Mechanism of ‘Inappropriate’ Sinus Tachycardia
Role of Sympathovagal Balance
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Background “Inappropriate” sinus tachycardia (IST) is an uncommon and poorly defined atrial tachycardia characterized by inappropriate tachycardia and exaggerated acceleration of heart rate with “normal” P wave. The mechanism of this tachycardia is unknown. The purpose of the present study was to determine the role of autonomic balance in the genesis of IST.

Methods and Results Six female patients aged 23 to 38 years with IST and 10 age- and sex-matched control subjects were assessed with the following autonomic function tests: (1) sympathovagal balance to the sinus node assessed by calculating the LF/HF (low frequency/high frequency) ratio using power spectral analysis both in the supine position and after 10 minutes of head-up tilt to 60°, (2) cardiovagal reflex assessed by cold face test (CFT), (3) β-adrenergic sensitivity as determined by calculating isoproterenol dose-response curves and isoproterenol chronotropic dose 25 (CD25), and (4) intrinsic heart rate (IHR) assessed after autonomic blockade with atropine 0.04 mg/kg and propranolol 0.2 mg/kg administered as an intravenous bolus. No significant differences in the LF/HF ratio both in the supine position (2.8±0.3 versus 2.6±0.4) and during upright tilt (8.7±1.3 versus 8.5±0.5) were observed between control subjects and IST patients. Cardiovagal response to CFT was markedly depressed in all patients (6.3% IST patients versus 24.2% control subjects, P < .001). β-Adrenergic hypersensitivity to isoproterenol was noted in all patients (mean CD25, 0.29±0.10 μg IST patients versus 1.27±0.4 μg control subjects; P < .001), and high IHR was noted in all cases. The patients were treated with high doses of β-blockers with adequate short-term control. Radiofrequency catheter ablation of the sinus node area was performed in one drug-refractory patient.

Conclusions These findings suggest that the mechanism leading to IST is related to a primary sinus node abnormality characterized by a high IHR, depressed efferent cardiovagal reflex, and β-adrenergic hypersensitivity. (Circulation. 1994; 90:873-877.)

Key Words • tachycardia • autonomic function • sinus node

Inappropriate sinus tachycardia (IST; nonparoxysmal sinus tachycardia, permanent sinus tachycardia) is an atrial tachycardia characterized by inappropriate tachycardia and exaggerated acceleration of heart rate during physiological stresses. The P wave morphology suggests origin in or very close to the sinus node.1-4 The mechanism leading to an exaggerated response of the sinus node to minimal physiological stress is incompletely understood. It is not clear whether the abnormality is an abnormal sinus node (or atrial pacemaker) or abnormal autonomic function with a normal sinus node. This study investigated the autonomic balance of the sinus node in 6 consecutive patients with IST.

Methods

Study Population
The study population consisted of 6 female patients aged 23 to 38 years with a history of tachycardia for a period of 3 or more months and 10 female control subjects aged 22 to 39 years. IST was defined by the following criteria: (1) atrial rate of ≥100 beats per minute at rest or triggered by minimal physiological stress, (2) “normal” P wave axis and morphology during tachycardia documented electrocardiographically, and (3) absence of orthostatic hypotension, diabetes mellitus, hyperthyroidism, or drug abuse. Verbal and written informed consent was obtained in all patients.

Clinical and Laboratory Examinations
All patients had a physical and neurological examination, a 12-lead ECG, ambulatory ECG monitoring for 24 to 48 hours, and a two-dimensional echocardiogram. Thyroid function and glucose levels were assessed in all patients. Exercise stress test was assessed in 4 patients.

Autonomic Function Tests
Subjects were studied in the postabsorptive state. All studies were performed at 8:30 AM. An intravenous line was inserted, and 5% dextrose in normal saline was started at a rate of 20 mL/hr. Continuous noninvasive assessment of blood pressure (Finapress, Ohmeda 2300) and ECG limb leads I, II, and III were recorded on a Graphix Thermal Array Corder (WR 3600). Two ECG leads were continuously recorded with a tape recorder (Zymed Tritrak 1100-5) for further analysis.

Sympathovagal Balance
Subjects were allowed 15 minutes in the supine position for stabilization. Sympathovagal balance in the supine position and during orthostatic stress was assessed by power spectral analysis of heart rate variability obtained from the tape-recorded ECG.5-10 Heart rate variability was assessed after 10 minutes in the supine position and after 10 minutes of upright
head-up tilt on an electronically driven table with footboard support to 60°. All tapes were digitally processed and manually scanned with a Zymed 1210 Holter system. Power spectral density was calculated by a fast Fourier transform algorithm producing a 512-point spectrum for the 0.01- to 1.0-Hz frequency band. Low-frequency (LF) power (0.04 to 0.15 Hz) and high-frequency (HF) power (0.15 to 0.5 Hz) were obtained, and the sympathovagal balance expressed as the LF/HF ratio was calculated.5-10 Ten age-matched (mean, 29±6 years), sex-matched healthy volunteers from our laboratory were used as control subjects.11

Cold Face Test

The cardiovagal reflex was evaluated by exploring the trigeminal-vagal response both in the study population as well as in the 10 control subjects. Bilateral cold pads (0°C) were applied over the ophthalmic branches of the trigeminal nerve for a period of 1 minute.13-14 Baseline heart rate was derived from the mean of the values recorded in the 2 minutes preceding the cold face test (CFT). The minimum heart rate during CFT was detected, and mean heart rate was calculated from 10 sinus beats (5 beats preceding and 5 beats after minimum heart rate). The magnitude of heart rate change is expressed as the percent reduction from mean baseline heart rate. The methodology and validation of this test has been previously reported by our laboratory and by others.12-15

Isoproterenol Sensitivity Test

β-Adrenergic sensitivity was assessed by calculating isoproterenol dose-response curves in each patient.16 Isoproterenol hydrochloride was given as a rapid 1-mL bolus. The initial dose used was always 0.25 μg and was thereafter doubled (0.5, 1.0, 2.0, and 4.0 μg) until an increase in heart rate of 35 beats per minute or a peak heart rate of 150 beats per minute was achieved. Ten minutes was allowed between each injection to allow return to baseline heart rate. The peak heart rate before and after each injection was calculated from the three shortest RR intervals of the ECG. Isoproterenol chronotropic dose 25 (CD25) was defined as the dose necessary to achieve an increase in heart rate of 25 beats per minute. The 10 control subjects underwent the same protocol, and data were pooled with that acquired from 5 healthy subjects previously reported.16

Intrinsic Heart Rate

Intrinsic heart rate (IHR) was assessed after bolus injection of propranolol 0.2 mg/kg and atropine 0.04 mg/kg.17 The IHR observed was compared with the predicted value for each patient by the formula IHR = 118.1 - (0.57×age).17,18

Statistical Analysis

Data are presented as mean±SD. Comparison between groups was assessed by one-way ANOVA. Continuous variables were assessed by a two-tailed unpaired t test. Differences were considered significant if the null hypothesis was rejected at the level of P<.05.

Results

All patients had normal physical and neurological examination. Thyroid function, glucose levels, and two-dimensional echocardiogram were normal in all patients. Heart rate response to low-grade exercise was markedly enhanced in the 4 patients assessed by exercise test, achieving a heart rate between 130 and 160 beats per minute (stage I Bruce protocol). Heart rates during tachycardia documented by Holter recordings in all patients varied between 140 and 185 beats per minute (Fig 1). Heart rate ranges during Holter recordings and heart rate response to head-up tilt and exercise treadmill are summarized in Table 1.

Autonomic Function Tests

Results of the autonomic function tests are shown in Table 2.

Sympathovagal Balance

Sympathovagal balance to the sinus node expressed as the LF/HF ratio in the supine position (2.8±0.3 versus 2.6±0.4) and after 10 minutes of upright tilt (8.7±1.3 versus 8.5±0.8) did not differ between control subjects and IST patients (P=NS).

Cold Face Test

The cardiovagal reflex was markedly abnormal in all patients (Table 2). Minor changes in percent heart rate were achieved: 6.3±2.1% in IST patients versus 24±8.5% in control subjects (P<.001), suggesting an impaired response of the sinus node to vagal stimulation.

Isoproterenol Sensitivity Test

β-Adrenergic hypersensitivity was observed in all patients. Dose-response curves showed an increased sensitivity to incremental dosages of isoproterenol (Fig 2). Similarly, CD25 was distinctively lower in IST patients than the mean dose required to achieve the same
TABLE 1. Heart Rate Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Awk HR</th>
<th>Asl HR</th>
<th>HR Rng (24 h)</th>
<th>HRS, bpm</th>
<th>HRT (1 min)</th>
<th>HRT (5 min)</th>
<th>BPS, mm Hg</th>
<th>BPT, mm Hg</th>
<th>ET-HR (1 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83</td>
<td>74</td>
<td>55-152</td>
<td>78</td>
<td>120</td>
<td>134</td>
<td>110/70</td>
<td>115/75</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>68</td>
<td>58-140</td>
<td>68</td>
<td>130</td>
<td>140</td>
<td>120/85</td>
<td>125/88</td>
<td>125</td>
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<td>78</td>
<td>70</td>
<td>62-145</td>
<td>78</td>
<td>110</td>
<td>118</td>
<td>103/68</td>
<td>110/75</td>
<td>118</td>
</tr>
<tr>
<td>4</td>
<td>84</td>
<td>76</td>
<td>58-168</td>
<td>88</td>
<td>145</td>
<td>154</td>
<td>108/62</td>
<td>115/72</td>
<td>128</td>
</tr>
<tr>
<td>5</td>
<td>94</td>
<td>88</td>
<td>70-155</td>
<td>96</td>
<td>140</td>
<td>155</td>
<td>105/72</td>
<td>110/78</td>
<td>134</td>
</tr>
<tr>
<td>6</td>
<td>105</td>
<td>94</td>
<td>88-185</td>
<td>106</td>
<td>152</td>
<td>164</td>
<td>105/80</td>
<td>110/88</td>
<td>NA</td>
</tr>
</tbody>
</table>

Asl indicates asleep; Av, average; Awk, awake; bpm, beats per minute; BPS, blood pressure supine; BPT, blood pressure tilt; ET-HR, exercise treadmill heart rate; HR, heart rate; HRS, heart rate supine; HRT, heart rate tilt; NA, not available; and Rng, range.

end point in healthy control subjects (0.29±0.10 µg in IST patients versus 1.27±0.4 µg in control subjects, P<.001).

Intrinsic Heart Rate

IHR observed was remarkably higher (±2 SD) than predicted in all patients (Fig 3). Despite complete autonomic denervation, response of the sinus node was significantly increased.

Therapy

All patients received propranolol (160 to 320 mg) or atenolol (100 to 200 mg) daily. Patients were followed for a period of 4 to 8 months. Only one patient (patient 6) persisted with IST. At electrophysiological study, sinus tachycardia at a rate of 145 beats per minute was induced by an isoproterenol infusion at a rate of 0.5 µg/min. A high to low atrial activation pattern originating in the area of the sinus node was documented. Earliest site of activation was mapped to the high posterolateral right atrium below the superior vena cava and right atrial junction. Atrial activation at this site preceded the surface P wave by 25 milliseconds, with the latest activation site recorded in the low lateral right atrium. Tachycardia was neither induced nor terminated by critically timed atrial extrastimuli or atrial pacing. Twenty radiofrequency energy applications were delivered to this area at a power level of 15 to 25 W, with a duration ranging between 30 and 60 seconds.

Radiofrequency energy application at this site was associated with transient sinoatrial exit block and junctional rhythm at the end of the procedure. Normal sinus rhythm was restored 48 hours after the procedure. After ablation, autonomic function tests demonstrated a normal β-adrenergic response and an IHR of 103 beats per minute compared with 140 beats per minute before ablation. Power spectral analysis of heart rate variability in the supine position and during 60° tilt remained unchanged. In contrast, CFT showed a tendency toward normalization (5.1% before ablation versus 12% after ablation). A 48-hour Holter monitor assessed 3 months after ablation documented resting heart rates ranging between 38 and 128 beats per minute. The patient has remained free of tachycardia for over 10 months.

Discussion

IST is a rare cause of supraventricular tachycardia that may be associated with incapacitating symptoms requiring aggressive therapy.1-4 IST may be related to one or a combination of the following mechanisms: (1) ectopic atrial focus in the sinus node region, (2) normal sinus node with increased sympathetic tone or failure to respond to vagal stimulation, or (3) intrinsic abnormality of the sinus node. The present study explored the role of autonomic balance in 6 patients meeting clinical criteria for IST.1-4

Sympathovagal balance at rest and after upright tilt was evaluated by power spectral analysis of heart rate

TABLE 2. Autonomic Function Tests

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>LF/HF S:T</th>
<th>Pr</th>
<th>Obs</th>
<th>NR, bpm</th>
<th>CFT, %HR</th>
<th>CD25, µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>2.6:8.1</td>
<td>100</td>
<td>125</td>
<td>84-116</td>
<td>2.4</td>
<td>0.50</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>2.4:8.2</td>
<td>96</td>
<td>122</td>
<td>80-112</td>
<td>8.8</td>
<td>0.25</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>2.6:8.3</td>
<td>104</td>
<td>134</td>
<td>88-120</td>
<td>8.5</td>
<td>0.25</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>2.8:8.5</td>
<td>101</td>
<td>125</td>
<td>85-117</td>
<td>7.2</td>
<td>0.25</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>3.2:9.8</td>
<td>103</td>
<td>130</td>
<td>87-119</td>
<td>5.8</td>
<td>0.25</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>2.2:8.4</td>
<td>104</td>
<td>140</td>
<td>88-120</td>
<td>5.1</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Mean 27±5 2.6:8.5 101 129 . . . 6.3±2.1 0.29±0.1

Control subjects 29±6 2.8:8.7 . . . . . . 24.2±8.5 1.27±0.4

bpm indicates beats per minute; CD25, chronotropic dose 25; CFT, cold face test; HR, heart rate; IHR, intrinsic heart rate; LF/HF, low-frequency/high-frequency ratio; NR, normal heart rate range; Obs, observed heart rate; Pr, predicted heart rate; S, supine position; and T, upright tilt.
variability. Previous reports have established the reliability of this method in assessing the autonomic balance to the sinus node.5-11 Sympathovagal balance, assessed by the LF/HF ratio both in the supine position and during upright tilt, was within normal ranges. These findings indicate that altered sympathovagal balance to the sinus node is not a major factor in the genesis of this tachycardia.

The sinus node response to β-adrenergic stimulation was markedly enhanced. Similarly, a markedly depressed cardiovagal response was noted in all patients. This finding suggests that the response to efferent vagal stimulation of the sinus node is impaired or that the integrity of the cardiovagal reflex is altered. The latter explanation appears to be unlikely given the fact that we observed normal sympathovagal balance both in the supine and upright positions, suggesting that the integrity of the baroreceptor reflex response is preserved. Impaired response of the sinus node to efferent vagal stimulation may enhance β-adrenergic sensitivity leading to increased sinus node response.

A striking increase in IHR was observed in all patients. Heart rate in the pharmacologically denervated heart reflects the intrinsic sinus node rate.17,18 This suggests that the mechanism leading to tachycardia in our patients was related to a primary sinus node abnormality resulting in a high IHR. Enhanced sinus node automaticity was potentiated by β-adrenergic hypersensitivity and impaired response to vagal stimulation.

Bauernfeind et al19 described the effects of autonomic modulation in 7 patients with "idiopathic chronic sinus tachycardia." The mechanism of increased sinus node response was related to alterations in either sympathetic (2 patients) or vagal control of resting heart rate (5 patients) associated with abnormalities of IHR in some patients. These findings agree with our study. However, we were unable to demonstrate an alteration in resting control of heart rate. This disparity may be attributed to several alternative explanations. Bauernfeind's patients had a history of chronic sinus tachycardia with increased resting heart rate documented in all cases in contrast to only one patient in our series. The duration of symptoms was also distinctively different, with a mean duration of 6 years in Bauernfeind's series compared with 10 months in our series. Interestingly, the only patient of our series with increased resting heart rate reported a symptom duration of 3 years. It is therefore possible that the increased resting heart rate reported in Bauernfeind's series is related to the chronicity of symptoms, representing one end of the spectrum of IST. On the other hand, this discrepancy may be related to the method chosen to determine autonomic balance of heart rate at rest. Bauernfeind et al determined changes in heart rate to pharmacological interventions (atropine/propranolol), and this may not reflect sympathovagal balance to the sinus node.19 Beat-to-beat variability of heart rate assessed by power spectral analysis provides an accurate estimate of the sympathovagal balance of the resting heart rate as well as during orthostatic stress.5-11

Schondorf and Low20 and Fouad et al21 have recently described a remarkably similar disorder predominantly observed in young women with otherwise normal hearts. Postural orthostatic tachycardia syndrome is characterized by a normal resting heart rate and exaggerated postural sinus tachycardia of 40 to 60 beats per minute elicited by upright tilt in the absence of orthostatic hypotension.20,21 Increased β-adrenergic sensitivity comparable to that reported in this series has also been reported.21 Similarly, respiratory sinus arrhythmia, which is an index of resting vagal efferent traffic, was normal in 16 patients with postural orthostatic hypotension.20 The striking clinical and functional similarities shared between IST, postural orthostatic tachycardia, and chronic nonparoxysmal sinus tachycardia syndromes raise the possibility that these disorders represent the spectrum of a homogeneous disease process. However, the possibility that these syndromes represent a heterogeneous disorder cannot be ruled out.

Patients with IST are usually controlled by medical therapy with β-blockers. However, some may develop intolerable adverse effects or may be refractory to

Fig 2. Isoproterenol dose-response curves for each patient are shown. Increased sensitivity to each individual dose was noted when compared with control subjects (broken line, n=15). BPM indicates beats per minute; HR, heart rate.

Fig 3. Line plot: Intrinsic heart rate. Predicted (Pre) and observed (Obs) intrinsic heart rates (HR) in each patient are shown. The predicted heart rate range and upper heart rate limit are indicated by the standard deviation (±2 SD) bar and dashed line, respectively, for all the patients. Intrinsic heart rate was increased in all patients. BPM indicates beats per minute.
medical therapy. Nonpharmacological therapy includes subtotal right atrial surgical exclusion. More recently, mechanical or chemical occlusion of the sinus node artery has been reported. Radiofrequency catheter ablation of the sinus node area was performed in one patient refractory to medical therapy. Junctional rhythm was observed for a period of 48 hours, and sinus rhythm was restored thereafter. This patient has remained free of symptoms despite recovering sinus rhythm. The explanation for this phenomenon is unclear. It is possible that ablation of a critical number of pacemaker cells involved in the development and maintenance of sinus tachycardia was achieved. Recovery of sinus rhythm after 48 hours of junctional rhythm may be due to resolution of edema induced by radiofrequency energy. Recently, modification of sinus node function by graded epicardial laser radiation has been reported in a dog model resembling IST. Widespread distribution of the atrial pacemaker complex has been documented in dogs and humans. It is possible that restoration of normal sinus rhythm in our case may be due to shifting of the atrial pacemaker complex to an alternate area in the vicinity of the sinus node.

Study Limitations

Electrophysiological studies were not performed in all patients. Nonetheless, all patients fulfilled the clinical criteria for IST, and electrophysiological study has not been shown to be helpful in elucidating the mechanism of this arrhythmia in previous studies. Furthermore, the response to autonomic tests would be unlikely in subjects with sinus node reentry or atrial tachycardia. However, it is impossible to rule out the presence of an abnormal ectopic atrial focus in the vicinity of the sinus node.

These data suggest that the mechanism leading to IST is related to a primary sinus node abnormality resulting in high IHR, potentiated by a depressed cardiovascular reflex and β-adrenergic hypersensitivity.

Acknowledgments

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References
