

ORIGINAL ARTICLE



Blood Pressure Regulation in Post-COVID POTS: Beyond Sinus Tachycardia

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BACKGROUND: Postural orthostatic tachycardia syndrome (POTS) is a frequently diagnosed cardiovascular disorder after COVID-19 infection. POTS is characterized by the presence of excessive sinus tachycardia on standing without a fall in blood pressure (BP). We investigated the BP profile using 24-hour ambulatory BP monitoring in patients with new-onset POTS after COVID-19 compared with prepandemic population-based controls.

METHODS: We performed a case-control study in 100 patients (mean age, 40.0±12.9 years; 85% women) with verified post-COVID-19 new-onset POTS diagnosed by a positive head-up tilt testing versus 100 controls from a population-based cohort with a negative active standing test, no history of syncope, POTS, or endocrine disease (mean age, 42.3±14.0 years; 78% women). Twenty-four-hour BP profile was assessed for circadian BP variation including hypotensive systolic BP (SBP) episodes (<80, <90, and <100 mm Hg).

RESULTS: Patients with post-COVID-19 POTS had significantly higher nighttime SBP, but not daytime SBP, and more daytime SBP hypotensive episodes compared with controls. Nondipping (34% versus 19%; $P<0.001$) and reverse dipping patterns (9% versus 0%; $P<0.001$) were more frequent in post-COVID-19 POTS. In the logistic regression, patients with post-COVID-19 POTS had significantly higher mean 24-hour SBP (odds ratio, 1.08 [95% CI, 1.04–1.11]; $P<0.001$) and nighttime SBP (odds ratio, 1.07 [95% CI, 1.04–1.10]; $P<0.001$), independent of age and sex.

CONCLUSIONS: Patients with post-COVID-19 POTS demonstrate higher mean 24-hour and nighttime SBP and show disruptions of circadian BP rhythm regulation compared with population-based controls, as well as more daytime hypotensive episodes. Future studies are needed to test whether patients with post-COVID-19 POTS may benefit from tailored BP therapy. (*Hypertension*. 2024;81:2540–2548. DOI: 10.1161/HYPERTENSIONAHA.124.23670.) • [Supplement Material](#).

Key Words: blood pressure ■ blood pressure monitoring, ambulatory ■ COVID-19 ■ post-acute COVID-19 syndrome ■ postural orthostatic tachycardia syndrome

The cardiovascular system may be substantially affected in the course of post-COVID-19 condition,¹ and the most prevalent circulatory disorder is postural orthostatic tachycardia syndrome (POTS), less known in the prepandemic era but now identified as a major health care burden.² Worldwide, about 20 million people may have developed POTS as a result of the COVID-19 pandemic, but the numbers may be underestimated due to diagnostic delay and a broad spectrum

of other post-COVID-19 symptoms diverting attention from the correct diagnosis.^{1,2}

POTS is a type of cardiovascular autonomic dysfunction characterized by abnormal heart rate increase on standing, symptoms of orthostatic intolerance without hypotension, along with reduced exercise capacity, fatigue, and other nonspecific symptoms such as headache, chest pain, or sleep difficulties, with a duration ≥ 3 months. Other possible pathogenesis should be excluded

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Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.124.23670>.

For Sources of Funding and Disclosures, see page 2546 and 2547.

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NOVELTY AND RELEVANCE

What Is New?

Our novel findings demonstrate that not only heart rate (manifested as sinus tachycardia) but also blood pressure control is affected in patients with new-onset postural orthostatic tachycardia syndrome after COVID-19 infection, compared with prepandemic population-based controls.

What Is Relevant?

We show that 24-hour ambulatory blood pressure monitoring can be a safe and cost-effective, noninvasive diagnostic tool that may aid in detecting signs of autonomic dysfunction and allow for early identification of disrupted blood pressure control in postural orthostatic tachycardia syndrome.

Clinical/Pathophysiological Implications?

The existence of a specific blood pressure profile in post postural orthostatic tachycardia syndrome may allow for the tailoring of treatment in this vexing condition.

Nonstandard Abbreviations and Acronyms

ABPM	ambulatory blood pressure monitoring
BP	blood pressure
DBP	diastolic blood pressure
MOS	Malmö Offspring Study
POTS	postural orthostatic tachycardia syndrome
SBP	systolic blood pressure

for the syndrome to be described as idiopathic,³ a view shared by the majority of experts.⁴

The steep rise in POTS diagnoses in the wake of the post-COVID-19 condition surge has created a unique opportunity to study the syndrome in detail, offering the hope of understanding that may lead to more effective therapy. In clinical practice, POTS has been seen as an essentially sinus tachycardia-related condition, meaning that taming the orthostatic tachycardia has been the main therapeutic target.⁴ However, POTS has also been suggested to be an inadequate blood volume condition with substantial disruption of the renin-angiotensin-aldosterone system affecting blood pressure (BP) control mechanisms.^{5–7} Interestingly, prominent research dating back to the late 90s demonstrated that orthostatic intolerance may be a disorder beyond sinus tachycardia and that the vascular autonomic control may be discordant from the cardiac autonomic control in adults with orthostatic intolerance.^{8–10} To treat the postulated hypovolemia and impaired vasoconstriction in POTS, some off-label therapeutics that address both vasculature (midodrine)¹¹ and blood volume control (fludrocortisone)¹² are applied, with weak rationale and without any detailed consideration given to baseline hemodynamics and the effects of therapy.

In recent years, new diagnostic entities comprising low BP phenotype and hypotensive tendency have been

proposed for patients experiencing recurrent vasovagal syncope.¹³ It has been demonstrated that treatment with vasoactive and volume-expanding agents may increase BP and eliminate hypotensive episodes on 24-hour ambulatory BP monitoring (ABPM), preventing syncopal recurrences.¹⁴ These may apply to some extent in long COVID and related cardiovascular disorders such as POTS as part of more comprehensive cardiovascular autonomic assessment.²

In this study, we aimed to assess the 24-hour BP profile in a cohort of untreated patients with post-COVID-19 POTS compared with population-based controls enrolled before the pandemic period, to explore circadian BP profile in POTS and identify new potential treatment targets.

METHODS

Data Availability

MOS (Malmö Offspring Study) is subject to ethical and legal restrictions related to the Swedish Biobanks in Medical Care Act (2002:297) and the Personal Data Act (1998:204). Data are available after filing an application to the Steering Committee of the Malmö Population-Based Cohorts: <https://www.malmo-kohorter.lu.se/malmo-cohorts>. Data from the post-COVID-19 cohort are available upon reasonable request from M.S.

Study Population

The flowchart is illustrated in Figure 1. We performed a case-control study in 100 patients with verified COVID-19 infection and new-onset POTS diagnosed by positive head-up tilt testing. Patients with post-COVID-19 POTS were recruited from a tertiary dysautonomia unit at the Department of Cardiology, Karolinska University Hospital in Stockholm.¹⁵ All patients were referred for cardiovascular autonomic testing due to prolonged and disabling symptoms with >50% sick leave for at least 6 months after acute COVID-19 infection and symptoms suggesting cardiovascular dysautonomia, such as orthostatic

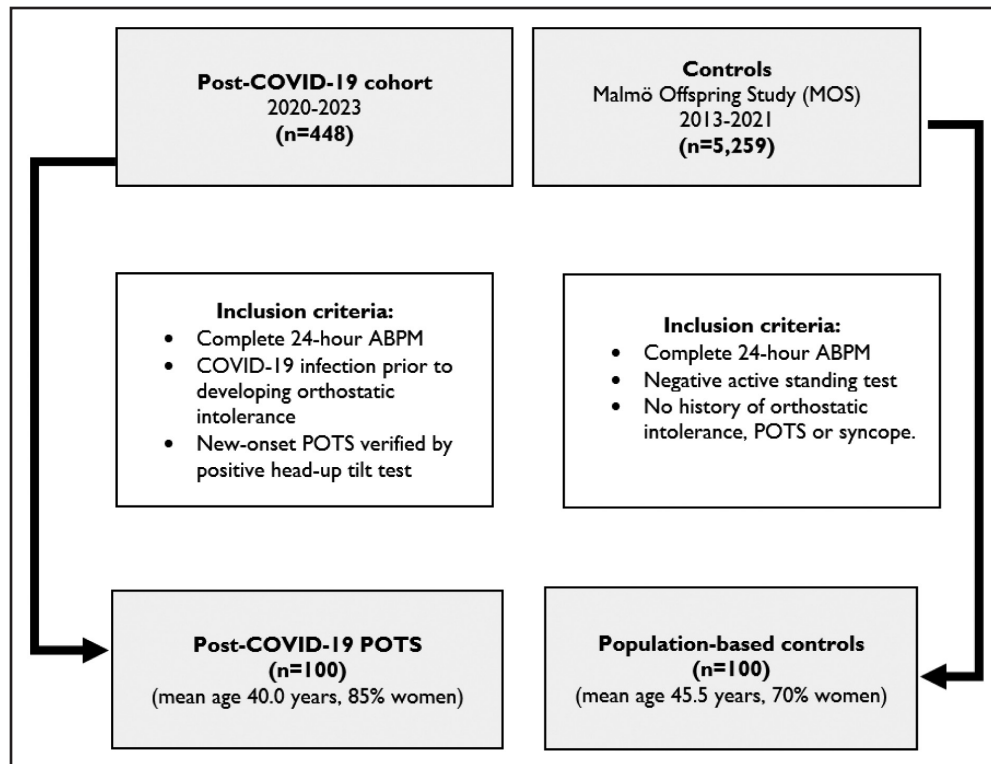


Figure 1. Flowchart.

MOS indicates Malmö Offspring Study; and POTS indicates postural orthostatic tachycardia syndrome.

intolerance, palpitations, chest pain, exercise intolerance, and dyspnea. The referred patients were previously diagnosed with post-COVID-19 syndrome by a multidisciplinary team at the study site between August 2020 and August 2023 in accordance with the current World Health Organization definition.¹⁶

Population-based controls were enrolled from the prospective population-based cohort MOS. Details of the cohort have been described elsewhere.¹⁷⁻¹⁹ A total of 5259 study participants were enrolled in MOS between 2013 and 2021. In the current study, a subset of 100 MOS participants were included with complete 24-hour ABPM data, enrolled before the start of the pandemic, that is, between 2013 and 2019, with a negative active standing test and without a history of orthostatic intolerance, POTS, or syncope.

Twenty-Four-Hour ABPM

Twenty-four-hour ABPM was assessed using automated and validated oscillometric devices (IEM Mobil-O-Graph; Stolberg, Germany²⁰ and Arteriograph 24; TensioMed, Ltd, Hungary^{17,21,22}). Brachial BP and heart rate were measured every 15 minutes during the day (07:00–22:00 in post-COVID-19 POTS; 06:00–22:00 in controls) and every 30 minutes during the night (22:00–07:00 in post-COVID-19 POTS; 22:00–06:00 in controls). A minimum of >70% and >75% valid recordings were required for population-based controls and patients with post-COVID-19 POTS, respectively. All medications impacting heart rate and BP were withheld before 24-hour ABPM measurement in patients with post-COVID-19 POTS, following the 4 half-lives rule, that is, between 48 and 72 hours before the measurement.

Definition of ABPM Variables

The following variables were retrieved from 24-hour ABPM records: mean 24-hour systolic BP (SBP), diastolic BP (DBP), and heart rate; mean nighttime SBP and heart rate; mean daytime SBP and heart rate; daytime and nighttime SBP hypotensive episodes through a detailed analysis of single measurements; and dipping status based on mean SBP during day and night.²³ Hypotensive tendency was defined as daytime SBP <80 mm Hg or daytime SBP <90 mm Hg, at least 1×, or daytime SBP <100 mm Hg, at least 2×, according to a previous study.¹³ Nocturnal dipping was defined as a nighttime SBP drop compared with daytime SBP: extreme dipping was defined as a nighttime SBP drop of ≥20%, normal dipping as 10% to 19%, nondipping as 0% to 9%, and reverse dipping as <0% (ie, SBP rise at night).

Definition of Other Clinical Variables

The symptom burden of patients with POTS was assessed by the Malmö POTS score,²⁴ which is a self-rating, 12-item score, with each item scoring between 0 and 10, and the total score ranges from 0 to 120 based on patient's own perception of symptoms through visual analog scale assessment. Physical activity in the post-COVID-19 POTS group was assessed before and after COVID-19 onset graded as: reduced, normal, or high. In the control group, physical activity was assessed only at study inclusion. Sleep quality (graded good, average, and poor) and sleep duration (assessed in hours of sleep per day) were self-reported and only available for controls.

Ethical Approval

MOS was approved by the Regional Ethical Review Board in Lund (No. 2012/594), and the post-COVID-19 POTS study (Characterization of Post-COVID Cardiovascular Manifestations Focus on Autonomic Dysfunction) was approved by the Swedish Ethical Review Authority in Uppsala (No. 2023-05391-01). All study participants gave written informed consent. The study conformed to the Declaration of Helsinki and its later amendments.

Statistical Analyses

Continuous variables are presented as mean±SD or median (interquartile range) and categorical variables as frequencies, as appropriate. Differences between groups were assessed using independent samples *t* tests for continuous variables and χ^2 tests for categorical variables. Logistic regression, adjusted for age and sex, was used to analyze the association between mean 24-hour SBP, nighttime SBP, and the presence of post-COVID-19 POTS. Hypotensive episodes (<80, <90, and <100 mm Hg) were analyzed using ANOVA. A subgroup analysis was performed, excluding subjects with diabetes and hypertension. Statistical significance was set at *P*<0.05 for all analyses. All statistical analyses were performed in IBM SPSS Statistics 29 (IBM Corporation, Armonk, NY).

RESULTS

Clinical characteristics of the study population are presented in the Table; Table S1 and S2. Compared with population-based controls, patients with post-COVID-19 POTS were younger (40 versus 46 years) and more frequently women (85% versus 70%).

Before COVID-19 infection, 10% and 31% of the patients with POTS reported reduced and high physical activity levels, respectively. Correspondingly, after COVID-19 infection, 68% of patients reported reduced physical activity levels and only 1% maintained a high physical activity level. Over 63% of all patients with post-COVID-19 POTS reported a high-symptom burden, with a Malmö POTS score of ≥61, whereas only 8% had mild symptoms (Malmö POTS score, 1–30).

The mean 24-hour SBP and DBP, as well as nighttime SBP, were higher in patients with post-COVID POTS compared with population-based controls (all *P*<0.05). The change (delta) in SBP between daytime and nighttime was blunted in patients with post-COVID-19 POTS (11.9±9.2 versus 18.4±8.1 mm Hg; *P*<0.001). In terms of nocturnal dipping, patients with post-COVID-19 exhibited a higher prevalence of non-dipping (34% versus 19%; *P*<0.001) and reverse dipping (9% versus 0%; *P*<0.001) patterns compared with controls.

Hypotensive Tendency in Post-COVID POTS

The overall prevalence of hypotensive episodes was significantly higher in patients with post-COVID-19 POTS

Table. Study Characteristics of the Population (n=200)

	Post-COVID-19 POTS, n=100	Controls, n=100	<i>P</i> value
Age, years±SD, age range	40.0±12.9 (17–82)	45.5±14.6 (19–70)	0.005*
Sex, women, %	85.0	70.0	0.01*
Hypertension, %	10.0	15.4	0.37
Diabetes, %	4.0	10.3	0.16
Office SBP, mm Hg±SD	119.8±14.9	119.7±16.3	0.96
Mean 24-h SBP, mm Hg±SD	117.2±12.1	112.2±11.7	0.003*
Mean 24-h DBP, mm Hg±SD	73.3±8.8	79.1±10.6	<0.001*
Mean 24-h HR, bpm±SD	76.8±12.0	71.1±7.9	0.001*
Mean daytime SBP, mm Hg±SD	119.8±12.1	120.9±11.0	0.51
Mean daytime HR, bpm±SD	79.9±12.6	73.2±8.3	<0.001*
Mean nighttime SBP, mm Hg±SD	107.9±13.5	102.6±11.2	0.003*
Mean nighttime HR, bpm±SD	67.4±11.8	63.6±8.0	0.03*
Δ SBP (daytime-nighttime), mm Hg±SD	11.9±9.2	18.4±8.1	<0.001*
Hypotensive tendency, %	59.0	34.0	<0.001*
Nocturnal dipping status, %			
Extreme dipping	9.0	22.0	<0.001*
Dipping	48.0	59.0	
Nondipping	34.0*	19.0	
Reverse dipping	9.0	0	

DBP indicates diastolic blood pressure; HR, heart rate; POTS, postural orthostatic tachycardia syndrome; and SBP, systolic blood pressure. *Statistically significant *P*<0.05.

than in population-based controls (59% versus 34%; *P*<0.001; Table). The distribution of SBP drops during daytime and nighttime is illustrated in Figure 2. Patients with post-COVID-19 POTS demonstrated significantly more daytime SBP drops to <100, <90, and <80 mm Hg than controls (all *P*<0.05), as well as more nighttime SBP drops to <100 mm Hg (*P*=0.006). No study participants had SBP drops to <80 mm Hg at night.

Patients with post-COVID-19 POTS with a hypotensive tendency were younger and presented with lower mean 24-hour SBP and DBP, daytime and nighttime SBP values (all *P*<0.001), and lower daytime heart rate (77±12 versus 83±12; *P*=0.042) compared with post-COVID POTS without a hypotensive tendency (Figure 3). The analysis of nocturnal dipping status in patients with post-COVID-19 POTS with and without hypotensive tendency revealed no statistically significant differences between the groups for the following categories: extreme dipping (*P*=0.19), dipping (*P*=0.47), nondipping (*P*=0.81), and reverse dipping (*P*=0.79).

In the logistic regression, post-COVID-19 POTS was associated with significantly higher mean 24-hour SBP (odds ratio, 1.08 [95% CI, 1.04–1.11]; *P*<0.001) and

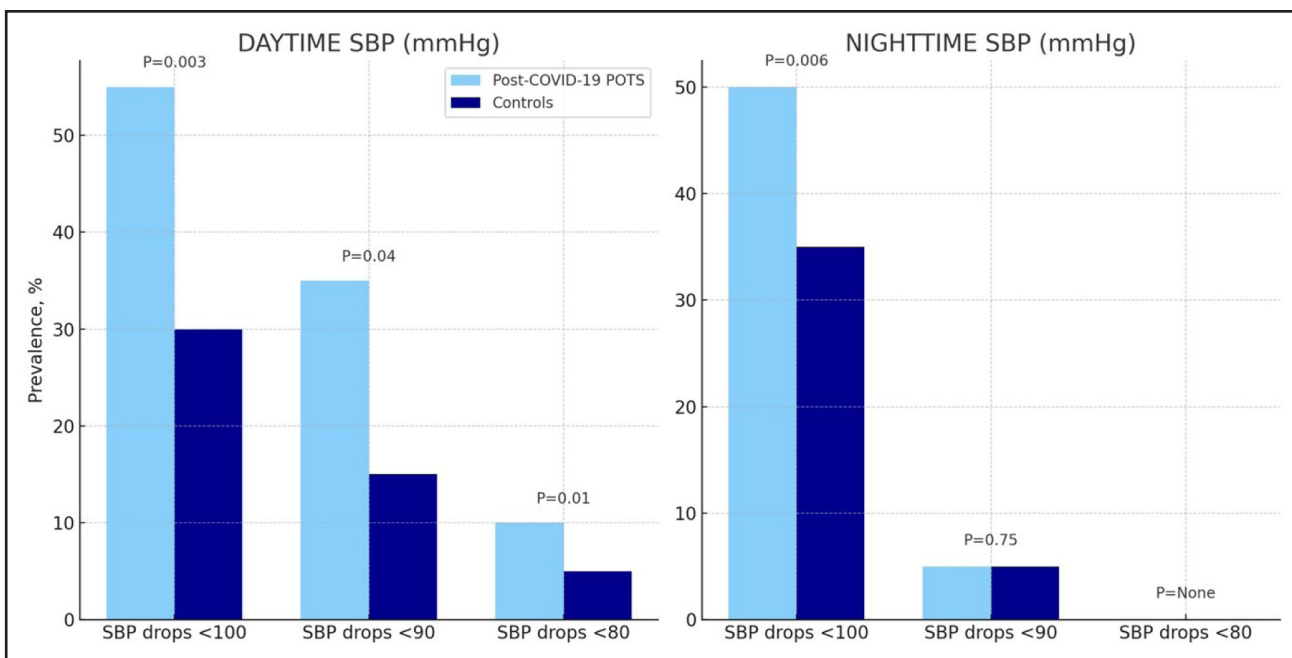


Figure 2. Hypotensive systolic blood pressure (SBP) drops during the day and night in post-COVID-19 postural orthostatic tachycardia syndrome vs population-based controls.

nighttime SBP (odds ratio, 1.07 [95% CI, 1.04–1.10]; $P < 0.001$), that is, a net increase of 8 and 7 mm Hg, respectively, independently of age and sex. In a subgroup analysis, exclusion of subjects with diabetes and hypertension did not result in significant changes to the overall findings.

DISCUSSION

Our study is the first to identify abnormal BP phenotypes in adult patients with new-onset post-COVID-19 POTS. We have observed that the majority of patients with post-COVID-19 POTS, predominantly younger and middle-aged women, demonstrate a more hypotensive tendency during daytime compared with population-based subjects, although their average 24-hour BP is higher. Moreover, the prevalence of nondipping and reverse dipping patterns is more common in post-COVID-19 POTS. Finally, patients with post-COVID-19 POTS with a hypotensive tendency are younger, have lower mean 24-hour BP, and have lower daytime heart rate. These findings may create a rationale for tailored therapy in this vexing condition.^{25,26}

POTS Is a Syndrome Beyond Sinus Tachycardia

To the best of our knowledge, only 2 studies have assessed 24-hour ABPM in children with POTS,^{27,28} and 1 small study has assessed 24-hour ABPM in 39 hypertensive adult patients with POTS before the pandemic. In accordance with our findings, a nondipping nocturnal pattern and higher daytime SBP were significant

predictors of POTS.²⁹ Traditionally, POTS is regarded as a syndrome characterized by an abnormal heart rate increase upon standing and the absence of orthostatic hypotension.^{30,31} Up till now, especially in the setting of post-COVID-19 sequelae, the BP profile of patients with POTS remains largely unexplored. Targeting the 24-hour BP profile may be of clinical relevance to optimize POTS treatment, and current consensus guidelines suggest several BP-influencing drugs as potential treatments for POTS.⁴

Nocturnal Dipping Profile in POTS

Our findings show that nocturnal nondipping and reverse dipping profiles are more prevalent in post-COVID-19 POTS, indicating that physiological circadian BP variability is disturbed. The regulation of the circadian rhythm is maintained by the autonomic nervous system. Previous studies have shown that nondipping and reverse dipping profiles are prospectively associated with increased cardiovascular events, end-organ damage, and metabolic abnormalities in normotensive and hypertensive middle-aged adults^{32,33} and are considered accurate predictors of dysautonomia in patients with Parkinson disease or undergoing hemodialysis.^{34,35} The pathophysiology of nondipping and reverse dipping profiles is linked to autonomic dysfunction.³⁶ For example, significantly higher plasma levels of norepinephrine at night, as well as increased α -1 adrenergic receptor activity, have been observed in nondippers compared with dippers.³⁷ These findings are in line with previous hypothetical pathological

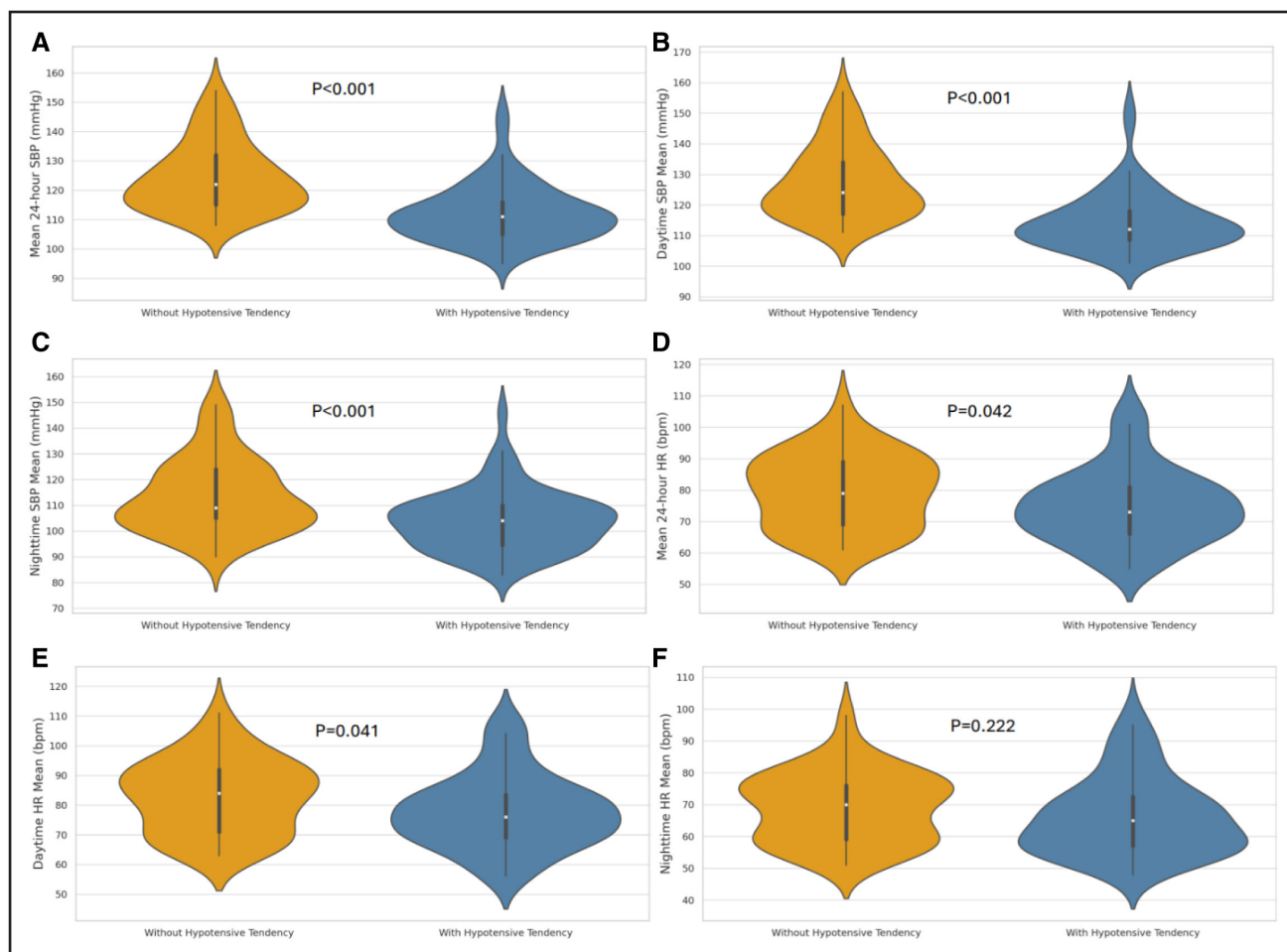


Figure 3. Blood pressure and heart rate profiles between patients with post-COVID-19 postural orthostatic tachycardia syndrome with and without a hypotensive tendency.

HR indicates heart rate; and SBP, systolic blood pressure.

mechanisms associated with POTS, considering that 90% of patients with POTS may have elevated autoantibodies against α -1 adrenergic receptors,³⁸ as well as higher mean plasma norepinephrine levels compared with controls.³⁹

Inverse 24-Hour ABPM Pattern in POTS Compared With Vasovagal Syncope

In contrast to the 24-hour ABPM pattern observed in patients with reflex (vasovagal) syncope (lower mean 24-hour SBP and higher mean 24-hour DBP),²³ our study showed an inverse pattern in patients with post-COVID-19 POTS, that is, higher 24-hour SBP and lower 24-hour DBP compared with controls. We hypothesize that the increase in 24-hour SBP observed in post-COVID-19 POTS may be driven by a significantly higher SBP at night, which in turn may be a result of a persistent hyperadrenergic state during sleep. Lower DBP may be a result of impaired peripheral vasoconstriction in POTS, as previously proposed.⁴⁰

Hypotensive Tendency in POTS

In our study, post-COVID-19 POTS exhibited a higher frequency of hypotensive tendency (or susceptibility) during daytime, with a higher number of SBP drops <80 , <90 , and <100 mm Hg compared with population-based controls. The change in SBP between daytime and nighttime was also markedly reduced in patients with post-COVID-19 POTS versus controls, suggesting underlying impairment in autonomic regulation.

Patients with post-COVID-19 POTS with a hypotensive tendency tend to be younger and have lower mean 24-hour SBP and DBP, as well as lower daytime and nighttime SBP values. They also exhibit a lower mean daytime heart rate compared with those without a hypotensive tendency. Despite these differences, nocturnal dipping status does not significantly differ between the 2 groups, suggesting that the mechanisms driving BP drops in patients with post-COVID-19 POTS with a hypotensive tendency may be different from those affecting nocturnal dipping patterns.

Future Perspectives

Future studies are warranted to explore whether patients with POTS may benefit from BP treatment regimens that counteract the hypotensive tendency during daytime and nondipping patterns at nighttime. Studies should also explore the distinct mechanisms driving daytime BP drops versus nocturnal dipping patterns. Additionally, developing targeted therapeutic interventions to stabilize BP and evaluating their effectiveness over time will be crucial. Longitudinal studies are needed to assess the impact of hypotensive tendency on the progression and severity of POTS, guiding better management strategies for this emerging and difficult-to-treat patient population.

Clinical Relevance

The hemodynamic effects of post-COVID-19 on the cardiovascular system are largely unexplored. Twenty-four-hour ABPM is a safe, cost-effective, noninvasive diagnostic tool, widely available, and may be helpful in detecting signs of autonomic dysfunction. Our study provides novel insights into the existence of a specific BP profile in POTS with a pronounced episodic hypotensive tendency during the daytime, a predominance of nocturnal nondipping, and reverse dipping patterns, as well as higher SBP on average. As the treatment of abnormal BP patterns has developed over the past decades, primarily to address the global hypertension epidemic, there are existing therapeutic measures that can be repurposed for patients with POTS.

Strengths and Limitations

To our knowledge, this is the first observational study to investigate circadian 24-hour BP profiles in post-COVID-19 POTS. It provides novel insights into the existence of a specific hemodynamic profile in POTS. The robustness of the study is further enhanced by strict adherence to a standardized examination protocol for all participants and by including a control group consisting of population-based individuals from the general population. This rigorous approach significantly reduces the likelihood of inaccurate diagnoses or undetected cases of POTS, thereby ensuring the reliability of our findings in establishing this association.

While our study provides relevant insights, its scope and impact are limited by its single-center background and observational design. Such a framework inherently introduces selection and referral biases, which significantly constrain the generalizability of our findings. Additionally, the cross-sectional design prevents conclusions about causality. Unfortunately, we lacked data on important variables such as family history of hypertension and sleeping habits in the post-COVID cohort. As such, we were not able to adjust for these possible confounding variables.

Similarly, we lacked data on heart rate in the supine and standing position among controls. Another important limitation is that we lack data on previous BP/heart rate phenotype before COVID-19 infection in POTS cases. Also, both cohorts used different study protocols and defined daytime and nighttime BP hours differently, ± 1 hour. The systematic biases in nighttime and daytime SBP and DBP were small when diurnal periods were defined by self-report, fixed time, or actigraphy.⁴¹ Thus, we speculate that our results would only change marginally. Future studies should aim at evaluating the possible treatment implications and specific ABPM hemodynamic profiles in POTS.

Perspectives

Our study demonstrates that not only heart rate but also BP control is affected in POTS as part of the long COVID condition. We provide novel insights into the existence of specific BP abnormalities in patients with post-COVID-19 POTS, providing further evidence that POTS is a disorder linked to overall cardiovascular autonomic dysfunction. ABPM is a cost-effective diagnostic tool that may allow early identification of signs of disrupted BP control in POTS, providing a better rationale for tailored treatment of this vexing condition.

ARTICLE INFORMATION

Received July 15, 2024; accepted October 4, 2024.

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Acknowledgments

The authors thank medical students Haia Sadek, Sara Hassan, and Sara Nawaz for their contributions in medical record reviews of patients with postural orthostatic tachycardia syndrome (POTS) and registered nurse Anna Rosenback for performing 24-hour ambulatory blood pressure monitoring in patients with POTS.

Author Contributions

Concept and design were handled by A. Fedorowski, with data acquisition contributed by A. Fedorowski, M. Ståhlberg, P.M. Nilsson, M. Johansson, and V. Hamrefors. Statistical analysis was conducted by M. Johansson and F. Ricci. The interpretation of data involved M. Johansson, F. Ricci, A. Fedorowski, M. Ståhlberg, P.M. Nilsson, V. Hamrefors, C. Lewinter, and R. Sutton. The article was drafted by M. Johansson, F. Ricci, and A. Fedorowski. Critical revision and final approval of the manuscript were provided by all authors.

Sources of Funding

The Malmö Offspring Study has been funded by the Research Council of Sweden (grant 521-2013-2756), the Heart and Lung Foundation (grant 20150427), and by funds obtained from the local Region Skåne County Council (Avtal om Läkarutbildning och Forskning [ALF]) to P.M. Nilsson. A. Fedorowski was supported by grants from the Swedish Heart Lung Foundation (No. 20220319) and the Swedish government and the Stockholm County Council Agreement (the ALF agreement No. 988024). F. Ricci was supported by the European Union—Next Generation EU, under the National Recovery and Resilience Plan, Mission 4

Component 2–M4C2, Investment 1.5–Call No. 3277 of 30.12.2021–The Italian Ministry of University and Research (MUR), award number: ECS00000041, project title: Innovation, Digitalisation and Sustainability for the Diffused Economy in Central Italy, concession degree No. 1057 of 23.06.2022 adopted by the MUR. CUP: D73C22000840006.

Disclosures

None.

Supplemental Material

Tables S1 and S2

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