Targeted Treatment of Inappropriate Sinoatrial Node Tachycardia Based on Electrophysiological and Structural Mechanisms

Carlo de Asmundis, MD, PhD[a,*], Luigi Pannone, MD[a], Dhanunjaya Lakkireddy, MD[b], Thomas M. Beaver, MD[c], Chad R. Brodt, MD[d], Randall J. Lee, MD, PhD[e], Antonio Sorgente, MD, PhD[a], Anaïs Gauthey, MD, PhD[a], Cinzia Monaco, MD[a], Ingrid Overeinder, MD[a], Gezim Bala, MD, PhD[a], Alexandre Almorad, MD[a], Erwin Ströker, MD, PhD[a], Juan Sieira, MD, PhD[a], Pedro Brugada, MD, PhD[a], Gian-Battista Chierchia, MD, PhD[a], Mark La Meir, MD, PhD[f], and Brian Olshansky, MD[g]

The purpose of this review is to determine the causal mechanisms and treatment of inappropriate sinoatrial tachycardia (IST), defined as a non-physiological elevation in resting heart rate. IST is defined as a resting daytime sinus rate >100 beats/minute and an average 24-hour heart rate >90 beats/minute. Potential causal mechanisms include sympathetic receptor hypersensitivity, blunted parasympathetic tone, or enhanced intrinsic automaticity within the sinoatrial node (SAN) pacemaker-conduction complex. These anomalies may coexist in the same patient. Recent ex-vivo near-infrared transmural optical imaging of the SAN in human and animal hearts provides important insights into the functional and molecular features of this complex structure. In particular, it reveals the existence of preferential sinoatrial conduction pathways that ensure robust SAN activation with electrical conduction. The mechanism of IST is debated because even high-resolution electroanatomical mapping approaches cannot reveal intramural conduction in the 3-dimensional SAN complex. It may be secondary to enhanced automaticity, intranodal re-entry, or sinoatrial conduction pathway re-entry. Different pharmacological approaches can target these mechanisms. Long-acting β blockers in IST can act on both primarily increased automaticity and dysregulated autonomic system. Ivabradine targets sources of increased SAN automaticity. Conventional or hybrid ablation may target all the described abnormalities. This review provides a state-of-the-art overview of putative IST mechanisms. In conclusion, based on current knowledge, pharmacological and ablation approaches for IST, including the novel hybrid SAN sparing ablation, are discussed. **(Am J Cardiol 2022;183:24−32)**

The purpose of this review is to determine the causal mechanisms and treatment of inappropriate sinoatrial tachycardia (IST), defined as a nonphysiological elevation in resting heart rate. IST is a chronic condition in which the sinus rate exceeds physiological needs and is otherwise unexplained by any specific trigger. IST is defined as a resting daytime sinus rate >100 beats/minute and average 24-hour heart rate >90 beats/minute.[1,2] Symptoms are heterogenous and may include palpitations, exercise intolerance, dyspnea, fatigue, syncope, chest pain, anxiety, and depression. Up to 90% of IST patients are young women with an average age of approximately 30 years.[3−6] Despite several basic and clinical studies, the electrophysiological mechanisms of IST remain heterogeneous. The increased heart rate is due to dysfunctional intrinsic sinoatrial node (SAN) pacemaker automaticity, abnormal function of the cardiac autonomic nerves, and/or various forms of macro or micro-reentry.[7,8] These anomalies may coexist in the same patient. Potential etiologies of IST require patient-specific treatments, with highly variable long-term success and safety.[9] The aim of this review is to provide a state-of-the-art overview of the putative mechanisms of IST. Furthermore, based on current knowledge, pharmacological and ablation strategies for IST are discussed (Figures 1 and 2).

[a]Heart Rhythm Management Centre, Postgraduate Program in Cardiac Electrophysiology and Pacing, Universitair Ziekenhuis Brussel - Vrije Universiteit Brussel, European Reference Networks Guard-Heart, Brussels, Belgium; [b]Kansas City Heart Rhythm Institute, Overland Park, Kansas, USA; [c]Division of Thoracic and Cardiovascular Surgery, Department of Surgery, University of Florida, Gainesville, Florida; [d]Sequoia Hospital, Palo Alto, California; [e]Section of Cardiology, University of California at San Francisco, San Francisco, California; [f]Cardiac Surgery Department, Universitair Ziekenhuis Brussel - Vrije Universiteit Brussel, Brussels, Belgium; and [g]Division of Cardiology, University of Iowa Hospitals, Iowa City, Iowa. Manuscript received May 9, 2022; revised manuscript received and accepted July 8, 2022.

Authors Mark La Meir and Brian Olshansky contributed equally as last authors.

Funding: None.

See page 29 for disclosure information.

*Corresponding author: Tel: (313) 972 4108; fax: (313) 972 1921.

E-mail address: carlodeasmundis@me.com (C. de Asmundis).

https://doi.org/10.1016/j.amjcard.2022.07.041

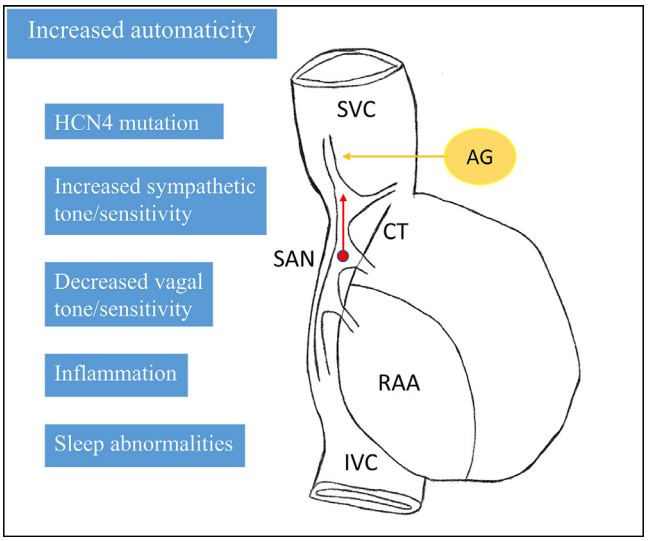

Figure 1. Inappropriate sinus node mechanism: increased automaticity. Increased automaticity can be secondary to increased sympathetic tone/sensitivity, decreased vagal tone/sensitivity, HCN4 mutation and, under certain circumstances, sleep abnormalities and inflammation. The increased automaticity can be the result of abnormalities in AG innervating SAN, (*yellow arrow, right side*); the result is an upward migration of the leading pacemaker (*red arrow, right side*). The SAN is represented with SACPs extending towards SVC, IVC and RAA, that is separated from the SAN by the CT. RAA = right atrial appendage.

Anatomy of Human SAN Pacemaker Complex

The SAN, located at the junction of the superior vena cava (SVC) and the right atrium, is a complex, multi-compartmental structure located at an intramural depth of approximately 1 to 3 mm and composed of small clusters of pacemaker myocytes arranged in parallel rows that frequently anastomose.[10–13] It is normally tilted such that the SAN head (superior third) is sub-epicardial, whereas the SAN tail (inferior third) is sub-endocardial. Clusters of specialized pacemaker cardiomyocytes are interspersed and electrically insulated within strands of dense connective tissue, nerve fibers, and capillaries to create a distinct SAN pacemaker complex.[10–13] These specialized SAN pacemaker cell clusters serve as pacemakers that initiate electrical activation.

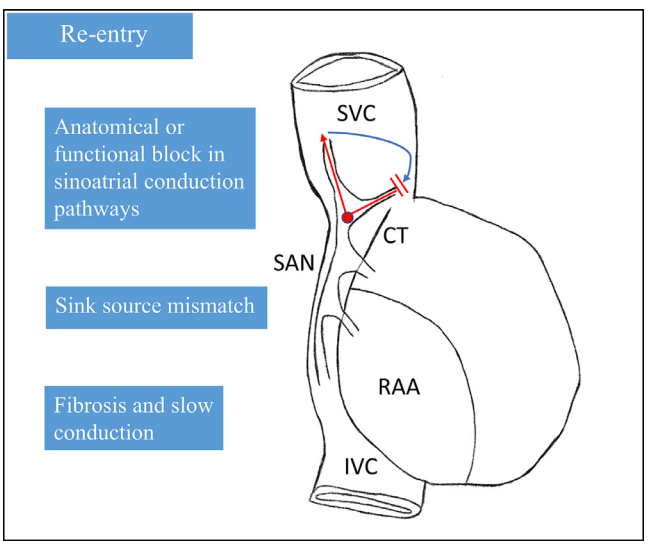

Figure 2. Inappropriate sinus node mechanism: re-entry. The SAN is represented with SACPs extending towards SVC, IVC and RAA, that is separated from the SAN by the CT. Re-entry can be secondary to anatomic or functional block in SACPs, block related to sink source mismatch, fibrosis and slow conduction. Hypothesized re-entrant mechanism through SACPs is shown: from the SAN the impulse travels towards SACPs (*red arrows, right side*), it blocks in one SACP that provides the pathway for the re-entrant wavefront (*blue arrow, right side*). RAA = right atrial appendage.

Sinoatrial conduction pathways

Recent ex-vivo human heart studies with intramural near-infrared optical mapping have clarified that distinct specialized sinoatrial conduction pathways (SACPs) structurally and functionally connect the SAN with the atria. Intramural near-infrared optical mapping is a biophotonic imaging technique that uses voltage- or calcium- sensitive dyes in the heart and light scattering optical mapping.[14] These studies revealed that the SAN is functionally insulated from the atria by fibrosis and fat except for 3 to 5 discrete SACPs that transmit electrical impulses to the atrial myocardium and correspond to discrete early atrial activation sites during sinus rhythm.[13,15] In nondiseased hearts, several discrete branching myofiber tracts are found to form the SACP structure, resulting in continuous, uninterrupted, physical connections between the SAN and the atria.[12] This continuous myofibrillar structure of the SACP is hypothesized to support normal function of the SAN by maintaining the source-sink relationship between SAN pacemaker cells and the atria.

Source-sink mismatch

The SAN has 2 functions, namely: pacing and driving the atrium. Pacing function requires a high resting potential (−60 mV) compared with surrounding atrial cells (−80 to 85 mV). This 20 to 30 mV voltage gradient in conditions of high cell-cell coupling drives an electrotonic current with a resulting suppression of the SAN and inhibits automaticity. In a landmark study, it was found that pacing was possible by increasing SAN resistivity.[16] Histological observations of SAN after removal of fat and connective tissues confirmed high SAN resistivity, reduced connexin43 expression in central SAN, and presence of gap junctions in SAN cells.[17,18] Although resistivity in surrounding atrial tissue is lower, an abrupt transition in resistive coupling would not allow the SAN to drive the atrium because of source-sink mismatch.

SAN-atrium coupling is the typical model of source-sink mismatch. The leading SAN pacemaker is a weak electrical source relying on I_{CaL} mediated upstroke.[19] The atrial cells behave as a large electrical sink with a more negative resting potential.[20] This apparent source-sink mismatch can be overcome by specialized SACPs. Conduction velocity is slow in SACPs, allowing SAN to develop a sufficient electrical charge to depolarize the atria. Furthermore, dissipation of electrical charge in the SAN is prevented by relative electrical uncoupling of SAN from the atria (Figure 2).

SACPs are identified based on their general anatomic locations (lateral/superior/middle/inferior, SVC, and septal

pathways).[21] During normal sinus rhythm, excitation originates in one of the intranodal pacemaker compartments, and it is preferentially delivered to the atria through either superior or inferior SACPs resulting in atrial activation with discrete early atrial activation sites. These sites could be 5 to 25 mm from leading intranodal SAN pacemaker activity seen on epicardial or endocardial electrograms.[22,23] New clinical simultaneous epicardial and endocardial multielectrode mapping studies of patients with cardiac disease and atrial fibrillation from 2 independent groups (de Groot[24] and Kalman[25]) confirmed ex-vivo near-infrared optical mapping observations of several discrete SACPs-early atrial activation sites.

INCREASED AUTOMATICITY

Automaticity in the SAN is the result of a complex interplay between ionic currents and autonomic modulation (Figure 1). The ionic currents responsible for the unique properties of SAN pacemaker cells, in terms of automatic depolarization and resting potential, are hyperpolarization-activated funny current (I_f) and rapid potassium current (I_{kr}) responsible for the "membrane voltage clock," and Na^+/Ca^{++} exchanger responsible for the "calcium clock."[26] The molecular alpha-subunits of the I_f are represented by hyperpolarization-activated cyclic nucleotide-gated channels (HCN1, HCN2 and HCN4).

In the human heart, HCN1 protein is primarily expressed only in the human SAN pacemaker cells. I_f is a mixed cationic current, activated by Phase 4 diastolic hyperpolarization and is responsible for the early depolarization of SAN cells leading to the opening of voltage gated Ca_L channels during Phase 0. The sympathetic nervous system modulates I_f through β-adrenergic receptor stimulation and binding of cyclic AMP (cAMP) to the channel, thus shifting the activation curve of the current to more positive voltages. Vagus nerve activation and muscarinic-induced inhibition of adenylate cyclase exerts opposite effects with bradycardic response.[27]

Familial form

A familial form of IST has been described and the pathogenic mutation has been identified in the HCN4 gene; the R524Q gain-of-function mutated HCN4 channel showed increased sensitivity to cAMP dependent activation, leading to a faster than normal pacemaker rate[28] (Figure 1).

Apart from the rare familial disease, various studies point toward autonomic dysfunction as the pathogenic mechanism of increased automaticity in IST (Figure 1). "Dysautonomia" may be caused by primary SAN disease with an abnormal response to the physiological autonomic tone or a dysregulated autonomic system.[29]

Autonomic dysfunction

In a canine model of IST, injection of epinephrine into the fat pad at the base of the right superior pulmonary vein containing autonomic ganglia (AG) innervating the SAN, induced IST for >30 min and subsided after autonomic ganglion ablation.[30] As the authors pointed out, complete SAN denervation might require another potential site residing in and around the root of the SVC near the junction with the right atrium, where AG have been found only in the humans.[31] Furthermore, in the canine model, stimulation of interganglionic nerve (coursing from the right stellate ganglion along the SVC to the heart) mimicked IST and moved the earliest SAN activation site superiorly and anteriorly.[32]

Based on clinical experience, Morillo et al[6] demonstrated in patients affected by IST, a β-adrenergic hypersensitivity to isoproterenol, a decreased cardiovagal reflex assessed by cold face test, and a high intrinsic heart rate assessed after autonomic blockade with atropine and propranolol. Autonomic dysfunction is associated with sleep disturbances, namely a reduced sleep quality, higher proportion of shallow Phase 2 sleep and, in some cases, the inability to reach Rapid eye movement (REM) phase.[33] The high heart rate, also present at night in patients with IST suggests that its mechanism resides primarily in the SAN, and the autonomic dysfunction can contribute as a modulator but is not the primary cause[6,34] (Figure 1).

The role of inflammation

The observation of IST in a transplanted heart further supports this hypothesis.[35] The cardiac transplant is a model of completely denervated heart; although reinnervation has been described, this had been excluded in the transplanted heart with IST. Furthermore, IST was not preexisting in the donor heart and it was hypothesized to be the result of the transplant operation that could have contributed to its occurrence (e.g., trauma, inflammation, or preservation injury to the SAN). However, effects of higher intrinsic rate because lack of vagal nerve cannot be excluded.

Inflammation can also play a role in the pathogenesis of IST. An association between viral illnesses (including SARS-CoV-2 infection) and IST has been described.[36,37] Furthermore, IST has been observed in noninfectious inflammatory diseases such as multiple sclerosis; notably, tachycardia subsided after intravenous methylprednisolone bolus.[38] The link between inflammation and IST is complex and not elucidated fully. Intravenous prostaglandin E1 infusion in humans increases heart rate by nearly 20 beats/minute; this effect lasts at least 15 minutes postinfusion with no change in blood pressure.[39,40] It might be attributable to an increase in cAMP with consequent effects on the HCN channels that has been demonstrated for prostaglandin E2 in a model of neuropathic pain.[41] Furthermore, inflammation increases sympathetic nerve activity and alters sympathovagal balance.[42] (Figure 1)

The role of anti β-adrenergic receptor antibodies

Finally, anti-β-adrenergic receptor antibodies have been described in a cohort of IST patientsand functionally characterized as stimulating the corresponding membrane receptors and increasing cAMP;[43] their role in the pathogenesis of IST is, however, unclear. Indeed, they have been found in only half of the cohort and their chronotropic role has been studied only on cultured neonatal rat ventricular myocytes. Further doubts are cast by the observation that they are not specific but observed in other diseases with an inflammatory response such as Chagas disease.[44] This raises the question whether they are really

pathogenetic or just a marker of inflammation, as already described with autoantibodies in Brugada's syndrome and arrhythmogenic cardiomyopathy.[45,46]

Re-entry and Fibrosis

Re-entrant arrhythmias need 2 conditions to occur: (1) anatomical or a functional block and (2) an excitable gap throughout the circuit.[7] These conditions can be easily found in the SAN-pacemaker-conduction complex. From a theoretical standpoint, 3D SAN-SACPs-atrium structure could harbor re-entry arrhythmias (Figure 2). A unidirectional block can occur because of source-sink mismatch, causing exit block; a low safety factor in SACPs-atrium junction can be explained by the discrepancy between a weak SAN source and a large atrial sink but also by the narrow curvature of the propagation wavefront in this region.[47] Furthermore, heterogeneous slowing of SAN conduction by sodium channel blockade, as well as extensive interstitial fibrotic strands have been shown to cause intranodal unidirectional block and initiated SAN micro- or macro-reentry[15] as follows: (1) SAN macro-re-entry: the initial SAN wave could propagate through one SACP and then excite atria and re-excite SAN pacemaker compartments via another SACP thus forming a macro-re-entry circuit with two main pathways, a slow intranodal and a fast atrial pathway located between exit and entrance SACPs.[48] (2) SAN micro-reentry: pivot waves anchored to a longitudinal conduction block in the SAN can produce not only tachycardia but even paradoxical bradycardia (due to exit block).[48]

These phenomena can be promoted by a cardiomyopathy/inflammation-induced fibrosis of the SAN and consequent conduction block.[49] (Figure 2) Importantly, SAN re-entry was not observed in human and canine hearts without structural fibrotic remodeling. Histological analysis revealed that these arrhythmias required intranodal fibrotic strands, not present in healthy hearts, indicating a critical role of a structural substrate for SAN macro- and micro-reentry.[13,50] Notably, fibrocytes and numerous active fibroblasts were found in the histological and ultrastructural analyses of the SAN excised from IST patients indicating extracellular fibrosis. Furthermore, pacemaker cells were observed to contain vacuoles laden with lipofuscin.[51]

However, spatial resolution of current clinical mapping systems is insufficient to diagnose the reported 1 to 3 mm microreentry circuit.[48] However, the minimum spacing recorded (electrode-electrode distance) for commercial contact mapping catheters is 2 to 2.5 mm.[52] Moreover, these re-entry tracks are often primarily intramural (1 to 3-mm depth), around intranodal interstitial fibrotic strands, which further makes visualization of these intramural SAN re-entry circuits track with surface-only clinical mapping approaches extremely challenging.

Embryology Hypothesis: Enhanced Automaticity or Re-entry

In clinical experience with hybrid SAN sparing ablation of IST, a difference between the postpacing interval and tachycardia cycle length <5 ms has been found at different sites near anatomical location of SAN.[53] Although this might be consistent with a re-entrant mechanism, the reset of an automatic focus cannot be excluded. The different anatomical sites, including SVC and inferior vena cava (IVC), can be explained by the embryological origin of SAN. When the heart is still a tubular structure, at early stage of embryogenesis, all cardiomyocytes can automatically initiate impulses.[54] Afterward, the sinus horn (embryological precursor of the SAN, SVC, IVC, and crista terminalis [CT]) finally develops into the sinus venous of the right atrium, a part of SVC and IVC, and the coronary sinus.[54] Potentially, pacemaker cells from a common embryological origin extending toward caval veins might explain the result of postpacing interval.

However, Kholova et al[55] studied morphological and morphometric characteristics of myocardial extensions in human caval veins and found that these extensions are structurally heterogeneous in the SVC; they did not find any specialized cells. In contrast, Chen et al[56] suggested that canine SVC cardiomyocytes could have distinct action potentials and ionic current profiles that might be responsible for arrhythmogenic activity in the SVC. Such structural heterogeneity could potentially support unidirectional circuitous repetitive activation around a line of block observed in the human SVC myocardial sleeve.[57] However, more studies are warranted to determine the structural and functional mechanisms of IST, specifically those that can support micro reentries near SAN-SACP borders and SVC (Figure 2).

IST Diagnostic Criteria

The diagnostic criteria for IST are summarized in Table 1. Other causes of sinus tachycardia must be excluded.[58] The differential diagnosis of IST include physiological sinus tachycardia, sinus tachycardia secondary to other medical conditions, and sinus node re-entrant tachycardia (Table 1).

Table 1
Differential diagnosis of inappropriate sinus node tachycardia

Inappropriate sinus node tachycardia	Sinus node reentrant tachycardia
Tachycardia is persistent and not paroxysmal with an associated loss of circadian variability of heart rate	Tachycardia episodes are paroxysmal
ECG shows a P wave morphology similar to normal sinus rhythm and atrial activation consistent with sinoatrial node area origin	P wave morphology and atrial activation consistent with sinoatrial node area origin
May not be induced or terminated with pacing maneuvers	Can be induced and terminated by atrial pacing maneuvers
Cannot be terminated by vagal maneuvers and adenosine	Can be terminated by vagal maneuvers and adenosine

Unlike several supraventricular tachycardias, including sinus node re-entrant tachycardia, IST may not be terminated by adenosine. In fact, Still et al[59], reported that in 18 patients with IST, regardless of the autonomic tone, adenosine only slightly slowed cycle length (500 vs 590 ms) compared with patients with normal sinus rhythm without SAN disease history. This suggested that the negative chronotropic (and dromotropic) response to adenosine is impaired in patients with IST.

Adenosine, an endogenous cardiac metabolite, activating purinergic A_1 cardiac receptors and GIRK channel mediated potassium current (I_KAdo.Ach), has different effects on the SAN and atrial tissue. In particular, it is known to cause sinus bradycardia (reduce SAN automaticity), SAN intranodal and SAN exit block due to hyperpolarization of SAN cells by activation of I_kAdo.Ach, and I_{CaL} inhibition.[13] If increased automaticity was the mechanism of IST, a reduction in heart rate would have been observed. In contrast, adenosine caused no significant lengthening of the sinus cycle length in the patients with IST, nor during pharmacological autonomic blockade.[59] This suggests that one mechanism of IST may be related to a lower expression or mutation of adenosine A1 receptor and/or GIRK1-4 protein.

IST Treatment

Pharmacological treatment

Pharmacological treatment of IST aims to reduce heart rate and symptoms but has relatively low success. Long-acting β blockers are used as first-line therapy. At 4 weeks Holter, Metoprolol succinate (mean dose 157 mg/day) reduced heart rate when compared with baseline (92.8 vs 114.3 beats/minute; $p < 0.001$).[60] However, dosing is of paramount importance to avoid excessive bradycardia during sleep and hypotension. Alternatively, nondihydropyridine calcium-channel blockers, including verapamil and diltiazem, have been used to treat IST.[61] Long-acting β blockers in IST can target different mechanisms, including primary increased automaticity and dysregulated autonomic system.

Ivabradine has been shown to be effective in treating IST with good tolerance.[62] It blocks HCN channels and specifically inhibits I_f, thereby targeting sources of increased SAN automaticity and possible latent cardiac pacemakers. In a small randomized, placebo-controlled crossover study, ivabradine was compared with placebo in 21 patients with IST. After 6 weeks of therapy, patients administered ivabradine (target dose 7.5 mg twice daily) had a 12 beats/minute reduction in resting heart rate and a 11 beats/minute reduction in mean 24-hour heart rate.[63] Re-entry or mechanisms other than automaticity could have been the cause in patients who did not respond to ivabradine. In particular, compared with metoprolol, a reduction in hypotension and bradycardia was seen with administration of ivabradine. Furthermore, a lower incidence of IST-related symptoms was reported with ivabradine versus metoprolol.[60] There are no studies on combined use of metoprolol and ivabradine.

However, ivabradine is not effective in symptom control of IST in up to 30% of patients.[60] While generally well tolerated, it is associated with hypotension and visual disturbances (diplopia, phosphenes).[62,64] Poor symptom control with drugs or drug intolerance are indications for IST catheter ablation (Figure 3), considering that there may be a disconnect between symptoms and heart rate in IST.

IST catheter ablation

Two ablation strategies have been described: the endocardial "SAN ablation" and the hybrid endo-epicardial "SAN sparing ablation." The former aims to target the SAN anatomical region directly with "SAN ablation" or "SAN modification" approaches to reduce heart rate >50% from the baseline, or a minimum of 25% reduction under catecholamine infusion. Rodríguez-Mañero et al[9] reported in their retrospective review a total of 9 studies of IST catheter ablation that included 153 patients. They found, at a mean follow-up interval of 28.1 ± 12.6 months, 86.4% of the patients were free of symptoms. However, this SAN modification approach is also associated with a pacemaker implantation rate as high as 50%.[65] Endocardial SAN ablation in symptomatic patients with IST can be technically challenging. Failure of endocardial SAN ablation may be either because of inadequate transmural lesion that affects the intramural SAN pacemaker compartments within thick (>10 mm) superior CT or because of the proximity of the phrenic nerve.[9] Jacobson et al[66] suggested that beacuse of the 3D intramural structure of the human SAN, a combined epicardial and endocardial approach to SAN ablation should be considered for refractory IST patients (Figure 3).

Hybrid SAN sparing IST ablation

More recently, a novel hybrid SAN sparing ablation approach for IST has been described (Figure 4). Briefly, a right side thoracoscopic approach is used. Epicardial lesions set includes: (1) A line between SVC and right atrium to electrically isolate the SAN from SVC, (2) A line between IVC and right atrium, and (3) An intercaval line along the CT.[53,65,67] Therefore, endocardial mapping is performed to assess line block and an endocardial ablation is eventually performed if a gap is found (Figure 4). In a nonrandomized multicenter prospective registry, 50 patients with IST were treated with hybrid approach.[65] The SAN sparing ablation demonstrated a rate of pacemaker implantation as low as 4% with 100% acute success rate and 8% recurrence at 12 months follow-up. In the same registry, the standard SAN modification approach was used in 50 patients with pacemaker implantation in 50% and a redo procedure performed in all patients.[67]

The efficiency of this strategy could be because of its potential targeting of increased automaticity (through local modulation of AG within the fat pad near the base of SVC and right pulmonary veins), SAN re-entry (through SVC, IVC and intercaval ablation lines targeting SACPs), and, eventually, caval latent pacemakers or micro-reentry (through electrical isolation of SVC and IVC). However, in a meta-analysis by Rodriguez-Manero,[9] the symptomatic benefits of ablation for IST wore off over time. This is important as only mid-term follow-up with the novel thoracoscopic ablation procedure is available. Further studies are eagerly awaited to confirm the promising outcomes of the hybrid IST approach at long-term follow-up.

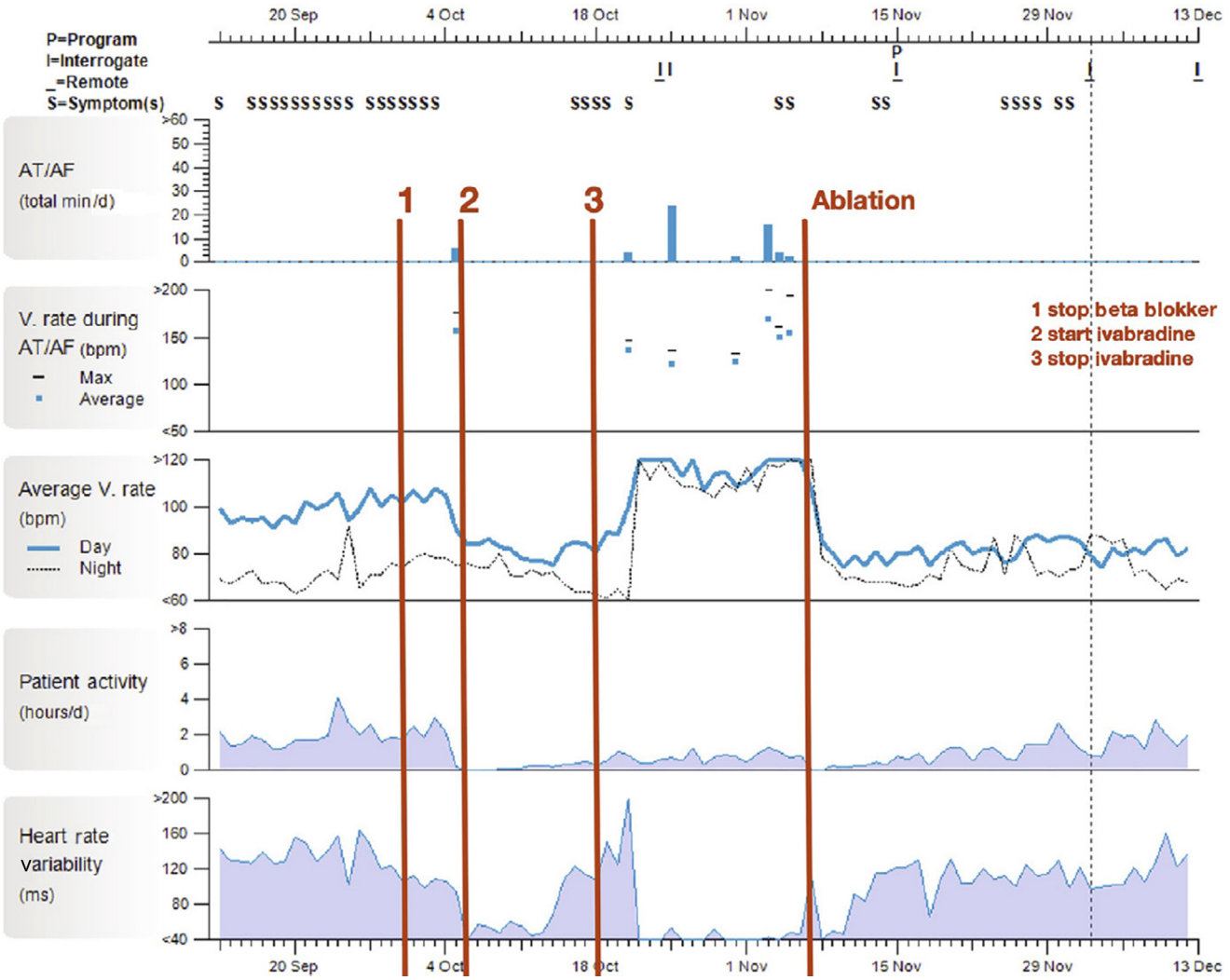

Figure 3. Hybrid sinus node sparing ablation after drug treatment failure. Loop monitoring of inappropriate sinus node tachycardia patient with different medications. Failure of 2 lines of pharmacological therapy, namely β blocker and ivabradine. Hybrid sinus node sparing ablation resulted in heart rate control with recovery of normal heart rate variability. AF = atrial fibrillation; AT = atrial tachycardia; V rate = ventricular rate. From: de Asmundis C, Chierchia GB, Sieira J, Ströker E, Umbrain V, Poelaert J, Brugada P, La Meir M. Sinus node sparing novel hybrid approach for treatment of inappropriate sinus tachycardia/postural orthostatic sinus tachycardia with new electrophysiological finding. *Am J Cardiol* 2019;124:224−232. doi: 10.1016/j.amjcard.2019.04.019 with permission.

Conclusions and Future Directions

The electrophysiological mechanisms for IST are still not fully elucidated. Preclinical and clinical data point toward an intrinsic abnormality of sinus node automaticity and concomitant autonomic dysfunction that might be primary or more probably secondary to IST. Different pharmacological approaches can target these mechanisms. Long-acting β blockers in IST can act on both primary increased automaticity and dysregulated autonomic system. Ivabradine targets sources of increased SAN automaticity. Conventional or hybrid ablation may target all the described abnormalities. However, SAN conventional ablation is associated with pacemaker implantation in up to 50% of cases. Novel hybrid SAN sparing ablation demonstrated a rate of pacemaker implantation as low as 4% with 100% acute success rate and 8% recurrence at 12 months follow-up. More studies are necessary to differentiate specific mechanisms of drug sensitive/resistant forms to develop better pharmaceutical interventions and ablation procedures. Furthermore, novel hypotheses of enhanced automaticity including inflammation and subsidiary pacemaker cells with pathologically enhanced automaticity outside the SAN and re-entry through SACPs, warrant validation in future studies.

Disclosures

Dr. de Asmundis receives research grants on behalf of the center from Biotronik, Medtronic, Abbott, LivaNova, Boston Scientific, AtriCure, Philips, and Acutus. Dr. de Asmundis received compensation for teaching purposes and proctoring from Medtronic, Abbott, Biotronik, Livanova, Boston Scientific, AtriCure, Acutus Medical Daiichi Sankyo. Dr. Lee is a part-time Medical Director at AtriCure, Inc. Dr. Chierchia

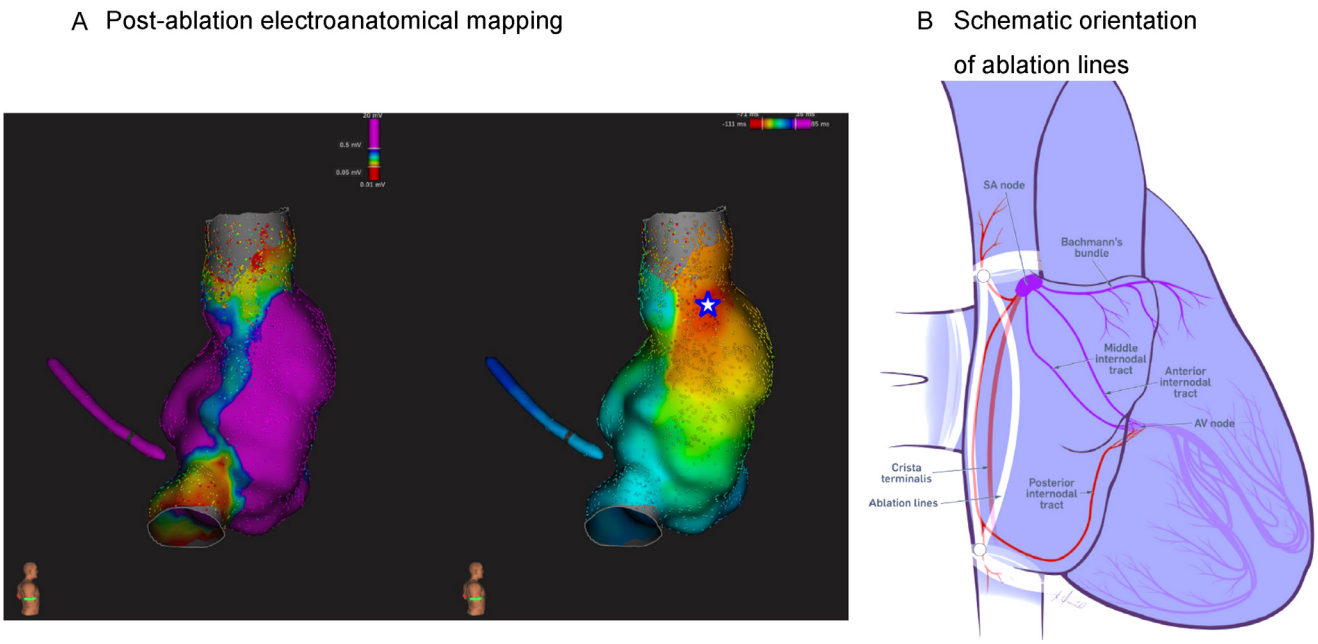

Figure 4. Hybrid sinus node sparing ablation lines. (*A*) Example of post-ablation right atrial electroanatomical voltage (*left*) and activation mapping (*right*). Ablation-induced isolation of the SVC and IVC and intercaval line conduction block. The earliest atrial activation site (*blue star*) is consistent with physiological sinoatrial node activation. (*B*) Anatomical representation of lesions set including: (*1*) A line between SVC and right atrium to electrically isolate the sinoatrial node from SVC; (*2*) A line between IVC and right atrium, and (*3*) An intercaval line along the CT. From de Asmundis C, Chierchia GB, Sieira J, Ströker E, Umbrain V, Poelaert J, Brugada P, La Meir M. Sinus node sparing novel hybrid approach for treatment of inappropriate sinus tachycardia/postural orthostatic sinus tachycardia with new electrophysiological finding. *Am J Cardiol* 2019;124:224−232. doi: 10.1016/j.amjcard.2019.04.019 with permission.

received compensation for teaching purposes and proctoring from Medtronic, Abbott, Biotronik, Boston Scientific, Acutus Medical. Dr. La Meir is a consultant for AtriCure. The remaining authors have no conflicts of interest to declare.

1. Olshansky B, Sullivan RM. Inappropriate sinus tachycardia. *J Am Coll Cardiol* 2013;61:793–801.
2. Olshansky B, Sullivan RM. Inappropriate sinus tachycardia. *Europace* 2019;21:194–207.
3. Still AM, Raatikainen P, Ylitalo A, Kauma H, Ikäheimo M, Antero Kesäniemi Y, Huikuri HV. Prevalence, characteristics and natural course of inappropriate sinus tachycardia. *Europace* 2005;7:104–112.
4. Lopera G, Castellanos A, Moleiro F, Huikuri HV, Myerburg RJ. Chronic inappropriate sinus tachycardia in elderly females. *Ann Noninvasive Electrocardiol* 2003;8:139–143.
5. Pellegrini CN, Scheinman MM. Epidemiology and definition of inappropriate sinus tachycardia. *J Interv Card Electrophysiol* 2016;46:29–32.
6. Morillo CA, Klein GJ, Thakur RK, Li H, Zardini M, Yee R. Mechanism of "inappropriate" sinus tachycardia. Role of sympathovagal balance. *Circulation* 1994;90:873–877.
7. Antzelevitch C, Burashnikov A. Overview of basic mechanisms of cardiac arrhythmia. *Card Electrophysiol Clin* 2011;3:23–45.
8. Baruscotti M, Bianco E, Bucchi A, DiFrancesco D. Current understanding of the pathophysiological mechanisms responsible for inappropriate sinus tachycardia: role of the If "funny" current. *J Interv Card Electrophysiol* 2016;46:19–28.
9. Rodríguez-Mañero M, Kreidieh B, Al Rifai M, Ibarra-Cortez S, Schurmann P, Álvarez PA, Fernández-López XA, García-Seara J, Martínez-Sande L, González-Juanatey JR, Valderrábano M. Ablation of inappropriate sinus tachycardia: a systematic review of the literature. *JACC Clin Electrophysiol* 2017;3:253–265.
10. James TN. Anatomy of the human sinus node. *Anat Rec* 1961;141:109–139.
11. Sánchez-Quintana D, Cabrera JA, Farré J, Climent V, Anderson RH, Ho SY. Sinus node revisited in the era of electroanatomical mapping and catheter ablation. *Heart* 2005;91:189–194.
12. Csepe TA, Zhao J, Hansen BJ, Li N, Sul LV, Lim P, Wang Y, Simonetti OP, Kilic A, Mohler PJ, Janssen PML, Fedorov VV. Human sinoatrial node structure: 3D microanatomy of sinoatrial conduction pathways. *Prog Biophys Mol Biol* 2016;120:164–178.
13. Li N, Hansen BJ, Csepe TA, Zhao J, Ignozzi AJ, Sul LV, Zakharkin SO, Kalyanasundaram A, Davis JP, Biesiadecki BJ, Kilic A, Janssen PML, Mohler PJ, Weiss R, Hummel JD, Fedorov VV. Redundant and diverse intranodal pacemakers and conduction pathways protect the human sinoatrial node from failure. *Sci Transl Med* 2017;9:eaam5607.
14. Efimov IR, Fedorov VV, Joung B, Lin SF. Mapping cardiac pacemaker circuits: methodological puzzles of the sinoatrial node optical mapping. *Circ Res* 2010;106:255–271.
15. Li N, Kalyanasundaram A, Hansen BJ, Artiga EJ, Sharma R, Abudulwahed SH, Helfrich KM, Rozenberg G, Wu PJ, Zakharkin S, Gyorke S, Janssen PM, Whitson BA, Mokadam NA, Biesiadecki BJ, Accornero F, Hummel JD, Mohler PJ, Dobrzynski H, Zhao J, Fedorov VV. Impaired neuronal sodium channels cause intranodal conduction failure and reentrant arrhythmias in human sinoatrial node. *Nat Commun* 2020;11:512.
16. Joyner RW, van Capelle FJ. Propagation through electrically coupled cells. How a small SA node drives a large atrium. *Biophys J* 1986;50:1157–1164.
17. Chandler NJ, Greener ID, Tellez JO, Inada S, Musa H, Molenaar P, DiFrancesco D, Baruscotti M, Longhi R, Anderson RH, Billeter R, Sharma V, Sigg DC, Boyett MR, Dobrzynski H. Molecular architecture of the human sinus node: insights into the function of the cardiac pacemaker. *Circulation* 2009;119:1562–1575.
18. Masson-Pevet M, Bleeker WK, Besselsen E, Mackaay AJC, Jongsma HJ, Bouman LN. On the ultrastructural identification of pacemaker cell types within the sinus node. *Dev Cardiovasc Med* 1982;17:19–34.
19. Bleeker WK, Mackaay AJ, Masson-Pévet M, Bouman LN, Becker AE. Functional and morphological organization of the rabbit sinus node. *Circ Res* 1980;46:11–22.
20. Boyett MR, Honjo H, Kodama I. The sinoatrial node, a heterogeneous pacemaker structure. *Cardiovasc Res* 2000;47:658–687.
21. Fedorov VV, Glukhov AV, Chang R, Kostecki G, Aferol H, Hucker WJ, Wuskell JP, Loew LM, Schuessler RB, Moazami N, Efimov IR.

Optical mapping of the isolated coronary-perfused human sinus node. *J Am Coll Cardiol* 2010;56:1386–1394.
22. Boineau JP, Canavan TE, Schuessler RB, Cain ME, Corr PB, Cox JL. Demonstration of a widely distributed atrial pacemaker complex in the human heart. *Circulation* 1988;77:1221–1237.
23. Sanders P, Morton JB, Kistler PM, Spence SJ, Davidson NC, Hussin A, Vohra JK, Sparks PB, Kalman JM. Electrophysiological and electroanatomic characterization of the atria in sinus node disease: evidence of diffuse atrial remodeling. *Circulation* 2004;109:1514–1522.
24. Kharbanda RK, Wesselius FJ, van Schie MS, Taverne YJHJ, Bogers AJJC, de Groot NMS. Endo-epicardial mapping of in vivo human sinoatrial node activity. *JACC Clin Electrophysiol* 2021;7:693–702.
25. Parameswaran R, Kalman JM, Royse A, Goldblatt J, Larobina M, Watts T, Walters TE, Nalliah CJ, Wong G, Al-Kaisey A, Douglas Anderson R, Voskoboinik A, Sugumar H, Chieng D, Sanders P, Kistler PM, Gerstenfeld EP, Lee G. Endocardial-epicardial phase mapping of prolonged persistent atrial fibrillation recordings: high prevalence of dissociated activation patterns. *Circ Arrhythm Electrophysiol* 2020;13:e008512.
26. Choudhury M, Boyett MR, Morris GM. Biology of the sinus node and its disease. *Arrhythm Electrophysiol Rev* 2015;4:28–34.
27. Difrancesco D. The role of the funny current in pacemaker activity. *Circ Res* 2010;106:434–446.
28. Baruscotti M, Bucchi A, Milanesi R, Paina M, Barbuti A, Gnecchi-Ruscone T, Bianco E, Vitali-Serdoz L, Cappato R, DiFrancesco D. A gain-of-function mutation in the cardiac pacemaker HCN4 channel increasing cAMP sensitivity is associated with familial inappropriate sinus tachycardia. *Eur Heart J* 2017;38:280–288.
29. Bauernfeind RA, Amat-Y-Leon F, Dhingra RC, Kehoe R, Wyndham C, Rosen KM. Chronic nonparoxysmal sinus tachycardia in otherwise healthy persons. *Ann Intern Med* 1979;91:702–710.
30. Scherlag BJ, Yamanashi WS, Amin R, Lazzara R, Jackman WM. Experimental model of inappropriate sinus tachycardia: initiation and ablation. *J Interv Card Electrophysiol* 2005;13:21–29.
31. Armour JA, Murphy DA, Yuan BX, Macdonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. *Anat Rec* 1997;247:289–298.
32. Zhou J, Scherlag BJ, Niu G, Hou Y, Lu Z, Zhang Y, Ding Y, Lazzara R, Jackman WM, Po SS. Anatomy and physiology of the right interganglionic nerve: implications for the pathophysiology of inappropriate sinus tachycardia. *J Cardiovasc Electrophysiol* 2008;19:971–976.
33. Mallien J, Isenmann S, Mrazek A, Haensch CA. Sleep disturbances and autonomic dysfunction in patients with postural orthostatic tachycardia syndrome. *Front Neurol* 2014;5:118.
34. Ptaszynski P, Kaczmarek K, Klingenheben T, Cygankiewicz I, Ruta J, Wranicz JK. Noninvasive assessment of autonomic cardiovascular activity in patients with inappropriate sinus tachycardia. *Am J Cardiol* 2013;112:811–815.
35. Ho RT, Ortman M, Mather PJ, Rubin S. Inappropriate sinus tachycardia in a transplanted heart-further insights into pathogenesis. *Heart Rhythm* 2011;8:781–783.
36. Sawalha K, Habash F, Vallurupalli S, Paydak H. Inappropriate sinus tachycardia following viral illness. *Clin Pract* 2021;11:219–222.
37. Arano Llach J, Bazan VBGV, Llados GLLG, Adelino RAR, Jesus Dominguez MJM, Massanella MMM, Bisbal FBF, Sarrias ASA, Bayes-Genis ABGA, Mateu LML. Villuendas Sabate RVSR. Inappropriate sinus tachycardia in post-covid-19 syndrome. *Eurospace* 2021;23:298.
38. Kundu A, Fitzgibbons TP. Acute symptomatic sinus bradycardia in a woman treated with pulse dose steroids for multiple sclerosis: a case report. *J Med Case Rep* 2015;9:216.
39. Bergström S, Duner H, von Euler U, Pernow B, Sjovall J. Observations on the effects of infusion of Prostaglandin E in man. *Acta Physiol Scand* 1959;45:145–151.
40. Bergström S, Carlson LA, Ekelund LG, Orö L. Cardiovascular and metabolic response to infusions of prostaglandin E1 and to simultaneous infusions of noradrenaline and prostaglandin E1 in man. prostaglandin and related factors 35. *Acta Physiol Scand* 1965;64:332–339.
41. Momin A, Cadiou H, Mason A, Mcnaughton PA. Role of the hyperpolarization-activated current Ih in somatosensory neurons. *J Physiol* 2008;586:5911–5929.
42. Patel KHK, Jones TN, Sattler S, Mason JC, Ng FS. Proarrhythmic electrophysiological and structural remodeling in rheumatoid arthritis. *Am J Physiol Heart Circ Physiol* 2020;319:H1008–H1020.
43. Chiale PA, Garro HA, Schmidberg J, Sánchez RA, Acunzo RS, Lago M, Levy G, Levin M. Inappropriate sinus tachycardia may be related to an immunologic disorder involving cardiac β andrenergic receptors. *Heart Rhythm* 2006;3:1182–1186.
44. de Oliveira SF, Pedrosa RC, Nascimento JH, Campos de Carvalho AC, MO Masuda. Sera from chronic chagasic patients with complex cardiac arrhythmias depress electrogenesis and conduction in isolated rabbit hearts. *Circulation* 1997;96:2031–2037.
45. Chatterjee D, Pieroni M, Fatah M, Charpentier F, Cunningham KS, Spears DA, Chatterjee D, Suna G, Bos JM, Ackerman MJ, Schulze-Bahr E, Dittmann S, Notarstefano PG, Bolognese L, Duru F, Saguner AM, Hamilton RM. An autoantibody profile detects Brugada syndrome and identifies abnormally expressed myocardial proteins. *Eur Heart J* 2020;41:2878–2890.
46. Chatterjee D, Fatah M, Akdis D, Spears DA, Koopmann TT, Mittal K, Rafiq MA, Cattanach BM, Zhao Q, Healey JS, Ackerman MJ, Bos JM, Sun Y, Maynes JT, Brunckhorst C, Medeiros-Domingo A, Duru F, Saguner AM, Hamilton RM. An autoantibody identifies arrhythmogenic right ventricular cardiomyopathy and participates in its pathogenesis. *Eur Heart J* 2018;39:3932–3944.
47. Boyle PM, Vigmond EJ. An intuitive safety factor for cardiac propagation. *Biophys J* 2010;98:L57–L59. Published correction appears in *Biophys J* 2013;105:2854.
48. Glukhov AV, Hage LT, Hansen BJ, Pedraza-Toscano A, Vargas-Pinto P, Hamlin RL, Weiss R, Carnes CA, Billman GE, Fedorov VV. Sinoatrial node reentry in a canine chronic left ventricular infarct model: role of intranodal fibrosis and heterogeneity of refractoriness. *Circ Arrhythm Electrophysiol* 2013;6:984–994.
49. Fedorov VV, Ambrosi CM, Kostecki G, Hucker WJ, Glukhov AV, Wuskell JP, Loew LM, Moazami N, Efimov IR. Anatomic localization and autonomic modulation of atrioventricular junctional rhythm in failing human hearts. *Circ Arrhythm Electrophysiol* 2011;4:515–525.
50. Lou Q, Hansen BJ, Fedorenko O, Csepe TA, Kalyanasundaram A, Li N, Hage LT, Glukhov AV, Billman GE, Weiss R, Mohler PJ, Györke S, Biesiadecki BJ, Carnes CA, Fedorov VV. Upregulation of adenosine A1 receptors facilitates sinoatrial node dysfunction in chronic canine heart failure by exacerbating nodal conduction abnormalities revealed by novel dual-sided intramural optical mapping. *Circulation* 2014;130:315–324.
51. Lowe JE, Hartwich T, Takla M, Schaper J. Ultrastructure of electrophysiologically identified human sinoatrial nodes. *Basic Res Cardiol* 1988;83:401–409.
52. Berte B, Zeppenfeld K, Tung R. Impact of micro-, mini- and multi-electrode mapping on ventricular substrate characterisation. *Arrhythm Electrophysiol Rev* 2020;9:128–135.
53. de Asmundis C, Chierchia GB, Sieira J, Ströker E, Umbrain V, Poelaert J, Brugada P, La Meir M. Sinus node sparing novel hybrid approach for treatment of inappropriate sinus tachycardia/postural orthostatic sinus tachycardia with new electrophysiological finding. *Am J Cardiol* 2019;124:224–232.
54. Anderson RH, Brown NA, Moorman AFM. Development and structures of the venous pole of the heart. *Dev Dyn* 2006;235:2–9.
55. Kholová I, Kautzner J. Morphology of atrial myocardial extensions into human caval veins: a postmortem study in patients with and without atrial fibrillation. *Circulation* 2004;110:483–488.
56. Chen YJ, Chen YC, Yeh HI, Lin CI, Chen SA. Electrophysiology and arrhythmogenic activity of single cardiomyocytes from canine superior vena cava. *Circulation* 2002;105:2679–2685.
57. Shah DC, Häissaguerre M, Jäis P, Clémenty J. High-resolution mapping of tachycardia originating from the superior vena cava: evidence of electrical heterogeneity, slow conduction, and possible circus movement reentry. *J Cardiovasc Electrophysiol* 2002;13:388–392.
58. Cossú SF, Steinberg JS. Supraventricular tachyarrhythmias involving the sinus node: clinical and electrophysiologic characteristics. *Prog Cardiovasc Dis* 1998;41:51–63.
59. Still AM, Huikuri HV, Airaksinen KE, Koistinen MJ, Kettunen R, Hartikainen J, Mitrani RD, Castellanos A, Myerburg RJ, Raatikainen MJP. Impaired negative chronotropic response to adenosine in patients with inappropriate sinus tachycardia. *J Cardiovasc Electrophysiol* 2002;13:557–562.
60. Ptaszynski P, Kaczmarek K, Ruta J, Klingenheben T, Wranicz JK. Metoprolol succinate vs. ivabradine in the treatment of inappropriate sinus tachycardia in patients unresponsive to previous pharmacological therapy. *Europace* 2013;15:116–121.

61. Foster MC, Levine PA. Use of verapamil to control an inappropriate chronic sinus tachycardia. *Chest* 1984;85:697–699.
62. Abed HS, Fulcher JR, Kilborn MJ, Keech AC. Inappropriate sinus tachycardia: focus on ivabradine. *Intern Med J* 2016;46:875–883.
63. Cappato R, Castelvecchio S, Ricci C, Bianco E, Vitali-Serdoz L, Gnecchi-Ruscone T, Pittalis M, Ambroggi L De, Baruscotti M, Gaeta M, Furlanello F, Francesco D Di, Lupo PP. Clinical efficacy of ivabradine in patients with inappropriate sinus tachycardia: a prospective, randomized, placebo-controlled, double-blind, crossover evaluation. *J Am Coll Cardiol* 2012;60:1323–1329.
64. Mason PK, DiMarco JP. New pharmacological agents for arrhythmias. *Circ Arrhythm Electrophysiol* 2009;2:588–597.
65. Lakkireddy D, Garg J, DeAsmundis C, LaMeier M, Romeya A, Vanmeetren J, Park P, Tummala R, Koerber S, Vasamreddy C, Shah A, Shivamurthy P, Frazier K, Awasthi Y, Chierchia GB, Atkins D, Bommana S, Di Biase L, Al-Ahmad A, Natale A, Gopinathannair R. Sinus node sparing hybrid thoracoscopic ablation outcomes in patients with inappropriate sinus tachycardia (SUSRUTA-IST) registry. *Heart Rhythm* 2022;19:30–38.
66. Jacobson JT, Kraus A, Lee R, Goldberger JJ. Epicardial/endocardial sinus node ablation after failed endocardial ablation for the treatment of inappropriate sinus tachycardia. *J Cardiovasc Electrophysiol* 2014;25:236–241.
67. de Asmundis C, Chierchia GB, Lakkireddy D, Romeya A, Okum E, Gandhi G, Sieira J, Vloka M, Jones SD, Shah H, Winner M, Patel D, Whalen SP, Beaty EH, Kincaid EH, Lee A, Brodt C, Taylor BJ, Colombowala I, Romano M, Morady F, Ströker E, Overeinder I, Bala G, Meeteren J Van, Krauthammer Y, Koerber S, Shults C, Thomaides A, Badhwar N, Gopinathannair R, Shah A, Tummala R, Bello D, Hoff S, Almorad A, Frazier K, Brugada P, Meir M La. Sinus node sparing novel hybrid approach for treatment of inappropriate sinus tachycardia/postural sinus tachycardia: multicenter experience. *J Interv Card Electrophysiol* 2022;63:531–544.