Case Report

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Efficacy of ranolazine in a patient with idiopathic dilated cardiomyopathy and electrical storm

Enrico Vizzardi[1,*], Antonio D'Aloia[1], Francesca Salghetti[1], Obaid Aljassim[2], Abdallah Raweh[3], Ivano Bonadei[1], Luca Bontempi[1], Antonio Curnis[1]

[1] *Cardiovascular Disease Section, Department of Applied Experimental Medicine, University of Brescia, Brescia, Italy;*
[2] *Dubai Hospital, Dubai, United Arab Emirates;*
[3] *IRCCS Policlinico San Donato, San Donato Milanese, Italy.*

ABSTRACT: A case of idiopathic dilated cardiomyopathy with an arrhythmic storm refractory to the usual antiarrhythmic therapy will be reported. The idiopathic structural heart disease of the patient is a vulnerable anatomic substrate in itself, for electrical instability and reentry mechanism, because of heterogeneous areas of scarred myocardium and low left ventricle ejection fraction. In this case, the ranolazine administration was safe and effective for the prevention of further electrical storms.

Keywords: Idiopathic dilated cardiomyopathy, electrical storm, anti-arrhythmic drugs refractoriness, ranolazine

1. Introduction

The term electrical storm (ES) describes a state of electrical instability of the heart characterized by a series of malignant ventricular arrhythmias in a short period of time (*1*). The most accepted definition is "Three or more distinct episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF) in 24 h, requiring the intervention of the defibrillator (anti-tachycardia pacing (ATP) or shock)" (*1,2*). According to the above-mentioned definition, the reported incidence of ES changes according to the studied populations: the incidence ranges from 10% to 28%, in those studies in which implantable cardioverter defibrillator (ICD) implantation is carried out for secondary prevention (*1*), but it is substantially lower − about 4% in the MADIT II study (*3*), which concerned primary prevention.

Electrical storm is, therefore, an increasingly common and life-threatening syndrome (*2*): the rapid succession of ventricular arrhythmias and multiple ICD shocks lead to increased mortality immediately after the event (*1*). Both arrhythmic events and repeated shocks can cause inflammation, remodelling, myocardial damage, left ventricular systolic dysfunction, progression of heart failure (*2*), and even anxiety, depression, and post-traumatic stress syndrome (*2*). Electrical storm is a very challenging clinical event and it is difficult to manage and to prevent.

At the moment amiodarone, sotalol, and β-blockers are the mainstay of therapy for the prevention of ventricular arrhythmias and electrical storm (*2,4*). Although they are usually effective, some patients are drug refractory, that means they have recurrent episodes of myocardial electrical instability, despite amiodarone and β-blockers combined (*2*). In addition, long-term amiodarone therapy is responsible for substantial side-effects (pulmonary fibrosis, hypothyroidism, liver toxicity, and corneal deposits) (*2*). Unfortunately no other antiarrhythmic drugs are currently available and efficacious to reduce the incidence of an electrical storm.

2. Case report

We describe the case of a 75 years old man, affected by idiopathic dilated cardiomyopathy and severe left ventricular systolic dysfunction (LVEF 30%), who received an ICD implantation for primary prevention in March 2010. The patient regularly carries out periodic outpatient controls at our Electrophysiology Center, to assess any tachi-arrhythmic episodes and the functional status of the device. In addition a remote monitoring system follows the device day by day.

From November 2011 to January 2012, an electrical storm and recurrent episodes of monomorphic VT have been reported (Figure 1). In particular, the electrical storm consisted of two subsequent fast monomorphic VT beating at a heart rate of 220 beats per minute (bpm), each sustained for 1 min and 40 sec and interrupted by two ICD interventions, followed by a slower VT (170

**Address correspondence to:*
Dr. Enrico Vizzardi, Cardiovascular Disease Section, Department of Applied Experimental Medicine, University of Brescia, Piazzale Spedali Civili 1, 25100 Brescia, Italy.
E-mail: enrico.vizzardi@tin.it

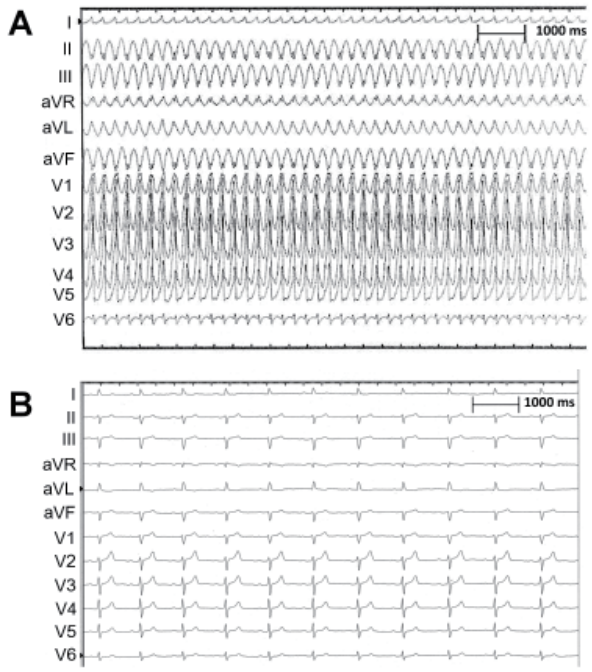

Figure 1. Twelve lead-electrocardiogram. (A) Monomorphic fast ventricular tachicardia (hear rate: 220 bpm); **(B)** Restoration of sinus rhythm after ICD-DC shock at 41 Joule.

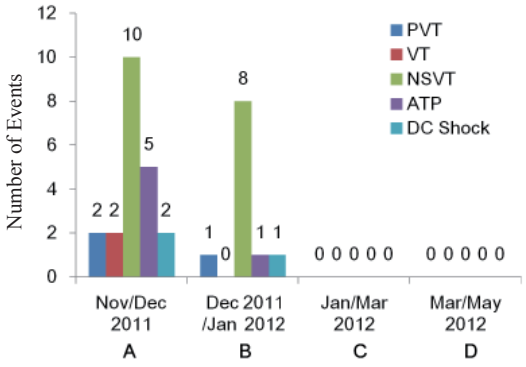

Figure 2. Diagram illustrating the relation between the ventricular events and drugs over time. Treatment regimens: **(A)** carvedilol 50 mg, amiodarone 200 mg, and ramipril 5 mg per day; **(B)** bisoprolol 10 mg, amiodarone 200 mg, flecainide 100 mg, and ramipril 5 mg per day; **(C)** bisoprolol 10 mg, amiodarone 200 mg, ranolazine 375 mg × 2, and ramipril 5 mg per day; **(D)** bisoprolol 10 mg, amiodarone 200 mg, ranolazine 375 mg × 2, and ramipril 5 mg per day. FVT, fast ventricular tachycardia; VT, ventricular tachycardia; NSVT, non-sustained ventricular tachycardia; ATP, anti-tachycardia pacing; DC shock, direct current shock.

bpm), ended by means of an ATP run. In that occasion the patients fainted, he was brought to the emergency room and then admitted to the cardiac Intensive Care Unit.

The most common triggers and risk factors of ventricular arrhythmias (acute myocardial infarction, worsening heart failure, electrolyte imbalance, chronic renal failure, hyperthyroidism, infections and fever, inherited arrhythmic syndromes) (*2*) were promptly excluded. Intracardiac electrocardiograms, that were recorded during the episodes, demonstrated that a premature ventricular complex, in the presence of an established heart disease, was the trigger.

Consequently, it was immediately decided to maximize the heart failure therapy, for the prevention of consequent ventricular arrhythmias. So, the patient was first treated with carvedilol 50 mg/die, amiodarone 200 mg/die 7 days/week, ramipril 5 mg/die, furosemide, and canrenoate potassium. Flecainide was added (100 mg/die) too, because of a single episode of atrial fibrillation with very high ventricular response, then degenerated in VF. Soon after, carvedilol was replaced by bisoprolol 10 mg/die and flecainide was suspended because of inefficacy. Despite the maximized antiarrhythmic therapy, the patient was drug refractory and still suffered from ventricular tachycardias' episodes. Therefore, considering the optimized heart failure therapy and the patient's clinical stability (NYHA I-II), ranolazine (375 mg tablets, twice daily) was introduced into the therapeutic scheme: it had been administered off label, as an antiarrhythmic agent (Figure 2). From January 2012 to May 2012, only few ventricular extrasystoles have been reported (neither ICD interventions nor FVT/VF) and the patient refers to feel well.

3. Discussion

Electrical storm is an increasingly common and life-threatening syndrome and a very challenging clinical event and it is difficult to manage and to prevent. Unfortunately, few antiarrhythmic drugs are currently available.

Ranolazine is an antianginal drug that inhibits a number of ion currents that are important in the genesis of the transmembrane cardiac action potential. It was initially developed as an antianginal agent, but it was found to additionally exert antiarrhythmic actions (*5*).

In the ventricles, ranolazine inhibits the late phase of inward sodium current (late INa), an expected effect to shorten action potential duration, and it reduces the rapidly activating delayed rectifier potassium current (IKr), an expected effect to lengthen action potential duration. In atria, in addition to blocking late INa and IKr, ranolazine inhibits the early or peak sodium channel current (peak INa) (*6*). It also has some effects on other currents, such as ICaL, INa-Ca, IKs. Based on its effects on these channels, some authors have proposed ranolazine as an antiarrhythmic agent (*5*).

In the ventricles, ranolazine effectively suppresses arrhythmogenesis associated with the reduced depolarization reserve caused by an increased late Ina, reduced IKr, or a combination of both (*6*). The group of Antzelevich *et al*. first pointed out the effect of ranolazine to suppress early after depolarizations (EADs) and delayed after depolarizations (DADs) (*6*). These observations first suggested an alleged role of ranolazine in preventing arrhythmias. In isolated perfused hearts of guinea pig and rabbit, ranolazine

has been shown to suppress EADs and VT induced by drugs that block IKr (*7*). Dhalla *et al*. observed that ranolazine reduced ventricular arrhythmias (such as ventricular premature beats, VT and VF) induced by ischemia and ischemia/reperfusion in an anesthetized rat model with transient (5 min) ligation of the left coronary artery, followed by reperfusion: in particular, ranolazine significantly reduced the incidence of ventricular fibrillation (67% in controls *vs*. 42% ($p = 0.414$), 30% ($p = 0.198$), and 8% ($p = 0.0094$) in ranolazine at 2, 4, and 8 μM respectively) (*8*). Similar results were obtained recently by Kloner *et al*. (*9*): they have for the first time compared ranolazine with other antiarrhythmic agents, like sotalol and lidocaine, as therapeutic doses, in an ischemia/reperfusion model. They observed that ranolazine was effective as much as sotalol or lidocaine in reducing reperfusion-induced ventricular arrhythmias: in fact, the incidence of ventricular arrhythmias in the sotalol, lidocaine, ranolazine, and control groups was 7/20, 10/20, 9/20, and 16/20, respectively.

In conclusion we describe a case of idiopathic dilated cardiomyopathy with an arrhythmic storm refractory to the usual antiarrhythmic therapy. Ranolazine, in association with carvedilol and amiodarone, suppresses arrhythmogenesis in this patient.

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