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ABSTRACT

Background

There is limited information on gender differences in patients with Brugada syndrome (BrS) who experienced arrhythmic events (AEs).

Objectives

To compare clinical, electrocardiographic (ECG), electrophysiologic (EP) and genetic characteristics between males and females in BrS-patients with their first AE.

Methods

The multicenter Survey on AE in BrS (SABRUS) collected data on first AE in 678 BrS-patients including 619 (91.3%) males and 59 (8.7%) females aged 0.27 to 84 (mean 42.5±14.1) years at the time of AE.

Results

After excluding pediatric patients, females were older than males (49.5±14.4 vs. 43±12.7 years, respectively, *P*=0.001). Higher proportions of females were observed in the pediatric and elderly populations. In Asians, male/female ratio of AE was ≈9-fold higher compared to Caucasians. Spontaneous type 1 BrS-ECG was associated with earlier onset of AE in pediatric females. A similar prevalence (≈65%) of spontaneous type 1 BrS-ECG was present in males and females above age of 60 years.

Females less frequently showed a spontaneous type-1 BrS-ECG (31% vs. 59%, *P*<0.001) or arrhythmia-inducibility at EP study (34% vs. 64%, P<0.001). An SCN5A mutation was more frequently found in females (47.6% vs. 27.8% in males, P=0.007).

Conclusions

This study confirms that female BrS-patients are much rarer, display less type 1 Brugada-ECG and exhibit lower inducibility rates than males. It shows for the first time that BrS females with AE have higher SCN5A mutation rates as well as the relationship between gender vs. age at onset of AE and ethnicity.

Keywords: Sudden cardiac death; *SCN5A* mutation; Ethnicity; Implantable cardioverter defibrillator; Brugada-ECG.

Brugada syndrome (BrS) is an inherited arrhythmic disorder that exposes patients with ostensibly normal hearts to sudden cardiac death (SCD).[1] Although the mode of inheritance has been recently questioned [2] , symptomatic BrS is surprisingly uncommon in females. The largest series include only 7-9 females with aborted cardiac arrest (CA) [3,4] and up to 4 females with AE after prophylactic ICD-implantation or follow-up of BrS-patients without ICD.[5-8]

We recently reported the results of a multicenter international survey on AE in BrS (SABRUS) on a large cohort of 678 BrS-patients with their first ever documented AE, including 59 females. [9,10]

The present study sought to compare males and females in the SABRUS patient population.

METHODS

CENTER SELECTION AND PATIENT RECRUITMENT

As detailed elsewhere[9] a total of 678 BrS-patients were recruited from 23 centers worldwide. These centers were located in 10 Western (415 patients, 61.2%) and 4 Asian countries (263 patients, 38.8%) and provided 7 to 105 patients per center. Sixteen centers (69.5%) reported their sole experience and 7 (31.5%) collected the experience of multiple institutions. All centers except two, declared no age limitation at patient recruitment.

The study was approved by the Research Ethics Boards of all participating institutions.

DATA ACQUISITION.

Anonymous patient information was retrospectively collected using a predefined questionnaire regarding the following: 1) gender; 2) age at the time of the first AE; 3) mode of AE documentation (Group A or Group B, see below); 4) ethnicity (Caucasian, Asian, other or unknown); 5) proband status; 6) family history of SCD; 7) prior history of syncope ; 8) presence of spontaneous or drug-induced Brugada-ECG type 1; 7) inducibility of sustained ventricular fibrillation (VF) at EP study (EPS) and 9) results of genetic testing for the presence of *SCN5A* mutation.

In addition all 23 SABRUS centers were requested to provide the gender and age distribution of the entire BrS-population followed at their own centers (with or without prior AE). The centers from Western and Asian countries were assumed to include Caucasian and Asian patients, respectively, based on initial SABRUS results.[9]

DEFINITIONS.

Arrhythmic events: Defined as any sustained ventricular tachyarrhythmia documented during initial aborted CA (group A) or triggering ICD-shock therapy after prophylactic implantation of an ICD (group B).

Age cut-offs: The rationale for using age cut-offs of 16 years for the pediatric patients and 70 years for the elderly has been explained elsewhere.[9]

Patient groups according to indication for ICD-implantation: Group B patients were subdivided by their indication for a prophylactic ICD-implantation as stated in the 2013 Expert Consensus Statement:[11]

- Group B1: Class IIa indication.

- Group B2: Class IIb indication.

- Group B3: Implanted with an ICD that subsequently proved to be justified (i.e. triggering appropriate ICD-shock therapy for AE) despite not complying with the above indications. These patients were further divided into 2 subgroups according to the EPS results: a) Group B3a: no arrhythmias inducible at EPS; b) Group B3b: EPS was not performed.

STATISTICAL ANALYSIS.

Differences between ages of different groups were assessed using a Mann–Whitney U test. Ratio differences were examined by a Chi-square test or a Fisher's exact test as appropriate. Scale variables are presented as mean±SD and nominal variables as N (Percentage). Statistical significance was defined as $P<0.05$. All calculations were performed using SPSS version 24 (IBM, Armonk, NY, USA).

RESULTS

The demographic, clinical, ECG, EPS and genetic findings of the patients in respect to gender are presented in **Table 1**.

Demographics. Out of 678 patients included in SABRUS, aged 0.27 to 84 years old, 619 were male (91.3%) and 59 (8.7%) were female. The vast majority (94.2%) of patients were 16 to 70 years old.

Gender distribution. The male to female (M/F) ratio was 10.4 for the whole group ranging from 25.2 in the 27-37 age group to 1.9 and 2.0 in the pediatric and elderly groups, respectively **(Figure 1A).** The proportion of females was highest among the pediatric (17% vs. 3% of males, $P<0.001$) and the elderly groups (5% vs. 1% of males, $P<0.05$) while that of males

was highest between ages 16-70 years (96% vs. 78% of females, *P*<0.001) **(Table 1).** In the pediatric group (n=29), there was a similar proportion of males and females in the 6-15 years group (42 and 40%, respectively) and in infants ≤5 years (58 and 60%, respectively). One of the 2 oldest study patients aged 84 years old was a female.

Age at time of AE. In the whole study-population the age at the time of the AE was not-normal distributed with no significant difference between males (41.9±14.0 years, Median [IQR] 42.0 [33.0-52.0]) and females (42.1±21.2 years, Median [IQR] 46.0 [28.0-58.0]) (*P*=0.225) **(Tables 1 and 2A).** Excluding the pediatric-patients from the entire cohort resulted in a normal age distribution with females being significantly older than males (49.5±14.4 vs. 43±12.7 years respectively, *P*=0.001) **(Table 2B)**. Similar gender related differences in age were observed in several subgroups in patients aged ≥16 years **(Table 2B).** In the pediatric group the ages of males and females at the time of AE were similar (6.2±4.9 and 5.8±6.2 years, respectively, *P*=0.636) **(Table 2C);** however, the presence of spontaneous type-1 BrS-ECG was associated with earlier onset of AE in the pediatric group in females as compared to males **(Table 2C).**

Mode of AE documentation. There was no gender difference in the proportion of patients belonging to groups A and B. There were similar rates of males (63%) and females (61%) in group A **(Table 1).**

Ethnicity. Compared to males, females were more frequently Caucasian (88% vs. 50%) and markedly less frequently of Asian origin (8% vs. 43%) (*P*<0.001). The M/F ratio was higher in Asians than in Caucasians (53 vs. 6) **(Table 1)** with a peak-ratio in the 38-48 year age-group for Asians and in the 27-37 year age-group for Caucasians **(Figure 2A).** Of

note, in the pediatric group, 25 of 26 patients with known ethnicity were Caucasian (16 males and 9 females) while there was a single Asian male. In the elderly group, 7 were Caucasian (4 males and 3 females) and the 2 Asians were male.

Proband status. Of the 678 study-patients 542 (496 males) were probands and 88 (76 males) were diagnosed during family screening. The proportions of probands in Caucasians and Asians were 83.5 and 91.5%, respectively, with no significant gender difference between the various age groups. **(Online Figure).**

Clinical history. A family history of SCD was noted in a similar proportion of patients of females (29%) and males (21%) (*P*=0.287) **(Table 1).** The 3 highest proportions of family history of SCD (40-50%) were noted in females **(Figure 3A).** A prior history of syncope was also noted in a higher proportion of females (47%) than males (38%) but the difference did not reach statistical significance (*P*=0.168) **(Table 1, Figure 3B).**

ECG. A spontaneous type-1 BrS-ECG was significantly more frequently observed in males (69%) than females (41%) (*P*<0.001) **(Table 1).** This difference was maintained up to 59 years of age at time of AE **(Figure 3C);** after age 60 years, a similar high incidence (≈65%) of spontaneous type-1 BrS-ECG was observed in both genders.

EPS. EPS was performed in a similar proportion of females and males (66% and 58%, respectively, *P*=0.246). The rate of VF-induction was significantly lower in females (36% vs. 66%, *P*<0.001) (**Table 1)** regardless of the patient's age at the AE **(Figure 3D).**

Genetic testing. Genetic testing was performed in a similar proportion of female and male patients (71% and 72%, respectively). In the whole patient group, an *SCN5A* mutation was found more frequently in females (47.6% vs. 27.8% in males, *P*=0.007)

(Table 1). However, in patients aged <16 years, mutation rates were similarly high (70% and 66.7% in females and males, respectively, *P*=0.86) whereas in patients ≥16 years, there was only a trend toward higher mutation rates in females (40.6% vs. 26.4%, *P*=0.082) **(Table 3, Figure 4)**. Both males and females had most of their mutations classified as pathogenic or likely pathogenic (89.9% vs. 78.9%, respectively) with no significant difference between genders (*P*=0.237).

Online Table 1 shows the main demographic, clinical, ECG and EP differences between 443 males and 42 females who underwent genetic testing in respect to the presence of an *SCN5A* mutation.

Data from the registry. Data on patient gender and age distribution were provided by 22 of the 23 SABRUS centers. Of note, only 5 of these 22 main centers were from Asian countries while the majority was from Western countries. The registry comprised 6441 patients (73.4% males and 26.6% females**) (Online Table 2).** The involvement of Asian patients was very low at high and low ends of the age spectrum (1% and 2% for the pediatric group and the elderly groups, respectively) while it ranged between 7.8 to 12.9% in the other age groups. The M/F ratios were the highest (3.8-3.9) in the 27-48 year age-group and the lowest at the pediatric and elderly age groups (1.2 and 1.8, respectively) **(Figure 1B).** In Western countries the M/F ratio ranged from 1 in both the pediatric and elderly groups to 3 in the 27-48 year age group. In Asian patients it ranged from 10 in the 49-59 year age-group to 86 in the 27-37 year age-group **(Figure 2B).**

Indications of prophylactic ICD-implantation. There was no difference between the proportions of males (37%) and females (39%) who underwent prophylactic ICD-

implantation (Group B). A higher proportion of females (8 of 23, 35% vs. 55 of 229, 24% of males) belonged to Group B3 **(Table 1);** however, this difference did not reach statistical significance (*P*=0.25).

DISCUSSION

The present study compares the clinical, ECG, EP and genetic characteristics of 619 male and 59 female BrS-patients with a first documented AE. The prior largest comparative study by Sacher et al[5] involved 11 European centers comprised 50 males (33 with aborted CA) and only 8 females (3 with aborted CA).

CONFIRMATORY STUDY RESULTS.

The results of our study confirmed several known characteristics of the female gender:[5,7,8]

Rarity of AE in BrS females. Our results confirm the rare occurrence of AE in female BrS-patients (M/F ratio of 10.4 in the survey) despite the non-negligible prevalence of the disease in that population (M/F ratio of 2.75 in the registry). Sieira et al.[8] reported on the highest AE-rate in females (6 of 23, 26%) in a series of 542 BrS-patients (42% females). They explained their large female cohort by a proactive search of BrS and an exhaustive familial screening program performed at their institution.

Lower prevalence of spontaneous type 1 Brugada-ECG. Out of a population of 58 patients with AE, Sacher et al.[5] found a spontaneous type-1 BrS-ECG at baseline in 36 men (72%) but in only 2 women (25%) (*P*=0.02). Sieira et al.[5] also found a low incidence rate (1 of 7, 14%) of spontaneous type-1 BrS-ECGs in females with AE. In contrast, in

PRELUDE[6] all 3 BrS-females who exhibited an AE after prophylactic ICD-implantation had spontaneous type-1 BrS-ECGs. In SABRUS a spontaneous type-1 BrS-pattern was observed in 69% of males and 41% of females with AE (*P*<0.001). Although our results confirm the lower female prevalence of spontaneous type-1 BrS-ECGs, the relatively high figure of 41% in females has never been reported previously.

Lower VF-inducibility rate. The lower VF-inducibility rate in BrS-females has been previously observed in all clinical settings of BrS.[5,7,8] In SABRUS, a similar lower percentage of VF-inducibility was observed in females (36% vs. 66% in males, *P*<0.001).

NEW STUDY FINDINGS.

Gender and age at onset of AE. Our study showed that gender distribution markedly varied in respect to patient age group at time of AE with a higher proportion of females among the pediatric and elderly age groups contrasting with a higher proportion of males between ages 16-70 years. Similar results were observed in the SABRUS-registry.

Gender and ethnicity. SABRUS also showed for the first time that gender distribution of AE was markedly dependent on patient ethnicity. The M/F ratio of AE in Asians was ≈9 fold higher than in Caucasians. Interestingly, analyzing the registry of the 22 main SABRUS centers showed a similar M/F risk ratio of 8 with M/F ratios of 19.2 and 2.4 in Asians and Caucasians, respectively. An electrophysiological mechanistic explanation of the extremely high M/F ratio in Asians compared to Caucasians may be due to the presence of modifier genes in Asians but not in Caucasians (12).

Earlier onset of AE in pediatric females. We found that the presence of spontaneous type-1 BrS-ECG's was associated with an earlier onset of AE in the pediatric group in

females as compared to males **(Table 2C).** This finding suggests that in the pediatric population, a spontaneous type-1 BrS-ECG in females might represent a significant arrhythmic risk marker.

Prevalence of spontaneous type-1 BrS-ECG. Contrasting with the higher prevalence of spontaneous type-1 BrS-ECG in males before age 60, a similar prevalence (≈65%) of spontaneous type-1 BrS-ECG was present in males and females above the age of 60 years **(Figure 3C).** This suggests that ageing is a relevant contributor to the development of a type-1 ECG, which could relate to an age-related development of (ultra)structural abnormalities, that has previously been shown in SCN5A-knockout mice.[13]

Gender and presence of *SCN5A* gene mutations. The most interesting finding in our present study relates to major gender differences in genetic characteristics. A recent Japanese study involving 97% of males showed that *SCN5A* mutation was a significant predictor of cardiac events in BrS *probands.*[14] In our study which involved 91.3% of males and 79.9% of probands, an *SCN5A* mutation was found more frequently in females (47.6%) than in males (27.8%) (P=0.007). Interestingly this was observed in all age groups at time of AE **(Figure 4).** Of note, when subdividing the population to above or below 16 years old, no difference in mutation rate was seen in the pediatric population and only a trend towards statistical significance was seen in adults probably due to relative small size of the female SABRUS group. Also, in our male SABRUS-patients the *SCN5A* mutation rate was slightly higher than that obtained in a large cohort of asymptomatic male BrS-patients from 4 of the largest centers cooperating in SABRUS (27.8% vs. 20.8%, P<0.001) **(Table 3).** However, in our female SABRUS-patients

the *SCN5A* mutation rate was markedly higher than in asymptomatic female BrS-patients (47.6% vs. 26.8%, *P*<0.001) **(Table 3).** Therefore, the relatively higher mutation rates observed in our female cohort with AE would suggest that the presence of an *SCN5A* mutation could represent an important risk marker for AE in the female patient population and to a much lesser extent in male patients.

Five (63%) of the 8 females of group B3 were *SCN5A* mutation carriers **(Online Table 1).** This could suggest that there might be additional value of genetic testing for deciding upon prophylactic ICD-implantation in females that should be assessed in prospective studies.

Clinical implications.

Arrhythmic risk stratification of BrS-patients is not an easy task in males and even more so in females. The present study suggests for the first time the possible predictive value of the presence of an *SCN5A* mutation in female patients that should be assessed prospectively.

Study limitations.

In addition to study limitations listed elsewhere[9,10] it is worthwhile emphasizing that despite the relatively large female cohort patient (n=59), our results from genetic testing derived from only 42 (71%) female patients. In addition, we acknowledge the problematic comparison in the pediatric and elderly groups due to a small sample size, and conclusion drawing must be done carefully.

A history of sinus node dysfunction was found by the Pedro Brugada group to represent a significant predictor of AE.[15,16] This parameter was not systematically assessed in our study.

Conclusion

Besides confirming previously known differences, this largest comparative study shows for the first time multiple important gender differences in BrS patients, especially the complex relationship between gender distribution and patient ethnicity with age at onset of AE as well as a possible worse prognosis associated with the presence of *SCN5A* mutation in females. It is important that all these factors will be taken into account in future studies on arrhythmic risk stratification in BrS.

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Table 1. Patients characteristics according to gender.

		Male	Female	P value
Number of patients		**619**	**59**	
Patient Age at AE (year)	Age range	0.27-84	0.36-84	
	All patients (n=678)	41.9±14.0	42.1±21.2	0.225
	< 16 years (n=29)	19 (3)	10 (17)	<0.001
	16-70 (n=639)	593 (96)	46 (78)	<0.001
	>70 years (n=10)	7 (1)	3 (5)	<0.05
Mode of AE documentation				
	Group A (n=426)	390 (63)	36 (61)	0.763
	Group B (n=252)	229 (37)	23 (39)	
	Group B1 (n=112)	102 (45)	10 (43)	
	Group B2 (n=77)	72 (31)	5 (22)	0.482
	Group B3 (n=63)	55 (24)	8 (35)	
	Subgroup B3a (n=33)	27 (49)	6 (75)	0.261
	Subgroup B3b (n=30)	28 (51)	2 (25)	
Ethnicity				
	Caucasian (n=364)	312 (50)	52 (88)	<0.001
	Asian (n=270)	265 (43)	5 (8)	
	Other/Unknown (n=44)	42 (7)	2 (3)	
Proband Status				
	Proband (n=542)	496 (80)	46 (78)	0.121
	Not Proband (n=88)	76 (12)	12 (20)	
	Unknown (48)	47 (8)	1 (2)	0.111
Family history of SCD				
	Yes (n=145)	128 (21)	17 (29)	0.287
	No (n=468)	427 (69)	41 (69)	
	Unknown (n=65)	64 (10)	1 (2)	<0.05
History of syncope				
	Yes (n=265)	237 (38)	28 (47)	0.168
	No (n=413)	382 (62)	31 (53)	
Spontaneous type-1 BrS-ECG				
	Yes (n=451)	427 (69)	24 (41)	<0.001
	No (n=227)	192 (31)	35 (59)	
VF inducibility				
	EPS performed (n=400)	361 (58)	39 (66)	0.246
	Inducible (n=253)	239 (66)	14 (36)	<0.001
	Not inducible (n=147)	122 (34)	25 (64)	
Presence of *SCN5A* mutation				
	Testing done (n=485)	443 (72)	42 (71)	0.825
	SCN5A mutation (n=143)	123 (28)	20 (48)	<0.01
	No *SCN5A* mutation (n=342)	320 (72)	22 (52)	

Abbreviations: n (%) unless otherwise indicated.

AE = arrhythmic event; BrS = Brugada syndrome; ECG = electrocardiogram; EPS = electrophysiologic study; Group A = cardiac arrest survivors; Group B = patients who received an appropriate shock from their ICD after prophylactic implantation; Group B1 = Class IIa indication (11); Group B2 = Class IIb indication (11); Group B3 = neither Class IIa nor Class IIb; Subgroup B3a = no inducible VF at EPS; Subgroup B3b = EPS not performed; SCD = sudden cardiac death; VF = ventricular fibrillation.

Table 2. Comparison of the age at time of AE between males and females in regard to the mode of AE documentation, ethnicity and various clinical characteristics.

2A. In all patients

		Male	Female	P-value
Number of patients		619	59	
Mean age at time of AE		41.9±14	42.1±21.2	0.255
Mode of AE documentation	Group A	39.5±14	37.5±23.5	0.783
	Group B	45.8±13.1	49.3±14.8	0.078
Ethnicity	Caucasian	41.2±15	41.9±21.4	0.222
	Asian	43.3±12.2	45±18.8	0.915
Clinical characteristics	Proband status	42±14	42.9±21.2	0.273
	Family history of SCD	41.7±14	38.4±21.3	0.909
	Prior history of syncope	41.3±15.2	45.2±19	0.061
	Spontaneous type-1 BrS-ECG	41.8±14.3	42.2±25	0.246
	Positive EPS	43.4±13	44.4±18.7	0.387
	Presence of *SCN5A* mutation	38.4±15.8	33.7±24.7	0.643

2B. In patients aged ≥ 16 years old.

		Male	Female	P-value
Number of patients		600	49	
Mean age at time of AE		43±12.7	49.5±14.4	0.001
Mode of AE documentation	Group A	41±12.4	47.9±16.8	0.029
	Group B	46.3±12.4	51.5±10.6	0.037
Ethnicity	Caucasian	43.1±12.9	49.6±13.8	0.002
	Asian	43.4±12.1	45±18.8	0.926
Clinical characteristics	Proband status	43±12.7	49.4±15.4	0.005
	Family history of SCD	42.6±13	48±13	0.120
	Prior history of syncope	43.3±12.9	50±13.5	0.009
	Spontaneous type-1 BrS-ECG	43.2±12.6	53.1±14.2	0.002
	Positive EPS	43.8±12.5	47.8±14.5	0.185
	Presence of *SCN5A* mutation	41.3±12.8	49.3±13.9	0.041

2C. In patients aged <16 years old.

		Male	Female	P-value
Number of patients		19	10	
Mean age at time of AE		6.2±4.9	5.8±6.2	0.636
Mode of AE documentation	Group A	5.8±5.3	6.3±6.4	0.978
	Group B	8.3±0.6	1.1±0	0.500
Ethnicity	Caucasian	6.2±5.2	4.8±5.6	0.419
	Asian	9±0	NA	NA
Clinical characteristics	Proband status	4.8±4.6	6.4±6.6	0.699
	Family history of SCD	6.7±5.7	7.3±7.5	0.857
	Prior history of syncope	6.2±5.1	5.6±5.3	0.900
	Spontaneous type-1 BrS-ECG	5.9±4.7	0.9±0.7	0.004
	Positive EPS	2.1±1.2	0.8±0	0.667
	Presence of *SCN5A* mutation	5.1±4.5	4.7±6.3	0.740

Abbreviations: AE = arrhythmic event; BrS = Brugada syndrome; ECG = electrocardiogram; EPS = electrophysiologic study; Group A = cardiac arrest survivors; Group B = patients who received an appropriate shock from their ICD after prophylactic implantation; SCD = sudden cardiac death.

Table 3. Comparison of *SCN5A* mutation rates in SABRUS and a Registry of Asymptomatic BrS Subjects in respect to gender

		Males	Females	P
Registry	< 16 yrs	26/91 (28.6%)	34/110 (30.9%)	0.71
	≥ 16 yrs	206/1025 (20.1%)	137/528 (25.9%)	0.0085
	All ages	232/1116 (20.8%)	171/638 (26.8%)	0.004
SABRUS	< 16 yrs	10/15 (66.7%)	7/10 (70%)	0.86
	≥ 16 yrs	113/428 (26.4%)	13/32 (40.6%)	0.082
	All ages	123/443 (27.8%)	20/42 (47.6%)	0.007

The Registry data originated from the following 4 SABRUS centers:

- L'Institut du Thorax, Service de Cardiologie, CHU de Nantes, Nantes, France (n=1104 sujects);
- Division of Cardiology, University of Torino, Torino, Italy (n=288 subjects);
- Heart Rhythm Management Centre, UZ-VUB, Brussels, Belgium (n=205 subjects);
- Pediatric Arrhythmias, Electrophysiology and Sudden Death Unit Cardiology Department, Hospital Sant Joan de Déu, Barcelona, Spain (n=157 subjects).

Figures legends

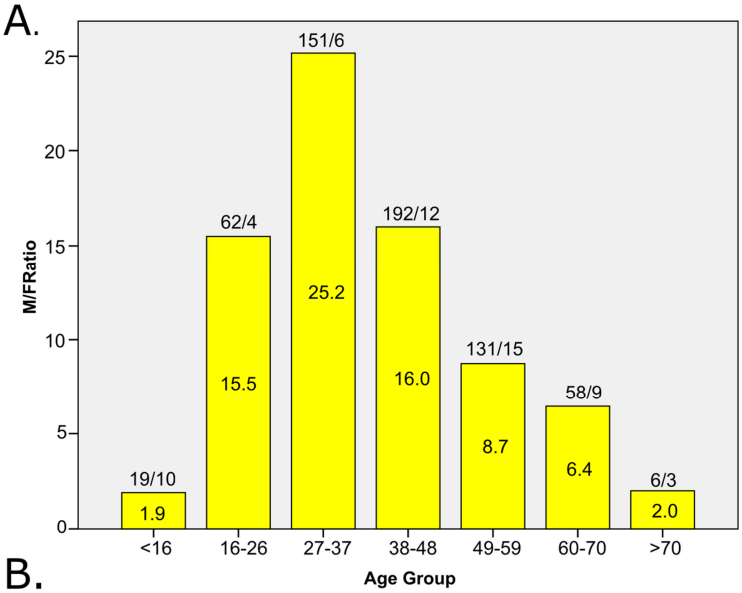
Figure 1. Male to female (M/F) ratio of arrhythmic event (AE) in various age groups in the 678 SABRUS patients (A) and in the 6441 patients of the Registry (B). The M/F ratio is indicated into the bars for each age group. The numbers above the bars indicate the absolute numbers of males and females, respectively, for each age group. In both SABRUS and the Registry, the M/F ratios were the highest in the 27-37 years age group. Note that the M/F ratio distribution is similar in both patient groups.

Figure 2. Male to female (M/F) ratio of arrhythmic event (AE) by ethnicity in various age groups in the 678 SABRUS patients (A) and in the 6441 patients of the Registry (B). The M/F ratio is indicated into the bars for each age group. In both SABRUS and the Registry, the M/F ratios were markedly greater in Asians than in Caucasians. The greatest M/F ratios were observed for Asians in the 38-48 years old age group in SABRUS (n=90) and in the 27-37 years old age group in the Registry (n=86).

Figure 3. Gender comparison of the proportions of patients with a family history of sudden cardiac death (panel A), prior history of syncope (panel B), presence of a spontaneous type 1 Brugada-ECG pattern (panel C) and inducibility of ventricular fibrillation at electrophysiologic study (panel D).

Figure 4. *SCN5A* mutations rates in SABRUS according to gender in respect to patient age group at the time of AE occurrence. Higher mutation rates were observed in females at all age groups with the highest figures (70% and 60%) observed in the pediatric and the 60-70 years age group, respectively. Of note the highest mutation rate in males (66.7%) was also found in the pediatric group.

A.



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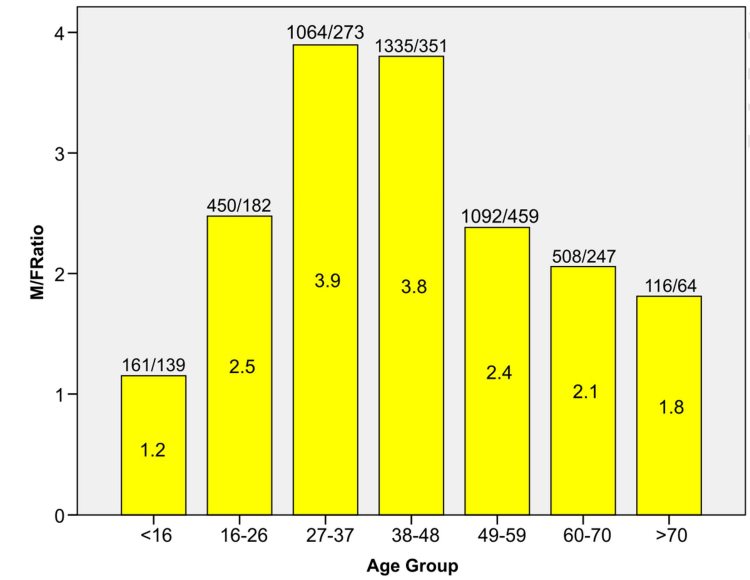

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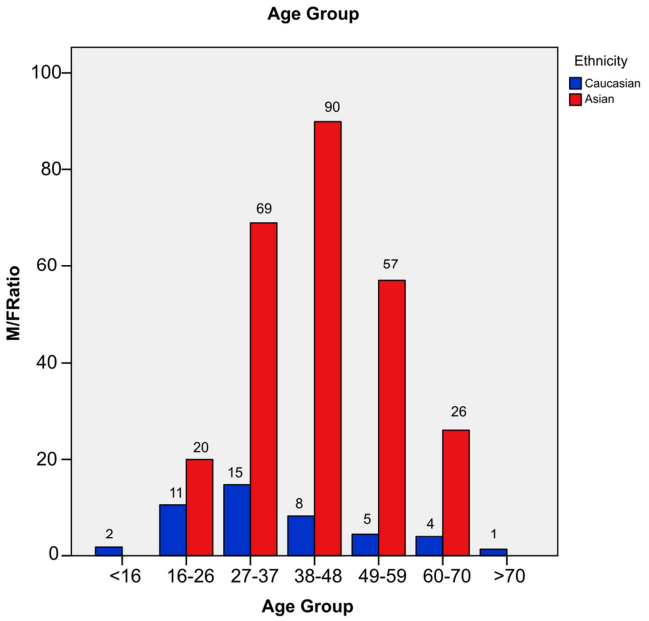

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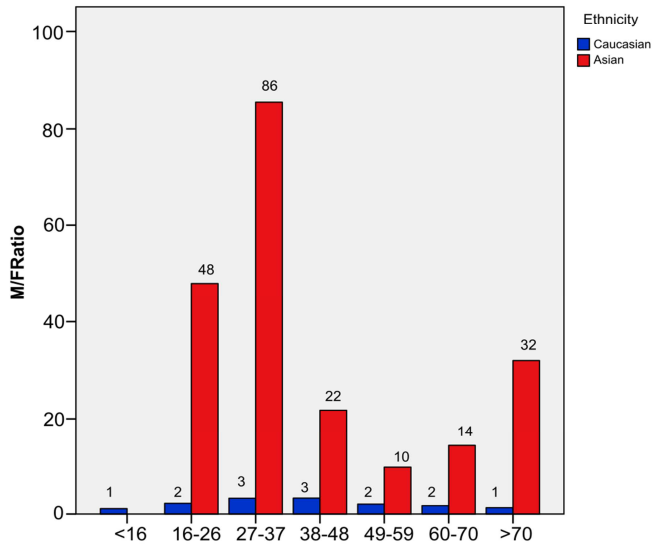

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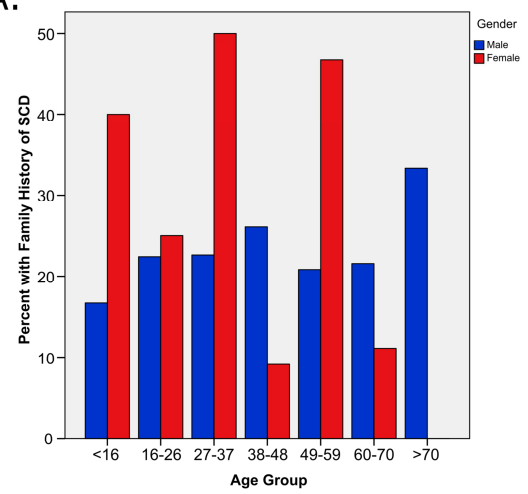
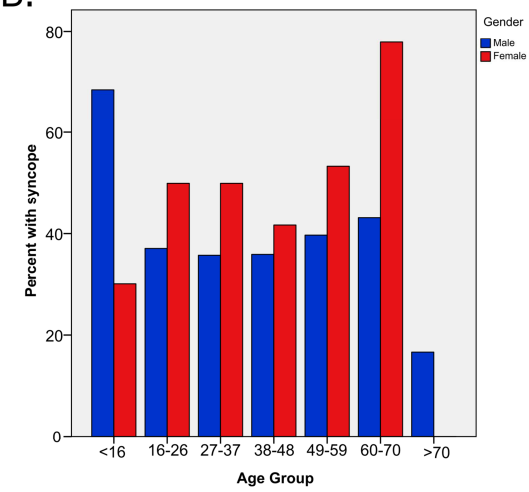
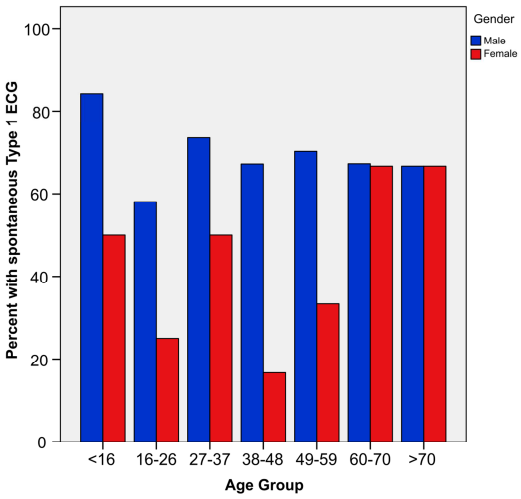

Gender
Male
Female
Percent with Family History of SCD
0
10
20
30
40
50
<16
16-26
27-37
38-48
49-59
60-70
>70
Age Group

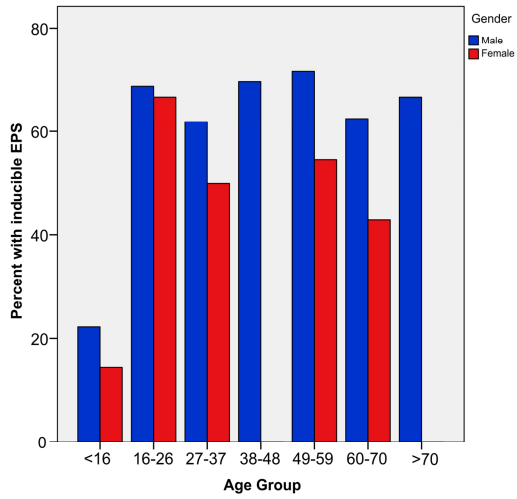
B.

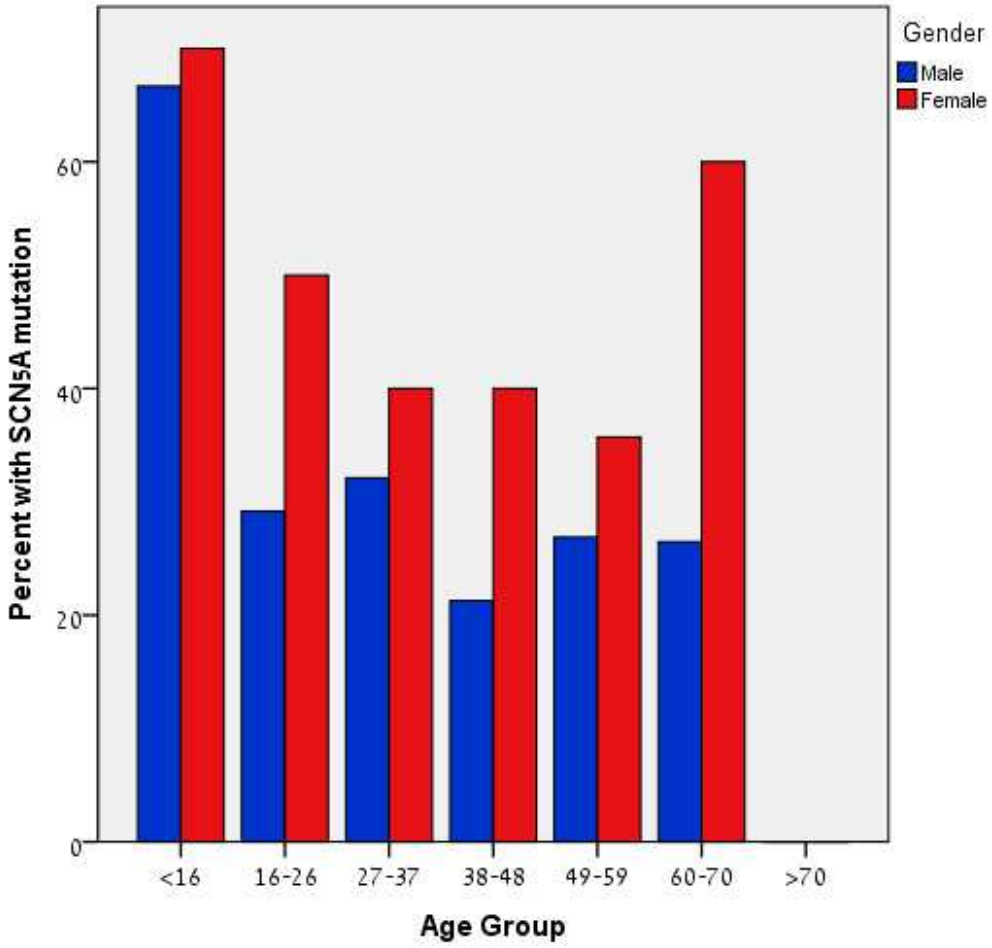

Gender
Male
Female
Percent with syncope
0
20
40
60
80
<16
16-26
27-37
38-48
49-59
60-70
>70
Age Group

C.


Gender
Male
Female
Percent with spontaneous Type 1 ECG
0
20
40
60
80
100
<16
16-26
27-37
38-48
49-59
60-70
>70
Age Group

D.


Gender
Male
Female
Percent with inducible EPS
0
20
40
60
80
<16
16-26
27-37
38-48
49-59
60-70
>70
Age Group


Gender
Male
Female
Percent with SCN5A mutation
0
20
40
60
<16
16-26
27-37
38-48
49-59
60-70
>70
Age Group