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INVESTIGATION OF AUTONOMIC FUNCTIONS IN ADULTS AFTER COVID-19 (SARS-COV-2) INFECTION USING SYMPATHETIC SKIN RESPONSE AND R-R INTERVAL VARIATION

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ABSTRACT The SARS-CoV-2 (COVID-19) pandemic has inflicted unparalleled morbidity and mortality on a global scale. Over time, as our understanding of the disease has grown, we have come to recognize the existence of long-term effects that transcend the initial acute phase. Sympathetic skin response (SSR) and R-R interval variability (RRIV) have been employed as methods to evaluate the function of the autonomic nervous system (ANS). Consequently, we have undertaken this study with the objective of investigating ANS function in patients who have recovered from COVID-19. **Methods** We enrolled a total of 51 individuals who had recovered from COVID-19 and 49 healthy individuals for this study. The assessment of autonomic function involved the evaluation of RRIV and SSR. **Results** In the case group comprising 51 individuals, 23 (45.1%) were male, and 28 (54.9%) were female. The age range of these patients varied from 21 to 86 years. Within the control group, consisting of 49 individuals, 24 (49%) were male, and 25 (51%) were female. Our findings revealed a notable correlation between COVID-19 infection and abnormal SSR parameters. However, when we examined RRIV, we did not find a statistically significant difference in RRIV parameters between the patient and control groups. **Conclusions** Our study suggests that abnormal SSR parameters could serve as a valuable indicator of ANS involvement in patients with COVID-19 infection. We did not find a significant difference in RRIV parameters between the case and control groups.

KEYWORDS : COVID-19, dysautonomia, heart rate variability, sympathetic skin response

1. INTRODUCTION

The global COVID-19 pandemic, precipitated by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has inflicted unparalleled morbidity and mortality across the globe. While the development and deployment of vaccines have offered a glimmer of hope, the repercussions of this disease persist, continuing to impact the lives of individuals affected. Over time, as we have garnered experience in combating this formidable adversary, our awareness of its extended effects has grown. Beyond the initial acute phase, we have begun to recognize a range of long-term consequences of COVID-19. Some of these clinical presentations are attributed to ANS involvement, adding to the complex landscape of COVID-19-related health issues. The terms 'Post-acute COVID' and 'Chronic COVID' have been coined to delineate these extended periods of symptomatology. 'Post-acute COVID' pertains to symptoms that manifest approximately three weeks after the initial COVID-19 infection, while 'Chronic COVID' refers to a more prolonged condition in which symptoms endure for a period exceeding 12 weeks (1,2). As we delve deeper into understanding the lingering effects of this virus, it becomes evident that the story of COVID-19 extends beyond its acute phase, and the challenges it poses for patients and healthcare providers are far-reaching. In this context, we embark on a journey to explore the nuances of the post-acute and chronic manifestations of COVID-19, with the aim of contributing to a comprehensive understanding of the virus's impact on individuals and communities. As the COVID-19 pandemic has unfolded, an increasing prevalence of post-acute and chronic manifestations has become apparent. Since the onset of the pandemic, a diverse array of neurological symptoms has been documented in patients, spanning from mild complaints such as anosmia, hypogeusia, and headaches to more severe conditions. Furthermore, it has become evident that COVID-19 can lead to the development of neurological diseases, including acute encephalomyelitis, ischemic strokes, polyneuropathy, and Guillain-Barre syndrome. These conditions may arise through various mechanisms, further underscoring the multifaceted nature of COVID-19's impact on the nervous system. Of particular interest, it is increasingly recognized that the ANS can also be affected by SARS-CoV-2 infection. Dysautonomia, a term used to describe disorders within the sympathetic or parasympathetic components of the ANS, presents with a wide spectrum of clinical manifestations. These can encompass irregular blood pressure, orthostatic hypotension, impotence, disturbances in bladder and bowel motility, incontinence, and sweating abnormalities. Dysautonomia may manifest acutely or chronically, often exhibiting a progressive nature. As the COVID-19 pandemic endures, there is growing evidence that the virus can impact the ANS, adding a new dimension to our understanding of its complex and diverse array of effects on human health. This realization underscores the importance of continued research and exploration in the field of COVID-19-related autonomic dysfunction (3). The connection between COVID-19 and the ANS is intricate and multifaceted. One example of this complexity is the potential for autonomic dysfunction resulting from autoimmune encephalitis. In such cases, symptoms can manifest across various domains of the ANS, including the cardiovascular and sudomotor systems (4). Additionally, the immune response triggered by COVID-19, characterized by a cytokine storm, plays a pivotal role in this relationship. Sympathetic activation due to COVID-19 results in the release of proinflammatory cytokines. This cascade of immune activity, driven by sympathetic activation, contributes to the complex interplay between the virus and the ANS, which can lead to a range of clinical manifestations and challenges in patient management (5). On the other hand, it's important to note that vagal stimulation has the opposite effect, triggering an anti-inflammatory response. Vagal stimulation can help counterbalance the proinflammatory response associated with sympathetic activation. This dynamic interplay between the sympathetic and parasympathetic branches of the ANS contributes to the regulation of inflammation in the body and has implications for understanding the immune response to COVID-19 (6).

The heightened activity of the sympathetic nervous system (SNS) results in the release of catecholamines, an increase in the body's metabolic rate, elevated blood flow, and heightened cardiac stress. Simultaneously, the influence of the parasympathetic nervous system (PNS) on the vagal anti-inflammatory reflex diminishes. Consequently, there is an increase in the release of proinflammatory cytokines, and

these cytokines are believed to be a key factor in the development of a cytokine storm. This intricate balance between sympathetic and parasympathetic activity can have profound implications for the body's response to COVID 19, including its effects on inflammation and immune responses (3,8,9). It's crucial to recognize that immune-mediated syndromes, such as orthostatic hypertension (OH) or postural orthostatic tachycardia syndrome (POTS), may also be associated with autoantibodies targeting specific receptors, including α-/β-adrenoceptors and muscarinic receptors. These autoantibodies can disrupt the normal functioning of the ANS, contributing to the complex and varied autonomic manifestations observed in individuals affected by COVID-19. This dual etiology, involving both direct viral effects and immune-mediated responses, underscores the multifaceted nature of autonomic dysfunction in the context of COVID-19. (7,10,11,12,13,14). Recognizing the significance of autonomic functioning in COVID-19 patients, the American Autonomic Association has recently released a comprehensive document emphasizing the importance of assessing autonomic function and recommending further testing in individuals affected by the virus. This underscores the need for ongoing research and clinical attention to better understand and manage autonomic dysfunction in the context of COVID-19 (15). This underscores the significance of ongoing scientific inquiry and the collaborative efforts of the medical and research communities in addressing the complex relationship between COVID-19 and the ANS. (16) Hence, considering the pressing need to further understand and characterize autonomic dysfunction following recovery from COVID-19, we have undertaken this study. Our primary objective is to evaluate the various dysfunctions that may affect the ANS in individuals who have recuperated from COVID-19. To achieve this, we will employ electrophysiological tests, including SSR and RRIV assessments. By conducting these tests, we aim to shed light on the intricate autonomic processes and potential irregularities that may persist or develop post-COVID-19.

2. MATERIALS AND METHODS

The study included patients who had previously recovered from COVID-19 and were admitted to the Neurology Outpatient Clinic of Balıkesir University Health Practices and Training Hospital between May and December 2021. The following criteria were applied for patient inclusion, patients should not display signs of autonomic disorders, should not have a history of additional diseases could potentially cause autonomic disorders. And patients should not be currently using treatments that could affect the test results.

The control group, comprising healthy individuals, had no history of systemic or neurological diseases, nor did they exhibit any autonomic symptoms. Additionally, they were not vaccinated. The age distribution of the control group was like that of the patient group, and their ages ranged between a certain range. Neither the patient group nor the control group had taken any medications that could influence the autonomic tests during the study or in the 24 hours leading up to the examinations. Prior to participation, written informed consent was obtained from all study participants. The post-COVID group consisted of 51 patients who had recovered from COVID-19, while the control group included 49 healthy individuals. All patients in the study had confirmed COVID-19 infections through RT-PCR and/or thorax CT reports. The electrophysiological examinations were conducted in the EMG laboratory of the Neurology Department. These evaluations were performed with the patient in a supine position, ensuring comfort, and within a room temperature range of 24-26 °C. The measurements were obtained using the VIASYS Medelec Synergy electromyography device. RRIV and SSR were assessed in participants whose nerve conduction studies were determined to be within the normal range. These evaluations aimed to investigate the ANS function in individuals who had recovered from COVID-19 and healthy controls.

2. 1 Sympathetic Skin Response (SSR)

SSR serves as an indicator of potential changes in the skin in response to either internal or external stimuli. This reflex is commonly utilized for assessing the activity of the SNS. In the SSR recordings, the active electrode was placed on the palm of the upper extremity and on the sole of the foot in the lower extremity. The reference electrode was positioned on the back of the hand in the upper extremity and on the dorsal surface of the foot in the lower extremity. Ground electrodes were secured around the wrist for the upper extremity and the ankle for the lower extremity. To record SSR, contralateral median nerve stimulation was performed by delivering brief electrical shocks with a duration of 0.2-0.5 milliseconds and an intensity ranging from 10 to 30 milliamperes. The analysis time for each recording was set to 10 seconds, during which a total of ten responses were recorded. The latency, measured in milliseconds, was determined from the onset of the stimulus artifact to the onset of the first negative deflection in the SSR recording. The amplitude, expressed in microvolts, was calculated from the peak-to-peak values. If no consistent voltage change was observed after three trials at the maximum stimuli intensity, the SSR response was considered absent. This determination was made using a sensitivity setting of 50 microvolts per division, indicating that the physiological response did not occur under these conditions.

2. 2 RRIV

RRIV is a method used to assess the functioning of the PNS, particularly during periods of rest and deep inspiration. Abnormalities in RRIV can indicate dysfunctions in cardiac PNS activity. In RRIV recording, ring electrodes were placed on both thumbs, while a ground electrode was securely wrapped around one of the patient's wrists. The electromyography device settings for RRIV recordings were configured with a filter setting of 20-50 Hz and a sensitivity of 0.5 millivolts per division. The fundamental principle underlying RRIV measurement involves tracking the time intervals between successive QRS complexes on an electrocardiogram (ECG). To perform RRIV assessment, a minimum of 20 QRS complexes were used for analysis. The procedure was conducted in two conditions: at rest and during deep inspiration, which was induced through hyperventilation (HV). In the study, participants were asked to perform six deep inspirations per minute during HV.

To calculate RRIV, two key parameters were considered: a) The difference between the shortest and longest intervals among the 20 R-R intervals. b) The time interval between the R peak of the fixed QRS complex and the mean value of the fluctuating QRS complexes. The mean percentage (%) of QRS complexes collected in each recording was calculated using the formula RRIV = (a / b) x 100. This percentage reflects the degree of RRIV and serves as an indicator of PNS function under different physiological conditions.

2.3 Statistics

For the statistical analysis of the data, the SPSS 23.0 software for Windows was utilized. Here is a summary of the statistical methods and procedures employed. Normality Analysis; the normality of continuous variables was assessed using the Kolmogorov-Smirnov test, along with a review of descriptive statistics such as skewness and kurtosis. Non-parametric tests were chosen for all analyses due to the absence of a normal distribution in at least one group for all the data. Descriptive statistics were used to summarize the data. Categorical variables were presented in terms of numbers and percentages, while numeric variables were described using the median and the range (minimum-maximum). Difference Analysis; the analysis aimed to identify differences in numeric

variables between two independent groups. To achieve this, the Mann-Whitney U test, a non-parametric test, was applied. This test is suitable for comparing two independent groups when the data do not follow a normal distribution. The statistical alpha significance level was established at $p < 0.05$, signifying that results with a p-value less than 0.05 were considered statistically significant.

3. RESULTS

This study included a total of 51 individuals who had previously contracted COVID-19 and 49 healthy individuals as the control group. The participants' ages in both the case and control groups ranged from 21 to 86 years. The mean age for the case group was 48 ± 14.5 years, and for the control group, it was 50.7 ± 18.3 years. There were no statistically significant differences in demographic variables, such as age and sex, between the two groups. In the case group, 23 individuals (45.1%) were male, and 28 individuals (54.9%) were female. Their ages ranged from 21 to 82 years. The control group comprised 24 males (49%) and 25 females (51%), with ages ranging from 24 to 86 years. This demographic information demonstrates that the study included a diverse range of participants in terms of age and gender, and efforts were made to ensure comparability between the case and control groups to minimize potential confounding factors related to these variables.

Table 1: Mean RRIV and SSR values for the case and control groups compairing genders. The p-values indicate the statistical significance of the differences observed.

Parameter	Case Group (mean/ median)	Control Group (mean/ median)	p-value (Group Comparison)	p-value (Gender Comparison)
Age (years)	49.8 / 49 (21-76)	51.2 / 50 (0-86)	0.775	0.481
SSR Median N latency (ms)	87.89 / 125 (12-167)	72.15 / 73 (0-198)	0.138	0.045
SSR Tibial N latency (ms)	96.21 / 23 (2-223)	115.38 / 145 (0-235)	0.822	0.502
SSR Median N amplitude (μV)	126.29 / 107 (1-351)	78.5 / 57 (0-264)	0.104	0.379
SSR Tibial N amplitude (μV)	54.36 / 48 (2-178)	82.42 / 48 (0-314)	0.904	0.575
R%	202 / 128 (10-1231)	185.24 / 129 (10-1401)	0.627	0.947
D%	269.11 / 236 (15-	254.38 / 249 (18-	0.689	0.089

SSR: sympathetic skin response, %R: RRIV during rest (%R), %D: RRIV values during deep breathing, N: nerve, Amp: amplitude, μV: microvolt

There were no statistically significant differences in age between the patient and control groups, both overall and within gender groups. The mean latency of the action potential recorded from the median nerve was significantly increased in the male case group compared to the control group (p=0.045).

For SSR Tibial N Latency, there was no statistically significant difference between patient and control groups.

For R%, there were no significant differences between patient and control groups or across genders. D%, there were no significant differences between patient and control groups.

Table 2: Mean RRIV and SSR values for the case and control group

	Case Group	Control Group	P
	mean±SD / median (min-max)		
Age	48±14,5 / 46 (21-82)	50,7±18,3 / 48 (24-86)	0,479
SSR Median N latency	99,31±57,44 / 129 (0-167)	71,73±64,22 / 61 (0-199)	0,013
SSR Tibial N latency (S)	89,25±90,51 / 23 (0-223)	104±87,31 / 139 (0-235)	0,534
SSR Median N amp (μV)	141,33±130,41 / 97 (0-521)	103,33±126,54 / 59 (0-581)	0,064
SSR Tibial N amp (μV)	64,37±62,51 / 48 (0-289)	90,65±97,4 / 59 (0-314)	0,659
R%	247,88±345,92 / 128,5 (0-1508)	170,94±201,86 / 142,5 (10-1401)	0,815
D%	302,44±395,47 / 221 (0-2398)	263,2±141,72 / 241 (18-536)	0,176

The SSR Median N latency was significantly longer in the case group. (p: 0,013) There was no statistically significant difference in SSR tibial n latency, median n latency between the case and the control group.

The R% and D% values in the case and the control group did not show a statistically significant difference.

Table 3: The subgroup analysis based on age (<50 years of age and ≥50 years of age) for both the case and control groups.

	<50 years of age		≥50 years of age		p values			
	Case Group	Control Group	Case	Control	Comparing case and control groups		Comparing age	
	mean±SD / median (min-max)				<50 years	≥50 years	Patient	Control
SSR Median N latency	1,29±0,27 / 1,32 (0-1,67)	1,21±0,34 / 1,27 (0-1,9)	1,38±0,1 / 1,4 (1,22-1,53)	1,31±0,46 / 1,32 (0-2)	0,13	0,581	0,09	0,297
SSR Tibial N latency (S)	1,94±0,47 / 1,98 (0-2,5)	1,69±0,44 / 1,8 (0-2,21)	2,08±0,17 / 2,06 (1,74-2,4)	1,72±0,5 / 1,87 (0-2,35)	0,002	0,002	0,161	0,779
SSR Median N amp (μV)	2,03±1,24 / 2 (0-4,4)	2,63±1,89 / 2,39 (0-7,8)	1,57±1,24 / 1,17 (0,2-5,21)	1,98±1,73 / 1,2 (0-7,1)	0,349	0,385	0,148	0,144
SSR tibial N amp (μV)	0,83±0,67 / 0,6 (0-2,89)	1,54±0,87 / 1,35 (0-3,14)	0,68±0,52 / 0,5 (0,2-2,41)	1,22±0,81 / 1,01 (0-3,14)	<,001	0,01	0,612	0,167
R%	14,76±5,96 / 12,85 (0-26)	20,19±11,12 / 18,55 (6,1-61)	12,31±5,02 / 12,05 (3,45-27)	14,96±7,25 / 13,5 (2,5-32,6)	0,035	0,18	0,096	0,03

D%	23,36± 8,46 / 22,6 (0-41)	31,76± 11,37 / 33,15 (12,4-53,6)	21,08± 6,87 / 21,15 (7,69-34,4)	25,34± 13,78 / 23,9 (3,8-53,3)	0,013	0,336	0,216	0,064

The mean latency of the action potential recorded from the median nerve was also significantly increased in the case group compared to the control group (p=0.013). The mean latency of the action potential recorded from the tibial nerve was significantly increased in both the case group under 50 years of age and over 50 years of age compared to the control group (p=0.002 for both groups).The mean amplitude of the action potential recorded from the tibial nerve was significantly decreased in both the case group under 50 years of age and over 50 years of age compared to the control group (p<0.001 for the under 50 years of age group, and p=0.010 for the over 50 years of age group).

R% was statistically increased in the case group under 50 years old. (p=0.035) D% was statistically increased in the case group under 50 years old (p=0.013).

4. DISCUSSION

HRV has emerged as a valuable non-invasive tool for assessing PNS function. A study conducted by Bail et al. has demonstrated that HRV can serve as a robust predictor for both short-term and long-term clinical outcomes, as well as respiratory complications arising from COVID-19 infection (17). In a complementary investigation by Kurtoglu et al., it was established that HRV, indicative of cardiac ANS dysfunction, is discernible in individuals with a prior history of COVID-19. Furthermore, their findings illuminate a notable impairment in cardiac parasympathetic function among those who have experienced COVID-19 (18).

Pan et al. have posited that HRV exhibits a substantial correlation with the severity of COVID-19, such that heightened disease severity corresponds to greater autonomic dysfunction, accompanied by the recording of abnormal HRV parameters through 24-hour dynamic electrocardiography (19). While it is worth noting that some studies did not identify a statistically significant relationship between HRV related parameters and COVID-19, it is essential to emphasize that these studies do not negate the potential influence of infection on ANS function. For example, one such study, conducted by Bellavia S. et al; found no discernible distinctions in HRV parameters between non-critically ill COVID-19 patients and healthy volunteers (20). Subsequently, two investigations delved into alterations in HRV parameters among individuals recovering from COVID-19 without exhibiting long COVID symptoms (21,22). Although both studies assessed four common HRV parameters, they consistently reported no significant changes in these HRV parameters. However, the interpretation of the results differed between the two studies. Aranyó et al. (21) observed a reduction in parasympathetic activity following COVID-19, while Asarcikli et al. (22) noted a predominance of parasympathetic activity. Based on these findings, they emphasized an overall increase in HRV following recovery from COVID-19. In our investigation, we did not find a significant difference in RRIV parameters between the patient and control groups. These findings suggest that the PNS remained unaffected in the COVID-19 patient group. Upon scrutinizing the medical histories of the COVID-19 patients participating in our study, it's noteworthy that only three of them had a prior hospitalization, and none had a history of intensive care unit admission. The relatively mild to moderate disease severity observed in these patients may have influenced the RRIV results. Also, none of the participants had symptoms of dysautonomia. Hence, it is prudent to consider including patients with a history of severe COVID-19 in future investigations focusing on RRIV. SSR represents an additional straightforward non-invasive method for evaluating unmyelinated axon involvement within the ANS, primarily by assessing sudomotor activity and voltage changes on the skin's surface. Nonetheless, there has been limited exploration into SSR abnormalities in individuals who have contracted COVID-19. Roshanzamir et al. conducted a study demonstrating a statistically significant correlation between COVID-19 infection and abnormal SSR parameters Notably, this effect was most pronounced in the latency prolongation of action potentials recorded from median and tibial nerves at the palms and soles.

According to Roshanzamir and colleagues, the extent of abnormal SSR parameters could serve as another valuable predictor of disease severity in patients with COVID-19, much like HRV indicators. (23). In a related investigation, Papadopoulou et al. conducted a case-control study to assess SSR in individuals with long COVID-19 syndrome, defined as the persistence of symptoms for at least three months. This research provides additional insights into the potential role of SSR in evaluating post-COVID-19 conditions (24). Furthermore, a study carried out by Emad et al. highlighted the significance of factors such as height and limb length in influencing SSR latency (25). Because these factors were not evaluated in our study it is a limitation of our study. In summary, our study has revealed an association between COVID-19 and sympathetic autonomic dysfunction, a phenomenon whose underlying mechanisms and prognostic implications warrant further investigation. The use of SSR measurement, characterized by its simplicity, noninvasiveness, and cost-effectiveness, could potentially emerge as a valuable tool in clinical practice for rapid diagnostic and prognostic purposes, although this requires thorough assessment in future research endeavors. While our findings suggest a promising role for SSR as a diagnostic and prognostic marker, the precise mechanisms driving autonomic dysfunction in COVID-19 and its broader clinical implications necessitate ongoing exploration to enhance our understanding of this complex interplay.

In summary, this investigation has discerned an association between COVID-19 and sympathetic autonomic dysfunction, the underlying mechanisms, and prognostic implications of which necessitate further comprehensive evaluation. Indeed, future studies are essential to provide a more comprehensive understanding of the changes in autonomic modulation observed in individuals experiencing dysautonomia following COVID-19. While some proposals regarding patho physiological mechanisms have been discussed, the existing data in the literature remain inconclusive. Understanding whether there is a correlation between these factors could shed light on the underlying mechanisms of autonomic dysfunction in patients with COVID-19. This deeper comprehension of autonomic dysfunction, along with the recognition of its association with inflammatory biomarkers in COVID-19 patients, has the potential to lead to more accurate diagnoses and improved prognostic assessments.

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