REVIEW

Diagnosis and Treatment of Inappropriate Sinus Tachycardia

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Abstract

Inappropriate sinus tachycardia (IST) is a syndrome of cardiac and extracardiac symptoms characterized by rapid sinus heart rate at rest (>100 bpm) or with minimal activity and disproportionate to the physiologic demands. Patients with this unique and puzzling arrhythmia may require restriction from physical activity. The responsible mechanisms for IST are not completely understood. IST and postural orthostatic tachycardia syndrome (POTS) are the 2 sides of the same coin. It is important to distinguish IST from so-called appropriate sinus tachycardia and from POTS, with which an overlap may occur. As 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. Beta-adrenergic blockers, considered a first-line therapy, are usually ineffective even at high doses; the same applies for most other medical therapies. Ivabradine seems to be more effective than beta-blockers especially in the non-hypertensive patients. 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. In this report, we will be review IST, explore its mechanisms and evaluate possible management strategies.

Rhythmos 2017;12(1):7-11.

Key Words: Inappropriate sinus tachycardia; postural orthostatic tachycardia syndrome; dysautonomias; autonomic nervous system

Abbreviations: IST = inappropriate sinus tachycardia; HR = heart rate, POTS = postural orthostatic tachycardia syndrome

Conflict of Interest: none declared

Manuscript submitted May 30, 2016; revised manuscript received November 22, 2016; Accepted December 27, 20-16

Introduction

Inappropriate sinus tachycardia (IST) is a unique type of automatic tachycardia originating in the sinus node. The syndrome of IST is defined as a sinus heart rate (HR)>100 bpm at rest (with a mean 24-hour HR>90 bpm, not due to primary causes) and is associated with a spectrum of symptoms including palpitations, weakness, fatigue, dizziness, or near syncope. The symptoms may not depend on HR. The acceleration in rate with minimal exercise is excessive and the recovery of the HR is prolonged.[1] Treatment of tachycardia alone may not ameliorate debilitating symptoms. IST is difficult to distinguish from the normal physiologic response on postural orthostatic tachycardia syndrome (POTS).[1, 2]

Epidemiology and Natural History

Inappropriate sinus tachycardia, a nonparoxysmal tachyarrhythmia, was originally described in 1939 by Codvelle and Boucher.[3] It has been recognized as a clinical condition since 1979, after the electrophysiological studies by Bauernfield et al which showed that a high-to-low right atrial activation sequence and atrial pacing neither terminated nor affected the tachycardia cycle length.[4]

Inappropriate sinus tachycardia is encountered more often in young female, otherwise healthy, patients, though the epidemiologic characteristics are not completely clear. Prior to the onset of IST, which often follows a viral illness or physical trauma, most of these patients will have been in excellent physical and emotional health. The causal relationship between IST and hypertension and/or hostile personality type remains speculative. IST is a chronic persistent condition which is probably related to an underlying autonomic imbalance, and can become quite debilitating. Using a definition of a resting HR of >90 bpm on 24-hour Holter monitoring, IST prevalence was 1.2% (7 of 604 middle aged subjects) including both symptomatic and asymptomatic patients in the OPERA study.[5]

The long-term outcome of the IST patients is not yet well understood, although it is believed to be a chronic condition, nevertheless it remains unknown whether patients improve and if so, how quick this improvement is. The episodes tend to become noted abruptly and to last months or years, but the natural history is obscure and the onset may be surreptitious.

The prognosis is generally benign. One reason of this fact is that although IST patients have faster HR, the rate does slow down during sleep and in various diurnal patterns.[8] The reported series are small in size and the long-term consequences are few while follow up is limited. IST rarely is associated with tachycardia-induced cardiomyopathy although isolated reports do exist.[10]

Diagnosis

Patients with IST range in presentation from asymptomatic to complaining of extremely debilitating symptoms, such as palpitations, weakness, chest pain, shortness of breath, fatigue, blurred vision, dizziness, or near syncope.[1-5]

Inappropriate sinus tachycardia is diagnosed via sequentially excluding other potential causes of

arrhythmia. Hence, if IST is suspected, a thorough medical history review and physical examination should be performed in order to rule out secondary causes for tachycardia such as infections, fever, myocardial infarction, heart failure, pulmonary issues, medications, illegal drugs, structural heart disease and/or thyroid disease. Low blood volume (hypovolemia) is another possible cause that should be considered and excluded. It should be noted that some individuals who have POTS have overlapping IST.[11] However, the elevated heart rate in POTS is mainly triggered by assuming the orthostatic posture, while heart rate is elevated in IST regardless of body position.

In order to confirm an IST diagnosis, physicians should obtain a 12-lead ECG (to rule out other arrhythmias), an echocardiogram, 24- or 48-hour Holter monitor, and an exercise stress test. In some cases, an electrophysiological study may be needed, particularly when the underlying cause of tachycardia is unclear, as well as a tilt table test.[1,7] Other tests that may be considered, as they can offer information on the patients' cardiovascular autonomic reflexes include heart rate responses to deep breathing, standing, Valsalva maneuver,[1,12] cold face test (diving test),[1,8] HR variability,[1,9,10] and baroreflex sensitivity.[1,10,15]

In a patient with IST the results of the above tests will demonstrate a resting HR of over 100 bpm and an exaggerated HR response to minimal activity (like going from lying down to standing position), while the heart rhythm is normal (sinus rhythm).[14] The echocardiogram should reveal a structurally normal heart, although rare cases of tachycardia-induced cardiomyopathy [35,36] and an association with mitral valve prolapse [37] have also been reported. Moreover, a treadmill exercise test (if performed) should document an exaggerated tachycardic response. The diagnostic strategy of IST is described in Table 1. The diagnostic electrocardiographic and electrophysiologic characteristics of IST are described in Tables 2 and 3. Furthermore, Figure 1 shows a pattern of intracardiac ECG recording during IST.

Table 1: Recommendations for diagnostic approach of IST [1,9,28]

1.	A complete history, physical exam and 12-lead ECG are recommended
2.	Complete blood analysis and thyroid function studies might be useful
3.	A 24-hour Holter monitoring might be useful
4.	Urine/serum drug screening might be useful
5.	Autonomic tests
6.	Treadmill exercise test

ECG = electrocardiogram; IST = inappropriate sinus tachycardia

Table 2: Electrocardiographic characteristics of IST [23]

1.	A resting sinus heart rate>100 bpm
2.	An exaggerated heart rate response to minimal activity, such as an increase in sinus rate of >25-30 bpm from supine to upright position
3.	Reduction or normalization of sinus rate during sleep
4.	P-wave morphology and axis during tachycardia similar to sinus rhythm

Table 3: Characteristics of IST during electrophysiological testing [23,38,41]

1.	Absence of other inducible supraventricular tachyarrhythmias
2.	During tachycardia, a gradual increase and decrease in sinus heart rate spontaneously, or with isoproterenol infusion, suggestive of automatic mechanism of IST
3.	Electroanatomic mapping showing endocardial atrial activation of the tachycardia similar to sinus rhythm in a craniocaudal fashion with the earliest activation localized at the superior aspect of the crista terminalis (estimated from fluoroscopic images, intracardiac echocardiography, or advanced 3D electroanatomic mapping techniques) and caudal migration of the earliest activation along the crista terminalis with a decrease in the tachycardia rate.

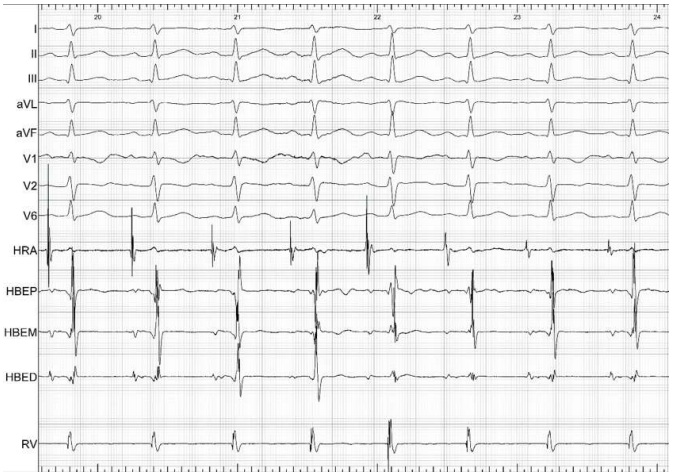

Figure 1: Intracardiac ECG recordings in IST. Surface leads I, II, III aVF V1, V2 and V6 and intracardiac recordings from the electrophysiology diagnostic catheters positioned in the high right atrium (HRA), His-bundle region (HIS) and right ventricular apex (RV). P-waves are upright in inferior leads and atrial activation sequence is high-to-low and similar to normal sinus rhythm.

Pathophysiology

The mechanisms leading to IST are not completely understood, [3] but there are several underlying pathologies that can result in this syndrome, including increased sinus node automaticity, beta-adrenergic hypersensitivity, decreased parasympathetic activity, and impaired

neurohumoral modulation.[1] The main question regarding theories of etiology, is whether IST is a primary disorder of the sino-atrial node, or whether is it is instead one of a class of disorders known as dysautonomias. Electrophysiologists tend to favour the former but the latter may be more precise.

The first theory is that IST is a primary sinus node disorder. As it is seen, the intrinsic heart rate is elevated, [5,6] suggesting that even in the absence of autonomic influence the sinus node displays enhanced automaticity. Moreover, patients with IST tend to have an abnormally enhanced HR response to epinephrine and evidence exist that the sinus node in patients with IST is structurally abnormal. If this theory stands, the ablation of the sinus node ought to cure the condition. The outcome from plenty of the sinus nodal ablations is very interesting. The immediate response is usually quite favourable, over 90% of patients no longer have IST immediately after sinus nodal ablation, but after 6 to 9 months recurrence is noted in about 80% of them.[17] The repetition of these electrophysiological studies showed a regeneration of the sinus node with IST-activity found inferior to the original site of ablation, across the crista terminalis. Furthermore, repeated ablations usually yield the same results, namely, early success and late failure.

The second theory is that IST is a form of dysautonomia. In this situation, the autonomic nervous system loses its normal balance, and at various times the parasympathetic or sympathetic systems become inappropriately predominant. Under the label of «dysautonomia» are grouped together the notions of chronic fatigue syndrome, vasovagal or neurocardiogenic syncope, panic attacks, anxiety, irritable bowel syndrome, POTS, fibromyalgia-and quite possible IST. Dysautonomias do not have a single cause. Some patients inherit the propensity to develop these syndromes and variations of dysautonomias often run in families. Viral illness, chemicals, chest or head trauma can trigger a dysautonomia syndrome.[20]

The fact is that IST patients might have been labelled as suffering from irritable bowel syndrome, POTS or chronic fatigue syndrome. Furthermore, the fact that something stimulates the successfully ablated sinus node to regenerate in IST patients suggests a more systemic problem than intrinsic sinus nodal disease. Electrophysiologists have noted that symptoms consistent with dysautonomia often persist even after successful ablation, i.e. during the period of time that normal HR has been achieved. An autoimmune mechanism mediated by the antiautonomic membrane receptor antibodies has been implicated as the pathogenesis of several cardiovascular disorders.[21]

In conclusion, it is generally accepted that the pathogenesis of IST is multifactorial, with the principal mechanism considered to be an enhanced intrinsic sinus node automaticity potentiated by altered sympathovagal balance. Other contributing mechanisms may include β-adrenergic hypersensitivity, M2 anticholinergic hyposensitivity, abnormal baroreflex activity and regional autonomic dysregulation.[6,13-14] Also, high intrinsic rate has been reported in many studies. [15,18]

Treatment

Inappropriate sinus tachycardia is frequently associated with significant impairment in quality of life. Unfortunately, there are no long-term, prospective, placebo controlled clinical trials of any therapeutic intervention that have demonstrated a substantial improvement in outcomes. Additionally, symptoms can continue despite heart rate control. [16,20]

Patients with IST require significant care and attention due to the nearly ubiquitous psychosocial distress and the complexity of their problems. Close attention and effective communication can improve outcome. Lifestyle changes should be discussed early on with all patients. There are very few treatments with solid evidence of efficacy for patients with IST.

Bate-adrenergic blockers are not usually effective and can cause adverse effects.[1,16] Other treatments have been suggested including fludrocortisone, volume expansion, pressure stockings, phenobarbital, clonidine, psychiatric evaluation, exercise training, and erythropoietin.[16] Ivabradine holds considerable promise for the treatment of IST. The drug blocks the I_f current and has a dramatic and generally well-tolerated effect on heart rate. At doses of 5–7.5 mg twice daily, the drug slows the heart rate by 25–40 bpm.[25,26] Several small case series have reported that ivabradine reduced heart rate and improved quality of life. The strongest evidence comes from a small, randomized crossover study in which 21 patients with IST were randomized to placebo or ivabradine 5 mg twice daily for a total of 12 weeks. Ivabradine eliminated symptoms in 70% of patients and increased exercise performance. Furthermore, the data suggested that combinations of metoprolol and ivabradine might be safe and effective.[24,28]

Several groups have described modification or ablation of the sinus node in IST. The clinical evidence is sparse and controversial due to a very small number of highly selective patients undergoing the procedure and the lack of a control patient population. Small case series support the option of sinus node modification by radiofrequency catheter ablation in patients with medically refractory IST. [37,38] There is no agreement on the optimal approach, including modification or ablation, open chest versus conventional intravascular access, and mapping methods.

During ablation, under a maximum adrenergic state and high-output pacing, the ablation catheter is positioned at the most cranial portion of the crista terminalis and radiofrequency energy is delivered in a craniocaudal direction at sites where local endocardial activation precedes the surface P-wave by 15–60 ms.[13,38]

Catheter ablation may be guided by intracardiac echocardiography[44] or 3D electroanatomic mapping.[42] Total sinus node ablation is defined as a reduction in HR of >50% of the tachycardia rate with a junctional escape rhythm. In general, primary success rates are reasonably good (76-100% in the short term), but there is a high rate of symptom recurrence, and the complication rates are significant. These complications include requirements for permanent pacing,[37] transient or permanent phrenic nerve paralysis, and transient superior vena cava syndrome. In addition, sinus node modification or ablation might not relieve all IST associated symptoms. Frequently, these patients are noted to have recurrence of IST, as well as occurrence of non-IST tachyarrhythmias at follow-up. In a study by Frankelet et al, 18% of the 33 patients who underwent sinus node modification over a mean follow-up of 2.0 ± 1.5 years were noted to have recurrence of IST, while 27% developed new non-IST tachyarrhythmias.[12]

Lastly, there is no evidence of symptomatic improvement over several years. Patients and referring physicians need to be aware that despite the potentially substantial symptoms and the patients' high motivation, the consequences of aggressive therapy might seriously outweigh any potential benefit. Given the young age of the patients and the highly invasive nature of ablation procedures, we do not recommend that they be part of routine care. However, ablation may be offered in highly select circumstances or as part of research protocols.

Table 4: **Recommendations-Treatment of IST**

1.	Treatment of reversible causes of sinus tachycardia, if identified
2.	Use of ivabradine
3.	Sinus node modification, sympathetic denervation, surgical ablation are not used in routine case

Conclusion

Sinus tachycardia is generally 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 aggressive treatment attempts in patients with IST because they may inflict serious complications that aggravate patient's condition.

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