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CASE REPORT

A Pediatric Case of Cardiomyopathy Induced by Inappropriate Sinus Tachycardia: Efficacy of Ivabradine

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Abstract We report the case of a 16-year-old boy with cardiomyopathy induced by inappropriate sinus tachycardia (IST). The patient was resistant to treatment with conventional rate-decreasing medications. Therapy with the selective sinus node I_f current inhibitor ivabradine was started. After 3 months of ivabradine therapy, an improvement in ejection fraction and a successful decrease in heart rate were observed. No side effects occurred. We suggest that ivabradine, currently used to treat stable angina, could be considered as a second-line treatment in patients with symptomatic and refractory IST.

Keywords Inappropriate sinus tachycardia · Ivabradine · Tachycardiomyopathy

Introduction

Inappropriate sinus tachycardia (IST) is an uncommon rhythm disorder characterized by an exaggerated increase in heart rate (HR) $\geq$100 bpm at rest or on minimal exertion. P waves are usually similar or identical to sinus P waves.

The clinical presentation of IST is extremely variable and ranges from short episodes of palpitations associated with dyspnea, atypical precordial pain, fatigue, cephalalgia, and occasional syncope and presyncope to incapacitating incessant tachycardia. As reported in current international guidelines [1], diagnosis of IST is usually made by exclusion. In general, treatment for IST has been limited to beta-blockers, calcium-channel blockers, antiarrhythmic drugs, and, sometimes, radiofrequency ablation [2, 4]. It is well known that incessant or chronic tachycardia may cause a deterioration of cardiac function known as "tachycardiomyopathy," which is partially or completely reversible on normalization of HR [9]. We report the case of a pediatric patient with IST and low left-ventricular ejection fraction (LVEF) treated with ivabradine.

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Case Report

In February 2010, a 16-year-old boy was referred to our center for cardiomyopathy induced by IST. On examination in October 2009, the patient was asymptomatic, but resting electrocardiogram (ECG) showed IST (average HR 145 bpm), and transthoracic echocardiography showed left-ventricular dilatation with decreased LVEF (35% to 40%). Several traditional rate-reducing medications (atenolol, verapamil, diltiazem, amiodarone, digoxin) associated with angiotensin-converting enzyme inhibitors (enalapril) were ineffective in controlling HR and improving left-ventricular function. The patient first underwent pharmacological cardioversion with amiodarone and then electrical cardioversion, but both attempts were unsuccessful.

On admission, the patient was completely asymptomatic; ECG was unchanged, whereas transthoracic echocardiography showed a bulbous appearance of the left ventricle, global hypokinesia with decreased LVEF (34%), and no left-ventricular dilatation (left-ventricular end-diastolic diameter 52 mm). Medical treatment included

ramipril 2.5 mg twice daily, flecainide 100 mg thrice daily, amiodarone 200 mg twice daily, and carvedilol titrated up to 25 mg twice daily. After 3 days, 24-hour Holter recording showed persistent IST with an average HR of 112 bpm (range 78 to 128) (Fig. 1a). Secondary systemic causes (e.g., hyperthyroidism, pheochromocytoma) were excluded. The cause of left-ventricular dysfunction was not identified, and the diagnosis of IST was made by exclusion. After one week of therapy, however, resting ECG showed recurrent IST (HR 128 bpm) in the absence of symptoms (Fig. 2a); transthoracic echocardiographic findings were unchanged. Sinus node modification by catheter ablation was considered. Owing to the potential adverse effects of this option, before catheter ablation we decided to test as second-line treatment the selective sinus node I_f current inhibitor ivabradine at an initial dose of 2.5 mg orally twice daily and titrated up to 7.5 mg twice daily. Simultaneously, the administration of angiotensin-converting enzyme inhibitors, beta-blockers, amiodarone, and flecainide was progressively decreased.

After 3 months of ivabradine therapy, when the patient was on no other medications, resting ECG showed normal sinus rhythm (HR 80 bpm) (Fig. 2b), F2> and transthoracic ECG showed normal cardiac dimensions with an improved LVEF of 50%. A 24-h Holter ECG showed sinus rhythm with an average HR of 78 bpm (range 49 to 122) (Fig. 1b). No side effects were observed.

Discussion

IST is an uncommon arrhythmia, the diagnosis of which is usually made by exclusion [1]. Our patient showed persistent tachycardia with an average HR >100 bpm. P-wave morphology and endocardial activation were identical to sinus rhythm.

Recent reviews on tachycardia-induced cardiomyopathy never included IST as a potential cause of the disease [5, 8]. This unique type of cardiomyopathy, however, is considered to be rate-dependent in that cases with greater rates manifest earlier. In our patient, the high average HR (145 bpm) and the duration of the arrhythmia (4 months) could have been the major contributors to cardiac dysfunction.

One of the interesting features of our case was the unusual mode of presentation; in particular, the patient never experienced symptoms, and the age of presentation was younger than classically described (38 ± 12 years) [1]. A review of the literature shows an unusual case of IST with advanced age of presentation (a 67-year-old female patient) [11].

Although no randomized, double-blinded, placebo-controlled clinical trials exist, beta-blockers, nondihydropyridine calcium-channels blockers, and antiarrhythmic drugs are traditionally considered the first-line therapy in patients with IST. In our patient, beta-blockers, flecainide, and amiodarone were ineffective. Actually, patients with IST are often refractory or intolerant to conventional medical management. For this reason, some investigators have proposed sinus node modification by catheter ablation. Nevertheless, the long-term success rate of this difficult technique remains unclear, and serious adverse effects have been reported (phrenic nerve injury, need for permanent pacing, pericarditis) [6, 8]. Recent evidence suggests that ivabradine may be effective in patients with IST [3, 4, 7, 12] by preventing the side effects induced by traditional medications. Ivabradine is a selective inhibitor of the I_f current, an important contributor to sinus node automaticity. This drug induces a selective and dose-dependent HR decrease in HR without modifying atrioventricular or intraventricular conduction or contractility. As a result, it is a pure HR-decreasing agent in patients with sinus rhythm.

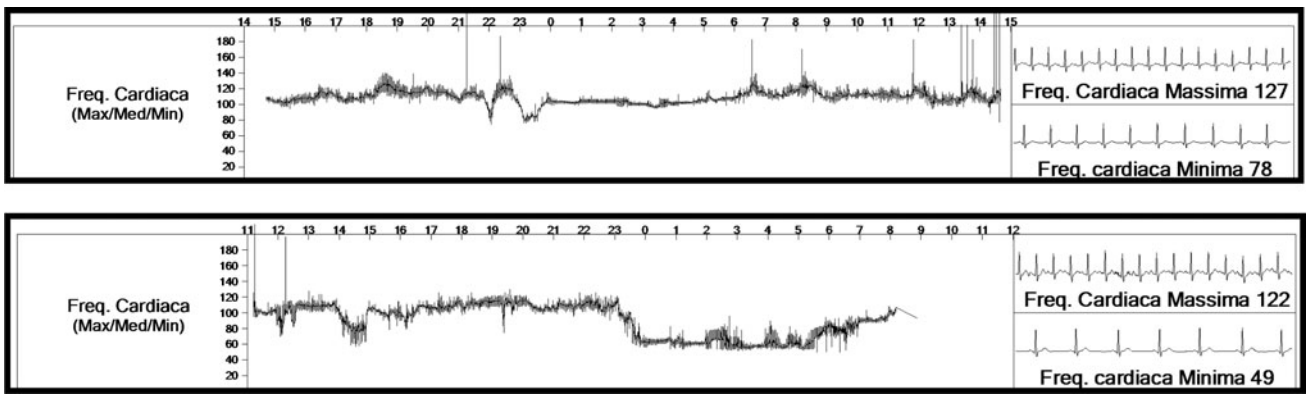

Fig. 1 **a** Results of 24-hour Holter ECG before ivabradine therapy. Daytime HR was ≥100 bpm (average HR 112 bpm). **b** Results of 24-h Holter ECG after 3 months of ivabradine therapy. The circadian slope was entirely shifted to values <100 bpm (average HR 78 bpm)

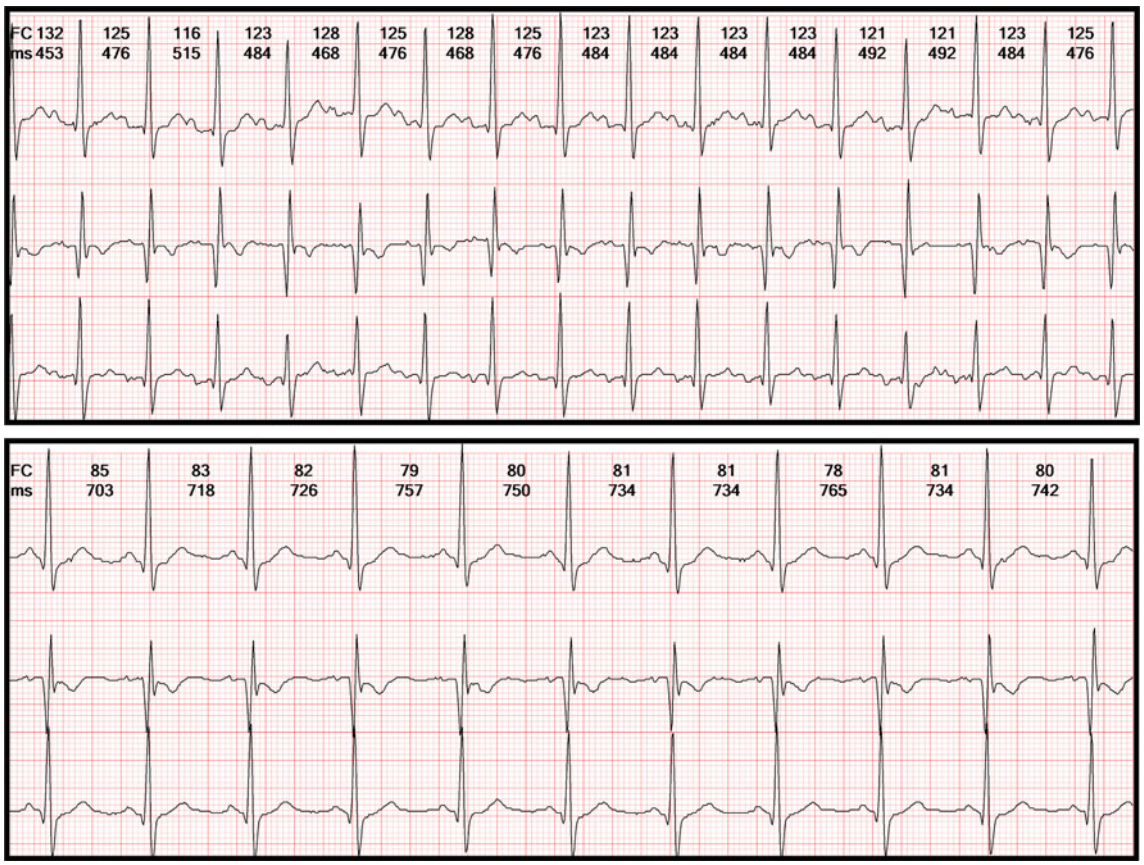

Fig. 2 **a** Resting ECG before ivabradine therapy showing sinus tachycardia (HR 125 bpm) and normal QRS. **b** Resting ECG after 3 months of ivabradine therapy showing normal sinus rhythm (HR 80 bpm)

HR decrease is associated with a significant improvement in cardiac function, symptoms, exercise capacity, and quality of life among patients with congestive heart failure. In our asymptomatic patient, who presented with IST and low LVEF, ivabradine therapy proved to be effective and safe, resulting in complete and stable HR normalization and functional recovery without the occurrence of adverse side effects.

In conclusion, in patients with an exaggerated increase in average HR, IST may favor the development of tachycardia-induced cardiomyopathy. In patients with IST resistant to traditional HR-lowering drugs, ivabradine could be considered as second-line therapy before catheter ablation. This could be particularly relevant for patients with functional cardiac repercussions. Previous experimental studies and some recent clinical trial have focused on the potential effects of ivabradine in congestive heart failure [8, 10]. In particular, in the SHIFT study, a randomized placebo-controlled study, the use of ivabradine in patients with hearth failure and systolic dysfunction, who were selected on the basis of having a baseline HR $\geq$70 bpm, significantly improved most cardiovascular primary end points.

Ivabradine is approved for use in chronic stable angina pectoris and heart failure in adults in Europe. The use of this medication is not approved in the United States. There are no trials of ivabradine in the pediatric age group.

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