Time-dependent responses to provocative testing with flecainide in the diagnosis of Brugada syndrome

David Calvo, MD, PhD,[*] José M. Rubín, MD, PhD,[*] Diego Pérez, MD,[*] Juan Gómez, PhD,[†‡] Juan Pablo Flórez, MD,[*] Pablo Avanzas, MD, PhD,[§] José Manuel García-Ruíz, MD,[§] Jesús María de la Hera, MD, PhD,[‡] Julián Reguero, MD, PhD,[§] Eliecer Coto, MD, PhD,[†‡] César Morís, MD, PhD[§]

From the [*]Arrhythmia Unit, Cardiology Department, [†]Department of Molecular Genetics, [‡]Red de Investigación Renal (REDINREN), and [§]Cardiology Department, Hospital Universitario Central de Asturias, Oviedo, Spain.

BACKGROUND Time-dependent variability of electrocardiogram (ECG) in patients with Brugada syndrome could affect the interpretation of provocative testing.

OBJECTIVE The aim of this study was to characterize ECG changes during and after flecainide infusion.

METHODS We studied 59 consecutive patients. The ECG was continuously analyzed during the first 30 minutes of provocative testing, and a single ECG was recorded 60 minutes later. We analyzed CYP2D6 and CYP3A5 variants affecting flecainide metabolism and performed blinded measurements at lead II.

RESULTS At baseline, ECG patterns were classified as follows: type II in 31 patients (53%), type III in 15 (25%), and normal ECG in 13 (22%). Because of induction of type I ECG, the percentage of responders progressively increased with longer recording time periods (6.8% in 10 minutes vs 11.9% in 20–30 minutes vs 18.6% in 90 minutes; $P < .01$). Four patients displayed a late response, which was evidenced 90 minutes after the initiation of provocative testing. QRS width differentially increased between responders and nonresponders ($P < .01$), with a maximum QRS width of 110 ms during the first 30 minutes being effective for identifying possible late responders (sensitivity 100%; specificity 85.6%; positive predictive value 88%; negative predictive value 100%). The incidence of CYP2D6 variants was lower in late responders than in early or delayed responders (0% vs 75% vs 100%; $P = .04$), while a homogeneous distribution of *CYP3A5*3/*3* was observed in our population.

CONCLUSION Response to flecainide exhibits time-dependent variability of ECG patterns and intervals. Longer periods of ECG recording increase the recognition probability of type I ECG.

KEYWORDS Brugada syndrome; Electrocardiogram; Provocative testing; Flecainide; Cytochrome P450

ABBREVIATIONS **BrS** = Brugada syndrome; **ECG** = electrocardiogram/electrocardiographic; **Het-EM** = heterozygous extensive metabolizer; **Hom-EM** = homozygous extensive metabolizer; **QTc** = corrected QT; **SD** = sudden death

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Introduction

Brugada syndrome (BrS) is a leading cause of sudden death (SD) in young people, with the type I electrocardiographic (ECG) pattern being an essential clue for diagnosis.[1] In patients with no spontaneous type I ECG, flecainide challenge has been promoted as a commonly used test in the clinic.[2] However, the time-dependent course of ECG patterns in patients with BrS display a well-known variability[3] that has not been appropriately analyzed in the context of provocative testing with sodium blockers.

Recently, 2 case reports[4,5] have described the occurrence of late positive responses after flecainide infusion. According to the standard recommendations for provocative testing performance (10–30 minutes of waiting time if the test has a negative result), these tests would have been considered as negative[2]; however, these results are false negatives, with implications for clinical management (ie, perform lifestyle measurements, avoid drugs with potential adverse effects, and prompt treatment of fever episodes). To quantify the incidence of late responses, we analyzed the time course of ECG changes during and 90 minutes after flecainide infusion. In addition, clinical, ECG, and genetic factors affecting flecainide metabolism were analyzed to describe predictors of time-dependent responses.

Address reprint requests and correspondence: Dr David Calvo Cuervo, Arrhythmia Unit, Cardiology Department, Hospital Universitario Central de Asturias, Calle Carretera de Rubín, s/n, 33011 Oviedo, Spain. E-mail address: dcalvo307@secardiologia.es.

Methods

Population and recording protocol

In the absence of a spontaneous type I ECG pattern, patients with suspected BrS were admitted for provocative testing

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with flecainide. According to the standard protocol used in our institution, the clinical profile and serum levels (creatinine and electrolytes) were previously obtained at the outpatient clinic, 1–3 months before the admission. Intravenous flecainide was continuously infused at a rate of 2.0 mg/kg bodyweight over 10 minutes (limited by a maximum dosage of 150 mg). Before flecainide infusion, we checked for the absence of type I ECG, both at the standard precordial position (V_1 and V_2 at the third intercostal space) and at the high precordial position (V_1 and V_2 at the second intercostal space). Thereafter, the standard 12-lead ECG was continuously recorded during 30 minutes in the electrophysiology laboratory (sample rate 1 kHz; bandpass filtered 0.05–150 Hz; EP Tracer v1.05.v3, CardioTek, Maastricht, The Netherlands) from the initiation of flecainide infusion, which enabled us to better characterize transitions between ECG patterns because types II and III were mainly defined at the standard precordial positions.[1] At the end of this period, we again explored the high precordial position for better sensitivity. Thereafter, the positions of the leads on the body surface were marked and a new ECG was recorded 60 minutes later (Figure 1). The study was approved by the ethics committee, and subjects gave informed consent.

ECG tracings were analyzed by 3 independent cardiac electrophysiologists and classified by consensus according to the published recommendations as type I, II, and III.[1] For the purpose of this study, we classified the normal ECG as category IV. This category also includes subtle deviations from normality as the incomplete right bundle branch block. The response to flecainide infusion was analyzed continuously during the first 30 minutes. ECG changes observed during flecainide infusion (first 10 minutes of the ECG recording) were considered to occur at the first stage of the test. The second and third stage changes were those changes that occurred between 10 and 20 minutes and between 20 and 30 minutes, respectively. Finally, the fourth stage changes were considered according to the single 12-lead ECG recorded 90 minutes after the initiation of flecainide infusion. In order to assign an ECG pattern as defining the result of the test at every stage, we selected the highest order pattern observed during the recording time, considering type I as the highest order pattern and category IV as the lowest one. Provocative testing was considered to display a positive response if the patient exhibited a type I ECG pattern anytime during the protocol. Those patients displaying a positive response during the first stage were defined as *early responders*. On the contrary, those patients displaying a positive response during the second and third stages were defined as *delayed responders*. Finally, those patients displaying a positive response only in the fourth stage were defined as *late responders*. All other patients were defined as *nonresponders*.

During the 30 minutes of continuous ECG recording, average heart rate, PR, QRS width, and corrected QT (QTc) intervals (Bazett's formula) were measured every 10 minutes from baseline (using integrated calipers over the digital records; speed 100 mm/s) at lead II. Measurements of 3 consecutive cycles were averaged. To avoid potential bias, interval measurements were performed blinded to the final result of provocative testing. Also, all ECG channels other than lead II were removed from the screen at this time to avoid the researcher perceiving the final result of provocative testing.

Genetic studies

According to current guidelines,[6] the whole coding sequence of *SCN5A* was amplified and sequenced in responders as described previously.[7] The nucleotide changes were classified as possible mutations if (1) reported previously (www.ensembl.org) or (2) they had an effect on the protein sequence, either by changing the amino acid or by introducing aberrant transcript sequences. Single amino acid changes were considered as mutations on the basis of the prediction programs SIFT (J. Craig Venter Institute, La Jolla, CA) and Polyphen (Harvard, Massachusetts).

In the whole cohort of responders and a randomly selected subset of nonresponders (5 patients), we also determined single nucleotide polymorphisms in *CYP3A5* and *CYP2D6* genes because they are mainly involved in flecainide metabolism.[4,8] The *CYP3A5*3* allele (SNP rs776746) was genotyped with a real-time TaqMan polymerase chain reaction assay (assay ID C_25201809_30, Applied Biosystems, California, USA) as reported previously.[9] To determine the *CYP2D6* genotype, we amplified and sequenced the 9 coding exons with primers specific for this gene (further details are available on request to the corresponding author).

Statistical analysis

Categorical variables are reported as numbers and percentages. For the purpose of the analysis and better clinical interpretation, we considered the ECG patterns as ordinal variables of arbitrary units by assigning a value from 1 to 4 to patterns I, II, III, and category IV, respectively. The ECG

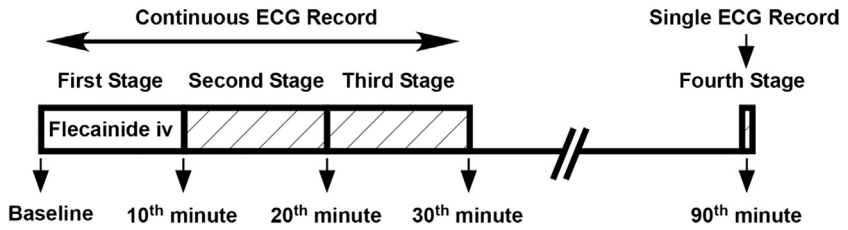

Figure 1 Study flowchart showing different stages of electrocardiographic (ECG) recording. Interval measurements were performed over the digital records at baseline, 10, 20, and 30 minutes (100 mm/s).

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