Inappropriate Sinus Tachycardia: Focus on Ivabradine

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Abstract

Inappropriate sinus tachycardia (IST) is an incompletely understood condition characterised by an elevation in heart rate (HR) accompanied by wide ranging symptoms, in the absence of an underlying physiological stimulus. The condition often takes a chronic course with significant adverse effects on quality of life. Currently there is no effective treatment for IST. Beta-blockers, generally considered the cornerstone of treatment, are often ineffective and poorly tolerated. Ivabradine is a novel sinus node I$_f$ “funny current” inhibitor which reduces the HR. It has been approved for the treatment of beta-blocker refractory chronic systolic heart failure and chronic stable angina, but more recently shown promise in the treatment of IST. This review provides an overview of IST prevalence and mechanisms, followed by an examination of the evidence for the role and efficacy of ivabradine in the treatment of IST.

Keywords: Inappropriate sinus tachycardia; Ivabradine
Introduction

Inappropriate sinus tachycardia is defined as a persistent non-paroxysmal elevation in the resting and exertional HR with no identifiable physiological or pathological stimulus(1). There is no formally accepted HR threshold for the definition of IST. This is, in part, related to the wide range of normal HR variation within the population, its dependency on age(2) and underlying physiological status. Population studies show that, in addition to an inverse correlation with age, mean intrinsic HR (HR under complete pharmacologic autonomic blockade or autonomic denervation) is independently associated with levels of physical activity, blood pressure, tobacco smoking, intake of caffeine and body height(3). The 2015 Heart Rhythm Society expert consensus statement defines IST as a “sinus heart rate >100bpm at rest (with a mean 24-hour heart rate >90 bpm not due to primary causes) and associated distressing symptoms of palpitations”(1, 4, 5). Other commonly described symptoms include dizziness, light headedness, dyspnoea and pre-syncope.

Prevalence and Clinical Course of IST

An Icelandic study of randomly sampled patients from insurance registries for hypertension reimbursement, described the prevalence and course of IST using the above definition(4). The largest of its kind, the study rigorously excluded differential diagnoses and mimics of the condition. However, the overall population was relatively small (604) and 149 subjects were on beta adrenoceptor antagonists for hypertension treatment. Of the 604 patient cohort, 7 fulfilled the definition for IST, yielding a prevalence of 1.16%. This is greater than the estimates for Wolff-Parkinson-White syndrome (0.15-0.31%)(6). No differences were
found between IST and control patients with regards to age, gender, smoking habits, alcohol intake, physical activity levels and adiposity. The mean age and 24-h ambulatory systolic pressure in the IST group was 47±7 years and 147±11 mmHg, respectively, noting the likely bias related to the cohort source (systemic arterial hypertension). After a mean follow-up of 6.0±2.4 years, the outlook for the condition was found to be benign, particularly for the development of tachycardia-mediated cardiomyopathy and survival. However, at follow-up, there was persistence of symptoms, elevated resting HR and elevated average daily HR.

Mechanisms in IST

The trigger and mechanism for the tachycardia in IST is unknown. Expert anecdotal evidence has suggested halogenated hydrocarbon exposure as one possible cause, although this is unsubstantiated(7). Peripheral and central neurohormonal mediators of autonomic control or their receptors have been implicated, however this remains speculative(8, 9). Notably, an exaggerated HR response to isoprenaline infusion occurs in less than one third of patients(10). This observation and the relative inefficacy of beta-blockade have led some investigators to believe that the condition may represent a sinus node channelopathy rather than an abnormality of autonomic modulation(11). Some clinical studies have pointed towards an elevation in intrinsic HR mediated by ATP sensitive potassium channels in sinus node tissue(12). A small study has identified greater plasma levels of beta adrenoceptor antibodies in patients with IST as compared to controls(11). The presence of these antibodies has been hypothesised to result in receptor activation function and second messenger mediated calcium influx and depolarisation. As yet there have been no reports of specific genetic abnormalities associated with IST.
Clinical Presentation and Diagnosis

Inappropriate sinus tachycardia often presents non-specifically with symptoms including pre-syncope, syncope, dyspnoea, exercise intolerance, dizziness, light-headedness, weakness and palpitations either chronically or in a relapsing and remitting pattern. Their severity may vary from mild to significantly disabling, and importantly may not parallel the severity of the tachycardia.

Essential to the diagnosis of IST is exclusion of underlying causes for an appropriate sinus tachycardia such as anaemia, cardiac failure, infection, stimulant intake, thyrotoxicosis, anxiety or psychosis. Therefore, in addition to undertaking a thorough general medical assessment, laboratory (serum thyrotropin levels and full blood count) tests, a 12-lead ECG and ambulatory cardiac rhythm monitors are required. The latter may be in the form of 24-hour, 48-hour, 7-day or longer ambulatory monitors which may reveal occult arrhythmias or allude to non-physiological phenomena such as lack of nocturnal vagal predominance. In accordance with expert consensus, the clinical diagnosis is made, after exclusion of differentials, in symptomatic patients with a persisting daytime sinus tachycardia.

Differential Diagnosis

Certain cardiac supraventricular tachycardias (SVT), which are amenable to curative treatment, may present with similar symptoms to IST. Electrocardiographic examples are shown in Figure 1 [Figure 1]. Accessory pathway mediated SVT and atrioventricular nodal re-entry tachycardia (AVNRT) almost always have a sudden onset and offset. The 12-lead
ECG in AVNRT is usually normal at baseline and subtle retrograde conducted P-waves are often seen during SVT. Accessory pathways may result in typical delta waves and short PR duration at baseline if conducting in the anterograde direction, and therefore it is manifest. Generally, if the accessory pathway conducts in the retrograde direction, features of pre-excitation are absent at baseline, and therefore it is concealed. Accessory pathway mediated SVT may be broad or narrow QRS complex, depending on the directionality of pathway conduction during SVT. One important pre-excitation syndrome mostly affecting children and teenagers is the permanent form of reciprocating junctional tachycardia (PJRT). This incessant form of long RP SVT commonly utilises an accessory pathway which is located in the right inferior paraseptal region and is often drug refractory. Its chronic nature and tachycardia rates as low as 130bpm may mask the diagnosis for months and subsequently promote a tachycardia-mediated cardiomyopathy. The latter is reversible after accessory pathway ablation(13) (14).

Atrial tachycardia (AT) on the other hand may oftentimes be difficult to differentiate from IST, particularly when arising from areas adjacent to the sinus node, such as superior crista terminalis or even within the sinus node in the form of re-entry. Although 12-lead ECG P wave axis and morphology will often provide vital clues to the AT site of origin, an AT focus close to the sinus node will generate a P wave morphology very similar or identical to that of sinus rhythm. The onset of tachycardia and symptoms, in addition to other clinical features, may point to either IST or AT.

Another condition to consider is Postural Orthostatic Tachycardia Syndrome (POTS), as both POTS and IST have overlapping clinical features. This increasingly recognised disorder is a condition of autonomic dysfunction characterised by a hyperadrenergic response to
orthostatic change in posture, with symptoms of dizziness, pre-syncope and diaphoresis (15). An exaggerated HR response to isoprenaline may be seen in both IST and POTS, and therefore a detailed clinical assessment is required to demonstrate the orthostatic relationship to symptoms and HR changes which occur in POTS. A head up tilt table test may be useful in demonstrating a 30 bpm HR rise (or tachycardia >120 bpm) on assuming the upright position from being supine. In the supine position, the 12-lead ECG in POTS patients is rarely >100 bpm whereas in IST the resting HR is often >100 bpm.

**Conventional Management Strategies for IST**

The use of negative chronotropic agents such as beta-blockers and calcium antagonists is often unsuccessful in controlling IST symptoms and HR(16). Intolerance to beta-blockade side effects may be particularly troublesome in this patient group. Clinicians have occasionally trialled beta adrenoceptor antagonists with intrinsic sympathetic activity (for example, pindolol or acebutolol). The goal with this approach is to suppress elevated HR whilst minimising anti-adrenergic related adverse effects. However, there is no evidence supporting an advantage for beta-blockers with intrinsic sympathetic activity over pure beta-blockers. There is an identified overlap of IST in some instances with anxiety disorders, which may also require specific treatment(1).

Invasive techniques are reserved for patients highly debilitated by drug-refractory symptoms. Limited experience exists for surgical or radiofrequency catheter modification of the sinus node zone in these patients. The effectiveness of catheter ablation in IST is at best modest. At an experienced centre, after a mean follow-up of 4 months, symptoms recurred
in 27% of patients deemed to have acute procedural success(17). Long term symptom control was not achieved in one third of patients despite repeat procedures. The risk of complications is low but not non-trivial. Sinus node dysfunction requiring permanent pacing, right phrenic nerve injury and superior vena cava syndrome are uncommon but serious complications.

The ablate and pace strategy is often undesirable in view of the sacrifice of atrio-ventricular conduction and complete reliance on permanent pacing in this younger demographic.

Ivabradine

Overview of Ivabradine

Ivabradine is a novel selective inhibitor of cardiac ionic channels which results in negative chronotropic effects through a reduced sinoatrial depolarisation rate, with negligible effects on contractility. The agent has been approved in Australia since 2006 primarily as a second line agent for patients with chronic stable angina who are intolerant of, or have a contraindication to beta-blockers, or as add-on therapy to beta-blockers in patients with inadequately controlled HR. The drug has been studied for its quantitative impact on exercise tolerance in patients with coronary artery disease and for its role in the treatment of chronic systolic (impaired ejection fraction) heart failure(18-23). Currently, Ivabradine is only covered by the Pharmaceutical Benefit Scheme (PBS) for its use in Heart failure and although approved for use in angina, this is currently only as a private prescription. In addition, emerging evidence has shown ivabradine to be of potentially significant benefit in patients with IST(24-26).
**Pharmacology of Ivabradine**

Sinoatrial nodal cells have an innate automaticity involving a slow inward current of sodium (and calcium), coupled with a slowly diminishing outward potassium current. This results in a cyclical drift of the resting membrane potential towards depolarization threshold, and is known as the pacemaker or “funny” current ($I_f$) [Figure 2]. It was dubbed “funny” because of its unique characteristics when compared to other cardiac membrane channels. The $I_f$ current is mostly generated through a non-selective voltage gated transmembrane cation channel known as the Hyperpolarization-activated cyclic nucleotide gated (HCN4) channel, which is strongly expressed in the sinus node region. Ivabradine is a chiral molecule with only the S-enantiomer showing voltage-dependent affinity to the HCN4/$I_f$ channel. Accessing the intracellular aspect of the channel, the drug blocks the transmembrane channel pore, selectively inhibiting inward cation movement. This slows the rate of pacemaker depolarization and thereby reduces sinus node beating rate with no appreciable effects on myocardial repolarisation or contractility. Ivabradine does not affect the QT interval on the surface electrocardiogram (ECG). In addition to a neutral effect on myocardial inotropy, no measurable changes are observed in systemic vascular resistance, cardiac output or coronary perfusion pressure. At therapeutic doses (5-7.5 mg twice daily oral dosing), resting and exertional HR are reduced by approximately 10 bpm, with a ceiling effect at doses of 20 mg twice daily. In the absence of food, an oral dose has only about 40% bioavailability due to extensive first pass hepatic metabolism by cytochrome P450 (CYP) 3A4. Potent CYP3A4 inhibitors such as macrolide antibiotics, azole antifungals and protease inhibitors may increase plasma levels. Additionally, concomitant use of moderately potent CYP3A4 inhibitors such as diltiazem and verapamil may result in a combined pharmacokinetic
(increased serum Ivabradine) and pharmacodynamic (potentiation of bradycardia effect) interaction.

Ivabradine is a weak inhibitor of CYP3A4 and is therefore unlikely to influence metabolism of other drugs, or their plasma levels. Food delays absorption but increases peak plasma levels and overall bioavailability to 70%. Trough plasma levels occur 12 hours after the last dose and on that basis, clinical studies into its quantitative effect on exercise tolerance are performed at this nadir state.

**Contra-indications and adverse reactions**

Ivabradine is generally contraindicated in the presence of resting bradycardia (<60 bpm), hypotension, and in sinus node dysfunction. Atrioventricular (AV) nodal disease is a relative contraindication however the drug may be used with caution in first and second degree AV block. Due to the lack of clinical studies into its safety or efficacy in atrial or ventricular tachyarrhythmias, Ivabradine should generally be avoided in those conditions. Finally, in conditions that predispose to an acquired long QT interval, Ivabradine should be avoided or used with careful monitoring to prevent excessive bradycardia and exacerbation of the polymorphic ventricular tachycardia risk.

Ivabradine is shown to be well tolerated, with dose-dependent predictable adverse reactions. The most common cardiovascular adverse reactions are bradycardia and hypotension whereas visual disturbances are the most common non-cardiovascular effects. Bradycardia (<60 bpm) was estimated at 4.2% in a randomised clinical study(31). This is comparable to but somewhat lower than the prevalence of bradycardia noted for the beta adrenoceptor antagonist, atenolol (5.8%). The combination of beta-blocker and Ivabradine
use results in an additive risk of bradycardia, with the SIGNIFY study showing a prevalence of 17.9% in a randomised double-blind multi-centre clinical trial setting(19). The most common adverse reaction overall is a phenomenon of visual phosphenes (14.5%)(27). This consists of bright illuminations at the periphery of the visual field exacerbated by sudden changes in the ambient level of brightness. This peculiar effect appears to be benign with the vast majority of patients reporting a mild to moderate level of intensity. The condition is self-resolving in >75% of patients within a matter of months without dose modification or treatment interruption(27). Less than 1% of patients reported having to stop treatment or modification of their daily activities to accommodate for this visual disturbance.

**Role of Ivabradine in IST**

With the development of ivabradine and insights into its pharmacologic mechanisms, some experimental use in IST has emerged(25). Early pilot work demonstrated the effectiveness of Ivabradine in reducing minimum, mean and maximum HR in addition to symptom improvement or complete resolution(27). In addition, the drug appeared to be well tolerated.

Several non-randomised open label studies of short to intermediate follow-up duration showed scope for the efficacy and tolerability of Ivabradine in IST. In 2010, an open label efficacy study in 18 subjects showed the drug to be well tolerated and associated with a significant reduction in maximal and median HR as well as greater workloads achieved on standard treadmill stress testing. One patient was excluded from the study due to persistent phosphenes despite dosage reduction(23).
In 2012 a small randomised and placebo controlled cross-over study compared Ivabradine to placebo in 21 patients with IST(28). After 6 weeks of therapy, patients taking Ivabradine (either 5 mg or 7.5 mg twice daily) experienced a 12 bpm reduction in resting HR, 18 bpm reduction on exercise, 16 bpm reduction on standing and 11 bpm reduction in mean 24 hour HR. These statistically significant improvements were associated with improved exercise tolerance and a quantitative reduction in symptom severity of >70%. Overall, more than 45% reported complete resolution of symptoms. In 2013, a study comparing long acting metoprolol (succinate) to Ivabradine in 20 patients was performed assessing changes in HR and quantitative symptomatology(16). Patients who had IST refractory to traditional beta-blockers were switched from metoprolol succinate to Ivabradine after 4 weeks of therapy. Although mean 24 hour HR reduction was similar between both agents, Ivabradine showed a greater reduction in daytime HR reduction. The metoprolol group experienced significantly greater troublesome bradycardia and hypotension requiring dosage reduction. Using an IST specific symptomatology scoring algorithm, Ivabradine treatment showed superior symptom attenuation as compared with metoprolol succinate.

An open label study of longer duration in 2013 showed favourable results and in addition, cessation of the drug after 1 year of therapy was associated with maintained HR benefits in 80% of patients(29). The latter observation points towards a possible mechanism beyond symptom suppression only but may represent prevention of the disease progression through favourable functional and/or structural cardiac remodelling.

The Ivabradine Versus Beta-blockers in the Treatment of Inappropriate Sinus Tachycardia (CIBIST; Clinical Trials Identifier NCT01657136) is an open label non-randomised study
comparing Ivabradine to the long half-life beta-blocker, bisoprolol. The phase III study primary outcome of HR reduction is expected to be released in 2016.

**Table 1** shows key findings of several important studies of different IST management modalities.

**Guideline Recommendations for IST Management**

The last focused ACC/AHA/ESC supraventricular arrhythmia guidelines in 2003 provided a class I recommendation for beta blockers, class IIa for calcium channel blockers and class IIb for catheter ablation, noting that all three treatments had level C evidence(30). However in 2015 the Heart Rhythm Society (HRS) expert consensus statement assigned a Class IIa recommendation for the use of ivabradine with level B-R evidence (moderate randomised trial) and removed recommendations for other pharmacotherapies. In addition, catheter ablation was actively recommended against with level E (consensus) evidence(5).

**Cost Implications if Ivabradine was subsidised for use in IST**

Inappropriate sinus tachycardia is an uncommon condition. Epidemiological estimates from Still et al put the prevalence at 1.16% with preponderance in middle aged adults (mean age 47±7 years)(4). Based on this and the comparative study between Ivabradine and Metropolol succinate, we provide a crude estimate of cumulative costs incurred for funding of Ivabradine by the PBS. The PBS is a program of the Australian Government that provides subsidised prescription drugs to residents of Australia. Of the 15.9 million Australians aged 15-65 years of age (Australian Bureau of Statistics, 2010), 184,440 individuals could feasibly satisfy conventional diagnostic criteria for IST. Based on comparative data from Ptaszynski et al(16), we posit that considering a worst case scenario, 50% of patients being treated for
IST could require step-up therapy from either beta-blockade or calcium antagonists to Ivabradine. The Food and Drug Administration of the United States recently approved Ivabradine for patients who have symptoms of heart failure that are stable with a resting HR of at least 70 beats per minute and are also taking beta-blockers at the highest dose they can tolerate. The European Medicines Agency had set the cut-off HR at 75 beats per minute for the same indication. In Australia, Ivabradine is approved for use in refractory chronic stable angina and chronic systolic heart failure. Current PBS subsidy indications for Ivabradine are for NYHA class II or III systolic heart failure (LVEF < 35%) in sinus rhythm, with a HR ≥77 beats per minute, despite maximum tolerated beta-blocker dosage. Economic recommendations submitted by Servier Laboratories Australia Pty Ltd to the PBS Advisory Committee (July 2012) for funding of Ivabradine for systolic heart failure, estimated a net cost to the government at $10-30 million by 5 years of listing. The incremental cost effectiveness ratio (ICER) expressed as a cost/quality adjusted Life Year (cost/QALY) is conservatively estimated at 65% for Ivabradine. In 2007-08, the prevalence of ischaemic heart disease and cardiac failure were 685,000 (Australian Institute of Health and Welfare [AIHW], 2012) and 276,250 (AIHW, 2011) respectively. Therefore, the $10-30 million 5 year cost for funding Ivabradine for the 961,250 patients with ischemic heart disease or cardiac failure may be used to model the anticipated costs for funding Ivabradine for the estimated 92,220 symptomatic patients with IST refractory to currently used pharmacotherapy (beta blockers and calcium channel antagonists). This 5 year estimate would be $1-2.9 million. It should be emphasized that the availability of Ivabradine as a potentially efficacious treatment option for IST would likely negate the need for invasive radiofrequency catheter modification of the sinus node, subsequently offsetting invasive treatment costs in patients with refractory symptoms. Moreover, in our experience, efficacious treatment in this
younger patient population can reduce indirect economic costs associated with the number of sick days, unemployment and disability claims.

Conclusion

Inappropriate sinus tachycardia is a condition with a best estimate prevalence of 1.16% in the general adult population. The condition has a wide spectrum of symptom severity and due to its predilection in the young, it has the potential to adversely impact daily activities, particularly effort tolerance and personal economic productivity, despite its overall benign course. Whilst it remains ill-defined on a cellular level, it appears that IST is probably a sinus node channelopathy in origin rather than a disease of altered autonomic modulation (as opposed to POTS, an important differential diagnosis). The mainstay of therapy has been beta-blockers. Despite some effect at reducing HR, these agents appear to have limited benefit and a significant adverse effect profile in this active younger group of patients.

Catheter ablation remains an evolving technique with modest results despite multiple procedures. In small clinical studies, Ivabradine has shown benefit in HR reduction, quantitative improvement in exercise capacity and subjective symptom burden amelioration. The drug is well tolerated and appears to carry a lower proarrhythmia risk. For a chronic condition often becoming clinically problematic in management, Ivabradine shows much promise as a potential therapy of choice for beta-blocker intolerant or sub-optimally responsive patients. Currently there are no large prospective randomised double-blinded placebo controlled studies examining the efficacy of the various treatment modalities. However the updated Heart Rhythm Society guidelines recommending Ivabradine with Class IIa, Level B-R evidence, reflects the progressively accruing evidence base for its use above all
other conventional treatment options. Given the low prevalence of IST and evidence for significant physiological and functional improvement with ivabradine, when considering suitability for prescription subsidy, ivabradine may well represent a cost-effective and relatively inexpensive treatment option.

References


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Figure legend

Figure 1: Electrocardiographic examples showing important differential diagnoses for

Inappropriate Sinus Tachycardia. A. An example of the permanent form of junctional reentrant tachycardia is shown. In this example, antegrade (atria to ventricles) conduction occurs through the atroventricular node (AVN) and retorograde conduction (ventricles to atria) through the accessory pathway. Retorograde conduction is relatively slow resulting in a long RP interval. This is most obvious in leads II and aVF. B. An example of the most common form of AV node reentrant tachycardia is shown. Retrograde conduction is very rapid, resulting in a P wave deforming the terminal portion of the QRS complex. This manifests as a pseudo-r’ in V1 and pseudo-s’ in II, III and aVF. C. An example of ventricular pre-excitation is shown with conduction over an atroventricular accessory pathway fibre. This results in an abbreviated PR interval and a delta wave (slurred QRS upstroke). D. An example of focal atrial tachycardia is shown. Like A, this is also a long RP tachycardia. The specific P wave morphology and polarity will depend on the precise location of the focus along the crista terminalis.

Figure 2: Overview of sinus node action potential profile. The pacemaker potential (diastolic depolarization, $I_f$ funny current) is responsible for the slow drift of the membrane potential (millivolts, mV) towards threshold (~40 mV). Once threshold is reached, rapid inward calcium ($I_{Ca}$) movement triggers membrane depolarization. Potassium efflux ($I_K$) subsequently repolarizes the membrane back towards subthreshold potential. Ivabradine accesses the cytoplasmic aspect of the $I_f$ channel, specifically inhibiting the pacemaker potential.
<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Population</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whalley, 2006(27)</td>
<td>Open label prospective evaluation. Treatment with Ivabradine and 7 months follow-up</td>
<td>7 patients with IST refractory to ≥2 drugs</td>
<td>Compared to baseline, significant reduction in mean, minimum and maximum 24 hour HR. Significant improvement in quality of life scores</td>
</tr>
<tr>
<td>Cappato, 2012(28)</td>
<td>Prospective randomized double-blind placebo-controlled cross-over evaluation. Treatment with placebo or Ivabradine for 6 weeks then cross-over</td>
<td>21 patients with IST</td>
<td>Compared with placebo, Ivabradine significantly reduced supine and orthostatic HR; reduced mean, minimum and maximum HR; increased exercise expenditure capability; reduced symptom severity scores</td>
</tr>
<tr>
<td>Ptaszynski, 2013(16)</td>
<td>Open label prospective evaluation. Treatment with metoprolol succinate for 4 weeks followed by Ivabradine</td>
<td>20 patients with IST resistant to previous therapy with either metoprolol tartrate or verapamil</td>
<td>Compared to metoprolol succinate, Ivabradine showed greater reduction in mean 24 hour HR, greater reduction in symptom severity scores and greater increase in exercise tolerance with treadmill stress testing</td>
</tr>
<tr>
<td>Benezet-Mazuecos, 2013(29)</td>
<td>Open label prospective safety and efficacy study. Treatment with Ivabradine twice daily, 5 mg or 7.5 mg dosage</td>
<td>24 patients with IST treated with Ivabradine and followed-up for 12 months</td>
<td>Ivabradine treatment significantly reduced (normalised) mean, maximum and minimum HR, and significant improvement in quality of life scores. At 12 months, 80% of patients remained free of IST criteria despite stopping the medication</td>
</tr>
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<td>Calo, 2010(23)</td>
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**Table 1:** Symptoms assessed by SF36 and/or European Heart Rhythm Association symptom score grades (I-IV). Heart rate trends assessed by 24 hour Holter monitoring. Metoprolol tartrate is a rapid acting twice daily dosed beta-blocker, whereas the succinate salt is the slow release once daily dosed formulation. HR: Heart Rate
Figure 1: Electrocardiographic differential diagnoses for Inappropriate Sinus Tachycardia
Figure 2: Overview of sinus node action potential profile.