Treatment of Inappropriate Sinus Tachycardia:
Still A Long Way To Go

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Inappropriate sinus tachycardia (IST) stands among the most challenging conditions to deal with in clinical practice. First described in 1939 by Codvelle and Boucher (1), IST is a benign syndrome in which symptoms occur in patients with sinus tachycardia. On the 12-lead ECG, the P wave morphology during tachycardia resembles that observed during normal heart rates, usually in the range between 60 and 90 beats per min. Sinus rates in affected patients tend to fluctuate above 90 beats per min for a dominant segment of the 24-hour heart beat activity (2).

The elusiveness of IST syndrome spreads across almost every aspect of its characterization, and likely accounts, at least in part, for our inability to treat effectively a considerable number of affected patients. Starting with definition, IST requires an average sinus rate exceeding 90 beats per min or a heart rate while awake and at rest equal to or higher than 100 beats per min. However, symptoms purportedly due to tachycardia may be present when sinus rates fall below 90 beats per min in some individuals whereas a multitude of subjects well above the estimated 1.2% prevalence of IST syndrome in the middle-ages population (3) exhibit sinus rates above 100 beats per min in the absence of any symptom. Exceeding sinus heart rates occur predominantly at rest, but several patients experience, alone or in combination with sinus tachycardia at rest, a disproportionally high (usually above 25 beats per min) almost immediate response to exertion, usually associated with a prolonged heart rate recovery after termination.

Symptoms in patients with IST also vary widely (4), with some being unlikely referable to tachycardia. If palpitation, shortness of breath, fatigue, dizziness, fainting, chest pain, and decreased ability to exercise can be correlated to increased sinus rates, other symptoms commonly reported such as anxiety, headaches, panic attacks and other psychiatric disorders appear to be less dependent on tachycardia. Response of symptoms to treatment is not always easy to interpret, as sometimes it does not correlate with drug-related reduction in sinus rate, whereas symptoms less dependent on increased sinus rate may benefit from drug treatment resulting in heart rate reduction (5).

Several mechanisms are potentially responsible for increased heart rate in patients with IST. While HCN4 pacemaker channel gain-of-function mutation has been recently shown to cause intrinsic dysfunction of the sinus node in family members (6), other mechanisms have also been suggested. Among them are beta-receptor stimulating autoantibodies, beta-adrenergic receptor super-sensitivity, muscarinic (M2) receptor autoantibodies or hyposensitivity, blunted response to adenosine, aberrant neuro-humoral modulation, impaired baroreflex control, alteration of baroreflex gain, impaired efferent parasympathetic function, vagal denervation and central autonomic overactivity (4). Identification of the mechanism responsible for IST in the individual patient is difficult, which may explain the wide variability in therapy and regimen prescriptions in these patients.

Several therapies have been investigated for the treatment of IST (7). Among medical therapies, beta-blockers, calcium-channel blockers, class I or III anti-arrhythmic drugs, fludrocortisone, midodrine, and,

most recently, ivabradine showed variably efficacy rates (2,7). Interventional therapies include sinus node modification or ablation, AV nodal ablation and permanent pacemaker implantation, stellate ganglion block and cardiac sympathetic denervation via minimally invasive or conventional thoracic surgery (2,7). Interpretation of results is challenging, as patient collectives in which these therapies are tested are usually scarce. Moreover, the methods used to evaluate therapeutic benefit vary among studies, with some being focused on changes in heart rate, others based on indicator assessment of symptom relief, others using individual scores adopted from other diseases (i.e., EHRA score) or multiple Quality-of-Life scores developed for different interpretation purposes. These variable methods notwithstanding, data collected in patients with IST show that symptom resolution and incomplete relief can be obtained in less than half and in about two-thirds of patients, respectively.

In this issue of the journal, Shabtaie et al. (8) provide a retrospective review on the outcome results of a large series of consecutive patients with IST referred to the authors' center between 1998 and 2018. Study data were extracted by means of prescribing patterns and symptom response to medical therapy and sinus node modification in 305 patients with a formal diagnosis of IST, i.e., after elimination of patients with sinus tachycardia secondary to identifiable causes. Four-hundred-fifty-one drug prescriptions were available for efficacy assessment in 259 patients (85%) of the authors' series during 3.6±4.6 years mean follow-up. Of these, 245 were available for efficacy assessment during treatment with beta-blockers (including acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, and propranolol), 93 during treatment with non-dihydropiridine calcium blockers (verapamil and diltiazem), 38 during treatment with class I of III anti-arrhythmic drugs, 21 during treatment with ivabradine, 19 during treatment with fludricortisone, and 35 during treatment with midrodine. Overall, elimination of symptoms was recorded in 4% of patients, improvement in 18%, no change in 71% and worsening or drug intolerance in 7%. Another 55 patients underwent 1.8±0.9 sinus node modifications, 12% of whom experienced peri-procedural major complications, whereas 8 patients, whether previously receiving drug prescription or sinus node modification, ultimately received AV nodal ablation with pacemaker implantation. Complimentarily, exercise and increased physical activity were recommended in more than two-thirds of patients, increasing fluid and salt liberalization or supplementation in about half of patients and compression stocking prescriptions in about one-fourth of patients.

The article by Shabtaie et al. (8) is warmly welcome on stage, as it provides, by far, the largest contribution on the effects of medical or interventional therapy in patients with this syndrome. Using a privileged observatory encompassing 20 years of clinical activity, the authors go across a wide range of therapy prescriptions that well reflect the clinical standards during the investigated period. Several original observations can be drawn from data analysis. First, referral to a high volume tertiary academic center of patients with IST occurred at a pace of about 1 patient per month during a long monitoring period. Second, beta-blockers and calcium channel blockers represented, in aggregate, about 75% of 451 drug prescriptions during an average 3.5-year measurable follow-up. Third, up to 11 different cardio-selective and 1 non-

selective beta-blockers were chosen by study investigators for sinus rate control, indicative of the current uncertainty related to therapy selection even within the same drug category. Of the beta-blockers prescribed, metoprolol was the one administered with largest incidence, followed by atenolol and propranolol. Fourth, sinus node modification, performed using an endocardial (90%) or epicardial approach (10%), resulted in elimination or attenuation of symptoms in 5% and 30% of patients, respectively. Such unsatisfactory outcome was further emphasized by the 4% rate of intra-procedural cardiac perforation, indicative of the aggressiveness required to achieve heart rate reduction in response sinus node ablation. Fifth, symptoms improvement did not appear to depend on drug-induced heart rate reduction, as heart rates of similar magnitude were recorded in responders and non-responders to drug therapy. Finally, and most striking on clinical perspective, about 80% of drug prescriptions provided no benefit, worsening of symptoms or medication intolerance during long-term follow-up.

In the context of an overall disappointing impact by medical and interventional therapies administered it is noteworthy that administration of oral ivabradine and ablation of the AV node with pacemaker implantation, especially in the group converted after failed sinus node modification, showed some trend towards a better clinical outcome. Of the 21 patients receiving ivabradine, 24% reported elimination of symptoms and another 33% experienced symptom attenuation. These results are consistent with previous reports exploring clinical outcome in patients with IST. In an open-label, observational comparative study conducted in 24 patients, Martino et al. (9) reported complete resolution of symptoms in 75% of patients receiving metoprolol and 90% of patients receiving ivabradine during 3-month follow-up. In a non-randomized, cross-over, open-label study conducted in 20 patients, Ptaszynski et al. (10) reported a clinical efficacy of 85% during treatment with metoprolol and 100% during treatment with ivabradine. During the same follow-up, 45% of patients in the former group and 70% in the latter group experienced resolution of all symptoms. In a placebo-controlled, cross-over, 12-week long study, Cappato et al. (5) reported elimination of 70% of baseline symptoms, with 43% of patients reporting elimination of all symptoms at 6-week follow-up. Table 1 summarizes the main characteristics of clinical trials providing comparative drug assessment in patients with IST. Among interventional therapies, AV nodal ablation provided a benefit similar to that reported with ivabradine, with 5 of 9 patients (55%) reporting resolution of symptoms during follow-up.

Although relevant to our knowledge, the contribution of this study suffers some important limitations, including the retrospective nature of data collection, reliance on available documentation from daily clinical practice, lack of outcome results from combined therapies, and data origin from a single center. To date, and in spite of the authors' valuable effort, most of our uncertainties about the causes of IST and the best therapies to be adopted in the individual case remain unresolved. In order to compensate for missing information, further studies are needed possibly based on large, multi-center, randomized evaluation of competitive therapies tested over long-term follow-up. (1,494)

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Table 1. Main characteristics of clinical trials providing comparative drug assessment in patients with inappropriate sinus tachycardia

	Patients (n)		Age (years)	Efficacy		Resolution		Follow-up		Symptom assessment
	B-blocker	Ivabradine		B-blocker	Ivabradine	B-blocker	Ivabradine	B-blocker	Ivabradine	
Ptaszynsky et al, 2013	20	20	36±10	17 (85%)	20 (100%)	9 (45%)	14 (70%)	1 month	1 month	EHRA score
Martino et al, 2015	12	12	16-62	-	-	9 (75%)	11 (90%)	3 months	3 months	No specification
Cappato et al, 2012*	-	21	37±13	-	15 (70%)	-	9 (43%)	1 month	1 month	Reduction of aggregate symptom estimate. Elimination of all symptoms.

*Control arm represented by placebo