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# Inappropriate Sinus Tachycardia Mistaken for Relapse of Reentrant Supraventricular Tachycardia in a Young Woman Treated Successfully with Ivabradine

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## Abstract

**Introduction:** Inappropriate Sinus Tachycardia (IST), first described in 1979, is a fast heart rhythm arising from the sinus node, the normal primary pacemaker of the heart but at an inappropriately high rate. Many treatments have been suggested for patients with IST; β-adrenergic blockers, even at high doses, generally are ineffective and tend to be associated with other symptoms.

Small studies and several case reports have demonstrated the potential value of Ivabradine, the first selective sinus node *If* channel inhibitor, to treat IST.

**Case Report:** We present a case of a young woman of 22 years old, treated with Ivabradine 5 mg twice a day.

The patient presents episodes of tachycardia compatible with an Atrioventricular Nodal Reentry Tachycardia (AVNRT), with a maximum heart rate of 210 bpm.

Many treatments were started without results. Two catheter ablations, (thermal and cryoablation) were performed. The second ablation has a good result, but one year ago, the tachycardia episodes reappeared and because the symptoms were very similar to those previously had before ablation procedure, even without seeing the ECG nodal reentrant tachycardia a new electrophysiological study was performed.

With surprise, the study did not show a double nodal curve. So treatment with Ivabradine was started with a complete resolution of symptoms. The drug was effective on heart rate but it does not affect blood pressure.

The control Holter monitoring shows a normal trend of heart rate with only a few episodes of sinus tachycardia during effort and no episodes at rest.

**Conclusion**: In conclusion the last Holter monitoring does not match IST diagnosis criteria. The quality of life of the patient improved significantly. The drug as in literature reports is effective, safe and well tolerated. The patient wishes to continue the drug after one year of treatment.

**Keywords:** Inappropriate Sinus Tachycardia; Ivabradine

## Introduction

Inappropriate sinus tachycardia (IST), first described in 1979 [1], is a fast heart rhythm arising from the sinus node, the normal primary pacemaker of the heart but at an inappropriate high rate. In a 24-hour Holter monitoring patients have an average daily heart rates exceeding 100 bpm but the P-wave morphology during tachycardia is nearly identical to that in sinus rhythm and usually have symptoms of pulsations in the neck, shortness of breath, light-headedness, fatigue, sweating, chest pain, non-paroxysmal palpitations at rest and/or early during exercise associated with a relative or absolute increase in sinus rate out of proportion to physiological need.

IST is a diagnosis based on the exclusion of all other pathologies causing tachycardia as anemia, pheochromocytoma, hyperthyroidism, anxiety disorder, medications and cardiomyopathy.

The pathophysiology of IST is poorly understood, although mechanisms such as excessive sympathetic influences, reduced parasympathetic influences, excessive intrinsic HR, ectopic activity of the sinus node, and β-receptor antibodies have been proposed as substrates for this arrhythmia

Many treatments have been suggested for patients with IST; β-adrenergic blockers, even at high doses, generally are ineffective and tend to be associated with other symptoms and other treatments (fludrocortisone, volume expansion, pressure stockings, phenobarbital, clonidine, and erythropoietin) may be harmful but not adequately tested [2].

Small studies [3,4,5] and several case reports have demonstrated the potential value of Ivabradine, the first selective sinus node *If* channel inhibitor, to treat IST. Ivabradine can have a dramatic effect on heart rate and can slow it from a mean 100 beats/min to fewer than 75 beats/min. The maximum heart rate can slow from a mean of 160 beats/min to 120 beats/min. The minimum heart rate also can slow over time.

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We present a case of young woman ablated for reentry supraventricular tachycardia that present recurrent episodes of tachycardia similar to the previous arrhythmias. So let us think about a recurrence of previous tachycardia, and a new electrophysiological study was perfumed without a double pathway. The treatment with Ivabradine completely resolves symptoms. This case report shows that the Ivabradine is not useful only in coronary heart disease, but its effect on Heart rate is important also if the drug is used off-label, and the normalization of heart rate improves the quality-of-life and this effect is maintained in the long-term follow-up.

## Case Report

The patient is a 22 year-old Caucasian female. At the age of 11-year-old she showed repeated episodes of tachycardia with sudden onset at rest, associated with dizziness and chest pain. The frequency of these episodes was around 5 a day. The first cardiological examination was performed at the age of 16. In the Holter monitoring some episodes of tachycardia were recorded compatible with an Atrioventricular nodal reentry tachycardia (AVNRT), with a maximum heart rate of 210 bpm (Figure 1). After the examination, the cardiologist decided to start a treatment with nadolol. Despite the increase in dosage of the beta blocker, the treatment did not prove to be effective. At the age of 19 (October 2011) was performed an electrophysiological study and catheter thermal ablation of the slow-fast pathway was done. Three months after the procedure the AVNRT episodes restarted with a heart rate lower than the previous episodes, around 180 bpm at rest, especially during the day compromising daily activities. A treatment with flecainide 200 mg was started but was ineffective then a new attempt with nadolol was performed, unsuccessfully. Second electrophysiological study and catheter cryoablation of the slow-fast pathway was performed at the age of 21 (January 2013). The procedure had a good outcome until December 2013 in which the patient began to have new episodes of tachycardia (5-6/die, at rest with sudden onset similar to the supraventricular tachycardia previous experienced the tachycardia was accompanied by presyncope, dizziness, shortness of breath and a new treatment with nadolol was started unsuccessfully. Despite the episodes of tachycardia were not registered with ECG, a new electrophysiological study was performed in June 2014 considering that symptoms were similar to previous. At baseline, the electrophysiological parameters are normal : Sinus cycle length (SCL or AA interval) 870 ms, conduction time of atrioventricular node (AH) 90 ms, and conduction time His-Purkinje( HV) 45 ms. The programmed ventricular pacing (600 drives) shows concentric retrograde decremental conduction pattern until PRE ventricular 260 ms without evidence of double nodal curve (Figure 2). The programmed atrial pacing (600 ms drive) shows retrograde conduction until atrial PRE 470 ms without a double atrial curve. The incremental atrial stimulus shows a Wenckebach point at 500 ms. No induction of arrhythmia with both single and double extrastimulii. After isoproterenol infusion until 4 mcg/kg/m started a sinus tachycardia 145 bpm that, the patient recognized as the clinical tachycardia. The ventricular pacing was repeated (drive 350 ms) and shows a concentric retrograde decremental conduction pattern until PRE ventricular 220 ms without evidence of double nodal curve. The programmed atrial pacing (350 ms drive) shows decremental conduction 250 ms without a double atrial curve. During incremental atrial stimulus, Wenkebach point is at 280 ms without Kay sign. No induction of an arrhythmia with both single and double extrastimulii. The electrophysiological study was repeated after stopping isoproterenol infusion without rising of arrhythmias. At the end of the procedure, sinus rhythm was 90 bpm. Holter monitoring shows an inappropriate sinus tachycardia at rest (Figure 3). Considering symptoms and the electrophysiological study that excluded a relapse of tachycardia, we started a treatment with Ivabradine (5 mg twice a day) with complete resolution of the tachycardia. Informed consent was obtained from the patient for off-label use of Ivabradine and for the publication of case reports. The Holter monitoring performed after one year of therapy shows a normal rest heart frequency with normal response during the effort. The echocardiogram was normal (Figure 4).

## Discussion

The prognosis of patients with IST is excellent: it does not shorten life; it does not cause death, stroke or myocardial infarction. It virtually never leads to tachycardiomyopathy.

IST is not fully understood yet and there are not universally accepted criteria to state a precise definition, which might have underestimated its real prevalence.

No specific heart rate best defines IST, yet patients with IST generally have resting daytime sinus rates of more than 100 beats/min and average 24-h heart rates of more than 90 beats/min that are not explained by physiologic demands or conditions known commonly to increase heart rate [6-10]. Invasive testing, such as electrophysiology studies, is not useful for making the diagnosis, although it may be useful to exclude the presence of a supraventricular tachycardia mechanism [11]. Several possible causes have been proposed, but none of them have been confirmed: autoantibodies to ganglionic acetylcholine receptor [11], anti-beta receptor immunoglobulin G antibodies [12], viral infection or toxin exposure as a trigger [13], an excess of hydrocarbon exposure or halogenated hydrocarbons which could sensitize the myocardium to catecholamines [14,15] but none of these have found enough proof to have any confirmation. To be noted that in one report, 100% of the patients with IST had some psychiatric diagnosis [16].

In IST, there is not one therapy which reduces heart rate and resolves symptoms completely and effectively, likely related to the complexity of the problem and the lack of full understanding of the causes [17]. The common treatment at the moment is a control of the high HR with negative chronotropic agents as beta-blockers and calcium channel blockers, which are often ineffective and, since are given at high doses to have a response, cause collateral effects. Even when they are effective in slowing down the HR they do not necessarily eliminate symptoms. When the pharmacological treatment is not effective, sinus node modification using a variety of catheter ablation techniques have been attempted [18-19]. Although the short-term results

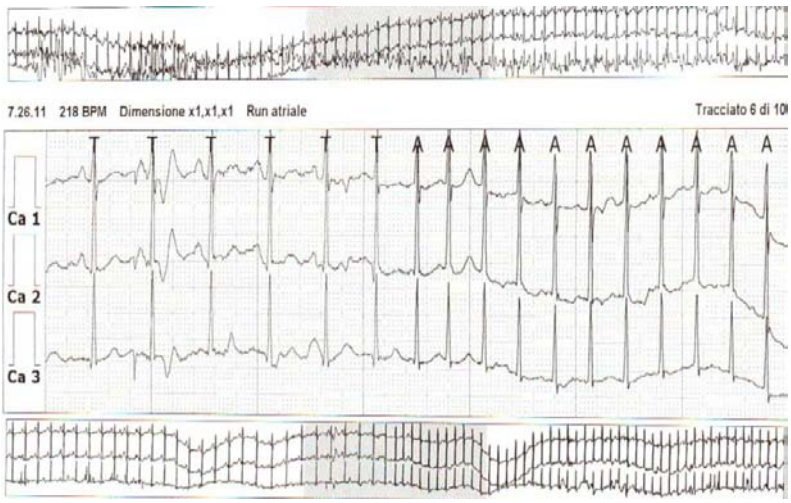


**Figure 1:** Strip Holter monitoring: Atrioventricular nodal reentry tachycardia (AVNRT).

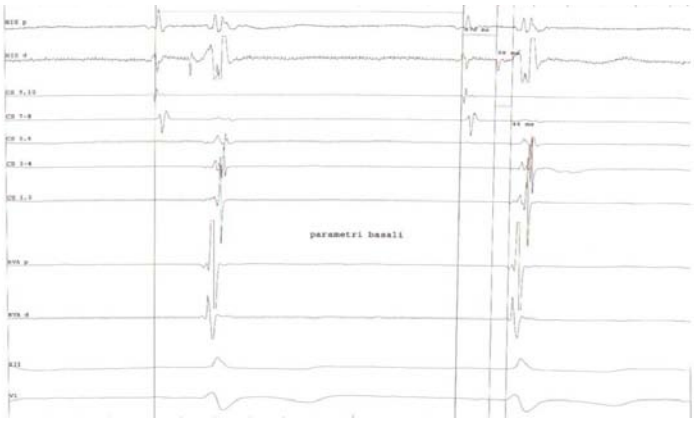


**Figure 2a:** Electrophysiological parameters: At baseline the electrophysiological parameters are normal:Sinus cycle length (SCL or AA interval) 870 ms, conduction time of atrioventricular node (AH) 90 ms, and conduction time His-Purkinje( HV) 45 ms.

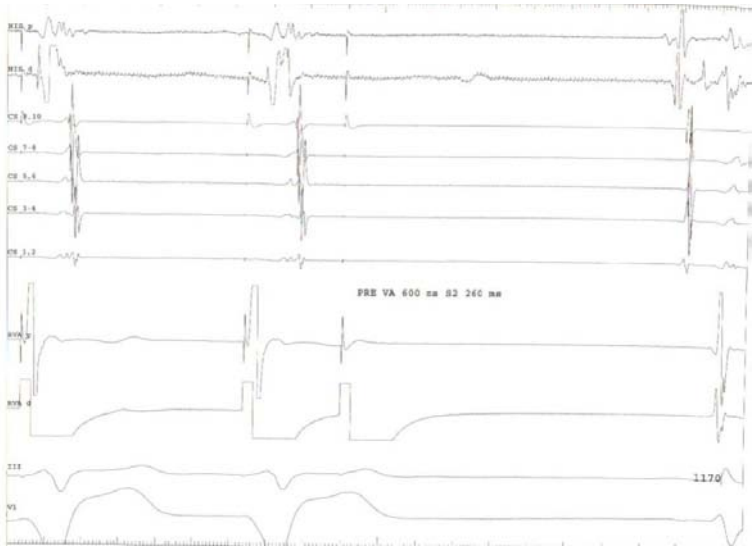


**Figure 2b:** Electrophysiological parameters: The programmed ventricular pacing (600 drives) shows concentric retrograde decremental conduction pattern until PRE ventricular 260 ms without evidence of double nodal curve.

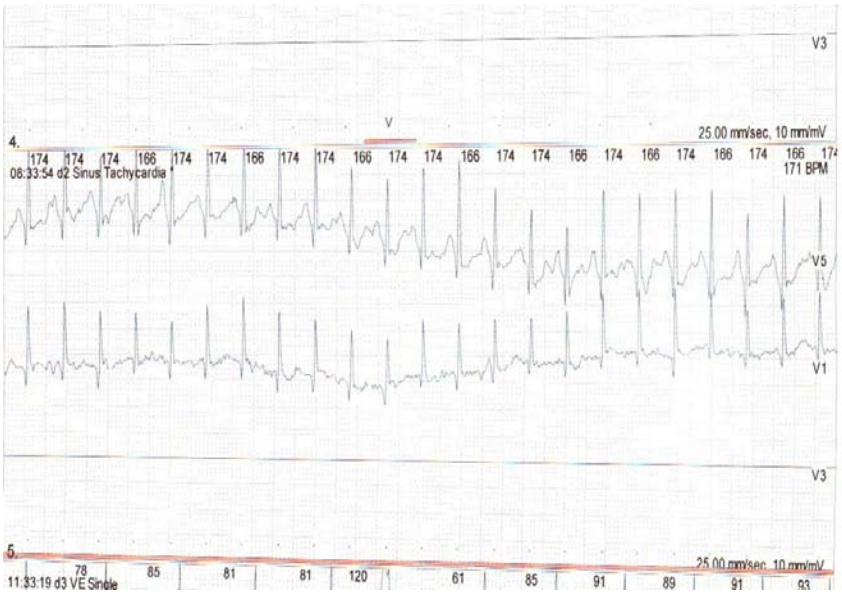


**Figure 3:** Strip Holter monitoring: Inappropriate sinus tachycardia at rest.

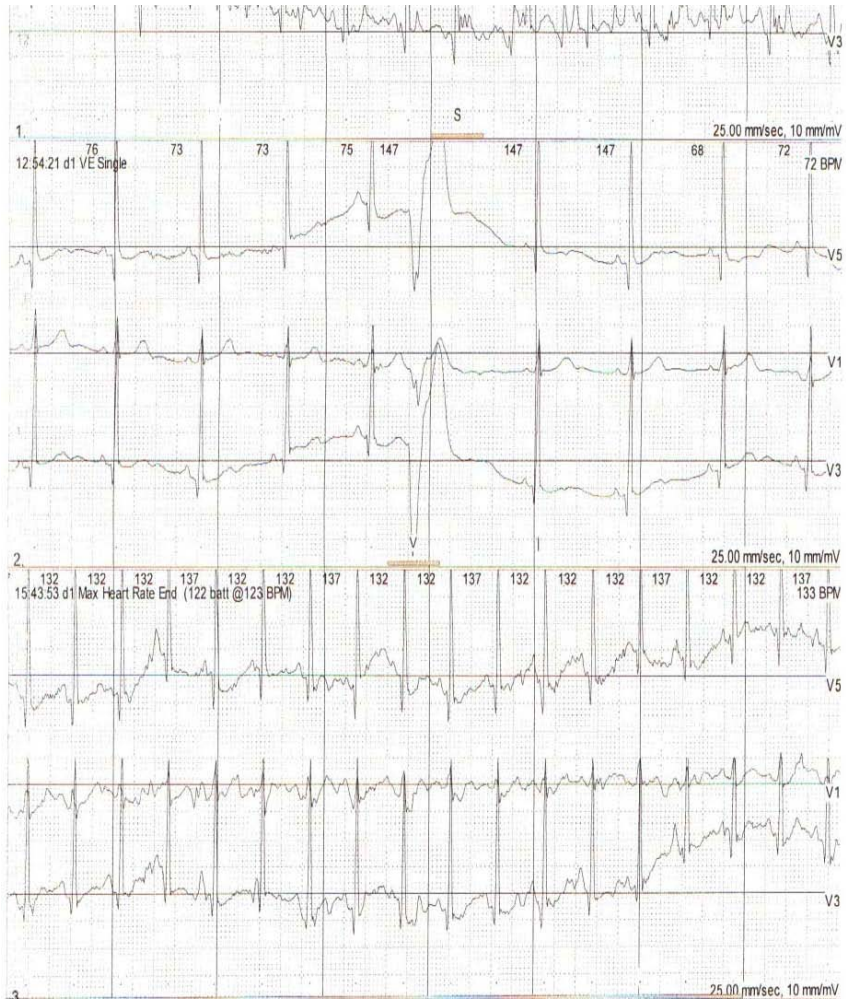


**Figure 4:** Sinus tachycardia during effort at Holter monitoring.

of ablation are generally good, symptoms and elevated heart rate commonly recur after successful sinus node modification. Revising the available literature regarding the subject, it is possible to find a handful of case reports and only a few studies about treating IST with a new category of drugs, the *If* blockers, especially Ivabradine. They all suggest that Ivabradine may be effective in IST treatment. The studies are mostly simple case-control based on a non significant number of subjects and follow-up, except the double-blind, randomized, placebo-controlled trial with a crossover design of Cappato et al. [20]. The patients were randomized to receive either Ivabradine or placebo for 6 weeks, with the following crossover after a brief washout period, permitting within-subject comparisons. Symptoms and heart rate parameters were determined for each patient on and off therapy. Seventy-five percent of IST-related symptoms were eliminated, with nearly 50% of patients having a sudden and complete resolution of all symptoms with Ivabradine. Adverse events are reported with only 1 patient presenting phosphenes, a known and reversible side effect of the drug. In other two studies, there are some follow up after the observational treatment. In one Calò et al. [21] reported the efficacy of Ivabradine administration in 16 consecutive patients followed up to 6 months. Data from this study suggest that Ivabradine significantly reduces the mean and maximum 24-h HR and that its impact on HR reduction tends to improve over time, as suggested by the greater degree of change observed at 6 months compared with that observed at 3 months. In the other study, Benezet-Mazuecost al. [22] followed up to 12 months 20 patients with ITS treated with Ivabradine. When they were proposed to interrupt the treatment, only 10 of them accepted. The other 10 patients preferred to remain on treatment because of significant clinical improvement. Patients who stopped Ivabradine were reevaluated with a 24-hour Holter recording 1 month later, when only two patients (20%) matched IST diagnosis criteria. In our case, the patient experimented some antiarrhythmic drugs as nadolol, that cause severe hypotension, flecainide that was ineffective and association with digoxin and nadolol that controlled for some period the heart rate. The other cause of tachycardia was excluded or corrected as anemia. We do not obtain an ECG during tachycardia, because the symptoms were similar to the previous. In fact, lower recurrence rate is achieved when cryoablation is performed at a younger age [23]. The patient experienced some antiarrhythmic drugs with an important side effect, so was started ivabradine with a complete resolution of symptoms. The drug was effective on heart rate but does not affect blood pressure which has always been a problem for hypotensive patient constitutionally, and that prevented the use of certain medications that adequately used could improve symptoms and control heart rate. The drug was well tolerated and the treatment is still in progress. The control Holter monitoring shows a normal trend of heart rate with only a few episodes of sinus tachycardia during effort and no episodes at rest.

## Conclusion

In conclusion, the last Holter monitoring does not match IST diagnosis criteria. Our case confirms the possibility to use ivabradine off-label in patients without coronary heart disease. There are controversy and a lack of consensus regarding the diagnostic criteria of this entity. It has been recently published in a case series comparing the effect of metoprolol and ivabradine [24] on resting HR and during exercise in IST patients. Ivabradine was more effective to relieve symptoms during exercise or daily activity and was better tolerated. Ivabradine is a drug that can control the HR, avoiding the side effects of other drugs. In the revised literature, the beneficial effect of Ivabradine persisted after 1 year on treatment. The patient wishes to continue it. The drug is effective and safe in rate control in patients with IST, especially as a second-line therapy in cases of lack of efficacy or intolerance of beta-blockers, Ivabradine was better tolerated without effect on blood pressure.

Future studies should clarify the potentially curative effects of Ivabradine in this entity, but we hope it will become the treatment of choice.

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