NATURAL HISTORY IN PATIENTS WITH THE BRUGADA SYNDROME

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Abstract.

Background. The prognosis of patients with the syndrome of right bundle branch block and ST segment elevation in the right precordial leads (Brugada syndrome) has been somewhat controversial, particularly for asymptomatic individuals. In this study, the largest cohort of patients with Brugada syndrome are reported and the prognostic significance of clinical and electrophysiological data are analyzed.

Patients. A total of 667 patients with the electrocardiographic characteristics of Brugada syndrome were analyzed.

Results. Mean age at diagnosis was 41±15 years, 160 were female and 507 male. The diagnosis was made due to the presence of a basal diagnostic electrocardiogram in 499 patients and in 168 the diagnostic electrocardiogram was noted only after antiarrhythmic drug administration. Sustained ventricular arrhythmias were induced during electrophysiological study in 231 out of 493 patients. During their lifetime 164 patients (25%) presented at least one episode of sudden cardiac death or documented ventricular fibrillation at a mean age of 43±15 years (2 to 77 years). Using multivariate Cox regression models, inducibility of sustained ventricular arrhythmias ($p<0.0001$, Hazard ratio 3.8, 95% CI 2.4-6.25), a male gender ($p<0.02$, Hazard ratio 1.9, 95% CI 1.03-3.4) and a basal abnormal electrocardiogram ($p<0.05$, Hazard ratio 1.9, 95% CI 1.01-3.7) were all predictors of occurrence of sudden cardiac death or ventricular fibrillation. Using a logistic regression model, the probability that a male, with a basal abnormal electrocardiogram and inducible has an event is 45% (CI 38-53%).

Conclusions. Patients with an electrocardiogram showing right bundle branch block and ST segment elevation in the right precordial have a high risk of ventricular arrhythmias and sudden death. Inducibility of sustained ventricular arrhythmias, a male gender and a spontaneously abnormal electrocardiogram are markers of a poor prognosis.

Key Words: Sudden Death, Inducibility, Electrocardiogram

Condensed Abstract

Natural history was studied in 667 individuals with the syndrome of right bundle branch block and ST segment elevation in the right precordial leads (Brugada syndrome). During their lifetime 164 patients suffered from sudden cardiac death or documented ventricular fibrillation. Inducibility of sustained ventricular arrhythmias, a male gender and a spontaneously abnormal electrocardiogram were markers of poor prognosis.

Introduction.

It has been demonstrated that patients with an abnormal electrocardiographic pattern of right bundle branch block and ST segment elevation in the right precordial leads, compatible with the diagnosis of Brugada syndrome have a high risk of sudden cardiac death (1-4). However, the prognosis of asymptomatic individuals and the value of clinical variables and some tests like programmed electrical stimulation are still a matter of discussion (5-7). We present here data on natural history and on the prognostic value of clinical and electrocardiographic variables in individuals with an electrocardiogram compatible with Brugada syndrome.

Patients and methods.

Data on 667 individuals with an electrocardiogram compatible with Brugada syndrome and no demonstrable structural heart disease were analyzed. The data are available thanks to the collaboration of many centers and physicians around the world (appendix). The electrocardiogram was defined as abnormal if a terminal r' wave, with a J point elevation of at least 0.2 mV, with a slowly descending ST segment in continuation with a flat or negative T wave (coved-type electrocardiogram) appeared spontaneously in leads V1 to V3 (figure1). The electrocardiogram was also defined as abnormal when the described electrocardiographic abnormalities became evident after the intravenous administration of an antiarrhythmic drug with potent sodium-channel blocking properties: ajmaline, flecainide or procainamide. Structural heart disease was excluded by clinical history, non-invasive (echocardiogram, stress test, nuclear magnetic resonance) and invasive methods (coronary angiography, left and right ventriculography and biopsy) used at the discretion of the treating physician.

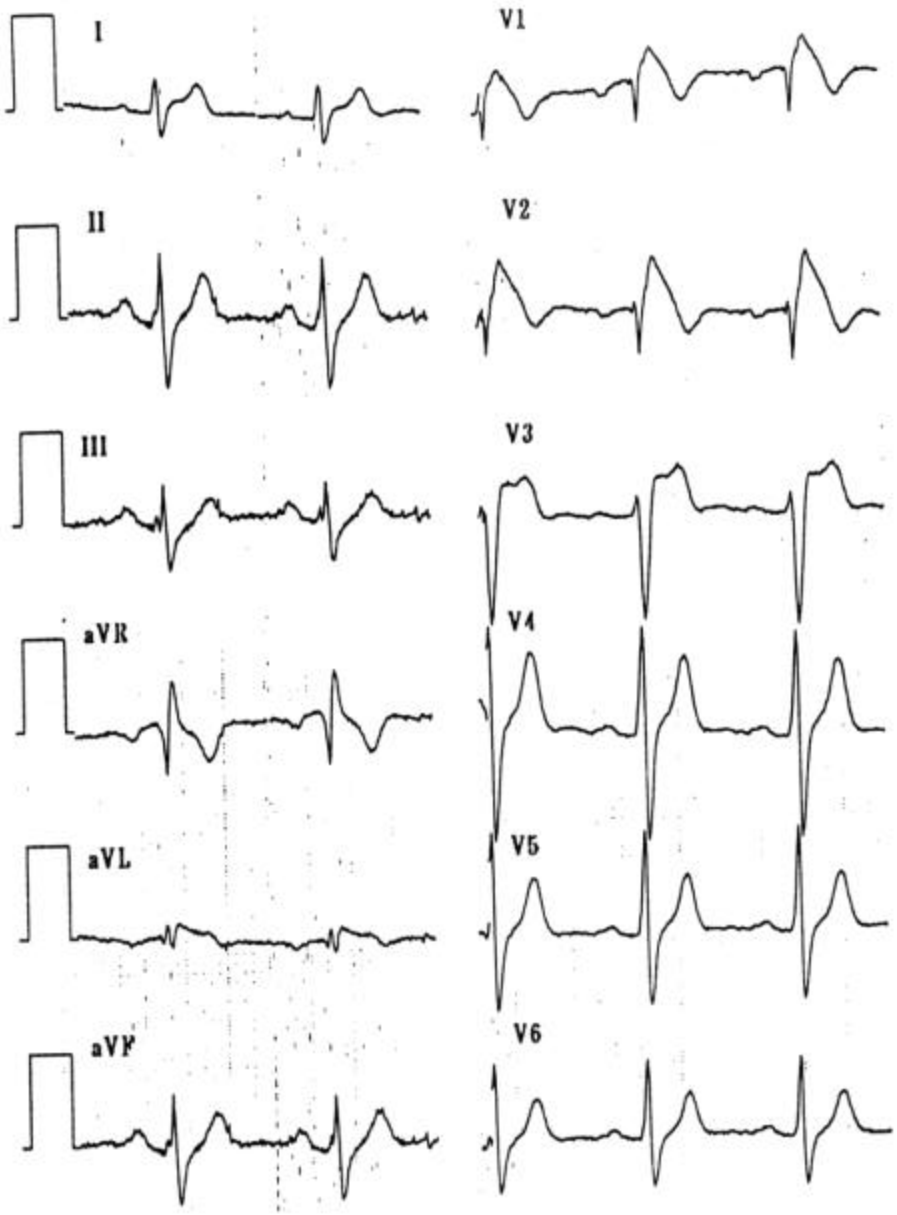

Figura 1

The abnormal electrocardiogram was identified after an episode of aborted sudden death in 120 patients, during study of a syncope of unknown origin in 124 patients, and in 423 asymptomatic patients the abnormal electrocardiogram was identified during routine electrocardiographic screening or during study of family members of patients with the syndrome.

Electrophysiologic study included basal measurements of conduction intervals and programmed ventricular stimulation. The protocol recommended used a single site of stimulation (right ventricular apex), three basic pacing cycles (600, 500 and 430 ms) and induction of 1, 2 and 3 ventricular premature beats down to a minimum of 200 ms. A patient was considered inducible if sustained ventricular arrhythmias (ventricular fibrillation, polymorphic ventricular tachycardia or monomorphic ventricular tachycardia lasting more than 30 seconds or requiring emergency intervention) were induced.

Statistical analysis.

Data were analyzed using the STATA Statistical Software (StataCorp., 1999, 7.0, College Station, TX). The Fisher exact test or the chi-square test was used for categorical variables. One-way analysis of variance (ANOVA) test was used for comparisons of continuous variables among the different groups. Survival curves were plotted using the Kaplan-Meier method and analyzed by the log-rank test. Cox regression models were used to analyze factors associated to occurrence of events. Those variables that were significant were used in a Logistic regression model to predict the probability of having an event. A p value less than 0.05 was considered statistically significant. Where applicable, data are presented as mean ± one standard deviation.

Results.

A total of 667 patients with the abnormal electrocardiogram were identified. Age at diagnosis (first abnormal electrocardiogram documented) was 41±15 years (2 to 85 years). A predominance of male patients was observed (507 vs 160). In 344 patients, a familial form of the disease was suspected. The electrocardiogram

was spontaneously abnormal in 499 cases and abnormal only after the administration of a class I antiarrhythmic drug in 168 patients. During electrophysiologic testing, 231 out of 493 patients were inducible into sustained ventricular arrhythmias. Demographic characteristics and results of the electrophysiologic testing are shown in table I.

Natural history

A total of 164 patients have presented at least one episode of sudden death or ventricular fibrillation during their lifetime (120 patients before the abnormal electrocardiogram was identified and 44 after).

Using multivariate analysis, inducibility of sustained ventricular arrhythmias, a male gender and the presence of a basal abnormal electrocardiogram were predictors of arrhythmia occurrence (table II).

The probability of having an event was studied using different combinations of these predictive factors (table III).

Follow-up

After the diagnosis was made, patients were followed a mean of 38±47 months.

In 105 patients at least one episode of sudden cardiac death or documented ventricular fibrillation has been documented. Using multivariate analysis, inducibility of sustained ventricular arrhythmias and the presence of a previous episode of sudden death or syncope were predictors of events (table IV).

References.

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome: A multicenter report. J Am Coll Cardiol 1992; 20:1391-6.

2. Brugada J, Brugada R, Brugada P. Right bundle branch block and ST segment elevation in leads V1 through V3. A marker for sudden death in patients without demonstrable structural heart disease. Circulation 1998;97:457-60.
3. Brugada R, Brugada J, Antzelevitch C, et al. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation 2000;101:510-5.
4. Atarashi H, Ogawa S, Harumi K, et al. Characteristics of patients with right bundle branch block and ST segment elevation in right precordial leads. Idiopathic ventricular fibrillation investigators. Am J Cardiol 1996;78:581-3.
5. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. J Am Coll Cardiol 1996;27:1061-70.
6. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST segment elevation. Circulation 1999;100:1660-6.
7. Shimizu W, Antzelevitch C, Suyama K, et al. Effects of sodium channel blockers on St segment, QRS duration, and corrected QT interval in patients with Brugada syndrome. J Cardiovasc Electrophysiol 2000;11:1320-9.
8. Dumaine R, Towbin JA, Brugada P, et al. Ionic mechanisms responsible for the electrocardiographic phenotype of the Brugada syndrome are temperature dependent. Circ Res 1999; 85:803-9.
9. Priori SG, Napolitano C, Gasparini M, et al. Clinical and genetic heterogeneity of right bundle branch block and ST-segment elevation syndrome. A prospective evaluation of 52 families. Circulation 2000;102:2509-15.
10. Hermida J, Lemoine J, Aoun FB, Jarry G, Rey J, Quiret J. Prevalence of the Brugada syndrome in an apparently healthy population. Am J Cardiol 2000;86:91-4.

Table I. Clinical characteristics of the patients

Clinical presentation	Sudden death or ventricular fibrillation	No sudden death or ventricular fibrillation	P
N	164	503	
Male/female	141/23	366/137	0.0001
Age (years)	42±15	43±15	NS
Basal abnormal ECG	150	349	0.0001
Family history of SCD	70	274	0.03
Inducible/non inducible	95/21	136/241	0.0001

ECG: electrocardiogram, SCD: sudden cardiac death

Table II. Probability of sudden death or ventricular fibrillation during lifetime depending on clinical and electrophysiological variables

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Inducible	4.76	3.03-7.69	0.0001	3.85	2.38-6.25	0.0001
Non inducible	1			1		
Basal ECG	3.85	2.17-7.14	0.0001	1.89	1.01-3.70	0.046
AAD ECG	1			1		
Male	2.4	1.56-3.80	0.0001	1.89	1.03-3.45	0.027
Female	1			1		
Family history	1.05	0.69-1.31	0.787			
No family history	1					

Basal ECG: basal abnormal electrocardiogram; AAD ECG: abnormal electrocardiogram only after antiarrhythmic drug administration.

Table III. Probability of having an event during lifetime

MALE patients

	Non inducible at EPS	Inducible at EPS
Abnormal ECG after AAD	4.4 (2.0 – 9.3)	23.4 (12.8 – 38.8)
Basal abnormal ECG	11.0 (7.0 – 16.8)	45.1 (37.9 – 52.5)

FEMALE patients

	Non inducible at EPS	Inducible at EPS
Abnormal ECG after AAD	3.0 (1.3 – 6.9)	17.0 (8.0 – 32.7)
Basal abnormal ECG	7.6 (3.8 – 14.8)	35.5 (21.8 – 52.1)

EPS: electrophysiologic study; ECG: electrocardiogram; AAD: antiarrhythmic drugs. Data are expressed in percentage (95% confidence intervals).

Table IV. Probability of sudden death or ventricular fibrillation during follow-up, after the diagnosis has been made, depending on clinical and electrophysiological variables.

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Inducible	11.1	4.54-25.0	0.0001	7.14	2.7-20.0	0.0001
Non inducible	1			1		
Basal ECG	3.70	1.75-7.69	0.0001			
AAD ECG	1					
Male	2.94	1.54-5.88	0.0001			
Female	1					
Family history	1.03	0.68-1.55	0.896			
No family history	1					
Asymptomatic	1		0.0001	1		0.0001
Syncope	2.60	1.43-4.76		2.41	1.16-4.99	
Sudden death	6.53	4.08-10.4		3.99	2.09-7.60	
HV<55 ms	1		0.494			
HV>55 ms	1.26	0.66-2.40				

Basal ECG: basal abnormal electrocardiogram; AAD ECG: abnormal electrocardiogram only after antiarrhythmic drug challenge.

Appendix 1.

Physicians and centers.

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