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Autonomic Modulation, Spontaneous Baroreflex Sensitivity and Fatigue in Young Men After COVID-19

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Summary

Impaired autonomic modulation and baroreflex sensitivity (BRS) have been reported during and after COVID-19. Both impairments are associated with negative cardiovascular outcomes. If these impairments were to exist undetected in young men after COVID-19, they could lead to negative cardiovascular outcomes. Fatigue is associated with autonomic dysfunction during and after COVID-19. It is unclear if fatigue can be used as an indicator of impaired autonomic modulation and BRS after COVID-19. This study aims to compare parasympathetic modulation, sympathetic modulation, and BRS between young men who had COVID-19 versus controls and to determine if fatigue is associated with impaired autonomic modulation and BRS. Parasympathetic modulation as the high-frequency power of R-R intervals ($lnHF_{R-R}$), sympathetic modulation as the low-frequency power of systolic blood pressure variability (LF_{SBP}), and BRS as the α-index were measured by power spectral density analysis. These variables were compared between 20 young men who had COVID-19 and 24 controls. Independent *t*-tests and Mann-Whitney U tests indicated no significant difference between the COVID-19 and the control group in: $lnHF_{R-R}$, P=0.20; LF_{SBP}, P=0.11, and α-index, P=0.20. Fatigue was not associated with impaired autonomic modulation or BRS. There is no difference in autonomic modulations or BRS between young men who had COVID-19 compared to controls. Fatigue did not seem to be associated with impaired autonomic modulation or impaired BRS in young men after COVID-19. Findings suggest that young men might not be at increased cardiovascular risk from COVID-19-related dysautonomia and impaired BRS.

Key words

COVID-19 • Parasympathetic modulation • Sympathetic modulation • Baroreflex sensitivity • Young men

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Introduction

The proliferation of Coronavirus Disease-2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1] has claimed many lives and continues to be a health problem worldwide. While many biological systems are associated with COVID-19, the association between COVID-19 and the autonomic nervous system (ANS) is particularly interesting. Given the ubiquitous nature of the ANS and the association between cardiovascular disease and the ANS, along with the high incidence of COVID-19-related cardiovascular death, such an interest is warranted.

The ANS has been hypothesized to be associated with COVID-19 [2,3,4], and there is a robust cytokine response associated with COVID-19 [5], which could be associated with sympathetic nervous system activity (SNA) [6]. As a result, of the possible association between SNA and the robust cytokine response, the use of α-1 adrenergic receptor antagonists has been suggested for the prevention of the cytokine storm syndrome observed in COVID-19 patients [7]. Conversely, the parasympathetic branch of the ANS is considered to be associated with the inhibition of inflammation responses [8]. Here, it has been suggested that the cholinergic anti-inflammatory pathway should be targeted in COVID-19 therapeutic considerations [9]. It has been hypothesized that autonomic balance determines the severity of COVID-19 courses [4], and it has been suggested that cardiovascular autonomic neuropathy should be accounted for during the assessment of COVID-19 patients [10].

An association between BRS and COVID-19 has also been suggested [10] and is being investigated [11], while impaired BRS has been observed in hospitalized COVID-19 patients [10]. Importantly, impaired autonomic modulation and BRS are associated with negative cardiovascular outcomes [12,13,14,15,16]. Studies have compared autonomic function and BRS between middle-aged individuals who had COVID-19 versus middle-aged individuals who never had COVID-19 [10]. However, one population that is underrepresented in research examining autonomic modulation and BRS after COVID-19 is young, healthy men who had COVID-19 with one persistent symptom of Long-COVID (fatigue) but were never hospitalized. Some prior works in this population have tested participants at different time intervals after COVID-19 diagnosis and have obtained data from participants with varying degrees of symptoms. This research underrepresentation is understandable, given that these individuals are considered young, otherwise healthy, and were never hospitalized for COVID-19. However, these considerations do not preclude young men from the adverse effects that impaired autonomic modulation and BRS could have on their cardiovascular system if they were to be present.

It could be assumed that fatigue could be a surrogate marker of impaired autonomic modulation and BRS in this group. Such a marker could aid when autonomic testing is not possible. The speculation that fatigue could serve as a marker of impaired autonomic modulation and BRS is plausible, given that fatigue and dyspnea have been proposed to be the most prevalent symptoms during and after COVID-19 [17], as in the case of Long-COVID, and given that Long-COVID is associated with autonomic dysfunction [1,3]. However, though this speculation is plausible, no research has examined whether there are concomitant impairments in autonomic modulation and BRS with fatigue in young men who have had COVID-19.

Understanding whether young, healthy men who have had COVID-19 are at increased cardiovascular risk from COVID-19-related impairment in autonomic modulation and BRS, and if fatigue can be used as a surrogate marker of these impairments is relevant. This knowledge could allow for timely interventions geared towards preventing cardiovascular disease and other adverse health outcomes later in this group. Therefore, the primary aim of this study is to compare parasympathetic modulation, sympathetic modulation, and BRS as related to cardiovascular function between young, healthy men who have had COVID-19 versus controls, and the secondary aim is to determine whether fatigue is associated with impaired autonomic modulation and BRS in young men after COVID-19.

Methods

Forty-four young men aged 18-27 years were recruited from Southern Connecticut State University and the surrounding community for this study. Twenty men were placed in a COVID-19 group, and twenty-four were placed in a control group. Inclusion criteria for the COVID-19 group were a positive COVID-19 result at least five weeks prior to being tested, being asymptomatic except for fatigue, and having never been hospitalized for COVID-19. Fatigue was determined using a 5-point

exertion scale (0=none, 1=heavy exertion, 2=moderate exertion, 3=slight exertion, 4=rest). This scale has been used previously in medical research [18]. Only participants who scored 2 on the scale were included in this study. Criteria for the control group were a negative serological test for SARS-CoV2 IgG and SARS-CoV2 IgM or negative COVID-19 diagnosis and no COVID-19 symptoms since January 2020.

All participants had normal EKG readings, were non-smokers, had no history of metabolic or cardiovascular disease, and were not on any medication. Participants reported for testing after a twelve-hour fast except for water and were instructed not to perform exercise 24 h prior to testing. All participants completed an informed consent form. The test protocols were approved by the Institutional Review Board at Southern Connecticut State University and were in compliance with the Declaration of Helsinki. Additionally, permission to conduct this face-to-face study and approval of our COVID-19 Safety Plan was obtained from the COVID-19 Advisory Committee at Southern Connecticut State University (2021-14-154).

Experimental measurements

Participants were instrumented with the Nexfin monitor (BMEYE, Netherlands), which is used to measure R-R intervals and beat-to-beat blood pressure.

Experimental protocol

On arrival for testing, participants were screened for COVID-19. If they had flu-like symptoms or an elevated temperature (above 100.4 °F or 38 °C), they would be excluded from testing. If they passed the COVID-19 screening, they were presented with a face mask. The information on the informed consent form was explained to the participants. They then read the informed consent form. Participants were asked to sign the consent form if they agreed with the conditions stated on the form.

Participants were then directed to sit in a quiet, comfortable temperature-controlled room (20-25 °C) with minimal stimuli for arousal for five minutes. Blood pressure measurements were then taken. Participants were then instrumented with a Nexfin monitor (BMEYE, Netherlands), which used EKG to determine continuous R-R interval measurements, and a finger blood pressure cuff to measure beat-to-beat blood pressure. Both measurements were taken for 8 min in a seated position at a sampling frequency of 1000 Hz. Participants were asked to breathe at 12 breaths·min^{-1} (0.2 Hz) guided by a light moving up and down on a computer screen. This breathing protocol was implemented to avoid the effect of a varied respiratory rate on spectral distributions [19]. Analysis of autonomic data was carried out in accordance with the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [20] *via* power spectrum analysis. Power spectrum analysis of heart rate fluctuation can be used as an indirect marker of autonomic function [21] and has been used in the analysis of autonomic data in prior studies [22]. Here, it involved the decomposition of a series of sequential R-R and systolic peak intervals into a sum of sinusoidal functions of different frequencies and amplitude. The power spectrum of the R-R intervals within the high-frequency band (0.15-0.4 Hz) is commonly used as an index of efferent vagal modulation [20], and the low-frequency band (0.04-0.15 Hz) is considered to be indicative of parasympathetic and sympathetic modulation. The spectrum of the systolic blood pressure (SBP) peaks within the low-frequency band (0.04-0.15 Hz) is considered to be an indicator of sympathetic vasomotor activity [23] and was used as an indicator of sympathetic modulation. Sympathovagal balance was calculated as the ratio of low-frequency (LF_{R-R}) to high-frequency modulation of the R-R intervals (HF_{R-R}), [24] denoted as LF/HF. However, this ratio has received criticism [25]. The absolute values of the HF_{R-R} and LF_{R-R} components were log-transformed to remove skewness and minimize the large standard deviation customarily present in this data and were indicated as $lnHF_{R-R}$ and $lnLF_{R-R}$.

Baroreflex sensitivity was determined as spontaneous BRS (sBRS) using the α-index. This index was derived as the square root of the ratio of low-frequency heart rate variability (LF_{R-R}) over the low frequency of systolic blood pressure variability (LF_{SBP}) when the coherence between both variables was 0.5 or greater. This method has been validated and was noticed to have a correlation of 0.94 with the phenylephrine method, which is considered to be a gold standard [26].

Statistical analyses

All data are presented as mean ± SD. Independent *t*-tests were used to determine differences in descriptive and dependent variables between the COVID-19 and the control group. The Mann-Whitney U test was used when a distribution was not normal (tested by the Shapiro Wilks test); $P<0.05$ was considered

significant. Statistical analyses were conducted using IBM. SPSS. Statistics (version 27; IBM Corp., Armonk, NY, USA).

Results

Means, ± standard deviations for the descriptive variables in the control and COVID-19 groups are illustrated in Table 1. Results for the descriptive variables indicated that except for DBP (P=0.02), there were no significant differences in age (P=0.41), height (P=0.58), weight (P=0.37), BMI (P=0.32), RHR (P=0.60), or SBP (P=0.08) between the groups. The time from SARS-CoV-2 infection to testing in the COVID-19 group is indicated in Table 1. Means, ± standard deviations for the dependent variables are illustrated in Table 2. There were no significant differences in $lnHF_{R-R}$ (P=0.20), LF_{SBP} (P=0.11), LF/HF (P=0.20), and α-index (P=0.20) between the COVID-19 and control groups. Additionally, though all the COVID-19 participants had fatigue as a symptom, we did not observe impairments in autonomic modulation or BRS in that group.

Table 1. Participants descriptive information.

Variables	Non-COVID-19 Group (n, 24)		COVID-19 Group (n, 20)		P
	Mean	SD	Mean	SD	
Age (years)	21.79	2.83	20.65	1.31	0.41
Height (cm)	175.17	6.51	176.40	8.09	0.58
Weight (kg)	79.13	18.31	83.70	19.33	0.37
BMI (kg/m^2)	25.56	5.03	26.89	5.84	0.32
RHR (bpm)	70.63	12.11	68.70	11.97	0.60
SBP (mm Hg)	113.67	7.75	117.30	6.06	0.08
DBP (mm Hg)	68.38	6.32	72.35	6.01	0.02
Days from infection to testing	-	-	185.14	128.02	-

Values in mean ± SD. BMI body mass index, RHR resting heart rate, SBP systolic blood pressure, DBP diastolic blood pressure. Statistical significance at P<0.05.

Table 2. Autonomic and sBRS parameters.

Variables	Non-COVID Group		COVID Group		P
	Mean	SD	Mean	SD	
$lnHF_{R-R}$ (ms^2)	7.41	1.09	7.77	0.82	0.20
LF_{SBP} (LF, mm Hg^2)	12.31	8.40	17.39	11.56	0.11
LF/HF	1.15	1.49	0.57	0.34	0.20
α-index (ms/mm Hg)	12.20	6.31	9.24	2.60	0.20

Values are indicated in mean ± SD. lnHFR-R log transformed high frequency from power spectral density analysis of R-R intervals from EKG. LFSBP low-frequency power from blood pressure variability, α-index indicator of spontaneous baroreflex sensitivity. Statistical significance at P<0.05.

Discussion

The current study demonstrated no differences in parasympathetic and sympathetic modulation in addition to BRS between young men who had COVID-19 versus young men who never had COVID-19. Additionally, though all the COVID-19 participants were experiencing fatigue at the time of testing, they did not demonstrate impairment in autonomic modulation or BRS.

It has been proposed that the ANS can be affected by COVID-19 [27]. Additionally, it has been proposed that an augmentation in SNA could be

associated with the cytokine storm associated with COVID-19 [6] and that impaired SNA has been observed during [10] and following SARS-CoV-2 infection [28]. However, we did not observe any difference in sympathetic modulation between young men who had COVID-19 versus controls. One prior research found elevated SNA *via* muscle sympathetic nerve activity (MSNA) in young COVID-19-positive participants versus controls within three to eight weeks of testing positive [28]. They later found no decrease in resting MSNA, throughout six months in the same population [29]. In that latter study, the results were obtained from a combined group of men and women; this reduced the possibility of understanding sex differences in SNA after recovery from COVID-19. Since the finding of no difference in sympathetic modulation between the groups in the current study was derived only from men, this allows for a fair understanding regarding these parameters in men, but the findings might not be generalizable to young women. Our finding suggested that the augmentation in SNA observed by earlier works could be transient and that normal sympathetic modulation could be re-established after COVID-19 in young, healthy men over time. Caution needs to be exercised with this speculation, as we tested our participants approximately 185 days after infection and were not able to assess sympathetic modulation at the onset of COVID-19 in the COVID-19 participants in the current study. Since elevated SNA is associated with negative cardiovascular health [30,31], the observed similarity in sympathetic modulation between the groups seem to suggest that young, healthy men who have had COVID-19 might not be at increased cardiovascular risk from COVID-19-related impairment in SNA.

Impaired parasympathetic nervous activity has been noted in middle-aged adults [10] during COVID-19, after recovery from COVID-19 [32], and in young men four to six weeks from the end of SARS-CoV-2 infection [33]. However, we did not observe a difference in parasympathetic modulation between groups. Our finding was corroborated by two prior studies demonstrating preserved HRV in young participants after COVID-19 [34,35]. It is worth noting that the mean age for the COVID-19 participants in the two middle-aged adult studies, which demonstrated impaired parasympathetic modulation, was greater than forty years [10,32]. However, the mean age of the COVID-19 participants in the current study was less than twenty-two years. Interestingly, the mean age of the participants in the two studies that corroborated the current study's finding was closer to the mean age of the participants in the current study. It is easy to speculate that age could be a factor affecting parasympathetic modulation after COVID-19. However, one prior study also demonstrated impaired parasympathetic modulation in young men four to six weeks from the end of infection [33].

Baroreflex dysfunction has been reported during COVID-19 in adults [10]. However, we found no difference in BRS between the COVID-19 and control groups after COVID-19. Since impairment of the baroreflex is associated with increased cardiovascular risk [12], our finding of no difference in BRS between these groups of young men suggests that young men who have had COVID-19 are not at increased cardiovascular risk from COVID-19-related impaired BRS. Since impaired BRS has been reported in the earlier phases of COVID-19 [10] and given that we did not examine BRS during the earlier phases, it is plausible to speculate that any earlier BRS impairment that might have been present in the COVID-19 participants in the current study could have been resolved over time. This speculation is particularly plausible given that the time from COVID-19 infection to testing in the COVID-19 group was approximately 185 days. Our finding has been corroborated, as it was proposed that COVID-19-related arterial stiffness and baroreflex dysfunction are partially reverted over time [36].

Impaired autonomic modulation has been linked to Long COVID [1,3] and COVID-19 [2,4]. All the COVID-19 participants in the current study reported fatigue at level 2 on the 5-point exertion scale, indicating fatigue during moderate exertion. Though autonomic dysfunction has been demonstrated to being associated with Long COVID and fatigue, and though the COVID-19 participants in the current study were experiencing fatigue, we did not observe impairments in BRS and autonomic modulation along with the fatigue observed in this group. Prior studies have examined BRS in young individuals with varying degrees of symptoms ranging from asymptomatic to symptomatic after COVID-19 [35,29]. However, to the best of our knowledge, the current study is the only study that examined BRS and autonomic modulation in young individuals who only had fatigue as a symptom after COVID-19. This distinction allows this study to help in determining if fatigue alone can be used as an indicator of impaired BRS and autonomic modulation in young men after COVID-19. The current finding of fatigue during moderate exertion

without concomitant impairment of autonomic modulation and BRS could be indicative that not all levels of fatigue are associated with impaired autonomic modulation and BRS after COVID-19 or that fatigue is not associated with those impairments. However, this finding seems to suggest that fatigue alone as a symptom might not be a good indicator of impaired autonomic modulation and BRS in young men after COVID-19.

Though the ANS is not the only system that is associated with COVID-19, symptoms of Long COVID and cardiovascular function, the ubiquitous nature of the ANS, and its association with cardiovascular disease allow it to be used as an indicator of potential cardiovascular risk from COVID-19. Given the robust association between the ANS and cardiovascular morbidity and mortality, our findings seem to suggest that young men who tested positive for COVID-19 approximately 185 days earlier, might not be at increased cardiovascular risk from COVID-19-related impairment in autonomic modulation and BRS. It has been suggested that medications such as amiodarone might reduce SARS-CoV-2 virus replication [37]. However, while, such works are relevant in the early phases of SARS-CoV-2 infection, it is of paramount importance that more works be done examining Long COVID and its impact on health.

Conclusions

Our findings indicated no difference in parasympathetic modulation, sympathetic modulation and BRS as related to cardiovascular function between young men who had COVID-19 versus young men who never had COVID-19. These findings suggest preserved ANS function and BRS in young men after COVID-19. Additionally, fatigue alone as a symptom does not seem to be associated with impaired autonomic modulation or impaired BRS in young men after COVID-19.

Limitations of the study

This study was started during a period when many institutions were closed due to COVID-19. During this period, many in-person research projects were halted. While we wanted to include women in this study, our early survey revealed that most women were not willing to take the chance to participate in any in-person research at that time. However, men were willing to participate. Therefore, we only included men in the study. Our study was limited as the findings could not be generalized to women. The secondary aim of this study was to determine whether fatigue is associated with impaired autonomic modulation and BRS in young men after COVID-19. Therefore, we only examined these associations with one symptom after COVID-19. If we had examined more symptoms perhaps more information could be obtained regarding symptoms after COVID-19 and cardiovascular health risk.

Conflict of Interest

There is no conflict of interest.

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