Tachycardia-induced cardiomyopathy secondary to incessant ectopic atrial tachycardia in two infants: Potential new indication for early initiation of enteral ivabradine

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ABSTRACT

This report describes two cases of tachycardia-induced cardiomyopathy secondary to incessant ectopic atrial tachycardia (EAT) in an infant presenting with severe left ventricular dysfunction and hemodynamic instability. The two cases were managed differently. The first required mechanical ventilation and was resistant to conventional antiarrhythmic drugs. After the initiation of enteral ivabradine (0.15mg/kg) the heart rate slowed with significant improvement in hemodynamics, peripheral perfusion and sinus rhythm was restored after 12 hours. Ivabradine was continued and the patient was discharged home after 10 days of hospitalization. The second case was managed by early initiation of ivabradine and resulted in restoration of sinus rhythm within 4 hours, thus avoiding trials of conventional anti-arrhythmic drugs with unstable hemodynamic profile. The infant was discharged after 5 days of hospitalization on ivabradine.

Keywords: Ectopic atrial tachycardia, infant, ivabradine, tachycardia-induced cardiomyopathy

INTRODUCTION

Increased automaticity is the underlying mechanism of several pediatric tachyarrhythmias including EAT. Ivabradine is a selective inhibitor of the hyperpolarization-activated cyclic nucleotide-gated channels involved in the funny current responsible for spontaneous depolarization of cardiac pacemaker cells. By inhibition of the funny current and reduction of automaticity, ivabradine represents a potential therapy for these conditions with hemodynamically neutral profile in contrast to many of the conventional antiarrhythmic drugs. Ivabradine demonstrates use dependence, resulting in a greater effect at higher heart rates. Ivabradine has been utilized so far in the literature for treatment in children with heart failure, EAT, multifocal atrial tachycardia, congenital, and postoperative junctional ectopic tachycardias.[1-7] We report here, the utility of ivabradine in two hemodynamically unstable infants with tachycardia-induced cardiomyopathy secondary to EAT. The two were managed differently, with earlier utilisation of ivabradine in the second patient, having learned from the first patient.

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CASE REPORT

Case 1

A 60-day-old male weighing 5 kg was referred for cardiac evaluation in view of suspicion of dilated cardiomyopathy. Physical examination revealed tachycardia and tachypnea with decreased pulses and peripheral perfusion. Chest radiograph showed a cardiothoracic ratio of 70%. The 12-lead electrocardiogram (ECG) showed a regular narrow QRS tachycardia with a rapid ventricular rate of 250 bpm with a long RP interval and abnormal peaked P-wave morphology. Differential diagnosis of ectopic atrial tachycardia (EAT) and permanent junctional reciprocating tachycardia were considered. The *P* waves were negative in V1 and aVR and positive in leads II, III, and aVF suggestive of EAT of superolateral crista terminalis origin [Figure 1]. Echocardiography showed severe left ventricular (LV) dysfunction with an ejection fraction (EF) of 17% with significant LV dilatation (LVIDd 3.58 cm [Z score + 5.60]).The coronary artery origins and aortic arch were normal. Serum electrolytes and renal function were normal. Severe acute respiratory syndrome coronavirus 2 polymerase chain reaction was negative and antibodies levels were normal. All serum inflammatory/cardiac markers were normal (C-reactive protein, ferritin, troponin I, and CK MB). The NT pro-BNP level was grossly elevated (31,500 pg/ml [normal <125]). Adenosine given during the tachycardia resulted in transient slowing of the heart rate from 250 to 187 bpm followed by reappearance of the tachycardia [Figure 2a and b]. The tachycardia persisted despite giving three doses of bolus intravenous metoprolol and metoprolol infusion. The infant was hemodynamically unstable with poor perfusion, decreased urine output, and low blood pressure (mean 20 mmHg). Hence, synchronized cardioversion with 5J was given with no benefit. Intravenous digoxin 15 μg/kg given over 30 min resulted in decrease in heart rate (107 bpm) followed by severe bradycardia (65 bpm) and cardiac arrest. ECG during the time of bradycardia showed multiple *P* waves with periods of flat isoelectric line confirming EAT [Figure 2c]. After cardiopulmonary resuscitation (0.4 ml of 1 in 10,000 dilution adrenaline single dose) and mechanical ventilation, heart rate picked up and tachyarrhythmia persisted. Furosemide (1 mg/kg/day), milrinone (0.5 mcg/kg/min), and amiodarone infusion (25 mcg/kg/min for 4 h followed by 15 mcg/kg/min for 24 h) were started in view of severe LV dysfunction and persistent tachyarrhythmia. There was no improvement in the hemodynamics and tachycardia persisted even after continuous metoprolol and amiodarone infusion for 2 h. Hence, enteral sotalol (1 mg/kg) was started. Despite all the above pharmacological interventions for 10 h since admission, the tachyarrhythmia persisted and the mean blood pressure was persistently low with poor urine output. Repeat synchronized cardioversion with 5J resulted in conversion of the rhythm to ventricular fibrillation. Unsynchronized cardioversion 10J thrice resulted in termination of VF and the EAT restarted. The child remained with a poor urine output (<0.3 ml/kg/hr) and hypotension, with mean blood pressure <25 mmHg for >6 h.

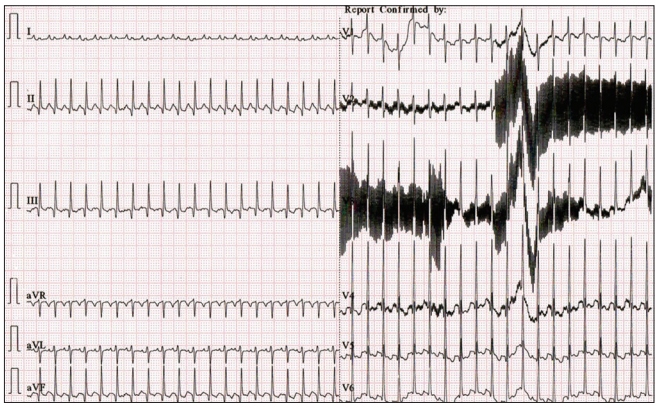

Figure 1: The 12-lead electrocardiogram showing a regular narrow QRS tachycardia with a rapid ventricular rate of 250 bpm with a long RP interval. The P waves were negative in V1 and aVR and positive in leads II, III, and aVF suggestive of ectopic atrial tachycardia of superolateral crista terminalis origin

Considering the hemodynamic instability and persistence of tachyarrhythmia despite using most of the conventional antiarrhythmic drugs, we administered enteral ivabradine. Within 45 min of the initiation of ivabradine (0.15 mg/kg), the heart rate slowed down to 190 bpm with significant improvement in the hemodynamics and perfusion (mean BP 40 mmHg). Metoprolol infusion was stopped and amiodarone infusion was continued for 24 h and then stopped. The heart rhythm became sinus after 12 h of enteral ivabradine and digoxin [Figure 3]. The LVEF improved from 17% to 33% after 24 h of ivabradine. The LVIDd started decreasing (LVIDd Z score + 4.26). He was extubated after 48 h of ventilation and put on high flow nasal cannula in view of respiratory distress and moderate LV dysfunction. He had one transient episode of tachyarrhythmia (250 bpm) which lasted for 2 min and terminated by itself. Hence, oral propranolol was added. Milrinone infusion was tapered and stopped with subsequent addition of enalapril. The LV function and LVIDd recovered completely (EF 58%; LVIDd 2 cm (Z score-0.22) after 7 days of achievement of sinus rhythm. The timeline of events which happened during the first 24 h was shown in Figure 4. He was discharged after 10 days of hospitalization on oral ivabradine (0.15 mg/kg twice a day), digoxin (5 μg/kg twice a day), and

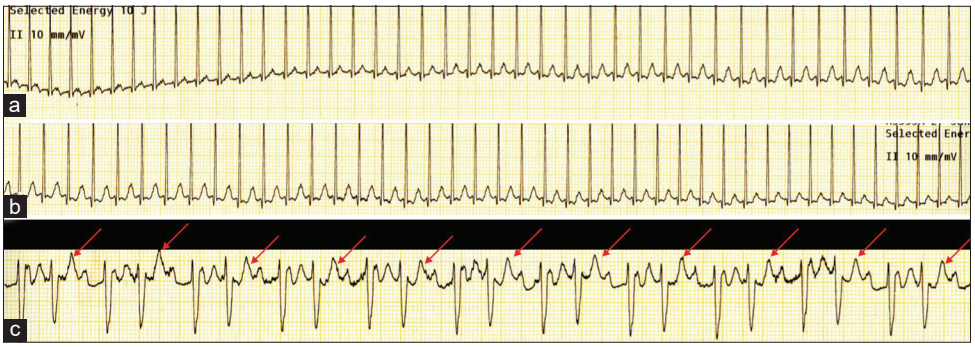

Figure 2: (a and b) Adenosine given during the tachycardia, resulting in transient slowing of the heart rate from 250 bpm to 187 bpm followed by reappearance of the tachycardia. (c) Electrocardiogram during the time of bradycardia following administration of intravenous digoxin showing multiple P waves with periods of flat isoelectric line confirming ectopic atrial tachycardia. (Ectopic P waves marked in red arrows)

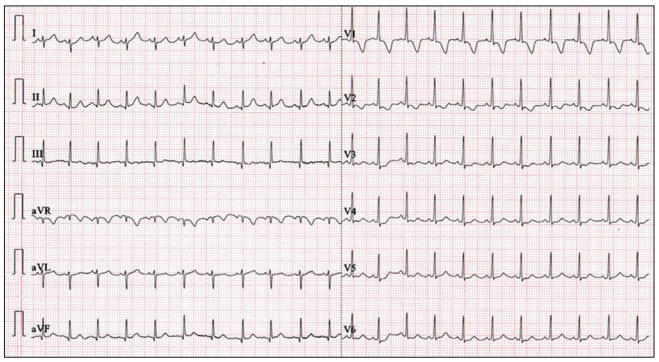

Figure 3: Electrocardiogram showing sinus rhythm

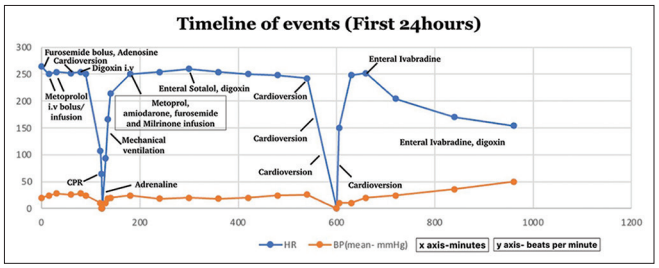

Figure 4: Timeline of events which happened during the 1st 24 h of management

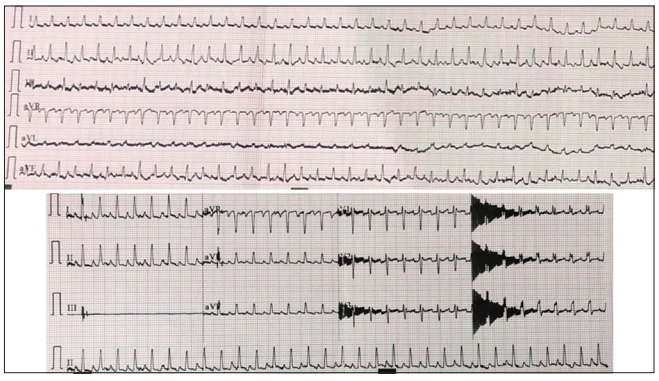

Figure 5: The 12-lead electrocardiogram (ECG) showing a regular narrow QRS tachycardia with a rapid ventricular rate of 187 bpm with long RP interval and abnormal peaked P wave morphology. The P waves were biphasic in V1 and positive in leads II, III and aVF suggestive of ectopic atrial tachycardia (EAT) of crista terminalis origin

propranolol (0.5 mg/kg twice a day). The efficacy of the treatment was monitored by patch ambulatory ECG (aECG) recorder for 7 days after discharge. The aECG recordings were predominant in sinus rhythm with short episodes of ectopic atrial rhythm. The average heart rate was 132 bpm (58–163). At follow-up after 3 months, ECG was in sinus rhythm and the LV function (EF 70%) is normal. The developmental milestones are appropriate for the age.

Case 2

A 30 day old boy weighing 3 kg was referred to our pediatric intensive care unit in view of significant respiratory distress and cardiogenic shock. Physical examination revealed tachycardia (200bpm), and tachypnoea with decreased pulses and poor peripheral perfusion. Blood gas showed severe metabolic acidosis (pH 6.9; HCO3 3.6 mol/L; PCO2 15mmHg). The baby was resuscitated with intravenous fluid and sodium bicarbonate correction. The 12-lead electrocardiogram (ECG) showed a regular narrow QRS tachycardia with a rapid ventricular rate of 187 bpm with long RP interval and abnormal peaked P wave morphology. The P waves were biphasic in V1 and positive in leads II, III and aVF suggestive of EAT [Figure 5]. Chest radiograph showed a cardiothoracic ratio of 75%. Echocardiography showed severe left ventricular (LV) dysfunction [ejection fraction (EF) 19%] with significant LV dilatation [LVIDd 2.5cm (Z score +3.18)]. SARS-CoV-2 PCR was negative and antibodies levels were normal. Adenosine given during the tachycardia, resulted in transient termination of the tachyarrhythmia followed by reappearance [Figure 6]. Enteral ivabradine (0.15mg/kg) was given resulting in gradual reduction of heart rate one hour after initiation and the rhythm became sinus after 4 hours. Enteral digoxin (10mcg/kg/day) was added one hour after ivabradine. There was significant improvement in the hemodynamics and perfusion (mean BP 25 mmHg). Blood gas after stabilization revealed improvement in the metabolic acidosis (pH 7.49; HCO3 16.6 mol/L; PCO2 22mmHg).

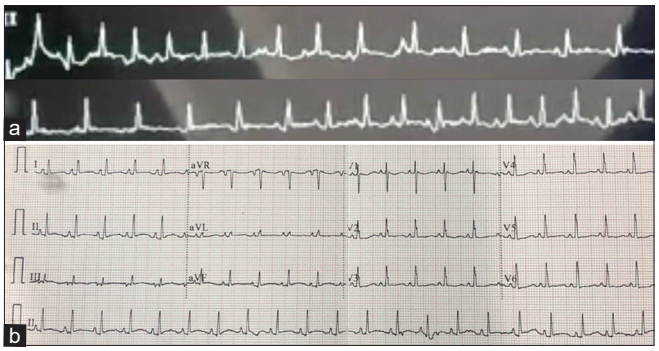

Figure 6: (a) Adenosine given during the tachycardia, showing transient termination of the tachyarrhythmia followed by reappearance. (b) ECG showing sinus rhythm after initiation of ivabradine

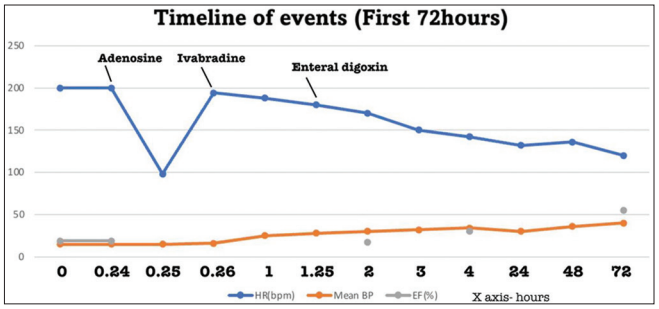

Figure 7: Timeline of events which happened during the first 72 hours of management in case 2

However the respiratory distress and LV dysfunction persisted. Supportive care including bubble continuous positive airway pressure, milrinone and furosemide infusion were provided for the LV dysfunction. He symptomatically improved with supportive care and it was weaned off after 24 hours. LV dimension [LVIDd 1.6cm (Z score -1.29)] and function (EF 55%) improved significantly after 72 hours. He was discharged after 5 days of hospitalization on oral ivabradine (0.15mg/kg twice a day), and digoxin (5mcg/kg twice a day). The timeline of events which happened during the first 72 hours is shown in the Figure 7.

DISCUSSION

EAT can be defined as a supraventricular tachycardia initiated and sustained by an automatic nonsinus atrial pacemaker, characterized by distinctly visible *P* waves with an abnormal frontal plane axis and atrial activation sequence.[8] EAT has a variable response to adenosine and may produce transient rate slowing, which is thought to be secondary to the antiadrenergic effect of adenosine. Adenosine A1 receptors are located on the SA node, AV node, and atrial myocytes. Activation of A1 receptor hyperpolarizes the cells of the SA node to give sinus slowing or arrest and on the AV node to give a transient heart block. Tachycardias originating in the atrium such as EAT do not rely on the SA or AV node and thus are not typically terminated by adenosine, although the transient AV block may help elucidate the tachycardia mechanism by allowing examination of the atrial electrical activity.[9] It can be resistant to conventional antiarrhythmic drugs and lead to tachycardia-induced cardiomyopathy (TCM). The incidence of TCM secondary to EAT was 22.6% in children.[10] Independent factors associated with a good response to pharmacological therapy include a younger age at presentation and nonincessant tachycardia. Children <3 years of age respond well to antiarrhythmic therapy and have a high incidence of spontaneous resolution of EAT and thus warrant a trial of antiarrhythmic therapy.[11,12] Pharmacological treatment is a safe and effective treatment strategy for infants with TCM which may avoid unnecessary ablation or at least postpone it till the procedure would be safer.[13] However, in medically resistant cases, radiofrequency catheter ablation in infants and small children is a promising alternative.[14] Ablation is successful in all ages. EAT recurrence was less common with electronanatomic mapping compared to conventional mapping techniques.[12]

From a clinical point of view, children with TCM will have features similar to dilated cardiomyopathy but with better prognosis with significant improvement of LV function after rhythm or rate control. It is characterized by significant changes in cardiomyocyte and mitochondrial morphology with reduced myocardial fibrosis and T cells when compared to dilated and ischemic cardiomyopathy. Internal organization of mitochondria and their distribution within the cardiomyocytes is critical for optimal production and distribution of ATP. In tachyarrhythmia, there is increased ATP demand resulting in suboptimal mitochondrial function leading to decreased myocardial contractility. Enrichment of mitochondria at intercalated discs was observed in the endomyocardial biopsy samples of TCM patients. These findings suggest that rate control or restoration of sinus rhythm will result in significant recovery of the LV function in children with TCM.[15] Factors associated with faster recovery include younger age, higher presenting heart rate, use of mechanical circulatory support, and higher LVEF.[16]

Our first case was refractory to most of the conventional antiarrhythmic drugs. Considering the age, hemodynamic instability, and unavailability of electrophysiology laboratory, we started oral ivabradine based on the literature, and this was associated with a good response.[2-4] While conversion to sinus due to a delayed effect of amiodarone cannot be completely excluded, this is unlikely as sustained sinus rhythm was achieved with ivabradine despite stopping amiodarone. This was again evident on the second case where early initiation of ivabradine resulted in early achievement of sinus rhythm.

Ivabradine is a specific inhibitor of HCN channels and a pure heart rate lowering agent. It has no effect on

action potential duration, intraventricular conduction, myocardial contraction, and relaxation at therapeutic levels. It inhibits both HCN4 and HCN1 isoforms in the human heart. It exhibits use dependence with greater effects at faster heart rates. Ivabradine is an established therapy for heart failure, junctional ectopic tachycardia, inappropriate sinus tachycardia and stable angina pectoris.[17] Ivabradine is effective in a subset of patients with incessant EAT originating in the atrial appendages than other atrial sites. Failure of complete atrialization of the sinus venosus might result in focal automaticity at ectopic atrial sites. Persistence of original embryonic cells with abnormal automaticity in the atrial appendages might be responsible for incessant EAT.[16]

In the first case apart from intravenous digoxin, enteral ivabradine was the only drug which reduced the heart rate without compromising the hemodynamics (which occurred with intravenous digoxin). Since ivabradine has a hemodynamically neutral profile when compared to many of the conventional antiarrhythmic drugs, it can be initiated early in the management plan in hemodynamically compromised patients due to severe LV dysfunction. This might have avoided unnecessary cardioversion and initiation of antiarrhythmic drugs with unstable hemodynamic profile and this was especially evident in the second case.[16,18] A recent report showed that enteral ivabradine was effective in an infant with multifocal atrial tachycardia with severe ventricular dysfunction requiring mechanical support.[7] Thus, early initiation of ivabradine in automatic tachyarrhythmias with severe LV dysfunction and unstable hemodynamics may avoid unnecessary cardioversion, invasive procedures, and initiation of antiarrhythmic drugs with unstable hemodynamic profile. The positive response to ivabradine potentially implicates the funny current in the pathogenesis of EAT.[16]

CONCLUSIONS

This case highlights the potential new role of ivabradine in hemodynamically compromised children with EAT. Further prospective studies are warranted to prove the benefit of early initiation of ivabradine in hemodynamically compromised infants.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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