

Advanced atrioventricular block due to hypervagotonia: Treatment with hyoscyamine



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Introduction

Hypervagotonia is an unusual condition that can be associated with significant symptoms usually due to sinus node dysfunction. We describe a 63-year-old male patient with episodic syncope due to hypervagotonia associated with advanced AV block that occurred during hot weather and was exacerbated by drinking cold water. We describe the use of hyoscyamine, a muscarinic receptor blocker, as an effective treatment strategy that avoided permanent pacemaker implant.

Case report

A 63-year-old man with episodic syncope or near syncope for the past 5 years presented to the emergency department because he felt particularly unwell that morning. At initial evaluation the baseline electrocardiogram (ECG) was normal (Figure 1), but on drinking cold water he could reproducibly self-precipitate periods of second-degree AV block (Figure 2). On hospital observation, he would display intermittent periods of advanced AV block that correlated with his symptoms (Figure 3). The episodes would be preceded by a sense of warmth and mild nausea. Historically, the episodes generally clustered in the late summer months, exacerbated by heat, and could be precipitated by drinking cold water. He had experienced these episodes for the past 5 years and after an evaluation at another institution 2 years ago, permanent pacing was recommended but the patient decided against this treatment option. This year, the symptoms were particularly bothersome and were occurring multiple times during the day. He initially had syncope with his first episodes 5 years ago, but now has identified warning signs and will sit or lie down when he has his prodrome and has

KEY TEACHING POINTS

- It is critical to identify the underlying cause for bradycardia.
- Hypervagotonia-associated bradycardia is usually due to sinus node dysfunction but in rare cases can present as AV block.
- Hyoscyamine can be a potentially effective therapy for hypervagotonia.

had no frank syncope for the past several years. The patient had no significant past medical history other than the episodic syncope and was not on medications. He does not smoke and rarely drinks alcohol.

Initial workup included thyroid stimulating hormone, erythrocyte sedimentation rate, C-reactive protein, and Lyme serology that were all within normal limits or negative. Cardiac magnetic resonance imaging and positron electron tomography scanning revealed normal cardiac function without structural abnormalities, and no scarring or other abnormalities were identified by late gadolinium enhancement. These tests helped rule out hypothyroidism, Lyme and other types of myocarditis, and cardiac sarcoidosis. Sleep evaluation demonstrated no evidence of sleep apnea. Tilt table testing demonstrated a normal hemodynamic response.

Careful evaluation of the ECGs and telemetry demonstrated that periods of advanced AV block were always preceded by sinus node slowing and thus suggestive of AV block owing to increased vagal tone (Figure 3). Different treatment options using a shared decision-making process were explained to the patient. While he was not completely against permanent pacing if necessary for treatment, he wished to avoid this option if possible. He was started on hyoscyamine first using short-acting and then extended-release formulations and low-dose treatment (0.125 mg twice a day) improved but did not eliminate his symptoms. On escalation of the hyoscyamine dosage to 0.375 mg twice a day, his

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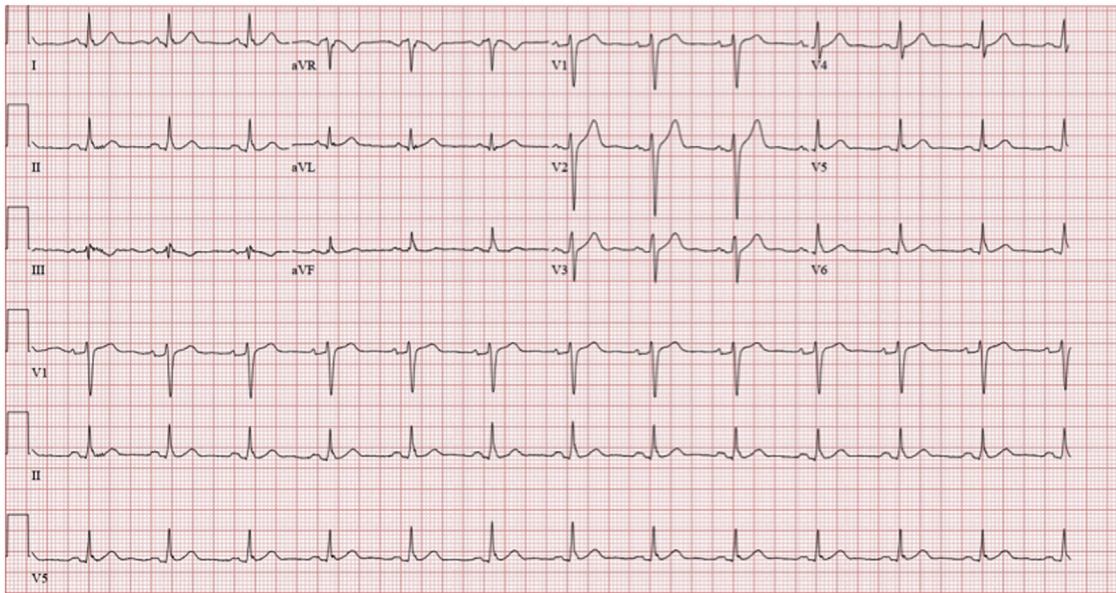


Figure 1 Baseline electrocardiogram initially obtained in the emergency department that demonstrates no significant abnormalities.

symptoms were eliminated, and extended ambulatory ECG monitoring confirmed the absence of AV block and stable heart rates without bradycardia despite attempts to self-induce symptoms by ingesting cold water. He noted some mild dryness in his mouth owing to hyoscyamine, but no other side effects. After a month of outpatient treatment, the hyoscyamine was gradually down-titrated and finally discontinued without recurrence of symptoms. After 6 months of follow-up the patient continues to do well. The current

plan is to restart the hyoscyamine next year during the summer when his symptoms begin to appear.

Discussion

This case report illustrates the importance of identifying the underlying etiology when caring for patients with symptomatic advanced AV block. The differential diagnosis for acquired AV block is traditionally further classified as either

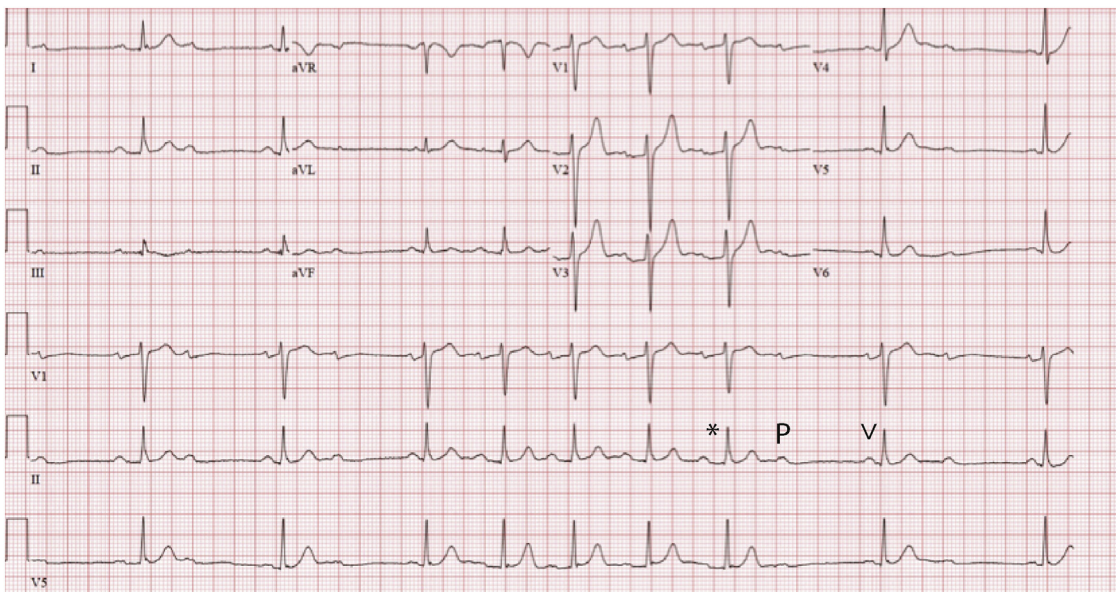


Figure 2 Electrocardiogram recorded while the patient was drinking cold water to induce his symptoms. In this case second-degree 2:1 AV block is observed in the first part of the recording, which is then followed by second-degree AV block Mobitz type I; notice that the PR interval (V) after the nonconducted P wave (P) is shorter than the PR interval (*) before the nonconducted P wave. In almost all cases second-degree AV block Mobitz type I identifies the AV node as the site of AV block rather than the His bundle.

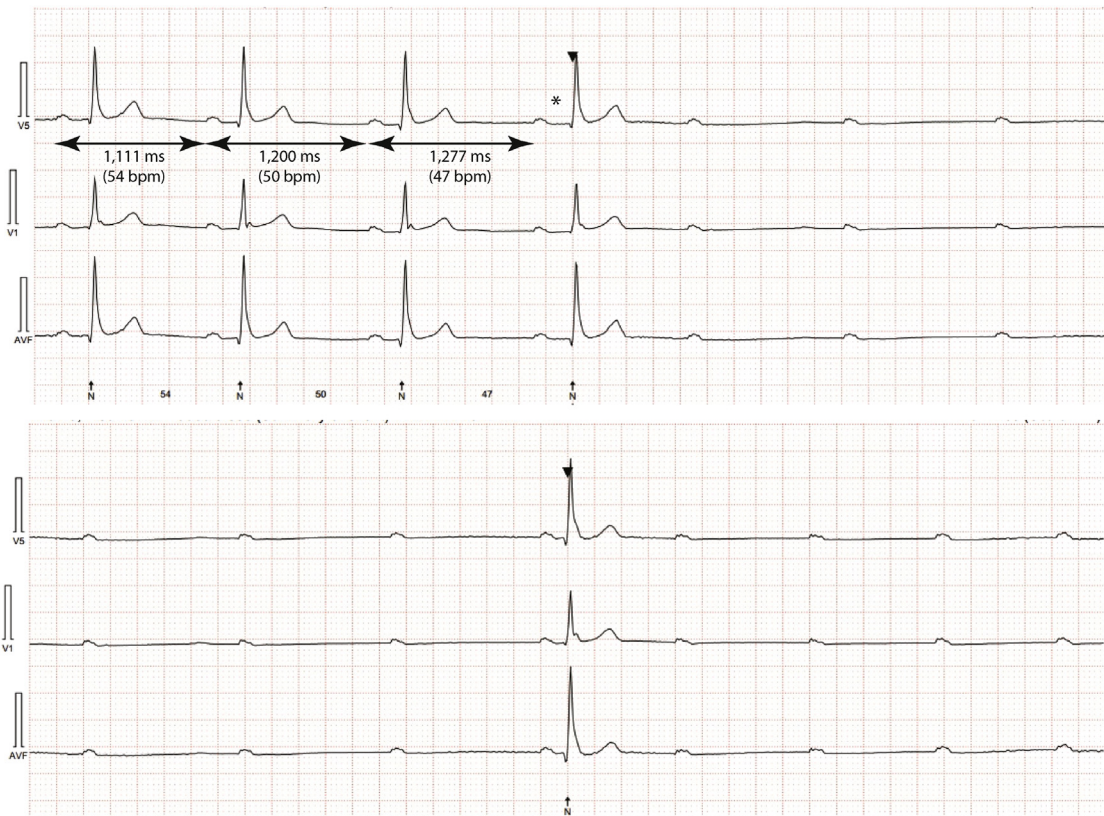


Figure 3 Rhythm strip during a period of advanced AV block. Advanced AV block is preceded by sinus node slowing, which provides evidence that the AV block is due to increased vagal tone. The last conducted PR interval before the advanced AV block (*) is prolonged compared to the preceding PR intervals.

intrinsic or extrinsic.¹ Intrinsic causes, diseases, or processes that directly affect or damage the AV node or His bundle include surgery or other cardiac procedures (eg, transcatheter aortic valve replacement), inflammation, infection, ischemia, or infiltrative diseases.² An important intrinsic cause of AV block is progressive cardiac conduction disease, traditionally referred to as Lev and Lenegre disease but now understood to have a genetic basis in some cases, with abnormalities identified in genes that encode for a number of different proteins (eg, ion channels, T-box transcription factors, protein kinases, bone morphogenetic protein, and many others).³ Extrinsic causes that can worsen AV conduction without direct damage include metabolic abnormalities such as hyperkalemia and hypokalemia, endocrine disorders such as hypothyroidism, or, as illustrated in this case, autonomic disturbances.

Hypervagotonia is an unusual cause for bradycardia that has been more commonly reported in younger patients, particularly athletes, and often in the setting of pain.⁴⁻⁶ Sinus node dysfunction manifested by sinus bradycardia and sinus pauses are the usual arrhythmias precipitated by hypervagotonia.⁴ Theophylline has been used for the treatment of hypervagotonia and in 1 study was 70% effective for eliminating symptoms associated with hypervagotonia, although permanent pacing was required in 1 patient with continued symptoms despite theophylline.⁴

Hyoscyamine is a naturally occurring alkaloid and plant toxin produced by plants in the Solanaceae family (eg, nightshade,

tomato, and potato), and is a levorotatory isomer of atropine with approximately 98% the strength of comparably dosed atropine.⁷ Hyoscyamine has an almost identical chemical structure to scopolamine and both are competitive nonselective muscarinic receptor antagonists. Prior clinical reports have described the use of hyoscyamine for treating lower abdominal and bladder disorders, particularly those that are associated with spasm, such as irritable bowel syndrome, diverticulitis, biliary colic, and interstitial cystitis.⁸ Hyoscyamine side effects are similar to other belladonna alkaloids and include diminished sweating, dizziness, blurred vision, mydriasis, gut immotility, palpitations, and tachycardia.^{7,8} Hyoscyamine is completely absorbable through oral routes and is available in sublingual and intravenous preparations for rapid onset of action, in oral elixir and pill forms, and as an extended-release oral pill. While the liver hydrolyzes the drug into tropic acid and tropine, the majority of the drug is excreted through the urine unchanged within 12 hours.⁷ The half-life of the oral compound is approximately 7 hours, and the recommended dose for the extended-release preparation is 0.375 mg twice daily, with a maximum dose of 1.5 mg daily regardless of preparation. In this patient, a lower dose was tried initially to evaluate the potential impact of hyoscyamine, and the standard recommended dose used for gastrointestinal and other problems was effective for treating the episodic AV block and relieving the patient's symptoms. Although permanent pacing is often recommended

and is effective for the treatment of many patients with advanced AV block, permanent pacing requires an indwelling device and can be associated with significant future morbidity owing to infection or lead and generator issues over a patient's lifetime.¹ This case report illustrates the potential use of hyoscyamine for the treatment of advanced AV block owing to hypervagotonia.

Conclusion

We describe a case of hypervagotonia causing advanced AV block that was treated effectively with hyoscyamine and obviated permanent pacemaker implant. Hyoscyamine is a particularly attractive treatment option for patients with hypervagotonia associated with a documented recurring stressor.

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