

## Treatment of inappropriate sinus tachycardia with ivabradine

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### Behandlung von inadäquaten Sinustachykardien mit Ivabradin

**Zusammenfassung.** *Hintergrund:* Inadäquate Sinustachykardien werden zumeist mit  $\beta$ -Blockern behandelt. Bei therapieresistenten Fällen wurde auch eine nicht-pharmakologische Behandlung versucht. Kürzlich haben Fallberichte bei manchen Patienten ein gutes Ansprechen auf Ivabradin gezeigt.

*Methoden:* Bei 13 Patienten (davon 11 Frauen) im Alter 27 bis 66 Jahren (MW:  $42 \pm 8$ ) wurden inadäquate Sinustachykardien mit Ivabradin in einer Dosierung von 15 mg/Tag behandelt.

*Ergebnisse:* Bei 12 Patienten (deren Vortherapie abgesetzt werden konnte oder die die vorher verordneten Medikamente nicht einnahmen) sank die mittlere Tagesfrequenz von  $94,0 \pm 10,0$  auf  $74,6 \pm 5,2$  Schläge/min (MW  $\pm$  SD). Bei 10 Patienten, bei denen wir verlässlich die höchste und niedrigste Tagesherzfrequenz erheben konnten, sanken die höchsten Frequenzen von  $150,3 \pm 13,4$  auf  $120,6 \pm 9,8$  und die niedrigsten von  $66,7 \pm 9,6$  auf  $54,8 \pm 6,9$ . Alle Unterschiede waren statistisch signifikant ( $p < 0,001$ ). Prozentuell korrelierte die Reduktion der Herzfrequenz mit der initialen Herzfrequenz ( $p < 0,005$ ). Bei einer Patientin, die seit mehr als 10 Jahren mit 300 mg Metoprolol/Tag behandelt wurde und die trotzdem eine Ruhfrequenz von 106/min aufwies wurde hinterher ohne Zwischenpause 15 mg Ivabradin/Tag verabreicht, was zu einer Verminderung von 4 Schlägen/min führte.

*Schlussfolgerungen:* Die Ergebnisse unserer Studie zeigen, dass Patienten mit inadäquaten Sinustachykardien erfolgreich mit Ivabradin behandelt werden können.

**Summary.** *Background:* Inappropriate sinus tachycardia is most often treated with beta-blockers; in resistant cases, nonpharmacologic treatment has been attempted. Recent case reports have shown a favorable response to ivabradine in some patients.

*Methods:* A total of 13 patients (11 women, 2 men) aged from 27 to 66 years (mean  $42 \pm 8$ ) and having inap-

propriate sinus tachycardia were treated with ivabradine 15 mg per day.

*Results:* In 12 patients whose previous therapy could be discontinued or who did not have previous medication the mean daily heart rate decreased from  $94.0 \pm 10.0$  to  $74.6 \pm 5.2$  bpm (mean  $\pm$  SD) after ivabradine treatment. In 10 patients in whom we could reliably measure the highest and lowest daily heart rates, the highest rate decreased from  $150.3 \pm 13.4$  to  $120.6 \pm 9.8$  and the lowest from  $66.7 \pm 9.6$  to  $54.8 \pm 6.9$ . All of the differences were statistically significant ( $P < 0.001$ ). The percentage of heart rate reduction correlated with the initial heart rate ( $P < 0.005$ ). The remaining patient, who had been treated with metoprolol 300 mg per day for more than 10 years and still had a resting heart rate of 106 bpm, switched to 15 mg of ivabradine daily without discontinuation of drug therapy. After this switch, a decrease of 4 bpm was noted in her mean daily heart rate.

*Conclusions:* The results of our study show that patients with inappropriate sinus tachycardia can be successfully treated with ivabradine.

**Key words:** Inappropriate sinus tachycardia, ivabradine, heart rate.

### Introduction

Inappropriate sinus tachycardia is an uncommon rhythm disturbance. It is diagnosed by a persistent, non-paroxysmal, daytime sinus rate  $> 100$  bpm and by excluding the more common causes for increased heart rate such as fever, hyperthyroidism and anemia [1–3]. Several causes of inappropriate sinus tachycardia have been proposed: enhanced sinus node automaticity, alterations in autonomic function (increased sympathetic activity or reduced parasympathetic activity), impaired baroreflex control, and increased levels of autoantibodies to beta-adrenergic receptors [1–5]. This arrhythmia is most often treated with beta-blockers. However, in resistant cases nonpharmacologic treatment such as transcatheter ablation [6–7] or even surgery [8] has been attempted. Apart from beta-blockers, other potentially effective drugs are nondihydropyridine calcium antag-

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onists and amiodarone. Ivabradine, a drug that selectively decreases heart rate, has recently become available; case reports have already shown a favorable response in reported patients [9–12].

### Patients and methods

Thirteen consecutive patients (11 women, 2 men) with inappropriate sinus tachycardia were studied. Their mean age was  $42 \pm 8$  years (mean  $\pm$  SD, range 27–66 years). All but one patient had been referred by general practitioners because of symptomatic sinus tachycardia and an average resting heart rate (in conventional electrocardiogram)  $>100$  bpm. The mean resting heart rate in all patients was  $109.6 \pm 12.4$  bpm (mean  $\pm$  SD). One patient presented with a Holter mean daily heart rate of 107 bpm. All patients had a daytime heart rate  $>100$  bpm (Holter). No variations in P-wave morphology were noted. All patients complained of palpitations and fatigue and were referred to our clinic because of high heart rates. Two patients (Nos. 3 and 12, Table 1) monitored their heart rate regularly; one with a sports wrist watch and the other (a nurse) by palpating her pulse. Three patients complained because of fatigue, but were not aware of their high heart rate until it was discovered by their physician; thereafter they also had palpitations. No patient had fever; hyperthyroidism was excluded for all by normal TSH measurements. No patient had clinical or echocardiographic signs of structural heart disease. All but one patient had a normal hemoglobin level; in one it was slightly decreased. All but one patient took no concomitant medication or dietary supplement; the remaining patient was on chronic, stable medication with clozapine, clonazepam and aripiprazole. The majority of patients (7/13) were pretreated with beta-blockers, although different drugs and different dosages were used, and in some patients treatment was discontinued because of side effects. For this reason, no reliable conclusion can be reached about the success of beta-blocker therapy in this group of patients. Twelve patients underwent Holter monitoring without any rate-lowering medication; this was repeated after two weeks of ivabradine 15 mg per day. The remaining patient was on medication with a high dose of metoprolol (300 mg per day). Nevertheless,

her resting heart rate was 106 bpm. This patient switched to treatment with ivabradine without interruption, and Holter monitoring results were compared for the beta-blocker and ivabradine treatments.

The following statistical methods were used: paired *t*-test and Pearson correlation coefficient.

### Results

Two weeks' treatment with ivabradine 15 mg per day in 12 patients with inappropriate sinus tachycardia resulted in a mean daily rate decrease of  $19.4 \pm 6.7$  bpm (mean  $\pm$  SD). The pretreatment heart rate was  $94.0 \pm 10.0$  bpm, the post-treatment rate  $74.6 \pm 5.2$  bpm. The highest and the lowest daily heart rates were reliably determined in 10 patients: the decrease in the maximal rate was  $29.7 \pm 10.4$  bpm (from  $150.3 \pm 13.4$  to  $120.6 \pm 9.8$ ); the decrease in the minimal rate was  $11.9 \pm 4.5$  bpm (from  $66.7 \pm 9.6$  to  $54.8 \pm 6.9$ ). Individual characteristics of the patients and the changes in their heart rates are shown in Table 1 and Fig. 1. Patients received ivabradine alone during the study; they received no beta-blockers or other rate-decreasing medication. Ivabradine did not cause any visual or other side effects in the patients and was well tolerated.

The percentage of heart rate reduction correlated well with the initial heart rate: in patients with a higher rate the reduction was greater ( $r = 0.75$ ,  $P < 0.005$ ).

In the patient who switched from treatment with metoprolol 300 mg daily to ivabradine without interruption, the mean heart rate decreased from 94 to 90 bpm. After six months of ivabradine therapy, this patient noticed an improvement of cold hands, feet sensation and overall feeling of wellbeing in comparison with beta-blocker treatment. She needed to take an angiotensin-converting enzyme inhibitor to control her blood pressure.

**Table 1.** Individual characteristics of patients treated with ivabradine

Case No.	Age (years)	Sex	HR	Holter 1	Holter 2	% rate reduction	Symptoms (years)	Previous $\beta$ -blocker therapy
1	68	F	110	84	70	17	6	–
2	47	F	104	82	67	18	4	metoprolol
3	45	F	112	87	68	22	4	atenolol
4	36	F	103	83	74	11	4	metoprolol
5	29	F	132	110	85	23	1	–
6	40	F	103	87	74	15	0.5	–
7	48	F	125	95	73	24	3	bisoprolol
8	43	F	123	97	76	22	1	–
9	49	M	109	104	73	30	5	metoprolol
10	50	F	102	107	82	23	1	–
11	34	M	125	103	77	25	1.5	–
12	28	F	136	89	76	15	3.5	metoprolol
Mean $\pm$ SD	$41 \pm 8$		$115.0 \pm 12.0$	$94.0 \pm 10.0$	$74.6 \pm 5.2$	$20 \pm 5$	$2.9 \pm 1.8$	

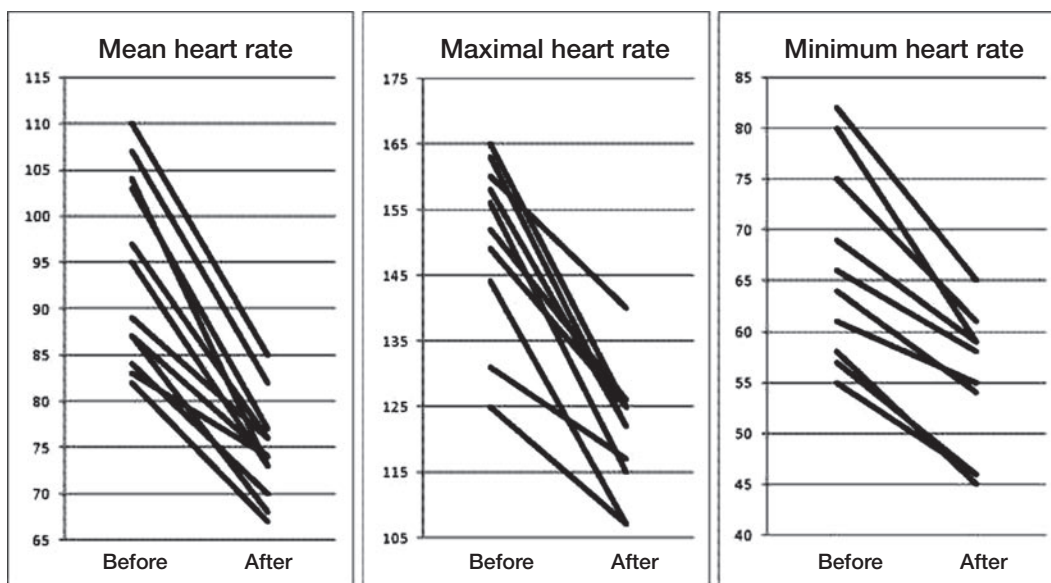
HR presenting heart rate (ECG); Holter 1 mean daily heart rate without rate-decreasing medication; Holter 2 mean daily heart rate after ivabradine; % rate reduction decrease in heart rate after ivabradine; Symptoms (years) duration before inclusion in the study.

## Discussion

Inappropriate sinus tachycardia is characterized by an elevated heart rate at rest and an exaggerated heart rate response to physical activity or emotional stress [1–3]. There is a characteristic drop in the nocturnal rate [13]. The condition is accompanied by palpitations and fatigue, possibly also by dizziness and other symptoms. Inappropriate sinus tachycardia is an uncommon arrhythmia and occurs in otherwise healthy people, predominantly younger women. Its cause is not well understood. Increased automaticity of the sinus node is the most plausible explanation for the underlying mechanism, although other mechanisms such as enhanced sympathetic and blunted parasympathetic tone, beta-receptor hypersensitivity, and brainstem dysregulation have been proposed. The diagnosis of inappropriate sinus tachycardia is made after other supraventricular tachycardias (atrial tachycardia with upright P waves in leads 1 and 2) and other medical disorders have been ruled out. Such disorders include hyperthyroidism, pheochromocytoma, high-grade anemia, fever and substance abuse. Physical deconditioning should also be excluded; regular physical activity should be recommended in these cases [14]. Inappropriate sinus tachycardia is usually treated with beta-blockers, the only drugs with class I recommendation for treatment of this condition [14]. Nondihydropyridine calcium-channel blockers with class IIa recommendation can be used in patients who do not tolerate beta-blockers. Often patients do not respond satisfactorily to any medical therapy [15] and resistant cases require transcatheter modification (ablation) of the sinus node [6, 7] (recommendation class I). However, the risk of bradycardia (requiring permanent pacing) and the fairly high rate of recurrence limit the usefulness of this treatment [16].

Although long-term successful outcome may be possible in some patients, symptoms of palpitations and autonomic characteristics frequently persist [6]. If all other treatments fail, surgical excision of the sinus node can be attempted [8]. Ivabradine is a relatively new drug registered for the treatment of stable angina pectoris. Its mode of action is by blocking the “funny” current ( $I_f$ ) responsible for spontaneous diastolic depolarization of pacemaker cells in the sinus node [17]. The therapeutic role of this drug in the treatment of sinus tachycardia therefore appears logical [18, 19], as confirmed in published case reports [9–12]. The experience with the group of patients in the present study shows that ivabradine can normalize the heart rate in patients with inappropriate sinus tachycardia. Traditionally, 70 or 72 bpm is considered the normal human diurnal heart rate, and these rates were therefore used in the early fixed-rate pacemakers. In another study, healthy volunteers (predominantly men) had a mean heart rate of 67 bpm [20]; in women, the heart rate is usually 3–5 bpm higher than in men [21]. Thus, the mean heart rate in our patients (predominantly women) after ivabradine therapy (74 bpm) was near normal. The same was true for the maximal and minimal daily heart rate.

Since the results of the “Beautiful” [22] and “Associate” [23] studies have proven that combined treatment with ivabradine and beta-blockers is feasible, such combined therapy could be used in resistant cases. It is difficult to speculate whether the results of the present study shed new light on the primary cause of inappropriate sinus tachycardia – increased automaticity of the sinus node or autonomic nervous dysregulation. Ivabradine was found to influence sinus node automaticity, but this does not rule out the possibility that the primary cause of the disorder might be autonomic dysregulation.



**Fig. 1.** Mean, maximal and minimal heart rate (bpm) before and after ivabradine treatment. All differences are statistically significant ( $P < 0.001$ )

### Limitations of the study

There are two definitions of inappropriate sinus tachycardia: one definition requires a daytime sinus heart rate >100 bpm [15], the other requires the same *or* a mean 24-h heart rate >90 bpm [25]. Though all presented patients fulfilled the criteria (because only one criterion is required), six patients had a daily heart rate <90 bpm. Since this is an observational study, it has some further limitations. No reliable comparison between treatment with ivabradine and with beta-blockers can be made. Only one patient received maximal beta-blockade before inclusion. All patients worked at least part time and were active; however, the degree of their physical activity was not studied in detail.

### Conclusion

Inappropriate sinus tachycardia can be successfully treated with ivabradine. This treatment may be especially useful in patients in whom beta-blockers are contraindicated or poorly tolerated.

### Conflict of Interest

The authors declare that there is no conflict of interest.

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