Autonomic dysfunction post–acute COVID-19 infection

Amar D. Desai, MPH,[*†1] Brian C. Boursiquot, MD,[*1] Catherine J. Moore, RN,[*]
Rakesh Gopinathannair, MD, FHRS,[‡] Marc P. Waase, MD, PhD,[*] Geoffrey A. Rubin, MD,[*]
Elaine Y. Wan, MD, FACC, FAHA, FHRS[*]

*From the *Department of Medicine, Division of Cardiology, Columbia University Vagelos College of Physicians and Surgeons, New York, New York, †Rutgers New Jersey Medical School, Newark, New Jersey, and ‡Kansas City Heart Rhythm Institute, Overland Park, Kansas.*

Introduction

SARS-CoV-2 infection, which causes the disease COVID-19, is most known for its severe respiratory complications. However, a variety of extrapulmonary effects have since been described, with cardiovascular complications being among the most common.[1] Those who recover from the acute phase of COVID-19 may be left with residual symptoms such as chest pain and dyspnea, resulting in a decreased quality of life and a syndrome sometimes described as "long COVID."[2] Recent evidence suggests that survivors with some of these chronic symptoms may have autonomic dysfunction (AD) with features of postural orthostatic tachycardia syndrome (POTS) and/or inappropriate sinus tachycardia (IST).[3,4] POTS is characterized by symptoms that occur with standing, an increase in heart rate of ≥30 beats per minute (bpm) (or heart rate >120 bpm) when moving from a supine to a standing position, and the absence of orthostatic hypotension.[5] IST is defined as a sinus heart rate >100 bpm at rest without an identifiable cause of sinus tachycardia.[6] Cardiac manifestations of AD lie on a wide spectrum and can therefore be classified as either POTS, IST, or other unspecified symptoms such as tachycardia and palpitations without a clear, single underlying pathologic mechanism.[7] The treatment of these arrhythmias includes nonpharmacologic management, such as increasing salt and fluid intake, as well as the use of oral medications. Beta blockers or off-label use of ivabradine have been reported to be used in both syndromes with the goal of controlling heart rate to reduce the symptoms.[8,9] Other

KEY TEACHING POINTS

- Autonomic dysfunction (AD) post–SARS-CoV-2 infection affects primarily female patients without a clear history of pre-existing conditions.
- AD post–SARS-CoV-2 affects patients showing a wide age distribution.
- Beta blockers and vaccines show strong efficacy in improving symptoms of suspected post-COVID AD.

therapies more common in POTS include fludrocortisone, midodrine, pyridostigmine, and alpha-2 agonists.[8]

There is a need to understand the patient characteristics and risk factors for developing AD as a sequela of COVID-19. Furthermore, there is limited management information specific to patients suffering from AD following COVID-19. It is unclear how treatment of these patients and their prognoses may differ from other cases of POTS or IST. In this study, we investigated a small cohort of patients diagnosed with suspected AD post SARS-CoV-2 infection to elucidate possible risk factors and treatment strategies in this population.

Case report

We identified patients ≥18 years old with a reported history of COVID-19 who were referred to outpatient cardiology at Columbia University Medical Center (New York, NY) and Kansas City Heart Rhythm Institute (Overland Park, KS) for evaluation of unexplained tachycardia, palpitations, chest pain, or orthostatic intolerance. Included patients must have met the definition of POTS, IST, or other cardiac autonomic dysfunction on evaluation by their cardiologist to be included in the study. Patients were considered to have confirmed COVID-19 if polymerase chain reaction (PCR) testing detected SARS-CoV-2 on nasopharyngeal swabs, or if they had symptoms suspicious for COVID-19 without available PCR testing and were later found to have detectable

SARS-CoV-2 antibodies on serologic testing. The date of COVID-19 diagnosis was defined as the date of positive PCR testing or, when unavailable, the date of initial symptom onset. Baseline symptoms were obtained from a combination of chart review and self-report via a phone-administered survey to which patients consented. We collected diagnostic information from laboratory reports as well as reports of any available imaging, including computed tomography scans, cardiac magnetic resonance imaging, and echocardiograms. Information on prescribed treatments was obtained from chart review, whereas data regarding symptomatic improvement following initiation of these treatments were obtained from the survey mentioned above.

Of 17 patients presenting with autonomic dysfunction in this time period suspected of having a history of COVID-19, 11 (64.7%) were confirmed to have contracted COVID-19 infection by the methods previously mentioned. In our case series of 11 patients (Table 1), the mean age was 46.0 ± 18.0 years. A majority of these patients were women (81.8%) without significant medical comorbidities. A minority of patients had hypertension and/or hyperlipidemia, but none had a history of prior autonomic dysfunction, arrhythmia, or other cardiovascular disease. The most common persistent symptoms following COVID-19 diagnoses were palpitations and fatigue (81.8% each), and most patients experienced chest discomfort (63.6%) and/or dyspnea (72.7%). The mean time from COVID-19 diagnosis to onset of these symptoms was 39.5 ± 57.3 days. The mean time from COVID-19 diagnosis to the first cardiology visit was 171.5 ± 119.0 days, and the mean time from diagnosis to the last cardiology follow-up was 260.5 ± 100.2 days. Serological evaluation was overall unremarkable and without signs of infection, anemia, thyroid disease, or systemic inflammation. A majority of patients (63.6%) had pulmonary embolism formally ruled out with either a normal D-dimer or a normal chest computed tomography with intravenous contrast, and the remaining patients did not have a formal evaluation for pulmonary embolism. All patients with available data had normal left ventricular ejection fractions, troponins, and brain natriuretic peptide levels. Eight patients (72.7%) underwent ambulatory cardiac monitoring and 2 patients (18.2%) underwent tilt table testing. Based on clinician impressions, 2 patients (18.2%) were diagnosed with IST, 2 (18.2%) were diagnosed with POTS, and the remaining patients (63.6%) either were still undergoing evaluation or did not meet formal criteria for IST or POTS.

Nine patients (81.8%) were prescribed medications and 2 (18.2%) were treated with lifestyle modification alone, including the use of compression stockings and increasing salt intake. Of these medications, beta blockers were the most common, with 5 patients (55.6%) being prescribed beta blockers. Three patients were prescribed metoprolol succinate, and 2 patients were prescribed metoprolol tartrate. Two of these patients had intolerance to metoprolol, in 1 case resulting in a switch to pindolol and in another case resulting in a switch to ivabradine. Of the remaining patients prescribed medications, 1 was prescribed midodrine, 1 was prescribed colchicine, and 2 were prescribed ibuprofen.

Upon follow-up phone survey of included patients (Table 2), 4 out of 5 patients treated with beta blockers (80.0%) reported improved or resolved symptoms and 1 out of 5 (20.0%) reported unchanged symptoms. The patient receiving midodrine reported improvement in symptoms. The patient receiving colchicine reported unchanged symptoms, while the 2 patients receiving ibuprofen reported improved or resolved symptoms.

From the cohort of patients, 6 patients (54.5%) reported they had received the COVID-19 vaccine. Of these 6 patients, 4 (66.7%) received the Pfizer vaccine, 1 (16.7%) received the Moderna vaccine, and 1 (16.7%) received an unknown vaccine. All patients received 2 injections of the vaccine they were administered. After receiving the vaccine, 3 of 6 patients (50.0%) reported an improvement of symptoms, while 3 of 6 (50.0%) reported no difference in symptom status. No patients reported a worsening of existing AD symptoms after taking the COVID-19 vaccine.

Discussion

From this small cohort of patients, several important findings can be derived that may impact the approach to suspected AD following COVID-19 infection. In terms of our study population, the majority of our cohort was young women, aligned with the typical population that suffers from POTS, IST, and post–acute COVID-19 AD.[3,4,10,11]

Of patients prescribed medications, a majority received beta blockers, which improved symptoms in 4 out of 5 patients. Anti-inflammatory medications were the second most common types of treatment and resulted in symptom improvement in 2 out of 3 cases. However, it is important to note that among patients who received medications, a majority still had ongoing symptoms at follow-up without complete resolution. This is consistent with a case series by Johansson and colleagues[4] that reported on 3 patients with post-COVID-19 POTS who all remained symptomatic despite pharmacologic management. Similarly, in Blitshteyn and Whitelaw's study on post-COVID AD,[10] a vast majority of patients received medications, but 85% of the cohort had residual symptoms greater than 6 months after initial COVID-19 diagnosis. These findings suggest that while these medications, especially beta blockers, certainly may improve symptoms of patients, post-COVID AD is consistent with the general prognosis of IST and POTS, which are both challenging to manage and often require ongoing management to reduce symptoms.[6,12] Further larger studies investigating the predominant presenting symptoms of patients and which medications they respond to may help improve our management.

Beyond receipt of medication, of 6 patients receiving the COVID-19 vaccine, 3 patients noticed improved symptoms and 3 patients noticed unchanged symptoms. Importantly, none of these patients experienced worsening of symptoms, a complication that was originally suspected and feared for both patients with long COVID and those with previous COVID infection during initial vaccine rollout.[13] This small

Table 1 Demographic and clinical characteristics of included patients from chart review

Parameter	Overall (N = 11)
Age (years), mean (SD)	46.00 (17.98)
Female, n (%)	9 (81.8)
Hypertension, n (%)	3 (27.3)
Hyperlipidemia, n (%)	2 (18.2)
Days to symptoms, mean (SD)	39.45 (57.30)
Palpitations, n (%)	9 (81.8)
Chest discomfort, n (%)	7 (63.6)
Dyspnea, n (%)	8 (72.7)
Fatigue, n (%)	9 (81.8)
Dizziness, n (%)	3 (27.3)
Symptoms worse when:	
Standing	1 (9.1)
Sitting	1 (9.1)
Same	4 (36.4)
N/A	5 (45.5)
Days to first cardiology clinic visit, mean (SD)	171.45 (119.02)
Left ventricular ejection fraction (%), mean (SD)	57.50 (4.51)
White blood cell count (per μL), mean (SD)	7546.25 (2362.41)
Hemoglobin (g/dL), mean (SD)	14.12 (1.10)
Thyroid stimulating hormone (mIU/L), mean (SD)	2.40 (1.97)
Erythrocyte sedimentation rate (mm/h), mean (SD)	17.00 (2.83)
C-reactive protein (mg/L), mean (SD)	0.85 (0.35)
Troponin, n (%):	
Normal	7 (63.6)
N/A	4 (36.4)
Brain natriuretic peptide, n (%):	
Normal	8 (72.7)
N/A	3 (27.3)
Pulmonary embolism formally ruled out, n (%)	7 (63.6)
Ambulatory heart rate monitoring, n (%)	8 (72.7)
Ambulatory monitor duration, n (%):	
<7 days	4 (36.4)
7–10 days	2 (18.2)
>10 days	2 (18.2)
N/A	3 (27.3)
Average heart rate (bpm), mean (SD)	86.25 (11.45)
Minimum heart rate (bpm), mean (SD)	51.38 (5.34)
Maximum heart rate (bpm), mean (SD)	154.25 (25.05)
Orthostatic vitals, n (%):	
Positive	1 (9.1)
Negative	4 (36.4)
Not checked	6 (54.5)
Tilt table test performed, n (%)	2 (18.2)
Diagnosis, n (%):	
Inappropriate sinus tachycardia	2 (18.2)
Postural orthostatic tachycardia syndrome	2 (18.2)
Other	7 (63.6)

bpm = beats per minute; N/A = not available.

Table 2 Results of patients from phone survey

Parameter	Frequency (%)
COVID-19+	11 (100.0%)
Prescribed medication from cardiologist	9 (81.8%)
Medication received:	
Beta blocker	5/9 (55.6%)
Midodrine	1/9 (11.1%)
Anti-inflammatory	3/9 (33.3%)
After receiving meds, symptoms _____:	
Resolved	2/9 (22.2%)
Improved	4/9 (44.4%)
Unchanged	3/9 (33.3%)
Worsened	0/9 (0.0%)
COVID-19 vaccination status:	
Vaccinated	6 (54.5%)
Unvaccinated	0 (0.0%)
Unknown	5 (45.5%)
Number of doses received:	
One	0 (0.0%)
Two	6/6 (100.0%)
Vaccine received	
Pfizer	4/6 (66.7%)
Moderna	1/6 (16.7%)
Unknown	1/6 (16.7%)
After vaccination, symptoms _____:	
Resolved	1/6 (16.7%)
Improved	2/6 (33.3%)
Unchanged	3/6 (50.0%)
Worsened	0 (0.0%)

halved when receiving both doses of the SARS-CoV-2 vaccine, supporting our findings.[14] While the exact mechanism for alleviation of these symptoms following immunization remains unclear, among many hypotheses, one that may be likely is that residual viral particles in tissues may be eliminated following administration of the vaccine, helping to alleviate lingering symptoms for the subset of patients who experience them. Further longitudinal studies comparing vaccinated individuals to those unwilling to take the vaccine should be conducted to evaluate the efficacy of these vaccines to resolve longer-term symptoms of COVID-19, including AD, in a larger and more controlled setting.

There are a few important strengths to note about this study. Unlike previous case studies of patients with cardiac complications COVID-19, we had 24-hour Holter monitor data, vaccination information, and follow-up phone survey data of patients, months after they had been seen by their cardiologist. This allowed for longitudinal assessment of patients with suspected AD over time, allowing us to understand characteristics of both the condition and the syndrome in ways otherwise not possible owing to our increased follow-up time. As long-haul COVID-19 syndrome has become more prevalent, these data offer valuable insights into what patients with suspected AD may encounter and benefit from.

There are some possible limitations to this study. Given a small overall sample size of 11 patients, despite the majority of patients having received medication or a vaccine, missing data for some patients is a significant limitation. Furthermore, there could have been considerable recall bias when taking phone surveys of included patients with regard to certain

cohort suggests the feasibility of vaccination in the population of patients suffering from suspected post-COVID AD, with no specific worsening of symptoms noted. A study of 6030 individuals in the United Kingdom revealed the odds of long COVID symptoms, including AD, were nearly

elements of their care (eg, medication prescribed by the cardiologist). There was also only a handful of patients who underwent tilt testing or had orthostatic vitals confirmed. Both patients who underwent tilt testing had increases in heart rate of over 30 bpm in the first 10 minutes of a 70-degree tilt, with considerable heart rate variability and subtle change in P-wave morphology on slower beats, suggestive of autonomically driven right atrial or sinus tachycardia originating in the superior and inferior aspect of the sinus node. Additional studies can possibly use tilt testing or ambulatory monitoring further as a means of confirming a suspected diagnosis of autonomic dysfunction. Our study also lacked serial routine testing for markers of inflammation or autoimmunity, which prevents us from making comparisons to other cohorts or testing the observation that POTS patients may have underlying autoimmune disease.[4,15] One-third of Blitshteyn's cohort had laboratory testing consistent with inflammation or autoimmunity, but a significant minority of patients in this cohort also had pre-existing autonomic symptoms even prior to COVID-19, so they may represent a different population than ours.[10]

Conclusion

In this small cohort of patients diagnosed with AD post SARS-CoV-2 infection, a majority were women, and few had preexisting conditions, suggesting the unpredictability of developing AD after COVID-19 infection. Beta blockers and vaccines both show efficacy in improving symptoms of suspected post-COVID AD. Further follow-up is necessary to assess efficacy of therapeutics, length of treatment, and time to recovery. Larger prospective studies with longer follow-up are needed to test efficacy of treatments for relief of AD symptoms following COVID-19. Lastly, as novel variants continue to arise, the impact of SARS-CoV-2 reinfection of previously infected individuals, including those with AD following their first bout of the virus, should be performed to specifically evaluate the impact of reinfection on long-term sequelae like AD.

References

1. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020;26:1017–1032.
2. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med 2021;27:601–615.
3. Shouman K, Vanichkachorn G, Cheshire WP, et al. Autonomic dysfunction following COVID-19 infection: an early experience. Clin Auton Res 2021; 31:385–394.
4. Johansson M, Stahlberg M, Runold M, et al. Long-haul post-COVID-19 symptoms presenting as a variant of postural orthostatic tachycardia syndrome: the Swedish experience. JACC Case Rep 2021;3:573–580.
5. Agarwal AK, Garg R, Ritch A, Sarkar P. Postural orthostatic tachycardia syndrome. Postgrad Med J 2007;83:478–480.
6. Olshansky B, Sullivan RM. Inappropriate sinus tachycardia. J Am Coll Cardiol 2013;61:793–801.
7. Wells R, Tonkin A. Clinical approach to autonomic dysfunction. Intern Med J 2016;46:1134–1139.
8. Sheldon RS, Grubb BP 2nd, Olshansky B, et al. 2015 Heart Rhythm Society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm 2015;12:e41–e63.
9. Desai AD, Boursiquot BC, Melki L, Wan EY. Management of arrhythmias associated with COVID-19. Curr Cardiol Rep 2020;23:2.
10. Blitshteyn S, Whitelaw S. Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. Immunol Res 2021;69:205–211.
11. Shabtaie SA, Witt CM, Asirvatham SJ. Natural history and clinical outcomes of inappropriate sinus tachycardia. J Cardiovasc Electrophysiol 2020;31:137–143.
12. Arnold AC, Ng J, Raj SR. Postural tachycardia syndrome - diagnosis, physiology, and prognosis. Auton Neurosci 2018;215:3–11.
13. Raw RK, Kelly CA, Rees J, Wroe C, Chadwick DR. Previous COVID-19 infection, but not Long-COVID, is associated with increased adverse events following BNT162b2/Pfizer vaccination. J Infect 2021;83:381–412.
14. Antonelli M, Penfold RS, Merino J, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study (published online ahead of print). Lancet Infect Dis 2021;09.01. https://doi.org/10.1016/S1473-3099(21)00460-6.
15. Goldstein DS. The possible association between COVID-19 and postural tachycardia syndrome. Heart Rhythm 2021;18:508–509.