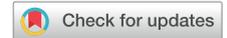


Autonomic dysfunction and post-COVID-19 syndrome: A still elusive link



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Infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is causing the long-lasting pandemic coronavirus disease 2019 (COVID-19), with dramatic clinical, social, and economic implications. Importantly, evolving experience consistently shows that, in addition to issues related to the acute phase, patients who recover from COVID-19 may present a wide variety of bothersome symptoms, which may be debilitating and significantly impair their quality of life. This condition, when it persists beyond 12 weeks after recovery, is defined as “post-COVID-19” or “long COVID-19” syndrome.¹

Some of the symptoms, including tachycardia/palpitations, chest pain, fatigue, and dyspnea with reduced effort tolerance, suggest a possible cardiovascular cause, whereas others (eg, muscle and/or joint pain, headache, memory loss, nausea, mood disturbances) suggest involvement of other systems. Symptoms may occur independently of the severity of COVID-19, although patients with more severe symptoms in the acute phase experience a higher rate of symptom persistence during follow-up.^{1,2}

Importantly, careful diagnostic assessment usually fails to identify specific causes of post-COVID-19 syndrome. However, it has been suggested that at least some post-COVID-19 symptoms, including those of potential cardiovascular origin, might be related to abnormalities of the autonomic nervous system (ANS).³ The pathophysiological mechanisms responsible for ANS impairment remain speculative and might include direct damage of the ANS (ganglia and/or nerve terminations) by the virus, a toxic effect of inflammatory cytokines released during the acute infection, and an immune-mediated response triggered by some viral component(s).^{1,3} Independent of the mechanism, the possibility of ANS involvement in SARS-CoV-2 infection is supported by the frequent occurrence of neurologic symptoms (eg, anosmia, dysgeusia) as well as the sporadic occurrence of clinical conditions typically related to ANS dysfunction

(eg, orthostatic hypotension, orthostatic tachycardia) in post-COVID-19 syndrome.³ Furthermore, patients with COVID-19, compared to healthy subjects, have been found to show reduced heart rate variability (HRV) parameters 20 weeks after recovery from the illness.⁴ However, a pathogenetic relationship between dysautonomia and post-COVID-19 syndrome remains to be demonstrated. Establishing such a relationship would be of importance because it might help guide the management of this clinical condition.

The study by Ladlow et al⁵ in this issue of *Heart Rhythm Journal* is welcome because it attempts to clarify whether any association exists between dysautonomia and symptoms, as well as objective evidence of exercise intolerance, in patients with post-COVID-19 syndrome. In their study, Ladlow et al enrolled 205 patients referred to a post-COVID-19 clinic who fulfilled specific eligibility criteria (hospitalization and desaturation $\leq 95\%$ on a Harvard step test or chest pain with electrocardiographic [ECG] changes during acute illness and life-limiting symptoms persisting for > 12 weeks). All patients underwent bicycle cardiopulmonary exercise testing (CPET) and were divided into 1 of 2 groups according to evidence or no evidence of dysautonomia.

Dysautonomia was diagnosed based on 3 heart rate (HR) parameters that Jouven et al⁶ found to be associated with total mortality and sudden death in a population of asymptomatic subjects: (1) resting HR > 75 bpm; (2) increase in HR during exercise < 89 bpm; and (3) HR reduction < 25 bpm during the first minute of recovery from peak exercise. HRV was also assessed by calculating the root mean square of the squared differences of adjacent RR intervals (RMSSD) on a 1-minute 12-lead ECG at rest and on 30-second ECGs during the first 3 minutes of recovery after peak exercise.

Patients were studied 183 ± 77 days (~ 6 months) from COVID-19 disease, and dysautonomia was found in 51 patients (25%). Per definition, these patients had higher HR at rest (95 ± 12 bpm vs 81 ± 12 bpm; $P < .001$) and lower HR increase during CPET (75 ± 12 bpm vs 96 ± 13 bpm; $P < .001$) and HR recovery after peak exercise (17 ± 4 bpm vs 31 ± 17 bpm; $P < .001$) compared to those without dysautonomia.

Patients with dysautonomia were older, had a higher body mass index (BMI) ($P = .013$) and waist circumference (WC) ($P = .003$), and had a lower basal RMSSD ($P < .001$).

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Furthermore, at rest, dysautonomic patients showed a higher breathing rate ($P = .006$) and lower forced vital capacity ($P = .031$), forced expiratory volume in 1 second ($P = .036$), and ventilatory efficiency (V_E/V_{CO_2}) ($P = .036$).

When assessing symptoms that showed prevalence $>25\%$, a significant association with dysautonomia was found for low mood ($P = .007$), headache ($P = .026$), and poor attention ($P = .047$). However, other symptoms, including some of potential cardiovascular origin (eg, shortness of breath, fatigue), showed no significant association with dysautonomia.

Patients with dysautonomia, however, showed a lower performance on CPET. In particular, HR at peak exercise (170 ± 13 bpm vs 177 ± 15 bpm; $P = .003$), maximal work rate (219 ± 37 W vs 253 ± 52 W; $P < .001$), and maximal oxygen consumption ($\dot{V}O_2$) (30.6 ± 5.5 mL/kg/min vs 35.8 ± 7.6 mL/kg/min; $P < .001$) all were significantly lower in patients with dysautonomia than in those without dysautonomia, suggesting a role of ANS dysfunction in their physical limitation.

Ladlow et al⁵ should be congratulated for performing this large study on post-COVID-19 syndrome. However, possible alternative interpretations of the data suggest caution in deriving definitive conclusions from their results.

Although the study shows the lack of significant relationship between dysautonomia and most post-COVID-19 symptoms, including, in particular, some symptoms of possible cardiovascular origin, the method applied to identify patients with an impairment of ANS function presents some limitations. Both higher HR at rest and lower HR recovery after exercise suggest an imbalance of sympathovagal tone toward adrenergic predominance in their patients with dysautonomia. However, rather than reflecting a primary impairment of the ANS, these findings simply might have been related to differences between the 2 groups with regard to some basal clinical characteristics, including higher BMI/WC, lower efficiency in respiratory function, and lower mood in dysautonomic patients. In addition, the lower increase in HR during maximal exercise in patients with dysautonomia might have been a mere consequence of their having a higher HR at rest and, given their older age, a lower maximal theoretical HR for age. The percent of predicted maximal HR for age achieved during CPET, in fact, did not differ between the 2 groups. The possibility that the differences in HR behavior might have not been related to a primary abnormality of the ANS is also suggested by the fact that, despite the basal difference, RMSSD values were

similar during exercise recovery in the 2 groups of patients, suggesting a similar ANS response to exercise interruption in the 2 groups.

Future studies should clarify whether different results regarding the relationship between ANS dysfunction and post-COVID-19 symptoms might be obtained using more comprehensive and better validated methods for the diagnosis of ANS dysfunction, such as standard tests of autonomic function⁷ and HRV assessed from its multiple (short-term and long-term) components.⁸

Of note, although the results of CPET in the study by Ladlow et al⁵ suggest lower performance by patients classified with dysautonomia, exercise tolerance was largely normal in these subjects, who achieved $>100\%$ of the predicted maximal oxygen consumption and an average maximal work rate of 219 W, with only small differences compared to patients without dysautonomia, possibly explained, again, and at least in part, by some demographic (age) and clinical (BMI, respiratory function) differences.

In conclusion, the study by Ladlow et al⁵ provides interesting data on the clinical characteristics and objective physical performance of patients with post-COVID-19 syndrome. However, the role of ANS in determining symptoms (particularly those of potential cardiovascular origin) and physical limitation in these patients still has not been fully elucidated by their data, making necessary further studies applying more comprehensive and valuable methods for the assessment of ANS function.

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