Prevalence, characteristics and natural course of inappropriate sinus tachycardia

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**Abstract**

Aims To study the prevalence, characteristics and natural course of inappropriate sinus tachycardia (IST).

Methods and results The prevalence and characteristics of IST were evaluated in a random sample of 604 middle-aged subjects. Seven of the subjects (1.16%) fulfilled the contemporary diagnostic criteria of IST. The systolic (147 ± 11 mmHg vs. 130 ± 13 mmHg, P < 0.001) and diastolic ambulatory blood pressures (92 ± 7 mmHg vs. 81 ± 8 mmHg, P < 0.001) were higher among the subjects with IST than among the controls. The other laboratory, echocardiographic and personality measurements, with the exception of the hostility score (10 ± 2 vs. 8 ± 3, P < 0.001), revealed no differences between the groups. The natural course and prognosis of the disorder was assessed among the subjects fulfilling the IST criteria and nine previously diagnosed IST patients. During a mean follow-up of 6.0 ± 2.4 years, none of the subjects developed any clinical or echocardiographic evidence of structural heart disease despite ongoing palpitations, and there was no significant reduction in the 24-h average HR (94 ± 2 bpm vs. 89 ± 8 bpm, P = 0.204).

Conclusion The prevalence of IST in a middle-aged population was higher than previously assumed. Despite the chronic nature of the disorder, the prognosis of IST was benign. The causal relationship between IST and hypertension and/or hostile personality type remains speculative.

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Introduction

Inappropriate sinus tachycardia (IST) is a nonparoxysmal tachyarrhythmia characterized by an increased resting heart rate (HR) and/or an exaggerated HR response to minimal exertion or a change in body posture [1]. HR is constantly above the physiological range with no appropriate relation to metabolic or physiological demands [2]. Thus, IST is neither a response to a pathological process such as heart failure, hyperthyroidism, hypovolaemia, anaemia, infection, diabetic autonomic dysfunction, phaeochromocytoma, orthostatic hypotension or reaction to the drugs accelerating HR nor a result of physical deconditioning [1]. Patients with IST have a wide spectrum of clinical presentations ranging from asymptomatic or minimally symptomatic sinus tachycardia noted during a routine physical examination to incapacitating incessant tachycardia.

IST was initially thought to be an uncommon disorder that could lead to total disability, but during recent years, it has been diagnosed with increasing frequency due to improved diagnostic techniques and more specific clinical characterization [3]. However, in spite of the extensive use of ambulatory ECG recordings in the diagnostic and prognostic evaluation of arrhythmia patients, there are no earlier reports on the prevalence of IST in the general population. Likewise, the characteristics of the patients and the natural course of IST in patients without specific treatment for the disorder are largely unknown. Therefore, this study was designed to: (1) evaluate the prevalence and characteristics of subjects fulfilling the diagnostic criteria of IST in a random sample of middle-aged subjects, and (2) assess the natural course and prognosis of IST during long-term follow-up.

Methods

Patient population

The prevalence of IST was assessed in a randomly assigned population of 604 middle-aged subjects (335 males). The population consisted of 290 hypertensive and 314 normotensive middle-aged subjects, who were originally enrolled for the Oulu Project Elucidating Risk of Atherosclerosis (OPERA) study. The OPERA is a population-based, epidemiological case–control study addressing the risk factors and disease end-points of cardiovascular diseases [4]. The entire OPERA study population consisted of 1200 subjects aged between 40 and 59 years at the time of enrolment. The subjects with hypertension (300 men and 300 women) were randomly selected by age stratification (15 male and 15 female subjects for each year of birth) from the National Social Insurance Institute register for the reimbursement of hypertension medication. The normotensive age- and sex-matched controls were obtained from the social insurance register covering the whole population of the city of Oulu [5]. Antihypertensive medication included agents with negative chronotropic action (e.g., betablocking agents) in 149 patients.

In the current analysis all subjects with abnormal P wave morphology or axis in 12-lead ECG, structural heart disease, diabetes or any pathological condition (e.g., anaemia, hypovolaemia, thyroid disease) or medication (e.g., thyroid hormone substitution, antiasthmatic drugs) known to accelerate HR were excluded. Furthermore, because several investigators have reported temporary elevation of sinus rate after catheter ablation [6–10], all patients with prior ablation of atrioventricular nodal reentrant or other supraventricular tachyarrhythmias were excluded [8].

During the years 1996–1998, nine of the patients referred to Oulu University Hospital for evaluation of symptomatic supraventricular tachyarrhythmias were diagnosed with IST. For the evaluation of the natural course and prognosis of IST, these nine patients were grouped together with the seven subjects from the random population who fulfilled the diagnostic criteria of IST. All subjects gave written informed consent, and the study protocols were approved by the local institutional ethics committee.

Definition of IST

According to the contemporary electrocardiographic criteria, IST is defined as a nonparoxysmal tachyarrhythmia with resting daytime heart rate higher than 100 bpm or an average heart rate higher than 90 bpm in 24-h ambulatory ECG recording with a similar P wave morphology and axis during normal sinus rhythm and tachycardia in a standard 12-lead ECG [3]. The syndrome is associated neither with structural heart disease nor with any secondary cause of sinus tachycardia. Here, only the random samples of middle-aged subjects who had both an average HR > 90 bpm during the ambulatory 24-h heart rate measurement and resting HR > 100 bpm in either a supine or a sitting position were considered to fulfil the criteria of IST.
**Measurement of heart rate**

In order to confirm the nonparoxysmal nature of the disorder and to avoid biases caused by temporary changes in sinus frequency, the HR in the random population was measured using three different methods on three separate days within one month: (1) Ambulatory 24-h HR was recorded using the SpaceLabs 90207 fully automatic oscillometric unit (SpaceLabs Inc., Redmond, New Jersey) during normal daily activities. HR and blood pressure were measured automatically every 15 min from 4:00 AM till midnight and every 20 min from midnight till 4:00 AM. (2) Ambulatory 45-min ECG was obtained in the morning (between 8 AM and 10 AM) using a Dynacord Holter Recorder (Model 420, DM Scientific, Irvine, CA, USA). Each subject was monitored for 15 min while quietly lying down and breathing normally, for 15 min in the sitting position and for 15 min during standardized quiet walking. (3) Standard 12-lead ECG was recorded after at least 15 min rest. Patients with hypertension continued their antihypertensive medication at the time of recordings.

In the symptomatic hospital patients, HR was measured from a 12-lead ECG recorded at rest and an ambulatory 24-h ECG recording with modified V1 and V5 lead placement during normal daily activities. All medications were discontinued at least four half-lives before the measurements. In addition to the non-invasive tests, four symptomatic inpatients underwent an invasive electrophysiological examination, but none of them was treated by radiofrequency catheter ablation.

**Heart rate variability**

The frequency domain measures of HR variability in the random population were analyzed using the methods recommended by the Task Force of the European Society of Cardiology [11]. Spectral power was quantified by fast Fourier transform analysis in two frequency bands 0.01–0.15 Hz (low frequency [LF]) and 0.15–0.40 Hz (high frequency [HF]) [12,13]. The LF and HF components during the 15 min period in supine and sitting positions and standardized walking were calculated as absolute units and LF/HF ratio was used as the index of sympatho-vagal balance.

**Other examinations**

All the subjects in the random population were interviewed by a physician, and a standardized health questionnaire of past medical history, smoking habits, alcohol consumption, physical activity and personality type was completed. Alcohol intake was converted into grams of absolute ethanol per week. Leisure-time physical activity was classified using a modification of the method described by Grimby [14]. Personality type was assessed by three different methods: Framingham type A behaviour pattern scale [15], Bortner’s short rating scale of behaviour pattern [16], and hostility scaling [17]. No systematic leisure-time physical activity testing or personality type scaling were conducted on the symptomatic inpatients with IST.

All patients with IST underwent a transthoracic echocardiographic examination with standard equipment and techniques. The measurements were obtained according to the guidelines of the American Society of Echocardiography [18]. Blood samples were drawn after an overnight fast to analyze the levels of haemoglobin, thyrotropin, glutamyl transferase and glucose. A 2-h oral glucose tolerance test (75 g) was used to identify latent diabetes in the random population.

**Follow-up of IST patients**

To assess the natural course and prognosis of IST, all available patient records were analyzed, and the clinical and echocardiographic examinations as well as the 12-lead ECG and 24-h ambulatory ECG were repeated 72 ± 29 months (range 36–133 months) after the initial examination. All medications that could affect HR were discontinued two days before follow-up visits. Patients with asthma medication were excluded from the follow-up.

**Statistical analysis**

The results are expressed as mean ± SD. Statistical analysis was performed using the SPSS for Windows version 10.1 software. The independent samples t-test was used to compare the two groups and the paired samples t-test to compare the HR and echocardiographic measurements between the baseline and control visits. The differences of frequencies between the class variables were tested by the Chi-square test and those between the non-normally distributed variables by the Mann–Whitney test. A value of \( P < 0.05 \) was considered to indicate statistical significance.
Results

Prevalence of IST

The distribution of the average 24-h HR in the random middle-aged population is described in Fig. 1. The distribution is clearly skewed to the right after a cutoff point of approximately 85–90 bpm. The average 24-h HR was over 90 bpm in 19 out of the 604 subjects (3.2%). Ten patients (1.7%) had HR > 100 bpm in a supine position and 15 patients (2.5%) in a sitting position, and 70 patients (11.6%) had HR > 100 bpm during walking. However, only seven of these subjects had both daytime HR > 100 bpm in a supine or sitting position and 24-h average HR > 90 bpm (95 ± 4 bpm), giving an overall prevalence of 1.16% for IST in the random middle-aged population.

Characteristics of the subjects with IST

The characteristics of the subjects fulfilling the diagnostic criteria of IST and the controls in the random middle-aged population are summarized in Table 1. The only demographic difference between the groups was personality type on the hostility scale (10 ± 2 vs. 8 ± 3, P < 0.001). In the random population, four subjects fulfilling the diagnostic criteria of IST were women (57%) and three were men. The mean age of the subjects was 47 ± 7 years. Five subjects (71%) had previously diagnosed hypertension, and two subjects (29%) were health care workers. The ambulatory systolic (147 ± 11 mmHg vs. 130 ± 13 mmHg, P < 0.001) and diastolic (92 ± 7 mmHg vs. 81 ± 8 mmHg, P < 0.001) blood pressures were significantly higher among those with IST. No significant differences were observed between the groups in the echocardiographic, laboratory and heart rate variability measurements, although there was a non-significant trend toward reduction of LF/HF ratio during walking compared with the supine position (Table 2).

In the symptomatic hospital population, the mean HR of the patients with IST was 110 ± 11 bpm (range 101–129 bpm) in the 12-lead ECG at rest and 94 ± 3 bpm (range 91–98 bpm) in the 24-h ECG recording. The mean age of the patients was 46 ± 7 years, and eight (89%) of them were female. Three patients had hypertension (33%), and one was a health care worker (11%). The results of the blood tests and M-mode and 2-D echocardiography were normal in all patients. When these patients were compared with those from the random sample who fulfilled the diagnostic criteria of IST, several parallel features were identified. There was no significant difference in the age (47 ± 7 vs. 46 ± 7 years) or the 24-h average HR (95 ± 4 bpm vs. 94 ± 36 bpm) between the random and hospital populations. Likewise, hypertension was a relatively common finding in both populations. However, in contrast to the random population, almost all the symptomatic hospital patients with IST were females (57% vs. 89%).

Natural course of IST

In the evaluation of the natural course and prognosis of IST, the subjects fulfilling the IST criteria in the random population (n = 7) and the symptomatic hospital patients (n = 9) were combined. All these patients were contacted by phone. Two subjects (one in each population) were excluded from further studies because they used sympathomimetic medication for asthma. Neither of them had any major cardiac symptoms. Two subjects in the random and one in the hospital population did not want to participate in the follow-up study. They all had some palpitations, but no other cardiac symptoms.

All the subjects (n = 11) who consented to attend the follow-up examinations, had symptoms of rapid heart rate during the control visit. In the random population, two subjects felt an increased heart rate during exercise, one had palpitations at rest, and one patient suffered from "strong heart beats". In the symptomatic hospital population, all patients had palpitations at rest or during minor exercise. There was no significant change in the HR
after a mean follow-up of 6.0 ± 2.4 years. The average heart rate in the 24-h ambulatory ECG recording was 94 ± 2 bpm (range 91–98 bpm) at the baseline examination and 89 ± 8 bpm (range 80–103 bpm, P = 0.204) at the follow-up visit (Fig. 2). Likewise, there were no significant differences in the resting HR measured from the 12-lead ECG between the baseline and the follow-up visit (104 ± 14 bpm vs. 98 ± 15 bpm, P = 0.068). However, despite the ongoing symptoms and the relatively high HR during the follow-up examination, only four of the 11 subjects still fulfilled the combined diagnostic criteria of IST, whereas the others’ average HR in the 24-h Holter recording had dropped below 90 bpm (Fig. 2).

The prognosis of IST was benign. All subjects were alive at follow-up, and none had symptoms or clinical findings of significant structural heart disease. There were no significant changes in the echocardiographic parameters between the baseline and follow-up examinations, although one subject in the random population had developed hypertension.

Discussion

This is the first study to describe the prevalence and characteristics of inappropriate sinus tachycardia (IST) in a random middle-aged population and to assess the natural course and prognosis of IST during long-term follow-up.

Prevalence of IST

The aim of the current study was to assess the prevalence of subjects fulfilling the contemporary electrocardiographic and clinical criteria of IST. Therefore, the diagnosis of the disorder was based on non-invasive measurements of HR by serial ECG and Holter recordings. Our results indicate that IST, defined as 24-h average HR > 90 bpm and HR > 100 bpm in a supine or sitting position, is a frequent finding among middle-aged subjects. The prevalence of IST (1.16%) exceeded that reported for the Wolff–Parkinson–White syndrome (0.15–0.31%), paroxysmal supraventricular tachycardia (0.23%) and ectopic atrial tachycardia (0.46%) [19–23]. In the random population, the distribution of 24-h average HR was clearly skewed towards the right. Thus, it is likely that the elevation of HR did not simply represent a continuum of the overall Gaussian distribution of sinus frequency in the general population.

The diagnosis of IST is difficult. It requires not only typical electrocardiographic findings but also careful exclusion of all reversible causes of sinus tachycardia [3,24]. Thus, it is obvious that
assessment of the actual prevalence of IST in a random population cannot be based on casual HR measurements. Here, all subjects with an abnormal P wave during tachycardia, structural heart disease, diabetes and any pathological condition or medication known to accelerate HR were excluded. In order to avoid biases caused by temporary changes in the sinus rate, the diagnosis of IST in the random population was based on three different HR measurements. Measurement of HR from casual 12-lead ECG significantly overestimated the prevalence of IST, and 24-h and 45-min ECG recordings under standard conditions also gave a much higher prevalence for IST than the use of combined diagnostic criteria. Furthermore, only patients with elevated HR both in supine and upright positions were included in the current study. If subjects with orthostatic intolerance (postural orthostatic tachycardia syndrome, POTS) [25] had been included, the prevalence of IST would have been even higher. These data question the specificity of the contemporary diagnostic criteria of IST and emphasize the importance of repeated ambulatory ECG recordings in the diagnosis of IST.

**Characteristics of subjects with IST**

The characteristics of the patients fulfilling the diagnostic criteria of IST have not previously been studied in a random population. According to the

| Table 2 | Haemodynamic and laboratory parameters in the random middle-aged population |
|-----------------|-----------------|-----------------|-----------------|
| **Heart rate (bpm)** | IST (n = 7) | Control (n = 597) | Significance |
| 12-lead ECG at rest | 87 ± 8 | 73 ± 13 | 0.005 |
| 24-h ambulatory recording | 95 ± 4 | 70 ± 10 | <0.001 |
| During a 15-min supine period | 94 ± 8 | 67 ± 10 | <0.001 |
| During a 15-min sitting period | 100 ± 8 | 71 ± 10 | <0.001 |
| During a 15-min walking period | 110 ± 4 | 83 ± 12 | <0.001 |
| **Heart rate variability** | | | |
| LF/HF ratio at rest | 2.03 ± 1.22 | 2.33 ± 1.45 | NS |
| LF/HF ratio on sitting | 1.99 ± 1.17 | 2.9 ± 2.27 | NS |
| LF/HF ratio on walking | 1.55 ± 1.45 | 2.47 ± 2.12 | NS |
| **Blood pressure (mmHg)** | | | |
| 24-h ambulatory systolic pressure | 147 ± 11 | 130 ± 13 | <0.01 |
| 24-h ambulatory diastolic pressure | 92 ± 7 | 81 ± 8 | <0.01 |
| **Echocardiographic measurements** | | | |
| Left atrial diameter (mm) | 40 ± 5 | 39 ± 5 | NS |
| Left ventricular diastolic diameter (mm) | 49 ± 5 | 52 ± 5 | NS |
| Fractional shortening (%) | 35 ± 6 | 35 ± 6 | NS |
| Left ventricular mass (g) | 175 ± 46 | 207 ± 62 | NS |
| **Laboratory measurements** | | | |
| Serum thyrotropin (mU/l) | 1.7 ± 0.8 | 2.1 ± 1.9 | NS |
| Serum haemoglobin (g/l) | 137 ± 15 | 143 ± 13 | NS |
| Fasting blood glucose (mmol/l) | 4.6 ± 0.4 | 4.4 ± 0.5 | NS |
| 2-h blood glucose (mmol/l) | 4.6 ± 1.1 | 5.4 ± 1.5 | NS |
| Total serum cholesterol (mmol/l) | 5.4 ± 0.97 | 5.7 ± 1.0 | NS |
| Serum triglycerides (mmol/l) | 1.1 ± 0.3 | 1.5 ± 0.9 | NS |

Abbreviations: IST = inappropriate sinus tachycardia, LF = low frequency and HF = high frequency domain in the spectral analysis of heart rate variability, respectively.
earlier reports, almost all highly symptomatic patients with IST have been women, many of them were hypertensive, and many have been health care workers \[6,24,26,27\]. The results of our study confirmed that elevated HR was more common among hypertensive than normotensive subjects. In the five series published earlier, about 90% of the patients with IST were females \[6,24,26,28\]. In the present study, no evident gender-related difference was seen in the random population, but most of the patients with IST in the symptomatic hospital population were women. The reasons for this difference are not clear, but it is possible that women with elevated HR may become more often symptomatic and/or seek more easily diagnostic examinations and treatment. Given the observation that there were no other differences in the patient characteristics, it is unlikely that the subjects fulfilling the diagnostic criteria of IST in the random sample and the symptomatic hospital population would have represented different diagnostic entities.

Besides the higher blood pressure among the subjects with IST, there were no other differences in the demographic characteristics, lifestyles, personality types, with the exception of hostility, laboratory values or echocardiographic parameters between the IST and control subjects. Thus, the elevation of HR could not be explained by abnormal glucose metabolism, obesity, higher thyroid activity or lower physical activity. Although IST may have some shared features with hypertension, a causal relationship between high blood pressure and elevated HR seems unlikely. The association between the hostility score and elevated HR remains speculative.

In some previous studies, high sinus rate and disabling symptoms such as palpitations, fatigue, lightheadedness and exercise intolerance have been related to orthostatic intolerance caused by mild autonomic dysfunction \[25\]. The characteristic feature in these patients is postural sinus tachycardia, i.e., the patients exhibit marked increase in HR after rising up from the supine position \[25\]. In the present study there were no differences in the response of HR to postural changes or standard walking between the IST and control subjects. Furthermore, no significant differences were observed in their sympatho-vagal balance (LF/HF ratio), assessed by spectral analysis of HR variability. Hence, altered autonomic input to the sinus node and postural changes appeared not to be a predominant cause of IST in this random population. These observations corroborate the elevation of HR in patients with IST being related to intrinsic enhancement rather than altered autonomic regulation of sinus node activity \[29\].

### Natural course of IST

There were only minor changes in the HR of the subjects with IST during a mean follow-up period of six years. Although some subjects no longer fulfilled the diagnostic criteria of IST, the average HR did not differ significantly between the baseline and control measurements. Most subjects complained of moderate symptoms of elevated HR at the control visit, but evident aggravation of the symptoms was rare.

It has been reported that nonparoxysmal supraventricular tachycardia may cause cardiomyopathy and impair the patient’s prognosis \[30\]. In the present study, none of the subjects with IST had any clinical or echocardiographic evidence of left ventricular dysfunction in the control examination. Furthermore, an extensive Medline search yielded only one case report in which chronic nonparoxysmal sinus tachycardia had caused severe left ventricular dysfunction \[31\]. In keeping with the above data and the findings of Lopera et al. \[32\] in elderly women, our observations indicate that, despite constantly elevated HR and persistent symptoms, the prognosis of IST is good.

### Limitations of the study

It is sometimes difficult to make a distinction between IST and other atrial tachyarrhythmias. Although no routine invasive electrophysiological testing was conducted, we feel that an overlap between IST and atrial tachyarrhythmias is unlikely because there were no ECG or clinical documentation of any atrial tachyarrhythmias. Likewise, the lack of any demonstrable orthostatic intolerance makes POTS an unlikely differential diagnostic option. On the other hand, it is possible that the present analysis underestimated the actual prevalence of IST among the hypertensive subjects in the random population, because 149 of 604 subjects were on betablocking medication at the baseline study. Finally, it should be noted that the study population was relatively small and some patients were lost to follow-up. Hence, some caution is required when interpreting the data on the characteristic and natural course of the patients with IST.

### Conclusions

IST appears to be a more common disorder than previously assumed. Despite the chronic nature of
the disorder and long-lasting symptoms, the natural course of IST is benign. Therefore, although early reassurance or medical treatment is essential, invasive therapy should be limited only to the most symptomatic patients as suggested in the ACC/AHA/ESC guidelines for the management of patients with IST [33].

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