



Comparison of paediatric patients evaluated for postural orthostatic tachycardia syndrome with and without tachycardia

Original Article

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Abstract

Introduction: Postural orthostatic tachycardia syndrome is a debilitating disorder. We compared paediatric patients with this dysautonomia presenting with and without peak upright heart rate > 100 beats per minute. **Materials and Methods:** Subjects were drawn from the Postural Orthostatic Tachycardia Syndrome Program database of the Children's Hospital of Philadelphia diagnosed between 2007 and 2018. Subjects were aged 12–18 years at diagnosis with demographic data, supine and peak heart rate from 10-minute stand, symptoms, and family history. Patients were divided into “low heart rate” (peak less than 100 beats/minute) and “high heart rate” (peak at least 100 beats/minute) groups. **Results:** In total, 729 subjects were included (low heart rate group: 131 patients, high heart rate group: 598 patients). The low heart rate group had later age at diagnosis (16.1 versus 15.7, $p = 0.0027$). Median heart rate increase was 32 beats/minute in the low heart rate group versus 40 beats/minute in the high heart rate group ($p < 0.00001$). Excluding palpitations and tachypalpitations, there were no differences in symptom type or frequency between groups. **Discussion:** Paediatric patients meeting heart rate criteria for postural orthostatic tachycardia syndrome but without peak heart rate > 100 demonstrate no difference in symptom type or frequency versus those who meet both criteria. Differences observed reached statistical significance due to population size but are not clinically meaningful. This suggests that increased heart rate, but not necessarily tachycardia, is seen in these patients, supporting previous findings suggesting maximal heart rate is not a major determinant of symptom prevalence in paediatric postural orthostatic tachycardia syndrome.

Tachycardia has been defined as “an abnormally rapid heart rate; thresholds for different age, gender, and patient populations exist.”¹ In the latest consensus document, postural orthostatic tachycardia syndrome includes in its list of the diagnostic criteria, “a sustained heart rate increment of not less than 30 beats/minute within 10 minutes of standing or head-up tilt.”² Notably, patients aged 12–19 years require at least a 40 beats per minute increase in heart rate.² However, do patients qualify for a diagnosis of postural orthostatic tachycardia syndrome if they demonstrate a sustained heart rate increase of at least 30 beats per minute while meeting all other diagnostic criteria, yet not becoming tachycardic by definition for age and gender? There are likely those in the field who would say no, saying that postural orthostatic tachycardia syndrome is defined, in part, by tachycardia, as it is included in the name of the syndrome. Under this more stringent definition of postural orthostatic tachycardia syndrome, these patients would be different and would not be able to be diagnosed as having postural orthostatic tachycardia syndrome, despite having significant clinical similarities to patients who otherwise would meet those criteria.

To further evaluate and assess this group of patients, we attempted to characterise their orthostatic heart rate response, symptom type and frequency, and family history. By doing so, it would give some insight into the similarities and differences between those groups who had an elevated heart rate response without tachycardia compared to those who met the commonly accepted definition of tachycardia. For the sake of our study, tachycardia is defined as > 100 beats per minute.

Material and methods

Subjects for this study were obtained from the Postural Orthostatic Tachycardia Syndrome Database created at the Children's Hospital of Philadelphia, a REDCap³ database that drew information from the electronic health record obtained during clinical evaluation of the patients. Patients were diagnosed and treated between 2007 and 2018 in the Postural Orthostatic Tachycardia Syndrome Program at the Children's Hospital of Philadelphia. A diagnosis of postural orthostatic tachycardia syndrome was made if the patient had at least 3 months of

Table 1. Signs and symptoms assessed

Sign/symptom	Description/definition
Abdominal pain	Painful sensation in the abdominal region
Blurred vision	The loss of visual acuity (sharpness of vision) resulting in a loss of ability to see small details
Brain fog	An informal designation used to refer to several different forms of cognitive dysfunction characterised by slowed mentation, memory loss or dysfunction, and/or difficulty concentrating
Chest pain	Discomfort felt in the upper abdomen, thorax, neck, or shoulders
Cold intolerance	An abnormal sensitivity to a cold environment or cold temperatures
Constipation	Difficulties in defaecation that include infrequent bowel movements, hard or lumpy stools, excessive straining, sensation of incomplete evacuation or blockage and, in some instances, the use of manual manoeuvres to facilitate evacuation
Diaphoresis	A clinical finding in which there is excessive or unpredictable sweating
Diarrhoea	A disorder characterised by passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual)
Dizziness	Light-headedness associated with a cardiovascular aetiology (i.e., relative hypotension), as compared to vertigo or a vestibular aetiology
Dyspnoea with activity	A subjective sense of shortness of breath with physical exertion
Early satiety	The sensation of feeling full or no longer hungry earlier while consuming a non-oversized meal or after eating less than usual preventing completion of a meal
Exercise intolerance	A condition of inability or decreased ability to perform physical exercise at the normally expected level or duration for people of that age, size, sex, and muscle mass
Fatigue	Overall tiredness and lack of energy that is not improved with rest
Headache	Pain in various parts of the head, not necessarily confined to the area of distribution of any nerve
Heat intolerance	A feeling of being overheated when the surrounding temperature rises
Hyperacusis	A disorder in which an individual has an abnormally low noise tolerance, and increased sensitivity to sounds
Insomnia	A sleep disorder characterised by difficulty in falling asleep and/or remaining asleep
Joint hypermobility	The capability that a joint (or a group of joints) has to move, passively and/or actively, beyond normal limits along physiological axes
Joint pain	Discomfort associated with musculoskeletal joints, either at rest or in motion
Muscle pain	Discomfort associated with the muscles, either at rest or in motion
Nausea	A difficult-to-describe sensation of sick or queasy feeling usually perceived as being in the stomach that can escalate in severity and may precede vomiting
Numbness	Decrease or loss of superficial sensation in an anatomic region of the body
Palpitations	Sensation of irregular, rapid, and/or forceful beating of the heart
Photophobia	Increased sensitivity of the eyes to light, which can result in the avoidance of light exposure
Syncope	A transient loss of consciousness and postural tone due to cerebral hypoperfusion, characterised by a rapid onset, short duration, and spontaneous complete recovery
Tachypalpitations	Increased heart rate associated with the sensation of palpitations
Venous pooling	The disproportionate accumulation of blood in the veins when a person changes position from supine to seated position or standing, especially in the lower extremities, that can appear as acrocyanosis with or without oedema
Vomiting	Forceful ejection of the contents of the stomach through the mouth

Where available, definitions taken from Boris JR, *et al.* Clin Auton Res 2023.⁴

chronic symptoms consistent with orthostatic intolerance, a sustained increase of at least 30 beats per minute on 10-minute standing test, with at least 3 measurements demonstrating this finding after five minutes supine position, no decrease in blood pressure by greater than 20/10 mmHg, and the absence of any other diagnoses that could cause orthostatic intolerance. Patients were on no medications that would affect heart rate response at the time of the standing test. Inclusion criteria for this study included being aged 12–18 years at the time of diagnosis with postural orthostatic

tachycardia syndrome. Subjects also needed to have available data that included supine and peak heart rate, the findings of an assessment of the signs and symptoms typically associated with postural orthostatic tachycardia syndrome (Table 1),⁴ and data obtained regarding family history, including the presence of postural orthostatic tachycardia syndrome, other orthostatic intolerance (e.g. light-headedness, syncope), joint hypermobility, and autoimmune disorders. Joint hypermobility was assessed using a Beighton scoring assessment.⁵

Demographic data, supine and standing heart rate, symptom frequency, and family history data were assessed. Supine heart rate was obtained after patients were supine for 5 minutes. Standing heart rate was the peak heart rate consistently noted during the 10-minute stand. Subjects were divided into two categories: those patients that had a peak heart rate on standing of less than 100 beats per minute (low heart rate group) and those that had a peak heart rate of at least 100 beats per minute (high heart rate group). Statistical associations between the binary outcome variable (< 100 beats per minute / ≥ 100 beats per minute) and each of the binary symptom variables were assessed using chi-squared tests and Fisher's exact tests on each 2×2 contingency table. To maintain a family-wise error rate at a standard statistical cut-off ($p < 0.05$), a Bonferroni correction was used, and the threshold for statistical significance was lowered to $p < 0.0018$. Further comparisons between patients with a 30–39 beats per minute increase versus ≥ 40 beats per minute increase within both the low heart rate and high heart rate groups were also performed.

Single variable logistic regression models were fit separately for each symptom (including one symptom and an intercept term per model). Probabilistic programming framework was employed to perform a Bayesian version of the single variable logistic regression analysis using a Bernoulli-logit likelihood function, with identical non-informative priors (Gaussian with mean of zero and standard deviation of 100) specified for the intercept and symptom terms. Visualisations of the coefficient posterior distributions, with demarcated 95% probability intervals, were used to assess coefficient significance. A multiple logistic regression analysis was performed, using the binary tachycardia threshold outcome variable, low heart rate or high heart rate, as the dependent variable, and using all measured binary symptom variables as independent predictors. Variance inflation factor analysis was performed to identify variables with problematic levels of correlation in the context of the model, which was re-run after removal of the predictor with the highest variance inflation factor. An equivalent Bayesian multiple logistic regression analysis was performed for comparison, with non-informative priors (as described above) for the intercept and coefficient terms. Bayesian variable selection and model comparison analysis were performed. Gaussian kernel density estimation was performed to assess the density of continuous variables for both of the tachycardia outcome variable groups. Student t-test p-values and non-parametric Mann-Whitney U-test p-values were used to test the null hypotheses. A Pearson correlation matrix was generated to examine pairwise correlations. Further analysis of collinearity was undertaken using a logistic principal component analysis.⁶ To highlight any potential non-linear interactions between symptoms with respect to their associations with the tachycardia outcome grouping, decision tree analysis was performed.

As these data were obtained in the course of clinical care and were de-identified, Institutional Review Board approval was waived.

Results

Out of 1464 patients seen in our clinic, 516 did not meet criteria for a diagnosis of postural orthostatic tachycardia syndrome. After 219 subjects were found to have insufficient data, a total of 729 patients met criteria for inclusion in this study, with 598 patients in the high

heart rate group, and 131 patients in the low heart rate group, based on a 10-minute stand peak heart rate. All patients with a diagnosis of postural orthostatic tachycardia syndrome had at least a persistent 30 beats-per-minute heart rate increase during standing testing.

The median age of symptom onset and age at diagnosis were statistically significantly higher in the low heart rate group (Table 2, Fig. 1), with symptom onset occurring at age 13.1 versus 13.0 years ($p = 0.044$) and age at diagnosis occurring at age 16.1 versus 15.7 years, ($p = 0.0027$). Although both groups had more female patients than males, the high heart rate group had significantly more females (81.3% versus 71.0%, $p = 0.0014$). There were no differences noted between most groups in race or ethnicity, with a predominance of White patients noted. Only patients reporting Asian and multiple races demonstrated statistically significantly different numbers, although these were very small total numbers of patients. The median difference in heart rate between the two groups was 32 in the low heart rate group, and 40 in the high heart rate group ($p < 0.00001$). Only 23 patients (17.6%) in the low heart rate group had a heart rate increase of 40 beats per minute, or more, whereas 314 patients (52.5%) in the high heart rate group had an increase of at least 40 beats per minute ($p < 0.00001$).

The frequency of 28 different symptoms (Table 1) was initially assessed individually (Table 3). As noted, the threshold for significance was set at $p < 0.0018$ following the appropriate Bonferroni correction without any correction for potentially correlated symptoms. Under these criteria, only the presence of palpitations and tachycardia were significantly different between groups, with palpitations more frequently seen (78.4% versus 61.1%, $p = 0.00003$) and tachypalpitations more frequently seen (62.0% versus 39.7%, $p < 0.00001$) in patients with the higher heart rate response on standing test.

Subgroup analysis was performed among those patients with a heart rate increase of 30–39 beats per minute and those with a ≥ 40 beats per minute increase. In addition to palpitations and tachypalpitations, insomnia and blurred vision had p values of 0.016 and 0.005, respectively, in the low heart rate group, and dizziness and insomnia had p values of 0.026 and 0.04, respectively, in the high heart rate group. However, no subgroup symptom comparison met the Bonferroni cut-off of 0.0018 (data not shown).

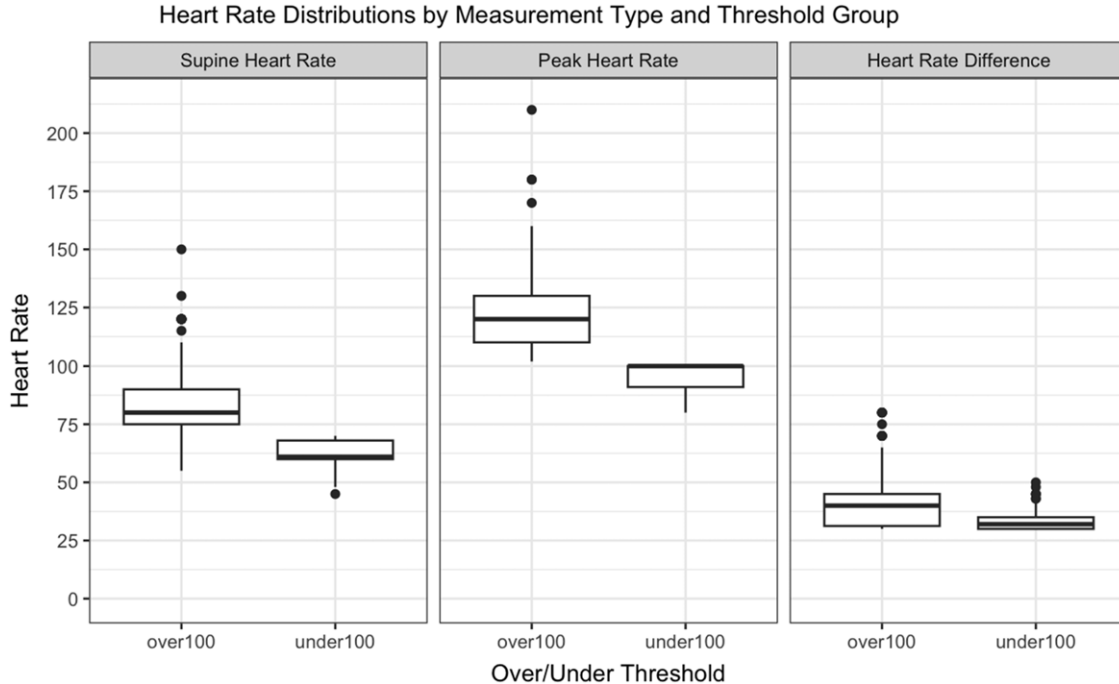
We assessed the relationship between symptom pairs using the Pearson correlation coefficient. Most symptoms were uncorrelated but we observed a high degree of correlation between tachypalpitations and palpitations ($r^2 = 0.62$), and between photophobia and hyperacusis ($r^2 = 0.53$) (Fig. 2). Logistic principal component analysis, optimised for use with binary variables, similarly did not reveal the presence of any systematic correlation. The variance explained plot showed that 15–20 principal components needed to be added before the variance explained by further additions began to plateau (Fig. 3). The data were plotted against the first two principal components (Fig. 4), with the points coloured by heart rate outcome group. Points of both colours were found evenly spread throughout the space, with none of the variation present in the first two principal components associated with the outcome variable, indicating that the dominant sources of variance in the dataset were unrelated to the heart rate outcome variable.

The mean number of symptoms per individual in the low heart rate group was 16.4, and that in the high heart rate

Table 2. Patient demographics and heart rate findings

	Peak HR ≤ 100	Peak HR > 100	p value
Age at diagnosis, y median (IQR)	16.1 (15.0, 17.1)	15.7 (14.2, 16.7)	0.0027
Age at symptom onset, y median (IQR)	13.1 (12.0, 15.0)	13.0 (11.2, 14.7)	0.044
Female, n (%)	93 (71.0)	486 (81.3)	0.0014
Male, n (%)	42 (29.0)	112 (18.7)	
			p < 0.008
White, n (%)	123 (93.9)	548 (91.6)	0.39
African-American, n (%)	0	8 (1.3)	0.59
Asian, n (%)	3 (2.3)	2 (0.3)	0.014
Native American/Alaskan, n (%)	0	1 (0.2)	0.24
Multiple, n (%)	3 (2.3)	2 (0.3)	0.014
Other, n (%)	8 (6.1)	33 (5.5)	0.79
Hispanic, n (%)	4 (3.1)	21 (3.5)	0.79
Supine HR, bpm median (IQR)	61 (60, 68)	80 (75, 90)	
Peak HR, bpm median (IQR)	100 (91, 100)	120 (110, 130)	
HR difference, bpm median (IQR)	32 (30, 35)	40 (31, 45)	<0.00001
Patients with a HR difference > 40 bpmn (%)	23 (17.6)	314 (52.5)	<0.00001
History of autoimmune disease n (%)	10 (7.6)	40 (6.7)	0.70

N = number; HR = heart rate; bpm = beats per minute; y = years; IQR = interquartile range.

**Figure 1.** Heart rate distributions by measurement type and threshold group.

group was 18 symptoms. Density plots of this variable coloured by outcome group are found in Figure 5. This difference was significantly different in terms of the corrected threshold, with a Student t-test ($p = 0.001$). If tachypalpatations and

palpitations were removed as symptoms, the mean number of symptoms per individual in the low heart rate group was 15.4 while the mean number in the high heart rate group was 16.6 ($p = 0.0092$).

Table 3. Symptoms, n (%)—low heart rate group versus high heart rate group; $p < 0.0018$

	Peak HR \leq 100	Peak HR $>$ 100	p value
Dizziness	128 (97.7)	582 (97.3)	0.80
Headache	118 (90.1)	561 (93.8)	0.13
Fatigue	114 (87.0)	560 (93.6)	0.009
Brain fog	111 (84.7)	500 (83.6)	0.75
Dyspnoea with activity	98 (74.8)	485 (81.1)	0.10
Insomnia	104 (79.4)	476 (79.6)	0.96
Palpitations	80 (61.1)	469 (78.4)	0.00003
Heat intolerance	89 (67.9)	457 (76.4)	0.052
Exercise intolerance	95 (72.5)	494 (76.0)	0.35
Nausea	104 (79.4)	436 (72.9)	0.13
Venous pooling	98 (74.8)	431 (72.1)	0.53
Early satiety	86 (65.6)	374 (62.5)	0.50
Joint hypermobility	66 (50.4)	373 (62.4)	0.011
Blurred vision	68 (51.8)	372 (62.2)	0.029
Tachycardia	52 (39.7)	371 (62.0)	<0.00001
Abdominal pain	77 (58.8)	366 (61.2)	0.61
Chest pain	70 (53.4)	366 (61.2)	0.10
Joint pain	61 (46.6)	307 (51.3)	0.32
Diaphoresis	70 (53.4)	306 (51.2)	0.64
Photophobia	48 (36.6)	289 (48.3)	0.015
Numbness	48 (36.6)	282 (47.2)	0.029
Constipation	52 (39.7)	265 (44.3)	0.33
Muscle Pain	41 (31.3)	259 (43.3)	0.011
Hyperacusis	38 (29.0)	221 (37.0)	0.09
Syncope	46 (35.1)	216 (36.1)	0.83
Cold intolerance	36 (27.5)	196 (32.8)	0.23
Diarrhoea	39 (29.8)	165 (27.6)	0.61
Vomiting	28 (21.4)	141 (23.6)	0.59
At least 10 symptoms	119/131 (90.8)	567/598 (94.8)	0.08
At least 15 symptoms	70 (53.4)	382 (63.9)	0.026
At least 20 symptoms	31 (23.7)	161 (26.9)	0.44

HR = heart rate.

Multiple logistic regression modelling, with all symptom variables input to the model, achieved ~82% accuracy. Figure 6 reveals that this number is mainly a result of the outcome group imbalance and that the actual classification ability of the model is very weak. The symptom coefficients that achieved significance in this model were fatigue ($p = 0.014$), nausea ($p = 0.035$), and tachycardia ($p = 0.05$). Variance inflation factors were calculated from this model, and even though none of these approached the accepted problematic threshold of five, the symptom with the highest variance inflation factor (tachycardia = 2.15) was removed, and the model was re-fit. This re-fit model's significant coefficients still included fatigue ($p = 0.014$) and nausea ($p = 0.033$), but now

featured palpitations as the most significant ($p = 0.001$). The predictive density plots show a minimal improvement in predictive accuracy (Fig. 7) resulting from the elimination of the pathological correlation between tachycardia and palpitations that allows two more patients to be classified correctly.

To confirm that these results were not test-specific, we used a Bayesian equivalent of the logistic regression model. Results demonstrated that fatigue, nausea, and tachycardia have 95% intervals that do not include zero (Fig. 8), i.e., these variables are statistically significant, as noted above. "Leave-one-out" cross-validated model comparison and variable selection identified the smallest model that approximates the performance of the full model containing all 28 symptom variables. The three most influential variables in order were tachycardia, palpitations, and fatigue (Fig. 9). While an appreciable amount of information was gained by adding tachycardia to the null model initially containing only the intercept term, very little information was gained by adding any other variable. By expressing performance as per cent accuracy, the model performance was never actually predicted to improve above the 82% provided by the null model, due to the outcome class imbalance.

Predictive decision trees to capture non-linear interactions between symptoms showed no predictive power. The cross-validated classification and regression tree algorithm, whereby 80% of the dataset is used to build a decision tree which is then tested on the remaining 20%, showed that none of the training sets were able to support the construction of a stable decision tree containing more than one symptom variable, which was tachycardia in all cases.

There was no difference between groups in the presence of a family history of postural orthostatic tachycardia syndrome, a family history of orthostatic intolerance, or a family history of an autoimmune disorder (Table 4). However, joint hypermobility was more likely to be seen in the higher heart rate group (31.1% versus 18.3%, $p = 0.0034$).

Discussion

Our data suggest that patients with postural orthostatic tachycardia syndrome who meet the formal criteria for tachycardia do not have a meaningful difference in symptom prevalence versus those who do not meet these criteria. We systematically looked for any potential differences using multiple distinct analytical statistical and data analysis approaches, both linear and non-linear, and found no specific consistent variances beyond palpitations and tachypalpitations. Palpitations are defined as the sensation of irregular, rapid, and/or forceful beating of the heart.⁴ Tachypalpitations refers specifically to the sensation of the heart beating faster. One would expect that these symptoms would be experienced more frequently with a higher heart rate response to upright position. Although postural orthostatic tachycardia syndrome is felt to be due to decreased core blood volume, increased venous pooling, and reduced cardiac output, the actual aetiology of these phenomena is unknown. Therefore, it is also difficult to address the reason that there is a difference in chronotropic response.

Those two differences aside, multiple different analyses demonstrated that there were either no differences or small inconsistent (and clinically irrelevant) differences between these two groups of patients, e.g., the 0.1-year difference in age of onset. Of note, the smaller percentage of patients in the low heart rate group demonstrating a 40 beats per minute increase as compared

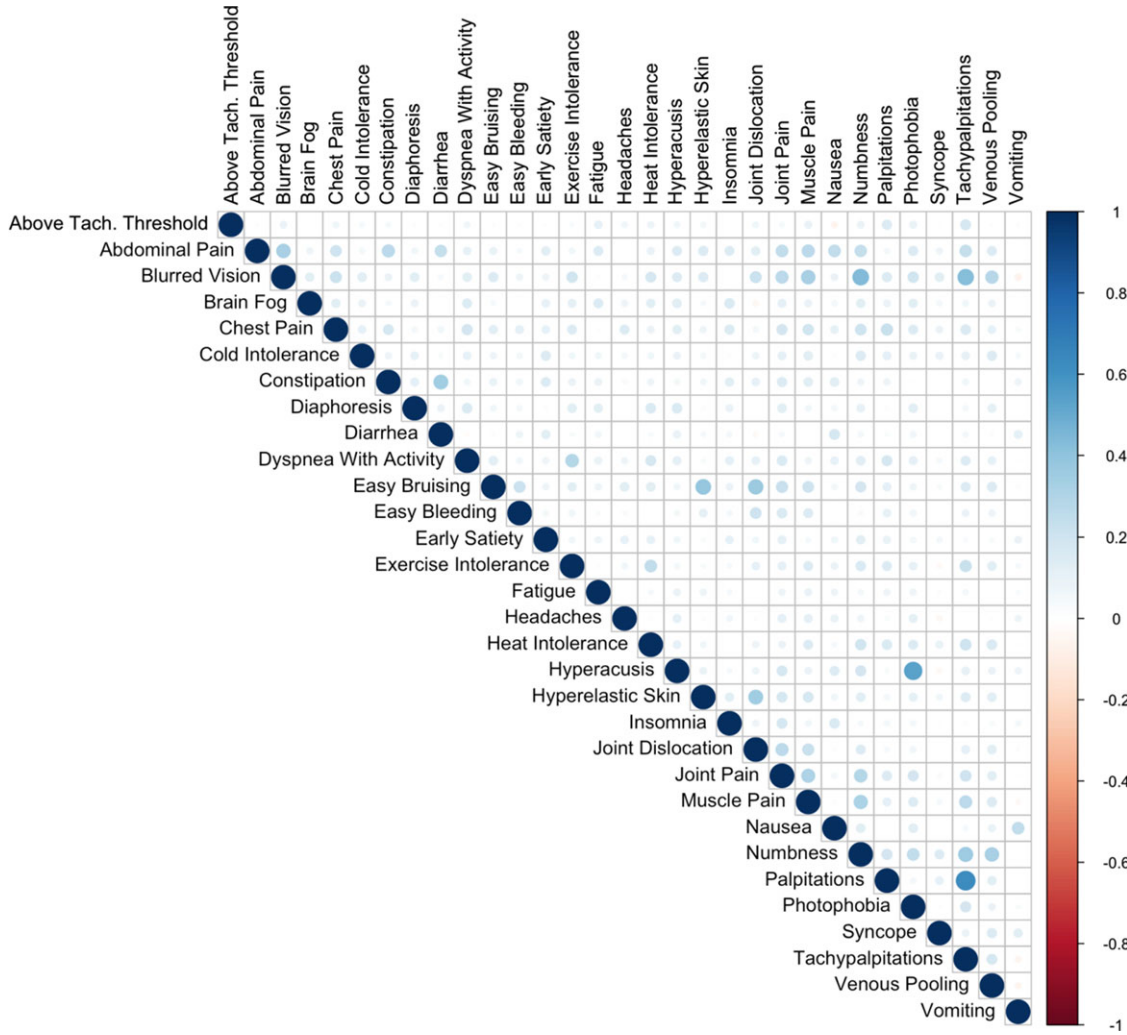


Figure 2. Correlations between symptom pairs.

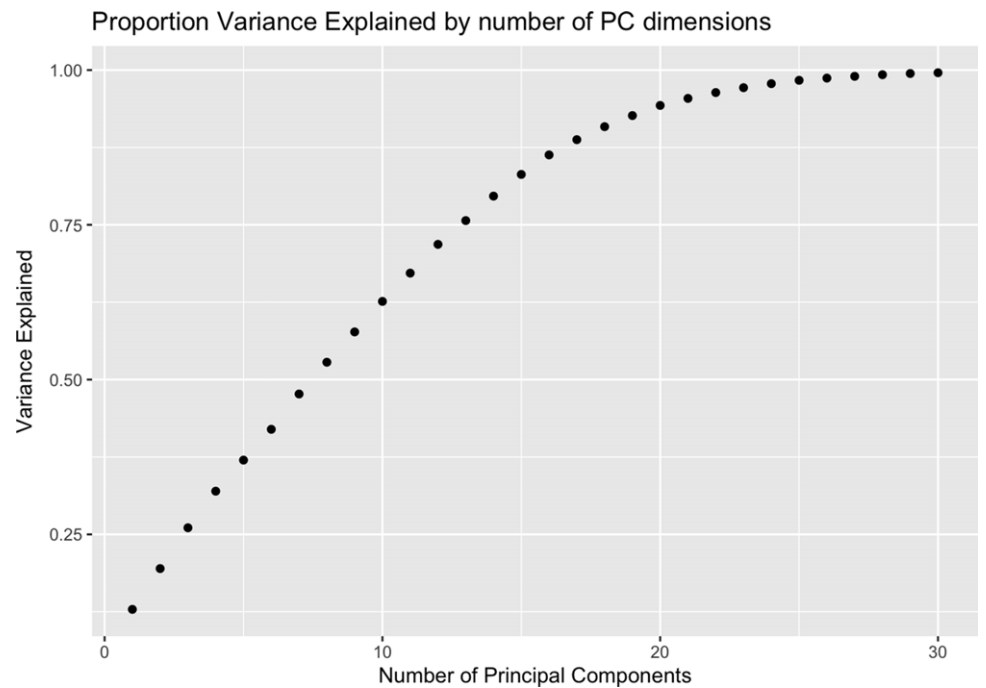


Figure 3. Cumulative proportion plot of variance explained by principal component dimension.

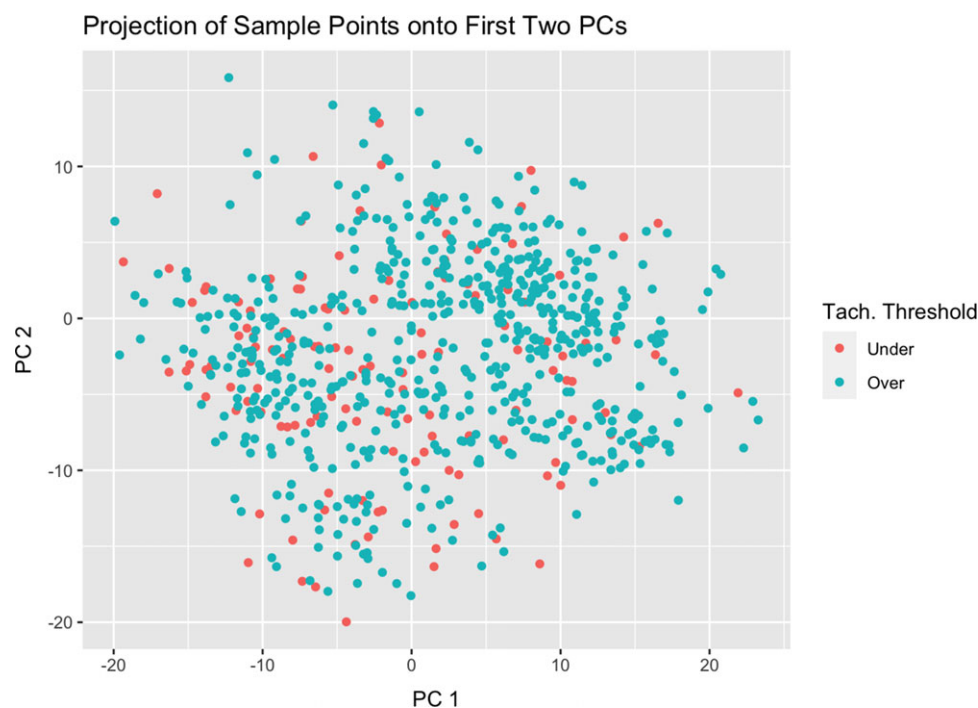


Figure 4. Projection plot of patients onto two most significant principal component axes.

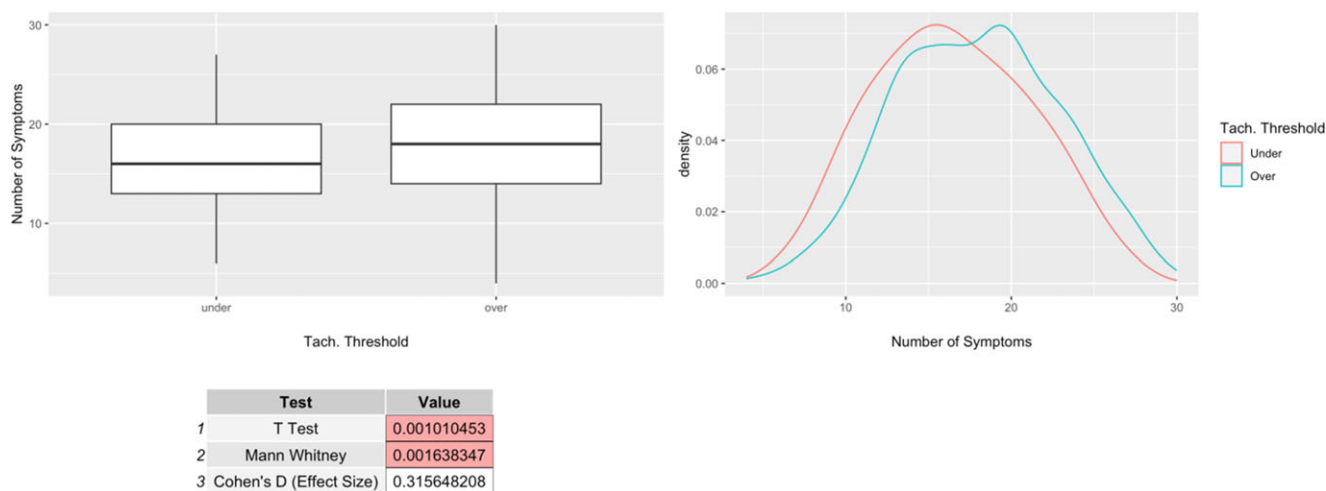


Figure 5. Distribution plots of total symptom number by tachycardia threshold status.

to the high heart rate group makes sense, in that a resting heart rate <60 would be needed to achieve a 40-point increase in heart rate in the low heart rate group. Although there were some patients that had this, most had resting heart rates greater than 60.

These data indicate that maximal heart rate on standing is unrelated to breadth of symptom burden in postural orthostatic tachycardia syndrome. Similar to what we published previously, in which paediatric patients with a 30–39 beats per minute increase on 10-minute standing test had indistinguishable symptoms from those with a ≥ 40 beats per minute increase,⁷ we have two groups of patients who appear identical except for these minute clinical differences. Our standard question panel did not account for symptom severity or frequency, so we could not assess for any difference in the degree of disability in these patients. However, based on what appear to be these slight variances, there appears to be no rationale for any differences in clinical management of these patients.

Specifically, although postural orthostatic tachycardia syndrome is not fully defined by a collection of symptoms, these findings imply that it is difficult to clinically differentiate between these two groups of patients and that the diagnostic criteria may not be capturing patients appropriately. The inappropriate exclusion from a postural orthostatic tachycardia syndrome diagnosis impacts these patients in several important ways. A diagnosis helps the patients and families to have validation for the multiple unexplained symptoms and disability that often leads to a delay in diagnosis after having seen multiple providers;⁸ its absence further prolongs this delay. A valid diagnosis helps to frame a therapeutic approach, as well as giving clues into comorbid diagnoses and prognosis. It also provides the ability to find a clinician familiar with these aspects of management, whose absence again may lead to provider confusion and delays in care for the patient. And, for some patients, having a diagnosis of postural orthostatic tachycardia syndrome may mean having access to governmental financial support in the setting of

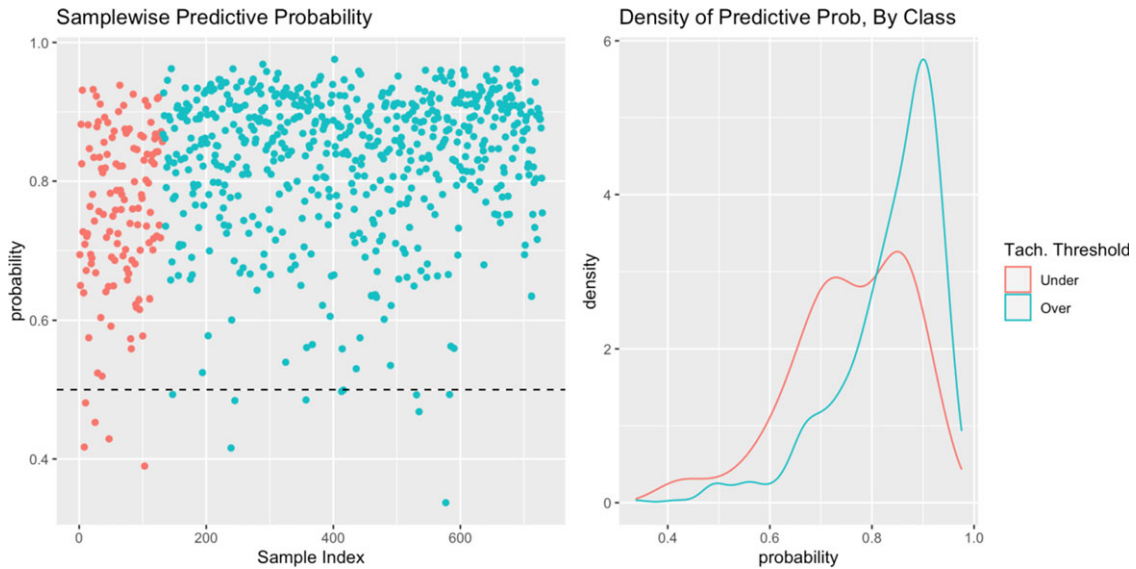


Figure 6. Predictive density plots from full multivariate model.

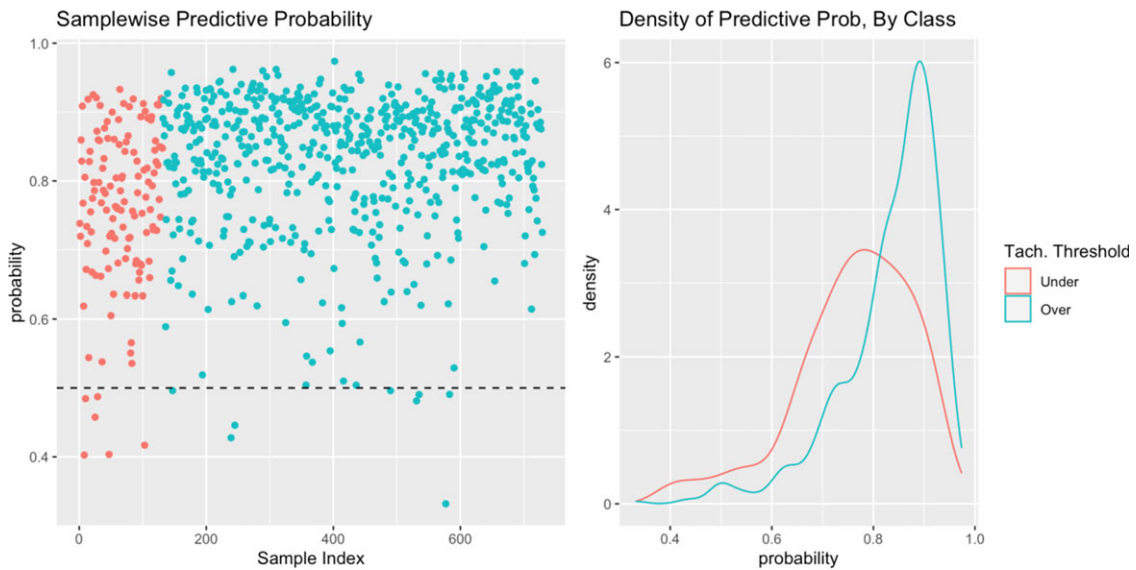


Figure 7. Predictive density plots from multivariate model excluding tachypalpitations.

severe and chronic disability,⁹ thereby mediating the impact of compounding stressors such as the financial burdens of dealing with a disability. We note that we considered the counterargument, i.e., that maintaining a strict definition of postural orthostatic tachycardia syndrome, including that of heart rate achieving a tachycardic response, must be preserved in order to ensure that postural orthostatic tachycardia syndrome isn't over-diagnosed so that it doesn't include a heterogeneous group of patients. It is immediately apparent, however, that if the criteria does not add useful information, or, arguably, adds only a false dichotomy, it is not meaningful to include it in the criteria.

These issues highlight the need for a more formalised set of specific diagnoses for the different presentations of what is currently termed postural orthostatic tachycardia syndrome. By its nature, postural orthostatic tachycardia syndrome is a heterogeneous collection of patients with varied symptoms. Some may be labelled hyperadrenergic, some hypovolemic, others partial

dysautonomic, and still others neuropathic.^{10–13} None of these definitions have consistently been shown to demonstrate any prognostic or therapeutic differences across groups. Definitions of syndromes can change over time, sometimes broadening,¹⁴ and other times narrowing diagnostic criteria,¹⁵ as a greater understanding of the manifestations is observed, a biological marker is identified, or a pathognomonic imaging modality is recognised to specifically and sensitively identify the disease process or evidence of it.

Notably, there also appears to be no difference in the frequency of family history of postural orthostatic tachycardia syndrome, orthostatic intolerance, or autoimmune disease. However, patients in the high heart rate group had 32% of family members with a history of joint hypermobility, which was just less than twice the frequency compared to those in the low heart rate group (Table 4). The reason for this is unclear, especially since as many as 61% of patients with postural orthostatic tachycardia syndrome have joint

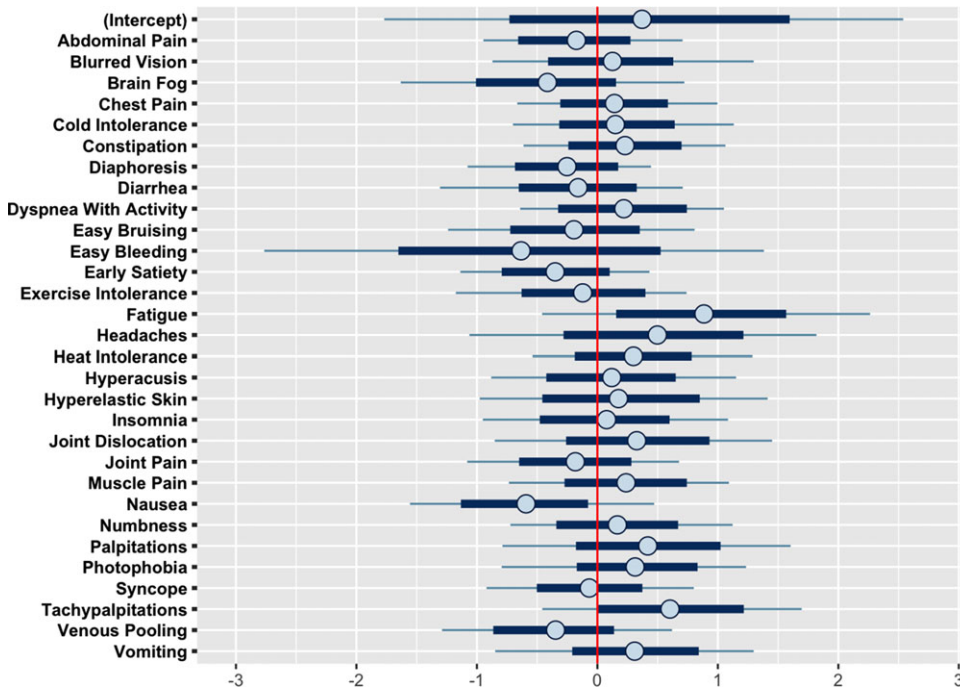


Figure 8. Bayesian coefficient estimation for full multivariate model.

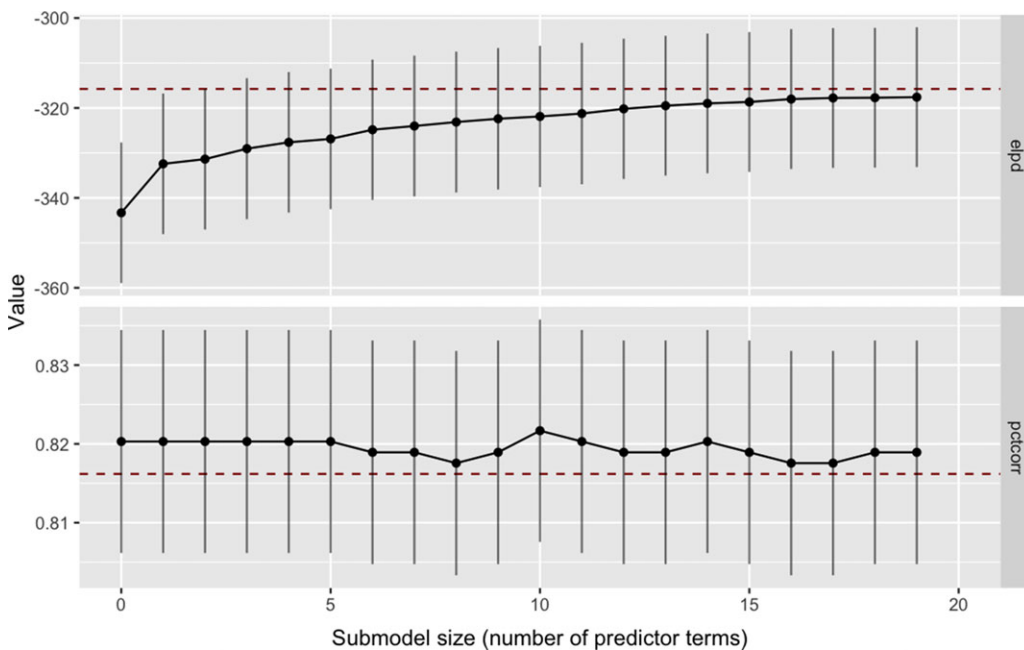


Figure 9. Bayesian variable selection using projection predictive feature selection.

hypermobility,^{16,17} and 20% of patients with postural orthostatic tachycardia syndrome have a family member with joint hypermobility.¹⁸ Joint hypermobility was seen in 62% of patients in the high heart rate group, but this was not found to be significantly different from the 50.4% found in the low heart rate group (Table 3). Both groups had a large number of patients with hypermobility. One could postulate that the connective tissue disorder that creates the hypermobility may also adversely affect vascular tone, leading to a greater likelihood of hypotension with secondary tachycardic response to maintain cardiac output. Notably, there is no statistical difference between the mean resting heart rate of patients with and without joint hypermobility (data not shown).

The study has limitations and strengths. Three primary limitations are that it only reports patients from a single practice, the lack of accepted markers for the phenotypes of interest and for postural orthostatic tachycardia syndrome itself, and use of qualitative description of symptoms that is non-informative as to severity/frequency. Another limitation is its utilisation of a 30 beats per minute increase in heart rate as the threshold for diagnosis of paediatric postural orthostatic tachycardia syndrome. Although the diagnostic criteria for patients aged 12–19 years include a 40 beats-per-minute threshold, prior research has shown no difference in symptomatology in a cohort of patients with a 30–39 beats per minute increase versus that of a cohort with a ≥ 40 beats-per-minute increase (Boris et al, 2019). As well, the diagnostic criteria

Table 4. Family history, n (%)—low heart rate group versus high heart rate group; $p < 0.013$

	Low heart rate	High heart rate	p value
POTS	17 (13.0)	96 (16.1)	0.38
Orthostatic intolerance	29 (22.1)	110 (18.4)	0.32
Joint Hypermobility	24 (18.3)	186 (31.1)	0.0034
Autoimmune disorder	81 (61.8)	379 (63.4)	0.74

POTS = postural orthostatic tachycardia syndrome.

that included a 40 beats-per-minute threshold were not published until 2011,¹⁹ after many of our patients were already being evaluated and managed. Also, although there are known differences between the degree of tachycardia induced by tilt table versus 10-minute stand,^{20,21} the 10-minute standing test has yet to be validated. The major strengths are that the use of records from a single practice improves intra-study coherence and common practices, and both the size of the population and the broad-based informatics approach that it enables, offers power which reduces the potential for false negative results.

In summary, patients with a > 30 beats per minute or > 40 beats per minute response to upright position, whether their peak heart rate rises above 100 beats per minute, or not, appear to have no difference in breadth of symptom burden between groups. This finding suggests it is important for practitioners to be alert to still consider a diagnosis of postural orthostatic tachycardia syndrome in those patients who have lower resting heart rates but a significant elevation in heart rate with upright position in conjunction with prolonged symptomatology associated with orthostatic intolerance.

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