The Use of Ivabradine in a Patient with Idiopathic Ventricular Arrhythmia Originating from the Left Ventricular Summit

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July 9, 2020

Abstract

Idiopathic ventricular arrhythmias (VA) are common and treatment options include anti-arrhythmic drugs (AAD) or catheter ablation. Patients presenting with idiopathic VA which is originating from the left ventricular summit (LVS) poses a particular challenge as the success for catheter ablation is low and AAD's may not be used long-term due to side effects. Ivabradine is an inhibitor of funny current (If) in cardiac pacemaker cells by blocking hyperpolarization-activated cyclic nucleotide-gated (HCN) and recommended for the treatment of heart failure with reduced ejection fraction and stable coronary artery disease. Recently, several cases described patients with atrial and junctional ectopic tachycardias who were successfully treated with ivabradine. In the present case, we reported the use of ivabradine in the treatment of idiopathic VA which was originated from the LVS and was resistant to multiple AAD's and catheter ablation.

Introduction

Idiopathic ventricular arrhythmias (VA) are frequently encountered in arrhythmia clinics and treatment options include anti-arrhythmic drugs (AAD) and catheter ablation. Limited efficacy and potential side effects restrict the long-term use of AAD's. On the other hand, catheter ablation is effective with relatively low complications rates and recommended as the first-line therapy by current guidelines[1]. However, despite the technologic advances in mapping techniques and ablation tools, catheter ablation fails to suppress VA in some patients. In this regard, VA's originating from the left ventricular summit (LVS) pose a particular challenge in the laboratory and are associated with lower procedural and long-term success rate due to its proximity to the bifurcation of left main coronary artery (LMCA), anatomical difficulties for advancing catheters and the necessity of epicardial approach in high proportion of cases.

Ivabradine is an inhibitor of funny current (I_f) in cardiac pacemaker cells by binding to hyperpolarization-activated cyclic nucleotide-gated (HCN) channels[2]. Ivabradine is currently indicated in the treatment of heart failure and stable coronary artery disease after being tested in large randomized clinical trials[3,4]. In addition, it is frequently used for treating patients with inappropriate sinus tachycardia and postural orthostatic tachycardia syndrome[5].

Previous case reports suggested promising role of ivabradin in the in pediatric population for treating junctional and atrial ectopic tachycardias in which increased automaticity were considered as the primary underlying mechanism[6-8]. Ivabradine offers a plausible treatment choice by effectively inhibiting I_f current and having relatively better safety profile compared to other anti-arrhythmic drugs (AAD) and catheter ablation.

Here we reported the use of ivabradine in the treatment of idiopathic VA which was originated from the LVS and resistant to multiple AAD's and catheter ablation.

Case Report

Eighteen years old female presented to our arrhythmia outpatient clinic with palpitation for past 12 months. Her symptoms were milder before but worsened during last weeks. She has been diagnosed with frequent premature ventricular contractions (PVC) and treated before with oral beta-blocker, isoptin, flecainide and amiodarone. The patient was referred to our center for catheter ablation after observing no improvement in her symptoms and failing in the suppression of PVC's.

Her medical and family history was unremarkable. Lab tests revealed normal complete blood count, cardiac troponins, biochemistry and thyroid hormone panel. 12-lead standard electrocardiography (ECG) revealed sinus rhythm with ventricular bigeminy **(Figure 1A)**. PVC's had inferior axis with R wave larger in DIII compared to DII, early precordial transition at V3 and slurring in the initial segment of the QRS which were suggestive of LVS and epicardial origin[9]. Transthoracic echocardiography (TTE) demonstrated normal left and right ventricular functions and no signs of any structural heart disease. Holter recording was performed for quantifying the burden of PVC's and revealed 96000 PVC's over 72 hours **(Figure 2A).** The patient was planned to undergo catheter ablation with 3D mapping system (EnSite Precision, Abbott, MN, USA). The mapping and ablation was performed by using 3.5-mm tip irrigated catheter. First, septal side of the right ventricular outflow tract (RVOT) region was mapped. No early ventricular signal could be recorded from these regions. We then assessed the coronary cusps and the left ventricle (LV) endocardial region below the left coronary cusp. However, we could not find early ventricular electrograms to proceed with ablation. Lastly, great cardiac vein (GCV)/anterior interventricular vein was mapped **(Figure 3).** An area with 26 ms pre-QRS signal (-26 ms) was found and pace mapping showed satisfactory match. Ablation was performed to this area after demonstrating more than 5 mm distance from coronary arteries. The power was set to 30 W with a maximum temperature 45 C° and aiming for a minimum 10 Ω drop in impedance. The power was titrated with 5 W up to 50 W in case impedance did not drop at least 5 Ω within the first 10 seconds. Although PVC's were transiently suppressed, they ensued following the cessation of the ablation. The procedure was ended after failing to achieve the suppression of PVC's.

In the morning after the procedure that patient was still complaining of palpitations and her ECG showed frequent PVC's. After considering various medications that were used by the patient previously, we started ivabradine 5 mg BID after counseling with the patient about the potential side effects of the drug. Two days later her complains improved significantly, the mean heart rate was 84 bpm and no side effects were observed. The dose was increased to 7.5 mg BID and the patient was discharged from the hospital with a planned outpatient clinical visit a week later. In the clinical visit she reported no palpitations, her ECG showed normal sinus rhythm with a mean heart rate 79 bpm **(Figure 1B)** and no PVC's. Seventy-two hour Holter recording demonstrated 12000 PVC's burden **(Figure 2B),** which was significantly lower compared to the one that was recorded prior to ivabradine treatment. Considering patient was asymptomatic, we did not increase the ivabradine dose to 10 mg BID for further suppressing PVC's. Serial clinical visits were planned for the evaluation of PVC burden and LV functions.

Discussion

The LV summit is a triangular region located at the most superior aspect of LV ostium. The apex of the triangle is bounded by the bifurcation of left anterior descending (LAD) and left circumflex (LCX) arteries and its base is formed by the arch between the first septal perforator of the LAD and LCX. The region is transected laterally by the great cardiac vein (GCV) at its junction with anterior interventicular vein (AIV) giving rise to two separate regions; a medial and more superior area which is inaccessible to catheter ablation and a lateral and more inferior area which is more easily accessible with ablation catheters. Arrhythmias that are originated from the LVS constitute approximately 14.5% of LV VA's[10]. Success rates of catheter ablation directing LVS VA's are lower compared to other outflow VA's due to inability to advance catheters to the site of interest, proximity to coronary arteries and high probability of epicardial site of origin[9].

Frequent PVC's are a well known risk factor for the development of cardiomyopathy in the absence of structural heart disease[11]. Although the time interval between the first diagnosis of PVC's and the occurrence of LV dysfunction has a wide range, several variables were proposed as the predictor of PVC induced cardiomyopathy including high PVC burden, male gender, epicardial origin, wide QRS and short coupling

interval[12]. LV dysfunction was not present in our patient but high PVC burden with LV epicardial origin and wide QRS increased the risk of developing PVC cardiomyopathy. Thus, suppressing PVC's not only provided symptom relief but also mitigated the risk of subsequent LV dysfunction. 72 hour Holter monitoring that was performed a week after the ivabradine treatment revealed 12000 PVC's. We did not increase the dose of ivabradine to 10 mg BID because the patient was asymptomatic. Serial clinical visits were planned for the further evaluation of PVC burden and LV functions. Frequent PVC's can be observed during the course of several cardiac conditions including sarcoidosis, arrhythmogenic right ventricular dysplasia (ARVD) and myocarditis. Absence of structural abnormalities in TTE, normal cardiac troponins and QRS configuration that was atypical for ARVD in our patient made these diagnoses less likely. We do not have cardiac magnetic resonance imaging (cMRI) in our hospital, which could be performed for the differential diagnosis.

Ivabradine binds to cytoplasmic side of the HCN channel and inhibits I_f current in cardiac pacemaker cells. Ivabradine blocks these channels only when they are in open state causing use dependent action explaining its greater effectiveness in higher heart rates[13]. HCN channels are of 4 isomers (HCN 1-4) and among them HCN 4 and HCN 3 are predominant through the sinoatrial and atrioventricular (AV) node respectively[14]. HCN 2 isoform is abundant in infant ventricular myocardium but its expression is much weaker in adult and healthy myocardium[15]. Their expression in ventricular myocardium can increase in certain conditions such as ventricular hypertrophy and dilated cardiomyopathy[16]. In addition, different isoforms are found in atrial appendages and pulmonary veins[17].

Previous reports demonstrated that ivabradine reduced the heart rate without negative inotropic effects in patients who are in sinus rhythm and atrial fibrillation by decreasing I_f current in the sinus node and AV node respectively[18]. In several cases and observational studies ivabradine was used successfully for treating patients with junctional and atrial tachycardias[6,7]. In their prospective single center study Banavalikar et al evaluated ivabradine treatment in patients with incessant focal atrial tachycardia and without structural heart disease[19]. Conversion to sinus rhythm was achieved in 17 out of 28 patients approximately 4 hours after ivabradine administration. All patients underwent subsequent electrophysiological (EP) study independent of their response to the treatment, which demonstrated that atrial tachycardias originating from the left and right atria appendage were more likely to convert to sinus rhythm. In a more recent report ivabradine was shown to successfully suppressed ventricular arrhythmias in a patient with catecholaminergic polymorphic ventricular tachycardia who was resistant to other AAD's or could not continue using them due to serious side effects[20]. In a patient with non-ischemic dilated cardiomyopathy ivabradine effectively suppressed PVC's that were resistant to beta blockers and optimized the response to cardiac resynchronization therapy by increasing the rate biventricular pacing[21].

Ivabradine has good safety profile with neutral effect on hemodynamics unlike other AAD's, which makes it an attractive option particularly in the context of tachycardia induced cardiomyopathy where most of AAD's are contraindicated. Although ivabradine can lead to QT interval prolongation by causing bradycardia and hERG inhibition, it is much less frequently observed compared to other AAD's[22].

Precise mechanisms underlying the efficacy of ivabradine in the treatment of tachycardias originating from areas other than sinus node and caused by increased automaticity is yet to be elucidated. One possible mechanism is that increased expression of HCN channels in ventricular myocytes may predispose to enhanced automaticity. Elevated β-adrenergic stimulus may increase the susceptibility of myocytes to early after-depolarization and spontaneous action potential through increased cAMP production, which can be prevented by ivabradine. However, it is not certain that which conditions trigger re-expression of genes that are responsible for coding HCN channels. Another potential explanation is that ivabradine may prevent triggered activity mediated arrhythmias by prolonging ventricular repolarization through its inhibitory effects on hERG/I_{Kr} channels. In their in vivo rat model, Mackiewicz et al. studied the effect of ivabradine on VA within 24 h after non-reperfused myocardial infarction[23]. They found that VA incidence and arrhythmic mortality were lower in rats that were administered ivabradine. This finding was further supported by that ivabradine partially prevented the increase in calcium sensitivity of ryanodine receptors and I_f current in the LV, HCN 4 up-regulation and heterogeneity in action potential duration between the remote LV wall and

infarct border zone, which all were observed within 24 h after myocardial infarction and were considered as major pro-arrhythmic mechanisms caused by ischemia.

In conclusion, with its acceptable safety profile ivabradine may be used in case other AAD's and catheter ablation fails to suppress idiopathic VA's. However, there are several issues to be addressed before recommending ivabradine in this context: i) What drives the increased expression of HCN in myocytes other pacemaker cells and how is it regulated? ii) What are the reasons for heterogeneity in clinical response to ivabradine among patients with cardiac arrhythmias? iii) Which isoforms of HCN channels in particular are contributory in the pathogenesis of specific arrhythmias and finally, iv) Randomized clinical trials are needed to better identify specific patient population that would benefit most from ivabradine and to determine optimal dosing strategies.

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Legends for Figures

Figure 1A: 12-Lead surface ECG recording of the patient prior to ivabradine treatment.

1B: 12-Lead surface ECG recording of the patient after ivabradine treatment.

ECG: Electrocardiography.

Figure 2A: 72-Hour Holter recording of the patient prior to ivabradine treatment.

2B: 72-Hour Holter recording of the patient after ivabradine treatment.

Figure 3: Top panel: Activation mapping in the 3-D system showing the site of the earliest activation in the distal GCV. **Bottom panel:** Local EGM's at the ablation catheter shows early signals (-26 ms) relative to the surface ECG QRS recordings.

3-D: Three dimensional, ECG: Electrocardiography, EGM: Electrogram, GCV: Great cardiac vein.