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Dysautonomia in post-COVID-19 patients: new insights

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ABSTRACT

Background: Increasing numbers of COVID-19 patients, continue to experience symptoms months after recovering from mild cases of COVID-19. Amongst these symptoms, several are related to neurological manifestations, including fatigue, anosmia, hypogeusia, headaches and hypoxia. However, the involvement of the autonomic nervous system, expressed by a dysautonomia, which can aggregate all these neurological symptoms has not been prominently reported. Here, we hypothesize that dysautonomia, could occur in secondary COVID-19 infection, also referred to as “long COVID” infection.

Methods: 39 participants were included from December 2020 to January 2021 for assessment by the Department of physical medicine to enhance their physical capabilities: 12 participants with COVID-19 diagnosis and fatigue, 15 participants with COVID-19 diagnosis without fatigue and 12 control participants without COVID-19 diagnosis and without fatigue. Heart rate variability (HRV) during a change in position is commonly measured to diagnose autonomic dysregulation. In this cohort, to reflect HRV, parasympathetic/sympathetic balance was estimated using the NOL™ index, a multiparameter artificial intelligence-driven index calculated from extracted physiological signals by the PMD-200™ pain monitoring system. Repeated-measures mixed-models testing group effect were performed to analyze NOL index changes over time between groups.

Results: A significant NOL index dissociation over time between post-COVID-19 participants with fatigue and control participants was observed ($p=0.046$). A trend towards significant NOL index dissociation over time was observed between post-COVID-19 participants without fatigue and control participants ($p=0.109$). No difference over time was observed between the two groups of post-COVID-19 participants ($p=0.904$).

Conclusions: Post-COVID-19 participants with fatigue may exhibit a dysautonomia characterized by dysregulation of the HRV, that is reflected by the NOL index measurements, compared to control participants. Dysautonomia may explain the persistent symptoms observed in post-COVID-19 patients, such as fatigue and hypoxia.

Trial registration : The study was approved by the Foch IRB: IRB00012437 (approval number: 20-12-02) on December 16, 2020.

Keywords: COVID-19, dysautonomia, long COVID, heart rate variability

INTRODUCTION

Increased numbers of COVID-19 patients, continue to experience symptoms several months after mild cases of COVID-19¹. Reported symptoms lead to disability with debilitating fatigue, breathlessness, headaches, muscle and/or joint pain, brain fog, memory loss, sensation of pressure on the chest, palpitations, nausea, dramatic mood swings in combination with exercise intolerance and a relapsing-remitting pattern of recurrence². Among these symptoms, several are related to neurological manifestations, including fatigue, anosmia, hypogeusia, and headaches³, and also respiratory symptoms, such as hypoxia⁴. Nevertheless, the involvement of the autonomic nervous system (ANS) which can aggregate all these neurological symptoms in COVID-19 infection has been under reported in the literature⁵. One of the last and recent hypotheses is that these symptoms could be the manifestation of a dysautonomia in post-COVID-19 infection⁶.

Dysautonomia, characterized by the failure or the increased activity of the sympathetic or parasympathetic components of the ANS, has several clinical symptoms, such as fatigue, orthostatic hypotension, labile blood pressure, dysregulation in the heart rate variability (HRV), impotence, bladder dysfunction, and alterations in bowel functions. Dysautonomia may be chronic or acute, progressive or reversible and has been shown to present numerous associated pathologies, such as alcoholism, diabetes, or either Parkinson's disease. Dysautonomia was also associated with viral infections, including hepatitis C virus, HIV, or Epstein-Barr virus⁵. Fatigue is one of the major clinical characteristic of dysautonomia in COVID-19 patients⁷⁻⁹.

HRV measurement is a commonly used method for cardiovascular follow-up in healthy participants, athletes and cardiovascular patients¹⁰. HRV is mainly related to emotional, social, cognitive and health levels¹¹. HRV is the main marker of the modulation of the sympathetic and parasympathetic branches of the ANS, and thus, of dysautonomia¹². The low-frequency band reflects the modulation of sympathetic and parasympathetic branches on the heart¹³ and has been considered as an index of the sympathovagal imbalance¹⁴. In the current study, we apply the nociception level (NOL) index to estimate HRV and overall ANS balance. The NOL algorithm (Medasense Biometrics, Ramat Gan Israel) is a multiparameter nonlinear combination of HR, HRV, amplitude of the finger photoplethysmogram, skin conductance level, and their time derivatives, obtained using a non-invasive finger probe, displayed on the monitor screen as a scale of 0-100 derived using a random forest regression¹⁵.

Here, we hypothesize that dysautonomia could occur in post-COVID-19 infection, also called "long COVID" infection. We aim to demonstrate this phenomenon by illustrating HRV dysregulation, reflected through the NOL index showing the sympathetic/parasympathetic

balance, in post-COVID-19 participants. We propose that the symptoms secondary to COVID-19 could be directly related to this virus or its immune-related dysregulation to the ANS, leading to transient or long-term dysautonomia.

METHODS

The present study prospectively included 39 participants from December 2020 to January 2021: 12 participants with COVID-19 diagnosis and fatigue, 15 participants with COVID-19 diagnosis without fatigue and 12 control participants without COVID-19 diagnosis and without fatigue. COVID-19 diagnosis was defined as positive polymerase chain reaction (PCR) test, serologic test or computed tomography (CT) scan. Participant's eligibility for inclusion in the study was assessed during their post-COVID follow-up in the Department of physical medicine and rehabilitation of the Foch hospital (Suresnes, France). This follow-up aims to enhance the participants in physical activity through a personalized program of exercises-post-COVID rehabilitation. Exclusion criteria were age inferior to 18 years, Nociception level unusable, vasoactive medication, toxicological or alcoholic participants, BMI superior to 35 and participants legally protected or deprived of their freedom.

HRV was reflected using the NOL index, initially developed in the operating theater to guide analgesia administration during surgery. The NOL index was calculated from the extracted signals by the PMD-200TM pain monitoring system. The NOL is based on a nonlinear combination of nociception-related physiologic parameters: HR, HRV (at the 0.15 to 0.4 Hz band power), amplitude of the photoplethysmography wave, skin conductance level, and their time derivatives ¹⁵ obtained continuously using a non-invasive finger probe. The NOL is based on the advanced statistical and machine learning techniques to combine multiple signals into a single composite index. The NOL is a multiparameter nonlinear combination of HR, HRV, PPGA and SCL derived from random forest regression displayed on a scale from 0-100. Random forest is an algorithmic modeling approach that enables combining multiple parameters of different origin and discovering their complex nonlinear interactions ¹⁶.

All study participants underwent the following protocol of measurements with the NOL index during their post-COVID follow-up consultation: step 1, five minutes lying down, step 2, five minutes standing, step 3, thirty seconds of flexion/extension and step 4, two minutes sitting down. Measures were performed each five seconds.

The study was approved by the Foch IRB: IRB00012437 (approval number: 20-12-02) on December 16, 2020. A non-opposed consent was obtained for all participants.

Parameters

The following clinical data were collected: age, gender, weight, height, body mass index (weight (kg) divided by height (m²)), heart rate, systolic, diastolic blood pressure, oxygen saturation, comorbidities (hypertension, diabetes and respiratory diseases), loss of taste and smell, previous oxygen therapy, and duration from first symptoms of COVID-19 diagnosis.

Fatigue was defined by clinicians as at least two of the following criteria: loss of body mass exceeding 10%, NIJMEGEN superior or equal to 23¹⁷, PCL-5 test superior to 20¹⁸ and 30 seconds of up and down test inferior to 3¹⁹.

Statistical analysis

Characteristics of the study population were described as median and interquartile range (IQR) for continuous variables. Categorical variables were described as absolute numerical values and proportions. Comparisons between groups were performed using Kruskal-Wallis test for continuous variables and Chi-squared test for categorical variables. Repeated-measures mixed-models testing group effect were performed to analyze NOL index changes over time between groups. Statistics were performed using SAS software (version 9.4; SAS Institute, Carry, NC). Significance was defined by a P value < 0.05.

RESULTS

Characteristics of the participants were described in **table 1**. No significant differences were observed for age, gender, comorbidities (hypertension, diabetes and respiratory diseases between the three groups of the study population). Moreover, no difference was observed for previous oxygen therapy, loss of taste and smell, and duration from first symptoms of post-COVID-19 between the post-COVID-19 participants with fatigue and thus without fatigue. Post-COVID-19 participants with fatigue presented higher values of NIJMEGEN and PCL-5 scores ($p=0.002$ and $p=0.001$, respectively) but not for loss of body mass exceeding 10% and the 30 seconds of up and down test ($p=0.632$ and $p=0.192$, respectively) than post-COVID-19 participants without fatigue.

Figure 1 shows the different curves of the NOL index for post-COVID-19 participants with and without fatigue compared to control participants. A significant dissociation over time between post-COVID-19 participants with fatigue and control participants was observed ($p=0.046$). A trend towards significant dissociation over time was observed between post-COVID-19 without fatigue and control participants ($p=0.109$). No difference over time was observed between the two groups of post-COVID-19 participants ($p=0.904$).

DISCUSSION

In our study, the NOL index, a non-invasively measured multi-parameter index, was used to highlight the dysautonomia hypothesis in post-COVID-19 participants. The variables that make up the NOL cover both sympathetic and parasympathetic activities of the ANS²⁰. We observed that HRV, reflected by the NOL index, was significantly different in post-COVID-19 participants with fatigue compared to control participants. HRV is one of the main markers of dysautonomia¹². Some etiologies may explain dysautonomia in post-COVID-19 patients including hypoxia, neurotropism and inflammation.

One of the aspects of COVID-19 patients' complications is the presentation of low blood oxygenation but no sensation of dyspnea²¹. This phenomenon has been called "happy hypoxemia"^{4,21}. This suggests that at least some sensory information could reach the brainstem to elicit a partial compensatory reflex respiratory response that is sufficient to lower the CO₂ level, which diffuses more rapidly across the alveoli than oxygen. Projections from the brainstem to the cortex allow the brain to process homeostatic afferent signaling. A signal of internal hypoxia was received by the brain to ensure a rise of sensation of "air hunger" and needing to breathe, which is curiously absent in severe COVID-19 patients⁴. Respiratory responses to hypoxia occur in the presence of sensory nerves in chemoreceptive areas. Internal environment was recognized by these nerves to stimulate the increase in the ventilatory drive. Respiratory pathology involves autonomic reflexes. Dyspnea is a conscious distressing symptom of breath difficulty²². Thus, the primitive brainstem reflex appears to be essential for survival and against a wide range of stimuli, such as hypoxia, hypercapnia, and acidosis.

COVID-19 infection could be responsible for direct invasion of the central nervous system (CNS) by a direct hematogenous and neural propagation²³. COVID-19 virus in the airways could pass by the epithelial barrier invading the blood and lymph circulation and thus, propagate towards the CNS. The diameter of the COVID-19 virus is 60 to 140 nm, allowing it to pass through the blood-brain barrier (BBB) and gain entry into the CNS²⁴. Other hypotheses highlighted a possible polarization of neurons leading to hyposmia due to conductive loss or neural loss²⁵. Possible damages to the afferent hypoxia-sensing neurons could be due to the direct effect of COVID-19 by binding ACE2 expressed in capillary endothelium of BBB to gain access into the CNS²⁶ or by indirect effect with cytokine storm on mitochondria or on nerve fibers²¹. Recent PET (positron emission tomography) scan findings have highlighted that COVID-19 neurotropism could occur in patients with impairment of olfactory bulb but also in other limbic structures, including thalamus/hypothalamus, cerebellum and the brainstem^{27,28}.

Moreover, the neuro-invasiveness of COVID-19 could have a direct role in hypoxia ²⁹. Excessive accumulations of acid metabolites in brain and anaerobic metabolites in mitochondria inducing edema and obstruction of the cerebral blood flow lead to hypoxia ³⁰.

The glossopharyngeal afferents, which innervate the carotid body and the vagal afferents enhancing the respiratory tract, present a key action in the monitoring organelle mechanism and modulating homeostasis by the stimulation of the ANS. Theses neurons are the primary sensory inputs of numerous reflex circuits modulating several major functions, such as HR, BP, and airway caliber ²². Pulmonary receptors expressed on afferent vagal nerve terminals in the lung have mechanical or chemical stimuli, which translocate in the brainstem by small-diameter myelinated (A δ) or unmyelinated (C)-fiber nerve axons. C-fiber afferents respond to inflammatory markers and could have a major role in prominent action in dyspnea and breath difficulty but also a major role in coughing ²². Vagal C-fiber afferents innervate the larynx response to laryngeal discomfort while the afferent information arrives from the vagal and glossopharyngeal nerves to merge at the nucleus of the tractus solitarius (NTS), a key site of critical homeostasis pathway. Thalamus, somatosensory cortex, amygdala and insular cortex were implicated in breath perception. However, the biological phenomenon underlying the dissociation between hypoxemia and overt dyspnea remain unknown in COVID-19 patients. Nevertheless, the observed disassociation could be present in patients presenting lesions in the glossopharyngeal or vagus nerves due to cranial nerve damages ⁴. Impairs of the HRV may be explained by the acute dysautonomia enhancing by afferent baroreflex failure. This mechanism leads to several damages at the afferent baroreceptor signaling, which starts from baroreceptors in carotid bodies to the vagal and glossopharyngeal nerve fibers, and then, to the NTS ⁵.

Moreover, the ANS responds quickly to changes in physiological states, it may offer signals, in the form of HRV, that can warn of an impending cytokine storm sooner than other currently employed laboratory tests ³¹. COVID-19 infection was associated with a cytokine storm characterized by the release of large amounts of pro-inflammatory cytokines and chemokines ^{32,33}. The relationship between HRV and inflammatory factors has been well extensively studied. Inflammatory factors might across the compromised BBB and cause brain damages. Thus, inflammation caused by viral infection could trigger and propagate chronic neuronal dysregulation ³⁴. A recent meta-analysis demonstrated an inverse relation between HRV and inflammation ³⁵. The measure of HRV was inversely correlated with CRP ³⁶. In the current COVID-19 infection, involvement of CRP became the vital monitoring patients' inflammatory factor ^{32,33}. Nevertheless, the biological mechanism for the relationship between ANS and immune system interacted to impact the HRV has not been well understood ³¹.

Limitations

The main strength of our study was the use of the NOL index, which is a validate parameter to estimate HRV ³⁷. The data were collected regarding standardized protocols that add validity to our study's results. Very few studies have investigated dysautonomia in COVID-19 participants and comparison to previous literature is difficult. One major limit was the relatively small sample size limiting the statistical power of the analyses. Consequently, we cannot exclude the possibility that some of the negative findings were due to lack of statistical power.

CONCLUSION

Post-COVID-19 participants with fatigue may exhibit a dysautonomia characterized by dysregulation of the HRV, reflected by the NOL index, compared to control participants. Dysautonomia may explain the persistent symptoms observed in post-COVID-19 participants, such as fatigue and hypoxia. Future clinical studies are needed to validate this hypothesis to allow better care of these participants during post-COVID-19 rehabilitation.

Compliance with Ethical Standards

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

IRB Approval

The study was approved by the Foch IRB: IRB00012437 (approval number: 20-12-02) on December 16, 2020. A non-opposed consent was obtained.

Consent for publication

A non-opposed consent was obtained for all participants.

Availability of data and materials

Not applicable

Competing interest

The authors declare they have no conflict of interest with this work.

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Authors' contributions

NB had the original idea and performed the participants' measurements. AV performed the design and the statistical analyses and the interpretation. AV wrote the article. NB, MLG, SR, PT and FH participate in the re-writing of the manuscript. All authors read and approved the final manuscript.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Table 1: Characteristics of the study population

Figure 1: NoL index changes over time according to the group of participants.

12 participants with COVID-19 and fatigue; 15 participants with COVID-19 without fatigue, 12 control participants.

Step 1: five minutes lying down; step2: five minutes standing; step 3: thirty seconds of flexion/extension and step 4: two minutes sitting down. Measures were performed each five seconds.

Figures

Figure 1

NoL index changes over time according to the group of participants. 12 participants with COVID-19 and fatigue; 15 participants with COVID-19 without fatigue, 12 control participants. Step 1: five minutes lying down; step2: five minutes standing; step 3: thirty seconds of flexion/extension and step 4: two minutes sitting down. Measures were performed each five seconds.