Electrocardiographic determinants of risk for Sudden Death and recurrence in Brugada Syndrome Patients.

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Introduction: In 1992 the Brugada brothers described a syndrome characterized by an electrocardiographic pattern resembling a right bundle branch block with a peculiar type of ST segment elevation in leads V1 to V3, polymorphic ventricular arrhythmias causing episodes of syncope or sudden death and a structurally normal hearts[1]. In 1996, Yan and Antzelevitch[2] described the cellular basis for the ST segment elevation (J wave) produced by a transmural voltage gradient secondary to an accentuation of the action potential notch and loss of the action potential dome in the epicardium of the right ventricle[3] [4]. In 1998 Chen et al[5] demonstrate the association with the mutation in the cardiac sodium channel gene SCN5A providing support to the hypothesis of a primary electrical disease.

Long term follow up of these patients have showed that symptomatic patients with an abnormal ECG, family history of sudden death and inducible ventricular arrhythmias in the electrophysiologic study are markers of poor prognosis[6]. The susceptibility to present ventricular arrhythmias is due to the marked transmural dispersion or repolarization and refractoriness and the development of a vulnerable window during which a premature impulse or extrasystole can induce a reentrant arrhythmia[2, 3, 7, 8 9]. Non-invasive markers in asymptomatic and symptomatic patients with basal ECG abnormalities suggesting Brugada syndrome are needed to identify patients at high risk of developing lethal ventricular arrhythmias. Since the ECG abnormalities constitute the hallmark of the syndrome, the aim of this study was to determine if the ECG analysis in patients with basal electrocardiographic abnormalities compatible with Brugada syndrome, might predict risk of sudden dead or Ventricular Fibrillation (VF) or risk of recurrent events at follow up.

Methods: Data on 164 individuals with a basal ECG compatible with Brugada syndrome and no demonstrable structural heart disease was analyzed. The data are available thanks to the collaboration of many centers and physicians around the world (Appendix). A single cardiologist - electrophysiologist blinded to the clinical information about the patients, analized the basal 12 lead ECG of all patients. Conventional interpretation of the ECG (Rhythm, QRS axis, Heart rate, P wave, QRS duration, QT intervals, etc) was performed. Specific measurements that could give

information about the degree of the degree of a posible conduction delay (Table 1) and changes compatible with the loss of the action potential dome in the epicardium (Table 2) were made.
ECG´s were classified and considered abnormal according to the proposed diagnostic criteria for the Brugada syndrome consensus report[10].

Table 1. - Variables Used to evaluate the degree of conduction delay.

Variables for Conduction delay	Unit	Lead	Measurement
TIDI	Milliseconds	V1, V2, V3	From the beginning of the QRS to the peak of R wave
QRS	Milliseconds	V1, V2, V3.	From the begining of the Q wave to the end of the S wave.
S wave	Milliseconds	V1, V2, V3	From the end of the R wave to the end of the S wave
		DI, DII, DIII	From the end of the R wave to the end of the S wave.
R'	Milliseconds	V1, V2.	From the end of the S wave to the J point.

TIDI: Time of inscription of the intrincecoid deflection. R':

Table 2. - Variable used to evaluate the degree of trasmural gradient.

Variables for transmural gradient.	Unit	Lead	Measurement
J point	Millivolts	V1, V2, V3	From the basal line to the beginning of the ST segment
ST segment	Millivolts	V1, V2, V3	At 120 ms from the Q wave
S wave	Millivolts	DI, DII, DIII	From the basal line to the peak of the S wave.

Structural Heart disease was excluded by clinical history, noninvasive (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. Individuals with diseases known to mimic the abnormal ECG of Brugada syndrome such as hypothermia, pericarditis, myocarditis, or acute ischemic events were excluded.

Tow groups were formed: Group A: Those with sudden death (SD) or ventricular fibrillation (VF) at any time in their lives. Group B no evidence of VF or SD at all. A second analysis was made to evaluate if this variables could predict recurrent events, so another two groups were formed. Group A: Recurrent events of documented VF or a proper ICD shock in patients with an ICD.

Statistical Analysis

Quantitative values are expressed by means ± SD. A Univariate analysis was performed for all variables analyzed. Variables significant were included in a multivariate analysis to identified variables for risk of Sudden death and risk of recurrent events. A P value < 0.05 was considered significant.

Results:

Mean age was 43 ± 15. There were 139 males (85%) and 25 (15%) females. Sixty-eight (42%) were asymptomatic and 96 (58%) had symptoms (syncope or sudden death) at diagnosis. Sudden death or VF at any time in the patient's life was found in 66 (40%) patients. Recurrent events (documented, VF or Polimorphic VT or a proper ICD shock) at follow up (29 ± 48 months) were found in 39 (24%) of patients. Out of the 164 patients 113 (69 %) had a type 1 ECG and 51 (31 %) a type 2 ECG.

Variables found more significant for the risk of sudden dead in the univariate analysis were ST segment elevation in lead V1, P= 0.04; maximal ST segment elevation in lead V1, P= 0.04; amplitud of the S wave in lead D1, P= 0.06, and the absence of a S wave in lead DII, 0.05 (Table 3). These variables were included in a Multivariate analysis showing that independent risk factors for sudden death were: ST segment elevation in lead V1 (OR 1.28, CI 95% 0.998 . 1.64, P= 0.05), Amplitude of the S wave in DI (OR 1.27, CI 95% 1 – 1.64, P= 0.04) and Absence of an **S wave in DII** (OR 0.4 , CI 95% 0.20 – 0.83), P= 0.01.

We realized the same analysis to see if the variable mentioned were also independent risk factors for recurrent events of VF or Polimorphyc VT and only the ST segment elevation in V1 was significant (OR 1.32, CI 95% 1 – 1.7, P= 0.032). None of the variables that measured the conduction delay were found to be significant for events.

Tabla 3. - General Electrocardiographic Measurements. .

	Suden death or VF					
	no (98)		si (66)		Total (164)	
	Mean	SD	Mean	SD	Mean	SD
TIDI V1	20.00	5.71	22.88	18.48	21.16	16.89
TIDI V2	26.17	0.47	28.41	12.68	27.07	11.43
TIDI V3	34.80	5.33	32.12	11.23	33.72	28.19
R' en V1	37.35	7.11	39.39	18.72	38.17	17.75
R' prima en V2	36.80	2.57	35.16	19.84	36.15	21.48
QT V1	392.39	1.62	389.23	49.73	391.12	57.01
QT V2	407.96	0.04	402.15	56.55	405.64	64.87
QT c	418.38	4.56	433.20	53.47	424.33	48.72
QT dispersion	62.68	9.77	54.46	30.47	59.38	30.23
J point V1	1.79	1.04	2.08	1.41	1.91	1.20
J point V2	2.83	1.42	2.98	1.83	2.89	1.59
J point V3	1.30	1.05	1.48	1.50	1.38	1.25
ST V1	1.22	1.05	1.66	1.66	1.40	1.34
ST V2	2.06	1.85	2.51	2.13	2.24	1.97
ST V3	1.17	0.98	1.28	1.31	1.22	1.12
S V1	104.49	3.01	106.46	16.53	105.28	14.50
S V2	107.86	2.62	104.17	33.54	106.39	27.46
S DI	0.95	1.33	1.45	1.93	1.15	1.61
S DII	1.95	1.69	1.86	2.24	1.92	1.92

Discussion:

Brugada Syndrome is responsible for about 50% of sudden death in young individuals with no structural heart disease[11]. Different clinical variables like previous history of sudden death or VF, syncope, induction of VF or polymorphic ventricular tachychardia (PVT) with programmed stimulation, and family history of SD had been identified as markers of poor prognosis in this patients[6]. Until now risk stratification for this patients is difficult and requires extensive work up, and some times the results are of difficult interpretation. The need for simple and easy-to-use markers of risk for sudden dead or FV-PVT in these patients are necessary. It is known that the loss of the action potential dome in epicardium but not endocardium, results in the development of a marked

transmural dispersion of repolarization and refractoriness, responsible of a vulnerable window during which a premature impulse or extrasystole can induce a reentrant arrhythmia[2-4]. The electrocardiographic representation of this transmural gradient is the elevation of the ST segment in right precordial leads (J wave)[3 4]. Some authors have investigated the prognostic value of the ST segment elevation and other electrocardiographic measurements in Brugada syndrome patients, but the number of patients is low and results are not constant. Atarashi et al.[9] analyzed the contribution of interventricular conduction delay to the risk of FV-PVT measuring the S wave in leads V1 and V2 and ST segment amplitud in V1 and V2, concluding that a S wave in V1 ≥ 0.08s and an amplitud of ST segment in V2 of ≥ 0.18 mv, are high risk criteria in patients with Brugada syndrome. In our study we found that the mean S wave in lead V1 for patients without sudden death or VF was 105 ± 13 ms, compared to 106 ± 16 ms in patients with sudden death of VF, and this did not reach statistical significance. It is interesting that the mean S wave in V1 in our series is significantly longer than that found by Atarashi et al. We also performed other measurements that represent the degree of the conduction delay (Table 2) in right precordial leads and in unipolar leads, and non of them were found significant.

Morita et al[8] found that asymptomatic patients with BS, in witch FV could be induced in the EP laboratory had a higher ST segment in V2, at rest, and after the administration of a sodium channel blocker.

In our series we found that the degree of the ST segment elevation in lead V1 is an independent risk factor for the presence of sudden death or VF and recurrence in patients with electrocardiographic basal abnormalities compatible with Brugada syndrome. This measurement represents the degree of the transmural gradient in the right ventricle, so the grater the gradient a bigger vulnerable window. This finding correlates with those of Morita[8] and Atarashi[9] ; but we also found that the amplitude of the S wave in lead DI is an independent risk factor for sudden death but not recurrence, until now there is no other report that acknowledge this variable as a marker of risk. The exact explanation for this is not well understood yet, but we think that if there is an alteration in the action potential of the epicardium of the right ventricle outflow tract, forces from this wall could have a more important expression, corresponding with the inscription of the S wave in lead DI. The probability of a conduction block of the right bundle branch cannot be ruled out, but the fact that in the majority of patients the typical electrocardiographic criteria for right bundle branch block is not present, and that this conduction block has not been proved by other investigators[12 13], makes this possibility improbable. It is also interesting that the type of the ECG (type 1 or 2) is not significant for the risk of sudden death or recurrence. This is important since up to day only the type 1 ECG is

considered diagnostic for Brugada syndrome, and type 2 ECG is referred as idiopatic electrocardiographic changes of Brugada syndrome. If we consider that the risk of developing ventricular arrhythmias is the ST segment elevation, this could be also true for type 2 ECG.

Finally, the constant changing of the ECG in these patients makes very difficult the correct assessment of the ECG; that is why we choose only those patients with basal abnormalities at diagnosis. The value of the degree of the ST segment elevation with Sodium channel blockers was not assessed.

Up to our knowledge this is the largest series that analyzes basal abnormalities of Brugada Syndrome patients; results are promising but more controlled studies are needed.

Conclusions:

The degree of the ST segment elevation in lead V1 and the amplitude of the S wave in lead DI are independent risk factors for sudden death or FV in patients with the Brugada Syndrome. The ST segment elevation in V1 is also a marker of recurrent events.

Table 4. – Clinical Variables

	Sudden Death or VF					
	no (98)		yes (66)		Total (164)	
	n	%	n	%	n	%
Male	83	84.69 %	56	84.85 %	139	84.76 %
Female	15	15.31 %	10	15.15 %	25	15.24 %
Symptoms	37	37.76 %	59	89.39 %	96	58.54 %
Inducibility	29	39.73 %	44	84.62 %	73	58.40 %
ICD	33	34.02 %	52	78.79 %	85	52.15 %
Recurrence	3	3.06 %	36	54.55 %	39	23.78 %
ECG type I	65	66.33 %	48	72.73 %	113	68.90 %
ECG type II	33	33.67 %	18	27.27%	51	31.1%
S in DII	58	59.18 %	29	43.94 %	87	53.05 %

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