

# Retrospective Analysis of Patients with Brugada Syndrome and Implantable Cardioverter Defibrillator

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## ABSTRACT

### Introduction

The Brugada syndrome is an inherited, electrical anomaly, with increased risk of sudden cardiac death. Automatic cardioverter defibrillators are the only effective treatment to prevent sudden cardiac death, while therapy management in asymptomatic patients is still controversial.

### Objectives

The aims of the study were to evaluate the incidence and causes of appropriate and inappropriate shocks and the complications related to the device, and to identify the relationship of clinical and electrophysiological study variables with the incidence of appropriate shocks.

### Methods

This was a single-center, retrospective registry of patients with type-1 electrocardiographic Brugada syndrome, either spontaneous or induced by ajmaline infusion, who were recipients of automatic implantable cardioverter defibrillator.

### Results

Twenty-one patients were included in the study; 18 men, with average age of 40 years. The device was indicated due to the following symptoms: nocturnal agonal respiration, syncope and resuscitated cardiac arrest, or positive electrophysiological study in asymptomatic patients.

There were no deaths during follow-up of 88 months, and the annual rate of appropriate shocks was 1.9%, below that of inappropriate shocks (7.5%).

Ten patients presented complications including device infection and psychiatric disorders. The only variable significantly related with the presence of appropriate shocks was history of fibrillation and atrial flutter.

### Conclusions

A low annual rate of appropriate shocks was observed. The difficulties in risk stratification, the high incidence of inappropriate shocks and the high frequency of complications indicate need of careful patient selection for the implantation of these devices until more reliable predictors of arrhythmic risk are found.

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## Key words

> Brugada Syndrome — Implantable cardioverter defibrillator — Atrial tachycardia.

## Abbreviations

> AF	Atrial fibrillation	ICD	Automatic implantable cardioverter defibrillator
AFL	Atrial flutter	IS	Inappropriate shocks
AS	Appropriate shocks	NAR	Nocturnal agonal respiration
BS	Brugada syndrome	PVT	Polymorphic ventricular tachycardia
EPS	Electrophysiological study	SD	Sudden death
FHSD	Family history of sudden death	VF	Ventricular fibrillation
HPL	High precordial lead		

## INTRODUCTION

The Brugada syndrome (BS) is an inherited electrical disease characterized by an electrocardiographic pattern of right bundle branch block with ST segment elevation in right precordial leads, absence of structural heart disease and increased risk of syncope or sudden death (SD) due to polymorphic ventricular tachycardia (PVT) or ventricular fibrillation (VF). (1)

In the presence of malignant arrhythmic events the automatic implantable cardioverter defibrillator (ICD) is the only available treatment for the prevention of SD, but there are controversies regarding risk stratification and the most appropriate therapeutic approach in asymptomatic patients. The low frequency of arrhythmic events in the latter patients and the high rate of device-related complications are a challenge for the correct identification of patients who will benefit from ICD. (2-5)

The objectives of the present study were: 1) To assess the incidence and causes of appropriate shocks (AS) or inappropriate shocks (IS) and device-related complications, and 2) To evaluate the relationship of various clinical, electrocardiographic and electrophysiological study (EPS) variables with the presentation of AS during follow-up.

## METHODS

This is a retrospective study including all patients with BS admitted in our cardiology service who received ICD between January 2001 and March 2013.

Based on the first BS consensus report, the type I pattern was defined as the presence of a convex ST segment elevation  $\geq 2$  mm, with coved descent followed by a negative or isoelectric T wave in at least one right precordial lead (V1-V3). The observation of this pattern exclusively in the third or second intercostal space (high precordial lead – HPL-) was also considered diagnostic.

The variables selected to determine their relationship with the presence of AS were: type of electrocardiographic pattern, presence of spontaneous variability (complete elimination of spontaneous type I pattern or its conversion to type II or III pattern), family history of sudden death (FHSD), (occurring in a first or second degree relative before 40 years of age, in the absence of structural cardiomyopathy or with confirmed diagnosis of BS), history of atrial fibrillation (AF) or atrial flutter (AFL) and the EPS result.

Following informed consent, all patients underwent an EPS, except two who refused its performance. A protocol with 3 baseline cycle intervals (600 ms – 500 ms – 400 ms) and up to three extra stimuli with a minimum coupling interval of 200 ms was used, from the apex and right ventricular outflow tract. A positive study was considered for induced PVT or AF.

Seventeen single-chamber and 4 dual-chamber devices were implanted. An unique zone of VF frequency detection was programmed at 190 beats/min with maximum energy electrical therapies and backup frequency of 40 beats/min.

A device electrical discharge in the presence of PVT, a monomorphic ventricular tachycardia or VT was considered an AS, and a device electrical discharge unrelated to a malignant arrhythmic even an IS.

Patients were evaluated at 30 days and then every six months, or in the presence of clinical symptoms or the

occurrence of electrical therapies.

## Statistical activity

Results are expressed as median and 25-75 interquartile range in the case of numerical variables and as number of observations and proportions for categorical or dichotomous variables.

Univariate analysis with the chi-square test with or without Yates correction was used to assess different variables as possible predictors of events. The Epi Info and Statistix 8 softwares were used to perform statistical analyses.

## RESULTS

Among the 43 BS patients, ICD was implanted in 21: 2 for resuscitated cardiac arrest, 1 for nocturnal agonal respiration (NAR), 13 for syncope and 5 asymptomatic with positive EPS. They all presented spontaneous type I electrocardiographic pattern or induced with 10 minute intravenous infusion of 1 mg/kg ajmaline. Table 1 shows clinical population characteristics.

No deaths occurred during mean follow-up of 88 months. The overall AS rate was 14% and the annual rate 1.9%. The average time from initial diagnosis to first AS was 16 months (range 4-40 months).

In patients presenting syncope the annual AS rate was 1.7%. Five patients underwent a tilt test which was positive in 4 of them and of the 4 event recurrences, only one showed AS.

Table 2 shows patient characteristics with and without AS. All patients with AS were men, with mean age of 27 years (range 22-31 years). They presented with spontaneous type I pattern (2 in HPL and 1 with simultaneous ST segment elevation in infe-

**Table 1.** Clinical characteristics of the population

Age average, years	40 (32-49)*
Male gender, n (%)	18 (85.7)
Average follow-up (months)	88
	<b>n (%)</b>
<b>Clinical presentation</b>	
Asymptomatic	5 (23.8)
Resuscitated cardiac arrest	2 (9.5)
Syncope	13(61.9)
Nocturnal agonal respiration	1 (4.7)
Family history of sudden death	7(33.3)
<b>History of AF/AFL</b>	
Atrial fibrillation	2(9.5)
Atrial flutter	2(9.5)
<b>Electrocardiogram</b>	
Spontaneous type I	14(66.6)
Induced type I	7 (33.3)
High precordial leads	2 (9.5)
Spontaneous variability	10 (47.6)
<b>Electrophysiological study</b>	
Positive electrophysiological study	7(36.8)

\* Median and 25-75 interquartile range.

AF/AFL: Atrial fibrillation/Atrial flutter

rior and right precordial leads). These patients were also symptomatic (2 syncope, 1 NAR), had history of AF/AFL and negative EPS and 2 patients presented FHSD.

None of the asymptomatic patients with induced type I electrocardiogram or positive EPS had AS.

The only variables with a statistically significant relationship with the presence of AS were history of AF/AFL ( $p = 0.002$ ) and AF ( $p = 0.046$ ) (Table 3).

Twelve patients had IS (Table 4), 10 with single-chamber ICD. Six patients presented sinus tachycardia, 2 AF and 2 AFL, treated with drugs for heart rate control and device reprogramming in a 210 beats/min VF zone. Two patients with IS required device replacement: one patient for loss of ventricular electrode catheter insulating material and the other for T wave oversensing.

Other complications related with the device occurred in 10 patients: pocket infection (1), bacterial endocarditis (1), catheter displacement (2) and 6 patients presented psychiatric disorders requiring specialized medical care.

## DISCUSSION

In our registry there were no deaths during follow-up and, similar to other studies, a low annual rate of AS (1.9 %) and a high annual rate of IS (7.5 %) was observed. (4-10) It is important to note that 17 out of the 21 devices were single-chamber, programmed with a single VF detection zone at a heart rate of 190 beat/min and no new IS were observed after their reprogramming at 210 beat/min.

Two out of 3 patients with AS presented spontaneous type 1 pattern exclusively in HPL. This highlights the importance of a systematic precordial mapping in the study of patients with syncope to identify this electrocardiographic modality called “high precordial variant”. (11)

The finding of ST segment elevation in the inferior and right precordial leads in the remaining patient is a rare electrocardiographic BS variety, probably associated to a larger “genetic damage” more susceptible to the development of malignant ventricular arrhythmias

Asymptomatic subjects or with an induced type I pattern represent a population at low risk of SD as none of them presented AS.

Syncope was the most common symptom for which ICD was indicated. According to our observations and those of other authors, many episodes would be associated with a neurocardiogenic, non-arrhythmogenic mechanism, which would also explain the low annual rate of AS observed in these patients (1.7 %). (12)

The EPS in BS risk stratification is a topic of permanent controversy (13-17) and was not a useful tool in our study. No patient with positive EPS presented arrhythmic events during follow-up, regardless of the number of extra stimuli by which inducibility was achieved, whereas all patients with AS had a negative study.

History of AFL and/or AF was the only variable that had a statistically significant relationship with the presence of AS, verified in the 3 patients who presented it. (18) Remarkably, in one subject, recurrent

**Table 2.** Patient characteristics with or without appropriate shocks

Variable	With appropriate shocks (n=3)	With inappropriate shocks (n=18)	p
Age, years*	30 (21-32)	42.2 (32-52)	ns
Male gender % (n)	100 (3)	88.8 (16)	ns
Follow-up (months)	120	86.8	ns
Asymptomatic % (n)	0	27.7 (5)	ns
RCA % (n)	0	11.1 (2)	ns
Syncope % (n)	66.6 (2)	61.1 (11)	ns
NAR % (n)	33.3 (1)	0	ns
FH of SD % (n)	66.6 (2)	27.7 (5)	ns
AF/AFL % (n)	100 (3)	11.1 (2)	0.002
AF % (n)	66.6 (2)	5.5 (1)	0.046
AFL % (n)	66.6 (2)	0	0.015
Spontaneous type I % (n)	100 (3)	61.1 (11)	ns
Induced type I	0	38.8 (7)	ns
SV % (n)	100% (3)	38.8 (7)	ns
EPS % (n)	100% (3)	83.3 (15)	ns
Positive EPS % (n)	0	46.6 (7)	ns

\* Median and 25-75 interquartile range.

RCA: resuscitated cardiac arrest. NAR: Nocturnal agonal respiration. FHSD: Family history of sudden death. AF: Atrial fibrillation. AFL: Atrial flutter. ECG: Electrocardiogram. SP: Spontaneous variability. EPS: Electrophysiological study

**Table 3.** Annual rate of appropriate shocks according to the variables analyzed

Variable	Annual rate of appropriate shocks	p
Age ≤40 years	4.09	0,09
Age ≥ 40 years	0	
Symptomatic	2.56	0,42
Asymptomatic	0	
FHSD (+)	3.9	0,24
FHSD (-)	1	
AF/AFL (+)	8.18	0,0075
AF/AFL (-)	0	
AF (+)	9.09	0,041
AF (-)	0.76	
Spontaneous type I ECG	2.93	0,27
Induced type I ECG	0	
Positive EPS	0	0,27
Negative EPS	2.93	

FHSD: Family history of sudden death. AF: Atrial fibrillation. AFL: Atrial flutter. ECG: Electrocardiogram. SP: Spontaneous variability. EPS: Electrophysiological study

**Table 4.** Incidence and cause of inappropriate shocks

	% (n)
Sinus tachycardia	54 (6)
Atrial flutter	18 (2)
Atrial fibrillation	18 (2)
Electromagnetic interference	9 (1)
T wave oversensing	9 (1)

episodes of atrial fibrillation were recorded immediately preceding a VF storm. (19) This statistical association poses a hypothesis that should be explored in future clinical trials.

Recent publications assess the complications and psychological impact of ICD in this population. (20) In this study a high incidence of device-related complications was observed, especially psychiatric disorders with a negative impact on the quality of life of these young subjects, most of which are under specialized medical care.

#### Study Limitations

Study limitations are the retrospective design, the small sample size, the relatively short follow-up in relation to life expectancy of the studied population and the low rate of events. It is also important to mention the difficulties in the interpretation of electrograms for the correct diagnosis of an event in patients carrying a single-chamber ICD.

#### CONCLUSIONS

In our study the rate of IS was significantly higher

than that of AS. Excluding the history of AF and AFL, no variable analyzed was significantly associated with the presence of AS.

Because of the difficulties associated with risk stratification, the high incidence of IS and the high rate of complications associated with these devices, a careful selection of patients for ICD implantation is recommended until more reliable predictors of arrhythmic risk in BS are found.

#### RESUMEN

#### Análisis retrospectivo de una población de pacientes con síndrome de Brugada y cardiodesfibrilador automático implantable

##### Introducción

El síndrome de Brugada es una anomalía eléctrica hereditaria con riesgo incrementado de muerte súbita. El cardiodesfibrilador automático implantable es el único tratamiento efectivo para la prevención de la muerte súbita, mientras que la conducta terapéutica en los pacientes asintomáticos continúa siendo controversial.

##### Objetivos

Evaluar la incidencia y las causas de choques apropiados e inapropiados y las complicaciones relacionadas con el dispositivo. Identificar la relación de variables clínicas y del estudio electrofisiológico con la ocurrencia de choques apropiados.

##### Material y métodos

Registro unicéntrico, retrospectivo de pacientes con síndrome de Brugada, con patrón electrocardiográfico tipo I espontáneo o inducido con infusión de ajmalina, a quienes se les colocó un cardiodesfibrilador automático implantable.

##### Resultados

Se incluyeron 21 pacientes, 18 hombres, con una mediana de edad de 40 años. El dispositivo fue indicado por síntomas respiración agónica nocturna, síncope y paro cardíaco resucitado o por un estudio electrofisiológico positivo en pacientes asintomáticos. En un seguimiento de 88 meses no hubo muertes; la tasa anual de choques apropiados fue del 1,9%, inferior a la de choques inapropiados (7,5%). Diez pacientes tuvieron complicaciones, que incluyeron infección del dispositivo y trastornos psiquiátricos. La única variable relacionada significativamente con la presencia de choques apropiados fue el antecedente de fibrilación y aleteo auricular.

##### Conclusiones

Se observó una tasa anual baja de choques apropiados. Las dificultades en la estratificación del riesgo, la alta incidencia de choques inapropiados y la elevada frecuencia de complicaciones hacen recomendable una selección cuidadosa para el implante de estos dispositivos hasta encontrar predictores más confiables de riesgo arrítmico.

**Palabras clave** > Síndrome de Brugada, -Desfibriladores implantables – Taquicardia ventricular.

##### Conflicts of interest

None declared.

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