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CASE REPORT
Electrophysiology

Ivabradine for inappropriate sinus tachycardia-induced symptomatic Mobitz type I atrio-ventricular block: a case summary

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Background Inappropriate sinus tachycardia (IST) is characterized by a continuum of symptoms, and the aetiology of IST is imprecise. IST-induced autonomic dysfunction is well known, but IST-induced atrio-ventricular block is not reported to our knowledge.

Case summary A 67-year-old female presented with a 4-day history of random intermittent difficulty in breathing, chest tightness, palpitations, and dizziness, with a recorded heart rate of 30 beats per minute (BPM) on home monitoring equipment. The initial electrocardiogram (ECG) demonstrated sinus rhythm with intermittent Mobitz type I second degree atrio-ventricular (AV) block, with continuous cardiac monitoring demonstrating frequent episodes of Wenckebach phenomenon throughout the day, with a sinus rate of 100–120 BPM. Echocardiogram showed no significant structural abnormalities. The patient was on bisoprolol, and hence, it was suspected Wenckebach may be due to that and so stopped. However, there was no tangible effect on rhythm 48 hours after stopping bisoprolol, leading to a suspicion of IST-induced Mobitz type I second degree AV block; and so decided to introduce ivabradine 2.5 mg twice daily. After 24 hours of Ivabradine, the patient remained in sinus rhythm with no documented episodes of Wenckebach phenomenon on cardiac monitor, a finding subsequently confirmed by 24-hour Holter monitoring. During a recent follow-up visit in clinic, the patient remained symptom-free, with an ECG demonstrating sinus rhythm at a physiological rate.

Discussion Mobitz type I second degree AV block is usually due to reversible conduction block at the level of the AV node whereby malfunctioning AV nodal cells tend to progressively fatigue until they fail to conduct an impulse. Under conditions of increased vagal tone and autonomic dysfunction, Wenckebach occurrence will be increased. Thus, selective impulse conduction within the sinoatrial (SA) node by ivabradine to reduce beat conduction to the AV node in patients with IST/dysautonomia-induced Mobitz type I AV will reduce the occurrence of Wenckebach.

Keywords Tachycardia • IST • Wenckebach • Inappropriate sinus tachycardia • Mobitz AV block • Ivabradine • Case report

ESC Curriculum 5.7 Bradycardia • 9.9 Cardiological consultations • 5.1 Palpitations

Learning points

- Inappropriate sinus tachycardia in the context of autonomic neuropathy affecting the sinoatrial node can lead to symptomatic Mobitz type I atrio-ventricular (AV) block.
- When monitored closely, selective inhibition of the sinoatrial node by ivabradine seems to be a safe and effective option to treat symptomatic Mobitz type I second degree AV block in patients with inappropriate sinus tachycardia.

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Introduction

Inappropriate sinus tachycardia (IST) is characterized by a spectrum of symptoms occurring as a result of an inappropriately increased sinus rate not related to the intensity of activity. The aetiology of IST remains unclear, comprising a complex and multi-factorial pathology from intrinsic sinus node overactivity as a consequence of channelopathy, autonomic dysfunction, increased sympathetic activity, and/or neurohormonal modulation.[1] Though IST-induced autonomic dysfunction is well-recognized, to our knowledge IST-induced atrio-ventricular (AV) block is not well-known. Here, we report on the case of a 67-year-old female with IST and symptomatic Mobitz type I second degree AV block (Wenckebach phenomenon), successfully treated with ivabradine through selective inhibition of the I_f channel.

Timeline

Date	Encounter type	Clinical events
13 May 2022	Inpatient	Admitted with symptoms of breathlessness, chest tightness, palpitation, and dizziness. Electrocardiogram (ECG) showed intermittent type 2 Mobitz I atrio-ventricular (AV) block, bisoprolol stopped
14 May 2022	Inpatient	ECG—intermittent type 2 Mobitz I block, given low creatine clearance related to chronic kidney disease, planned to wait for another 24 hours for bisoprolol to wash out
15 May 2022	Inpatient	Initiated ivabradine 2.5 mg twice daily
16 May 2022	Inpatient	Symptom-free, ECG, and cardiac monitor showed sinus rhythm, no documented Wenckebach phenomenon
24 May 2022	Outpatient	Symptom-free, Holter showed sinus rhythm with mean heart rate of 77 beats per minute, no evidence of Mobitz type I AV block
07 December 2022	Outpatient	Symptom-free, ECG showed sinus rhythm

Case report

A 67-year-old female presented with a history of shortness of breath for the preceding 4 days, associated with intermittent chest discomfort, palpitations, and dizziness. She recorded her heart rate of 30 beats per minute, upon which she was conveyed to the emergency department. She described her palpitations primarily as 'skipped beats' and became unsteady on her feet, requiring family assistance to mobilize. There was no history of falls, collapse, or loss of consciousness. Past medical history included treated Takayasu's arteritis, bullous pemphigoid (on long-term prednisolone 5 mg once daily), hypertension, dyslipidaemia, chronic kidney disease, inflammatory arthritis, and type II diabetes mellitus. At functional baseline, she was able to mobilize around the house with a walking frame and cook independently with minimal assistance. Her relevant medication with regards to presentation included bisoprolol 5 mg once daily.

Weight was recorded as 133 kg, with a height of 168 cm, and a calculated body mass index of 47.3. Physical examination revealed no significant abnormality. Investigations revealed a mild anaemia (haemoglobin—112 g/dL), chronic kidney disease (creatinine—147 μmol/L and creatinine clearance 69 ml/minute by using Cockcroft-Gault calculation), and negative troponin levels. The initial electrocardiogram (ECG) demonstrated sinus rhythm with intermittent Mobitz type I second degree AV block with a sinus rate of 100–110 beats per minute (*Figure 1*). Cardiac monitoring revealed frequent episodes of Wenckebach phenomenon (Mobitz type I second degree AV block) throughout the day with no heart rate variability on postural change. Echocardiogram showed normal bi-ventricular size and function, dilated bi-atrial size, moderate mitral regurgitation, and mild tricuspid regurgitation. A previous 24-h ambulatory ECG in 2021 showed normal sinus rhythm with no significant tachybrady arrhythmia.

It was at first theorized that her symptoms were the result of beta-blockade; therefore, her bisoprolol was ceased. Following a washout period of 48 h, there was no appreciable effect on ECG complex morphology/rhythm or heart rate, and multiple episodes of Mobitz type I were documented throughout the day. On telemetry, a rhythm pattern with intermittent sinus tachycardia at rest at a rate of 130 beats per minutes and intermittent Mobitz type I second degree AV block was demonstrated over a period of 20 min (*Figure 2*).

The following day, the patient was noted to be hypertensive; therefore, candesartan was increased to 4 mg once at night, and amlodipine 2.5 mg once daily was initiated. These interventions had the desired effect of lowering blood pressure; however, there was no demonstrable effect on the incidence of Mobitz type I episodes on telemetry. At this stage, we deduced a provisional diagnosis of IST-induced Wenckebach phenomenon, relating possibly to autonomic dysfunction with a differential diagnosis of multi-factorial pathology, possibly related to diabetes or long-term steroid use. Thereafter, ivabradine was initiated at a dose of 2.5 mg 12-h with close monitoring. Twenty-four hours following first administration of ivabradine, the heart rate was noted to be at a persistent physiological rate of 70–80 beats per minute at rest, in normal sinus rhythm with no documented episodes of Wenckebach phenomenon on the cardiac monitor or on 12-lead ECG (*Figure 3*), with no detectable nocturnal episodes. There were no pauses or evidence of high-grade AV block on telemetry. Since ivabradine makes symptoms and rhythm better, decided to continue ivabradine alone at this stage. The patient noted an improvement in her condition, with no further symptoms. She was thereafter deemed medically fit and discharged on 16 May 2022.

An outpatient 24-h ambulatory ECG monitor obtained a week following discharge demonstrated sinus rhythm with regular diurnal variation and a mean heart rate of 77 beats per minute with no further symptoms recorded during either the follow-up or 24-h recording period. Additionally, there was no evidence of Wenckebach phenomenon or high-grade AV block during the 24-h recording period. No adverse effects attributable to ivabradine were noted during the follow-up period. The patient was reviewed in outpatient clinic a few months post-discharge; the patient had remained symptom-free from a cardiac perspective and ECG demonstrated sinus rhythm.

Discussion

Here, we report the case of a 67-year-old lady with symptomatic Mobitz type I second degree (Wenckebach pattern) AV block and IST, successfully treated with ivabradine. We believe that this case represents the first reported instance of utilizing ivabradine to selectively reduce impulse conduction within the sinoatrial (SA) node to reduce beat conduction to the AV node in a patient with symptomatic Mobitz type I second degree AV block as a result of dysautonomic sinus

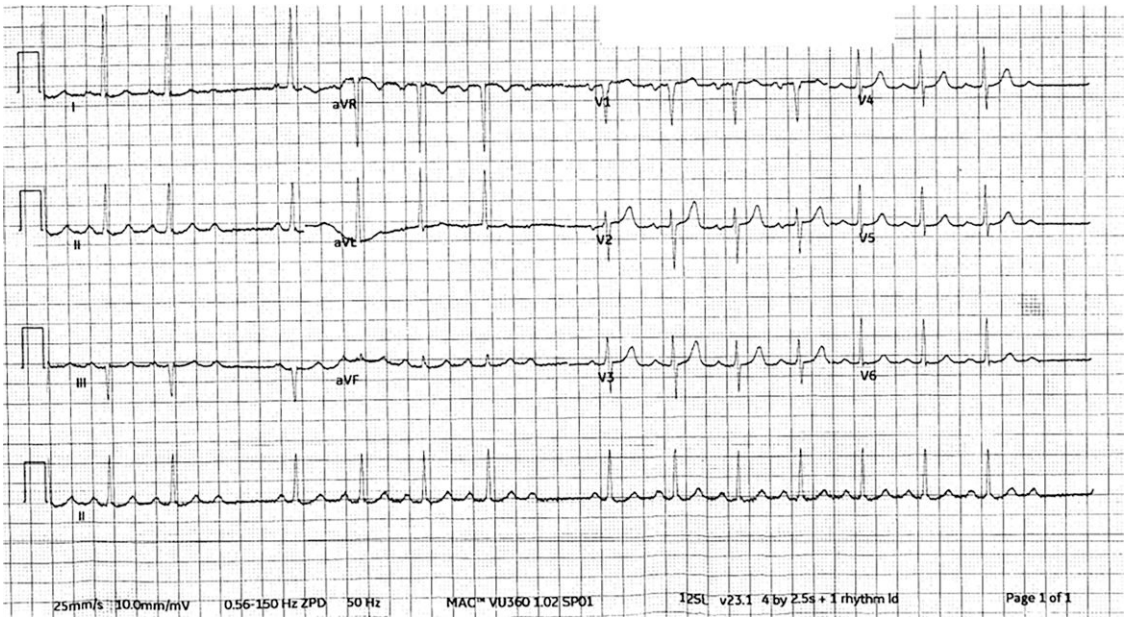

Figure 1 Intermittent Mobitz type I atrio-ventricular block. Sinus rate of 100–110 beats per minute.

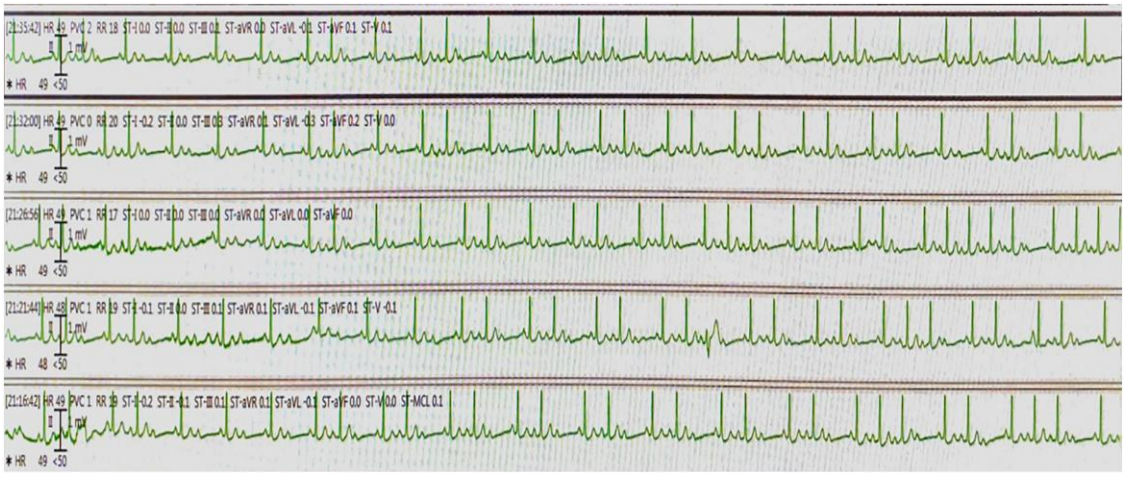

Figure 2 Cardiac monitor demonstrating multiple episodes of intermittent Mobitz type I atrio-ventricular block and inappropriate sinus tachycardia within a 20-min period.

tachycardia, to in turn cease the incidence of Wenckebach phenomenon.

The atria and ventricles are electrically isolated from one another by the AV node located at the base of right atrium within the triangle of Koch. The AV node acts as the gatekeeper of the ventricles to delay conduction that in turn preserves cardiac filling, and to promote sequential activation of the atria and ventricles through a process of decremental conduction. The AV node however does not act in a binary fashion with regards to atrial stimulus and indeed is fully integrated into a system of neurohormonal stimulation and acts under the influence of the autonomic nervous system. The underlying mechanism of the Wenckebach phenomenon is caused by a reversible conduction block at the AV node predicated by progressive fatigue of impaired AV nodal cells, leading to failure of impulse conduction. Hence within the pathological setting of inappropriately increased vagal tone and autonomic dysfunction, Wenckebach occurrence will be increased.[2]

IST can occur due to an intrinsic increase in sinus node automaticity or perhaps due to extrinsic factors such as neuro-hormonal modulation, autonomic dysfunction, or increased vagal tone.[3] Ivabradine is a selective inhibitor of I_f channels within cells of the SA node. It provokes a reduction

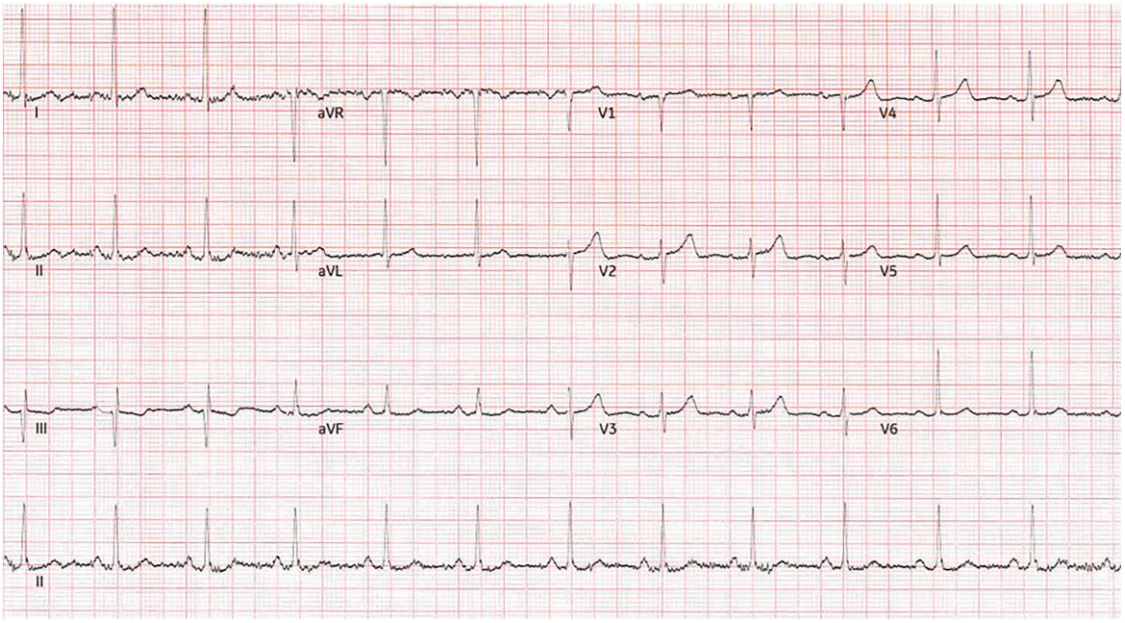

Figure 3 Normal sinus rhythm at a physiological rate of 70–80 bpm measured 24 h following first ivabradine administration.

in heart rate by prolonging the diastolic depolarization that in turn slows firing within the SA node, without resultant effect on blood pressure.[4] Ivabradine has been utilized in the treatment of IST without adverse side effects.[3]

Tachycardia in this instance was deemed to represent a manifestation of cardiovascular autonomic neuropathy, secondary to diabetes, where a resting tachycardia and exercise intolerance occurred secondary to inadequate heart rate response.[5] Indeed in our patient, longstanding steroids and diabetes were theorized to have synergistically contributed to an autonomic neuropathy preferentially affecting the SA node, in turn resulting in persistent sinus tachycardia. This was noted to induce an abnormally high rate of Wenckebach behaviour in the AV node secondary to IST. The rationale therefore to treat these frequent Wenckebach patterns with ivabradine was to lower the sinus rate and in turn induce dissipation of the Wenckebach behaviour.

In this first reported case, we have demonstrated that ivabradine is a safe and effective treatment for symptomatic Mobitz type I second degree AV block, where the aetiology is an IST predicated by autonomic dysfunction. The future use of ivabradine in this clinical setting mandates further studies.

Conclusions

IST in a patient with high risk of autonomic neuropathy could affect the SA node can lead to symptomatic Mobitz type I second degree AV block. This can be treated with selective inhibition of the SA node by ivabradine, with close cardiac monitoring.

Limitations

Though our patient underwent continuous cardiac monitoring from time of admission through to discharge, dedicated 24-h ambulatory ECG monitoring did not take place prior to our intervention of the administration of ivabradine.

Lead author biography

Lead author, Dr Korolewicz, worked in the cardiology unit at Hammersmith Hospital in his role as an internal medicine resident. The corresponding and senior authors have published several papers in academic cardiology. Dr Lim is a senior Consultant Cardiologist and Electrophysiologist in a leading tertiary care cardiac centre, Hammersmith Hospital, London.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: We obtained consent from the patient in accordance with COPE guidelines.

Conflict of interest: None declared.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

References

1. Olshansky B, Sullivan RM. Inappropriate sinus tachycardia. *EP Europace* 2019;**21**:194–207.

2. Hansom SP, Golian M, Green MS. The Wenckebach phenomenon. *Curr Cardiol Rev* 2021;**17**: 10–16.
3. Gee ME, Watkins AK, Brown JN, Young EJA. Ivabradine for the treatment of postural orthostatic tachycardia syndrome: a systematic review. *Am J Cardiovasc Drugs* 2018;**18**: 195–204.
4. Sulfi S, Timmis AD. Ivabradine—the first selective sinus node if channel inhibitor in the treatment of stable angina: ivabradine in the treatment of stable angina. *Int J Clin Pract* 2006;**60**: 222–228.
5. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007;**115**: 387–397.