

## Gender Differences in Clinical Manifestations of Brugada Syndrome

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- Objectives** We sought to assess differences in phenotype and prognosis between men and women in a large population of patients with Brugada syndrome.
- Background** A male predominance has been reported in the Brugada syndrome. No specific data are available, however, concerning gender differences in the clinical manifestations and their role in prognosis.
- Methods** Patients with Brugada syndrome were prospectively included in the study. Data on baseline characteristics, electrocardiogram parameters before and after pharmacological test, and events in follow-up were recorded for all patients.
- Results** Among 384 patients, 272 (70.8%) were men and 112 (29.2%) women. At inclusion, men had experienced syncope more frequently (18%) or aborted sudden cardiac death (6%) than women (14% and 1%, respectively,  $p = 0.04$ ). Men also had greater rates of spontaneous type-1 electrocardiogram, greater ST-segment elevation, and greater inducibility of ventricular fibrillation ( $p < 0.001$  for all). Conversely, conduction parameters and corrected QT intervals significantly increased more in women in response to sodium blockers ( $p = 0.03$  and  $p = 0.001$ , respectively). During a mean follow-up of  $58 \pm 48$  months, sudden cardiac death or documented ventricular fibrillation occurred in 31 men (11.6%) and 3 women (2.8%;  $p = 0.003$ ). The presence of previous symptoms was the most important predictor for cardiac events in men, whereas a longer PR interval was identified among those women with a greater risk in this series.
- Conclusions** Men with Brugada syndrome present with a greater risk clinical profile than women and have a worse prognosis. Although classical risk factors identify male patients with worse outcome, conduction disturbances could be a marker of risk in the female population. (J Am Coll Cardiol 2008;52:1567-73) © 2008 by the American College of Cardiology Foundation

Brugada syndrome was first described in 1992 as a clinical syndrome presenting with a characteristic electrocardiogram (ECG) morphology (incomplete right bundle branch block associated with ST-segment elevation) and susceptibility to ventricular arrhythmias and sudden cardiac death (SCD) (1). After few initial clinical reports, the first mutations responsible for the syndrome were described in 1998 in the SCN5A gene, which encodes the cardiac sodium channel (2). Functional studies of these and other subsequent mutations described on the same gene showed that the

Brugada phenotype appeared as a consequence of a loss of function in the sodium channel (2-4). Recently, a new mutation in the glycerol-3 phosphate dehydrogenase-1 like (GPD1-L) gene that decreases the trafficking of sodium currents also has been connected to the syndrome (5). Both SCN5A and GPD1-L genes are on chromosome 3 and, thus, are not presumably linked to gender (2,5). Indeed, Brugada syndrome presents an autosomal-dominant mode of transmission with low penetrance (6).

Despite the syndrome not being linked to gender, the Brugada phenotype has been reported to be up to 8 to 10 times more prevalent in men than in women (6,7). In fact, 71% to 77% of the patients included in the main clinical studies of Brugada syndrome are men (8-11). The same clinical studies have shown that compelling clinical events such as SCD or ventricular fibrillation (VF) tend to occur more frequently in men than in women (8-12). These data do nothing other than to confirm what was already known

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**Abbreviations  
and Acronyms**

<b>CI</b>	= confidence interval
<b>ECG</b>	= electrocardiogram
<b>EPS</b>	= electrophysiological study
<b>GPD1-L</b>	= glycerol-3 phosphate dehydrogenase-1 like
<b>HR</b>	= hazard ratio
<b>ICD</b>	= implantable cardioverter-defibrillator
<b>Ito</b>	= potassium current
<b>QTc</b>	= corrected QT interval
<b>SCD</b>	= sudden cardiac death
<b>SUDS</b>	= sudden unexplained death syndrome
<b>VF</b>	= ventricular fibrillation

in some Southeast Asian villages regarding sudden unexplained death syndrome (i.e., SUDS), considered now to be the same disorder as Brugada syndrome (13), where men used to dress in female bedclothes given that SUDS was thought to be a female spirit searching for young men at the time of sleep.

Several hypotheses have been raised to explain the gender differences in Brugada syndrome, supporting either constitutional differences in ionic currents between genders (14), or a role of sex hormones since the time of puberty and throughout life (15,16). However, despite the general agreement of a male predominance in the Brugada syndrome phenotype, specific data on how gender influences the

clinical manifestations and prognosis of patients are lacking. Moreover, no information regarding differences in risk markers according to gender has been available thus far. In this study, we sought to establish, in a large population of patients with Brugada syndrome, the clinical phenotype of both men and women and to compare their clinical evolution.

## Methods

**Study population.** Patients for this study were recruited either in Hospital Clinic of Barcelona or in UZ Brussel Hospital and followed prospectively. Although both study hospitals are international referral centers for Brugada syndrome, only those patients directly evaluated and followed by 1 of the 2 centers were included in the study to minimize high-risk selected population bias (inclusion period 1992 to 2007). Patients from other centers who had been referred for evaluation and/or a second opinion but had not subsequently been followed by the 2 centers and patients who were referred for the international database were excluded. This process guaranteed a more representative population and that all patients underwent the same study protocol.

A spontaneous or induced (after sodium-blocker administration) coved-type ECG pattern (type-1 ECG) was required in all patients. Type-1 ECG was defined as descendent ST-segment elevation  $\geq 2$  mm in right precordial leads followed by a negative T-wave, as stated in the consensus (17). Sodium-blocker administration was performed with ajmaline (1 mg/kg of body weight), flecainide (2 mg/kg of body weight), or procainamide (10 mg/kg of body weight) according to drug availability in the 2 centers. An echocardiography, chest X-ray, and other cardiac explo-

rations when needed were performed to definitely rule out structural heart disease.

**Clinical data.** At baseline, clinical data regarding age, family history, symptoms at presentation, and ECG were collected. Baseline ECG was defined as type 1, type 2, or type 3/normal patterns. Baseline PR interval, QRS duration, and QT interval corrected for the Bazett's formula (QTc) were measured in milliseconds. Analysis of ST-segment elevation was performed in lead V<sub>2</sub> at 40 ms from the J point. The same measurements (PR interval, QRS duration, QT interval, and ST-segment elevation) were obtained after pharmacological test, provided it was performed.

All patients were recommended to undergo electrophysiological study (EPS). The protocol was identical for all. At baseline and in the absence of any drugs, conduction intervals were obtained. Ventricular stimulation was performed at a single site (right ventricular apex), with induction of 1, 2, or 3 ventricular premature beats down to a minimum of 200 ms, over basal rhythm, and over pacing cycle lengths of 600, 500, and 430 ms.

Single- or dual-chamber implantable cardioverter-defibrillators (ICDs) were indicated in accordance with the current recommendations (17), that is, in high-risk patients presenting with SCD (class I), in patients presenting with syncope with spontaneous (class I) or induced (class IIa) type-1 ECG, or in asymptomatic patients with family history of SCD and inducibility of VF at the EPS, either with spontaneous type-1 ECG (class IIa) or with induced type-1 ECG (class IIb).

All patients were directly followed by 1 of the 2 participating centers. Cardiac events were defined as SCD or documented VF, and recorded for all patients during follow-up. Syncope was not included in the definition because we sought to record only confirmed life-threatening events.

**Statistical analysis.** Results are reported as mean  $\pm$  SD or frequency as appropriate. Comparisons between groups were performed with the Student *t* test or chi-square analysis. Differences of ECG parameters before and after the administration of sodium-blockers were tested with the use of a paired Student *t* test. The relationship between baseline data and the time to event during follow-up was evaluated with survival analysis methodology (i.e., Cox regression models). Variables were included in the multivariable analysis with the use of a forward stepwise procedure with a criteria of  $p < 0.05$  for inclusion and  $p > 0.10$  for removal from the model. Cumulative event rates were estimated by Kaplan-Meier estimation, and plots were compared by the log-rank test. A  $p$  value of  $<0.05$  was considered statistically significant. Statistical analyses were performed using SPSS 14.1 software package (SPSS Inc., Chicago, Illinois).

## Results

**Baseline clinical data.** A series of 384 patients were included in the study; 272 were men (70.8%) and 112 were

women (29.2%). This male predominance is in accordance to previous studies (8–11) and confirms that Brugada syndrome more frequently is diagnosed among men than women. The general characteristics of the study population are summarized in Table 1. Most patients were asymptomatic at the time of diagnosis, although men presented more frequently with symptoms as compared with women. This difference was more remarkable regarding SCD, which was present in 17 of 272 men (6%) and only in 1 of 112 women (1%,  $p = 0.01$ ). Interestingly, of the 18 patients who first came with SCD, 9 had had previous syncope. Previous atrial fibrillation did not significantly differ between men and women.

Baseline ECG showed typical features of Brugada syndrome more frequently in men, given that type-1 ECG, the only definite diagnostic ECG pattern of Brugada syndrome, was present in 128 men (47%), whereas it was present in only 26 women (23%,  $p < 0.001$ ). Likewise, ST-segment elevation in basal ECG among those patients who spontaneously showed a type-1 ECG was significantly greater in men as compared with women ( $3.5 \pm 1.8$  mm vs.  $2.5 \pm 0.7$  mm,  $p < 0.001$ ).

The EPS was performed in 350 patients (91.1%). Two patients did not undergo EPS because 1 presented with SCD as the first symptom and died during the same hospital admission and other developed severe brain damage after cardiac arrest. In 1 patient, VF requiring cardiopulmo-

nary resuscitation occurred during the pharmacological test with sodium blockers, and EPS was not performed. Additionally, the EPS was not performed in 11 asymptomatic children with spontaneous normal ECG and age  $< 16$  years. Another 20 patients refused to undergo the procedure, mainly given their low risk profile (asymptomatic with normal ECG at baseline). Despite identical protocols of ventricular stimulation for both men and women, the rate of inducibility of ventricular arrhythmias was significantly higher in males (32% vs. 12%,  $p < 0.001$ ). No differences were observed in basal conduction intervals during EPS between the 2 groups.

The effects of the administration of a sodium-blocker on the ECG parameters are depicted in Table 2. Note that only patients who underwent the pharmacological test are presented ( $n = 312$ ). In the presence of pharmacological sodium-blockade, the PR interval, QRS duration, QTc interval, and ST-segment elevation significantly increased in both men and women. This increase was greater in women regarding conduction parameters (PR interval, a trend in QRS duration) and QTc interval, whereas the increment of ST-segment elevation did not significantly differ between men and women.

Overall, men displayed a greater risk-profile at baseline than women. Indeed, male gender increased by 7.4 the risk of presenting with SCD at the time of diagnosis (95% confidence interval [CI]: 1.0 to 55.5), by 2.9 the risk of displaying spontaneous type-1 ECG (95% CI: 1.8 to 4.8), or by 3.5 the rate of inducibility of ventricular arrhythmias at the EPS (95% CI: 1.8 to 6.9), with regard to women. Given their greater risk profile, men were more likely to receive an ICD than women (38% vs. 22%,  $p = 0.002$ ).

**Clinical outcomes.** In the entire study population, cardiac events defined as SCD or documented VF occurred in 34 of 384 (8.9%) patients during a mean follow-up of  $58 \pm 48$  months. Specifically, 27 appropriate ICD discharges, 6 SCD (nonresuscitated), and 1 (resuscitated) documented VF were recorded. The rate of events was significantly greater among those patients who had presented with syncope (10 of 65 events, 15.4%) or aborted SCD (11 events of 18, 61.1%) at the time of diagnosis than among previously asymptomatic patients (13 events of 301, 4.3%,  $p < 0.001$ ).

Despite similar follow-up periods in both genders (Table 1), cardiac events appeared in 31 men (11.6%) but only in 3 women (2.8%,  $p = 0.003$ ). Kaplan-Meier estimate of cardiac event-free survival according to gender is represented in Figure 1. With the use of univariable analysis, we found that gender was significantly related to cardiac events (hazard ratio [HR]: 4.45, 95% CI: 1.36 to 14.58,  $p = 0.014$ ), along with other variables such as symptoms at the time of diagnosis, spontaneous type-1 ECG, inducibility of VF during EPS, or atrial fibrillation (Table 3). However, the use of multivariable analysis did not confirm gender as an independent predictor of cardiac events during follow-up (Table 3).

**Table 1** General Characteristics of the Study Population

	Men (n = 272)	Women (n = 112)	p Value
Age at diagnosis, yrs	45 ± 14	48 ± 18	0.09
Family history of SCD, n (%)	82 (31)	50 (45)	0.007
Symptoms at diagnosis, n (%)			0.04
None	206 (76)	95 (85)	
Syncope	49 (18)	16 (14)	
Aborted SCD	17 (6)	1 (1)	
Previous AF, n (%)	26 (10)	14 (12)	0.2
Baseline ECG			
Normal or type-3, n (%)	68 (25)	69 (62)	<0.001
Type-2, n (%)	76 (28)	17 (15)	
Type-1, n (%)	128 (47)	26 (23)	
PR interval, ms	176 ± 31	176 ± 35	1
QRS duration, ms	107 ± 17	98 ± 19	<0.001
QTc interval, ms	422 ± 47	422 ± 49	1
ST-segment elevation, mm*	3.5 ± 1.8	2.5 ± 0.7	<0.001
Pharmacological test, n = 312 (%)	210/272 (77)	102/112 (91)	0.001
Drug (ajmaline/flecainide/ procainamide)	133/65/12	73/28/1	0.09
EPS, n = 350 (%)	259/272 (95)	91/112 (81)	<0.001
Inducible, n (%)	84 (32)	11 (12)	<0.001
Noninducible, n (%)	175 (68)	80 (88)	
HV interval, ms	48 ± 10	47 ± 8	0.4
ICD, n (%)	103 (38)	24 (22)	0.002
Follow-up, months	57 ± 52	60 ± 40	0.48

\*Only for patients with spontaneous type-1 electrocardiogram (ECG) ( $n = 154$ ).  
AF = atrial fibrillation; EPS = electrophysiological study; ICD = implantable cardioverter-defibrillator; QTc = corrected QT interval; SCD = sudden cardiac death.

**Table 2** ECG Parameters in Those Patients Who Underwent the Pharmacological Test: Values Before and After Administration of the Sodium-Blocker

	Men			Women			p Value†
	Baseline	After Sodium-Blocker	p Value*	Baseline	After Sodium-Blocker	p Value*	
PR interval, ms	173 ± 31	204 ± 34	<0.001	173 ± 35	211 ± 43	<0.001	0.03
QRS duration, ms	105 ± 16	130 ± 24	<0.001	98 ± 16	128 ± 27	<0.001	0.06
QTc interval, ms	417 ± 45	458 ± 51	<0.001	418 ± 47	486 ± 47	<0.001	0.001
ST-segment elevation, mm	2.3 ± 1.6	4.2 ± 1.9	<0.001	1.6 ± 1.0	3.4 ± 1.5	<0.001	0.8

\*p value in the paired t test for intragroup comparisons of ECG parameters before and after the pharmacological test. All ECG parameters significantly increased in both men and women after the administration of sodium-blockers. †p value in the t test for intergroup comparisons (men vs. women) of the increment in ECG parameters after pharmacological test. In women, the increment of PR and QTc intervals was significantly greater than in men, and a trend also was observed for the QRS duration. ST-segment elevation increased equally in men and in women.

Abbreviations as in Table 1.

Because the clinical presentation was notoriously different in men and women, we analyzed separately the 2 populations to assess the characteristics of patients at risk for both genders. The results are summarized in Table 4. Male patients who developed cardiac events were more likely to be previously symptomatic and had more frequently spontaneous type-1 ECG, inducibility of VF, and history of previous AF ( $p < 0.05$ ) than male patients who did not develop cardiac events. The presence of symptoms at the time of diagnosis defined those patients at greater risk for events, which occurred in 18.4% of patients with previous syncope, in 64.7% of those with previous aborted SCD and only in 5.5% of previously asymptomatic patients ( $p < 0.001$ ). In fact, symptoms were the only independent predictor for a worse prognosis in the multivariable analysis (HR: 3.4, 95% CI: 1.3 to 8.1 for syncope,  $p = 0.01$ ; and HR: 13.8, 95% CI: 5.5 to 34.6 for SCD,  $p < 0.001$ ) for the male population.

Conversely, in the presence of an extremely low rate of cardiac events in women (2.8%), none of the classically

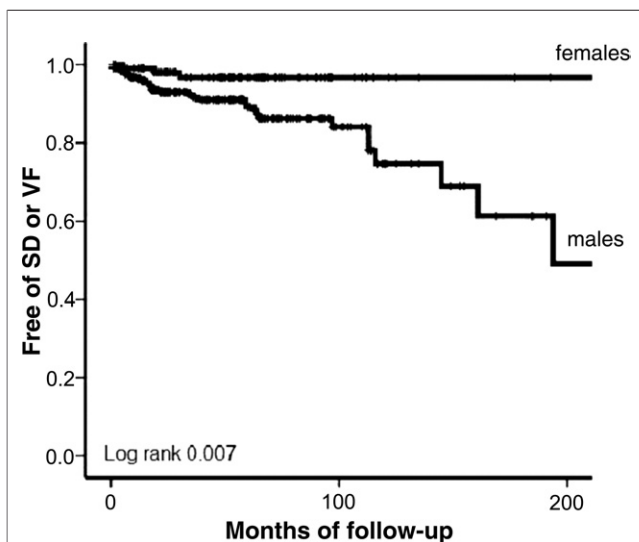
reported risk markers (8–12) showed enough power to identify those female patients with worse outcome. For example, 2 of the 3 events appeared in previously asymptomatic women (Table 4). Interestingly, conduction parameters such as the PR interval or the HV interval were significantly longer in female patients who developed cardiac events (Table 4). The former, with the limitations as a result of the scarce number of events, was actually the only independent predictor for cardiac events in the female population (multivariable analysis: HR 1.03 per each ms of increase in the PR interval, 95% CI: 1.01 to 1.05,  $p = 0.03$ ).

### Discussion

In this study, we aimed to analyze the differences in clinical manifestations of Brugada syndrome according to gender. In a series of 384 patients with Brugada syndrome, men were predominant (70.8%) and displayed a higher risk profile as compared with women, as well as a greater event rate in follow-up. In the male population, cardiac events were more frequent among patients with previous symptoms, spontaneous type-1 ECG, or inducibility of VF in the EPS. Women showed more conduction disturbances and longer QTc interval in response to sodium blockers. In the presence of a very low event rate, conduction parameters appeared to be related to a worse outcome in the female population.

To date, several hypotheses have been raised to explain the gender differences in Brugada syndrome. The role of specific mutations seems to be of minor influence because, on the one hand, patients with and without identified SCN5A mutations display a similar male predominance (7,18,19) and, on the other hand, the same single mutation has been described for both a family with male predominance and another one with female phenotypic predominance (13,20). In addition, no evidence exists of a gender influence of the new reported mutation on the GPD1-L gene (5). Two other hypotheses seem more likely to play a role in the gender distinction of Brugada phenotype, perhaps interacting with each other: the gender-related intrinsic differences in ionic currents and the hormonal influence.

Di Diego et al. (14) elegantly demonstrated that transient outward potassium current (Ito) density quantified by



**Figure 1** Kaplan-Meier Estimate of Cardiac Event-Free Survival According to Gender

Kaplan-Meier analysis of cardiac events in follow-up, defined as sudden cardiac death (SCD) or documented ventricular fibrillation (VF), in male and female patients.

**Table 3 Variables Related to the Occurrence of Cardiac Events During Follow-Up in the Entire Population (Cox Regression Model)**

	Overall Population					
	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Gender	4.45	1.36-14.58	0.014	2.82	0.64-12.41	NS
Previous AF	2.63	1.24-5.58	0.012	2.16	0.93-5.03	0.07
Symptoms at diagnosis						
Syncope	3.43	1.5-7.83	0.003	1.86	0.7-4.97	NS
Aborted SCD	11.59	5.01-26.79	<0.001	8.45	3.17-22.55	<0.001
Spontaneous type-1 ECG	2.7	1.3-5.58	0.008	1.4	0.59-3.33	NS
Inducibility of VF (EPS)	5.33	2.34-12.15	<0.001	2.93	1.14-7.55	0.02

Cardiac events are defined as SCD or documented VF.

CI = confidence interval; ECG = electrocardiogram; HR = hazard ratio; VF = ventricular fibrillation; other abbreviations as in Table 1.

whole-cell patch-clamp techniques was significantly greater in male than female right ventricle epicardia of arterially perfused canine heart preparations, thus explaining the deeper notch in phase 1 of the action potential in men as compared with women. The electrophysiological implications of these findings were assessed in the same model by the administration of a sodium-calcium blocker and subsequently confirmed by other groups (21). Two effects were noted: the use of terfenadine induced, first, transmural dispersion of repolarization, thus leading to the characteristic ST-segment elevation of Brugada syndrome, and, second, epicardial dispersion of repolarization that might facilitate all-or-none repolarization, thus favoring phase-2 re-entry and VF (14). Both phenomena were mainly observed in male samples because of their deeper Phase 1 magnitude at baseline.

In our study, we provide clinical confirmation of these experimental findings. In accordance with the work of Di Diego et al. (14), our male population displayed more pathological ECGs at baseline as compared with our female population. Type-1 ECG at diagnosis was significantly more frequent in men than in women (47% vs. 23%,  $p < 0.001$ ) and, among patients displaying spontaneous type-1 ECG, ST-segment elevation also was significantly greater in men ( $3.5 \pm 1.8$  mm vs.  $2.5 \pm 0.7$  mm,  $p < 0.001$ ). On the other hand, men also had a significantly greater rate of

VF than women, both before the diagnosis (6% vs. 1%,  $p = 0.01$ ) and during follow-up (11.6% vs. 2.8%,  $p = 0.003$ ), although in our series, male gender per se was not an independent predictor of cardiac events. Our findings are also in the same line than the ones from other clinical works in which men are reported to display more ST-segment elevation (22) and greater events in follow-up (12).

This study also demonstrates that, despite similar baseline ECG parameters, women experience a greater increase of PR interval, QRS duration, and QTc interval after exposure to sodium-blockers than men (Table 2). Cardiac conduction disturbances have been reported in sodium loss-of-function conditions and specifically combined with Brugada syndrome within the same family (23). Interestingly, a gender-related difference could be observed in this family, in which men predominantly presented with Brugada phenotype and women with isolated conduction disturbances (23). Subsequent experimental studies demonstrated that, in the presence of sodium blockade, the smaller Ito in women predisposes them to progressive conduction disorders, whereas the greater Ito in men explains their greater ST-segment elevation (24). Accordingly, in our clinical study, the exposure to a sodium-blocker produced a greater increase in conduction parameters in females as compared with men. However, the differences of increase in ST-segment elevation were not statistically significant between both genders.

**Table 4 Characteristics of the Patients With Cardiac Events in Male and Female Populations**

	Male Population			Female Population		
	No Events (n = 241)	Events (n = 31)	p Value	No Events (n = 109)	Events (n = 3)	p Value
Symptoms at diagnosis, n (%)	46 (19)	20 (64)	<0.001	16 (15)	1 (33)	NS
Previous AF, n (%)	18 (7)	8 (26)	0.005	12 (11)	2 (67)	0.04
Spontaneous type-1 ECG, n (%)*	105 (43)	21 (67)	0.01	23 (21)	2 (67)	NS
PR interval, ms*	175 ± 30	178 ± 40	NS	173 ± 32	240 ± 62	0.001
QRS duration, ms*	107 ± 17	110 ± 18	NS	97 ± 16	130 ± 62	NS
QTc interval, ms*	421 ± 48	432 ± 42	NS	420 ± 49	486 ± 47	0.06
ST-segment elevation*†	3.6 ± 2	3 ± 1	NS	2.4 ± 1	3.2 ± 1	NS
Inducibility of VF, n (%)	64/232 (28)	20/27 (74)	<0.001	10/89 (11)	1/2 (50)	NS
HV interval	48 ± 10	46 ± 7	NS	46 ± 8	60 ± 11	0.02

Cardiac events are defined as SCD or documented VF. \*Indicates parameters in the basal ECG. †Indicates parameters exclusively in patients with spontaneous type-1 ECG. Abbreviations as in Tables 1 and 3.

On the other hand, experimental works have shown that female rabbit ventricular myocytes have significantly lower IKr and IK1 current densities (25) and greater epicardial ICaL (26) than male rabbits, which could explain the greater susceptibility of women to develop longer QT intervals and early afterdepolarizations or torsades de pointes (21,27). Thus, the differences in IK currents between genders are expected to be the basis for the greater prolongation of the QTc interval observed in our female population after exposure to sodium blockers, because all the 3 drugs used in this study (ajmaline, flecainide, and procainamide) have known IKr blocking effect.

Hormonal influence might also play a role in the phenotypic manifestations of Brugada syndrome (28), which would explain the regression of the typical ECG features reported in castrated men (15) and the greater levels of testosterone present in Brugada male patients as compared with control patients (16). Some experimental data point out that hormones could modify the ionic membrane currents, with estrogens having been reported to inhibit Ito expression and trafficking (29) and testosterone to increase IKs slow potassium currents (30). Consequently, with this hypothesis, the few available data existing thus far of Brugada syndrome in children have not shown a difference in phenotypic presentation between boys and girls (31). The population in this study mainly was of adult patients (95.6% were >18 years of age). Thus, conclusions about a gender distinction in Brugada syndrome during childhood, and specifically before the hormonal influence of adolescence, cannot be taken from these data.

Identifying the markers of risk of SCD in patients with Brugada syndrome has been a matter of great interest in the last years (8-12). In contrast to the previous series of our group, embracing patients from the international database (8,10), this study included only those patients directly studied and followed by the 2 participating centers, because we sought to minimize a high-risk selected population bias and to ensure an identical study protocol for all patients. Interestingly, in this study we assessed the characteristics of patients at risk separately in men and women. In accordance to the results reported for previous mixed populations (8-12), high-risk male patients had more previous symptoms, more spontaneous type-1 ECG, and more inducibility of VF at the EPS. On the other hand, the event rate in the female population appeared considerably lower than that of the male population. Despite the inclusion in our study of the largest population of female patients described thus far, in the presence of such low rate of cardiac events, only the conduction parameters consistently differ between women who experienced SCD or VF and those who did not. Specifically, the PR interval was the best marker of risk for the female population in our series, although this result should be interpreted cautiously given the small number of events. One plausible interpretation is that longer PR intervals reflect greater sodium channel dysfunction and,

thus, a deeper defect leading to greater susceptibility for ventricular arrhythmias.

**Study limitations.** Changes on ECG parameters after exposure to sodium blockers were evaluated for the overall population, even though not all patients received the same drug. The possible bias due to these differences was attenuated by the fact that the percentage of the drugs administered in men and women did not significantly differ.

## Conclusions

In this prospective 2-center study including 384 patients with Brugada syndrome, men (70.8%) were the predominant gender represented and displayed a greater risk profile at baseline as compared with women, with more pathological ECG features, a greater rate of symptoms, and a greater inducibility of ventricular arrhythmias at the EPS. Women showed greater conduction intervals and a corrected QT interval in response to sodium-blockers. Cardiac events in the longest follow-up reported thus far were significantly greater in men, although gender was not an independent predictor of a worse outcome. Classic risk factors identified male patients with worse outcome, being the presence of previous symptoms the most important predictor of events in the male population. Conversely, conduction disturbances appeared to be a marker of risk in this female population. This study confirms that men have a worse prognosis than women with Brugada syndrome.

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**Key Words:** Brugada syndrome ■ gender ■ sudden cardiac death.