Postural Tachycardia Syndrome and Inappropriate Sinus Tachycardia: Role of Autonomic Modulation and Sinus Node Automaticity

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Background—Inappropriate sinus tachycardia (IST) and postural tachycardia syndrome (POTS) are disorders characterized by sinus tachycardia. It is debated whether the pathophysiology of IST and POTS results from abnormal autonomic regulation or abnormal sinus node function. We hypothesized that intrinsic heart rate (IHR) after autonomic blockade would be increased in patients with IST but not POTS.

Methods and Results—We enrolled 48 POTS patients, 8 IST patients, and 17 healthy control (HC) subjects. Intravenous propranolol and atropine were given to block the sympathetic and parasympathetic limbs of the autonomic nervous system in order to determine the IHR. Patients with IST have a higher sympathetic contribution to heart rate when compared with POTS patients (31±13 bpm versus 12±7 bpm, P<0.001) and HC (8±4 bpm; P<0.001) and a trend to less parasympathetic contribution than POTS and HC (IST: 31±11 bpm versus POTS: 46±11 bpm versus HC: 48±11 bpm, ANOVA P=0.108). IHR was not significantly different between IST and either POTS or HC (IST: 111±11 bpm versus POTS: 108±11 bpm versus HC: 106±12 bpm, ANOVA P=0.237).

Conclusions—IST patients have more sympathetic tone when compared with either POTS or HC, but IST patients do not have abnormal sinus node automaticity. These data suggest that the treatment of IST and POTS should focus on sympatholysis, reserving sinus node modification for patients with continued debilitating symptoms after beta-blockade and possibly ivabradine.


Key Words: autonomic nervous system • inappropriate sinus tachycardia • postural tachycardia syndrome • sinus node • sympathetic nervous system

Inappropriate sinus tachycardia (IST) and postural tachycardia syndrome (POTS) are syndromes with overlapping clinical features of excessive sinus tachycardia. While the elevated heart rate (HR) in POTS is predominantly triggered by orthostatic stress, HR is elevated in IST without regard to body position. In both disorders, HR can increase greatly in response to minimal activity.

The role of the autonomic nervous system in driving the high HR in IST and POTS is not well characterized. One theory is that the underlying problem is abnormally high intrinsic sinus node automaticity rates due to ion channel perturbations. If so, a radiofrequency sinus node modification procedure to eliminate these abnormally firing cells, or treatment with ivabradine, which modulates the funny channel (If), may be optimal. Alternatively, the high HR could be driven by alterations in autonomic nervous system tone, with a shift to excess sympathetic nervous system tone and decreased cardiovascular tone. In this latter scenario, IST and POTS patients might be more likely to benefit from pharmacologic treatments that blunt the sympathetic nervous system response, such as propranolol. To better define the influence of autonomic modulation on HR in IST and POTS, we performed acute autonomic blockade to determine the intrinsic heart rate (IHR). We hypothesized that IHR would be increased in IST, but not in POTS, compared with healthy subjects.
Methods

Subjects

Patients referred to the Vanderbilt University Autonomic Dysfunction Center with POTS or IST between June 2006 and March 2010 were candidates for inclusion in this study. Patients met criteria for IST with a daytime resting HR >100 bpm or a 24-hour average HR >90 bpm in the absence of any acute physiologic demand or conditions known commonly to increase HR. This was determined by a clinical Holter monitor prior to arrival on the Vanderbilt Clinical Research Center. Patients with POTS had an increase in HR ≥30 bpm within 10 minutes of standing in the absence of orthostatic hypotension (a fall in blood pressure [BP] ≥20/10 mm Hg), and accompanied by orthostatic symptoms. All patients were ≥18 years, and had at least a 6-month history of symptoms in the absence of other disorders known to cause orthostatic intolerance.

Healthy control (HC) subjects were recruited from the Vanderbilt University Clinical Research Center volunteer database and local advertisements. HC subjects had no concomitant cardiovascular disease or other major illnesses, and none were current smokers. Pregnancy was excluded in female subjects with a urine or serum pregnancy test.

The Vanderbilt University Investigational Review Board approved this study, and written informed consent was obtained from each subject before study participation. The data reported are a part of “The Pathophysiology of Orthostatic Intolerance Study,” which is registered with www.clinicaltrials.gov (NCT00608725).

Study Conditions

Study investigations were performed at the Elliot V. Newman Clinical Research Center at Vanderbilt University. Patients consumed a methylxanthine-free diet containing 150 mEq/day of sodium and 70 mEq/day of potassium for at least 3 days prior to testing. Medications that are known to alter HR or BP were stopped at least 5 half-life periods prior to the study. Oral contraceptive pills and chronic selective serotonin reuptake inhibitors were allowed.

Study Testing

Posture study

A baseline “Posture Study” was performed for subject characterization. After an overnight fast, HR, BP, and fractionated plasma catecholamines were measured with patients in the supine position and with standing up to 30 minutes (as tolerated). BP was measured intermittently with an automated sphygmomanometer cuff (Dinamap, GE Healthcare). For the catecholamine measurements, blood was collected in plastic syringes, and immediately transferred to chilled vacuum tubes with sodium heparin (BD), and placed on ice. Plasma was separated by centrifugation at −4°C and stored at −70°C in collection tubes with 6% reduced glutathione (Sigma-Aldrich, Inc) until the assay was performed. Concentrations of norepinephrine (NE), epinephrine (EPI), and dihydroxyphenylglycine (DHPG) were measured by batch alumina extraction followed by high-performance liquid chromatography for separation with electrochemical detection and quantification. Plasma NE and EPI are reported in SI units. To convert from nmol/L to the more conventional pg/mL, multiply 169.18 for norepinephrine (1 nmol/L = 169.18 pg/mL) or by 183.2 for epinephrine (1 nmol/L = 183.2 pg/mL). DHPG/NE ratio is a marker of NE transporter activity with a higher ratio representing increased activity.

Intrinsic heart rate (IHR) protocol

Digital data acquisition. The surface ECG lead II was amplified, and no additional filters were applied. ECG and blood pressure were digitized with 14-bit resolution and 500-Hz sample frequency, and recorded using the WINDAQ data-acquisition system (D1720; DATAQ). BP was measured with an automated oscillometric brachial cuff (Vital-Guard 450C; Ivy Biomedical Systems) and by the volume clamp method (Nexfin; BMEYE). HR and respiratory rate were determined from continuous ECG monitoring (Vital Guard 450C; Ivy Biomedical Systems). Data were analyzed offline using a customized program for data analysis written in PV-Wave (Visual Numerics Incorporated) by one of the authors (A.D.).

Pharmacologic testing for IHR. Studies were performed with the subjects supine. After a 10-minute baseline recording, subjects were given propranolol IV 0.2 mg/kg (in 4 equal divided doses at least 3 minutes apart) to block the HR response to the sympathetic limb of the autonomic nervous system. Subjects were then given atropine 0.04 mg/kg IV (in 4 equal divided doses at least 3 minutes apart) to block the HR response to the parasympathetic arm of the autonomic nervous system. A Valsalva maneuver was performed after the 3rd dose of atropine. If the HR was fixed, this was taken as an indication that the subject was autonomically blocked and the 4th dose of atropine was not administered. IHR was defined as the HR following the final doses of both propranolol and atropine (Figure 1). The sympathetic contribution to HR (SYM) was defined as the decrease in HR from baseline to post-propranolol. The parasympathetic contribution to HR (PSYM) was defined as the increase in HR from the post-propranolol assessment to the IHR.
Heart rate variability (HRV), blood pressure variability (BPV) and baroreflex sensitivity (BRS)

HRV, BPV, and BRS were calculated from the quiet supine baseline prior to pharmacologic intervention. A QRS detection algorithm, modified from Pan and Tompkins, was used to generate beat-to-beat values. The nonequidistant event time series of RR intervals were interpolated, low-pass filtered (cutoff: 2 Hz), and resampled at 4 Hz. Data segments of 300 seconds, recorded during stable resting conditions, were used for spectral analysis. Linear trends were removed, and power spectral density was estimated with the fast Fourier transform-based Welch algorithm, using segments of 256 data points with 50% overlapping and a Hanning window. The power in the algorithm, using segments of 256 data points with 50% estimated with the fast Fourier transform-based Welch method, so the $P$ value significance threshold was 0.017 for the comparisons of IST versus POTS, IST versus HC, and POST versus HC. Statistical analyses were performed using SPSS for Windows version 19 (IBM Corp). GraphPad Prism version 5.02 (GraphPad Software Inc) was used to create the figures.

Results

Patient Characteristics

Eight IST patients (36±12 years, BMI 30±7 kg/m$^2$), 48 POTS patients (30±8 years, BMI 23±4 kg/m$^2$), and 17 HC subjects (27±8 years, BMI 22±3 kg/m$^2$) met the study inclusion criteria. All subjects were female. IHR data was available on all subjects. The digital data recordings were too noisy to reliably perform spectral analysis in 6 POTS patients and 3 HC subjects. Therefore, heart rate variability and baroreceptor sensitivity assessments were completed in 8 IST patients, 42 POTS patients, and 14 HC subjects.

The supine and standing data from the posture study are presented in Table 1. While supine, IST patients had a significantly higher HR when compared with POTS patients (88±10 bpm versus 73±10 bpm, $P=0.010$) and HC (72±21 bpm, $P=0.019$). POTS patients had a higher orthostatic increase in HR than HC (48±23 bpm versus 13±23 bpm, $P<0.001$). Although there was a larger orthostatic HR increase in POTS patients compared with IST patients, however, this did not reach statistical significance (48±23 bpm versus 38±14 bpm, $P=0.825$). There was no difference between IST patients and HC (38±14 bpm versus 13±23 bpm, $P=0.088$).

Supine SBP was highest among IST patients when compared with POTS and HC, but did not reach statistical significance (IST: 120±11 mm Hg, versus POTS: 107±12 mm Hg, $P=0.021$ versus HC: 102±15 mm Hg, ANOVA, $P=0.145$). The DBP was significantly higher among IST patients when compared with POTS and HC (IST: 77±10 mm Hg versus POTS: 65±8 mm Hg, $P=0.040$ versus HC: 64±10 mm Hg, $P=0.041$).

The mean supine plasma NE was not different among the 3 groups (IST: 1.6±1.1 nmol/L [269±191 pg/mL] versus POTS: 1.1±0.7 nmol/L [179±110 pg/mL] versus HC: 0.8±0.2 nmol/L [133±39 pg/mL] ANOVA, $P=0.106$). Plasma supine EPI level was highest in IST patients.
Table 1. Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>POTS N=48</th>
<th>IST N=8</th>
<th>HC N=17</th>
<th>ANOVA P Value</th>
<th>POTS vs HC P Value</th>
<th>IST vs HC P Value</th>
<th>POTS vs IST P Value</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>30±8</td>
<td>36±12</td>
<td>27±8</td>
<td>0.044</td>
<td>0.431</td>
<td>0.044</td>
<td>0.172</td>
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<tr>
<td>Height, cm</td>
<td>168±6</td>
<td>163±8</td>
<td>167±6</td>
<td>0.142</td>
<td>0.812</td>
<td>0.409</td>
<td>0.147</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>65±11</td>
<td>83±23</td>
<td>63±9</td>
<td>0.003</td>
<td>0.900</td>
<td>0.006</td>
<td>0.005</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>23±4</td>
<td>30±7</td>
<td>22±3</td>
<td>&lt;0.001</td>
<td>0.863</td>
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**Supine**
- HR, bpm: 73±11, 88±10, 72±21 (0.011), 1.000, 0.019, 0.010
- SBP, mm Hg: 107±12, 120±11, 102±15 (0.145)
- DBP, mm Hg: 65±8, 77±10, 64±10 (0.035), 1.000, 0.041, 0.040
- NE, nmol/L: 1.1±0.7, 1.6±1.1, 0.8±0.2 (0.106)
- EPI, nmol/L: 0.09±0.06, 0.19±0.2, 0.08±0.04 (0.007), 1.000, 0.008, 0.009
- DHPG/NE: 7.6±2.9, 5.7±2.3, 8.0±1.8 (0.655)

**Standing**
- HR, bpm: 120±24, 114±30, 85±19 (<0.001), <0.001, 0.071, 1.000
- SBP, mm Hg: 107±23, 128±26, 98±17 (0.168)
- DBP, mm Hg: 72±14, 79±12, 67±13 (0.619)
- NE, nmol/L: 4.0±2.7, 5.3±3.1, 2.3±0.7 (0.022), 0.084, 0.038, 0.471
- EPI, nmol/L: 0.3±0.4, 0.9±1.6, 0.4±0.5 (0.018), 1.000, 0.030, 0.016
- DHPG/NE: 3.1±1.1, 2.3±1.1, 3.9±1.8 (0.138)

**Change from supine to standing**
- HR, bpm: 48±23, 38±14, 13±23 (<0.001), <0.001, 0.088, 0.825
- SBP, mm Hg: 0.1±23, 6±22, −3±9 (0.917)
- DBP, mm Hg: 6±13, −2±11, 3±12 (0.062)
- NE, nmol/L: 2.8±2.3, 3.5±2.8, 1.6±0.7 (0.061)
- EPI, nmol/L: 0.2±0.4, 0.8±1.5, 0.2±0.3 (0.018), 1.000, 0.022, 0.019

Analysis of variance (ANOVA) was used to determine the P value for the overall difference between the 3 groups after adjusting for age and BMI. P<0.05 was considered significant. Post-hoc Bonferroni testing was performed to adjust for multiple comparisons for the pair-wise comparisons, with a threshold P value of <0.017. Data are presented as mean±standard deviation. ANOVA indicates analysis of variance; DBP, diastolic blood pressure; DHPG, dihydroxyphenylglycine; EPI, epinephrine; HC, healthy control; HR, heart rate; IST, inappropriate sinus tachycardia; NE, norepinephrine; POTS, postural tachycardia syndrome; SBP, systolic blood pressure.

(0.19±0.2 nmol/L [35±42 pg/mL]) and this was significantly greater than HC subjects (0.08±0.04 nmol/L [14±8 pg/mL], P=0.008) and POTS patients (0.09±0.06 nmol/L [18±11 pg/mL], P=0.009). Upon standing, plasma NE was highest in IST patients (5.3±3.1 nmol [902±525 pg/mL]) and was significantly greater than HC subjects (2.3±0.7 nmol/L [393±122 pg/mL], P=0.038) but not with POTS (4.0±2.7 nmol/L [675±455 pg/mL], P=0.471). The standing EPI level showed a similar trend, highest among IST patients (0.9±1.6 nmol/L [158±298 pg/mL]) than HC 0.4±0.5 nmol/L [66±88 pg/mL], P=0.030 and POTS 0.3±0.4 nmol/L [61±73 pg/mL], P=0.016.

**Intrinsic heart rate (IHR)**

The IHR (primary endpoint) was not different among the 3 groups (ANOVA P=0.237, IST: 108±13 bpm, POTS: 108±11 bpm, HC: 106±12 bpm) (Table 2; Figure 2A).

**Sympathetic tone contribution to IHR (SYM)**

Patients with IST showed a larger HR reduction after sympathetic blockade with propranolol when compared with POTS patients (31±13 bpm versus 12±7 bpm, P<0.001) and HC subjects (31±13 bpm versus 8±4 bpm, P<0.001). There was no difference between POTS patients and HC subjects (P=0.160) (Table 2; Figure 2B).

**Parasympathetic contribution to IHR (PSYM)**

The vagal contribution to HR was assessed as the HR change in response to atropine. IST patients had a smaller parasympathetic contribution to HR than POTS patients (31±11 bpm...
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<th>Table 2. Intrinsic heart rate and Spectral Analysis</th>
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<td><strong>Intrinsic HR parameters</strong></td>
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<tr>
<td>Start HR, bpm</td>
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<td>SYM contribution to IHR, bpm</td>
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<td>PSYM contribution to IHR, bpm</td>
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<td>IHR, bpm</td>
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**Heart rate variability parameters**

|        | POTS | IST | HC | ANOVA   | POTS vs HC | IST vs HC | POTS vs IST |
|        | n=42 | n=8 | n=14 | P Value | P Value | P Value | P Value |
| HR, bpm | 74±11 | 100±19 | 65±8 | <0.001 | 0.055 | <0.001 | <0.001 |
| Respiratory rate (breath/min) (range) | 17±3 (12 to 28) | 18±3 (14 to 20) | 16±3 (11 to 22) | 0.417 |
| RRI, ms | 828±126 | 619±119 | 933±113 | <0.001 |
| pNN50, % | 17.1±17.5 | 5.02±9.7 | 36.5±25.5 | 0.006 |
| LF RRI, ms² | 891±786 | 416±466 | 1144±1093 | 0.547 |
| HF RRI, ms² | 595±777 | 181±284 | 2147±3688 | 0.030 |

**Blood pressure variability & baroreceptor sensitivity**

|        | POTS | IST | HC | ANOVA   | POTS vs HC | IST vs HC | POTS vs IST |
|        | n=42 | n=8 | n=14 | P Value | P Value | P Value | P Value |
| LF SBP, mm Hg² | 8.7±9.1 | 22.4±28.3 | 6.7±5.4 | 0.001 | 1.000 | 0.002 | 0.002 |
| Baroreceptor sensitivity, mm Hg/ms | 9.5±5.7 | 4.5±3.5 | 12.5±7.6 | 0.104 |

Analysis of variance (ANOVA) was used to determine the P value for the overall difference between the 3 groups after adjusting for age and BMI. P<0.05 was considered significant. Post-hoc Bonferroni testing was performed to adjust for multiple comparisons for the pair-wise comparisons, with a threshold P value of <0.017. Values are presented in mean ± standard deviation. ANOVA indicates analysis of variance; HC, healthy control; HF, high frequency; HR, heart rate; IHR, intrinsic heart rate; IST, inappropriate sinus tachycardia; LF, low frequency; POTS, postural tachycardia syndrome; PSYM, parasympathetic; RRI, RR interval; SBP, systolic blood pressure; SYM, sympathetic.

versus 46±11 bpm, unadjusted P=0.003) and HC subjects (31±11 bpm versus 48±11 bpm, unadjusted P=0.002), but these differences were no longer significant after adjusting for age and BMI (ANOVA, P=0.108) (Table 2; Figure 2C).

Mean respiratory rates were not different among the 3 groups (IST: 18±2 breaths/min versus POTS: 17±3 breaths/min versus HC: 16±3 breaths/min; ANOVA P=0.435). All but 1 POTS patient (at 28 breaths/min), and all of the IST patients had respiratory rates <24 breaths/min.

**Heart rate variability and Blood pressure variability**

In the time-domain, pNN50 (a marker of cardiovagal tone) was significantly reduced in both IST patients (P=0.042) and POTS patients (P=0.008) compared with HC subjects (Table 2).

The RRI-HF variability power spectrum component, also a marker of parasympathetic tone, was reduced in POTS patients compared with HC subjects (595±777 ms² versus 2147±3688 ms², P=0.034). The absolute value for RRI-HF was even lower in IST patients (181±284 ms²), but this did not achieve statistical significance when compared with HC (P=0.170). There was no difference between IST and POTS (P=1.000; Figure 3A).

The SBP-LF power spectrum component, a marker of sympathetic tone, was highest among the IST patients (22.4±28.3 mm Hg) when compared with either POTS (8.7±9.1, P=0.002) or HC subjects (6.7±5.4 mm Hg, P=0.002). There was no difference between POTS and HC (P=1.000; Figure 3B).

Mean cardiovagal baroreceptor sensitivity gain was lowest among IST patients (4.5±3.5 mm Hg/ms) that was significant when compared with HC (12.5±7.6, P=mm Hg/ms P=0.015) but not with POTS (9.5±5.7 mm Hg/ms, P=0.107). This significant difference was lost after adjusting for age and BMI. (ANOVA P=0.104).

**Discussion**

The present study provides evidence that suggests a stronger autonomic influence in the pathophysiology of IST than POTS, without significantly abnormal sinus node automaticity. This is supported by 2 main new findings (1) IHR is not different between patients with POTS and IST and HC subjects, and (2) patients with IST have more sympathetic tone and less parasympathetic tone than POTS patients or HC subjects. The
pathophysiology of IST remains incompletely understood, and is most likely multifactorial in nature as suggested by other researchers.3,4 Our knowledge of this syndrome, continues to evolve since its first description by Bauernfeind and colleagues over 3 decades ago.5

The natural history of IST is not well defined but symptoms are chronic and debilitating, with the cardiac prognosis considered mostly benign,6 although tachycardia-induced cardiomyopathy has been reported in a few patients.16,17 Understanding the physiology underlying this disorder remains of paramount importance in establishing effective treatments and providing relief to these patients. The management of IST remains controversial, with radiofrequency sinus node modification being a major treatment approach.3,18–20 If IST and POTS share similarities in their pathophysiology with increased sympathetic tone, then it is possible that patients with POTS and IST may benefit from treatment approaches targeting sympathetic blockade.

**Sinus Rate Regulation**

The primary pacemaker of the heart is the sinoatrial (SA) node, which is under the control of several mechanisms involving ion channel distribution under the influence of the autonomic nervous system.21 The autonomic nervous system continuously regulates the sinus rate closely.22 Stimulation of adrenergic receptors increases \(I_{Ca,L}\) and the \(I_f\) channel.
currents and increases HR, while cholinergic stimulation decreases the $I_{Ca,L}$ and $I_f$ channel currents and decreases HR. Our study found that the sympathetic nervous system contribution to IHR was exaggerated in both IST and POTS patients. Further, IST patients had exaggerated sympathetic tone and a trend to less parasympathetic tone than POTS patients (Figure 4). This exaggerated sympathetic tone may reflect an increase in circulating anti-adrenergic receptor antibodies previously reported. Of note, we were able to show this significant difference even with only a small number of IST patients, suggesting a strong role for autonomic perturbations in its pathophysiology.

Intrinsic Heart Rate (IHR) IST Patients

The IHR test evaluates automaticity of the sinus node after pharmacologic denervation. The peak HR measured during combined pharmacologic autonomic blockade reflects intrinsic sinus node function. Morillo et al observed an increase in IHR among patients with IST. In this and other IST studies, patients with POTS may have been included in the IST group. The present study clearly and distinctly defined IST and POTS. This study showed no significant differences in intrinsic HR between these 2 disorders and HC subjects, suggesting that abnormal sinus node automaticity does not play an important pathophysiological role in IST or POTS.

Clinical Implications

The treatment of IST and POTS remains challenging due to a limited understanding of their pathophysiology. The practice of radiofrequency sinus node modification and ablation continues in a subgroup of patients despite limited evidence of its utility. Unfortunately, many of these patients remain symptomatic even with lower heart rates. Ivabradine, a pharmacological inhibitor of the sinus node $I_f$ current, has been shown to improve both HR and symptoms in IST patients, and may prove beneficial in patients with POTS.

Our study confirms the presence of abnormal autonomic modulation in IST, with excess sympathetic tone and reduced cardiovagal tone. This appears similar to the autonomic dysfunction in POTS. In view of these findings, it is likely that pharmacologic therapy with an adrenergic antagonist such as propranolol, which is used to treat POTS, may be of clinical benefit in IST patients.

Study Limitations

The main limitation of this study is the small sample of patients with IST. Despite the sample size, we were still able to show significantly increased sympathetic tone among IST patients, suggesting a large and important effect. The effect was sustained even after adjusting for age and BMI in the analysis. We selected IST patients based upon their meeting prespecified HR criteria. It is possible that patients who undergo catheter ablation may represent a sicker or different subgroup of patients with IST.

Conclusions

Patients with both IST and POTS appear to have abnormal autonomic modulation, with elevated sympathetic tone and diminished parasympathetic tone. This is more marked in IST patients than POTS patients. IST patients do not have increased sinus node automaticity (as reflected by the intrinsic HR). These data suggest that the treatment of IST and POTS should focus on sympatholysis, rather than procedures such as sinus node modification, reserving sinus node modification with catheter ablation for patients who continue to have debilitating symptoms after failure of adequate beta-blockade and possibly ivabradine.

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Disclosures

None.
References


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