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Review

Inappropriate sinus tachycardia: a review

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Inappropriate sinus tachycardia (IST) has been defined as a resting heart rate of >100 beats per minute and an average 24-hour heart rate >90 bpm with distressing symptoms resulting from the persistent tachycardia. IST is prevalent in 1% of the middle-aged population, mostly females. Rarely can elderly patients also present with IST. Possible mechanisms of IST include intrinsic sinus node abnormality, beta-adrenergic receptor stimulating autoantibody, beta-adrenergic receptor supersensitivity, muscarinic receptor autoantibody, or hyposensitivity, impaired baroreflex control, depressed efferent parasympathetic/vagal function, nociceptive stimulation, central autonomic overactivity, aberrant neurohumoral modulation, etc. Symptoms associated with IST are palpitations, chest pain, fatigue, shortness of breath, presyncope, and syncope. Despite these distressing symptoms, IST has not been associated with tachycardia-associated cardiomyopathy or increased major cardiovascular events. Various treatment options for patients with IST are ivabradine, beta-adrenergic blockers, calcium channel blockers, psychiatric evaluation, and exercise training. Although, endocardial radiofrequency ablation targeting the sinus node has been used as a treatment modality for otherwise treatment-refractory IST, the results have been dismal. The other modalities used for refractory IST treatment are endocardial modification of the sinus node using radiofrequency energy, combined endo and epicardial ablation of the sinus node, thoracoscopic epicardial ablation of the sinus node, sinus node sparing thoracoscopic and endocardial hybrid ablation. The goal of this review is to provide the readership with the pathophysiological basis of IST and its management options.

Keywords

Autonomic dysfunction; Inappropriate sinus tachycardia; Ivabradine

1. Introduction

Inappropriate sinus tachycardia (IST) is a clinical syndrome characterized by persistently increased resting heart rate (HR) and a further exaggerated increase with minimal physiologic stimuli. 2015 Heart Rhythm Society (HRS) expert consensus statement defines IST as a resting sinus HR of >100 beats per minute (bpm), an average 24-hour HR >90 bpm without any identifiable cause, and distressing symptoms resulting from the persistent tachycardia [1].

Some experts have divided IST patients into three groups based on the HR pattern (a) normal resting heart rate (<85 bpm) with an exaggerated increase in HR in response to minimal stimuli, (b) moderately increased resting HR (>85 bpm) with an exaggerated increase in HR in response to minimal stimuli and (c) markedly elevated resting HR with a graded response to physiologic stimuli [2].

2. Epidemiology

Epidemiological data regarding IST is scarce. A prospective, population-based case-control study found a prevalence of 1.16% (n = 7; Male:Female, 1:4) in 604 middle-aged subjects. The mean age of the IST patients was 47 $\pm$ 7 years [3].

In a single-center, retrospective study of Holter recordings, 63 patients (4.98%) out of 1265 patients were diagnosed with IST according to the Heart Rhythm Society (HRS) criteria [4]. The authors did not include 33 patients with a mean HR of $\geq$90 bpm and resting HR of <100 bpm in the IST cohort, which may have underestimated the true IST prevalence in the symptomatic population. The mean age of patients was 39.7 years, and 60% of the patients were females.

In a retrospective analysis of 305 IST patients, the mean age of patients was 33 years at the time of diagnosis, and 92.1% (n = 281) were females [5].

Although most patients are young females, IST has been diagnosed in elderly patients as well. Lopera *et al.* [6] have reported on four women in whom IST was diagnosed in the 6th or 7th decade of life. One of the main issues with their methodology was that they included an increase in HR of $\geq$25 bpm on standing from a supine position as an inclusion criterion which may indicate an overlap between IST and postural orthostatic tachycardia syndrome (POTS) [7].

Some reports indicate that a disproportionate number of IST patients are healthcare workers [8, 9]. Two of the seven IST patients (29%) in the OPERA study were health-

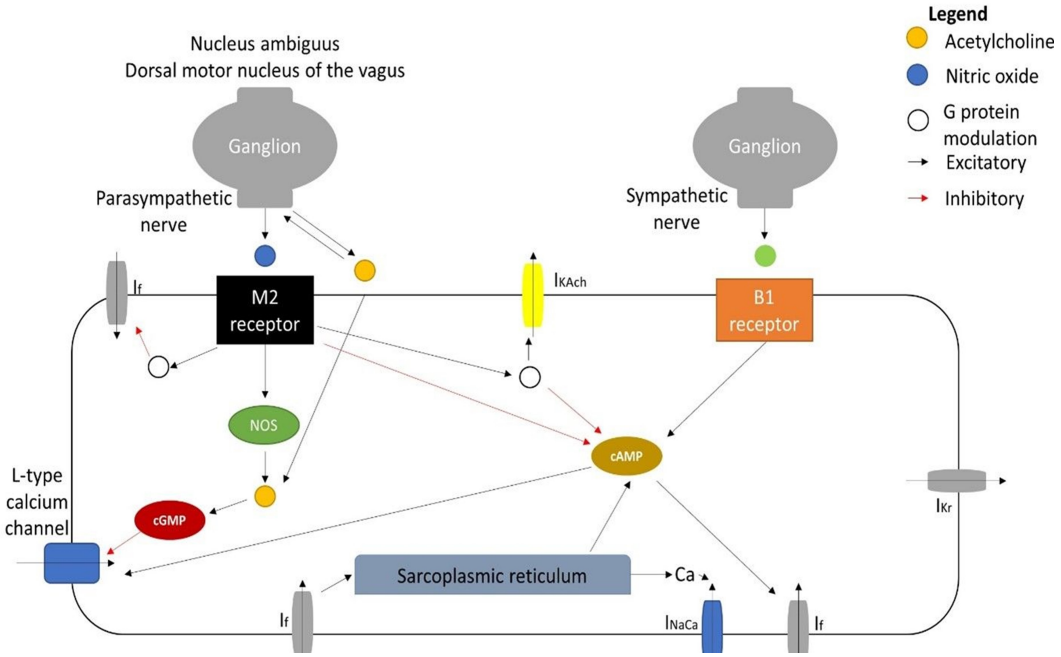

Fig. 1. Heart rate control via the autonomic nervous system. Sinus node activation is managed by cellular currents, including I_{KAch}, I_{NaCa}, I_{Kr}, and L-type calcium channels, among others. Moreover, calcium released from the sarcoplasmic reticulum plays a role in the setting of the sinus rate. The parasympathetic system helps determine the rate at rest through acetylcholine and nitric oxide, and parasympathetic activation affects the muscarinic receptor (M2). If: funny current. I_{NaCa}, sodium/calcium exchange current; I_{Kr}, delayed rectifier potassium current; I_{KAch}, inward-rectifier potassium channel.

care workers [3]. The exact reason for this phenomenon is unknown, but one possibility is that the healthcare workers may be quick to recognize the tachycardia when it occurs and seek medical care for this.

3. Pathophysiology

The funny current (If) or the pacemaker current is a mixed Na^+/K^+ inward current mediated by hyperpolarization-activated cyclic nucleotide-gated (HCN) channels found in heart cells with pacemaking ability. The funny If current is activated during hyperpolarization and is responsible for spontaneous diastolic (phase 4) depolarization which leads to pacemaker cell depolarization. Sympathetic stimulation via beta-adrenergic activation increases the funny current by increasing cyclic adenosine monophosphate (cAMP), leading to an increased firing rate of pacemaker cells. Vagal stimulation leads to decreased pacemaker activity by decreasing cAMP levels. HCN channels most common in the human sinoatrial node are HCN4 [10] (Fig. 1).

Morillo *et al.* [11] found that in 6 IST patients, there was increased sinus node automaticity, beta-adrenergic hypersensitivity, and decreased response to vagal stimulation. Intrinsic heart rate in IST patients after autonomic blockade with propranolol and atropine was significantly higher, which means that patients with IST have an intrinsic sinus node abnormality despite adrenergic hypersensitivity and vagal hyporesponsiveness. IST patients also have a markedly reduced vagal efferent tone [12].

Wising in 1941 first described a familial form of IST that was labeled as familial, congenital sinus tachycardia [13]. A gain-of-function mutation (arginine-to-glutamine; R524Q) in the HCN4 gene has been reported in a family of IST patients. This mutation leads to an increased affinity of the HCN4 channels to cAMP, thus mimicking beta-adrenergic stimulation [14].

Chiale *et al.* [15] found circulating anti-beta-adrenergic IgG antibodies in 11 of 21 (52%) patients (21 females; mean age 37 years). These antibodies had a positive chronotropic effect by increasing cAMP levels which was abolished by propranolol in all but one patient. This study proved that the immunologic phenomenon might be responsible for IST in half of the IST patients, which still doesn't explain the pathogenesis of IST in a significant number of patients in which there may be other mechanisms responsible for IST. In this study, the chronotropic effect of anti-beta-adrenergic IgG antibodies could not be reversed by propranolol in one patient leading the authors to hypothesize that beta-adrenergic receptors may not be the only target of such antibodies.

Adenosine typically has a biphasic response on sinus node activity: an initial reduced sinus node firing rate followed by reflex sinus tachycardia. But in IST, both of these responses are impaired with or without pharmacologic autonomic blockade with propranolol and atropine. Interestingly, Still *et al.* [16] in their study also reported that transient second degree or third-degree atrioventricular block after adenosine administration was less frequent in IST patients in comparison to healthy controls leading the authors to pos-

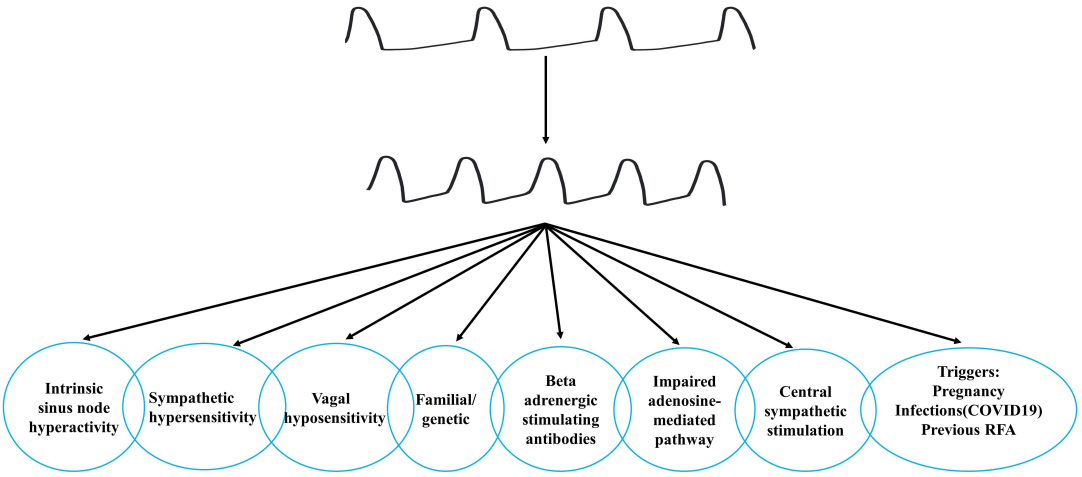

Fig. 2. Schematic of inappropriate sinus tachycardia pathogenesis. Please see the text for details.

tulate that impaired function of acetylcholine-sensitive and adenosine-sensitive potassium channels ($I_{KAch,Ado}$) may be the cause of IST. These observations also suggest that autonomic system anomalies present in IST patients may not be the primary cause of the tachycardia.

IST has also been reported in a 53-year-old man who developed IST one year after receiving a bicaval heart transplant. Sympathetic reinnervation of the donor's heart was ruled out using I^{123} metaiodobenzylguanidine (MIBG) scintigraphy, pointing out that IST can develop in a heart that has no autonomic innervation [17].

Other factors proposed for IST pathogenesis are beta-adrenergic receptor supersensitivity, muscarinic receptor abnormality, central and peripheral nociceptive effects, neurohormonal modulation, hypothalamic paraventricular nucleus stimulation, and non-muscarinic, non-adrenergic, vagally-mediated tachycardia [18] (Fig. 2).

In a significant number of patients, a precipitating event initiating the tachycardia has been reported. The most common triggers identified in IST patients are pregnancy (7.9%), antecedent infectious illness (5.9%), emotional stress (3.6%) [5].

Multiple reports have documented IST after radiofrequency ablation (RFA) for various supraventricular tachycardias (SVT) [19–22]. The possible explanations for this phenomenon are autonomic modulation to the heart by ablation of vagal ganglia and increased awareness of heart rate after an ablation procedure. In atrioventricular nodal reentrant tachycardia (AVNRT) ablation procedures, one possibility remains that the patients were having symptoms of increased heart rate because of dual AV nodal physiology, which was ablated and were then labeled as AVNRT [5].

As the COVID-19 epidemic runs rampant across various nations, there is increasing evidence that one of the sequelae of COVID-19 infection is autonomic dysfunction as a component of the post-COVID syndrome [23]. Huang *et al.* [24] reported that at 6-months follow-up, 9% (154 out of 1655) of patients who had recovered from COVID-19 reported palpitations. Ståhlberg *et al.* [25] report that 25–50% of patients had palpitations or tachycardia persisting 12 weeks or longer, and they have proposed the term "post-COVID-19 tachycardia syndrome" for the persistent symptomatic tachycardia after COVID-19 illness. POTS and IST have been reported as a spectrum of this syndrome [23, 26, 27].

4. Clinical features and diagnosis

Palpitations are the most common symptom in around 90% of patients. Other symptoms include chest discomfort, fatigue, shortness of breath, presyncope, and syncope. Depression and anxiety each are found in a quarter of the patients with IST. Almost a quarter of patients have a documented arrhythmia other than IST, most commonly atrial tachycardia, followed by AVNRT and AF [5].

The occasional case reports of tachycardia-induced cardiomyopathy notwithstanding, the overall prognosis of IST is favorable. One of the reasons these patients do not develop cardiomyopathy is that the normal diurnal variation in HR is preserved in these patients [28].

IST is a diagnosis of exclusion. Evaluation should be aimed at ruling out secondary causes of sinus tachycardia, e.g., anemia, hyperthyroidism, heart failure, etc. Evaluation of an IST usually requires a 12-lead electrocardiogram (EKG), 24-hour Holter monitoring, echocardiography. The further non-invasive evaluation may require an exercise test to assess the severity of symptoms and diagnose patients who have normal resting heart rates, as already pointed out in the introduction section [1].

Tilt table testing is required to rule out the presence of POTS. In the study by Shabtaie *et al.* [5], 24% of patients were diagnosed as having POTS.

According to the HRS expert consensus statement [1], various tests for cardiac autonomic responses like Valsalva, heart rate variability, cold face test, and baroreflex sensitivity are not routinely indicated because of unproven clinical benefits.

An invasive cardiac electrophysiology study is indicated if the diagnosis is in doubt or another tachycardia mechanism is suspected [29].

IST and sinus node reentrant tachycardia have similar EKG findings. The two can be differentiated by initiation and termination with a premature atrial contraction, termination by adenosine, or various vagal maneuvers characteristic of sinus node reentrant tachycardia [30].

5. Management

Reassurance and avoidance of cardiac stimulants are an integral part of IST management [29].

Pharmacotherapy usually involves beta-blockers, ivabradine, and calcium channel blockers. Some of the other drugs that have been used in IST are flecainide, sotalol, fludrocortisone, midodrine, etc.

Beta-blockers are the most widely used drugs for IST, but the improvement in the symptoms is modest. In a retrospective analysis, only about 25% of patients reported improved symptoms, and 4% reported complete resolution of symptoms with beta-blockers [31].

Evidence of the benefit of nondihydropyridine calcium channel blockers in IST is limited but are nevertheless used. The overwhelming majority of IST patients report no improvement or worsening symptoms after using these agents [31].

Ivabradine reduces sinus node firing rate by inhibiting If current. It has the most evidence regarding its usage in IST. In a pooled analysis of 9 prospective studies involving 145 patients, ivabradine significantly reduced resting HR and peak HR, leads to significant improvement in symptoms, and is better tolerated [32].

An observational, non-randomized study with a 1-month follow-up compared ivabradine with metoprolol succinate. Ivabradine resulted in a similar reduction in HR, better symptomatic relief, increased exercise duration and maximal workload, and better safety profile [33].

In a prospective, open-label study involving 40 patients with a follow-up of 24 months, Annamaria *et al.* [34] compared ivabradine to bisoprolol. Ivabradine was superior to bisoprolol in reducing daytime and night-time mean HR, increasing exercise capacity, and improving quality of life, and as shown in previous studies, was tolerated better.

Ivabradine can be used along with beta-blockers or calcium channel blockers. A combination of ivabradine and metoprolol succinate was better than metoprolol monotherapy in an observational study of twenty IST patients who received metoprolol for 4 weeks followed by the combination therapy for another 4 weeks [35].

Caution is warranted in the co-administration of ivabradine, and calcium channel blockers as verapamil and diltiazem inhibit the CYP3A4 enzyme system, which metabolizes ivabradine [36].

Another non-pharmacological measure found effective in IST is exercise training. Exercise training and beta-blockers increase exercise capacity, reduce average HR, and improve symptoms and overall quality of life [37]. Management of accompanying depression and anxiety may lead to symptom amelioration [18].

6. Invasive

Many patients remain symptomatic even after using all the aforementioned treatment options, or their use is restricted because of the disabling adverse effects. Invasive treatment is reserved after the exhaustion of all the other treatment options.

Various invasive treatment options that have been reported are:

(a) endocardial radiofrequency ablation (RFA) targeted at the sinus node.

(b) combined endo and epicardial ablation of the sinus node.

(c) thoracoscopic epicardial ablation of the sinus node.

(d) sinus node sparing thoracoscopic and endocardial hybrid ablation.

The most commonly used treatment modality with available data to make an informed decision has been endocardial sinus node modification using radiofrequency energy.

In the retrospective study by Shabtaie *et al.* [31], over a period of 20 years, 55 out of 305 IST patients underwent a sinus node modification procedure. 91% of the procedures were endocardial, and 9% were epicardial RFA procedures. Within 6 months of the procedure, 58% of patients reported any improvement; 66% didn't report any long-term improvement even with multiple procedures (mean procedures per patient: 1.8 ± 0.9). The mean follow-up of these patients was 4.8 ± 5.2 years. Procedural complications included pacemaker implantation requirement (31%), cardiac perforation (3.6%), acute kidney injury (1.8%), myocardial infarction (1.8%), cerebrovascular event (1.8%), pericardial effusion (1.8%), and deep venous thrombosis (1.8%).

In a systematic review of nine studies that included 153 patients, Rodríguez-Mañero *et al.* [38] reported acute procedural success in 90%. 86% of patients reported long-term improvement in symptoms. Various complications reported in 8.5% were: phrenic nerve injury, superior vena cava syndrome, arteriovenous fistula, retroperitoneal bleed, cardiac tamponade, right ventricular puncture, and pericarditis [38]. After a mean follow-up of 28.14 ± 12.64 months, 86% of patients reported improvement in symptoms, and 19.6% of patients had a recurrence. 15 patients (10%) underwent pacemaker implantation during the follow-up.

Table 1. Studies of invasive treatment in IST.

Study	Year	Number of patients	Type of study	Treatment strategy	Results	Remarks
Shabtaie *et al.* [31]	2021	55	Single-center retrospective case series	Endocardial RFA SNM (91%) Epicardial RFA SNM (9%)	58% showed improvement in symptoms in 6 months 5% showed long-term (>6 months) resolution of symptoms	See text for details
Lakkireddy *et al.* [39]	2021	100 (82 females)	Multicenter prospective registry	50: Hybrid strategy 50: endocardial RFA	Restoration of normal sinus rhythm and rate: 100% vs. 84% 78% vs. 0% of patients were able to stop their rate-reducing drugs RFA group was associated with multiple repeat procedures and more adverse effects	See text for details
Daher *et al.* [40]	2020	39 (37 females)	Single-center retrospective case series	Endocardial RFA based SNM	37 patients had symptom resolution after at least 1 SNM 21 required >1 SNM procedure 13 required postprocedure rate control medications	13 patients required PPM implantation 2 patients had phrenic nerve injury 6 patients had postprocedure pericarditis
Reissmann *et al.* [41]	2020	3 (all females)	Single-center retrospective case series	Endocardial RFA based SNM	100% acute success rate. 2 of the 3 patients had relief of symptoms after a mean FU of 424 days	1 required PPM implantation after SN ablation
Aalaei-Andabili *et al.* [42]	2019	10 (8 females)	Single-center retrospective case series	Minimally invasive thoracoscopic surgery All patients had recurred after at least 1 endocardial RFA based SNM	100% acute success rate 2 IST recurrences after a median FU of 13 months 88% freedom from reintervention at 6 months 4 repeat interventions (3 endocardial RFA, 1 minimally invasive surgery)	1 pericarditis 1 pulmonary embolism No PPM implantation
Khiabani *et al.* [43]	2019	18 (16 females)	Single-center retrospective case series	Surgical isolation of sinus node 15 patients had recurred after endocardial RFA based SNM	100% acute success rate No IST recurrence in 17 patients after a mean FU of 11 years	5 patients required PPM implantation on FU 2 patients required RFA for atrial flutter and AT
de Asmundis *et al.* [44]	2019	50 (41 females; 39 IST, 11 POTS)	Single-center retrospective case series	Sinus node sparing hybrid thoracoscopic ablation	Preablation HR in IST 119 $\pm$ 10 bpm HR on day 1 postablation 65 $\pm$ 13 After a mean FU of 28 months, 100% of patients had significantly slower HR (74 $\pm$ 9 bpm) All patients stopped rate-reducing medications during FU	Pericarditis was the most common complication (39/50) No requirement of PPM during FU No phrenic nerve injury
Ibarra-Cortez *et al.* [45]	2015	13 (all females)	Single-center retrospective case series	Endocardial RFA based SNM. Pericardial access in 10 patients for phrenic nerve preservation.	100% acute success rate 84.6% (11 out of 13) relief of symptoms after a mean FU of 811 days	1 pericardial bleeding which required surgery 1 PPM implantation

Table 1. Continued.

Study	Year	Number of patients	Type of study	Treatment strategy	Results	Remarks
Jacobson *et al.* [46]	2014	5 (All females)	Single-center retrospective case series	Epicardial SN ablation in patients who had failed an endocardial approach.	100% acute success rate 100% relief of symptoms after a FU of 30 months	3 cases of pericarditis 1 case of RV puncture 3 patients already had a device implanted
Frankel *et al.* [47]	2012	33 (31 females)	Single-center retrospective case series	Endocardial RFA based SNM	6 patients (18%) had an IST recurrence after a mean FU of 2 years	Non-IST tachycardias were found in 42% before the SNM procedure (most common was AVNRT) and in 27% after the procedure (most common was AT) 4 patients required PPM implantation on FU
Takemoto *et al.* [48]	2011	6 (3 females)	Single-center case series	Endocardial RFA based SNM	SNM success 100% 1 patient had a recurrence after a mean FU of 29 months	
Lin *et al.* [49]	2007	7 (6 females)	Single-center case series	Endocardial RFA based SNM	SNM success 100% 6 patients had no recurrence over a mean FU of 13 months	1 patient required PPM implantation
Marrouche *et al.* [50]	2002	39 (35 females)	Single-center case series	Endocardial RFA based SNM	SNM success 100% 21% had recurrence over a mean FU of 32 months None of the patients required PPM implantation after the procedure	1 SVC syndrome 3 patients presented with atrial tachycardia after the procedure
Man *et al.* [51]	2000	29 (26 females)	Single-center case series	Endocardial RFA based SNM	76% acute success 55% (16) free of symptoms after a mean FU of 32 months	1 right diaphragmatic palsy 6 patients received a PPM on FU (5 after AVNJ ablation)
Callans *et al.* [52]	1999	10 (9 females)	Single-center, retrospective case series, studied SVC obstruction post RFA for IST	Endocardial RFA based SNM	84% (11) acute success in 13 procedures 3 (30%) recurrences No FU data	5 patients had a $\geq$30% decrease in SVC-RA junction diameter 1 PPM implantation after SN ablation
Lee *et al.* [9]	1995	16 (15 females)	Single center case series	Endocardial RFA based SNM (n = 12)/SN ablation (n = 4)	100% acute success 87% symptom relief at 20 months follow-up 2 recurrences 4 patients were deemed to be as partial success on FU 2 patients developed ectopic atrial tachycardia	Right phrenic nerve palsy (n = 1, transient) SVC syndrome (n = 1, transient) 3 patients received a PPM 3 patients had already received a PPM after AVNJ ablation

AT, atrial tachycardia; AVNJ, atrioventricular node junction; AVNRT, atrioventricular nodal reentrant tachycardia; SN, sinus node; SNM, sinus node modification; FU, follow-up; PPM, permanent pacemaker.

The evidence regarding RFA based sinus node modification in IST so far (Table 1, Ref. [9, 31, 39–52]) can be summarized as moderate acute procedural success, minimal long-term benefits, and an increased risk of complications. That is why the HRS expert consensus document [1] (Class III recommendation) and ESC guidelines [29] do not recommend RFA as a routine treatment for IST. It should be reserved for the most symptomatic patients in which all the available conservative therapeutic measures have failed.

Evidence suggests two distinct and dominant sinus nodes in human hearts: a superior sinus node near the SVC and an inferior sinus node near the IVC. So, a procedure for IST will lead to HR control only if sympathetic innervation to both these sinus nodes is interrupted [53].

This concept has led to sinus-node-sparing thoracoscopic isolation of SVC and IVC from the right atrium. This procedure involves thoracoscopic ablation at the SVC-RA junction (sparing the sinus node after identifying it by endocardial three-dimensional electroanatomic mapping), IVC-RA junction, and the third ablation line along crista terminalis connecting these two ablation lines (Fig. 3).

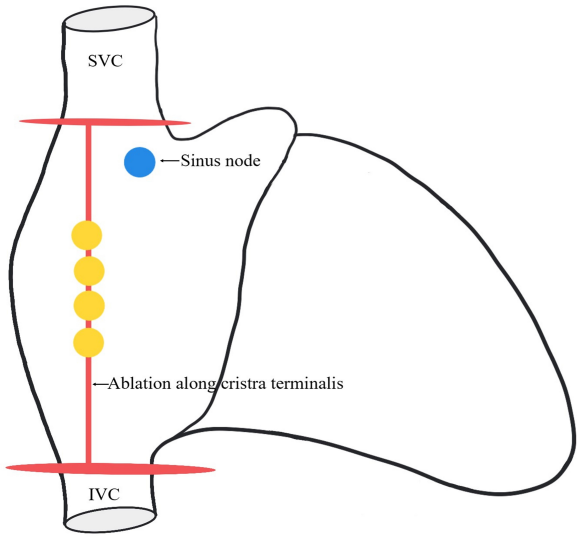

Fig. 3. Thoracoscopic sinus node sparing ablation strategy. Ablation lesions (red-colored oval circles and straight line) are created at SVC-RA junction, IVC-RA junction, and along crista terminalis by using a bipolar radiofrequency clamping device. If any, the gaps along the crista terminalis ablation line are endocardially ablated (yellow dots).

In 39 consecutive IST patients, who underwent the hybrid procedure, the mean HR decreased from 119 $\pm$ 10 bpm before the procedure to 65 $\pm$ 13 bpm on the first day post-ablation and was 74 $\pm$ 9 bpm at 24 months follow-up. All patients stopped their rate-reducing drugs during the follow-up. The most common complication during the follow-up was pericarditis. None of the patients required pacemaker implantation, and none of the patients developed phrenic nerve injury.

In a multicenter, prospective registry, the hybrid ablation procedure was compared with RFA based endocardial sinus node modification in 100 IST patients. The patients' mean number of procedures was 1.02 in the hybrid group and 2.44 in the endocardial ablation group. Mean resting HR before the procedure was 122 and 121 bpm, respectively. Mean HR after the procedure, at 12 months follow-up, and after 6-minute walk test at 12 months was 61 vs. 82.9 bpm ($p <$ 0.001), 72 vs. 88 bpm ($p < 0.001$), and 107 vs. 115 bpm ($p =$ 0.01) [39].

78% of patients in the hybrid group could stop all of their rate-reducing drugs, while none of the patients in the endocardial RFA group was able to do so. Quality of life (QoL) scores showed a significant improvement in both groups, but the hybrid group had better QoL scores than the endocardial RFA group.

The hybrid procedure was associated with significantly more extended ICU stay (1 vs. 0.2 days) and acute pericarditis (92 vs. 48%). The endocardial RFA procedure was associated with a significantly longer non-ICU hospital stay (4.2 vs. 2.9 days), more rehospitalizations during the 12-month follow-up (54 vs. 6%), more right hemidiaphragm stunning (14 vs. 0%), and more permanent pacemaker implantations during the follow-up (50 vs. 4%).

HRS expert consensus document [1] recommends Class III indication for surgical ablation (along with sinus node modification and sympathetic denervation) as a part of routine care for IST patients. Although unlikely to become a part of routine care, for patients with drug-refractory IST, hybrid ablation offers a safer and more effective treatment option than endocardial sinus node modification using radiofrequency energy.

Some of the other treatment options that have been utilized in drug-refractory IST are stellate ganglion block and cardiac sympathetic denervation [54], renal sympathetic denervation [55], surgical ablation of the sinus node [43], thoracoscopic epicardial ablation of the sinus node [42], surgical excision of the sinus node [56], partial cardiac denervation and sinus node modification via right thoracotomy [57].

7. Conclusions

IST is a clinical syndrome with distressing symptoms mainly affecting younger females, is challenging to treat, but has a favorable long-term prognosis. Ivabradine has shown better results and is tolerated better than other rate-reducing drugs. RFA aimed at sinus node modification has dismal results. Sinus node sparing thoracoscopic ablation aimed at isolation of sinus node has shown promising results.

Author contributions

MA, AH, AK were involved in literature search and drafting of the manuscript, BPG and KK approved the draft and were involved in final editions of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest. Dr. Kanjwal is the consultant for St Jude Medical and Bio sense webster.

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