PREVALENCE AND CHARACTERISTICS OF ECTOPIC ATRIAL TACHYCARDIA AND INAPPROPRIATE SINUS TACHYCARDIA

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OULU 2004
Still, Aino-Maija, Prevalence and characteristics of ectopic atrial tachycardia and inappropriate sinus tachycardia
Department of Internal Medicine, University of Oulu, P.O.Box 5000, FIN-90014 University of Oulu, Finland
2004
Oulu, Finland

Abstract

This research was designed to assess the prevalence, characteristics, natural course and autonomic regulation of ectopic atrial tachycardia (EAT) and inappropriate sinus tachycardia (IST) and the response of IST to adenosine.

The prevalence of EAT, as estimated from the electrocardiograms (ECG) of males applying for a pilot's licence, was 0.34%. During a mean follow-up time of 8 years among 10 asymptomatic subjects and 7 years among 17 symptomatic patients, a majority of the subjects showed a reduction of the heart rate (HR), either with restoration of sinus rhythm (SR) (37%) or with a change in P wave morphology (37%).

The prevalence of IST in a random sample of 604 middle-aged subjects was 1.16%. The systolic and diastolic ambulatory blood pressures were higher among the subjects with IST than subjects with SR (P < 0.001). The other laboratory, echocardiographic and personality measurements, with the exception of the hostility score (P < 0.001), revealed no differences between the groups. During a mean follow-up of 6 years, none of the subjects with IST developed any evidence of structural heart disease despite ongoing palpitations, and there was no significant reduction of the 24-hour average HR.

In an analysis of R-R interval variability from 24-hour ECG recordings in 12 patients with incessant EAT, 12 subjects with IST and 24 subjects with SR, the time- and frequency-domain measures of HR variability did not differ between the subjects with EAT and IST. However, the short-term fractal HR behaviour differed between EAT and IST.

In studies of the effects of adenosine in 18 patients with IST and 18 subjects with SR, adenosine prolonged significantly the sinus interval (P < 0.001) in the control subjects, but did not cause any significant changes of atrial cycle length in the patients with IST.

Conclusions: 1. EAT has a tendency towards gradual degeneration over time. 2. The prevalence of IST is higher than previously assumed, but the overall prognosis is good. 3. EAT and IST seem to be under similar autonomic regulation as the sinus node, but the firing of ectopic atrial foci shows more random behaviour. 4. The usual negative chronotropic effect of adenosine is impaired in subjects with IST.

Keywords: adenosine, arrhythmia, electrocardiography, prognosis
To my family
Acknowledgements

This work was carried out at the Department of Internal Medicine, University of Oulu. Part of the patients were gathered from Kuopio University Hospital, Kuopio, Finland, Central Military Hospital, Helsinki, Finland, and University of Miami School of Medicine, Miami, Florida, USA.

I wish to express my gratitude to Professor Antero Kesäniemi, M.D., Ph.D., who both as the head of the Department and as a co-worker has supported me during my work for this thesis.

I am deeply grateful to Docent Juha Mustonen, M.D., Ph.D., and Docent Markku Mäkijärvi, M.D., Ph.D., for their valuable comments and constructive criticism during the preparation of the final manuscript.

My warmest and deepest gratitude is due to my doctoral supervisor Professor Heikki Huikuri, M.D., Ph.D., for introducing to me this subject and for his excellent guidance during the process. I am also grateful for the possibility to be a member of his research team.

I sincerely thank Docent Pekka Raatikainen, M.D., Ph.D., my second supervisor, for his enthusiastic and valuable contribution to this work during the recent years.

I owe my special thanks to Docent Juhani Airaksinen, M.D., Ph.D., my other supervisor, for his warm and positive attitude towards research work and colleagues.

My sincere gratitude is also due to Professor Agustin Castellanos, M.D., Docent Juha Hartikainen, M.D., Ph.D., Professor Markku Ikäheimo, M.D., Ph.D., Docent Jouko Karjalainen, M.D., Ph.D., Docent Heikki Kauma, M.D., Ph.D., Docent Raimo Kettunen, M.D., Ph.D., Docent Juhani Koistinen, M.D., Ph.D., Associate Professor Raul Mitani, M.D., Professor Robert Myerburg, M.D., Docent Timo Mäkikallio, M.D., Ph.D., and Antti Ylitalo, M.D., Ph.D. who were my co-workers.

I want to thank our research team: Vesa Jokinen, M.D., Ph.D., Kai Lindgren, M.D., Juha Perkiömäki, M.D., Ph.D., Sirku Pikkujämsä M.D., Ph.D., Jari Tapanainen, M.D., Ph.D., and Mikko Tulppo, Ph.D., for their existence and help. Pirkko Huikuri, R.N., Päivi Karjalainen, R.N., Marja Hietaniemi, R.N., Maire Kukkonen, R.N., Ms. Anne Lehtinen, Ms. Anne Salovaara and Mirja Peltola, M.Sc. are most sincerely acknowledged for their technical assistance.
I wish to express my warmest thanks to all colleagues and the staff in the Cardiovascular Laboratory for both clinical and scientific help. Especially Markku Linnaluoto, M.Sc., is acknowledged.

I express my thanks to Mrs. Sirkka-Liisa Leinonen for her prompt revision of the English language of this thesis.

My deepest gratitude is due to my mother and my late father for their love and continuous encouragement during my life and their love and important help to my family. I wish to thank my sister Minna and her family for love and support. I thank my aunt Arja for her love towards our family and for her help in our home to make this thesis possible. I want to thank all of my relatives and friends for their support and encouragement during these years.

Finally, I owe my most loving thanks to my husband Jari especially for his love and support. I also thank him for giving me new interesting perspectives into life. Our wonderful children Emil-Aleksi, 4, and Jenni-Julia, 3, are really the centre of my life.

This study was financially supported by AstraZeneca, Masala, Finland, The Finnish Foundation for Cardiovascular Research, The Commemorative Foundation of Maud Kuistila, Orion Corporation Research Foundation, Oulu University Hospital and the Oulu University Scholarship Foundation.

Oulu, April 2004

Aino-Maija Still
### Abbreviations

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<th>Description</th>
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<tr>
<td>ACL</td>
<td>atrial cycle length</td>
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<tr>
<td>AT</td>
<td>atrial tachycardia</td>
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<td>AV</td>
<td>atrioventricular</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<td>BPM</td>
<td>beats per minute</td>
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<td>EAT</td>
<td>ectopic atrial tachycardia</td>
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<tr>
<td>ECG</td>
<td>electrocardiography</td>
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<td>HR</td>
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<td>HRV</td>
<td>heart rate variability</td>
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<tr>
<td>$I_{K_Ach,Ado}$</td>
<td>acetylcholine- and adenosine-sensitive potassium channel</td>
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<td>IHR</td>
<td>intrinsic heart rate</td>
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<td>IST</td>
<td>inappropriate sinus tachycardia</td>
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<tr>
<td>LF</td>
<td>low frequency</td>
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<tr>
<td>HF</td>
<td>high frequency</td>
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<td>LVH</td>
<td>left ventricular hypertrophy</td>
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<td>RF</td>
<td>radiofrequency</td>
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<td>R-R interval</td>
<td>interval between consecutive ventricular beats</td>
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<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SR</td>
<td>sinus rhythm</td>
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<tr>
<td>SVT</td>
<td>supraventricular tachycardia</td>
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List of original articles

This thesis is based on the following publications, which are referred to in the text by their Roman numerals:


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References
1 Introduction

Supraventricular tachycardias (SVTs) are common rhythm disturbances and were previously clustered together into one diagnostic category. Based on the knowledge gained from invasive electrophysiological studies, it has become possible to differentiate between the various SVT subtypes, mainly by the mechanisms involved (1). Clinically, part of these arrhythmias can be diagnosed by means of 12-lead ECG, and new and effective methods of treatment can be devised, as necessary. The precipitants of the subtypes of SVTs vary with age, sex and associated comorbidity. This study was designed to focus on ectopic atrial tachycardia (EAT) and inappropriate sinus tachycardia (IST).

EAT is often manifested as incessant tachycardia that originates outside the sinus node, showing abnormal P waves in ECG (2). IST is non-paroxysmal tachycardia characterized by an increased resting heart rate (HR) or an exaggerated HR response to minimal exertion (3) without an appropriate relationship with metabolic or physiologic demands (4).

Even though ambulatory electrocardiographic monitoring has been increasingly used to provide data concerning arrhythmias in different age groups, there are no earlier studies on the prevalence of EAT or IST. The clinical importance of EAT and IST is that they may cause severe symptoms and be resistant to traditional antiarrhythmic medications. In addition the increasing prevalence of congestive heart failure has highlighted the importance of the search for potentially reversible etiologies of cardiomyopathy, which has been associated with incessant EAT, especially in children (5–8). There are some earlier studies on the natural course of EAT with varying spontaneous resolutions (2,9–16). The prognosis of IST is largely unknown, and the mechanism of this arrhythmia is poorly understood.

Experimental and clinical evidence suggests a strong relationship between the autonomic nervous system and the occurrence of atrial tachyarrhythmias (17). The analysis of heart rate variability (HRV) is a useful tool for indirect assessment of autonomic effects on the heart and may have implications for understanding the arrhythmogenic mechanism. HRV reflects the neural regulation of normal pacemaker tissue and is well characterized (18–28), but there is little information of the autonomic nervous regulation of abnormal atrial foci originating outside the sinus node.

Adenosine is an endogenous purine nucleoside that has become an important agent for the diagnosis and treatment of cardiac arrhythmias (29). The efficacy of intravenous ade-
nosophine for the termination of tachycardias requiring the atrioventricular (AV) node as part of their reentrant circuit is well established (30,31), but there is much less data on the response to adenosine in patients with arrhythmias involving the sinus node.

This study was designed to evaluate the prevalence and natural course of EAT in symptomatic inpatients and in asymptomatic subjects. We also estimated the prevalence and characteristics of subjects fulfilling the criteria of IST in a random sample of hypertensive and normotensive middle-aged subjects and assessed the natural course of IST both in the random sample and in symptomatic hospital patients with documented IST. HRV analyses were used to determine the possible differences in HR behaviour between sinus rhythm (SR), IST and EAT. Finally, the response of IST to adenosine was systematically assessed.
2 Review of the literature

2.1 General aspects of the nervous regulation of heart rate

The sinus node, atrioventricular node and specialized conduction system of the heart possess the inherent ability for spontaneous, rhythmic initiation of the cardiac excitation impulse. Autonomic nervous system also influences the rate of spread of the excitation impulse, the depolarization and repolarization of the myocardium, and the contractility of both the atria and the ventricles (32).

The parasympathetic innervation of the heart originates in the medulla and passes through the right and left cardiac nerves. Two sets of cardiac nerves arise from each vagus nerve: the superior (superior and inferior cervical) cardiac nerves, which arise from the vagi in the neck, and the inferior (thoracic) cardiac nerves, which arise from either the vagus nerves or the recurrent branches of the vagi. The sympathetic innervation of the heart passes from the spinal cord to the upper four or five thoracic ganglia. Some fibers from the upper thoracic ganglia pass up the cervical sympathetic to the superior, middle, or inferior cervical ganglia. The superior (cervical), middle (cervical), and inferior (cervical) cardiac nerves originate from their respective ganglia and pass downward through the deep and superficial parts of the cardiac plexus to the heart (32).

Most of the parasympathetic nerves are distributed near the sinus node and AV conduction tissue, to a lesser extent to muscle of the two atria, and even less to the ventricular muscle. The right and left vagi are distributed differentially to the various cardiac structures. The right vagus nerve affects the sinus node predominantly. Stimulation slows sinus nodal firing or may even stop it for several seconds. The left vagus nerve mainly inhibits AV conduction tissue to produce various degrees of AV block. However, the efferent vagal fibers overlap. Cardiac parasympathetic impulses are transmitted by acetylcholine (33,34).

The postganglionic cardiac sympathetic fibers approach the base of the heart along the adventitial surface of the great vessels. On reaching the base of the heart, these fibers are distributed to the various chambers as an extensive epicardial plexus. They then penetrate the myocardium, usually accompanying the coronary vessels. Sympathetic fibers are dense to the epicardial coronary arteries and veins and are moderate to intramural ves-
sels. The sympathetic nerves are distributed to the same areas as parasympathetic nerves, but with a strong presentation to the ventricular muscle as well as to the other parts of heart. Sympathetic stimulation to the heart is largely mediated by the release of norepinephrine. The effect of stimulating these nerves is to increase the rate at which the heart beats. Maximal sympathetic stimulation can almost triple the resting heart rate. Conduction time through the AV node is also reduced (32–34).

Both sympathetic and parasympathetic fibers influence the sinus node, the AV node, and both the atrial and ventricular myocardium. The sinus node is usually under the tonic influence of both divisions of the autonomic nervous system. The sympathetic system enhances automaticity, whereas the parasympathetic system inhibits it. Changes in heart rate usually involve a reciprocal action of the two divisions of the autonomic nervous system. Thus an increased heart rate is produced by a diminution of parasympathetic activity and concomitant increase in sympathetic activity; deceleration is usually achieved by the opposite mechanisms. Under certain conditions the heart rate may change by selective action of just one division of the autonomic nervous system, rather than by reciprocal changes in both divisions. In healthy individuals the heart rate at rest is dominated by the parasympathetic innervation. When physiological circumstances require the heart to beat more rapidly, as in exercise, the activity of the parasympathetic nerves is inhibited, while that of the sympathetic nerves is enhanced. Sympathetic activity alters heart rate and AV conduction much more slowly than does vagal activity. Therefore, vagal activity can exert beat-by-beat control of cardiac function, whereas sympathetic activity cannot. In general, sympathetic stimulation increases the strength of heart muscle contraction, whereas parasympathetic stimulation decreases it (32–34).

### 2.2 Ectopic atrial tachycardia

#### 2.2.1 History

EAT was first described as early as 1922 by Gallavardin (35). A variety of names, including automatic atrial tachycardia, (uni)focal atrial tachycardia and ectopic atrial tachycardia, have been used, but because of the uncertainty concerning the mechanism of this tachycardia, the term EAT is preferred. In 1947, Parkinson and Papp (36) introduced the attribute “repetitive” to describe this type of tachycardia, and they also described a persistent variety of arrhythmia (37,38), which is referred to as “sustained” by other authors (39). In children with chronic EAT or atrial tachycardia (AT) with AV block, the condition most probably also includes forms of tachycardia other than EAT, such as the permanent form of junctional reciprocating tachycardia, multifocal AT and atrial flutter, and thus there is no homogeneous entity (39–44).

The development of invasive electrophysiological techniques has enabled better classification, diagnostic and therapeutic possibilities of ATs. The electrophysiological properties of EAT have been elucidated by Goldreyer et al (45) and Gillette and Garson (46). Later on, the literature on EAT in children and adults has been enriched by reports on
clinical aspects and medical, surgical and catheter ablative treatments (10,12,13,16,47–55).

The results of antiarrhythmic drug therapy, and even cardiac surgery, have been suboptimal in EAT. Since chronic tachycardias, such as EAT, are among the few reversible causes of cardiomyopathy, alternative treatment options have been explored aggressively. Radiofrequency (RF) catheter ablation was adopted quickly for the management of EAT, and its efficacy has been proven during the past decade (50–55). A new interesting electrophysiological issue is the association between EAT and focal atrial fibrillation (56,57).

2.2.2 Prevalence

EAT may occur as a primary disturbance of cardiac rhythm in a structurally normal heart or develop as a complication of other cardiac or pulmonary disorders. Although an association with atrial neoplasms has been described, patients with EAT typically show no evidence of any defined organic heart disease (58). Even though EAT may present at any age, it is predominantly seen in young infants, children and young adults. Onset may even be prenatal (7,11,12).

EAT is thought to be an uncommon rhythm disorder, but its true prevalence in the general population has not earlier been assessed. In the previous studies, approximately 20% of SVTs in children (5) and 25% in adults have been nonparoxysmal (59). EAT has been electrophysiologically identified in 5–20% of children (60,61) and approximately 5% of adult patients with symptomatic SVTs (62). The prevalence of asymptomatic subjects with EAT and the occurrence of EAT in patients with structurally normal hearts is not known. A positive family history of tachycardia has been reported with this arrhythmia (46). Pooling of the results of the previously published sixteen series indicates that the distribution between the genders is quite equal (198 females and 192 males) (2,10,12–14,16,45,46,53,55,63–68).

2.2.3 Pathophysiology

EAT is defined as a SVT arising from the atrial muscle that does not include the sinus node. It is characterized by inappropriate rapid frequency of atrial activation, which starts rhythmically in a very small area (focus) and spreads centrifugally (46,69–72). When the firing rate of the ectopic focus exceeds that of the sinus node, it becomes the predominant pacemaker of the heart. The mechanism of focal ectopic activity has been a subject of debate. Most data suggest that EAT is caused by abnormal automaticity of atrial cells to undergo spontaneous diastolic depolarization and to initiate an electrical impulse in the absence of external electrical stimulation (62,73–75). In one study, microelectrode recordings from left atrial appendage tissue obtained at the time of surgical excision of an EAT focus revealed a high resting membrane potential and spontaneous phase 4 automaticity (73). Further support for automaticity as the mechanism may be found from the use of RF catheter therapy. It has been observed that EAT almost always involves a small
area of tissue, since it is eliminated within several seconds of the onset of RF energy application (54,60). Secondly, just prior to successful elimination of the foci, the ectopic rate often accelerates, consistently with the enhanced automaticity observed in response to RF energy in other tissues (76). Finally, the foci seem to cluster in a few specific areas. These findings all suggest that EAT involves subtle electrical changes in otherwise normal tissue from trabeculated atria or connections between the atria and the systemic veins (54). Other possible mechanisms of EAT include triggered activity (early and delayed after potentials) and micro re-entry (70,74,77,78). Most of the above hypotheses are based on imperfect surrogate markers, such as the response to pacing or pharmacological maneuvers, and are fraught with problems. Further work is needed to evaluate the cellular mechanism of EAT.

EAT may arise from any site in the right or left atrium. The foci are not randomly distributed, but rather tend to cluster in certain anatomical zones (7,51,52,60,77,79,80). In the right atrium, the most frequent locations of the foci are along the crista terminalis (2/3), in the para-Hisian region and around the ostium of the coronary sinus (80). In addition, ATs originating from around the tricuspid annulus have been characterized (81). In the left atrium, the most frequent location of the foci seems to be at the junction (or inside) the pulmonary veins. There are also isolated reports of left atrial tachycardia originating from the mitral annulus (68,82). The distribution of EAT foci may differ, depending on the patient population (75). In several studies, the ectopic foci have been reported to occur in the right atrium (2,12,49). One of the primary differences between adult and pediatric patients with EAT is the predominance of right-sided foci in adults, whereas both left- and right-sided ones are seen in children (15,60).

There are some studies of histological features of the ectopic foci. Most cases have been not associated with any specific pathologic abnormalities of cardiac or skeletal muscle (83) or resected atrial tissue near the focus (15). Moro et al found fibrous plaque with some degenerated myocytes (84). However, they suggested it could also be a fibrotic lesion due to a previous inflammatory process. In other studies, the occasional pathological findings have been restricted to nonspecific fibrosis, cellular hypertrophy and patchy fatty infiltrates. All of these changes may be secondary to tachycardia-induced myopathy, but in some cases the tissue examined was completely normal (85).

What most of these foci seem to have in common is a region of structural inhomogeneity. An interesting question is why the large bulk of surrounding myocardium does not electronically inhibit the firing of a small focus. Lesh (75) speculates that, in addition to abnormal automaticity, a region of relatively poor cell-to-cell coupling is required for the initiation and perpetuation of EAT. Accordingly, a cell or a small cluster of cells with abnormal automaticity well coupled with the surrounding normal atrium could not be able to manifest that tendency due to electrotonic interactions. However, if the region of abnormal automaticity exhibits poor cell-to-cell coupling, a reduced electrotonic influence allows these cells to manifest and maintain their abnormal firing. Fractionated electrograms often seen at a successful EAT ablation site may be markers of the requisite non-uniformly anisotropic substrate (75). For example, the crista terminalis contains cells that have very sparsely distributed transverse gap junctions as well as cells with automatic properties (86).
One expanding field of research is the identification of patients with focal atrial ectopy which triggers atrial fibrillation. This special type of atrial fibrillation is initiated by a burst of rapid EAT with subsequent degeneration to atrial fibrillation (56,57).

### 2.2.3.1 The etiology of ectopic atrial tachycardia

The etiology of EAT is unknown. Most reports support the hypothesis that myocardial dysfunction is a result rather than the cause of incessant EAT (7,12,87,88). The exact pathophysiological mechanisms of this dysfunction are not fully understood. The most notable feature of tachycardia-induced myopathy is a prompt reversal of ventricular dysfunction when tachycardia is eliminated (89). In animal models, dilated cardiomyopathy can be induced within 30 days when the atrium is paced chronically at rates that are approximately 3 times normal, and recovery occurs in about 2 weeks when pacing is terminated (90). It is now known that ventricular dysfunction is truly related to depressed contractile performance of individual myocytes instead of being simply a phenomenon due to excess preload or high afterload. Multiple factors, such as alterations in cellular calcium homeostasis, changes in cell ultrastructure including decreased myofibril content, alteration in the Na+, K+-ATPase system and changes in beta-adrenergic receptor function, have been implicated as causes of tachycardia-induced myopathy (85). The central biochemical derangement that includes these changes has not yet been identified. One possible explanation is that long-standing tachycardia causes chronic depletion of myocardial high-energy phosphate (5,6,87,88,91–93). Although AV dyssynchrony may play some role, normal AV synchrony with a normal PR interval may still lead to ventricular dysfunction. Immature or developing myocardium may be more vulnerable to the deleterious effects of chronic EAT than mature myocardium, possibly because the rate of AV conduction tends to be quite brisk through a younger patient's AV node, although the exact explanation for this age-related difference is uncertain (94).

### 2.2.3.2 Autonomic regulation of ectopic atrial tachycardia

**Pharmacological maneuvers**

Several pharmacological agents have been used to aid the diagnosis of EAT (Table 1).

*Isoproterenol.* During an invasive electrophysiological examination, administration of isoproterenol as an adrenergic stimulator is commonly used to initiate or accelerate EAT in a similar way as it accelerates SR. The intravenous infusion rate of isoproterenol should increase HR by at least 20–40 % or above 100 bpm to ensure arrhythmia induction (54,66). Typically, this requires an infusion rate of 0.01 to 0.04 µg/kg/min (62,66). Epinephrine and aminophylline can also be used to provoke ectopic focus (62).
Table 1. Pharmacological agents in the diagnosis of ectopic atrial tachycardia.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of effect</th>
<th>Dose</th>
<th>Clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoproterenol</td>
<td>β-receptor agonist</td>
<td>0.01–0.04 µg/kg/min infusion</td>
<td>HR increase</td>
</tr>
<tr>
<td>Adenosine</td>
<td>$I_{K_{ACh,Ado}}$-channel activation</td>
<td>0.1–0.15 mg/kg i.v. quick bolus</td>
<td>Transient slowing or termination of EAT No effect Transient AV block</td>
</tr>
<tr>
<td>Calcium channel blockers (verapamil)</td>
<td>L-type calcium current blocker</td>
<td>Verapamil 5 mg i.v. slow bolus</td>
<td>AV block No effect on EAT rate No termination of EAT</td>
</tr>
<tr>
<td>Atropine</td>
<td>Muscarin receptor antagonist</td>
<td>0.04 mg/kg i.v. bolus</td>
<td>HR increase AV conduction time decreases</td>
</tr>
</tbody>
</table>

**Adenosine.** Adenosine is an endogenous purine nucleoside that has become an important agent for the diagnosis and treatment of cardiac arrhythmias (29). Adenosine acts on supraventricular tissue via two cellular mechanisms: 1) It activates the acetylcholine-sensitive and adenosine-sensitive potassium channel ($I_{K_{ACh,Ado}}$), which results in hyperpolarization of the membrane potential towards the potassium equilibrium potential ($\approx$ -90 mV) and shortening of the action potential duration by increasing potassium conductance (95). 2) Adenosine also has indirect antiadrenergic effects. It decreases intracellular cAMP, which results in inhibition of the L-type calcium current ($I_{Ca(L)}$) as well as the transient inward current ($I_{T1}$) (30). The effect of adenosine on EAT depends on the mechanism of the arrhythmia. These effects are consistent with transient suppression of EAT attributable to enhanced automaticity (70,96,97). The findings on the effects of adenosine on EAT are complex. Previously reported responses of EAT to adenosine include an absence of effect (98–100), transient slowing and termination (101–104). These differences may be due to the different mechanisms of tachycardia or related to the tachycardia focus. Chen et al showed septal AT to be more sensitive to adenosine than free-wall AT (66). Marrouche et al (105) reported insensitivity of left septal AT to adenosine. In the study of Engelstein et al, all patients showed suppression of tachycardia after an adenosine-induced transient AV nodal block (96). A rebound effect of adenosine with acceleration of AT rate has also been reported in EAT (70). Thus, adenosine may help to confirm the diagnosis of EAT as the ACL (atrial cycle length) will remain unchanged in the face of a transiently increased AV block or marked shortening of ACL (106), and the P wave axis and morphology can be evaluated (107). In clinical practice, the potent negative dromotropic action of adenosine helps the diagnosis of EAT.

**Calcium channel blockers.** Intravenous administration of verapamil may cause an AV block but does neither affect the rate of AT nor terminate EAT (62,96).

**Atropine.** In their earlier studies, Morton & Thomas and Jose & Taylor (108,109) found that intravenous atropine (0.04 mg/kg) increased sinus rate by 20% to 50%. There are no published studies of the anticholinergic effects of atropine on EAT.

**Heart rate variability.** HR is normally determined by the rate of depolarization of the fastest cardiac pacemaker. Because temporal changes in cardiac interbeat intervals are mediated by phasic vagal and sympathetic outflow, measurement of HRV from ECG
recordings has considerable potential to assess the role of the autonomic nervous system in the regulation of pacemaker tissue (18–23). Beginning with the original observations of Akselrod et al (18) on the typical spectral patterns of HRV during normal SR, a large amount of data have been published on the characteristics of HRV in healthy subjects and patients with various cardiac diseases (19–23).

The neural regulation and dynamics of the richly innervated sinus node are well characterized (18–28), but there is little information on the dynamic behaviour of pacemakers originating outside the sinus node.

Both experimental and clinical evidence suggests that there is a strong relationship between the autonomic nervous system and the occurrence of atrial tachyarrhythmias. Either vagal or sympathetic stimulation can produce arrhythmogenic effects on atrial tissues. Therefore, any fluctuations in autonomic tone or sympathovagal imbalance may produce atrial tachyarrhythmias. In addition, there is heterogeneous autonomic innervation, and there are frequent and complex interactions between the sympathetic and parasympathetic nervous systems, which may produce spatially and temporally inhomogeneous autonomic effects. These spatial and temporal inhomogeneities of autonomic effects may play important roles in the genesis of various atrial tachyarrhythmias. Furthermore, persistent atrial tachyarrhythmias may result in remodelling of the autonomic nervous system and lead to a vicious circle. Development of new methods to explore the subtle modulation of the autonomic nervous system may have implications for understanding the arrhythmogenic mechanism and providing effective therapy (17).

HRV can be analyzed from short-term and long-term (usually 24-hour) ECG recordings. Long-term recordings are better reproducible than short-term recordings. Short-term recording of HRV should be done in controlled situations, in order to improve reproducibility. These recordings are often applied with maneuvers affecting the activity of the autonomic nervous system, e.g. during the Valsalva maneuver, orthostatic test or deep breathing. Huikuri et al (110) showed in their study that 45-minute ECG recording (15 minutes while quietly lying down and breathing normally, 15 minutes in the sitting position and 15 minutes while walking) gives a reasonable correlation with the 24-hour measures of HRV.

The variation in HR may be evaluated by a number of methods. Recently, methods of analysis based on nonlinear dynamics have been developed to describe the complex behaviour of cardiac interbeat intervals (24–26,111,112). The studies using these new methods have shown typical self-similar or fractal-like features in the R-R interval dynamics of normal SR (24–28) and have also implicated abnormal HR behaviour in patients with structural heart disease (25–28).

### 2.2.4 Symptoms and characteristics

Clinical features of EAT have been described by few investigators (2,12,13). Symptoms consist of tachypnea and feeding problems in infants and toddlers, while older patients experience fatigue, syncope, shortness of breath, palpitation and exercise intolerance. There are also two reports of patients with chronic EAT and stroke (39,41). Although EAT is usually more significant symptomatically than hemodynamically, a case of cardi-
ac arrest due to hemodynamic derangement during EAT with extremely rapid AV conduction has been reported (58). Another case report suggested that incessant EAT resulted in the occurrence of aborted sudden cardiac death by spontaneous ventricular fibrillation (113), but in that particular case, it was not possible to exclude the residual action of amiodarone and flecainide or the residual peripartum cardiomyopathy.

In contrast to most re-entrant SVTs, EAT often presents as an incessant or frequently repetitive tachycardia. In the repetitive type, the activity from the atrial focus is episodic and the tachycardia is frequently interrupted by short periods of SR, but the ectopic rhythm still accounts for more than 50% of the atrial rhythm over a 24-hour period (62). With incessant/sustained tachycardia, although the firing rate of the ectopic focus may vary, sinoatrial activity is not apparent for long periods of time, tachycardia being constantly present for months or years without evidence of sinus activity (39). Transition from one form to another may occur (39). The repetitive type may be tolerated well for years, causing symptoms only in cases of exclusive HR during phases of tachycardia and only rarely inducing dilated cardiomyopathy. In contrast, the incessant type is usually severely symptomatic, though some patients may be asymptomatic for many years. Symptoms of heart failure may appear very late, only after the left ventricular shortening fraction has reduced to less than 15% (64) or when ventricular dysfunction eventually leads to low cardiac output and pulmonary edema (62). Left ventricular end-diastolic dimension is the first echocardiographic index to become abnormal (114), and then the decreased left ventricular shortening fraction is seen in echocardiography, suggesting dilated cardiomyopathy (2).

2.2.5 Diagnosis and differential diagnosis

2.2.5.1 Clinical evaluation

Clinical evaluation of the patient with suspected EAT includes a careful medical history, cardiovascular examination, 12-lead ECG, echocardiography and 24-hour ECG recording. Antiarrhythmic medication should be discontinued for at least two days before the examinations. The diagnosis of EAT may be suspected from the surface ECG. The ECG characteristics of EAT are summarized in Table 2. A typical example of EAT is presented in Figure 1. Atrial rate is often between 130 and 240 bpm, but possibly as low as 90 bpm or as high as 300 bpm (4). In children, the 24-hour average HR is often within 140–170 bpm (62). Atrial rate may increase during exercise (115) and is accelerated by adrenergic stimulation (2,62). In HR trend analysis, different patterns can be observed, depending on the type of EAT (Figure 2, 3A and 3B).
**Table 2. The ECG and diagnostic characteristics of EAT and IST.**

<table>
<thead>
<tr>
<th></th>
<th>EAT</th>
<th>IST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Inappropriate for age and activity</td>
<td>≥ 100 bpm at rest or with minimal stress</td>
</tr>
<tr>
<td></td>
<td>Highly variable rate of atrial tachycardia depending on the state of activity and autonomic state</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Narrow complex SVT with distinctly visible P waves, sometimes aberrant ventricular conduction</td>
<td></td>
</tr>
<tr>
<td>P wave</td>
<td>Abnormal P wave morphology and inferior, right or left deviation axis, a normal or minimally prolonged PR interval, but PR&lt;RP, a clearly defined isoelectric baseline between P waves in all leads</td>
<td>P wave axis and morphology during tachycardia similar or identical to that during SR or P wave positive in ECG leads I, II and aVF</td>
</tr>
<tr>
<td>Onset/termination</td>
<td>Onset of tachycardia with a P wave identical to subsequent P waves</td>
<td>Gradual over 1–3 minutes</td>
</tr>
<tr>
<td></td>
<td>Gradual shift of the pacemaker from the sinus node to the ectopic focus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warm-up (gradual shortening of the P wave CL over the first few beats after the onset of tachycardia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cool-down (gradual rate decrease before tachycardia termination sometimes associated with exit block at termination)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second-degree AV block without interruption of the tachycardia, occurring especially at rest or at asleep</td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>Incessant/repetitive</td>
<td>Chronic, nonparoxysmal</td>
</tr>
<tr>
<td>Notable</td>
<td>Exclusion of secondary causes of sinus tachycardia (e.g. physical deconditioning, heart failure, hyperthyroidism, anemia, hypovolemia, infection, diabetes mellitus with evidence of autonomic dysfunction, pheochromocytoma, orthostatic hypotension or drug abuse including thyroid hormone, diuretics and stimulants)</td>
<td>Exclusion of atrial tachycardias Correlation of symptoms with documented tachycardia</td>
</tr>
</tbody>
</table>

CL=cycle length
Fig. 1. ECG of a symptomatic 42-year-old woman with incessant ectopic atrial tachycardia. Her heart rate was 110 bpm. Notice negative P waves in leads II, III, aVF and V2-6. In the electrophysiologic study the ectopic focus was localized in the right ventricle, near atrioventricular node.
Fig. 2. 24-hour heart rate trend analysis of a symptomatic 42-year-old woman with incessant ectopic atrial tachycardia. Average heart rate was 104 bpm (range 93-164 bpm) and the profile of the curve is monotonic.

Fig. 3. (A) 24-hour heart rate trend analysis of a 41-year-old woman with repetitive type of ectopic atrial tachycardia with average heart rate 84 bpm (range 57-163 bpm). During EAT paroxysm heart rate increases clearly.

Fig. 3. (B) The closer view of the EAT paroxysm shows gradual increase in heart rate.

Evaluation of the surface P wave configuration during EAT can provide only a general guide to AT localization (Table 3). Tang et al. showed that a positive biphasic P wave in aVL suggests a right atrial origin with 88% sensitivity and 79% specificity, whereas a positive P wave in V1 and a negative P wave in lead aVL suggest a left atrial origin with 93% sensitivity and 88% specificity (116). A very low amplitude (isoelectric) P wave in the leads aVL and I suggests a focus close to the septum (68). Lateral right EAT demonstrates upright P waves in the leads I and aVL (81), and left atrial or pulmonary vein foci
tend to be inverted in these leads (although they may also be isoelectric in lead I) (117). However, it is well recognized that a positive P wave in lead aVL is also consistent with a right pulmonary vein origin (117). Negative P waves in the inferior leads II, III and aVF are suggestive of a caudal origin, whereas positive P waves in the inferior leads are seen when the origin is cranial (116). Chen et al (66) reported that a negative or biphasic P wave in lead V1 and a positive or biphasic P wave in all inferior leads were related to anteroseptal AT. A negative or biphasic P wave in lead V1 and a negative P wave in at least two of the three inferior leads suggested mid-septal AT, and a positive P wave in lead V1 and a negative P wave in all three inferior leads indicated posteroseptal atrial tachycardia. Recently, Marrouche et al found out that no specific 12-lead ECG P wave morphology appears to be associated with left septal atrial tachycardia (118). It has also been suggested that multi-lead body surface potential recording can be used to help localize the site of origin of the tachycardia (119).

Table 3. Evaluation of the surface P wave configuration during ectopic atrial tachycardia.

<table>
<thead>
<tr>
<th>Focus location</th>
<th>P wave morphology and lead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial EAT</td>
<td>Positive V1 and negative aVL&lt;br&gt;Left atrial or pulmonary vein: negative I and aVL, or isoelectric in I&lt;br&gt;Right pulmonary vein origin: positive aVL</td>
</tr>
<tr>
<td>Right atrial EAT</td>
<td>Positive, biphasic in aVL&lt;br&gt;Lateral: positive I and aVL</td>
</tr>
<tr>
<td>Septal EAT</td>
<td>Isoelectric aVL and I</td>
</tr>
<tr>
<td>Anteroseptal EAT</td>
<td>Negative or biphasic V1 and positive or biphasic in all inferior leads</td>
</tr>
<tr>
<td>Mid-septal EAT</td>
<td>Negative or biphasic V1 and negative in at least 2/3 inferior leads</td>
</tr>
<tr>
<td>Posteroseptal EAT</td>
<td>Positive V1 and negative in all 3 inferior leads</td>
</tr>
<tr>
<td>Left septal EAT</td>
<td>No specific changes</td>
</tr>
<tr>
<td>Caudal origin EAT</td>
<td>Negative II, III and aVF</td>
</tr>
<tr>
<td>Cranial origin EAT</td>
<td>Positive II, III and aVF</td>
</tr>
</tbody>
</table>

2.2.5.2 Electrophysiologic evaluation

An invasive electrophysiological test is often needed to confirm the diagnosis of EAT. If possible, the index arrhythmia should be well documented before invasive testing, because aggressive programmed atrial stimulation will at times induce non-clinical tachycardias (75). The electrophysiological evaluation should be made in a non-medicated state, and sedation should be minimized. EAT is sensitive to autonomic state, and sedation may suppress inducibility in a way that cannot always be overcome with the infusion of isoproterenol (75).

Baseline electrophysiological study consists of measurement of conduction intervals, followed by determination of atrial and AV nodal refractory periods. The diagnostic catheters are positioned in the lateral portion of the high right atrium, the His position, the
coronary sinus and the right ventricular apex (Figure 4). The electrophysiological properties of EAT have been elucidated by Goldreyer et al in adults (45) and confirmed by Gillette and Garson in children (46). ACL during tachycardia is usually ≥ 250 ms, but can be as short as ≤ 200 ms (4). Over a prolonged period of observation, ACL may exhibit important variations (45). EAT does not terminate with external direct current (DC) cardioversion, and vagal maneuvers do not terminate the tachycardia because it is not AV junction-dependent (62). EAT is independent of intra-atrial conduction delay. Usually, EAT cannot be initiated or terminated with atrial electrical stimulation, not even by overdriving, but there is one report of the inducibility of EAT with programmed stimulation (97). The reset behaviour of the EAT focus in response to single premature extrastimuli can be nearly identical to that of the normal sinus node. VA dissociation during ventricular pacing easily excludes the possibility of AV reentrant tachycardia (66).

As described earlier, P wave morphology on ECG can be used to target the endocardial mapping to specific anatomic structures determined before electrophysiological study (68,116). Endocardial mapping is started by placing specific multipolar catheters along the regions of most likely tachycardia origin (120–122). In the clinical setting, bipolar recordings with short interelectrode distance (≤ 2 mm) offer sufficient spatial resolution for most tachycardias. Activation mapping with a rowing catheter is used to determine the exact site of tachycardia by recording the earliest presystolic onset of local atrial activation during the tachycardia. Atrial activation preceding the onset of the P wave by 20–60 ms in the bipolar recording mode is used to locate the zone of origin (60). Endocardial mapping can trace the origin of activation to a specific area, from which it spreads centrif-
ugally to both atria (4). Unipolar recordings are helpful by showing negative (QS) pattern with sharp initial deflection at the location of the focus. The spread of activation from the focus or origin is not always uniformly radial, as conduction can be directed by anatomical or functional pathways and barriers (123). During EAT there is generally an electrically silent period in ACL in surface ECG, and intra-cardiac mapping will show significant portions of the cycle length without recorded activity. Left atrial mapping is best performed via transseptal approach when the foramen ovale is closed (124). The atrial activation sequence will vary, depending on the site of the atrial focus. When the focus is located high in the crista terminalis, the atrial activation sequence will not be very different from that during SR or IST. In these cases, only sharp changes in the rate with minor, but significant, changes in the activation sequence will permit EAT diagnosis (80). Pace mapping to match the surface P wave during tachycardia can be used adjunctively, but because of the difficulty in clearly discerning the surface P wave morphology, activation mapping is more accurate (52).

There are also novel computerized approaches to the mapping of EAT. The electromagnetic mapping system (CARTO™ Biosense, Biosense Ltd., Israel) is based on a sequential mapping technology allowing detailed 3-dimensional reconstruction of the chamber geometry and the exact endocardial activation sequence (55,125–127). In the CARTO system, the endocardial activation sequence must be constructed point by point (128), whereas the non-contact mapping system (129,130) (EnSite™, Endocardial Solutions, USA) allows simultaneous acquisition of electrical signals of the whole chamber by a single-beat analysis. The use of intracardiac echocardiography might be helpful in discerning the anatomical substrate for EAT (80,131).

2.2.5.3 Differential diagnosis

While most left atrial foci are usually easy to diagnose based on P wave morphology, right atrial foci and right pulmonary vein foci are sometimes difficult to distinguish from sinus tachycardia. Whereas most SVTs have a sudden onset and termination, in EAT the shift of the pacemaker from the sinus node to the ectopic focus is more gradual. In early stages this may evade detection and be misinterpreted as sinus tachycardia (132). The variability of the tachycardia rate from minute to minute and from hour to hour is extremely helpful in differentiating EAT from reentrant SVT. If the P wave axis and morphology are normal, the differentiation of sinus tachycardia is difficult. On the other hand, any change in the P wave axis or morphology from normal SR should suggest an ectopic focus (132). In cases with negative P waves in the standard leads II, III and aVF and a PR/RR ratio < 0.5, the differential diagnosis between EAT and the permanent form of junctional reciprocating tachycardia or uncommon AV nodal reentrant tachycardia may be difficult (2). Normally intermittent second-degree AV block effectively differentiates these arrhythmias from EAT. Other forms of SVT possibly confounded with EAT are intra-atrial or sinus node re-entry tachycardia, which can be excluded with certainty only by invasive electrophysiologic study (2) (Table 4). They are, however, clinically characterized, intermittent rather than chronic, initiated by atrial extra-stimuli and usually without a "warm-up phenomenon". In the electrophysiological examination, it is noteworthy
that relatively small re-entry circuits may resemble focal AT, especially if a limited number of endocardial recordings are collected (4).

It is important to differentiate EAT with secondary left ventricular dysfunction from primary dilated cardiomyopathy with sinus tachycardia (133). The rate of tachycardia (faster in patients with EAT), the P wave axis in the horizontal plane (more posterior in patients with EAT), the presence of a second-degree AV block (more frequent in patients with EAT) and a decreased shortening fraction (more severe in patients with idiopathic cardiomyopathy) may be helpful in differentiating between these two entities (134).

Table 4. Electrophysiologic differentiation of EAT, IST and sinus node re-entry.

<table>
<thead>
<tr>
<th></th>
<th>EAT</th>
<th>IST</th>
<th>SNRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>Adrenergic stimulation</td>
<td>Adrenergic stimulation</td>
<td>Extrastimulation</td>
</tr>
<tr>
<td></td>
<td>Atropine</td>
<td></td>
<td>Easily induced</td>
</tr>
<tr>
<td>Rate response</td>
<td>Warm-up over a few</td>
<td>Gradual over seconds/</td>
<td>Immediate</td>
</tr>
<tr>
<td>at onset</td>
<td>beats</td>
<td>minutes</td>
<td></td>
</tr>
<tr>
<td>Shift in focus</td>
<td>Gradual</td>
<td>Gradual</td>
<td>Sudden</td>
</tr>
<tr>
<td>Local electrogram</td>
<td>Fractionated</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Termination</td>
<td>Cool down</td>
<td>Gradual</td>
<td>Sudden</td>
</tr>
<tr>
<td>Vagal maneuvers</td>
<td>Usually no effect</td>
<td>Slowing/inferior shift</td>
<td>Abrupt termination</td>
</tr>
<tr>
<td>Inducible by pacing</td>
<td>Slowing without change in focus</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Terminated by pacing</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

SNRT = sinus node re-entry

2.2.6 Natural course

Spontaneous resolution of EAT has been reported after successful pharmacologic control of the arrhythmia. In nine previous studies, the average rate of spontaneous resolution of EAT was 31% (2,9–16). Spontaneous resolution is common in infants less than 6 months old (up to 90%) (11), but quite rare in elderly patients (9). The wide variation in these rates appears to be due to a combination of factors, but is probably most influenced by age at presentation, with 72% of the spontaneous resolutions occurring in patients < 6 months of age. Low spontaneous resolution rates were not associated with shorter follow-up in nine studies, but overall, the arrhythmia was long-term in two thirds of patients (2,9–16). Klersy et al (16) reported in their study that age at the onset of arrhythmia was the single covariate able to predict the possibility of remission independently. Disappearance of arrhythmia was noted in 55% of the patients aged less than 25, compared to 14% of the patients aged 26 or older.

EAT is usually chronic tachycardia persisting for months and years. Untreated incessant type of EAT, especially with rapid ventricular response may cause cardiomyopathy impairing the patient's prognosis (91,135) and these patients need urgent treatment (2). Functional left ventricular myopathy is also present in up to 50–75% of cases (5,9,15,62)
especially in children, but appears to be less common in the older adult population who first present with EAT (52). The onset of dysfunction occurs over a variable period, depending on the rate of tachycardia, the percentage of time the patient has tachycardia and the patient’s age.

The ventricular rate that causes tachycardia-induced cardiomyopathy has not been determined, although any prolonged episode of HR greater than 100 bpm may be important in adults (93), and in the published pediatric series, mean heart rates of about 150–176 bpm were seen in the patients with depressed cardiac function, compared to about 90–136 bpm in those with well preserved ventricular performance (15,62,89). Children with chronic tachycardia rates of more than 140 bpm should be followed up closely (136). If the tachycardia is intermittent and present for less than 50 % of the day, ventricular dysfunction usually does not occur (64). When the tachycardia is terminated, symptoms are often relieved immediately (137). Ventricular function normalizes over weeks to months. The shortening fraction normalizes first, but left ventricular size lags behind by months (114). Normalization of ventricular function occurs regardless of whether tachycardia is stopped by pharmacological or nonpharmacological means (138). There are no earlier reports of the mortality of patients with EAT.

2.2.7 Treatment and outcome

2.2.7.1 Medical therapy

Acute treatment. In acute treatment of hemodynamically stable EAT adenosine is usually used and other antiarrhythmic medications can also be attempted. Electrical cardioversion can be tried in hemodynamically unstable EAT (Table 5).

Long-term treatment. There is widespread agreement that the traditional antiarrhythmic drugs are of little help in EAT. Virtually every class of antiarrhythmic agents has been used, but no single class or agent appears to be universally effective. Digoxin may slow down the atrial rate in some cases, but it usually has no permanent effect (12,13). The catecholamine sensitivity of EAT suggested that beta-blocking agents should be therapeutic. They indeed slow down atrial tachycardia in some patients (12), but are considered ineffective in others (13). Class I A antiarrhythmic agents, particularly quinidine and procainamide, have been disappointing in the treatment of EAT. In contrast, they may even increase the rate of EAT in some cases (12). Class I C agents, encainide, propafenone and flecainide, have shown their usefulness in EAT in several studies (13,48,139–141). Finally, amiodarone, a complex class III agent, seems to be the most effective agent in the treatment of EAT (12,47). The value of amiodarone is limited by the frequency of undesired side-effects, which may lead to discontinuation of the drug. Severe side-effects, however, appear to be less frequent in infants and children than in adults (47,142). Naheed et al reported that the most successful drug combinations were amiodarone with beta-blockers or verapamil (10). One report describes effective EAT treatment in children with racemic sotalol, which associates class III with beta-blocking properties (143). In a series of
35

54 young patients treated for EAT, Garson et al found an effective drug in only 50% of cases (15). At best, medication slows the rate by 5 to 10% and prevents some of the symptoms of myocardial failure (136). Table 5 describes the latest ACC/AHA/ESC guidelines for the management of EAT (144).

Table 5. ACC/AHA/ESC recommendations for treatment of focal atrial tachycardia\(^a\) (141).

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Recommendation</th>
<th>Classification</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute treatment(^b)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Conversion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodynamically unstable patient</td>
<td>DC cardioversion</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Hemodynamically stable patient</td>
<td>Adenosine</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Verapamil, diltiazem</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Procainamide</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Flecainide/propafenone</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Amiodarone, sotalol</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>B. Rate regulation (in absence of digitalis therapy)</td>
<td>Beta blockers</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Prophylactic therapy</td>
<td></td>
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<tr>
<td>Recurrent symptomatic AT</td>
<td>Catheter ablation</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Betablockers, calcium-channel blockers</td>
<td></td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Disopyramide(^c)</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Flecainide/propafenone(^c)</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Sotalol, amiodarone</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic or symptomatic incessant ATs</td>
<td>Catheter ablation</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Nonsustained and asymptomatic</td>
<td>No therapy</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Catheter ablation</td>
<td>III</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

See references in detail ref. 141

\(^a\)Excluded are patients with multifocal atrial tachycardia, in whom beta-blockers and sotalol are often contraindicated due to pulmonary disease. \(^b\)All listed drugs for acute treatment are administered intravenously. \(^c\)Flecainide, propafenone and disopyramide should not be used unless combined with an AV-nodal-blocking agent.

AT indicates atrial tachycardia; DC, direct current.

The levels of the evidence are ranked as follows: Level A (highest): derived from multiple randomized clinical trials; Level B (intermediate): data on the basis of a limited number of randomized trials, nonrandomized studies, or observational registries; Level C (lowest): the primary basis for the recommendation was expert consensus.

The format for classifying indications, summarizing both evidence and expert opinion:

- Class I: Conditions for which there is evidence and/or general agreement that the procedure or treatment is useful and effective;
- Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment;
- Class IIa: The weight of evidence or opinion is in favour of the procedure or treatment;
- Class IIb: Usefulness/efficacy is less well established by evidence or opinion;
- Class III: Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and may even be harmful in some cases.
2.2.7.2 Invasive therapy

Surgical resection or ablation of the ectopic focus was first attempted in 1973 (145). Since then, different surgical procedures (electrocoagulation, excision, cryoablation of the ectopic focus or electric isolation of an atrial portion) with variable success rates have been described (7,39,49,79,123,137,146–151). The problems related to open heart surgery and intra-operative mapping have shifted the interest in the invasive therapy of EAT from arrhythmia surgery to catheter ablation.

The earliest catheter ablation method involved direct current (DC) ablation of the normal AV conducting system with permanent VVIR pacemaker implantation. This approach controlled the ventricular rate, but permitted the atrial tachyarrhythmia to persist (152). Direct ablation of the EAT focus was first reported by Silka et al 1984 using DC energy (153). DC ablation did not gain wide acceptance as a treatment of EAT, primarily due to the risk of perforation from barotrauma in the relatively thin-walled atrium. The introduction of RF current as an ablation energy source caused a resurgence of interest in catheter therapy for EAT. Studies by Lee et al (154) and other investigators (155,156) in animal models demonstrated the transmural nature of RF lesions at the atrial level, which healed with well-organized fibrous scars and did not result in acute or late perforation. The technique was quickly applied to both adult (157) and pediatric patients (60,158) with EAT during the last decade.

The response of the EAT focus to successful RF application is rapid and similar to that seen with a correctly positioned catheter in patients undergoing ablation for accessory pathways (62). The most common response to successful ablation is transient acceleration of the atrial rate followed by abrupt termination of the tachycardia, but occasionally heat may also increase the firing rate of the ectopic focus (62,75). Once tachycardia terminates, energy application should be continued for 60–100 seconds (75), and power can be titrated to achieve a tip/tissue interface temperature of 65–70°C, which is high enough to ensure proper lesion formation without boiling, coagulum formation and impedance rises (159,160).

Following a successful RF application, the patient is usually observed in the EP laboratory with the catheters in place for another 30 to 60 minutes. Isoproterenol infusion and sometimes programmed stimulation are used to ensure that there is no ectopic activity left (62).

The acute success rate of catheter ablation of EAT guided by conventional fluoroscopic methods is 70–90% (51,53,54,78). A single focus and right atrial origin are important predictors of successful ablation. Mapping targeted to the anatomic structures most commonly involved in EAT has yielded high ablation success rate even without the use of sophisticated three-dimensional mapping techniques (62,80,81). On the other hand, Weiss et al reported a 100% acute success rate by using the CARTO system in the management of EAT (67). The reported recurrence rates after successful ablation vary between 9 and 14% in different studies with different follow-up time (54,62,67,68).

Catheter ablation of EAT is safe. The rate of minor complications in different studies is approximately 3% (51–54,60,70–72,78,161,162). Despite the generally thin atrial wall, cardiac perforation is uncommon and probably no more frequent than with the ablation of other SVTs. However, the thin atrial wall frequently does not limit lesion growth beyond the myocardium, so damage to noncardiac structures may occur, most notably damage to
the right or left phrenic nerve with ablation of the right or left lateral atrial freewall, superior vena cava, and left pulmonary vein tachycardias. Other site-specific ablation risks include the risk of sinus node dysfunction after ablation of EAT arising from the sinus node region and complete heart block after ablation in the anteroseptal region. Recent findings suggest that the ablation of pulmonary vein tachycardias may result in pulmonary vein stenosis and occlusion (163). In children, the size of an atrial lesion produced by RF energy may increase with age. Whether this lesion expansion creates clinical problems is unknown (124).

Our knowledge of the sequence of onset of ventricular dysfunction allows us to tailor our treatment: According to earlier comments (64), medical treatment could be carried out until ventricular dilatation occurs. The shortening fraction should not be allowed to fall below normal. Ablation therapy is also a treatment option for patients who are intolerant of drug treatment or who do not want to long-term therapy.

2.3 Inappropriate sinus tachycardia

2.3.1 History

Inappropriate sinus tachycardia, which has also been called chronic nonparoxysmal sinus tachycardia or permanent sinus tachycardia, was first described in 1939. Codvelle and Boucher reported a case of an apparently healthy young man who, for two years, had resting sinus rates in the range of 160 bpm (164). Subsequently, Wising (165) reported four members of a single family who had unexplained sinus tachycardia of long duration. In 1979, the syndrome of IST was defined by Bauernfeind and colleagues (166) as chronic nonparoxysmal sinus tachycardia in otherwise healthy individuals, and they further studied the mechanism of IST. This arrhythmia received little attention until 1994, when Morillo and colleagues (167) published their studies of the mechanism of IST. In recent years, IST has been increasingly recognized and studied as a clinical entity, and the therapeutic possibilities of IST have been a subject of great interest lately (1,3,105,168–180).

2.3.2 Prevalence and characteristics

IST has been thought to be relatively uncommon among the general population, but there are no earlier studies concerning the prevalence of IST. The syndrome is not associated with structural heart disease. The majority of patients with this clinical syndrome are young, 20–45 years old (105,171,175) and over 90% of patients in the earlier published series have been female (3,105,166,167,170,171,174,177,181). In addition, there is a disproportionate occurrence of IST in health care professionals, such as cardiac nurses and physiotherapists (167,170). The explanation for these findings is lacking, but it can be selection bias. Recently, Lopera et al. (180) reported four elderly females (aged 61–71
years) with long-standing IST, representing them as a unique subgroup within the IST patient population. Thus, IST can be present in a wide spectrum of patient populations, including elderly as well as younger subjects.

2.3.3 Pathophysiology

2.3.3.1 Sinus node anatomy and physiology

The sinus node is a collection of morphologically and electrically distinct cells (182,183). The central portion of the sinus node, which houses the dominant pacemaking function, contains cells with longer action potentials and faster rates of phase 4 diastolic depolarization than other cardiac cells (183,184). As early as 1911, Lewis (185) et al. and subsequently Meek and Eyster (186) showed that the site of origin of the impulse is located in the region between the superior vena cava and the right atrial appendage. Boineau et al (187,188) later noted, both in animal and in human studies, that the sinus node actually comprises a wide complex of pacemaker cells distributed along the lateral aspect of the right atrium. Using extensive intraoperative mapping techniques, they elegantly showed that the sinus node in humans is a structure approximately 7.5x1.5 cm in size and distributed along the long axis of the crista terminalis, extending from its superior aspect at the junction of the superior vena cava and the right atrium almost to its inferior extent at the junction of the right atrium and the inferior vena cava. Furthermore, Anderson et al (189) demonstrated that sinus pacemaker tissue may also be found in the superior and medial aspects of the crista terminalis where it crosses anterior to the superior vena cava. The sinus node complex is anatomically situated subepicardially within the terminal groove (sulcus terminalis), and the analogous endocardial structure is the crista terminalis (171,189).

The sinus node complex responds to changes in autonomic balance with changes in the rate of firing. It has also been shown that a change in HR correlates with a change in the site of origin in atrial depolarization. That is, an increase in HR associated with sympathetic activation causes a cranial shift in the pacemaker location, whereas vagal stimulation, resulting in slowing down of HR, causes a caudal shift along the crista terminalis (188,190). The sinus pacemaker may be shifted over a distance of up to 3 cm along the region of the sulcus terminalis (188,191). This dynamic behaviour is helpful when evaluating patients suspected of having IST.

2.3.3.2 Pathophysiology of inappropriate sinus tachycardia

IST is focal tachycardia originating in the sinus node at rates above the physiologic range, but without any appropriate relation to the metabolic or physiologic demand. The pathophysiologic mechanisms of IST are not well understood, and the differences between the
studies on its mechanism suggest that this may possibly be a heterogeneous condition. Bauernfeind et al (166) originally suggested that the tachycardia results from abnormal autonomic influence on the sinus node, i.e. either excessive sympathetic tone or blunted vagal activity. In their series of 7 patients, only one had an elevated intrinsic heart rate (IHR). Others have found a decrease in HRV in IST patients and have suggested decreased vagal tone (174).

Another possible mechanism for the syndrome of IST is a primary abnormality of the sinus node. Although no causative links have been established, it is suggestive that a primary cellular abnormality may be present. Pathological analysis of sinus nodes surgically removed from patients with medically refractory IST showed an increased number of lipofuscin-laden vacuoles in the transitional cells of the sinus node. This finding is consistent with cell degeneration (192). Morillo et al (167) studied 6 patients with IST. Their autonomic balance as assessed by HRV was normal, but the intrinsic heart rate (IHR) was significantly elevated in all patients. In addition, the patients demonstrated beta-adrenergic hypersensitivity as assessed by dose-response curves to isoproterenol and a depressed efferent cardiac vagal reflex in the cold pressor test. These data suggest that, at least in these patients, the mechanism involved a primary abnormality of sinus node function manifested as enhanced automaticity, perhaps worsened by a depressed vagal response or an exaggerated response to catecholamines. More recently, the report by Marrouche et al (105) was consistent with a combined mechanism involving both increased sympathetic hypersensitivity and intrinsic automatic behaviour. The fact that women have higher IHR than men after autonomic blockade (109) also suggests that the difference in HR is not related to a gender difference in autonomic tone but to the intrinsic properties of the sinus node. It is conceivable that very young patients have a different mechanism with predominant hyperactivity of the sympathoadrenergic system (105). Some patients with IST may also have a psychological component of hypersensitivity to somatic input.

Several investigators have reported IST in patients after RF catheter ablation, particularly after atrioventricular node modification (170,193–196). In large series of patients, the incidence appears to be approximately 10 % (193,194). However, the tachycardia usually persists for less than one month and rarely requires therapy (193,194). In some instances, the tachycardia may require medical or ablative therapy (170). Some studies of HRV after ablation have suggested vagal withdrawal (194,195). Although sympathovagal imbalance is one possible mechanism, the precise mechanism of this phenomenon is unknown.

Patients with the IST syndrome are likely to represent heterogeneous etiologies of abnormal sinus automaticity, abnormal autonomic influences and automatic focal ATs arising near the sinus node, and different pathophysiologic mechanisms may show similar clinical pictures (171). One possibility is that IST may represent autonomic neuritis or part of a spectrum of more general autonomic neuropathy. Differentiation between the mechanisms may help to guide therapy in a given patient. Clearly, further research into the etiology of IST is required.
2.3.3.3 Autonomic regulation

Pharmacological maneuvers

Autonomic testing in inappropriate sinus tachycardia. Autonomic testing is useful in individual patients to clarify the mechanism of IST and may assist in the choice of therapy. This includes determination of IHR during complete beta-adrenergic and cholinergic blockade (109,197). Jose and Taylor have demonstrated that complete cardiac denervation can be produced chemically by bolus injections of propranolol (0.2 mg/kg) and atropine (0.04 mg/kg) (109). The IHR measured is compared with the predicted value for each patient by the formula: \( IHR = 118.1 - (0.57 \times \text{age}) \) (197). Because vagal influences predominate, administration of a large dose of atropine normally results in a relatively large (mean 53 bpm) increment in resting HR. Normally, there is relatively little resting beta sympathetic tone, and administration of a large dose of propranolol results in only a small (mean 9 bpm) decrement in resting heart rate (198). A bolus injection of atropine (1 mg) alone can also be administered to assess the maximum HR (199).

Assessment of the HR response to graded isoproterenol infusion is a part of autonomic testing (167). Adrenergic stimulation by isoproterenol is occasionally required for the initiation of tachycardia during electrophysiological testing. Intravenous infusion of isoproterenol is administered, starting at 0.5 to 1 µg per minute and titrated every 3 to 5 minutes to a maximum dose of 6 µg/minute with serial assessment of sinus cycle length.

Adenosine. The efficacy of intravenous adenosine for the termination of tachycardias requiring the AV node as a part of their re-entrant circuit is well established, but there are much less data on the response to adenosine in patients with arrhythmias involving the sinus node. Adenosine is known to cause transient slowing of physiologic sinus tachycardia (200) and to terminate sinus node re-entrant tachycardia (96,201). Earlier, only Glatter et al have studied the effects of adenosine on IST. In their study, adenosine failed to relieve tachycardia, although some increase in the tachycardia cycle length was seen in all patients (106).

Heart rate variability

There are few studies dealing with autonomic regulation of IST. Morillo et al (167) attempted to evaluate sympathovagal balance by measuring the LH/HF ratio for only 10 minutes before and 10 minutes after upright tilt (i.e., a total of 20 minutes). They found that the ratio was normal and no difference existed between the control and study patients. The results of the studies of Castellanos et al (179) confirmed this, but they also reported that 24-hour ECG recording-based time- and frequency-domain indexes of HRV were markedly reduced in a population of young, mainly female patients with IST. It is noteworthy that the LF/HF ratio only expresses the relation between the numerator and the denominator regardless of their absolute values (179). Also, Sgarbossa et al (174) and recently Lopera and colleagues (180) found similar changes in the traditional indices of HRV. These changes have been traditionally considered to be due to abnormally low parasympathetic tone or increased sympathetic tone and/or to indicate, as several studies have suggested, that secondary increases in sinus rates by themselves, regardless of their causes (high-dose isoproterenol, exercise and so forth), can decrease overall HRV (202–206). Castellanos et al (179) also observed the decrease in traditional HRV parameters.
after attempted normalization to a rate of 75 bpm, suggesting an overall 24-hour decrease in parasympathetic activity and possible short periods of increased vagal tone seen at the AV nodal level in IST.

It is possible that analysis of traditional HRV is not able to support a primary sympathetic or parasympathetic mechanism. Non-linear indices, such as approximate entropy and detrended fluctuation analysis, may be more useful in this respect (180).

2.3.4 Symptoms

The symptoms of IST syndrome include palpitations with or without dizziness, (pre)syncope, light-headedness, chest pain/discomfort, shortness of breath, anxiety and reduction in exercise capacity. Patients with IST have a spectrum of clinical presentations ranging from minimally symptomatic palpitations to incessant and incapacitating tachycardia. In many cases, the symptoms are disproportionate to the degree of tachycardia (199). Occasionally, the patient may be completely asymptomatic and is found to have resting tachycardia during a routine physical examination (1).

2.3.5 Diagnosis and differential diagnosis

2.3.5.1 Clinical evaluation

The diagnostic criteria of IST have been in a state of evolution. The diagnosis must be based on the complete clinical picture and exclusion of other atrial tachycardias. Because symptoms are frequently intermittent, serial evaluation may be required (3).

The clinical evaluation of the patient includes a careful medical history, cardiovascular examination, 12-lead ECG, echocardiography, 24-hour ECG recording and a treadmill test. Antiarrhythmic medication should be discontinued at least two days before the evaluation. The ECG characteristics of IST are summarized in Table 2, and a typical ECG example of IST is shown in Figure 5.
Fig. 5. ECG of a 36-year-old woman with inappropriate sinus tachycardia. Her heart rate at rest was 101 bpm. P wave axis and morphology are similar as in sinus rhythm.
Fig. 6. Examples of different 24-hour heart rate trend analyses of patients with inappropriate sinus tachycardia. A) The heart rate trend of a 29-year-old woman with average heart rate 101 bpm (range 82-141 bpm). The variation of heart rate during activities was modest. B) The heart rate trend of a 23-year-old woman with average heart rate 84 bpm (range 68-205 bpm). The resting heart rate was mostly in the physiologic range of 65 to 85 bpm. Inappropriate sinus rate
response was seen with modest activity. C) The heart rate trend of a 26-year-old woman with average heart rate 109 bpm (range 96-165 bpm). The resting heart rate was elevated, and inappropriate sinus rate response was associated with mild exertion. D) The heart rate trend of a 36-year old woman. The average heart rate was 97 bpm (range 70-157 bpm). An exaggerated heart rate response was seen during the waking hours and a near-normal heart rate during sleep.

24-hour ambulatory ECG recording characteristically demonstrates, in a non-medicated state, a mean HR above 90–95 bpm (169,179). A daytime resting HR is usually higher than 95 bpm, and an increase in sinus rate from supine to upright position of more than 25–30 bpm have been reported (179). Generally, patients have a near-normal resting HR during sleep and an exaggerated HR response during the waking hours. However, the 24-hour HR trend analysis in patients with IST may have a wide spectrum (178) (Figure 6). The bicycle test reflects the exaggerated HR response to minimal exercise. Within the first 90 seconds of a standard Bruce protocol in a bicycle test, patients with IST have a HR response greater than 130 bpm to this minimal workload (169). Echocardiography is usually normal, although there have been occasional instances of mild tachycardia-induced cardiomyopathy in patients with long-standing IST (169). The syndrome of IST is rarely associated with mitral valve prolapse (170).

2.3.5.2 Electrophysiologic evaluation

The sole purpose of the diagnostic invasive electrophysiological examination is the exclusion of other atrial arrhythmias in a patient who has a clear documentation of excessive HRs with concomitant symptoms and is considered for nonpharmacologic therapies (199). In patients who are mildly symptomatic and do not require therapy or are responsive to medical therapy alone, electrophysiological evaluation is not necessary.

The electrophysiological diagnosis of IST includes (1) exclusion of arrhythmias initiated or terminated by programmed atrial stimulation or overdrive pacing, (2) intracardiac atrial electrogram recordings that reveal a cranio-caudal pattern of activation, with the earliest recordings occurring at the superior aspect of the crista terminalis despite autonomic manipulation (atropine or isoproterenol), (3) a gradual increase and decrease in HR at the initiation and termination of tachycardia, and (4) shifts at the earliest site of activation along the crista terminalis in response to changes in the tachycardia rate (170).

The basic electrophysiological examination is done in the way described in the section on EAT (see pages 30 and 31). The normal physiology of the sinus node distinguishes IST from other atrial arrhythmias. Sinus node function, as assessed by automaticity of the sinus node, is within the normal limits. This is determined by overdrive suppression of the sinus node and by noting the recovery time after atrial pacing at high rates. Intra-atrial, AV nodal and His-Purkinje conduction times are also normal (1). The approach described by Kalman et al and Lee and co-workers involves a combination of electrophysiological mapping and an anatomic approach. For activation sequence mapping, a multipolar catheter is placed along the crista terminalis in addition to the catheter used for a routine electrophysiological evaluation (coronary sinus, His bundle region and right ventricular apex). Intracardiac echocardiography is useful because the crista terminalis not visible by
fluoroscopy and has a varied course in patient populations. Intracardiac echocardiography readily identifies the crista terminalis and its proximity to a catheter. HR and the site of the earliest crista terminalis activation are noted at the baseline and during graduated isoproterenol infusion (199). Under maximal adrenergic stimulation with isoproterenol and parasympathetic blockade with atropine, the superior portions of the crista terminalis are revealed as the earliest site of activation. Programmed atrial stimulation can be attempted to induce tachycardia at the baseline and after catecholamine infusion. Detailed endocardial atrial activation mapping during tachycardia should reveal the earliest activation in this region, showing a high-to-low and right-to-left sequence and thus suggesting origin in or around the sinus node (1,171). In some laboratories, aminophylline is also used in initiating IST (105). Advanced mapping technologies, such as the 3-dimensional electro-anatomical mapping system (105) or the non-contact mapping system (207), may have advantages in identifying and tracking the RF application site and reducing procedural time.

2.3.5.3 Differential diagnosis

In the differential diagnosis, it is important to exclude sinus node re-entrant tachycardia, an AT which originates in the sinus node region, physiologic sinus tachycardia and posture tachycardia syndrome. The inclusion of symptoms as the criteria of IST differentiates this syndrome from severely deconditioned individuals who might fulfill the criteria for "inappropriate" sinus tachycardia based on rate alone (170). Secondary causes of sinus tachycardia, as described earlier (Table 2), should be excluded. The differentiation of sinus tachycardia from AT or sinus node re-entry tachycardia is usually made in the electrophysiological laboratory, but it may be difficult even there. Documentation of the arrhythmia on 12-lead ECG often enables differentiation of IST from EAT. Programmed stimulation is useful to exclude sinoatrial re-entrant tachycardia, because, in contrast to sinoatrial re-entrant tachycardia, atrial pacing neither initiates nor terminates IST. Table 4 shows the electrophysiological differentiation of IST, EAT and sinus node re-entry. In general, in IST the site of origin of activation changes and moves down along the crista terminalis as a function of changes in autonomic tone, whereas in focal tachycardia site of origin remains fixed. The borderline between IST and focal AT originating in crista terminalis is relatively imprecise. During ablation, AT appears to be a focal disorder, which may be successfully ablated with a single well-targeted RF application. IST is a diffuse disorder, and successful ablation requires targeting of the tissue over a considerable region of the pacemaker complex. The intracardiac atrial electrograms associated with AT are generally fractionated, whereas the intracardiac atrial electrograms of IST are not fractionated (3).

Postural tachycardia syndrome is characterized by a high sinus rate and disabling symptoms, such as palpitations, fatigue, light-headedness and exercise intolerance, related to orthostatic intolerance caused by mild autonomic dysfunction (208). The characteristic feature in these patients is postural sinus tachycardia, i.e. the patients exhibit marked increase in HR upon rising up from a supine position (208) in the absence of orthostatic hypotension and improved by fludrocortisone (209). In some patients, there may be an
overlap between IST and postural tachycardia syndrome or neurocardiogenic (vasovagal) syncope and chronic fatigue syndrome. The similarities to panic and anxiety disorder may prevent a proper diagnosis. In fact, many patients with IST referred for electrophysiological evaluation carry a primary psychiatric diagnosis, being managed with various anxiolytic agents (1).

2.3.6 Natural course

Only one previous report suggests that the prognosis of these patients may be excellent (165), although dilated cardiomyopathy may develop in some patients with chronic untreated ATs, impairing the patient's prognosis (91,135). The risk of tachycardia-induced cardiomyopathy in treated patients with IST is unknown, but is likely to be small (144).

Reported cases of IST deal predominantly with young females and with symptoms of relatively short-to-intermediate duration (167,169,171,174,179). Recently, Lopera et al (180) published a study of four elderly females with long-standing (at least 15 years) IST. All these patients had developed systemic hypertension after many years of sustained cardiac symptoms of palpitations and documented high resting HRs. The investigators did not observe dilated cardiomyopathy in any of their patients. Although a cause-effect relation between chronic IST and systemic hypertension cannot be established based on the results of that study, it is possible that treatment of the IST could facilitate the treatment of the underlying systemic hypertension. There are no earlier studies on the mortality of patients with IST.

2.3.7 Treatment and outcome

2.3.7.1 Medical and other therapies

According to the ACC/AHA/ESC guidelines for the management of patients with IST (Table 6) (144), initial therapy should be pharmacological, and the agents most frequently used as first-line therapy are beta-blockers. Because no comparative studies of management exist for IST, therapy is empirical and tailored to individual patients. Incessant forms of IST are particularly problematic to treat. The patient's response to exercise or isoproterenol infusion may be useful in both guiding the choice of therapy and assessing its efficacy. Nondihydropyridine calcium-channel blockers, such as verapamil and diltiazem, are an alternative and may be more useful in patients with an elevated IHR and a normal response to isoproterenol (210). In general, these drugs have no serious side effects. More aggressive medical therapy with drugs that affect sinus node automaticity, such as amiodarone or propafenone, may be indicated in selected patients. However, their potentially serious side effects must be considered before initiating this therapy in a patient population comprising mostly young people (210). Newer agents that slow HR by
inhibiting the hyperpolarization-activated (I_f) current are investigational and have not been used in patients with IST (211–218).

Table 6. ACC/AHA/ESC recommendations for treatment of inappropriate sinus tachycardia (141).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recommendation</th>
<th>Classification</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>Medical</td>
<td>Beta-blockers</td>
<td>I</td>
<td>C</td>
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<tr>
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<td>Verapamil, diltiazem</td>
<td>Ila</td>
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</tr>
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<td>Interventions</td>
<td>Catheter ablation - sinus node</td>
<td>IIb</td>
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<tr>
<td></td>
<td>modification/elimination*</td>
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*used as a last resort. See references in detail ref. 141. The levels of the evidence are ranked and the formats for classifying indications are as in Table 5.

Earlier studies have indicated that teenagers may represent a selected group of subjects with IST who may respond to aerobic exercise programs (219), but in adults monitored aerobic exercise reducing the resting HR did not abolish inappropriate paroxysms of sinus tachycardia (105).

2.3.7.2 Invasive therapy

Surgical and nonelectric ablation. Asymptomatic or minimally symptomatic patients who are not seeking treatment or respond to pharmacologic therapy do not usually require invasive investigations and therapy. Medically refractory patients have been managed surgically with the use of a right atrial exclusion technique, leaving the patient with a junctional escape rhythm (220). Likewise, reports of sinus node ablation with the use of intracoronary ethanol have documented success in eradicating IST (221). Intraoperative cryoablation or percutaneous catheter ablation of the His bundle have also been used in the management of patients refractory to medical therapy. The main limitation of these techniques is that most patients are rendered pacemaker-dependent (78,169,222). Furthermore, in the case of His bundle ablation, the atria continue to beat at a fast rate, which might cause the patient to continue experiencing symptoms as well as create dual-chamber pacemaker problems with the ventricles “tracking” the high atrial rate or cause symptoms during mode switching or a high-rate block (1,199).

Radiofrequency catheter ablation. The recognition that the sinus node region is a large complex exhibiting rate-dependent site differentiation has allowed targeted ablation to eliminate the fastest sinus rates while maintaining the pacemaker function of the sinus node (199). Animal studies have shown the feasibility of performing sinus node modification with high-frequency current (223) and Nd:YAG laser photocoagulation (224). More recently, RF energy was found to be quite effective in patients with IST (191,225). The appropriate site for lesion delivery is dictated by activation mapping. By maneuvering a mapping/ablation catheter throughout the high right atrium, it is possible to record electrograms from the distal portion of the ablation catheter that precede the surface P wave, as well as all other recorded electrograms, during the tachycardia. The local endocardial
activation time preceding the onset of the surface P wave by 25 to 45 ms has been associated with an increased probability of HR being decreased after the application of RF energy (178). This portion of the crista terminalis is then targeted for ablation. Progressively superior portions of the crista terminalis are then ablated until the target HR reduction is achieved. Power should be adjusted to achieve a catheter tip temperature of 55°C to 70°C. Speeding up of the sinus HR followed by a marked subsequent HR reduction or the appearance of a junctional rhythm during ablation are indicators for successful ablation sites, at which the delivery of ablation energy should be continued for at least 60–90 seconds (199). Because of the complex sinus node structure, the sinus node ablation procedure is usually time-consuming, and several RF applications are normally required (178). The clinician must take care to ablate the superomedial portion of the crista terminalis as it courses anterior to the superior vena cava to insert on the intra-atrial septum. By using 3-dimensional electroanatomical mapping, Marrouche and colleagues (105) estimated the ablated area to measure 12±4mm x 195mm. After ablation, the site of the earliest activation along the crista terminalis, even during maximal adrenergic stimulation, is inferior. This is also shown by the superiorly directed P wave axis on the 12-lead ECG. This approach has been demonstrated to be acutely effective to achieve a significant reduction in sinus rate and yet to maintain chronotropic competence (170,191).

HR control may have been achieved by either destruction of pacemaker tissue or interruption of autonomic neural inputs or both. Histological examination of the canine sinus node after RF catheter ablation demonstrated an area of fibrosis with complete loss of both nodal cells and sympathetic innervation (191). The demonstration of decreased IHR after RF ablation is consistent with the destruction of sinus node cells and/or sympathetic innervation to the sinus node complex.

Results of sinus node modification. The definitions of successful short-term outcomes are not uniform. The baseline sinus rate usually varies greatly from patient to patient and sometimes varies in a given patient from time to time during the procedure. In some laboratories, they titrate isoproterenol infusion to raise HR above 120 bpm, and a sinus node modification is defined as successful when HR decreases by 30 bpm during isoproterenol infusion (178) and atropine (199). Other investigators have defined short-term success as reduction of the baseline sinus rate to less than 90 bpm and the sinus rate during isoproterenol infusion by more than 20% (177) or by 25% (170). In the total sinus node ablation, a reduction of HR by more than 50% of tachycardia HR with a junctional escape rhythm has been defined as a successful outcome (170). Short-term clinical benefits have not been demonstrated clearly by ICE (178). Overall, sinus node modification/ablation can achieve short-term success in 70% to 100% of treated patients (105,170,175,177,226).

The long-term clinical outcomes have been disappointing in these patients, although no precise definition of successful long-term clinical outcome has been established. Outcomes could be measured objectively by the HR response or subjectively by the patient's symptoms during follow-up. Previously, studies on RF catheter ablation of IST have reported a wide range of long-term success rates (23–83%) and a sizable risk of complete sinus node abolition (105,169,170,175,177,227). One of the factors contributing to limited long-term cure was the inability to target with precision the sites of impulse origin using conventional mapping (177). Recently, RF ablation guided by intracardiac echocardiography has also appeared to reduce the risk of inadvertent sinus node damage (227–
However, this technique seems to be associated with a poor success rate (23%) at long-term follow-up (227). Ren and colleagues (181) got 70% predictive value of the characteristic intracardiac echocardiography signature, suggesting transmural/epicardial damage for long-term IST control. One must realize that sinus node modification is not a focal ablation, but requires complete abolition of the cranial portion of the sinus node complex, which seems to show automatic behaviour. Although a successful long-term outcome may be achieved in a few patients, symptoms of palpitations and autonomic characteristics frequently persist.

There was a high rate (30–77%) of symptom recurrence in the series with sinus node modification (3,227,230). Most recurrences occurred 1–6 months after the procedure following apparent early success (3,227). Recurrence may be classified into 1 of 2 general categories. Symptomatic recurrence or persistence of symptoms in the absence of documented IST and despite persisting evidence of a successful electrophysiological outcome has been observed in some cases. The second category is electrophysiological and tachycardic recurrence after an initially successful procedure (3). It appears that complete ablation of the sinus node resulting in junctional rhythm has better long-term success (72%), but requires pacemaker insertion (227,230). Also, the important recognition is the relatively frequent association with other atrial tachycardias, which require ablation to maximize procedural success (105).

Complications of sinus node modification. Early complications of RF modification of sinus node function include the need for permanent pacemaker implantation due to extensive total sinus node ablation, transient junctional rhythm persisting for up to approximately 48 hours, transient right phrenic nerve palsy and transient superior vena cava syndrome caused by ablation around the junction of the superior vena cava and right atrium (210). This complication could be diminished by using intracardiac echocardiography for accurate guidance of the procedure (228).

Indications of sinus node modification. Sinus node modification could be considered in symptomatic patients with IST with persistently increased HR. Definition of autonomic features is critical before any attempt at sinus node modification. In certain laboratories, sinus node modification or total sinus node ablation is not recommended for patients with IST and evidence of postural orthostatic tachycardia (178).

The personality of patients with IST is complex, and it is therefore important to discuss thoroughly the realistic expectations and beneficial effects of the procedure. Marrouche et al (105) had many study patients with psychiatric disorders, which improved following ablation in about 66% of them. They also showed that patients with no symptoms other than palpitation and early ablation after the onset of the rhythm disorder were more likely to perceive the procedure as beneficial and to experience complete symptom resolution. After ablation, counselling and easy access to experienced allied professionals increase the positive impact of this procedure on the use of health care resources. Apparently, earlier identification and treatment could improve the quality of life of the patients with IST (180). Given the relatively low rate of long-term success in relieving symptoms despite electrophysiological modification of sinus node function, further studies are needed to identify the optimal extent of ablation and the cohort of patients most likely to benefit from such procedure (199).
3 Aims of the study

The purposes of the present study were to assess the prevalence, characteristics and natural course of EAT and IST.

The specific aims were:

1. to assess the prevalence and natural course of EAT in an asymptomatic, healthy male population and in symptomatic hospital patients (I).
2. to assess the prevalence and characteristics of subjects fulfilling the diagnostic criteria of IST in a random sample of middle-aged subjects and to assess the natural course and prognosis of IST during long-term follow-up (IV).
3. to determine whether there are differences in HR behaviour between normal SR, IST and EAT (II).
4. to systematically study the response of IST to adenosine (III).
4 Subjects and methods

4.1 Subjects

A total of 41 patients with EAT and 46 patients with IST and 42 control patients with SR were recruited (Articles I–IV). Some of the patients took part in more than one study. The study protocols were approved by the local institutional ethical committees. All patients and control subjects gave their written informed consent for the study. Demographic data of the patients are presented in Table 7.

The resting 12-lead ECGs of consecutive young males applying for a pilot’s licence during the years 1981–1993 were analysed retrospectively at the Central Military Hospital in Helsinki, Finland, to assess the prevalence of EAT in an asymptomatic population. To assess the prevalence of EAT in symptomatic patients, all the ECGs of in and outpatients with arrhythmia at the Oulu and Kuopio University Hospitals in the years 1987–1995 were analysed, using five different arrhythmia diagnosis codes according to the ICD9-classification (4270A, 4272A, 4278X, 7850A, 7851A) to cover all possible EAT patients. The patients with ECG evidence of EAT were invited for a control visit. (I)

To evaluate the HRV of tachycardias originating from the ectopic foci and the sinus node, inpatients and outpatients of Oulu University Hospital (n=19) and the University of Miami School of Medicine (n=5) with fast HR in standard 12-lead ECG and in 24-hour ambulatory recordings were included in the study. All patients had elevated HRs observed incidentally (n=3) on a routine examination or brought to attention because of their symptoms (n=21), causing referral to a hospital. Twelve patients had EAT and 12 IST. The control group with normal SR consisted of 24 age- and sex-matched healthy subjects without clinical or echocardiographic evidence of structural heart disease. These subjects were enrolled from the cross-sectional study undertaken earlier and described in detail previously (231–233). (II)
The effects of adenosine were studied in a population consisting of 18 patients referred for evaluation of IST to Oulu University Hospital, Kuopio University Hospital or Miami University Medical Center. Most of the patients presented with incapacitating symptoms, such as palpitations, weakness and light-headedness. The mean duration of the symptoms attributable to IST was 6.9±5.6 years. The age- and sex-matched control group consisted of 18 patients with SR who were referred for an elective electrophysiological examination because of a narrow complex SVT. In the IST and control groups, 7 and 12 patients underwent an invasive electrophysiological study, respectively. (III)

The prevalence of IST was assessed in a randomly assigned population of 604 middle-aged subjects (335 males and 265 females). 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 project is a population-based, epidemiological case-control study addressing the risk factors and disease end-points of cardiovascular diseases (234). 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 picked from the social insurance regis-
ter covering the whole population of the City of Oulu (235). 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., anemia, hypovolemia, thyroid disease) or medication (e.g., thyroid hormone substitution, antiasthmatic drugs) known to accelerate HR were excluded. Patients with hypertension continued their antihypertensive medication at the time of the primary recordings. (IV)

During the years 1996–1998, nine of the patients referred to Oulu University Hospital for evaluation of symptomatic SVTs were diagnosed with IST. For the evaluation of the natural course and prognosis of IST, these 9 patients were pooled together with the 7 subjects from the random population who fulfilled the diagnostic criteria of IST. (IV)

4.2 Definitions of tachycardias

Incessant EAT was defined according to the following criteria: (1) resting daytime HR ≥ 90 bpm, (2) average HR > 90 bpm on 24-hour ECG recordings, and (3) an abnormal P wave axis and/or abnormal P wave morphology in ≥ 2 precordial leads and in ≥ 1 bipolar limb lead on 12-lead ECG (2,236). P wave morphology was described biphasic if P wave had two positive phases. P wave was diphasic if P wave had one negative and one positive phase or one positive and one negative phase. During the follow-up, the rhythm was defined as EAT if the P wave morphology was similar and the rate > 90 bpm in the repeat ECG without a change (<10°) in the frontal P wave axis. If the P wave morphology was abnormal, but the rate < 90 bpm, the rhythm was defined as slow ectopic rhythm. If the P wave morphology and/or axis was clearly different in the repeat ECG, the rhythm was defined as a fusion of ectopic and sinus rhythms. The criteria of normal SR were complete normalization of P wave morphology and axis, with a rate < 90 bpm. The ECGs of all subjects were inspected by the author and by another experienced cardiologist.

IST was defined as a resting daytime HR > 100 bpm with a normal P wave morphology and axis obtained from standard 12-lead ECGs recorded on ≥ 2 separate days and an average HR of > 90 bpm on 24-hour ECG recording (169). In the middle-aged random sample (IV) only the subjects with an average HR > 90 bpm during the ambulatory 24-hour HR measurement and resting HR > 100 bpm in either a supine or a sitting position were considered to fulfill the criteria of IST.

4.3 Collection of clinical data and follow-up

The study subjects were interviewed by the same physician. In the medical history, special attention was given to arrhythmia symptoms, previous diseases and medications. In the middle-aged random sample (III) a standardized health questionnaire on smoking habits, alcohol consumption, physical activity and personality type was also filled in. Alcohol intake was converted into grams of absolute ethanol per week. On the basis of leisure-time physical activity, four groups were formed, using a modification of the method described by Grimby (237). Personality type was evaluated on (1) the Framingham
type A behaviour pattern scale (238), (2) Bortner’s short rating scale of behaviour pattern (239) and (3) the hostility scale (240).

All the patients with evidence of EAT or IST were invited for a control visit, during which the following parameters were checked: clinical history, physical examination, 12-lead ECG, 24-hour ambulatory ECG recording and echocardiography (I–IV). Antiarrhythmic medications were stopped for at least four half-lives before the control visit.

4.4 Electrocardiographic measurements

4.4.1 12-lead ECG

Resting HR was measured and P wave morphology and axis were evaluated from standard 12-lead ECG recordings at a paper speed of 50 mm/s after at least 15 minutes’ rest.

4.4.2 Ambulatory ECG recordings

The short-term ambulatory ECGs (IV) were recorded with a Dynacord Holter Recorder (Model 420, DM, Scientific, Irvine, CA, USA) with a sample frequency of 256 Hz. Each subject was monitored for 15 minutes while quietly lying down and breathing normally, for 15 minutes in a sitting position and for 15 minutes while walking (IV).

Twenty-four-hour HR ambulatory ECGs were recorded using an Oxford Medilog 4500 Holter recorder (Oxford Medical Ltd., England) (II–IV). All patients were encouraged to continue their normal daily activities during the recordings. The data were sampled digitally and transferred to a microcomputer for an analysis of the average 24-hour HR and HRV. Before the HRV analysis, all recordings were carefully edited in order to eliminate segments with intermittent AV block and premature ectopic beats in the patients with IST and sinus beats in the patients with EAT. For details, see Article II.

4.4.2.1 Heart rate variability

Only recordings with qualified beats for at least a 16-hour period and with > 80 % qualified ectopic or sinus beats, respectively, were included in the analyses of HRV. HRV measures were analysed with custom-made analysis programs (Hearts, Hearts Signal Co, Kempele, Finland) as described in detail the previously published papers (27,28,231–233).

Time- and Frequency-Domain Analysis of HRV. The time- and frequency-domain measures of HRV were analysed by the methods recommended by the Task Force of the European Society of Cardiology (22). The SD of all normal-to-normal R-R intervals
(SDNN) and the difference between the maximum and minimum hourly HR (circadian rhythm) were computed as standard time-domain measures of HRV. Spectral power was quantified both by fast Fourier transform analysis and by autoregressive analysis in 4 frequency bands (232,233): ≤0.0033 Hz (ultra low frequency [ULF]), 0.0033 to 0.04 Hz (very-low frequency [VLF]), 0.04 to 0.15 Hz (low frequency [LF]), and 0.15 to 0.40 Hz (high frequency [HF]). ULF and VLF spectral components were computed over the entire recording interval by the fast Fourier method (233). LF and HF components were computed from the segments of 512 R-R intervals by the autoregressive method, and the average values of the entire recording interval were calculated for the components. The LF and HF components were calculated as both absolute and normalized units, which we obtained by dividing the power of these components by the total variance from which the DC component had been subtracted and multiplying this value by 100 (21). In the 45-minute ECG recordings the LF and HF components during the 15-minute period at supine and sitting position and standardized walking were calculated as absolute units and LF/HF ratio was used.

Time domain measures of HRV correlate well with vagal activity (20,241–244). In spectral HRV analysis, respiration is related to the high frequency (HF) power (21). Reflecting the predominantly parasympathetic origin of the HF component, this band can be minimized with atropine or vagotomy (18,19,21,241,243,245). The LF peak of HRV has been attributed to sympathetic activity with vagal modulation, but there are discrepant findings dividing the opinions on the genesis of LF oscillation (18,19,21,243,245,246). Studies on muscle sympathetic nerve activity have suggested that LF and HF may, respectively, reflect sympathetic and vagal outflow (247,248). As a result, the relationship between LF power and HF power (LF/HF ratio) has often been referred to as a specific marker of sympathovagal balance (21,23), but this idea has been seriously criticized (249). The origin of the ULF and VLF components is not clear. Vagal activity (18,21), thermoregulation and peripheral vascular resistance have been suggested as the cause for fluctuation in the VLF region (250–253).

Poincaré plot analysis. A Poincaré plot analysis is a diagram in which each R-R interval is plotted as a function of the previous R-R interval. Both visual analysis and of the graphic display and quantitative analysis of the plots can be used to describe R-R interval dynamics. The quantitative 2-D analysis of these plots has been described in detail previously (232). The Scattergrams of successive R-R intervals were plotted for the entire 24-hour period, and the SD of instantaneous R-R interval variability (SD1) and of continuous variability (SD2) were then analysed. The shape of the plot was also classified as complex, torpedo-shaped, or normal, as described previously (232).

Fractal and complexity analysis of R-R interval variability. The power-law relationship of R-R interval variability was calculated from the frequency range 10^{-4} to 10^{-2} Hz. The point power spectrum was logarithmically smoothed in the frequency domain and the power integrated into bins spaced 0.0167 log (Hz) apart. A robust line-fitting algorithm of log (power) on log (frequency) was then applied to the power spectrum between 10^{-4} and 10^{-2} Hz, and the slope of this line was calculated (β). This spectral range was chosen on the basis of previous observations regarding the linear relationship between log (power) and log (frequency) in this frequency band in human HR time series data (25). The details of this method have been described previously (25,233).
The detrended fluctuation analysis technique was used to quantify the fractal scaling properties of short-term and intermediate-term R-R interval time series. This method is a modified root-mean-square analysis of random walk that quantifies the presence or absence of fractal correlation properties and has been validated for nonstationary time series (111). In this method, the root-mean-square fluctuation of integrated and detrended time series is measured at each observation window and plotted against the size of the observation window on a log-log scale. The fractal-like signal (1/f signal spectrum) results in an exponent value of 1 ($\alpha=1.0$). The details of this method have been described elsewhere (26,28,111). In the present study, the HR correlations were defined separately for short-term (<11 beats, $\alpha_1$) and long-term (>11 beats, $\alpha_2$) R-R interval data (scaling exponents) on the basis of the previous finding of a crossover point on the log-log plot. Both $\alpha_1$ and $\alpha_2$ were analysed from segments of 8000 R-R intervals and averaged to obtain mean values for the entire recording period.

Approximate entropy. Approximate entropy is a measure that quantifies the regularity or predictability of time series. The details of the method used have been described earlier (27,112). The parameters $m$ and $r$ of the method must be fixed to calculate approximate entropy, and $m=2$ and $r=20\%$ of the SD of the data sets were chosen on the basis of previous findings of statistical validity. Approximate entropy values were computed from 8000 R-R interval segments and averaged to obtain a mean value of approximate entropy characterizing the entire recording (27).

4.4.3 Ambulatory blood pressure and heart rate recordings

Ambulatory 24-hour BP and HR were recorded using the fully automatic SpaceLabs 90207 oscillometric unit (SpaceLabs Inc., Redmond, New Jersey) during normal daily activities (IV). Measurements were performed automatically at every 15 minutes from 4:00 AM till midnight and at every 20 minutes from midnight till 4:00 AM. The mean value of HR during the ambulatory measurement was used in the analysis.

In order to avoid biases caused by temporary changes in sinus frequency, the HR in the random sample (IV) was measured using three different methods on three separate days within one month: 1) ambulatory 24-hour HR recording, 2) 45-minute ECG recording and 3) standard 12-lead ECG.

4.5 Electrophysiological studies

Electrophysiological examinations were performed based on clinical indications. Quadripolar catheters were positioned in the high right atrium, the His bundle position, in the coronary sinus and in the right ventricular apex. In some patients with IST, a 20-pole catheter was also positioned along the tricuspid valve annulus in the right atrium, with the tip of the catheter at the coronary sinus ostium. Intracardiac electrograms, filtered from 30 to 250 Hz, were printed on an electrostatic paper at a paper speed of 100 mm/s or stored on an optical disk using a digitized amplifier/recorder system.
Detailed mapping and ablation of the EATs were performed using a 7 F deflectable ablation catheter with a 4-mm distal tip electrode. The criteria of incessant EAT during the electrophysiological examination were: (1) an endocardial activation sequence inconsistent with a sinus node origin, (2) inability to terminate or reset the tachycardia with appropriately timed premature atrial extrastimuli or rapid atrial pacing, (3) exclusion of intra-atrial, AV and AV nodal re-entry and (4) sudden restoration of SR after RF ablation of tachycardia. The earliest local intracardiac activation in relation to the P wave on the surface ECG was used to select the target site for ablation. RF energy was applied at the appropriate target sites in a range of 20 to 40 W power for 40 to 60 seconds until termination of EAT.

IST was defined by (1) an activation sequence consistent with a sinus origin (i.e., earliest endocardial activation in the lateral high right atrium obtained with the halo catheter) and (2) exclusion of re-entry by inability to terminate or reset tachycardia by atrial extrastimuli or rapid atrial pacing. None of the IST patients were treated by sinus node modification/ablation.

### 4.6 Echocardiographic measurements

A Hewlett Packard Sonos 500 ultrasound system (Hewlett Packard Company, Massachusetts, USA) was used for the echocardiographic examinations. M-mode measurements were obtained under 2-D guidance according to the recommendations of the American Society of Echocardiography (254). The left ventricular mass was calculated according to the formula of Troy et al (255). Fractional shortening was calculated by dividing the difference between the left ventricular dimensions in diastole and systole by the diastolic dimension and then multiplying it by 100.

### 4.7 Pharmacological maneuvers

#### 4.7.1 Autonomic blockade

Because the electrophysiological effects of adenosine are influenced by autonomic tone (116,256,257), in a subset of 5 patients with IST and 5 patients with SR, the direct effects of adenosine were assessed under complete beta-adrenergic and cholinergic blockade. Autonomic blockade was achieved pharmacologically by abolishing all beta-adrenergic and cholinergic receptor input to the heart with intravenous propranolol (0.2 mg/kg) and atropine (0.04 mg/kg), respectively. The adenosine sensitivity test during autonomic blockade was carried out 10 minutes after the drugs were injected. The expected IHR was calculated according to a previously described regression equation (197): \( \text{IHR} = 118.1 - (0.57 \times \text{age}) \). The IHR was compared to the actual atrial rate during autonomic blockade.
4.7.2 Atropine

An intravenous atropine bolus injection was given continuously and gradually at a dose of 0.02 mg/kg to the patients with EAT and IST. HR was continuously recorded at a paper speed of 25 mm/s until no increase in the average HR was observed during the 2-minute period. The difference between baseline HR and maximum HR after atropine was calculated and compared with the normal reference values obtained in the previous studies (108,109).

4.7.3 Adenosine

During IST, adenosine was given as a rapid bolus injection (0.1 and 0.15 mg/kg) followed by a 10-mL bolus of normal saline into a large antecubital vein at bedside or into the femoral vein during the electrophysiological studies. The higher dosage was used only if the first bolus did not cause a high-degree AV block. During each study, 6- or 12-channel ECG was recorded continuously at a paper speed of 50 mm/s or using a computer-based digitized recording system (CardioLab EP System; Prucka Engineering, Inc., Houston, TX, USA), until the effect of adenosine disappeared (minimum of 3 min). Following the adenosine bolus, ACL was measured beat-to-beat until it and the AV nodal conduction time returned to baseline. Statistical comparisons within and between the groups were made before the adenosine injection (=baseline), at the time of the maximal effect (=peak) and during the maximal reflex acceleration of sinus rate (=rebound). In the event that no apparent effect on ACL was detected, the time of the maximal AV delay was used to pinpoint the peak effect of adenosine. In the control subjects, adenosine was given during normal SR either after successful catheter ablation or during bedside testing to unmask latent pre-excitation.

4.8 Laboratory methods

All the blood samples were drawn after a 12-hour requested fast. A two-hour oral glucose tolerance test was performed to identify latent diabetes, and the levels of haemoglobin, thyreotropin, glutamyl transferase and glucose were analyzed using standard laboratory methods (IV). In the other study populations, laboratory tests were made by the clinical indications.

4.9 Statistical analyses

All parametric data are reported as mean ± SD (I–IV). Statistical analyses were performed using SigmaStat 2.03 (SPSS Science, Chicago, IL)(II) or SPSS for Windows ver-
sion 7.5–10.1 (I, III, IV). Paired Student's t-test was used to compare HR at baseline and at follow-up (I, IV). Analysis of variance by Bonferroni’s *post hoc* test was used to compare the duration of follow-up time (I). Within-subject differences between the groups were assessed with ANOVA for repeated measurements followed by a *post hoc* t-test with Bonferroni correction (II, III). Continuous variables were compared with Student’s t-test for unpaired samples, and comparisons of categorical data were made with the Mann-Whitney Rank Sum test (III). 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 (IV). A value of $P < 0.05$ was considered statistically significant.
5 Results

5.1 Ectopic atrial tachycardia

5.1.1 Prevalence
Out of a total of 3554 12-lead ECGs of healthy asymptomatic males aged between 17 and 21 years (mean 19±1 years), which were analysed retrospectively at the Central Military Hospital, 12 showed evidence of EAT (prevalence 0.34%). All ECGs had been interpreted as normal by the primary physician. The ECGs of 17 out of the 3700 symptomatic inpatients with arrhythmia (prevalence 0.46%) examined between the years 1980 and 1993 pointed to EAT.

5.1.2 Natural course
A repeat ECG was obtained in 10 males after a follow-up time of 8±3 years (range 3–11 years). Nine of the subjects were still asymptomatic, but one had developed symptoms of palpitation. Two subjects were lost to follow-up. None of the subjects had ever had any antiarrhythmic medication. In all symptomatic arrhythmia patients, a repeat ECG was recorded after a mean follow-up of 7±3 years (range 3–16 years) at a mean age of 26±17 years (eight females and nine males).

Seven of the 27 patients (26%), both asymptomatic (n=10) and symptomatic (n=17), continued to have similar or different ectopic atrial rhythm at follow-up, and 10 (37%) had SR. Ten patients (37%) showed a clear change in P wave morphology in at least two leads and in the frontal axis of the P wave without its complete normalization, suggestive of a fusion of ectopic atrial and sinus rhythms (Figure 7). HR was significantly slower on the repeat ECG (81±19 bpm vs. 109±17 bpm, P<0.001). Only three patients (11%) had faster EAT.
Fig. 7. Left: the primary ECG of an asymptomatic 18-year-old male applying for a pilot’s licence. The heart rate was 97 bpm; in lead aVL the P wave is negative, in leads V1-2 diphasic and in lead V3 biphasic. Four and a half years later he is still asymptomatic and in the repeat ECG heart rate is slower 87 bpm. The P wave morphology has changed; in lead aVL the P wave is positive, isoelectric in leads II and V1 and notched in V2 suggestive of fusion of ectopic atrial and sinus rhythms. Biphasic=P wave with two positive phases, diphasic=P wave with one negative and one positive phase or with one positive and one negative phase.
The follow-up time tended to be longer in the patients who were in SR (mean 92±41 months) compared to those with fusion rhythm or EAT (81±34 months), but the difference was not statistically significant. Five patients had used sotalol and one patient propranolol regularly. One patient had used metoprolol and one propranolol if needed. EAT was the only arrhythmia documented in each case, and none of the patients developed heart failure during the follow-up time. None of the 27 patients had a positive family history of EAT.

5.1.3 Heart rate variability

5.1.3.1 Time- and frequency-domain measures of heart rate variability

Table 8 shows the time- and frequency-domain measures of HRV. None of these measures differed between the patients with EAT and IST. However, all traditional HRV measures expressed in absolute units, including the measures obtained by quantitative analysis of Poincaré plots, were reduced in the patients with EAT compared to those with normal SR (see examples in Figure 8). Despite the reduced overall HRV, the Poincaré plots showed normal comet-shaped characteristics in the cases with EAT. The LF/HF ratio or the LF and HF components analysed in normalised units did not differ from normal in EAT. There was no difference between the maximum and minimum HRs (amplitude of the circadian rhythm) between the study groups (Table 8).
### Table 8. Twenty-four-hour heart rate variability data.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EAT (n=12)</th>
<th>IST (n=12)</th>
<th>Normal sinus rhythm (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24-h HR (bpm)</td>
<td>109±12†</td>
<td>106±9†</td>
<td>72±8</td>
</tr>
<tr>
<td>Minimum HR (bpm)</td>
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<tr>
<td>Maximum HR (bpm)</td>
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<td>121±15</td>
<td>95±14</td>
</tr>
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<td>Difference between maximum and minimum HR (bpm)</td>
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<td>31±8</td>
<td>40±14</td>
</tr>
<tr>
<td>SD1 (ms)</td>
<td>17±12†</td>
<td>15±6†</td>
<td>37±12</td>
</tr>
<tr>
<td>SD2 (ms)</td>
<td>56±33*</td>
<td>67±14†</td>
<td>146±29</td>
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<tr>
<td>SDNN (ms)</td>
<td>75±28†</td>
<td>77±16†</td>
<td>176±39</td>
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<tr>
<td>SDNNi</td>
<td>13±4†</td>
<td>13±3†</td>
<td>21±5</td>
</tr>
<tr>
<td>HF power (ms²)</td>
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</tr>
<tr>
<td>Ln (ms²)</td>
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<td>4.2±0.8†</td>
<td>6.7±0.9</td>
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<td>39±6</td>
<td>38±7</td>
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<td>LF power (ms²)</td>
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<td>1611±960</td>
</tr>
<tr>
<td>Ln (ms²)</td>
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<td>55±8</td>
<td>60±7</td>
<td>61±6</td>
</tr>
<tr>
<td>LF/HF ratio</td>
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<td>1.9±0.9</td>
</tr>
<tr>
<td>VLF power (ms²)</td>
<td>517±472</td>
<td>556±289</td>
<td>2792±1358</td>
</tr>
<tr>
<td>Ln (ms²)</td>
<td>5.3±1.3†</td>
<td>5.8±0.6†</td>
<td>7.8±0.6</td>
</tr>
<tr>
<td>ApEn</td>
<td>1.13±0.22</td>
<td>1.05±0.33</td>
<td>1.15±0.16</td>
</tr>
<tr>
<td>α₁</td>
<td>0.71±0.16†§</td>
<td>1.16±0.13</td>
<td>1.19±0.11</td>
</tr>
<tr>
<td>α₂</td>
<td>1.06±0.21</td>
<td>1.04±0.19</td>
<td>1.08±0.16</td>
</tr>
<tr>
<td>β</td>
<td>−1.39±0.22</td>
<td>1.39±0.22</td>
<td>−1.26±0.15</td>
</tr>
</tbody>
</table>

SD1=short-term SD and SD2=long-term SD analysed from Poincare plots; SDNNi=SDNN normalized with R-R interval length; Ln=natural logarithmic of absolute values, NU=normalized units; ApEn=approximate entropy. SDNN= standard deviations of all R-R intervals. β=slope of regression line of log(power)-log(frequency) of HR variability between frequencies 10⁻² and 10⁻⁴. HF=high-frequency power component of heart rate variability. LnHF=logarithmic high-frequency power component of heart rate variability. LF=low-frequency power component. LnLF=logarithmic low-frequency power component. VLF=very-low-frequency power component. LnVLF=logarithmic very-low-frequency power component of heart rate variability. α₁=short-term scaling exponent. α₂=long-term scaling exponent.

Values are mean ± SD. †P value <0.001 and *P<0.01 compared with normal sinus rhythm with ANOVA and Bonferroni post hoc analysis, §P<0.001 between EAT and IST.

See details in Article II.
Fig. 8. Examples of power spectral analysis of R-R-interval variability of patient with ectopic atrial tachycardia (EAT) without random beat-to-beat R-R-interval dynamics, patient with inappropriate sinus tachycardia (IST) and subject with normal sinus rhythm (SR). Typical spectral pattern with LF and HF oscillations of R-R-interval variability can be observed in EAT and IST, but absolute values of spectral components are smaller in magnitude in EAT and IST than in SR. Power-law slope of R-R-interval dynamics does not differ between EAT, IST and SR.

5.1.3.2 Fractal and complexity measures of R-R interval variability

Approximate entropy, the long-term scaling exponent $\alpha_2$ and the power-law slope in cases with EAT did not differ from those with SR. However, the short-term scaling component $\alpha_1$ was significantly lower in EAT than in either IST or normal SR (Table 8 and Figures 8 and 9).

Fig. 9. Individual values of short-term scaling exponent of patients with ectopic atrial tachycardia (EAT), inappropriate sinus tachycardia (IST), and normal sinus rhythm (SR). Short-term scaling exponent was reduced ($\alpha_1<0.95$) in all but 1 of the patients with EAT.
Full disclosures of Holter recordings and ECG printouts of patients with EAT showed sudden, abrupt prolongations in R-R intervals (exit blocks from ectopic foci) without evidence of a change in P wave morphology or AV block in 6 patients throughout the 24-hour recordings. In 5 cases with low $\alpha_1$ value, no abrupt changes in R-R intervals were observed, but the ectopic foci showed continuous instability in beat-to-beat behaviour during the entire recording period. Unstable beat-to-beat R-R interval behaviour and exit blocks were more commonly observed during sleep than in the daytime.

5.1.4 Heart rate responses of ectopic atrial tachycardia to intravenous atropine

HR increased from $104\pm16$ bpm to $134\pm11$ bpm ($p<0.001$) after intravenous atropine administration in the patients with EAT. The mean increase of HR was $30\pm14$ beats (range 11–65 bpm). In 2 patients, the increase in HR was smaller than the reference values reported for healthy subjects with normal SR (>20% increase from baseline).

5.2 Inappropriate sinus tachycardia

5.2.1 Prevalence

The distribution of the average 24-hour HR in the random middle-aged population is shown in Figure 10. The distribution is clearly skewed to the right after a cutoff point of approximately 85–90 bpm. The average 24-hour HR was over 90 bpm in 19 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-hour average HR > 90 bpm (95±4 bpm), giving an overall prevalence of 1.16 % for IST in the random middle-aged population.
5.2.2 Characteristics of the subjects with inappropriate sinus tachycardia

The characteristics of the subjects fulfilling the diagnostic criteria of IST and the controls in the random middle-aged population are shown summarized in Table 9. 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, 4 subjects fulfilling the diagnostic criteria of IST were women (57%) and 3 were men. The mean age of the subjects was 47±7 years. Five subjects (71%) had previously diagnosed hypertension, and 2 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 HRV measurements, although there was a non-significant trend towards reduction of the LF/HF ratio during walking as compared to the supine position (Table 10).
<table>
<thead>
<tr>
<th></th>
<th>IST (n=7)</th>
<th>Control (n=597)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47±7</td>
<td>51±6</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>4/3</td>
<td>332/265</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27.1±3.3</td>
<td>27.4±4.4</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.86±0.97</td>
<td>0.87±0.86</td>
</tr>
<tr>
<td>Current smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No smoking</td>
<td>4 (57%)</td>
<td>421 (71%)</td>
</tr>
<tr>
<td>Moderate smoking (&lt;20/day)</td>
<td>2 (29%)</td>
<td>154 (25%)</td>
</tr>
<tr>
<td>Heavy smoking (&gt;20/day)</td>
<td>1 (14%)</td>
<td>22 (4%)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No drinking</td>
<td>1 (14%)</td>
<td>89 (15%)</td>
</tr>
<tr>
<td>1–100 g/week</td>
<td>4 (57%)</td>
<td>369 (61%)</td>
</tr>
<tr>
<td>&gt;100 g/week</td>
<td>2 (29%)</td>
<td>143 (24%)</td>
</tr>
<tr>
<td>Leisure time physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No activity</td>
<td>2 (29%)</td>
<td>24 (4%)</td>
</tr>
<tr>
<td>Mild activity</td>
<td>2 (29%)</td>
<td>166 (28%)</td>
</tr>
<tr>
<td>Moderate activity</td>
<td>1 (14%)</td>
<td>198 (33%)</td>
</tr>
<tr>
<td>Heavy activity</td>
<td>2 (29%)</td>
<td>208 (35%)</td>
</tr>
<tr>
<td>Personality type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Framingham</td>
<td>27±7</td>
<td>26±5</td>
</tr>
<tr>
<td>Bortner</td>
<td>22±3</td>
<td>22±3</td>
</tr>
<tr>
<td>Hostility</td>
<td>10±2 *</td>
<td>8±3</td>
</tr>
</tbody>
</table>

*p < 0.001. See details in Article IV.
Among the hospital population, the mean HR in the subjects with IST was 110±11 (range 101–129) bpm in the 12-lead ECG at rest and 94±3 (range 91–98) bpm in the 24-hour 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 to those from the random sample who fulfilled the diagnostic criteria of IST, several parallel features were identified. There was no significant difference in age (47±7 vs. 46±7 years) or the 24-hour 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 inpatients with IST were female (57% vs. 89%).

Table 10. Haemodynamic and laboratory parameters in the random middle-aged population.

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

LF=low-frequency and HF=high-frequency domain in the spectral analysis of heart rate variability, respectively. See details in Article IV.
5.2.3 Natural course

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 inpatients (n=9) were combined. Eleven of the 16 subjects consented to participate in a follow-up examination at 72±29 months (range 36–133). Two subjects (one in each population) were excluded because of asthma medication at the time of the control visit, and two subjects in the random and one in the symptomatic hospital population were lost to follow-up. All subjects who consented to attend the follow-up examinations had symptoms of rapid HR at the time of the control visit. In the random population, two subjects felt an increased HR 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 HR after a mean follow-up of 6.0±2.4 years. The average HR in the 24-hour ambulatory ECG recording was 94±2 bpm (range 91–98 bpm) at baseline and 89±8 bpm (range 80–103 bpm) at follow-up. Likewise, there were no significant differences in the resting HR measured from the 12-lead ECG between the baseline and follow-up visit (104±14 bpm vs. 98±15 bpm, P=0.07). However, despite the persistent symptoms and the relatively high HR at the follow-up examination, only 4 of the 11 subjects still fulfilled the combined diagnostic criteria of IST, whereas the other subjects’ average HR in the 24-hour Holter recording had dropped below 90 bpm.

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 (Table 6), although one subject in the random population had developed hypertension.

5.2.4 Heart rate variability

5.2.4.1 Time- and frequency-domain measures of heart rate variability

All traditional HRV measures were reduced in the patients with IST compared to the subjects with normal SR (Table 8). Despite the reduced overall HRV, the Poincaré plots showed normal comet-shaped characteristics in cases with IST. The LF/HF ratio or the LF and HF components analysed in normalised units did not differ from normal in IST.
5.2.4.2 Fractal and complexity measures of R-R interval variability

The short- and long-term scaling exponents $\alpha_1$ and $\alpha_2$, the power-law slope $\beta$ and approximate entropy did not differ between the subjects with IST and those with normal SR (Table 8).

5.2.5 Heart rate responses of inappropriate sinus tachycardia to intravenous atropine

In the subjects with IST, HR increased from 108±15 to 137±18 bpm after the administration of intravenous atropine. The mean increase of HR was 29±13 bpm (range 15–49 bpm). Two subjects with IST had a smaller increase in HR than the normal reference range.

5.2.6 Electrophysiological effects of adenosine in inappropriate sinus tachycardia

Basic ECG measurements (III) showed that the resting HR was significantly higher in the patients with IST (114±17 bpm) than in the control subjects (79±11 bpm), P<0.001. The average HR of the IST patients during a 24-hour ECG recording was 94±3 (range 91–104) bpm and showed an unusually high sinus rate during minimal physical activity.

During autonomic blockade, the atrial rate was 132±11 (range 120–145) bpm in the IST patients and 101±13 (range 88–122) bpm in the control patients (P<0.01). Thus, the atrial rate was significantly higher in the IST than in the control group, not only under the baseline conditions but also during autonomic blockade. Moreover, the atrial rate during complete autonomic blockade was significantly higher than the expected range of IHR in the patients with IST (132±11 vs. 88±4 bpm, P<0.001), but not in the control subjects (101±13 vs. 93±8 bpm, p=0.28).

IST, unlike many other SVTs, was resistant to the antiarrhythmic actions of adenosine. The nucleoside failed to terminate the tachycardia in all the patients with IST. In the patients with IST, the first dose of adenosine (0.1 mg/kg) had no significant negative chronotropic action, whereas in the control subjects, it prolonged ACL by 210±159 ms (P<0.001). The highest dose of adenosine increased ACL from 780±128 msec to 984±225 msec (P<0.001) in the control group. Although the maximum dose of adenosine was significantly greater in the IST (0.13±0.03 vs. 0.11±0.02 mg/kg, P=0.014) than in the control group, it caused no significant slowing down of atrial rate. More specifically, in the patients with IST, there was only a minor increase in ACL (526±69 msec to 590±149 ms, P>0.05) even with the maximum dose of adenosine (Figure 11). A comparison of the IST patients to the control subjects indicated that adenosine prolonged ACL significantly less in the patients with IST. In the IST and control groups, adenosine increased ACL by 11±16% and 27±26% (P=0.037), respectively. Adenosine had little or no effect on the
atrial activation sequence (Figure 12). In the control subjects, the effect of adenosine on ACL was clearly biphasic, i.e., the initial slowing down of the atrial rate was rapidly followed by a reflex shortening of ACL. Similar to the peak negative chronotropic effect, the rebound effect caused by adenosine was significantly greater in the control than the IST group. The maximum change in ACL between the baseline and the rebound effect was 47±51 msec in the IST group and 173±96 msec (P<0.001) in the control group (Figure 11B).

Fig. 11. Effect of adenosine on atrial cycle length in patients with inappropriate sinus tachycardia (IST) and control subjects under baseline conditions. A. Typical example of the beat-to-beat changes in atrial cycle length after adenosine. B. Mean changes in atrial cycle length. The dose of adenosine was significantly greater in the IST group (0.13±0.03 mg/kg vs. 0.11±0.02 mg/kg, P=0.014) than in the control group. IST vs. control: ***P<0.001. Peak/rebound vs. baseline: †† P<0.01, † P<0.05.
Fig. 12. Effect of adenosine on atrial activation sequence in a patient with inappropriate sinus tachycardia (IST). Adenosine had minimal to no effect on atrial activation sequence in patients with IST. Shown are surface lead I and bipolar intracardiac ECGs from high right atrial (hRA), tricuspid annulus (TA), and coronary sinus (CS) before and after adenosine (0.15 mg/kg) bolus. Electrodes TA1 and TA7 are located at CS ostium and the sinus node area, respectively.

Because the metabolism of adenosine in human blood is extremely rapid, the effective amount of the drug delivered to the myocardium may vary according to the injection site. In our study, adenosine was injected into either a large antecubital vein (bedside subgroup) or a femoral vein (electrophysiology subgroup). In the electrophysiology subgroup, there was a statistically significant difference between the groups, i.e. adenosine prolonged ACL significantly more in the control subjects than in the patients with IST (211±213 msec vs. 25±48 msec, P=0.032). In the bedside subgroup, there was a clear tendency for adenosine to prolong ACL more in the control subjects than in the patients with IST (194±117 msec vs. 88±117 msec, P=0.142). Thus, the results of the subgroup analysis corroborated that the chronotropic response to adenosine was impaired in the patients with IST.

During pharmacological beta-adrenergic and cholinergic receptor blockade, adenosine prolonged ACL from a baseline value of 523±60 ms to a peak value of 785±243 ms (P=0.048) in the control subjects. In the patients with IST, the adenosine-induced change from the baseline was significantly smaller, i.e., from 461±60 to 487±67 ms (P>0.05). Compared with the baseline conditions, there were no significant differences between the peak effects of adenosine, but the magnitude of the rebound effect tended to be impaired during the autonomic blockade (p=0.061).

The dromotropic effects of adenosine: The maximum dose of adenosine caused a transient second- or third-degree AV block in 44% of the IST patients and in 77% of the con-
trol subjects (P<0.001). Interestingly, adenosine caused apparent prolongation of the AV conduction time or a high-degree AV block without affecting ACL in 8 (44%) of the IST patients, whereas in all the control subjects, lengthening of the AV conduction time always concurred with slowing down of the sinus rate.

There were no significant differences in the incidence of adverse effects between the IST group and the control subjects. No major side effects occurred in either group under the baseline conditions or during the pharmacological autonomic blockade. Minor adverse effects, such as facial flushing and brief chest discomfort, were rather common in both groups. In two patients with IST, the highest dose of adenosine (0.15 mg/kg) caused a brief, hemodynamically stable, self-terminating episode of atrial fibrillation.
6 Discussion

6.1 Ectopic atrial tachycardia

6.1.1 Prevalence

Even though EAT was described as early as 1922 by Gallavardin (35), its prevalence has not been well studied. In particular, there are no data on its prevalence among asymptomatic subjects. The present observations show that the prevalence of asymptomatic EAT is higher than that reported for Wolff-Parkinson-White syndrome in young healthy males (258–260). It is evident that EAT is not well known among physicians and therefore often escapes diagnosis. In fact, none of the present subjects applying for a pilot's licence had been diagnosed as having EAT. In the earlier studies, researchers have felt confident that, in most patients, the diagnosis of EAT can be established by clinical characteristics, standard electrocardiogram and 24-hour ECG recording as long as one adheres strictly to the criteria mentioned above (Table 2) (2,12,261).

6.1.2 Natural course

There have been no previous studies on the natural course of EAT in asymptomatic patients and only a few on incessant, symptomatic EAT in paediatric patients.

It has been noticed that spontaneous remission of symptomatic EAT is not rare, being reported in approximately 31% of cases (9). The present results in young adult subjects agree with the earlier findings in younger subjects suggesting that spontaneous remission is common.

During the follow-up, a change in P wave morphology in at least two leads suggestive of a fusion of sinus and ectopic atrial rhythms was observed in some subjects. These observations suggest that the ectopic foci gradually slow down and degenerate over time rather than there being any sudden restoration of SR. This observation is supported by the
rarity of the diagnosis of EAT in middle-aged or elderly people without concomitant structural heart disease (262,263).

6.1.3 Heart rate variability

6.1.3.1 Abnormalities in time- and frequency-domain heart rate variability

Autonomic regulation of EAT and IST can be compared by traditional analysis methods because of the similar average HR between the two rhythms. The present results suggest that vagal outflow both to ectopic foci and to sinoatrial cells and their responsiveness to the vagal input are similar, because phasic vagal tone is the major factor in the genesis of HRV (18–23). This concept is also supported by the observation that atropine resulted in a similar increase in average HR during EAT and IST. HRV analysed in absolute units was reduced in EAT compared with normal SR. The mechanism for differences in overall HRV is difficult to interpret, however, because the traditional HRV analysis methods may fail to reveal specific autonomic abnormalities in cases with markedly elevated HR (203,206). Several factors that increase HR itself, regardless of the cause of increase, reduce the overall HRV (203,264). Therefore, the pattern of reduced overall R-R interval variability in patients with EAT may result not only from a reduced vagal input but also from enhanced intrinsic automaticity of pacemaker cells or an increased sympathetic input. The traditional methods of analyzing HRV in absolute units may not be able to document the specific autonomic disturbance as a mechanism of arrhythmias in these cases. Notably, the LF/HF ratio and the LF and HF components expressed in normalized units did not differ from normal in EAT, which suggests that there are no marked abnormalities in the phasic influences of the autonomic nervous system on ectopic foci. The increase in HR was within the normal limits after atropine in the majority of patients with ectopic tachycardias, which also suggests that abnormal vagal function may not be the predominant autonomic disturbance in this tachycardia (167).

6.1.3.2 Abnormalities in short-term correlation properties of R-R interval dynamics

An increase in the randomness of short-term HR behaviour, expressed as a reduction of the short-term scaling exponent, was a typical feature of the EATs and resulted either from abrupt prolongations in the R-R intervals or from continuous instability in the beat-to-beat behaviour of R-R intervals. An ECG analysis of Holter recordings revealed that the prolongations in R-R intervals resulted from abrupt exit blocks due to the ectopic foci. Anecdotal cases of exit blocks due to ectopic atrial foci have also been reported previously in short-term ECG recordings (265).
Two potential mechanisms may explain the unstable or random R-R interval behaviour of EATs. First, it is possible that the exit blocks from the ectopic foci result from a specific electrophysiological abnormality similar to that observed in the diseased sinus node. Second, there may be a specific autonomie mechanism behind this abnormality. Accentuated sympathovagal interaction caused by high sympathetic outflow together with a concomitant increase in phasic vagal outflow may result in uncorrelated short-term HR behaviour. Experiments in healthy volunteers have shown that incremental doses of norepinephrine infusion with baroreflex-mediated vagal activation result in similar abrupt prolongations of sinus intervals as observed in the present patients with EAT (266). A reduced short-term scaling exponent and random beat-to-beat HR dynamics have also been observed in patients with heart failure with high levels of norepinephrine (26,267). A complex interaction between norepinephrine and acetylcholine at the presynaptic and postsynaptic levels of the target tissue has been described (268), which may facilitate the random firing of both normal and abnormal pacemakers.

6.2 Inappropriate sinus tachycardia

6.2.1 Prevalence

Our study was the first to describe the prevalence and characteristics of IST in a random middle-aged population and to assess the natural course and prognosis of IST during long-term follow-up. Our results indicate that IST, defined as 24-hour 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 SVT (0.23%) and EAT (0.46%) (269–273). In the random population, the distribution of 24-hour average HR was clearly skewed towards the right. Thus, it is likely that the elevation of HR does 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 (169,171). 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-hour and 45-minute 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 in both a supine and an upright position were included in the current study. If subjects with orthostatic intolerance (postural orthostatic tachycardia syndrome) (208) had been included,
the prevalence of IST would have been even higher. These data emphasize the importance of repeated ambulatory ECG recordings in the diagnosis of IST.

### 6.2.2 Characteristics of subjects with inappropriate sinus tachycardia

The characteristics of patients fulfilling the diagnostic criteria of IST have not previously been studied in a random population. According to the earlier reports, almost all highly symptomatic patients with IST have been women, many of them have been hypertensive, and many have been health care workers (166,167,170,171). The results of our study confirmed the higher prevalence of elevated HR among hypertensive than normotensive subjects. In the five series published earlier, about 90% of the patients with IST were females (166,167,170,171,174). 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 have been related to orthostatic intolerance caused by mild autonomic dysfunction (208). The characteristic feature of these patients is postural sinus tachycardia, i.e., they exhibit a marked increase in HR upon rising from a supine position (208). 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 sympathovagal balance (LF/HF ratio) as assessed by spectral analysis of HRV. Hence, altered autonomic input to the sinus node and postural changes did not appear to be a predominant cause of IST in this random population. These observations corroborate that the elevation of HR in patients with IST may be related to an intrinsic enhancement rather than altered autonomic regulation of sinus node activity (274).
6.2.3 Natural course

There were only minor changes in the HR of the subjects with IST during a mean follow-up period of 6 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 SVT may cause cardiomyopathy and impair the patient’s prognosis (135). 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 showing that chronic nonparoxysmal sinus tachycardia had caused severe left ventricular dysfunction (275). These observations confirm that, despite the constantly elevated HR and persistent symptoms, the prognosis of IST is good.

6.2.4 Heart rate variability

6.2.4.1 Abnormalities in time- and frequency-domain heart rate variability

HRV analysed in absolute units was reduced in IST compared with normal SR. Reduced overall HRV in IST has also been reported previously (179) and may result from a reduced vagal input and/or from enhanced intrinsic automaticity of pacemaker cells or an elevated sympathetic input. The LF/HF ratio and the LF and HF components analysed in normalized units did not differ from normal in IST, suggesting that there are no marked abnormalities in the phasic influences of the autonomic nervous system on sinoatrial cells causing IST.

6.2.4.2 Short-term correlation properties of R-R interval dynamics

The randomness of the short-term HR behaviour of IST did not differ from normal SR.

6.2.5 Pharmacological maneuvers

6.2.5.1 Autonomic blockade

The results of the baseline electrophysiological measurements corroborated and expanded the observations made previously in other laboratories. It was found that not only the
resting HR but also IHR was significantly higher in the patients with IST than in the control subjects. Likewise, in the patients with IST but not in the control subjects, HR after the abolition of autonomic input with propranolol and atropine was significantly higher than IHR calculated according to the equation of Jose and Collison (197).

6.2.5.2 Adenosine

There have been few data on the effects of adenosine on tachyarrhythmias involving the sinus node. To our knowledge, only Glatter et al (106) studied the effects of adenosine on IST. Similar to their study, adenosine failed to terminate the tachycardia in all of the IST patients in our study. Thus, in contrast to sinus node re-entrant tachycardia (96,201), IST was found to be resistant to the antiarrhythmic actions of adenosine. This is in contrast with the anticipated greater negative chronotropic effect of adenosine in subjects with a higher atrial rate (rate-dependent action) (29). Despite a shorter initial cycle length and a larger dose of adenosine, the negative chronotropic response to adenosine was smaller in the patients with IST than in the control subjects. Glatter (106) et al found slight prolongation of the tachycardia cycle, but many of their patients had isoproterenol infusion at the time of the adenosine test (personal communication). Under such conditions, it is likely that the indirect negative chronotropic (antiadrenergic) effect of adenosine is augmented. In keeping with their results, we observed that adenosine caused only a modest, if any, shift in the atrial activation sequence.

The electrophysiological effects of adenosine may vary, depending on the autonomic nervous system tone and the injection site (29). The depressant effect of adenosine on the sinus node is accentuated by the heightened vagal (256) and beta-adrenergic tone (257). Therefore, to eliminate the influence of background autonomic tone, we studied the effects of adenosine during pharmacologic beta-adrenergic and cholinergic receptor blockade. In the control subjects, autonomic blockade had minimal to no effect on the direct negative chronotropic response to adenosine, although reflex tachycardia tended to be blunted. These data indicate that, in control subjects, adenosine exerts a significant negative chronotropic effect regardless of autonomic tone. In contrast, adenosine did not have any significant effect on IST cycle length either under baseline conditions or during autonomic blockade. Consequently, the direct (i.e., cAMP-independent) negative chronotropic effect of adenosine is expected to be diminished in patients with IST. The unusual pharmacokinetic properties of adenosine (e.g., extremely rapid metabolism and biphasic effect on sinus rate) (29) preclude steady-state dose-response measurements and may cause site-dependent variation in the response to adenosine injection. Nevertheless, the results of our subgroup analysis demonstrated that, regardless of the injection site, adenosine prolonged ACL more effectively in the control subjects than in the patients with IST, i.e., the negative chronotropic response to adenosine was impaired in the patients with IST.

Numerous experimental (29,30) and clinical (276) investigations have showed that the negative dromotropic effect of adenosine is dose- and rate-dependent. In this study, adenosine elicited a transient second- or third-degree AV block more frequently in the control subjects (i.e., subjects with slower atrial rate) than the IST patients. Hence, not only the
negative chronotropic but also the dromotropic response to adenosine were impaired in patients with IST. On the other hand, several findings suggest that purinergic and parasympathetic control is more evident in the sinus than in the AV node (277). Consistent with this notion, we found that adenosine increased the AV nodal conduction time (or caused a high-degree AV block) with virtually no effect on ACL in eight patients with IST. In another study, it was seen that the phenylephrine-induced increase in vagal tone can provoke a second-degree AV block without causing any distinct change in the IST rate (166).

6.2.6 Potential mechanism(s) of inappropriate sinus tachycardia

During the recent years, it has become apparent that inheritable ion channel abnormalities play an important role in the pathogenesis of several cardiac tachyarrhythmias, such as the long QT syndrome (278). In addition, Lerman et al (279) showed that a mutation in the inhibitory branch of the cAMP signal transduction pathway may result in idiopathic right ventricular outflow tract tachycardia that is unresponsive to adenosine. Wising (165) previously provided evidence that IST is a heritable disorder, and knockout of the \( I_{K_{Ach,Ado}} \) protein in mice causes a state that closely resembles IST (280,281). Hence, it is tempting to speculate that a specific gene mutation controlling the function of the \( I_{K_{Ach,Ado}} \) protein is the basic abnormality behind IST. Nevertheless, the underlying cause(s) of IST may be heterogeneous (173).

The present data provide new insight into the possible mechanism(s) of IST. First, the resistance of IST to the antiarrhythmic action of adenosine argues against triggered (96,201) activity as the principal mechanism of IST. Second, the higher than normal IHR supports the previous notion that the mechanism(s) of IST involve(s) a primary abnormality of the sinus node rather than abnormal autonomic modulation (29). Given the accentuation of the effect of adenosine on the sinus node by beta-adrenergic stimulation (257), the impaired response to adenosine makes excessive sympathetic input unlikely as a primary mechanism of IST. Third, at the cellular level, an impaired negative chronotropic effect to adenosine suggests that either the indirect (anti-\( \beta \)-adrenergic) or preferably the direct \( \text{Gi}_0 \)-protein-mediated signal transduction pathway is malfunctioning in patients with IST. Accordingly, we postulate that IST may result from a deficient function of the \( I_{K_{Ach,Ado}} \) channel. Because the A1-adenosine receptors and the muscarinic cholinergic system share the same receptor-effector pathway (277), this could explain not only the impaired negative chronotropic response to adenosine but also the blunted response to vagal input in the patients with IST (1,171). This interpretation is supported by several experimental findings. Clapham’s group showed that \( I_{K_{Ach,Ado}} \)-deficient GIRK4 knockout mice exhibited a significantly faster sinus rate than wild-type mice (280). They also reported that the bradycardic response to purinergic and cholinergic agonists and HRV are decreased in mice without functional \( I_{K_{Ach,Ado}} \) channels (281). As in patients with IST, the effect of adenosine on AV nodal conduction was influenced less than the effect on sinus rate (281).
6.3 Limitations of the study

The asymptomatic population sample with EAT comprised only young males. Therefore, the prevalence figures may not be applicable to other populations. It was evident, however, that EAT is not an uncommon finding in asymptomatic young adults, and its prevalence may be even higher in younger subjects. A cut-off HR of 90 bpm was used in this study to define EAT. This definition is based on the recommendations by Spodick et al. (236), who defined 50 bpm and 90 bpm as the extremes of normal resting sinus HR in adult populations, which should improve the sensitivity of the tachycardia threshold. The definition of normal P wave morphology may also be problematic. We attempted to avoid overestimating the prevalence of EAT by including only patients with an abnormal P wave in at least three leads, including one bipolar limb lead.

The diagnosis of IST was based on non-invasive measurements of HR by serial ECG and Holter recordings. Nevertheless, although no routine invasive electrophysiological studies were made, we feel that an overlap between IST and other atrial tachyarrhythmias is unlikely because there was no ECG or clinical evidence of such 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 the 604 subjects were on beta-blocking and/or 62 patients on calcium-channel medication at the baseline. The population studied with symptomatic IST is rather small, but confirms the good prognosis of IST recently reported by Lopera et al. in elderly females.

Finally, we must add that a variety of genetic and other mechanisms may be responsible for the clinical syndrome, and there may be some overlap between IST and chronic orthostatic intolerance.

6.4 Implications of the study

Our results suggest that invasive therapy, such as catheter ablation, may not be indicated in asymptomatic or mildly symptomatic patients with EAT because of the higher probability of spontaneous remission of arrhythmia than of the occurrence of symptoms or heart failure.

The results of our study are consistent in suggesting that early reassurance or medical treatment is essential, while 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.

Analysis of the fractal characteristics of cardiac interbeat dynamics revealed abnormal dynamic behaviour that was not revealed by the traditional methods of HRV analysis, which confirms that the new analysis methods based on fractals and nonlinear dynamics add significantly to the diagnostic performance of the conventional methods used to assess abnormal HR behaviour. Long-term ECG recordings may also help to differentiate between IST and EAT in cases where 12-lead ECG does not yield a definitive diagnosis.
Our data suggest that adenosine may be a useful noninvasive probe in the evaluation of patients with suspected IST. Because adenosine markedly decelerates physiological sinus tachycardia (200,257) and terminates sinus node re-entrant tachycardia as well as triggered atrial tachycardias (96,201), intravenous adenosine is likely to help in differentiating between these arrhythmias and IST.

6.5 Future perspectives

In the future, studies with larger patient populations and application of molecular biology techniques will be required to validate the exact mechanism and pathophysiology of IST. New electroanatomical techniques (CARTO, Ensite) may also help in assessment of exact localization of both IST and EAT and facilitate in the catheter ablation of these arrhythmias. Especially symptomatic patients with EAT can perhaps be more easily examined and treated by new mapping techniques. In IST, Ensite technique can also record the exact intra-atrial activation sequence, which could possibly give new information of this arrhythmia.

Because these arrhythmias are relatively rare, a national arrhythmia register might help in further evaluation of these arrhythmias in a larger sample size. Patient follow-up, clinical outcomes and given treatment would be easily available for each patient. In addition, national guidelines of SVTs in Finland would expand the knowledge of EAT and IST among the medical community. Guidelines in native language would highlight this rather rare issue and offer information to a larger group of physicians.
7 Conclusions

1. Asymptomatic EAT is not an uncommon finding among young males. In the majority, the atrial rhythm slows over time, leading to either restoration of SR or fusion of ectopic atrial and sinus rhythms. This suggests that the ectopic foci gradually degenerate over time.

2. IST appears to be a more common disorder than previously assumed. Despite the chronic nature and long-lasting symptoms of this disorder, its natural course is benign.

3. HRV values obtained by time- and frequency-domain analysis methods over a 24-hour period did not differ between EAT and IST, which suggests that atrial arrhythmic foci are under similar long-term phasic regulation as the sinus node. In contrast, short-term correlation properties of R-R interval behaviour were not similar during IST and EAT. These differences may result from a specific autonomic disturbance that controls the discharge of the ectopic foci or from an intrinsic electrophysiological abnormality of these foci.

4. IST is resistant to the antiarrhythmic actions of adenosine. Unlike several other SVTs, IST is not terminated by adenosine and, regardless of the autonomic tone, the negative chronotropic response to adenosine is impaired in patients with IST. These findings are expected to have important diagnostic implications and to provide new insight into the pathophysiologic mechanism(s) of IST.
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