

Deepalakshmi Kaliyaperumal*, Karthikeyan RK, Murali Alagesan and Sudha Ramalingam

Characterization of cardiac autonomic function in COVID-19 using heart rate variability: a hospital based preliminary observational study

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Abstract

Objectives: The novel corona virus disease, which was initially reported in China in late 2019, has become a global pandemic affecting 330 million cases. COVID-19 affects predominantly the respiratory system, in addition to other organ systems, mainly the cardiovascular system. One of the hypotheses is that virus entering the target cells by binding to angiotensin converting enzyme 2 affecting hypothalamic pituitary axis could lead to dysautonomia which is measured by heart rate variability (HRV). HRV is a non-invasive measure of autonomic function that facilitates identification of COVID-19 patients at the risk of developing cardiovascular complications. So, we aimed to assess HRV in COVID patients and compare between COVID patients and normal controls.

Methods: In a case control design, we compared 63 COVID-19 infected patients with 43 healthy controls matched for age and gender. Along with clinical characterization, heart rate variability was evaluated using ambulatory 5 min ECG in lead II and expressed in frequency and time domain measures. Statistical analysis was performed using SPSS 17.0.

Results: Mean age of the study population was 49.1 ± 14.2 years and 71 (66.9%) were males. Frequency domain measures high (HF) and low (LF) frequency powers were significantly decreased in COVID-19 patients compared to controls. HF/LF and LF/HF ratios were not different between groups. Time domain measures rMSSD (root mean

square of successive RR interval differences) and SDNN (standard deviation of NN intervals) were significantly increased among COVID-19 subjects. COVID-19 infection was associated with increased parasympathetic activity as defined by $rMSSD > 40$ {adjusted odds ratio 7.609 (95% CI 1.61–35.94); $p=0.01$ } and $SDNN > 60$ {adjusted odds ratio 2.620 (95% CI 1.070–6.44); $p=0.035$ } after adjusting for age, gender and comorbidities.

Conclusions: Our study results showed increased parasympathetic tone in COVID patients. Early diagnosis of autonomic imbalance in COVID patients is needed to plan management and limit progression of disease.

Keywords: heart failure; pulmonary hypertension; right heart.

Introduction

In December 2019, a novel coronavirus disease (nCoV) epidemic emerged in Wuhan City, Hubei Province, China. Owing to its high transmissibility and infectivity rate it spread across the world and WHO declared it as a pandemic on March 11, 2020 [1, 2]. As this virus predominantly affects the respiratory system it has been renamed as severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) and the disease caused by this virus has been named as corona virus disease 19 (COVID-19) [3].

COVID-19 shows wide range of clinical presentations ranging from asymptomatic/mild symptoms (fever, cough, dyspnea, myalgia, fatigue, anosmia, dysgeusia and diarrhea) to severe illness like acute respiratory distress syndrome (ARDS), arterial and venous thrombosis, myocarditis and varieties of neurological manifestations [4–7]. A report from WHO says that “80% of infections are mild or asymptomatic, 15% are severe infections and 5% are critical infections” [8]. Co-morbid conditions like obesity, type 2 diabetes mellitus, coronary artery disease, chronic liver disease, chronic kidney disease and chronic respiratory disease are known to be risk factors for developing severe disease [9–11]. Wide spectrum of manifestations is explained by SARS CoV-2 having target cells in multiple organs and systems like respiratory tract including lung parenchyma,

*Corresponding author: Deepalakshmi Kaliyaperumal, MD, Physiology, PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore, Tamil Nadu, 641004, India, E-mail: drdeepalakshmik@gmail.com

Karthikeyan RK, Respiratory Medicine, PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India

Murali Alagesan, Internal Medicine, PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India

Sudha Ramalingam, Research and Innovation, PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India

ileum, bladder, esophagus, heart, kidney, hypothalamus, pituitary, adrenal glands etc. These target cells have angiotensin converting enzyme-2 (ACE2) receptors in their cell wall. ACE2 binding affinity of the SARS CoV-2 spike protein ectodomain is one of possible mechanisms by which entry to these cells is facilitated [1, 12]. Histopathological and immune histochemical studies have clearly demonstrated a direct assault on these organs/systems by the SARS CoV-2 virus [13].

Though main portal of entry is respiratory system and hence the dominantly affected one, SARS CoV-2 reaches other systems through mechanism yet unknown. Neuro-invasive potential of SARS CoV-2 has been discussed in recent literature in the context of plausible explanation for variety of neurological manifestations of COVID-19 [14–16]. Earlier studies have demonstrated that SARS CoV-1 and MERS CoV (Middle east respiratory syndrome CoV) have the potential to enter and invade central nervous system, dominantly in brainstem structures [12, 17, 18]. Owing to the similarities in viral structure and receptor binding domain, neurotropism of SARS CoV-2 can be speculated from the evidence found from SARS CoV-1. Though sparse, direct evidence of neurotropism of SARS CoV-2 is emerging in literature. A recent report by Paniz–Mondolfi et al. [19], demonstrated by electron microscopy, presence of viral particles in postmortem brain tissues of a COVID-19 patient. Another report by Moriguchi et al. [20], evidenced the presence of SARS CoV-2 in cerebrospinal fluid. It has been postulated that SARS CoV-2 can enter the central nervous system by several mechanisms such as invasion through olfactory epithelium [21], synapse-connected route from terminal nerve endings [22] and transmission across blood-brain barrier by endothelial damage [19]. Clinical implications of neuropropensity of SARS CoV-2 range from mild symptoms like headache, dizziness etc., to severe manifestations like seizures, encephalitis, Guillain-Barre syndrome and cerebrovascular events. Involvement of autonomic nervous system (brainstem and hypothalamus) can lead to dysfunction of vital organs including cardiovascular system, thereby significantly influencing the outcome in COVID-19 patients. Cardiovascular system is also affected by the virus leading to manifestations like acute myocardial infarction, myocarditis and arterial & venous thrombosis. Monitoring the cardiac autonomic function of patients with COVID-19 can help us identify the individuals who are at risk of developing adverse cardiovascular outcomes.

Autonomic dysfunction has been reported in viral infections like retrovirus (human immunodeficiency virus, human T-lymphotropic virus), herpes viruses, flavivirus, arbovirus, enterovirus 71 and lyssavirus [23]. Current

literature on autonomic dysfunction in COVID-19 patients is very sparse, barring a few case reports [24, 25]. Though various other methods were employed in these clinical settings to elicit dysautonomia, heart rate variability (HRV) measurement was seldom used for this purpose. During last two decades, HRV is considered most objective, reproducible and validated tool for demonstration of autonomic dysfunction [26]. Frequency and time domain measures of HRV have emerged as the most promising markers of balance between parasympathetic and sympathetic activity of autonomic nervous system that controls homeostasis of all vital organs.

Eliciting an association between autonomic dysfunction and COVID-19 could clarify the genesis of many clinical manifestations and importantly the unpredictable natural course of the illness. In this study, we intended to evaluate for autonomic imbalance and the direction of its deviation in COVID-19 subjects by measuring HRV and comparing the differences in HRV metrics between SARS CoV-2 positive and negative individuals.

Methods

This was an analytical cross-sectional study involving adult COVID-19 patients admitted for treatment in PSG Institute of Medical Sciences, Coimbatore, a specialized COVID-19 treating center in South India during March to June 2020. Sample frame during this period was approximately 500 inpatients whose COVID-19 status was confirmed by reverse transcription-polymerase chain reaction (RT-PCR) test of nasopharyngeal and oropharyngeal swab. Eligible inpatients (test group) of both genders, aged between 25 and 60 years were recruited from the sample frame by convenient sampling method. Patients with uncontrolled hypertension, coronary artery disease, cerebrovascular accident, family history of young myocardial infarction were excluded. Similarly, those patients on treatment with beta-blockers, inhaled or oral beta-mimetics, theophylline and other drugs with potential chronotropic effects were excluded. Patients with severe disease (those requiring oxygen support and/or intensive care) were also excluded. The comparison group included age and gender-matched healthy individuals from among the employees of medical school who tested negative for SARS CoV-2 by RT-PCR of their nasopharyngeal and oropharyngeal swab and fulfilled above mentioned selection criteria. This study was cleared by the institutional human ethics committee, and all study participants gave written informed consent. All such subjects recruited for the study underwent a detailed clinical examination.

Assessment of HRV

Study participants in both the groups were instructed to refrain from smoking, caffeine intake for 2 h and alcohol intake for 36 h. They should have had adequate rest, at

least 8 h of uninterrupted sleep on the night before the assessment of HRV and normal breakfast on the day of assessment. They were made to lie quietly in a couch in supine position for 5 min to alleviate the anxiety in a sound attenuated room with dim lighting and the temperature ranging from 20 to 25 °C.

After explaining the procedure to the subject, HRV, a quantitative marker of the autonomic activity was assessed using an ambulatory ECG system (INCO digital NIVIQUIRE, Bangalore, India) in lead II for 5 min. It is a multichannel digital data acquisition system which enables to acquire, analyze and store ECG data. ECG data was obtained at a sampling rate of 1,024 Hz in standard lead II configuration. The interface RS232C-compatible module was used to transfer data from the recording unit to the computer. The transferred data was analyzed using inbuilt software system. The series of RR intervals obtained were subjected to frequency and time domain analysis. Time domain indices of HRV indicate the amount of variability in measurements of interbeat interval (IBI), which represent time period between successive heartbeats. Time domain measures include standard deviation of NN intervals (SDNN), root mean square of successive RR interval differences (rMSSD) and percentage of successive RR intervals (pNN50). Frequency domain measurements estimate the distribution of absolute or relative power into frequency bands. Frequency domain measures include low frequency (LF) and high frequency (HF) [26]. HF component indicates the parasympathetic activity, whereas LF represents both sympathetic and vagal activity, and SDNN, rMSSD and pNN50 measure parasympathetic activity [26, 27].

Statistical analysis

The data were examined initially for normality of distribution and homogeneity of variance and expressed in terms of mean \pm SD or percentage. Data with wide dispersion were expressed in log transformed values. Data from continuous variables were compared between study groups using Student's *t*-test whereas categorical variables were compared using Chi-Square test. Mann-Whitney *U* test was performed for variables that were not normally distributed. HRV variables that were significantly different between the groups were used as dependent variables for logistic regression analysis. For this purpose, HRV measures were dichotomized to categorical variable (artificial categorization using median split [28]) using an arbitrary cut-off value that was close to the median as reported by Nunan et al. [27] in their systematic review of studies involving normal subjects. Stepwise logistic regression

analysis was employed to identify significant covariates and to evaluate association between HRV measures and SARS CoV-2 status after adjusting for important confounders like age, gender and comorbidity. Subgroup analysis was performed to characterize clinical and HRV profiles of SARS CoV-2 infected subjects based on symptom status. A *p* value of <0.05 was considered significant. All statistical analyses were carried out using SPSS version 17 software.

Results

In total, 106 participants were recruited for the study, which included 63 (59.4%) COVID-19 subjects and 43 (40.6%) healthy individuals who tested negative for SARS CoV-2. Among COVID-19 patients 33 (52.3%) had mild to moderate symptoms and 30 (47.6%) were asymptomatic. Mean age of the study population was 49.09 ± 14.21 years with 71 (67%) male subjects and 35 (33%) female subjects (Figure 1).

Comparing COVID-19 patients and healthy subjects, both groups were age and gender matched. Vital parameters like heart rate, SPO_2 at room air, systolic and diastolic blood pressure showed no difference between the study groups. Among frequency domain HRV parameters, HF and LF powers were significantly decreased among COVID-19 patients as compared to healthy individuals. HF/LF ratio and LF/HF ratio were not different between the groups (Table 1). Among time domain parameters, mean rMSSD was significantly higher in the COVID-19 group compared to healthy individuals (Figure 2). Mean SDNN value was higher among COVID-19 subjects with a trend toward statistical significance.

In the above graphical representation, the box spans the interquartile range, ends of the box represent upper and lower quartiles, bold horizontal line within the box represents the median value and the whiskers show the

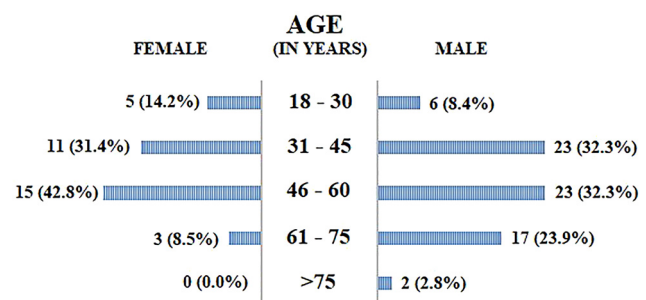


Figure 1: Age and gender distribution of study population.

Table 1: Comparison of clinical profile and heart rate variability parameters between COVID-19 subjects and healthy individuals. Data shown as mean \pm SD and frequency {n (%)}.

Variables	COVID-19 subjects (n=63)	Healthy subjects (n=43)	p-Value
Age, years	48.39 \pm 16.3	50.1 \pm 10.5	0.517
Gender			0.449
Male	44 (69.8%)	27 (62.8%)	
Female	19 (30.2%)	16 (37.2%)	
SPO ₂ in room air, %	95 \pm 6	97 \pm 1	0.678
Systolic BP, mmHg	124 \pm 15	121 \pm 6	0.386
Diastolic BP, mmHg	77 \pm 7	77 \pm 4	0.818
HR	84 \pm 15	81 \pm 15	0.151
HF ^a	1.79 \pm 0.15	2.09 \pm 0.39	0.0001*
LF	33.47 \pm 20.31	77.46 \pm 50.8	0.0001*
HF/LF ratio	4.16 \pm 4.56	2.34 \pm 1.89	0.248
LF/HF ratio	0.70 \pm 0.71	0.64 \pm 0.35	0.282
pNN50	4.45 \pm 8.12	1.99 \pm 3.23	0.561
rMSSD ^a	1.49 \pm 0.58	1.15 \pm 0.29	0.019*
SDNN ^a	1.89 \pm 0.33	1.73 \pm 0.10	0.10
rMSSD>40	19 (30.6%)	2 (4.7%)	0.001 ^b
SDNN>60	27 (45.0%)	11 (25.6%)	0.044 ^b

SPO₂, oxygen saturation; BP, blood pressure; HR, heart rate; SDNN, standard deviation of NN intervals; rMSSD, root mean square of successive RR interval differences; pNN50, percentage of successive RR intervals; LF, low frequency power; HF, high frequency power.

*Mann-Whitney *U* test, level of significance 0.05. ^aLog transformed values. ^bChi square test, level of significance 0.05.

minimum and maximum values. The circles with numerals are outliers.

Based on the published data on range of observations and median value of normal subjects, we defined parasympathetic overtone when subjects had rMSSD more than

Table 2: Stepwise logistic regression analysis of association between COVID-19 infection and parasympathetic overtone as defined by rMSSD>40 or SDNN>60.

Parasympathetic overtone	Odds ratio (95% CI)	p-Value
rMSSD>40		
Unadjusted	9.058 (1.98–41.35)	0.004
Adjusted for age and gender	8.670 (1.86–40.30)	0.006
Adjusted for age, gender and diabetes mellitus type 2	8.174 (1.75–38.22)	0.008
Adjusted for age, gender and presence of comorbidities	7.609 (1.61–35.94)	0.01
SDNN>60		
Unadjusted	2.380 (1.014–5.58)	0.046
Adjusted for age and gender	2.427 (1.020–5.77)	0.045
Adjusted for age, gender and diabetes mellitus type 2	2.417 (1.002–5.83)	0.049
Adjusted for age, gender and presence of comorbidities	2.620 (1.070–6.44)	0.035

40 and SDNN more than 60 [27]. These dichotomous variables indicated that COVID-19 patients had higher parasympathetic overtone than the healthy subjects (Table 1). Stepwise logistic regression analysis revealed a significant association between SARS CoV-2 infection status and parasympathetic overtone after adjusting for age, gender, T2DM or the presence of one or more comorbidities (Table 2).

Subgroup analysis was performed comparing the characteristics between symptomatic and asymptomatic subjects with COVID-19 (Table 3). Symptomatic COVID-19 patients were elderly and predominantly males as compared to asymptomatic patients. Symptomatic patients more frequently had at least one co-morbidity. Common

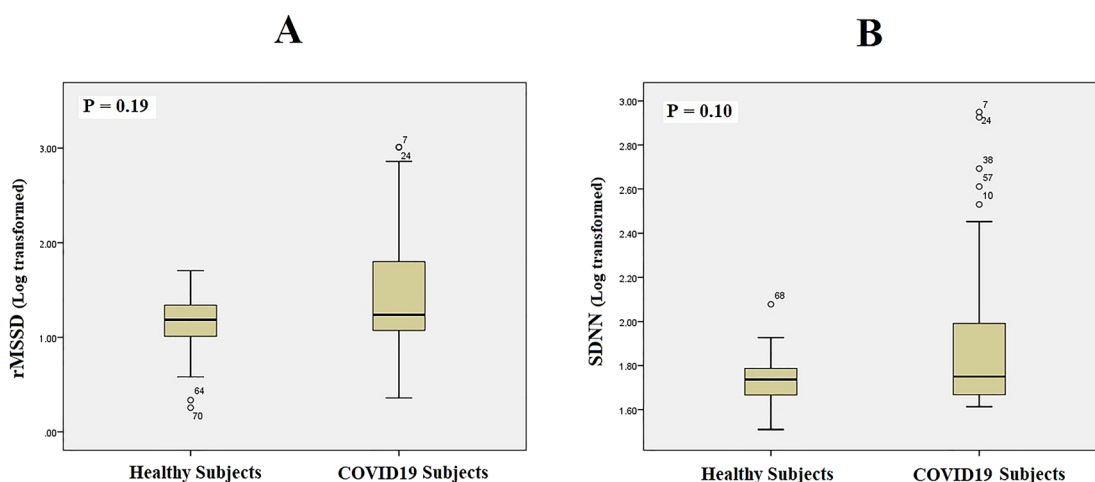


Figure 2: Boxplot graphical representation of rMSSD (A) and SDNN (B) among COVID-19 patients and healthy subjects.

Table 3: Subgroup analysis of clinical profile and heart rate variability parameters among symptomatic and asymptomatic COVID-19 subjects. Data shown as mean \pm SD and frequency {n (%)}.

Variables	Symptomatic COVID-19 subjects (n=33)	Asymptomatic COVID-19 subjects (n=33)	p-Value
Age, years	57.59 \pm 13.5	38.57 \pm 13.1	0.0001 ^c
Gender			0.006 ^b
Males	28 (84.8%)	16 (53.3%)	
Females	5 (15.2%)	17 (46.7%)	
SPO ₂ in room air, %	94 \pm 9	97 \pm 1	0.072
Systolic BP, mmHg	128 \pm 16	121 \pm 15	0.097
Diastolic BP, mmHg	77 \pm 7	77 \pm 8	0.763
Comorbidities			
DM type 2	11 (36.7%)	7 (23.3%)	0.260
Systemic hypertension	10 (33.3%)	2 (6.7%)	0.010 ^b
Any one or more of above comorbidities	20 (66.7%)	8 (26.7%)	0.002 ^b
HR	88.14 \pm 17.11	80.55 \pm 12.98	0.055
HF	64.61 \pm 21.22	68.58 \pm 19.33	0.442
LF	35.38 \pm 21.22	31.37 \pm 19.40	0.437
HF/LF ratio	3.82 \pm 4.35	4.54 \pm 4.83	0.518
LF/HF ratio	0.79 \pm 0.83	0.61 \pm 0.55	0.650
pNN50	4.58 \pm 8.73	4.30 \pm 7.53	0.358
rMSSD ^a	1.41 \pm 0.62	1.56 \pm 0.53	0.086 [*]
SDNN ^a	1.87 \pm 0.36	1.91 \pm 0.3	0.135

SPO₂, oxygen saturation; BP, blood pressure; HR, heart rate; SDNN, standard deviation of NN intervals; rMSSD, root mean square of successive RR interval differences; pNN50, percentage of successive RR intervals; LF, low frequency power; HF, high frequency power.

*Mann–Whitney *U* test, level of significance 0.05. ^aLog transformed values. ^bChi square test, level of significance 0.05. ^cStudent's *t*-test, level of significance 0.05.

co-morbidities among symptomatics were DM type 2 (36.7%), Systemic hypertension (33.3%), obesity (10%), hypothyroidism (13.3%) and psychomorbidity (10%). Both frequency and time domain HRV parameters showed no difference between the subgroups.

Discussion

Our study clearly demonstrated an increased parasympathetic activity in COVID-19 patients, independent of important confounders like age, gender and comorbidities including diabetes mellitus. Autonomic dysfunction in COVID-19 subjects in our study was best demonstrated by time domain measures of HRV namely rMSSD and SDNN with predefined cut-off values. HF and LF powers in frequency domain were significantly decreased in COVID-19 subjects, though their ratios were not significantly different when compared to the healthy uninfected subjects. In a

subgroup analysis of COVID-19 subjects, HRV measures were not different between asymptomatics and mild to moderate symptomatic. To our knowledge, our study was the first to demonstrate higher rate of autonomic imbalance among COVID-19 patients as compared to uninfected healthy group.

Our search through literature yielded scanty reports on autonomic dysfunction among COVID-19 patients. Ritwik Ghosh et al. [24] reported in one case of COVID-19, clinical features of autonomic dysfunction in the form of sinus arrhythmia, postural hypotension, intermittent profuse sweating, constipation, erectile dysfunction and squeezing sensation in the chest. Cardiac dysautonomia was not studied in this report. In another case report, Reiner Buchhorn et al. [25], studied a 58-year-old COVID-19 patient with 24 h ECG monitoring and found a significant decrease in heart rate and a paradoxical decline in HRV. But for these two case reports suggesting a possible autonomic dysfunction, no studies have yet, evaluated the presence of this important physiological disharmony in COVID-19 patients.

Though scanty in the context of COVID-19, plethora of evidence available in the literature demonstrating autonomic dysfunction in other infectious diseases like human immunodeficiency virus [29–31] human T Cell lymphotropic virus [32], Epstein Barr virus [33], cytomegalovirus [34], West Nile virus [35], Chagas disease [36, 37], diphtheria [38], leprosy [39], dengue [40], tetanus [41] and botulism [42]. Methodological differences in evaluating autonomic function as well as variations in study design do not allow head-to-head comparison of these studies with our findings in COVID-19 patients. In our search through literature, we found only two reports using HRV to link autonomic dysfunction with infection. Jeevagan Vijayabala et al. [43] postulated sympathetic dysfunction as one of the pathogenetic mechanisms in Dengue shock syndrome. Robert Carter et al. [40] examined HRV of 27 children during defervescence in dengue viral infection and found that cardiac parasympathetic activity was the major cause for reduction in heart rate during this period of illness. Their observations were mainly based on frequency domain measures of HRV after correcting for baseline changes in heart rate. Contradictory to the above observations, La-Orkhun et al. [44] found no significant changes in various time and frequency domain metrics of HRV at least 24 h after defervescence, and follow-up conducted at least 14 days after defervescence. Our findings are consistent with Jeevagan Vijayabala et al. and Robert Carter et al., that we too found an increased parasympathetic activity in COVID-19 patients as demonstrated by the increase in time domain variables of HRV. This study further substantiates

two cases as cited above that reported autonomic dysfunction due to COVID-19. Proposed mechanisms of viral infection induced autonomic dysfunction include invasion of the central nervous system and the direct viral, toxin-mediated or immune-mediated involvement of the peripheral and autonomic nervous system [45].

Unlike the time domain variables, we found that frequency domains of HRV, specifically the LF/HF ratio were not different between the COVID-19 subjects and the healthy subjects. Traditionally LF/HF ratio was considered a marker of sympatho-vagal balance in cardiovascular system. However recent evidence this ratio merely indicates one part of complex non-linear interaction between sympathetic and parasympathetic nervous systems confounded by multiple physiological and mechanical factors [46]. Some of these confounders may have been missed in our study protocol. Also, smaller sample size may explain our inability to detect subtle difference in LF/HF ratio between the groups.

Our study involved a standardized measurement of heart rate variability using an ambulatory 5 min ECG recording in lead II. Precision of our evaluation was further augmented by stringent selection of subjects and optimal conditions for HRV measurement during conduct of the study. Our study is limited by participation of only asymptomatics and mild to moderate symptomatic patients with SARS CoV-2 infection. Severely ill COVID-19 patients were excluded from the study because we believed that factors like stress, cytokine storm, drugs like steroids, vasopressors etc., positive pressure ventilation, prolonged hospitalization and related psych morbidity that typically characterize these patients may have a confounding effect on our observations. None of our study subjects had any of these factors that could have possibly altered our findings. Sample size of the study was not adequate to provide enough statistical power to our findings. But we believe that this preliminary report can serve a stimulus for future research in this direction. A larger sample size could have facilitated further evaluation of association between symptoms and autonomic function in our subjects.

In conclusion, this study has found that COVID-19 is associated with autonomic dysfunction whose mechanism and prognostic implications need to be evaluated further. HRV measurement, being a simple, noninvasive, inexpensive tool, its utility in clinical practice as a possible rapid diagnostic and prognostic marker needs to be assessed in future research.

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Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: This study was cleared by the local institutional human ethics committee and all study participants gave written informed consent.

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