**Characteristics of patients with spontaneous vs drug-induced Brugada ECG.**

**Sub-analysis from the SABRUS**

**Running Title: Spontaneous vs drug-induced Brugada patients**

Anat Milman MD PhD1,2, Avi Sabbag MD1,2, Giulio Conte MD PhD3, Pieter G. Postema MD PhD4.5,Antoine Andorin MD4,6, Jean-Baptiste Gourraud MD PhD4,6, Frederic Sacher MD7, Philippe Mabo MD8, Sung-Hwan Kim MD9, Shingo Maeda MD PhD10, Yoshihide Takahashi MD PhD10, Tsukasa Kamakura MD PhD11, Takeshi Aiba MD PhD11, Jimmy JM Juang MD PhD12, Yoav Michowitz MD13, Eran Leshem MD1,2, Yuka Mizusawa MD4,5, Elena Arbelo MD PhD4,14,15, Zhengrong Huang MD PhD16, Isabelle Denjoy MD17, Carla Giustetto MD18, Yanushi D. Wijeyeratne MD4,19, Andrea Mazzanti MD4,20, Ramon Brugada MD PhD15,21,22, Ruben Casado-Arroyo MD PhD23 ,Jean Champagne MD24, Leonardo Calo MD25, Georgia Sarquella-Brugada MD PhD26, Jacob Tfelt-Hansen MD DMSc4,27,28, Silvia G. Priori MD PhD4,20, Masahiko Takagi MD PhD29, Christian Veltmann MD30, Pietro Delise MD31, Domenico Corrado MD PhD4,32, Elijah R. Behr MD4,19, Fiorenzo Gaita MD18, Gan-Xin Yan MD PhD33, Josep Brugada MD PhD14, Antoine Leenhardt MD17, Arthur A.M. Wilde MD PhD4,5, Pedro Brugada MD PhD3, Kengo F. Kusano MD PhD11, Kenzo Hirao MD PhD10, Gi-Byoung NamMD PhD34, Vincent Probst MD PhD4,6, Bernard Belhassen MD35

1 Leviev Heart Institute, The Chaim Sheba Medical Center, Tel Hashomer, Israel

2 Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

3 Heart Rhythm Management Centre, UZ-VUB, Brussels, Belgium

4 European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart

5 Amsterdam UMC, University of Amsterdam, Heart Center; department of Clinical and Experimental Cardiology, Amsterdam, The Netherlands

6 Service de Cardiologie, CHU de Nantes, Nantes, France

7 Hôpital Cardiologique du Haut-Lévêque & Université Bordeaux, LIRYC Institute, Bordeaux, France

8 Cardiology and Vascular Disease Division, Rennes University Health Centre, Rennes, France

9 Division of Cardiology, College of Medicine, The Catholic University of Korea, Seoul, Korea

10 Heart Rhythm Center, Tokyo Medical and Dental University, Tokyo, Japan

11 Division of Arrhythmia and Electrophysiology, National Cerebral and Cardiovascular Center, Osaka, Japan

12 Cardiovascular Center and Division of Cardiology, National Taiwan University Hospital and University College of Medicine, Taipei, Taiwan

13 Cardiology Department, Shaare Zedek Hospital, Affiliated to the Faculty of Medicine, Hebrew University, Jerusalem, Israel.

14 Arrhythmia Section, Cardiology Department, Hospital Clínic, Universitat de Barcelona and bIDIBAPS, Institut d’Investigació August Pi i Sunyer (IDIBAPS), Barcelona, Spain

15 Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain

16 Department of Cardiology, the First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China

17 Service de Cardiologie et CNMR Maladies Cardiaques Héréditaires Rares, Hôpital Bichat, Paris, and Université Paris Diderot, Sorbonne, Paris, France

18 Division of Cardiology, University of Torino, Department of Medical Sciences, Città della Salute e della Scienza Hospital, Torino, Italy

19 Cardiovascular Sciences, St. George's University of London and Cardiology Clinical Academic Group St. George's University Hospitals NHS Foundation Trust, London, UK

20 Molecular Cardiology, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy

21 Cardiovascular Genetics Center, University of Girona-IDIBGI, Girona, Spain

22 Medical Science Department, School of Medicine, University of Girona, Girona, Spain

23 Department of Cardiology, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium

24 Quebec Heart and Lung Institute, Quebec City, Canada

25 Division of Cardiology, Policlinico Casilino, Roma, Italy

26 Pediatric Arrhythmias, Electrophysiology and Sudden Death Unit Cardiology, Department Hospital Sant Joan de Déu, Barcelona - Universitat de Barcelona, Spain

27 The Heart Centre, Copenhagen University Hospital, Copenhagen, Denmark

28 Department of Forensic Medicine, Faculty of Medical Sciences, University of Copenhagen, Copenhagen, Denmark

29 Division of Cardiac Arrhythmia, Kansai Medical University Medical Center, Moriguchi, Japan

30 Hannover Heart Rhythm Center, Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany

31 Division of Cardiology, Hospital of Peschiera del Garda, Veneto, Italy

32 Department of Cardiac, Thoracic and Vascular Sciences University of Padova, Padova, Italy

33 Lankenau Medical Center, Wynnewood, Pennsylvania, USA

34 Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

35 Heart Institute, Hadassah University Hospital, Jerusalem, Israel.

**Address for correspondence:** Anat Milman, MD PhD

Davidai Arrhythmia Center, Leviev Heart Center, Sheba Medical Center,

Tel Hashomer 5265601, Israel.

 Telephone: +972-54-3166651

 Email: anatmilman@gmail.com

**Nonstandard Abbreviations and Acronyms:**

BrS - Brugada syndrome

S – spontaneous

DI - drug-induced

AE – arrhythmic events

SCD - sudden cardiac death

SABRUS - Survey on Arrhythmic events in Brugada Syndrome

ICD – implantable cardiac defibrillator

VF – ventricular fibrillation

Patients with Brugada syndrome (BrS) may display either a spontaneous (S) or a drug-induced (DI) ECG pattern. The latter group is considered at a lower risk of arrhythmic events (AE) and sudden cardiac death (SCD). The only study that compared these two groups in BrS associated with AEs comprised a small cohort of 44 patients (1).

The SABRUS (Survey on Arrhythmic events in Brugada Syndrome) gathers the largest cohort of patients with BrS and AEs published to date (2). The data that support the findings of this study are available from the corresponding author upon reasonable request. Patients were divided into 2 groups according to their AE presentation: group A presented with aborted cardiac arrest prior to diagnosis of BrS and group B were Brugada patients implanted prophylactically with an ICD which proved to be justified during follow up. The present study compares DI-BrS and S-BrS patients from SABRUS. **The study was approved by the Institutional Committee on Human Research at the Tel Aviv Sourasky Medical Center.** Continuous variables are presented as mean±SD or median (interquartile range) and compared using the student’s t-test or Mann-Whitney U test as appropriate. Categorical variables are presented by absolute numbers and proportions and compared using the χ2 test or Fisher exact test. All tests were 2-tailed, and a P < 0.05 was considered statistically significant.

Of the 678 SABRUS patients, 451 (66.5%) had S-BrS ECG and 227 (33.5%) had DI-BrS ECG (Table 1). Females predominated in the DI-ECG group (15.4% vs 5.3% in the S-ECG group, p<0.001), with less Asians than Whites (33.9% vs 42.8% in the S-ECG group, p=0.036). Higher inducibility rates of ventricular fibrillation (VF) at electrophysiologic study (EPS) were found in the S-ECG group (67.3% vs 55%.7 in the DI-ECG groups, respectively, p=0.022), with a similar rate of EPS performed in both groups (61.7% in the DI-ECG group vs 57.6% in the S-ECG group, p=0.315). There were no differences between DI-BrS ECG and S-BrS ECG patients regarding age at AE, proband status, history of syncope, AE presentation, family history of sudden cardiac death (SCD), fever related events and genetic analysis.

To the best of our knowledge this is the first study comparing BrS patients with S-ECG and DI-ECG in a large population cohort with AEs. Although a previous paper by Tadros et al. (3) showed that 8% of patients tested by drug provocation for BrS could have false positive results, we assume, based on our findings of the SABRUS cohort (4) that all our patients with DI-ECG have proven BrS, and that the results of our study should be taken in this context only.

Syncope combined with a spontaneous type 1 Brugada ECG has been shown to be useful for identifying Brugada patients at risk for AE. However, this is not relevant when a DI-ECG is encountered. In addition, the use of programmed ventricular stimulation has shown conflicting results. In a large series of patients with DI-BrS ECG, Sieira et al. (5) showed that VF inducibility rate was significantly lower than in patients with S-BrS ECG (13.2% vs 42.4%, respectively, p<0.01), however their cohort comprised a minority of patients with AEs. In our cohort comprising only patients with AEs, the lower inducibility rate is confirmed (55.7%. vs 67.3%, respectively, p=0.022). These findings suggest that EPS is less useful for the management of BrS patients with DI-ECG, and do not inform necessarily on risk stratification strategies. These findings could actually represent a difference in the mechanism of arrhythmia generation of the two subgroups of Brugada patients, and future studies should test whether this could explain the lower arrhythmic risk of DI-ECG patients.

Females predominated in our DI-ECG group. This is in line with the study by Nagayama et al. (1) in a smaller cohort.

For the first time, SABRUS showed that Asians with AEs displayed significantly less DI-ECG compared to whites. This may suggest that a genetic predisposition of Asians plays a role in the occurrence of the S-BrS ECG type.

No difference in the presence of *SCN5A* gene mutation was found between the DI-ECG and S-ECG groups. These findings agree with those reported by Nagayama et al. (1) in a similar, although significantly smaller patient cohort.

In conclusion, DI-BrS patients represented a third of BrS cohort with AEs. They differed from S-BrS patients in gender, ethnicity, and VF inducibility rates. The most important observation is that this group of patients is less studied and identifying high-risk DI-BrS patients is not an easy task. We encourage seeking new risk markers in this group in future studies.

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**Table 1. Patient characteristics according to Brugada ECG type.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |   | **Drug-induced BrECG** | **Spontaneous BrECG** | **P value** |
|  |   | (n=227, 33.5%) | (n=451, 66.5%) |
| **Age at AE, years (mean±SD)** |   | 42 ±14 | 42±15 | 0.969 |
|  | Age at AE ≤16 | 9 (4) | 23 (5.1) | 0.532 |
|  | Age at AE >16 | 218 (96) | 428 (94.9) |
| **Gender** | Male  | 192 (84.6) | 427 (94.7) | <0.001 |
|  | Female | 35 (15.4) | 24 (5.3) |
| **Ethnicity** | White | 130 (57.3) | 234 (51.9) | 0.036 |
|  | Asian | 77 (33.9) | 193 (42.8) |
|  | Other/ Unknown  | 20 (8.8) | 24 (5.3) |
| **Arrhythmic event documentation** | Group A | 150 (66.1) | 276 (61.2) | 0.214 |
|  | Group B | 77 (33.9) | 175 (38.8) |
| **Proband status**  |   | 181 (85.4) | 361 (86.4) | 0.736 |
| **History of syncope**  |   | 82 (36.1) | 183 (40.6) | 0.262 |
| **Fever during AE** |   | 11 (5.9) | 24 (6) | 0.961 |
| **Family History of SCD** | Yes | 46 (20.3) | 99 (22) | 0.851 |
|  | No | 158 (69.6) | 310 (68.7) |
|  | Unknown  | 23 (10.1) | 42 (9.3) |
| **EPS performed**  |   | 140 (61.7) | 260 (57.6) | 0.315 |
| **VF inducibility during EPS** |   | 78 (55.7) | 175 (67.3) | 0.022 |
| **Genetic analysis performed** |   | 158 (69.6) | 327 (72.5) | 0.429 |
| **SCN5A mutation present** |   | 41 (25.9) | 102 (31.2) | 0.235 |

Abbreviations: AE = arrhythmic event, BrECG = Brugada electrocardiogram, EPS = electrophysiologic study; SCD = sudden cardiac death; SD = standard deviation; VF = ventricular fibrillation.

**150-character tweet representing manuscript:**

Drug induced Brugada patients represented a third of the SABRUS cohort. They differed from spontaneous type 1 Brugada patients in gender, ethnicity, and VF inducibility rates.