Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 8, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.07.074

STATE-OF-THE-ART PAPER

Inappropriate Sinus Tachycardia

Brian Olshansky, MD,* Renee M. Sullivan, MD†
Iowa City, Iowa; and Columbia, Missouri

Inappropriate sinus tachycardia (IST) is a syndrome in which the sinus heart rate is inexplicably faster than expected and associated symptoms are present. The heart rate at rest, even in a supine position, can exceed 100 beats/min; minimal activity accelerates the rate rapidly and substantially. Patients with IST may require restriction from physical activity. Mechanisms responsible for IST are understood incompletely. It is important to distinguish IST from so-called appropriate sinus tachycardia and from postural orthostatic tachycardia syndrome, with which overlap may occur. Because the long-term outcome seems to be benign, treatment may be unnecessary or may be as simple as physical training. However, for patients with intolerable symptoms, therapeutic measures are warranted. Even at high doses, β-adrenergic blockers, the first-line therapy, often are ineffective; the same is true for most other medical therapies. In rare instances, catheter- or surgically- based right atrial or sinus node modification may be helpful, but even this is fraught with limited efficacy and potential complications. Overtreatment, in an attempt to reduce symptoms, can be difficult to avoid, but is discouraged. (J Am Coll Cardiol 2013;61: 793–801) © 2013 by the American College of Cardiology Foundation

Inappropriate sinus tachycardia (IST), a syndrome characterized by unexpectedly fast sinus rates at rest, with minimal physical activity, or both, is manifest by a spectrum of symptoms including palpitations, weakness, fatigue, dizziness, or near syncope. Acceleration in rate with minimal exercise is excessive and heart rate recovery is prolonged. Sinus tachycardia, even if excessively fast, generally is a transient and reversible condition with an explainable cause and a rate appropriate for the circumstance (caffeine ingestion, anxiety, deconditioning, and so on.) (1). IST is a more long-standing problem that is not as easy to explain. Herein, we review IST, explore its mechanisms, and review management strategies.

What Is a Normal Sinus Rate?

Healthy, normal individuals, at rest, have sinus rates of 50 to 90 beats/min, generally lower than the intrinsic sinus rate (i.e., devoid of autonomic influence), in part because of vagal tone (2–4). In 432 otherwise normal medical staff and prisoners, the intrinsic resting sinus rate was age dependent (3). Individuals 15 years of age had an average intrinsic heart rate of more than 118 beats/min; 15% of those 15 to 30 years of age had intrinsic rates of more than 115 beats/min. There was a greater distribution of faster intrinsic rates in younger individuals. For those older than 45 years, 15% had an intrinsic sinus rate of more than 100 beats/min. Rates were reproducible, not dependent on time of day, and only slightly dependent on exercise.

In CORDIS (Israeli Cardiovascular Occupational Risk Factors Determination in Israel Study), the percent difference in mean heart rate (supine to standing) in 5,428 subjects (mean age: 40.4 ± 11.5 years, 74% blue collar, 58% physically active) was greater among women than men (12.7% vs. 11.6%, $p < 0.03$). Heart rate was associated independently with height ($p < 0.0001$), cigarette smoking ($p < 0.0001$), and coffee drinking ($p < 0.001$) and was associated inversely with age ($p < 0.002$), blood pressure elevation ($p < 0.0005$), and physical activity ($p < 0.0001$) (5).

Inappropriate Sinus Tachycardia: The Clinical Presentation

No specific heart rate best defines IST, yet patients with IST generally have resting daytime sinus rates of more than 100 beats/min and average 24-h heart rates of more than 90 beats/min that are not explained by physiologic demands or conditions known commonly to increase heart rate. Patients with IST often have multiple, incapacitating symptoms including palpitations, dyspnea, dizziness, lightheadedness, and near syncope, but the symptoms may not be dependent on heart rate. Associated emotional and psychiatric problems often are identified, but any relationship to IST is uncertain. Treatment of tachycardia alone may not ameliorate debilitating symptoms, the predominant problem in this condition. IST may be difficult to distinguish from a

From the *Department of Internal Medicine, Division of Cardiovascular Medicine, University of Iowa Hospitals and Clinics, Iowa City, Iowa; and the †Department of Internal Medicine, Division of Cardiovascular Medicine, University of Missouri, Columbia, Missouri. Dr. Olshansky is a consultant for Boston Scientific, Medtronic, BioControl, Sanofi-Aventis, Boehringer Ingleheim, and Amarin. The income derived from each of these companies is separately < $10,000. Dr. Sullivan has reported that she has no relationships relevant to the contents of this paper to disclose.

Manuscript received January 19, 2012; revised manuscript received July 19, 2012, accepted July 31, 2012.

JACC Vol. 61, No. 8, 2013
February 26, 2013:793–801

Abbreviations and Acronyms

HRV = heart rate variability

IST = inappropriate sinus tachycardia

POTS = postural orthostatic tachycardia syndrome

normal physiologic response or postural orthostatic tachycardia syndrome (POTS).

Epidemiology of Inappropriate Sinus Tachycardia

Most patients are young and female, but the epidemiologic characteristics are uncertain. Episodes tend to become noticed abruptly and persist over months or years, but the natural history is obscure and the onset may be surreptitious. The prognosis generally is benign. Perhaps one reason for a benign prognosis is that although IST patients have faster heart rates, the rate slows somewhat during sleep and in various diurnal patterns (6). Long-term consequences are few, yet reported series are small, follow-up is limited, and populations are diverse. IST rarely is associated with tachycardia-induced cardiomyopathy (7), although isolated reports do exist (8,9).

Still et al. (10) identified 7 of 604 middle-aged subjects from OPERA (Oulu Project Elucidating Risk of Atherosclerosis) as meeting criteria for IST (resting daytime sinus rate >100 beats/min or average 24-h rate > 90 beats/min). Personality measurements (except hostility scores) were normal. Over 6.0 ± 2.4 years, these and 9 IST patients diagnosed previously had a benign course, although they had palpitations and fast average heart rates (90 ± 2 beats/min vs. 89 ± 8 beats/min) over the long term. IST has been identified in older individuals, as well (11). In this group, no significant differences in echocardiographic parameters were noted between baseline and follow-up examinations.

Regulation of the Sinus Rate

As a multicomponent hierarchical structure, the sinus node is complex and tightly controlled (12) by more than 16 regionally varying, autonomically influenced currents. The role of calcium cycling (13) versus I_f (14) remains controversial (15). The I_f current is commonly regarded as the predominant current responsible for sinus rate, but this is clearly a simplification (13). No specific channelopathy is implicated in IST, although some have been suspected (16).

Parasympathetic regulation of resting sinus rate depends on M2 muscarinic receptor-mediated activation of I_{KAch} via G protein-coupled, inwardly rectifying potassium channels (Fig. 1) (17). M2 receptors activate L-type calcium channels ($I_{Ca\text{-}L}$), negatively influencing adenylate cyclase and having a stimulatory effect on G1 proteins to suppress I_f.

Calcium clocks and cellular membrane voltage, driven by β-adrenergic sympathetic nervous system activation or extrinsic catecholamines, can be blocked, in part, by I_f blockade. Although several drugs and ions can block the I_f current, their effects are nonspecific. Other I_f blockers have been developed, but only ivabradine is available commercially. Subsidiary pacemakers, residing in the superior portion of the sinus node, are activated by sympathetic stimulation such that a depolarizing shift in the I_f activation curve, a potentiation of $I_{Ca\text{-}L}$, a potentiation of I_K, a hyperpolarized shift in I_K activation curve, an acceleration of the deactivation of I_K, and a potentiation of I_{ST} occur (14).

Although phasic vagal (parasympathetic) activation supersedes sympathetic activation (called accentuated antagonism) (18), tonic sympathetic activation overshadows intermittent vagal activation. Catecholamine excess or sympathetic activation, with or without vagal inhibition, could cause IST.

Mechanisms Responsible for Inappropriate Sinus Tachycardia

Explanatory mechanisms for IST (Table 1), likely multifactorial and complex, amount to a form of dysautonomia (19), an intrinsic sinus node problem, or both. A viable, consistent, unified mechanism has yet to be identified.

Animal Models

Catecholamine injections into the sinus node fat pad containing autonomic ganglia (20) or high-frequency stimulation of the anterior right ganglionated plexi (21) accelerate the sinus rate, but so do many things. Thus, we find these data unconvincing as a mechanism for IST in patients (1). Hyposensitivity of muscarinic receptors (22); central and peripheral nociceptive effects (23,24); depressed efferent vagal activation (25); neurohormonal modulation (26); nonmuscarinic, nonadrenergic, vagally mediated mechanisms (27); or hypothalamic paraventricular nucleus stimulation (28) likewise can cause sinus tachycardia.

Vasointestinal peptide, twice as potent as norepinephrine (29) and more potent than epinephrine (30), can increase sinus rate. Central gamma-aminobutyric acid (GABA)-nergic (31) and serotonin 1-A receptor activation (32) in the medullary raphe and parapyramidal regions affecting autonomic outflow can initiate sinus tachycardia. Histamine (33), neuropeptides (29) (including neuropeptide Y), phenyl-histidine-isoleucine, substance P (34), α-opioid receptor activation (35), or other mediators (36) may be involved. M2 receptor abnormalities, sinus node channelopathies, or circulating mediators could cause IST, but none have been identified. Indeed, much remains to be learned about inappropriate and, for that matter, appropriate sinus tachycardia.

Clinical Studies

Clinical reports include small, select populations of patients with IST. Autoantibodies to ganglionic acetylcholine receptors, described in POTS (37), have been postulated to be responsible for, but have not been identified in, IST. Chiale et al. (38) suspected anti-β-receptor immunoglobulin G antibodies as a cause for IST. Studying 21 IST patients versus 15 controls, β-anti-adrenergic receptor antibodies

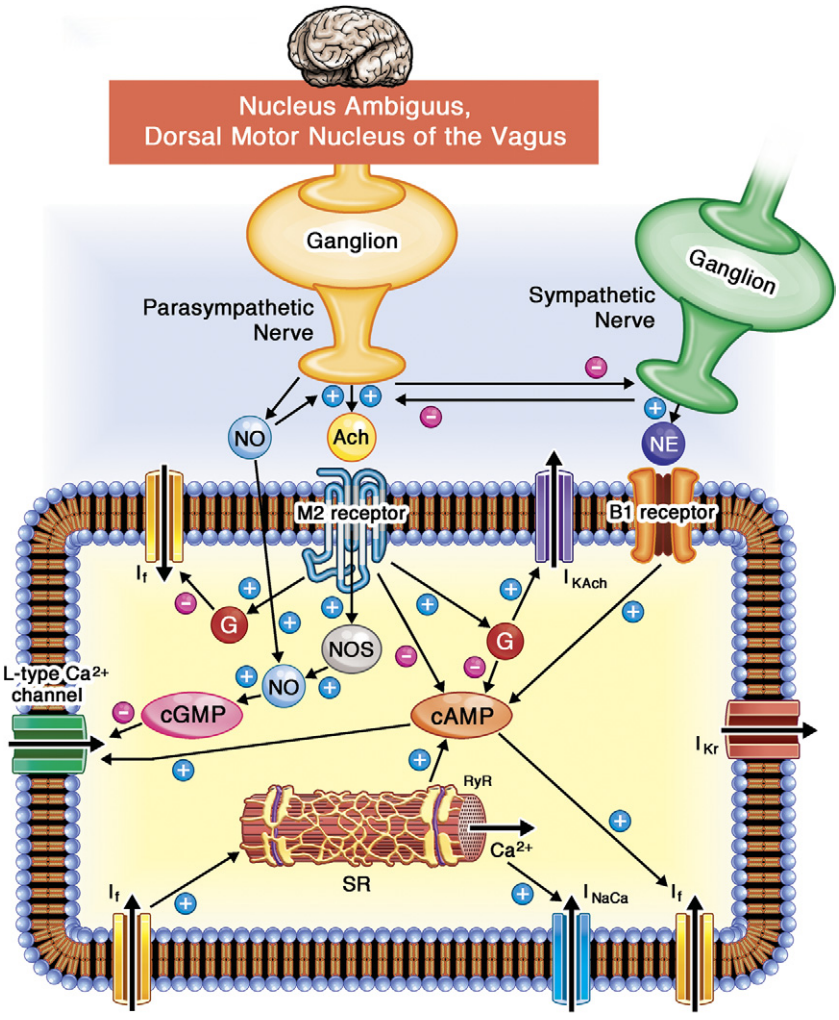

Figure 1 **Heart Rate Control via the Autonomic Nervous System**

Predominant (not all-inclusive) regulators of the sinus rate are depicted. Sinus node activation is under the control of various cellular currents, including I_{KAch}, I_f, I_{NaCa}, I_{Kr}, and the L-type calcium (Ca2+) channel, among others, regulated in part via G protein modulation (G). Additionally, the so-called calcium clock, involving ryanodine receptor (RyR) Ca2+ release from the sarcoplasmic reticulum (SR), has an important role in sinus rate determination. Further regulation and modulation of rate (particularly at rest) involves parasympathetic activation via acetylcholine (Ach) and nitric oxide (NO), in part via nitric oxide synthase (NOS). Parasympathetic nerve activation affects the muscarinic (M2) receptor via Ach and works by affecting intracellular cyclic GMP (cGMP) and cyclic AMP (cAMP) in part. Sympathetic activation stimulates β-1 receptors via norepinephrine to increase cAMP. Both limbs of the autonomic nervous system are regulated and interact at multiple levels, including the central nervous system and peripheral nerve terminals. There are multiple checks and balances throughout the entire regulatory system and, despite the simplifications shown here, they are extraordinarily complex. Presently, it is not clear what part(s) of the system is the predominant driver of increased rates in inappropriate sinus tachycardia. I_{Kr} = delayed rectifier K+ current; I_f = funny current; I_{NaCa} = sodium/calcium exchange current; NE = norepinephrine; + = stimulates; − = inhibits.

were identified in 11 IST patients. Immunoglobulin G fractions showing anti-β-receptor antibodies caused long-lasting increases in cyclic AMP. In 5 IST patients (and 5 controls), immunoglobulin G fractions were evaluated using COS-7 cells transfected with genes encoding for the β-1 and β-2 adrenergic receptors. No anti-M2 cholinergic receptor antibodies were identified.

Heart rate variability (HRV) in IST patients is inconsistent. In one report, all temporal and power spectral HRV parameters were reduced, suggesting reduced parasympathetic tone, after correcting for heart rate (39). However, some data support sinus rate elevation in IST independent of an autonomic mechanism (40). In another report, the low-frequency HRV spectrum was higher in IST patients (consistent with higher sympathetic tone) versus controls, but no consistent pattern was observed, and results may be dependent on population and age (11).

Morillo et al. (41) evaluated 6 women with IST (age range 23 to 38 years) and 10 controls. HRV low to high frequency ratio in supine and head-up tilt positions was similar in both groups. The cardiovagal response measured by the cold-face test was seen less frequently in IST than in controls (6% of IST patients vs. 24% of controls, $p < 0.001$). Patients with IST were hypersensitive to isoproter-

JACC Vol. 61, No. 8, 2013
February 26, 2013:793–801

Table 1 Potential Mechanisms of Inappropriate Sinus Tachycardia

Intrinsic sinus node overactivity: channelopathy
Autonomic influence
Decreased parasympathetic activity
Hyposensitivity of muscarinic receptors
Decreased efferent vagal activation
Increased sympathetic activity
β-receptor autoantibodies
Combined
Baroreceptor activity
Neurohormonal modulation
Vasoactive intestinal polypeptide
Histamine
Norepinephrine
Epinephrine
Serotonin 1-A receptor activation
Central GABA-nergic activation
Substance P

GABA = gamma-aminobutyric acid.

enol. However, intrinsic heart rates were higher in IST patients. In these patients, β-blockers often were effective (41); this is not our general experience.

Leon et al. (42) investigated whether baroreflex gain differed in 8 IST patients versus 9 controls. Individuals with IST had a higher mean heart rate (78.8 ± 5.3 beats/min vs. 58.5 ± 4.2 beats/min) and blood pressure, but heart rates for IST patients were not in the range many consider IST. Baroreflex gain during orthostatic stress was reduced significantly in IST patients, and the change in baroreceptor gain during head-up tilt stabilization was blunted markedly in those considered to have IST. The intrinsic heart rate (3) observed in 7 of 8 patients was faster than predicted (115.7 ± 2.7 observed beats/min vs. 110.6 ± 1.4 expected beats/min, $p < 0.01$). Only 25% considered to have IST showed a hypersensitive response to catecholamines, pointing to the sinus node as the problem, rather than the autonomic nervous system.

Still et al. (16) studied the response to adenosine after β-adrenergic and cholinergic blockade in 18 IST patients (mean age 46 ± 15 years) versus controls (114 ± 17 beats/min vs. 79 ± 11 beats/min). Adenosine did not stop or slow the sinus rate. After adenosine, reflex increase in the sinus rate was greater in controls than in IST patients (21.2 ± 9.7% vs. 8.5 ± 8.8%, $p < 0.001$), supporting the tenet that an accelerated intrinsic sinus rate may be the primary abnormality. They postulated that IST may be the result of deficient function of the acetylcholine-sensitive and adenosine-sensitive potassium channel. In clinical studies, β-adrenergic receptor supersensitivity (43), M2 receptor blockade (44,45), or the role of neuropeptide neurotransmitters (46) have been considered. Variations in diurnal patterns have been speculated to help to characterize forms of IST (6).

Ultimately, the causal mechanism for the abnormally fast sinus rate is unknown. The initial event may be a trigger, such as a viral infection or toxin exposure (47), but evidence is scant. In our experience, excess hydrocarbon exposure may be one mechanism; halogenated hydrocarbons can sensitize the myocardium to catecholamines and can increase the sinus rate (48,49). The problem, however, may lie in the sinus node itself. Lipofuscin-laden vacuoles have been identified as an ultrastructural marker noted in 3 patients with IST for whom the sinus node was excised (50).

Causes for Sinus Tachycardia

Critical to the diagnosis of IST is the need to exclude specific physiological and psychological triggers for appropriate sinus tachycardia, including exercise, anxiety, panic attacks, and pain. Anticholinergics, catecholamines, alcohol, caffeine, cocaine, tobacco, β-blocker withdrawal, and supraventricular tachycardia ablation causing vagal denervation increase sinus rate (51–54). Several medical conditions can explain sinus tachycardia as well (Table 2). Central mechanisms may be responsible for sinus tachycardia caused by insults to the brain, including head trauma, especially to the brainstem.

Most IST patients are otherwise completely healthy. Because IST seems to be more common in health care providers (55), consideration of access to stimulants and other drugs (e.g., insulin) must be considered in the evaluation of appropriate versus inappropriate sinus tachycardia. Occult substance abuse and psychiatric causes such as panic attacks must be considered in the differential diagnosis. In one report, 100% of patients with IST had some psychiatric diagnosis (schizophrenia, depression, panic disorder, or somatoform disorder) (56).

Diagnosing Inappropriate Sinus Tachycardia

The diagnosis of IST is based on persistent or recurrent sinus tachycardia on 12-lead electrogram or by long-term

Table 2 Explainable Causes of Sinus Tachycardia to Consider Before Diagnosing Inappropriate Sinus Tachycardia

Drugs, Substances, Medications, Interventions	Medical Conditions
Anticholinergics	Anemia
Catecholamines	Dehydration
Alcohol	Exercise
Caffeine	Anxiety
Tobacco	Pain
Cocaine	Pulmonary embolus
β-blocker withdrawal	Fever
Supraventricular tachycardia ablation	Pericarditis
	Aortic or mitral regurgitation
	Myocardial infarction
	Pneumothorax
	Hyperthyroidism
	Hypoglycemia

monitoring that is not otherwise explainable. Invasive testing, such as electrophysiology studies, is not useful for making the diagnosis, although it may be useful to exclude a concomitant supraventricular tachycardia mechanism (57). The evaluation of sinus tachycardia must take into account whether the rhythm is paroxysmal or persistent. Careful analysis of a 12-lead electrocardiogram should consider P-wave morphological features. If the P-wave is the same or similar to that in normal sinus rhythm, IST is possible. If paroxysmal, atrial tachycardia, including sinus node reentry, should be excluded. If tachycardia occurs gradually with postural change, a tilt-table test may indicate POTS; with tilting, the increase in heart rate is nearly immediate in IST (58). If tachycardia is persistent and an underlying cause can be determined, IST is not present. In the patient with generally persistent episodes for which no cause can be determined, however, IST may be diagnosed. IST is a diagnosis of exclusion.

Commonly, there is confusion between IST and POTS; overlap between the 2 exists (Table 3) (59). Tachycardia in IST is not postural as it is in POTS. In POTS, there is a persistent increase in heart rate by more than 30 beats/min or a rate of more than 120 beats/min within 10 minutes of changing from a supine to an upright position in the absence of orthostatic hypotension. As with IST, patients with POTS often have multisystem symptoms. There is venous (including splanchnic) pooling, α-hypersensitivity and β-hypersensitivity, baroreceptor dysfunction, hypovolemia, the presence of brainstem dysregulation, or a combination thereof. One has to wonder: is tachycardia in POTS inappropriate? Probably so.

Treatment of Inappropriate Sinus Tachycardia

Managing IST (controlling symptoms and reducing rate) remains a substantial challenge, especially because the syndrome itself is nebulous. Heart rate control, however, does not necessarily eliminate symptoms. Controlling the sinus rate in asymptomatic patients with IST is controversial because the treatment may be worse than the syndrome itself. In IST, no one therapy reduces heart rate and symptoms completely and effectively, likely related to the complexity of the problem and the lack of full understanding of the causes.

Many treatment recommendations have been made for patients with IST, but these therapies have not been well tested. β-adrenergic blockers, even at high doses, generally are ineffective and tend to be associated with other symptoms. Other treatments (fludrocortisone, volume expansion, pressure stockings, phenobarbital, clonidine, psychiatric evaluation, erythropoietin) have been suggested, but may be harmful and have not been proven (59).

A study of 19 patients with POTS supported the use of exercise training to improve quality of life and to maintain upright cardiac output compared with the use of propranolol (60). We suspect that exercise training also may help IST patients. Benzodiazepines may be helpful, but this drug class has not been evaluated carefully. It is likely that many IST patients have a superimposed anxiety disorder. Although not reported, benzodiazepine and β-blocker combinations, in the hands of an empathetic physician, may be effective for many IST patients (Coghlan CH, personal communication). Indeed, effective patient communication and attention seem to improve outcomes (56).

Radiofrequency Catheter Ablation

Radiofrequency ablation in attempts to modify the sinus node or eliminate sympathetic inputs, at best, is partially effective, but has been tested only in small populations. Early reports suggested that ablation had value; we remain tentative and do not recommend aggressive attempts to ablate the sinus node in patients with IST on a routine basis.

In 16 drug-refractory, highly symptomatic patients with IST, total sinus node ablation (n = 4) or sinus node modification (n = 12) was performed via radiofrequency energy delivery to sites of earliest atrial activation. For those who had sinus node modification, a chronotropic response was still present with a reduction in maximal heart rate (132.8 $\pm$ 6.5 beats/min vs. 179.5 $\pm$ 3.6 beats/min, $p < 0.001$). Holter monitoring showed a decrease in maximal and mean heart rate (167.2 $\pm$ 2.6 beats/min vs. 96.7 $\pm$ 5.0 beats/min, $p < 0.001$, and 125.6 $\pm$ 5.0 beats/min vs. 54.1 $\pm$ 5.3 beats/min, $p < 0.001$, respectively) with long-term benefits. Two patients required pacing, one had transient right diaphragmatic paralysis and another had transient superior vena cava syndrome (61).

In a report of 29 IST patients, ablation reduced sinus rates to less than 90 beats/min acutely in 22 patients (62). For 13 acutely successful ablations, radiofrequency ablation at the site of earliest endocardial activation resulted in migration of earliest activation from the high lateral right

Table 3 Inappropriate Sinus Tachycardia Versus Postural Orthostatic Tachycardia Syndrome

	Inappropriate Sinus Tachycardia	Postural Orthostatic Tachycardia Syndrome
Definition	Abnormally fast sinus rhythm at rest or minimal activity that accelerates beyond expectations and is out of proportion to physiologic necessity not resulting from an explainable underlying cause	Condition of orthostatic intolerance leading to abnormal increase in heart rate with change in position
Heart rate	Resting daytime heart rate exceeds 100 beats/min and average heart rate on 24-h Holter monitor exceeds 90 beats/min	Persistent increase in heart rate by more than 30 beats/min or absolute pulse of more than 120 beats/min within 10 min of moving from a supine to upright position in the absence of orthostatic hypotension
Diagnosis	Diagnosis of exclusion	Tilt table

atrium with a progressive reduction in rate. For the other 9 patients with a successful acute outcome, reduction in rate occurred abruptly. Symptoms recurred 4.4 ± 3 months after the procedure in 6 of 22 patients, but after additional procedures in 3 patients, symptoms were eliminated successfully (62).

In a more recent report, long-term results of 3-dimensional map-guided ablation of IST were reported in 39 patients (35 women, mean age 31 ± 9 years) (56). The shift in the earliest sinus node activation site after β-adrenergic blockade was compared with the shift after ablation. After ablation, the mean sinus rate normalized (72 ± 8 beats/min) with a more pronounced shift in caudal activation along the crista terminalis than with esmolol, but 21% of patients experienced recurrent IST and underwent repeat ablation. The authors concluded that adrenergic hypersensitivity is not the only mechanism responsible for IST and that 3-dimensional guidance helped facilitate ablation (56). In some cases, with a thick terminal crest, an epicardial ablation approach has been used (63). Ablation of the arcuate ridge in a combined epicardial and endocardial approach has been described (63,64).

Although we agree that detailed 3-dimensional mapping helps to identify sinus nodal sites to ablate in patients with IST, including the use of noncontact mapping (65,66), we have observed migrating tachycardia rates with progressive ablation at superior sites in the sinus node in patients with IST. We are not convinced that a single 3-dimensional mapping approach, even one that uses unipolar mapping, in an attempt to derive the origin of the sinus node activation, is any better than bipolar mapping (66,67).

Such ablation can be fruitless because tachycardia ultimately may come from other sinus nodal sites or from the atrioventricular junction after complete sinus node obliteration. This has been observed in surgical ablations and even after sinus node removal (68). Furthermore, symptoms can persist despite sinus node slowing, and the benefits may be only short term (69).

It becomes extraordinarily important to distinguish the potential mechanisms responsible for sinus tachycardia, because for patients with POTS, radiofrequency ablation of the sinus node will have devastating effects, exacerbating symptoms or making hemodynamics worse. If POTS was the original problem, incorrectly diagnosed as IST, blunting the acceleration in heart rate during position change by sinus node ablation could prevent the needed sinus response to overcome inappropriate vasodilation or lack of appropriate vasoconstriction. Severe postural hypotension therefore may ensue.

Narrowing of the superior vena cava (70), damage to the phrenic nerve (71), and bradycardia requiring a pacemaker can occur. The latter complication may develop days after ablation. Because complications are probably underreported, these devastating outcomes for an otherwise young healthy person who may continue to have symptoms and tachycardia should raise serious concerns about proceeding with interventional approaches. Patients and referring physicians must be cognizant that although symptoms may be substantial and patients may be highly motivated, consequences of aggressive therapeutic attempts may seriously outweigh any potential benefit.

Surgical Ablation

Surgical ablation of the sinus node may be ineffective because in patients with IST, escape rhythms, including those from the atrioventricular junction, also may be inappropriately fast. Over a 17-year period, 9 medically refractory patients (mean age 33 ± 6 years) with symptoms lasting 13.4 ± 10.9 years underwent median sternotomy (cardiopulmonary bypass time 73 ± 25 min) for surgical isolation of the sinus node, cryoablation, or both; 2 patients underwent radiofrequency ablation via a right inframammary incision. Over a mean of 6.4 ± 5.9 years, 4 underwent repeat postoperative ablation attempts; 1 required a pacemaker (72). Other methods have been used to ablate the sinus node surgically, either using a thoracoscopic approach (68,73), an off-pump beating-heart sinus isolation and ablation through a minithoracotomy (72), or direct complete removal of the sinus node (74). Partial cardiac denervation and sinus node ablation have been attempted (75).

Complete surgical sympathectomy has not been well tested yet. However, innervation may remain via the intrinsic cardiac nervous system (76). Even complete sympathectomy may not address the primary problem, and therefore may treat IST ineffectively. Further, IST has been observed after heart transplantation even after complete central autonomic denervation (77). Surgical ablation is not recommended, except for patients who are completely debilitated symptomatically and for whom everything else has failed. The aggressiveness of the surgical therapies testifies to the fact that patients with IST can be highly motivated to pursue substantial and risky procedures to eliminate their symptoms.

Emerging Therapy for Inappropriate Sinus Tachycardia

Small studies (78–80) and several case reports have demonstrated the potential value of the I_f blocker ivabradine to treat IST; the drug is not available in the United States. Ivabradine can have a dramatic effect on heart rate and can slow it from a mean of 100 beats/min to fewer than 75 beats/min. The maximum heart rate can slow from a mean of 160 beats/min to 120 beats/min. The minimum heart rate also can slow over time.

Ivabradine was evaluated in 10 female patients (median age 32.5 years, range: 12 to 57 years) with IST (78). Ivabradine (5 to 7.5 mg twice daily) with a β-blocker (n = 3) or as monotherapy (n = 7) reduced maximum and mean heart rates (baseline: maximal heart rate 176 ± 45 beats/min, mean heart rate: 84 ± 11 beats/min; ivabradine: maximal heart rate: 137 ± 36 beats/min, mean heart rate:

74 ± 8 beats/min, both $p < 0.05$). The minimum heart rate did not change, but symptoms were ameliorated or suppressed in all 8 contacted after a mean of 16 ± 9 months (78).

In another report (79), the efficacy and safety of ivabradine were tested in 18 consecutive symptomatic patients (mean age: 45 ± 15 years); 16 completed the study. There was a significant reduction of median and maximal heart rates over 6 months, with small changes in the minimal heart rate. There was improvement in exercise tolerance. Phosphene toxicity limited use of the drug in small numbers of patients, but otherwise, it was well tolerated.

Ivabradine may precipitate excess bradycardia (especially in combination with β-blockers or calcium-channel blockers) and may cause headaches or other side effects. It should not be used with strong CYP 3A4 inhibitors or in patients with liver or severe renal dysfunction. It should be avoided in patients who are hypotensive, pregnant, or breastfeeding. These latter are of most concern for the IST patient.

A General Approach

Our general approach to patients in whom sinus tachycardia is present and IST is presumed includes the following:

1. Determine if, and when, sinus tachycardia is present and if the problem is reproducible and persistent. Consider if any explainable cause of tachycardia exists and determine if symptoms are postural, because this may be the result of POTS, or exacerbated by physical activity. Consider psychiatric issues, exclude substance abuse, and carefully counsel the patient on the risks and benefits of any interventional therapy. Consider that there is no necessity to move to aggressive ablation interventions if simpler approaches do not work. Ensure the patient is aware that the therapeutic options, including ablation, have limited value and may cause tremendous harm.
2. If IST is diagnosed, determine if there is a trigger or an event that precipitated the symptoms because this may help to determine the longevity of the problem. For some, a postviral syndrome can be associated with POTS and this may be short lived. If the patient is otherwise young and healthy, the problem may last 5 years or more before dissipating.
3. Patients with IST often have symptoms independent of heart rate. It is critical to determine if the heart rate is associated directly with the symptoms, because in this setting, treatment of the heart rate likely will make a difference. Consider a multidisciplinary approach to rule out psychiatric issues that may be exacerbating the symptoms and may be alleviated by other approaches.
4. Treatment begins with modest doses of β-blockers. No specific β-blocker is more effective than another. Exercise training is recommended. Potential stimulants in the diet (such as caffeine or alcohol) should be eliminated.
5. Ivabradine at a dose of 5.0 to 7.5 mg twice daily, if available, may be highly effective and should be considered.
6. Consider radiofrequency ablation only if sinus rates are extremely fast, the patient clearly has IST with symptoms resulting from sinus tachycardia, and all other therapies have failed.

Conclusions

Sinus tachycardia generally is explainable. When it is not, it may be the result of IST, a difficult to characterize, symptomatic condition that represents a spectrum of disorders related to increased sinus node automaticity, disordered autonomic activation, or both. There may be an overlap between conditions caused by orthostatic intolerance (e.g., POTS) or anxiety. Evaluation of patients with this condition begins with assessment and exclusion of all possible explainable causes for sinus tachycardia. In some cases, this may require long-term follow-up to determine presence of substance abuse or psychiatric abnormalities.

For the remaining patients, it is critical to distinguish POTS from IST because inappropriate treatment of suspected IST with sinus node ablation (when it is actually misdiagnosed POTS) will have a devastating effect. Treatment can be as simple as avoiding triggers of tachycardia and exercise training. Because tachycardia-induced cardiomyopathy develops rarely, the primary reason to treat IST is to improve symptoms. Caution is advised to limit aggressive treatment attempts in patients with IST because the cure often can be worse than the condition itself.

Acknowledgment

The authors thank Mark Chapleau, PhD, University of Iowa and Veterans Affairs Medical Center, for his expert guidance and review of our manuscript.

Reprint requests and correspondence: Dr. Brian Olshansky, Department of Medicine, University of Iowa Hospitals and Clinics, 4426a JCP, 200 Hawkins Drive, Iowa City, Iowa 52242. E-mail: brian-olshansky@uiowa.edu.

REFERENCES

1. Olshansky B. What's so inappropriate about sinus tachycardia? J Cardiovasc Electrophysiol 2008;19:977–8.
2. Marcus B, Gillette PC, Garson A Jr. Intrinsic heart rate in children and young adults: an index of sinus node function isolated from autonomic control. Am Heart J 1990;119:911–6.
3. Jose AD, Collison D. The normal range and determinants of the intrinsic heart rate in man. Cardiovasc Res 1970;4:160–7.
4. Alboni P, Malcarne C, Pedroni P, Masoni A, Narula OS. Electrophysiology of normal sinus node with and without autonomic blockade. Circulation 1982;65:1236–42.
5. Kristal-Boneh E, Harari G, Weinstein Y, Green MS. Factors affecting differences in supine, sitting, and standing heart rate: the Israeli CORDIS Study. Aviat Space Environ Med 1995;66:775–9.
6. Rubenstein JC, Freher M, Kadish A, Goldberger JJ. Diurnal heart rate patterns in inappropriate sinus tachycardia. Pacing Clin Electrophysiol 2010;33:911–9.
7. Nerheim P, Birger-Botkin S, Piracha L, Olshansky B. Heart failure and sudden death in patients with tachycardia-induced cardiomyopathy and recurrent tachycardia. Circulation 2004;110:247–52.

8. Winum PF, Cayla G, Rubini M, Beck L, Messner-Pellenc P. A case of cardiomyopathy induced by inappropriate sinus tachycardia and cured by ivabradine. Pacing Clin Electrophysiol 2009;32:942–4.
9. Romeo E, Grimaldi N, Sarubbi B, et al. A pediatric case of cardiomyopathy induced by inappropriate sinus tachycardia: efficacy of ivabradine. Pediatr Cardiol 2011;32:842–5.
10. Still AM, Raatikainen P, Ylitalo A, et al. Prevalence, characteristics and natural course of inappropriate sinus tachycardia. Europace 2005; 7:104–12.
11. Lopera G, Castellanos A, Moleiro F, Huikuri HV, Myerburg RJ. Chronic inappropriate sinus tachycardia in elderly females. Ann Noninvasive Electrocardiol 2003;8:139–43.
12. Boyett MR, Honjo H, Kodama I. The sinoatrial node, a heterogeneous pacemaker structure. Cardiovasc Res 2000;47:658–87.
13. Rosen MR, Nargeot J, Salama G. The case for the funny current and the calcium clock. Heart Rhythm 2012;9:616–8.
14. DiFrancesco D. The role of the funny current in pacemaker activity. Circ Res 2010;106:434–46.
15. Lakatta EG, DiFrancesco D. What keeps us ticking: a funny current, a calcium clock, or both? J Mol Cell Cardiol 2009;47:157–70.
16. Still AM, Huikuri HV, Airaksinen KE, et al. Impaired negative chronotropic response to adenosine in patients with inappropriate sinus tachycardia. J Cardiovasc Electrophysiol 2002;13:557–62.
17. Cifelli C, Rose RA, Zhang H, et al. RGS4 regulates parasympathetic signaling and heart rate control in the sinoatrial node. Circ Res 2008;103:527–35.
18. Kimura T, Uchida W, Satoh S. Predominance of postsynaptic mechanism in vagal suppression of sympathetic tachycardia in the dog. J Pharmacol Exp Ther 1985;235:793–7.
19. Low PA. Autonomic neuropathies. Curr Opin Neurol 1998;11:531–7.
20. Scherlag BJ, Yamanashi WS, Amin R, Lazzara R, Jackman WM. Experimental model of inappropriate sinus tachycardia: initiation and ablation. J Interv Card Electrophysiol 2005;13:21–9.
21. Zhou J, Scherlag BJ, Niu G, et al. Anatomy and physiology of the right interganglionic nerve: implications for the pathophysiology of inappropriate sinus tachycardia. J Cardiovasc Electrophysiol 2008;19: 971–6.
22. Dunstan R, Jackson DM. The demonstration of a change in responsiveness of mice to physostigmine and atropine after withdrawal from long-term haloperidol pretreatment. J Neural Transm 1977;40:181–9.
23. Boscan P, Pickering AE, Paton JF. The nucleus of the solitary tract: an integrating station for nociceptive and cardiorespiratory afferents. Exp Physiol 2002;87:259–66.
24. Cheng Z, Powley TL, Schwaber JS, Doyle FJ 3rd. Vagal afferent innervation of the atria of the rat heart reconstructed with confocal microscopy. J Comp Neurol 1997;381:1–17.
25. Hildreth CM, Padley JR, Pilowsky PM, Goodchild AK. Impaired serotonergic regulation of heart rate may underlie reduced baroreflex sensitivity in an animal model of depression. Am J Physiol Heart Circ Physiol 2008;294:H474–80.
26. Hill MR, Wallick DW, Mongeon LR, Martin PJ, Levy MN. Vasoactive intestinal polypeptide antagonists attenuate vagally induced tachycardia in the anesthetized dog. Am J Physiol 1995;269: H1467–72.
27. Prud'homme MJ, Houdeau E, Serghini R, Tillet Y, Schemann M, Rousseau JP. Small intensely fluorescent cells of the rat paracervical ganglion synthesize adrenaline, receive afferent innervation from postganglionic cholinergic neurones, and contain muscarinic receptors. Brain Res 1999;821:141–9.
28. Kawabe T, Chitravanshi VC, Nakamura T, Kawabe K, Sapru HN. Mechanism of heart rate responses elicited by chemical stimulation of the hypothalamic paraventricular nucleus in the rat. Brain Res 2009; 1248:115–26.
29. Rigel DF. Effects of neuropeptides on heart rate in dogs: comparison of VIP, PHI, NPY, CGRP, and NT. Am J Physiol 1988;255:H311–7.
30. Lundberg JM, Hokfelt T, Schultzberg M, Uvnas-Wallensten K, Kohler C, Said SI. Occurrence of vasoactive intestinal polypeptide (VIP)-like immunoreactivity in certain cholinergic neurons of the cat: evidence from combined immunohistochemistry and acetylcholinesterase staining. Neuroscience 1979;4:1539–59.
31. Salome N, Ngampramuan S, Nalivaiko E. Intra-amygdala injection of GABAA agonist, muscimol, reduces tachycardia and modifies cardiac sympatho-vagal balance during restraint stress in rats. Neuroscience 2007;148:335–41.
32. Ngampramuan S, Baumert M, Beig MI, Kotchabhakdi N, Nalivaiko E. Activation of 5-HT(1A) receptors attenuates tachycardia induced by restraint stress in rats. Am J Physiol Regul Integr Comp Physiol 2008;294:R132–41.
33. Skovgaard N, Moller K, Gesser H, Wang T. Histamine induces postprandial tachycardia through a direct effect on cardiac H2-receptors in pythons. Am J Physiol Regul Integr Comp Physiol 2009;296:R774–85.
34. Wharton J, Polak JM, McGregor GP, Bishop AE, Bloom SR. The distribution of substrate P-like immunoreactive nerves in the guinea-pig heart. Neuroscience 1981;6:2193–204.
35. Irnaten M, Aicher SA, Wang J, et al. Mu-opioid receptors are located postsynaptically and endomorphin-1 inhibits voltage-gated calcium currents in premotor cardiac parasympathetic neurons in the rat nucleus ambiguus. Neuroscience 2003;116:573–82.
36. Boscan P, Allen AM, Paton JF. Baroreflex inhibition of cardiac sympathetic outflow is attenuated by angiotensin II in the nucleus of the solitary tract. Neuroscience 2001;103:153–60.
37. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. N Engl J Med 2000;343:847–55.
38. Chiale PA, Garro HA, Schmidberg J, et al. Inappropriate sinus tachycardia may be related to an immunologic disorder involving cardiac beta andrenergic receptors. Heart Rhythm 2006;3:1182–6.
39. Castellanos A, Moleiro F, Chakko S, et al. Heart rate variability in inappropriate sinus tachycardia. Am J Cardiol 1998;82:531–4.
40. Zhang JQ, Holden AV, Monfredi O, Boyett MR, Zhang H. Stochastic vagal modulation of cardiac pacemaking may lead to erroneous identification of cardiac "chaos." Chaos 2009;19:028509.
41. Morillo CA, Klein GJ, Thakur RK, Li H, Zardini M, Yee R. Mechanism of 'inappropriate' sinus tachycardia. Role of sympathovagal balance. Circulation 1994;90:873–7.
42. Leon H, Guzman JC, Kuusela T, Dillenburg R, Kamath M, Morillo CA. Impaired baroreflex gain in patients with inappropriate sinus tachycardia. J Cardiovasc Electrophysiol 2005;16:64–8.
43. Low PA, Sandroni P, Joyner M, Shen WK. Postural tachycardia syndrome (POTS). J Cardiovasc Electrophysiol 2009;20:352–8.
44. Andersson KE, Campeau L, Olshansky B. Cardiac effects of muscarinic receptor antagonists used for voiding dysfunction. Br J Clin Pharmacol 2011;72:186–96.
45. Olshansky B, Ebinger U, Brum J, Egermark M, Viegas A, Rekeda L. Differential pharmacological effects of antimuscarinic drugs on heart rate: a randomized, placebo-controlled, double-blind, crossover study with tolterodine and darifenacin in healthy participants > or = 50 years. J Cardiovasc Pharmacol Ther 2008;13:241–51.
46. Beaulieu P, Lambert C. Peptidic regulation of heart rate and interactions with the autonomic nervous system. Cardiovasc Res 1998;37: 578–85.
47. Skoczynska A, Szechinski J, Juzwa W, Smolik R, Behal FJ. Carotid sinus reflexes in rats given small doses of lead. Toxicology 1987;43: 161–71.
48. Jiao Z, De Jesus VR, Iravanian S, et al. A possible mechanism of halocarbon-induced cardiac sensitization arrhythmias. J Mol Cell Cardiol 2006;41:698–705.
49. Mariussen E, Fonnum F. Neurochemical targets and behavioral effects of organohalogen compounds: an update. Crit Rev Toxicol 2006;36: 253–89.
50. Lowe JE, Hartwich T, Takla M, Schaper J. Ultrastructure of electrophysiologically identified human sinoatrial nodes. Basic Res Cardiol 1988;83:401–9.
51. Moreira JM, Curimbaba J, Filho HC, Pimenta J. Persistent inappropriate sinus tachycardia after radiofrequency ablation of left lateral accessory pathway. J Cardiovasc Electrophysiol 2006;17:678–81.
52. Skeberis V, Simonis F, Tsakonas K, Celiker A, Andries E, Brugada P. Inappropriate sinus tachycardia following radiofrequency ablation of AV nodal tachycardia: incidence and clinical significance. Pacing Clin Electrophysiol 1994;17:924–7.
53. Pappone C, Stabile G, Oreto G, et al. Inappropriate sinus tachycardia after radiofrequency ablation of para-Hisian accessory pathways. J Cardiovasc Electrophysiol 1997;8:1357–65.
54. Kocovic DZ, Harada T, Shea JB, Soroff D, Friedman PL. Alterations of heart rate and of heart rate variability after radiofrequency catheter ablation of supraventricular tachycardia. Delineation of parasympathetic pathways in the human heart. Circulation 1993;88:1671–81.

55. Krahn AD, Yee R, Klein GJ, Morillo C. Inappropriate sinus tachycardia: evaluation and therapy. J Cardiovasc Electrophysiol 1995;6:1124–8.
56. Marrouche NF, Beheiry S, Tomassoni G, et al. Three-dimensional nonfluoroscopic mapping and ablation of inappropriate sinus tachycardia. Procedural strategies and long-term outcome. J Am Coll Cardiol 2002;39:1046–54.
57. Frankel DS, Lin D, Anastasio N, et al. Frequent additional tachyarrhythmias in patients with inappropriate sinus tachycardia undergoing sinus node modification: an important cause of symptom recurrence. Procedural strategies and long-term outcome. J Cardiovasc Electrophysiol 2012;23:835–9.
58. Shen WK, Low PA, Jahangir A, et al. Is sinus node modification appropriate for inappropriate sinus tachycardia with features of postural orthostatic tachycardia syndrome? Pacing Clin Electrophysiol 2001;24:217–30.
59. Brady PA, Low PA, Shen WK. Inappropriate sinus tachycardia, postural orthostatic tachycardia syndrome, and overlapping syndromes. Pacing Clin Electrophysiol 2005;28:1112–21.
60. Fu Q, Vangundy TB, Shibata S, Auchus RJ, Williams GH, Levine BD. Exercise training versus propranolol in the treatment of the postural orthostatic tachycardia syndrome. Hypertension 2011;58:167–75.
61. Lee RJ, Kalman JM, Fitzpatrick AP, et al. Radiofrequency catheter modification of the sinus node for "inappropriate" sinus tachycardia. Circulation 1995;92:2919–28.
62. Man KC, Knight B, Tse HF, et al. Radiofrequency catheter ablation of inappropriate sinus tachycardia guided by activation mapping. J Am Coll Cardiol 2000;35:451–7.
63. Koplan BA, Parkash R, Couper G, Stevenson WG. Combined epicardial-endocardial approach to ablation of inappropriate sinus tachycardia. J Cardiovasc Electrophysiol 2004;15:237–40.
64. Killu AM, Syed FF, Wu P, Asirvatham SJ. Refractory inappropriate sinus tachycardia successfully treated with radiofrequency ablation at the arcuate ridge. Heart Rhythm 2012;9:1324–7.
65. Takemoto M, Mukai Y, Inoue S, et al. Usefulness of non-contact mapping for radiofrequency catheter ablation of inappropriate sinus tachycardia: new procedural strategy and long-term clinical outcome. Intern Med 2012;51:357–62.
66. Lin D, Garcia F, Jacobson J, et al. Use of noncontact mapping and saline-cooled ablation catheter for sinus node modification in medically refractory inappropriate sinus tachycardia. Pacing Clin Electrophysiol 2007;30:236–42.
67. Bonhomme CE, Deger FT, Schultz J, Hsu SS. Radiofrequency catheter ablation using non-contact mapping for inappropriate sinus tachycardia. J Interv Card Electrophysiol 2004;10:159–63.
68. Beaver TM, Miles WM, Conti JB, et al. Minimally invasive ablation of a migrating focus of inappropriate sinus tachycardia. J Thorac Cardiovasc Surg 2010;139:506–7.
69. Shen WK. Modification and ablation for inappropriate sinus tachycardia: current status. Card Electrophysiol Rev 2002;6:349–55.
70. Callans DJ, Ren JF, Schwartzman D, Gottlieb CD, Chaudhry FA, Marchlinski FE. Narrowing of the superior vena cava-right atrium junction during radiofrequency catheter ablation for inappropriate sinus tachycardia: analysis with intracardiac echocardiography. J Am Coll Cardiol 1999;33:1667–70.
71. Vatasescu R, Shalganov T, Kardos A, et al. Right diaphragmatic paralysis following endocardial cryothermal ablation of inappropriate sinus tachycardia. Europace 2006;8:904–6.
72. Kreizel D, Bailey M, Lindsay BD, Damiano RJ Jr. A minimally invasive surgical treatment for inappropriate sinus tachycardia. J Thorac Cardiovasc Surg 2005;130:598–9.
73. Shandling AH, Rieders D, Bethencourt DM. Thoracoscopic microwave epicardial ablation: feasibility for the treatment of idiopathic sinus node tachycardia. Ann Thorac Surg 2007;83:300–2.
74. Esmailzadeh B, Bernat R, Winkler K, Meybehm M, Pfeiffer D, Kirchhoff PG. Surgical excision of the sinus node in a patient with inappropriate sinus tachycardia. J Thorac Cardiovasc Surg 1997;114:861–4.
75. Taketani T, Wolf RK, Garrett JV. Partial cardiac denervation and sinus node modification for inappropriate sinus tachycardia. Ann Thorac Surg 2007;84:652–4.
76. Saburkina I, Ryzevaite K, Pauziene N, et al. Epicardial neural ganglionated plexus of ovine heart: anatomic basis for experimental cardiac electrophysiology and nerve protective cardiac surgery. Heart Rhythm 2010;7:942–50.
77. Ho RT, Ortman M, Mather PJ, Rubin S. Inappropriate sinus tachycardia in a transplanted heart—further insights into pathogenesis. Heart Rhythm 2011;8:781–3.
78. Zellerhoff S, Hinterseer M, Felix Krull B, et al. Ivabradine in patients with inappropriate sinus tachycardia. Naunyn Schmiedebergs Arch Pharmacol 2010;382:483–6.
79. Calo L, Rebecchi M, Sette A, et al. Efficacy of ivabradine administration in patients affected by inappropriate sinus tachycardia. Heart Rhythm 2010;7:1318–23.
80. Kaplinsky E, Comes FP, Urondo LS, Ayma FP. Efficacy of ivabradine in four patients with inappropriate sinus tachycardia: a three month-long experience based on electrocardiographic, Holter monitoring, exercise tolerance and quality of life assessments. Cardiol J 2010;17:166–71.

Key Words: arrhythmia ■ sinus ■ tachycardia.