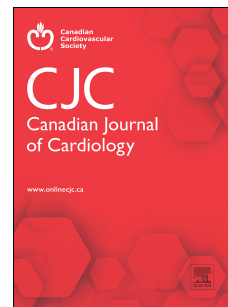


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Cardiovascular autonomic abnormalities in patients with Post-acute Sequelae of COVID-19: don't miss that target!

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Short title: High prevalence of CV dysautonomia in PASC

Cardiovascular dysautonomias in the post-COVID landscape

A massive and sustained world-wide spread of the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has triggered a pandemic that has lasted for three years now and generated > 600 million reported cases around the globe. It has been increasingly evident that a substantial portion of patients who develop Corona Virus Disease 2019 (COVID-19) do not recover completely but rather experience lingering symptoms for months to years. This novel clinical syndrome is has been termed Long COVID or Post-acute Sequelae of COVID-19 (PASC), and has been defined by the World Health Organization as ongoing symptoms beyond three months from the acute illness due to confirmed or suspected SARS-CoV-2 infection that cannot be explained by other diseases¹. The prevalence of PASC in patients with COVID-19 varies based on definition and setting and has been reported to be between 68% in hospitalized ² and 13% in non-hospitalized patients ³. It's beyond any doubt that this novel clinical syndrome has profound negative effects on individual patients, healthcare sectors and whole societies.

Case reports and smaller observational cohort studies have indicated that PASC can be associated with cardiovascular (CV) autonomic dysfunction including postural orthostatic tachycardia syndrome (POTS), inappropriate sinus tachycardia (IST), and orthostatic hypotension (OH)⁴⁻⁷. This is important since CV dysautonomias are conditions that often can be successfully treated with substantial symptom improvement, while virtually no evidence exists for effective treatment of PASC itself. The prevalence of CV autonomic dysfunction in PASC remains largely unknown but is important to comprehend since it will highlight dysautonomia as a specific sequelae of acute COVID-19, establish pre-test likelihood and guide the development of diagnostic work-up protocols for unsorted PASC patients.

Cardiovascular dysautonomia is common in PACS: more women but no difference between hospitalized and non-hospitalized patients

Hira and colleagues should be complimented for the effort to determine the occurrence of cardiovascular autonomic abnormalities in PACS patients. In their study published in this issue⁸, 70 PASC patients completed a thorough investigation including active standing test, autonomic function testing (quantitative sudomotor axon reflex testing, deep breathing, and Valsalva maneuver) as well as symptom reports at a median of 399 days after a primary PCR-confirmed SARS-CoV-2 infection. A majority of included patients were females (80%) and did not require hospital treatment during the acute COVID-19 disease (87%). However, comorbidities, disease history and current medications as well as the exact inclusion criteria were not detailed. The authors report a high prevalence of CV dysautonomia in the overall cohort (73%), with the most prevalent abnormality being initial orthostatic hypotension (61%) and POTS (30%). Inappropriate sinus tachycardia was uncommon (1.4%) but it should be emphasized that prolonged ECG monitoring was not a part of study protocol, thus reducing the diagnostic accuracy for this specific abnormality.⁹ Moreover, tilt testing and 24-hour ambulatory blood pressure monitoring were not performed, which potentially may have affected the detection rate of delayed orthostatic hypotension and vasovagal syncope susceptibility, common dysautonomic conditions.^{7, 10, 11} POTS was found more frequently in females (36%) compared to males (7%, $p=0.0037$), and the overall prevalence of

cardiovascular dysautonomia was similar in hospitalized and non-hospitalized patients which implies that initial disease severity is not a risk factor for developing dysautonomia in PASC patients.

Strengths and weaknesses of the study

The study has several strengths. Previous data on the prevalence of specific forms of CV dysautonomia in PASC relied mostly on case reports, case series, smaller observational studies, and symptom questionnaires. In contrast, the current paper includes a fairly large patient cohort that are well characterized in terms of hemodynamic response to active standing test, and by other autonomic tests as well as by presence and severity of symptoms common in dysautonomia. Patients were evaluated on average one year after the primary SARS-CoV-2 infection which is important when interpreting the results. Persistence of CV dysautonomia long time after initial infection suggests that these symptoms and hemodynamic findings are in many unlikely to resolve shortly after the initial infection. One might suspect that the number of patients affected by CV autonomic abnormalities may have been higher at three or six months after acute illness but that some may have recovered before the evaluation one year after. It is also our clinical experience that symptoms and hemodynamic findings during orthostatic tests may change over a longer follow-up period. Therefore, an important study limitation is that testing for CV dysautonomia was performed only once.

In general, to describe accurately prevalence of a disease in population, a larger number of evaluated subjects is needed. The study by Hira and colleagues is therefore limited by the relatively small number of included patients. It is additionally difficult to draw conclusions on sex differences (only 20% males) and importance of hospitalization (only 13% were hospitalized) as these subgroups were even smaller. Furthermore, most patients were recruited from referral centers (dedicated PASC centers and/or dysautonomia clinics) which likely makes the study population highly selected. Consequently, it's difficult to extrapolate these findings onto general PASC population. One can assume that patients evaluated at these centers experienced longer PASC duration and more severe functional impairment compared with an average PASC patient thus biasing the study toward a sicker population. Therefore, the prevalence numbers reported by Hira and colleagues should be interpreted with

caution as representative for specialized post-COVID centers, not the general PASC population. The proportions of POTS, for instance, reported here are however in line with our personal experience from a similar tertiary center, and find support in previous reports.¹² Importantly, the present study included only Caucasians from the same geographical region and hence, studies in other races and geographical regions are needed to establish the global impact of CV dysautonomia on PASC. Two other aspects we wish to highlight as important when interpreting these results are that 80% of patients were evaluated before COVID-19 vaccination and that data on when the initial COVID-19 disease occurred were not presented. First, COVID-19 vaccination itself can induce prolonged symptoms and physical findings consistent with CV dysautonomia although POTS is diagnosed at a much lower rate after vaccination than after contracting the virus¹³. Second, the SARS-CoV-2 has mutated several times during the pandemic, and it is unknown whether different SARS-CoV-2 strains are more prone to trigger CV dysautonomia. Thus, the prevalence of dysautonomia in PASC population may change after vaccination or according to the viral strand causing the primary infection. However, we consider it unlikely that these factors would have a decisive effect on the overall incidence of autonomic disturbances in the study.

Conclusion

Although some limitations exist, the study constitutes an important contribution to our understanding of the role of cardiovascular autonomic dysfunction in the post-COVID condition. Patients were systematically evaluated and majority were diagnosed with at least one objective, symptomatic and potentially treatable autonomic abnormality. These findings highlight the need for specialized autonomic clinics and imply that a high suspicion of cardiovascular dysautonomia should be raised in patients not recovering swiftly from acute COVID-19.

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