whom between the ages of 18-45 were included in the study and divided into three groups: Group 1(participants have never had Post-Covid Syndrome), Group 2 (recovered after Covid-19) and Group 3 (participants who had never Covid-19 infection). A 5-minute heart rate variability measurement was performed in the resting position for the patients in each group. A statistically significant low Stress Index score was found in Group 1 (participants have never had Post-Covid Syndrome) ($p<0.05$). While a significant low measurement was observed in the SNS index in Group 1($p<0.05$), a significant high score was observed in Group 3 ($p<0.05$), which consisted of participants who had experienced PCS. The RMSSD and HF variable, a significant low score was observed in Group 3 ($p<0.05$).

As a result of this study, it was observed that sympathetic activity dominance clearly emerged and caused autonomic dysfunction in participants with PCS, compared to individuals who had never had Covid 19 infection and recovered from Covid 19 infection.

Keywords: Autonomic Nervous System Disorders, Heart Rates, Long COVID, Post-Acute COVID syndrome.

1. Introduction

SARS-CoV-2 virus, which becomes evident with severe acute respiratory tract infection and pneumonia, can turn into a chronic disease that can cause permanent symptoms in recovering individuals [1]. Long Covid syndrome or Post-Covid syndrome (PCS) is defined as symptoms that develop in addition to respiratory symptoms, lasting longer than 12 weeks, in individuals with Covid-19 infection [2]. Many symptoms can be seen in PCS, e.g. fatigue, headache, cognitive impairment, dyspnea, heart palpitations, heat intolerance, digestive system disorders, sleep disorders, dermal problems, and orthostatic intolerance [3]. The Covid-19 infection can affect the autonomic nervous system (ANS) and there may be a possible association between PCS and ANS dysfunction [4,5]. It is known that the cytokine storm caused by Covid-19 is related to sympathetic activation that induces the release of proinflammatory cytokines, and also the virus is associated with autoantibodies against α(alpha) and β(beta) adrenoceptors and muscarinic receptors; in this case, it turns into an autoimmunological disorder together with ANS dysfunction [6]. With its craniosacral parasympathetic fibers and cervicothoracic sympathetic fibers, the ANS has a complex network structure that maintains the homeostasis of the body [7]. The parasympathetic nervous system predominates in "rest and digest" conditions, while the sympathetic nervous system drives the "fight or flight" response in stressful situations [8]. Heart rate variability (HRV) measurement method can be used to evaluate ANS activity [9]. HRV is a non-invasive method and is a measure of the change in heart rate over a period of time [10]. HRV is a scalar quantity that shows the time between two beats of the heart and defines the oscillations between the R-R intervals [11]. In HRV, time-dependent and frequency-dependent measurement results are obtained and from these data, time-dependent RMSSD (square root of the square of the difference of the R-R intervals), frequency-dependent high-frequency (HF) and low frequency (LF) measurement components are mostly used in relation to predict the sympathetic nervous system (SNS) and parasympathetic nervous system (PSS) activities [12]. HRV is measured generally in 3 different time intervals , as ultra short-term (<5 minutes), short-term (5 minutes) and long-term (24 hours), , and these values provide different results from each other [13]. While 24-hour long-term measurements are preferred in cardiac diseases with a risk of mortality, short-term and ultra short-term measurements may be preferred in measuring the effect of chronic and metabolic diseases on HRV [14,15]. The aim of this study is to reveal the possible relationship between PCS and ANS dysfunction.

2. Material and Methods

2.1. Study Design

The study was carried out after Iğdır University Clinical Ethical committee approval (Date: 14/02/2023 and Number: 2023/3). Written informed consent was obtained from every participant. In addition sociodemographic information was obtained from the participants in the form of a questionnaire and the symptoms experienced by the participants were recorded. Firstly, an application was made for the Clinical Trials code from the National Library of Medicine and the study was started with the ID number NCT05502094. Patients were evaluated once during the study with a 5-minute HRV measurement using the Polar H7 device. Participants were warned not to exert excessive effort and not to take any medication or treatment before the measurement. In the research form given to the patients, the symptoms of individuals with PCS (fatigue, headache, cognitive impairment, dyspnea, heart palpitation, heat intolerance, digestive system disorders, sleep disturbance, dermal problems, orthostatic intolerance.) were marked and the percentage of these symptoms was calculated.

2.2. Subjects

A total of 60 participants whom between the ages of 18-45 (mean age 25, male n=10, female n=10) were included in the study. Study participants were divided into three groups i) participants who had never Covid-19 infection (n=20), ii) recovered after Covid-19 (n=20) and iii) Experienced Post Covid Syndrome (n=20) (Table 1). Considering that the estrogen level and menstrual cycle in the body can affect the ANS among female patients, female participants in pre-menopausal, post-menopausal and pregnancy conditions were excluded from the study. At the same time, taking into account the change in estrogen during the menstruation period, the measurement date of women in the menstruation period was postponed until the end of this period. Participants who used medication in the last six months for the treatment of ANS dysfunction were also excluded from the study.

Table 1: Participants Characteristics

Participants	n	F/M
Have never had Covid-19 infection (Group 1)	20	10/10
Fully recovered after Covid-19 (Group 2)	20	10/10
Experienced Post Covid Syndrome (Group 3)	20	10/10

n: Number of Participants, F/M: Female to male ratio

2.3. Procedure

All subjects participating in the study completed the 5-minute HRV measurement test with the Polar H7 device. It was stated to the participants that they should avoid heavy physical activities on the day of the test, get enough sleep, not consume cigarettes, alcohol and caffeinated beverages, and not consume high-calorie foods until two hours before the test. Before the measurement, male patients were advised to shave the hair tissue in the chest area. The electrode part of the wearable belt-shaped device was cleaned with alcohol and moistened with water before use on each patient. The measurements of the participants were completed in a long sitting position on a back-supported stretcher for five minutes without any movement or speech in a comfortable way.

The Polar H7 wearable HRV measurement technology, which we used in our study and produced by Polar Electro company, is a device that helps to measure the R-R interval at rest and at different activity intensities. In the study conducted by Schweizer et al., it was shown that the Polar device had 99.6% R-R interval signal quality during five different activities [16]. In this study, the measurements made with the Polar H7 device were analyzed with Kubios Software 3.5.0 program in computer environment.

With this program, it is possible to apply time dependent, frequency dependent and nonlinear analysis method. The variables used in time-domain measurements and frequency-domain measurements are given in Table-2.

PNS and SNS indexes provide information about parasympathetic and sympathetic nervous system dominance respectively, [17]. The PNS is responsible for lowering Heart Rate and increasing heart rate variability. The SNS is responsible for increasing Heart Rate and decreasing Heart Rate Variability. PNS and SNS scores, which are considered normal between -2 and +2, give information about PNS and SNS dominance according to the direction of influence as the deviation from this range increases [18]. Stress index, which is a measure of HRV, which reflects the stress of the cardiovascular system directly affected by the SNS, reveals a decrease in heart rate variability and high sympathetic cardiac activation at high scores [19]. The root mean square of successive (RMSSD) is defined as the mean squared of the temporal differences between heartbeats and is calculated in milliseconds [20]. RMSSD reflects the parasympathetic activation And low scores are associated with increased risk of morbidity [21]. Frequency domain analyzes are used to distinguish between PNS and SNS effects. It has been revealed that SNS activity affects the low frequency band (LF) of HRV between 0.04 and 0.15 Hz, while PNS predominantly affects the high frequency band (HF) between 0.15 and 0.4 Hz [22].

A numerically low score for the LF/HF ratio reflects parasympathetic dominance, while a high numerical ratio indicates sympathetic dominance [23].

Table 2: HRV parameters calculated by Kubios HRV software

Variable	Characteristics
Stress Index	The stress of the cardiovascular system directly affected by the SNS
PNS Index	Parasympathetic nervous system dominance
SNS Index	Sympathetic nervous system dominance
Time Dependent	
RMSSD (ms)	The square root of the mean square of differences in the RR intervals.
Frequency Dependent	
LF (ms^2)	0.04-0.15 Hz
HF (ms^2)	0.15-0.4 Hz
LF/HF (ms^2)	Sympathetic/Parasympathetic Balance

2.4. Data Analysis

SPSS 20.0 program was used to analyze the obtained data. The normality test was performed with the Kolmogorov-Smirnov test to find out which test the obtained data would be analyzed. The mean comparison of the measurements taken in the groups was evaluated with One-way ANOVA in the parameters showing normal distribution.

2.5. Blinding

One of the researchers played a role in determining the participants to be included in the study, while the other researchers independently completed the HRV measurements and data analysis, respectively.

3. Results

3.1. Sample Size and Demographic Data

The demographic data of the participants are compiled in Table 3.

Table 3: Demographic data of participants

Variable	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Group 3 (Mean±SD)
Age (Years)	23.35±1.461	26.55±7.571	25.10±9.539
Height (cm)	171.45±9.539	172.50±10.665	171.80±11.687
Weight (kg)	61,85±9.235	65,40±13.926	67.05±12.751
BMI (kg/cm^2)	19.10±6.406	21.70±2.639	22.60±2.811

Abbreviations: cm (Cantimeters), kg (kilograms), BMI (Body mass index)

The research was completed with a total of 60 people, 20 participants in each group. The numerical data of the participants included in the three groups were found to be normal, and there were no significantly differences in age (F=1.412, p= 0.252), height (F =0.050, p= 0.951), weight (F = 0.959, p= 0.389) and BMI (F=3,590, p=0.064) between groups.

3.2. Symptoms

The percentages (%) of the symptoms for in Group 3 (n=20) were shown in Chart-1.

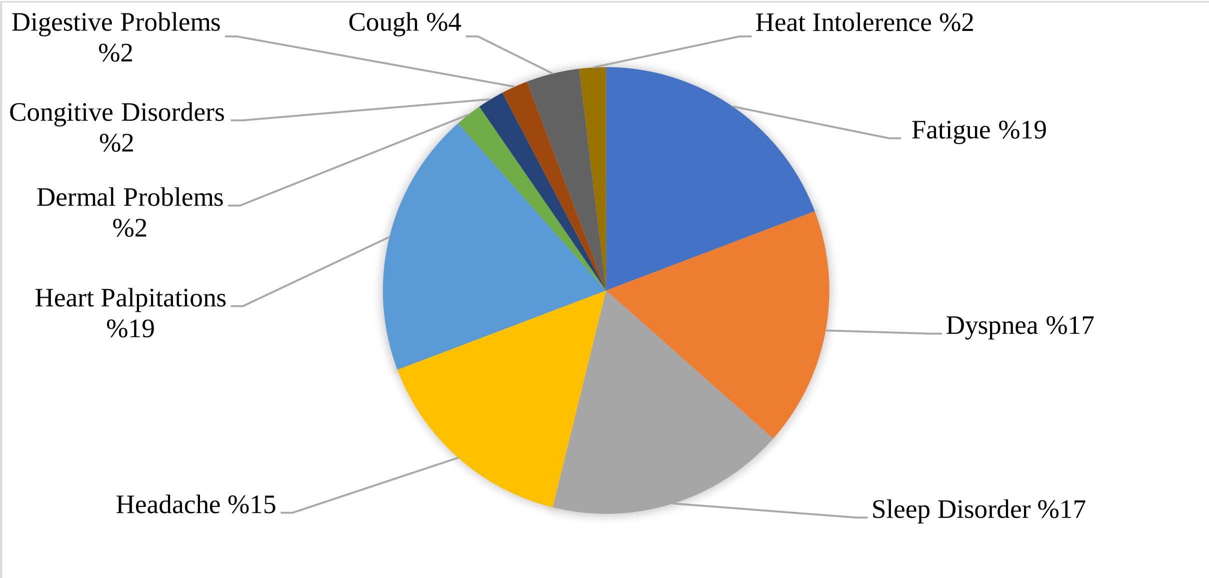

Figure 1: Distrubution of Symptoms (%)

3.3. HRV parameters

The differences in HRV parameters between the groups are given in Table 4. These data were obtained using ANOVA and Post-Hoc analyses.

3.3.1. Indexes

A statistically significant low Stress Index score was found in Group 1 (26.020 ±4.391) with participants who have never had covid 19 infection ($p<0.05$). No statistically significant difference exists between the three groups in the PNS index. While a significant low measurement was observed in the SNS index in Group 1(4.324 ±1.517, $p<0.05$), a significant high score was observed in Group 3 (17.287 ±26.781, $p<0.05$), which consisted of participants who had experienced PCS.

3.3.2. Time Domain Analysis

The RMSSD variable was significantly low in Group 3 (6.865 ±2.892, $p<0.05$),

3.3.3. Frequency Domain Analysis

There was no statistically significant difference between the three groups in the LF and LF/HF variables. In the HF variable, a significant low score was observed in Group 3 (20.80 ±16.832, $p<0.05$).

Table 4: ANOVA table for the Stress, PNS, SNS indexes, frequency domain analysis and time domain analysis of heart rate variability between groups.

	Group 1 (Mean ±SD)	Group 2 (Mean ±SD)	Group 3 (Mean ±SD)	*F*	df	*p* value
Stress Index	26.020±4.391*	27.385±7.096	49.125±51.239	3.741	2	0.030
PNS Index	-2.137± 0.628	-2.579±1.744	-2.205±0.549	0.910	2	0.408
SNS Index	4.324±1.517*	4.780±2.163	17.287±26.781*	4.483	2	0.016
RMSSD	7.641± 1.740	14.197±16.980	6.865±2.892*	3.248	2	0.046
LF	122.45±81.010	136.75±126.196	235.60±288.269	2.157	2	0.125
HF	24.40±16.763	56.55±79.761	20.80±16.832*	3.356	2	0.042
LF/HF	6.260± 3.686	5.334±3.055	7.095±3.393	1.352	2	0.267

*Values are group mean ± SD, *p < 0.05; post-hoc analyses, values compared between groups.*

4. Discussion

In our study, HRV was measured in three groups of participants who have never had Covid, who have had a Covid infection and have fully recovered, and who have experienced Post-Covid symptoms for more than 12 weeks after Covid infection. As a result of these measurements, when the stress index is examined, a significant low score was seen in the group of participants who had never had Covid, compared to those who had recovered completely and had Post-Covid symptoms. This may show the relationship between the dominance of sympathetic activity, and the increase in the stress index score after Covid infection together with the presence of Post-Covid symptoms. In the study of Kim et al., it was revealed that the HRV measurement and the stress index score reflect the stress caused by the person's sympathetic dominance [24].

High stres index can be an indicator of sympathetic hyperactivation which is an important component of autonomic dysregulation in infections and is associated with hyperinflammatory states [25]. It can be stated that the dysfunctional state in the ANS activity (increased sympathetic activity, suppressed parasympathetic activity) contributes to morbidity and mortality in COVID-19 patients, and the solution of this problem can be a goal in treatment. In animal studies, surgical vagotomy increases alveolar damage due to overproduction of inflammatory cytokines such as IL-6 [26].

When the PNS and SNS indices are examined among the three groups , the low SNS index score in group 1 is compatible with the stres index score. However, no statistically significant difference was found between the groups in the PNS index. This may show that Covid infection is mostly related to SNS and has little or no effect on PNS. But When the subvariables depending on time and frequency were examined, a significant low measurement was observed in the group with Post Covid symptoms in the RMSSD score. This may be due to formulation differences in parameters such as PNS index and RMSSD reflecting PNS activity or because of the heterogeneity of Post-Covid symptoms. Many underlying mechanisms have been proposed for post covid/long covid autonomic dysfunction; direct invasion of the ANS by the COVID-19 (autonom neuropathy), autoimmunity disorder against ANS, prolonged bed rest, microangiopathy, secondary to another pathology such as covid-induced stroke or encephalitis, both psychological and physiological stress caused by the disease itself (in adaptive, compensatory context) [27,28]. We encountered different Post-Covid symptoms not all related with heart as in Figure 1 and low scores in the RMSSD are associated with decreased vagal cardiac activity control [29].

A significant decrease in the HF variant was observed in individuals experiencing PCS and this was compatible with the result of RMSSD In the study conducted by Vreijling et al., low HF scores were found to be lower in individuals with chronic fatigue syndrome, irritable bowel syndrome and fibromyalgia compared to healthy people and this may indicate that low HF score is a biomarker in chronic diseases [30].

When the literature was examined, it was seen that HRV variables showed a higher chance of survival in patients with Covid 19 infection, while low HRV increased the risk of intensive care unit admission [31]. In the study of Pan et al., a significant relationship was found between the severity of the symptoms of the disease and low LF/HF scores in patients who had Covid 19 infection [32]. Similar to our study, in the study conducted by Ballering et al., 90-150 days later, it has been revealed that symptoms such as feeling hot and cold, aggravation in the arms or legs, general fatigue, chest pain, difficulty in breathing, pain when breathing, muscle pain, smell and taste disorders, tingling in the extremities, lump in the throat, alternating symptoms in patients with Covid 19 infection were found [33].

According to symptoms in PCS, it can be said that ANS is heterogeneously affected by Covid –19 virus and its infection. Larsen et al define orthostatic intolerance, palpitations/tachycardia, temperature intolerance, labile blood pressure, new-onset hypertension, gastrointestinal symptoms (e.g., abdominal pain, bloating, nausea) as symptoms suggestive of autonomic dysfunction. However, fatigue, headache, cognitive impairment (brain fog) were not associated with autonomic dysfunction in the study [27]. Similarly, Townsend et al, in their evaluation of post-covid patients with and without chronic fatigue, stated that fatigue was not associated with autonomic dysfunction but was associated with anxiety. They applied heart rate variability (HRV), 24-hour blood pressure monitoring, prefrontal cortex oxygenation with infrared spectroscopy to evalute ANS activity [34]. Lo argue that COVID-19 related chronic fatigue may be due to hypotension but Barizien and colleagues directly linked fatigue to autonomic dysfunction in long COVID-19 patients [35,36]. In fact, fatigue may accompany conditions with autonomic dysfunction such as bradycardia or tachycardia, in which hypoactivity or hyperactivity of the branches of the ANS can be seen [37]. Since the ANS has many roles in the body and Covid-19 infection does not only affect the upper respiratory tract, functional changes in the branches of the ANS and in different parts of the body may differ from patient to patient. This may explain the differences in HRV parameters even though HRV is a heart rate measurement.

The fact that measurements were not taken at different time intervals for the purpose of verification is a limitation of this study. Although it is known that very short-term (< 5 minutes), short-term (5 minutes) and long-term (24-hour) measurements give different results, a measurement time of five minutes was preferred because it was seen that it was difficult to analyze the 24-hour measurements of the patients. In addition, the difference in HRV parameters for each post covid symptom could be looked at by keeping the number of participants high.

5. Conclusion

As a result of this study, it was observed that sympathetic activity dominance clearly emerged and caused autonomic dysfunction in participants with PCS, compared to individuals who had never had Covid 19 infection and recovered from Covid 19 infection. The dominance of sympathetic activity may be due to the persistence of symptoms and increased cardiovascular stress. Regardless of the situation, regulating autonomic activity can help control post-COVID syndrome.

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