Giuseppe Mascia ORCID iD: 0000-0002-7069-4015

Brugada syndrome and syncope: a systematic review

Short title: The role of syncope in the Brugada syndrome

Giuseppe Mascia MD [1 2]; Roberta Della Bona MD [1 2]; Pietro Ameri MD [1 2]; Marco Canepa MD [1 2]; Italo Porto MD [1 2]; Michele Brignole MD [3]

[1] Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy

[2] Department of Internal Medicine, University of Genoa, Italy

[3] IRCCS Istituto Auxologico Italiano, Faint & Fall Programme, Ospedale San Luca, Milan, Italy

All authors: [1] made substantial contributions to the research design, acquisition and interpretation of data; [2] revised the paper critically; [3] approved the submitted and final versions.

Funding: None

Disclosures: None

Acknowledgements: no sources of support.

Corresponding author: Italo Porto MD, PhD. Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, University of Genoa, Italy

e-mail: italo.porto@gmail.com; Mob: +39 3332545285; Fax: +39 0105556695

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jce.14787.

Abstract

Introduction: Distinguishing syncope due to malignant arrhythmias from an incidental benign form in Brugada syndrome (BrS) is often difficult. Through systematic literature review, we evaluated the role of syncope in predicting subsequent malignant arrhythmias in BrS.

Methods: A comprehensive literature search was performed on PubMed (MeSH search terms “Brugada syndrome”and “syncope”). Overall, 9 studies for a total of 1347 patients were included. Patients were stratified as affected by suspected arrhythmic syncope (SAS), undefined syncope (US) or neurally-mediated syncope (NMS).

Results: Overall, 15,7% of the 279 patients with SAS had malignant arrhythmic events during a mean follow-up of 67 months, corresponding to 2.8 events per 100/person year. At the same time, 7% of the 527 patients affected by US had malignant arrhythmias during a mean follow-up of 39 months, corresponding 2.2 events per 100/person year. Conversely, 0.7% of 541 patients with NMS had malignant arrhythmic events at follow-up, corresponding to 0.13 events per 100/person year, (p=0.0001 NMS versus SAS and US pooled).

Conclusions: In BrS population,the risk of arrhythmic events in the follow-up may be stratified according to the clinical evaluation.The "relatively" low predictive value of the clinical diagnosis of SAS warrants for a more accurate multi-parametric assessment, in order to restrict the number of candidates for implantable cardioverter-defibrillator therapy.

Keywords: Syncope; Brugada syndrome; Ventricular arrhythmias; Sudden cardiac death

Manuscript

The occurrence of syncope in patients with Brugada syndrome (BrS) complicates their clinical management, since distinguishing syncope due to arrhythmias from an incidental benign form is often difficult, unless an electrocardiogram is recorded during the episode [1]. We performed a systematic review to evaluate the role/contribution of syncope in predicting malignant arrhythmic events in BrS. The protocol was registered in Prospero (ID: 200151). A comprehensive literature search of PubMed including all English publications from 1992 to 2020 was performed using the Medical Subject Headings search terms "Brugada syndrome" and "syncope". From the initial 135 results, we excluded case reports, reviews, replicated populations, editorial comments, and we found 21 articles that assessed arrhythmic events in BrS which included syncope at baseline. Among them, 11 articles that did not have a detailed definition of syncopal episodes at baseline, or included unexplained syncope as arrhythmic endpoint in the follow-up, as well as one duplicate pubblication, were excluded. The remaining 9 articles were included in the meta-analysis and mostly reported the results of large multicentre registries [2-10] (Table 1). All studies had a homogeneous definition of malignant arrhythmic events at follow-up, defined as documented ventricular fibrillation (VF), or appropriate implantable cardioverter-defibrillator (ICD) shock, or sudden cardiac death (SCD). The definition of suspected arrhythmic syncope (SAS) was relatively homogeneous in 6 studies [4-5,7-10] and included: 1) abrupt onset without prodrome and/or triggers; 2)short duration and prompt recovery during sleep; 3)concomitant use of drugs known to facilitate

arrhythmias in BrS. When patients did not meet any of these characteristics, syncope was classified as neurally mediated syncope (NMS) in the presence of typical triggers and prodroms, or as undefined syncope (US) if clinical features did not fit into one of the above categories. Two studies [2,6] defined the study population as affected by SAS, but did not give a precise definition of it and were included into the US category. Finally,one study [3] included only patients with US. Pooled together, 44/279 (15.7%) patients with SAS had arrhythmic events during a median follow-up of 67 months, corresponding to 2.8 per 100/person year. US patients had a rate of arrhythmic events slightly lower than patients with SAS: 37/527 (7.0%) during a median follow-up of 39 months, corresponding to 2.2 per 100/person year. In the NMS group, 4/541 patients (0,7%) had malignant arrhythmic events during a median follow-up of 70 months, corresponding to 0.13 per 100/person year (Table 1, p= 0.0001 with chi-square test for NMS versus SAS and US pooled). In interpreting these data, the pooled number of BrS patients with SAS and US was unrealistically higher than those with NMS (806 versus 541, respectively). Due to the relative rarity of BrS, the registries were assembled by few tertiary centres, collecting cases from several different referrals. We suppose that many cases of typical NMS were not referred to tertiary BrS centres, configuring a selection bias: by diluting the arrhythmic events among the general population of patients with syncope, the prognostic yield of syncope is likely to be even lower, pointing to the need for a precise definition of the nature of the syncopal event. Clues from history taking (syncope occurring during fever, without prodromes, without typical triggers for reflex syncope, or in the presence of drugs associated with BrS) have been previously proposed by Olde Nordkamp et al [7] in their single-centre registry, in order to identify truly arrythmic syncope in BrS and to guide ICD implantation. Our results

extend this observation to a larger and more complex BrS sample (1347 patients from several centers in different nations) and to a longer follow-up, showing that the risk of arrhythmic events in the follow-up could be stratified based on the initial clinical assessment. Another novel observation is that the probability of malignant arrhythmia is exceptionally low in patients with NMS, even lower than that observed in asymptomatic patients, reported to range from 0,4 per 100/person year from Olde Nordkamp et al [7] to 1 per 100/person year [11]. ICD could be definitely avoided in these patients. On the other hand, the relatively low predictive value of SAS for malignant arrhythmias warrants a more accurate multi-parametric assessment to restrict the number of candidates for ICD therapy. A more comprehensive and robust risk stratification model for patients with BrS without obvious aborted cardiac arrest is sorely needed.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Short description of each authors' contribution: GM, RDB, PA, MC, IP, MB: all six authors contributed equally to this paper

Acknowledgements: no sources of support.

References

1. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martín A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG; ESC Scientific Document Group. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018 Jun 1;39(21):1883-1948.

2. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F, Giustetto C, Schulze-Bahr E, Borggrefe M, Haissaguerre M, Mabo P, Le Marec H, Wolpert C, Wilde AA. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. Circulation 2010;121:635–643.

3. Delise P, Allocca G, Marras E, Giustetto C, Gaita F, Sciarra L, Calo L, Proclemer A, Marziali M, Rebellato L, Berton G, Coro L, Sitta N. Risk stratification in individuals with the Brugada type 1 ECG pattern without previous cardiac arrest: usefulness of a combined clinical and electrophysiologic approach. Eur Heart J. 2011 Jan;32(2):169-76.

4. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, Giordano U, Pappone C, Mascioli G, Rossetti G, De Nardis R, Colombo M. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol. 2012 Jan 3;59(1):37-45.

5. Sacher F, Arsac F, Wilton SB, Derval N, Denis A, de Guillebon M, Ramoul K, Bordachar P, Ritter P, Hocini M, Clémenty J, Jaïs P, Haïssaguerre M.

Syncope in Brugada syndrome patients: prevalence, characteristics, and outcome. Heart Rhythm. 2012 Aug;9(8):1272-9.

6. Takagi M, Aonuma K, Sekiguchi Y, Yokoyama Y, Aihara N, Hiraoka M; Japan Idiopathic Ventricular Fibrillation Study (J-IVFS) Investigators. The prognostic value of early repolarization (J wave) and ST-segment morphology after J wave in Brugada syndrome: multicenter study in Japan. Heart Rhythm. 2013 Apr;10(4):533-9.

7. Olde Nordkamp LR, Vink AS, Wilde AA, de Lange FJ, de Jong JS, Wieling W, van Dijk N, Tan HL. Syncope in Brugada syndrome: prevalence, clinical significance, and clues from history taking to distinguish arrhythmic from nonarrhythmic causes. Heart Rhythm. 2015 Feb;12(2):367-75.

8. Giustetto C, Cerrato N, Ruffino E, Gribaudo E, Scrocco C, Barbonaglia L, Bianchi F, Bortnik M, Rossetti G, Carvalho P, Riccardi R, Castagno D, Anselmino M, Bergamasco L, Gaita F. Etiological diagnosis, prognostic significance and role of electrophysiological study in patients with Brugada ECG and syncope. Int J Cardiol. 2017 Aug 15;241:188-193.

9. Flórez JP, García D, Valverde I, Rubín J, Pérez D, González-Vasserot M, Reguero J, de la Hera JM, Avanzas P, Gómez J, Coto E, Morís C, Calvo D. Role of Syncope in Predicting Adverse Outcomes in Patients With Suspected Brugada Syndrome Undergoing Standardized Flecainide Testing. Europace. 2018 Jun 1;20(FI1):f64-f71.

10. Hernandez-Ojeda J, Arbelo E, Jorda P, Borras R, Campuzano O, Sarquella-Brugada G, Iglesias A, Mont L, Brugada R, Brugada J. The role of clinical

assessment and electrophysiology study in Brugada syndrome patients with syncope. Am Heart J. 2020 Feb;220:213-223.

11. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ; ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015 Nov 1;36(41):2793-2867.

Table 1: Selected studies evaluating patients with syncope in Brugada syndrome

Study	Study type	Patients with syncope (% of total population)	Median FU (months)	Syncope type	Arrhythmic events during FU *	Remark
Probst et al. FINGER Registry [2]	Inclusion of consecutive patients	313 (30%)	34	Suspected arrhythmic (undefined)	19 (6%) 2.2 per 100/person year	Other forms of syncope (number unknown) were probably included in the "asymptomatic group". The arrhythmic event rate in such patients was 10/654 (1.5%) corresponding to 0.5 per 100/person year. VAs during EPS was not predictive of arrhythmic events.
Delise et al.[3]	Prospective registry	105 (34%)	40	Any syncope	10 (10%) 2.9 per 100/person year	Possible selection bias (patients with typical vasovagal syncope were not enrolled in the registry). Among total patient population major arrhythmic events occurred in 14% of subjects with positive EPS, in no subjects with negative EPS, and in 5.3% of subjects without EPS
Priori et al. PRELUDE registry [4]	Prospective registry	64 (21%)	34	Suspected arrhythmic (abrupt loss of consciousness at rest or during sleep with agonal respiration reported by bystander)	7 (11%) 2.5 per 100/person year	Other forms of syncope (number unknown) probably included in the "asymptomatic group". The arrhythmic event rate in such patients were 7/244 (0.3%). The combination of spontaneous type-1 Brugada pattern and syncope were the

						strongest predictor of arrhythmic events (hazard ratio: 4.2) EPS was unable to identify high-risk patients
Sacher et al.[5]	Prospective registry	57 (28%)	65	Suspected arrhythmic (no prodrome, no trigger, short duration, prompt recovery): 23 (40%) Typical vasovagal syncope: 17 (30%) Doubtful origin (intermediate clinical features): 17 (30%)	6 (26%) 1.1 per 100/person year 0 (0%) 0 (0%)	Seventeen patients underwent EPS (56 % had inducible VAs: no statistical difference was observed in terms of inducibility between three groups). Thirty-eight percent of patients had positive tilt test. Two patients had a recurrent syncope not related to VAs, emphasizing that the co-presence of malignant VAs and vasovagal syncope in patients with BrS is not rare. Among 32 patients with ICD, 28% had complications: in particular, inappropriate shock occurred in 25% of patients Sixteen patients underwent EPS (19% inducible). Seventy-nine percent of patients had positive tilt test Fourteen patients underwent EPS (43% inducible). Twenty-seven percent of patients had positive tilt test
Takagi et al.[6]	Prospective multicentric registry	109 (24%)	50	Suspected arrhythmic (not specified)	8 (7%) 1.7 per 100/person year	The incidence of cardiac events was not different in patients with (11%) or without (8%) a J wave.

Olde Nordkamp et al.[7]	Retrospective plus systematic interview. Diagnosis of syncope adjudicated by expert committee	118 (84%)	54	Likely arrhythmic (during fever, no prodrome and no trigger, iatrogenic drugs): 33 (28%) Likely vasovagal (ESC guidelines on syncope criteria): 67 (57%) Unknown cause (intermediate clinical features): 18 (15%)	4 (12%) 2.7 per 100/person year 0 (0%) 0 (0%)	No difference in the inducibility of VAs during EPS between patients with arrhythmic and non-arrhythmic syncope Non-arrhythmic syncope recurred in 14/67 patients (21%) initially assigned to the vasovagal group
Giustetto et al.[8]	Consecutive patients prospectively collected	195 (100%)	62	Suspected arrhythmic (during fever, no prodrome and no trigger, iatrogenic drugs: 77 (39%) Neurally-mediated (ESC guidelines on syncope criteria): 118 (61%)	7 (9%) 1.7 per 100/person year 2 (2%) 0.3 per 100 person/year	EPS positive in 7 patients, tilt test positive in 1 patient. No loop recorder events were documented EPS positive in 2 patients, tilt test positive in 1 patient. No loop recorder events were documented
Florez et al. [9]	Single centre	251 (100%)	74	Suspected arrhythmic (no prodrome, no trigger): 16 Neurally-mediated: 235	4 (25%) 4.0 per 100/person year 1 (0.4%) 0.03 per 100/person year	Possible selection bias (inclusion was based on flecainide test) In attempt to improve risk stratification, 59 patients underwent EPS after diagnosis. Of these, 19 patients had inducible, sustained VAs requiring external defibrillation and one ICD was implanted
Hernandez-Ojeda et al.[10]	Prospective registry Diagnosis of syncope adjudicated by expert committee	135 (28,5%)	92	Suspected arrhythmic (no prodrome, no trigger, short duration, prompt recovery): 66 (48.9%)	16 (24%) 3.1 per 100/person year	EPS positive in 53%. Arrhythmic events during follow-up in 21% of EPS-positive patients and in 8% of EPS-negative

	(specific questionnaire)		Vasovagal 51 (38%) Undefined 18 (13%)	1 (2%) 0.2 per 100/person year 0 (0%)	patients (p=0.04) EPS positive in 12%. Three patients received a loop-recorder due to recurrent episodes. EPS positive in 0%. Five patients underwent a loop recorder implant: none of these patients had another syncope event during follow-up
Total	1347	67 39 70	Suspected arrhythmic syncope: 279 (21%) Undefined syncope: 527 (39%) Neurally-mediated syncope: 541(40%)	44 (15.7%) 2.8 per 100/person year 37 (7.0%) 2.2 per 100/person year 4 (0.7%) 0.13 per 100/person year	

* Arrhythmic events were defined as SCD or appropriate ICD shock

FU=follow up; ICD= implantable cardioverter defibrillator; SCD=sudden cardiac death; ESC= European Society of Cardiology; VA= ventricular arrhythmia; EPS = electrophysiology study;