Syncope in Brugada syndrome: Prevalence, clinical significance, and clues from history taking to distinguish arrhythmic from nonarrhythmic causes

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BACKGROUND Syncope in Brugada syndrome (BrS) patients is a sign of increased risk for sudden cardiac death and usually is ascribed to cardiac arrhythmias. However, syncope often occurs in the general population, mostly from nonarrhythmic causes (eg, reflex syncope).

OBJECTIVE The purpose of this study was to distinguish arrhythmic events from nonarrhythmic syncope in BrS and to establish the clinical relevance of nonarrhythmic syncope.

METHODS We reviewed the patient records of 342 consecutively included BrS patients and conducted systematic interviews in 141 patients with aborted cardiac arrest (ACA) or syncope.

RESULTS In total, 23 patients (7%) experienced ECG-documented ACA and 118 (34%) syncope; of these 118, 67 (57%) were diagnosed with suspected nonarrhythmic syncope. Compared to suspected nonarrhythmic syncope patients, ACA patients were older at first event (45 vs 20 years), were more likely to be male (relative risk 2.1) and to have urinary incontinence (relative risk 4.6), and were less likely to report prodromes. ACA was never triggered by hot/crowded surroundings, pain or other emotional stress, seeing blood, or prolonged standing. During follow-up (median 54 months), ACA rate was 8.7% per year among ACA patients and 0% per year among suspected nonarrhythmic syncope patients.

CONCLUSION Syncope, especially nonarrhythmic syncope, often occurs in BrS. The high incidence of nonarrhythmic syncope must be taken into account during risk stratification. Arrhythmic events and nonarrhythmic syncope may be distinguished by clinical characteristics (absence of prodromes and, particularly, specific triggers), demonstrating the importance of systematic history taking.

KEYWORDS Brugada syndrome; Syncope; Ventricular arrhythmia

ABBREVIATIONS **ACA** = aborted cardiac arrest; **BrS** = Brugada syndrome; **ECG** = electrocardiogram; **ESC** = European Society of Cardiology; **ICD** = implantable cardioverter-defibrillator; **RR** = relative risk; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia

(Heart Rhythm 2015;12:367–375)

Introduction

Brugada syndrome (BrS) is characterized by sudden cardiac death at a relatively young age and signature ST-segment elevation in the right precordial electrocardiogram (ECG) leads (type 1 BrS ECG). The associated life-threatening tachyarrhythmias (ventricular tachycardia/ventricular fibrillation [VT/VF]) may manifest as cardiac arrest or syncope.[1]

Accordingly, syncope is a sign of increased risk for life-threatening arrhythmias (along with type 1 BrS ECG at baseline, ie, in the absence of provoking drugs), as indicated by studies on risk stratification of BrS.[2] Yet, syncope in BrS patients constitutes a diagnostic dilemma. Although syncope in (suspected) BrS patients is often ascribed by default to cardiac arrhythmia in this setting, syncope also may stem from other causes. In the general population, reflex syncope is by far the most frequent cause of syncope, especially in the young, with a cumulative incidence of 40% by the age of 21 years.[3] It is difficult to establish whether syncope events in BrS patients are caused by arrhythmia or nonarrhythmic syncope.[4] The European Society of Cardiology (ESC) guidelines for syncope are inadequate for risk stratification in relatively young patients with a high risk for ventricular arrhythmias.[5] Clearly, it is important to distinguish these types of syncope because the updated consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes[6] recommends implantable cardioverter-defibrillator (ICD) placement only in BrS patients with syncope judged likely to be caused by

Dr. Tan was supported by Grant ZonMW Vici 918.86.616 from the Netherlands Organization for Scientific Research. **Address reprint requests and correspondence:** Dr. Hanno L. Tan, Department of Cardiology, Heart Center, Academic Medical Center, University of Amsterdam, PO Box 22700; 1100 DE Amsterdam, The Netherlands. E-mail address: h.l.tan@amc.uva.nl.

ventricular arrhythmias, given the risk of ICD complications[7] and costs.

In an effort to distinguish arrhythmic from nonarrhythmic syncope in BrS patients and to establish the clinical relevance of nonarrhythmic syncope in these patients, we asked the following questions: (1) How many BrS patients sustain arrhythmias and/or nonarrhythmic syncope? (2) Can clinical characteristics be identified to distinguish arrhythmic events from nonarrhythmic syncope in BrS? (3) What is the risk of future arrhythmias in BrS patients with nonarrhythmic syncope?

Methods

Study population

We conducted a cohort study at the Academic Medical Center, a large tertiary referral center in the Netherlands, of BrS patients consecutively included between January 1, 2001, and April 1, 2011. BrS was diagnosed when a type 1 BrS ECG was observed in >1 right precordial lead in the presence or absence of a sodium channel-blocking drug (flecainide or ajmaline).[1] The institutional review board waived the requirement for informed consent.

Study design

All living patients who had experienced syncope or aborted cardiac arrest (ACA) by the time of diagnosis, as indicated in their medical records, underwent a telephone interview to obtain details on this event. The interview was conducted by one investigator (A.V.) and consisted of a standardized systematic history taking of the event similar to the ESC guidelines on syncope (Online Supplementary Appendix 1).[5] This questionnaire was developed to determine the diagnostic yield of initial evaluation of syncope and includes the number of previous (pre)syncope/syncope events, triggers and prodromes, duration, and some general information about orthostasis, other cardiac diseases, medication and intoxications, diet, and family history of syncope.[8] In addition, clinical data were collected from the patient records, including historical data and additional cardiac testing such as Holter monitoring, exercise testing, and cardiovascular reflex testing. Also, data on the occurrence of severe injury requiring medical attention or intervention as a result of the syncope or ACA were collected.

With these data, an expert committee, consisting of a cardiologist specialized in BrS (H.T.) and a physician specialized in syncope (W.W.), independently made 1 of 4 baseline diagnoses in descending order of severity: (1) ACA, (2) suspected arrhythmic syncope, (3) suspected nonarrhythmic syncope, or (4) unknown. The diagnosis was accepted if both experts agreed. Patients for whom no agreement was reached were discussed in a face-to-face meeting between both experts and attended by a third expert, another cardiologist who specialized in BrS and syncope (A.W.). In this meeting, the 3 experts agreed on a final diagnosis. Patients with multiple events were diagnosed according to the diagnosis with the highest severity. In the absence of a "reference standard" to determine the cause of syncope, long-term follow-up was used to validate the accuracy of the diagnoses made.

Definitions

ACA was defined as loss of consciousness due to an unexpected circulatory arrest with ECG/Holter-documented arrhythmia (VT/VF or bradyarrhythmia such as AV block).[9]

Syncope was defined as transient loss of consciousness caused by a fall in systemic blood pressure resulting in global cerebral hypoperfusion.[5] Suspected arrhythmic syncope was defined as syncope highly likely to be caused by arrhythmia but without ECG/Holter documentation of arrhythmia. The sensitivity for this diagnosis was set high in order to minimize the possibility of false-negative results. This diagnosis was made particularly when syncope occurred during fever, with sudden onset without prodromes, without typical triggers for reflex or situational syncope, or in the presence of drugs associated with BrS ECG and/or arrhythmias (www.brugadadrugs.org). Suspected nonarrhythmic syncope was the composite of the following entities: certain or highly likely[5] reflex syncope and orthostatic hypotension without ECG/Holter documentation of arrhythmia. It was defined according to the criteria of the separate entities described in the ESC guidelines as transient loss of consciousness with spontaneous complete recovery specifically associated with ≥ 1 typical prodrome in addition to ≥ 1 typical trigger.[5] Prodromes were nausea, vomiting, pallor, diaphoresis, abdominal discomfort, yawning, sighing, or hyperventilation. Typical triggers were emotional distress, prolonged standing, being in crowded and/or hot places or after exertion, cough, gastrointestinal stimulation, or micturition. A temporal relationship with start or changes of vasodepressive drugs leading to hypotension or the presence of autonomic neuropathy were also considered triggers for nonarrhythmic syncope.

Statistical analysis

All data were analyzed using SPSS 20.0 (SPSS, Chicago, IL). Categorical data are displayed as percentage and compared between groups using the χ^2 test or Fisher exact test. The Shapiro–Wilk test was used to verify whether continuous data followed a normal distribution. Normally distributed continuous data are reported as mean $\pm$ SD and were compared between groups using the Student t test. Continuous data not normally distributed are expressed as median (quartiles and range) and were compared between groups using the Mann–Whitney U test.

Clinical characteristics, prodromes, and triggers were compared between the ACA group and the suspected nonarrhythmic syncope group. The suspected arrhythmic syncope group was not used for this comparison to avoid circular reasoning, because this diagnosis was partly defined by the absence of specific prodromes and triggers. However, we assume that the clinical features of ACA can be extrapolated to arrhythmic syncope. In patients with both ACA and suspected nonarrhythmic syncope, only the

Table 1 Patient characteristics

	All patients	Symptomatic patients	Asymptomatic patients	
	(N = 342)	(N = 141)	(N = 201)	*P* value*
Male	205 (60%)	85 (60%)	120 (60%)	.87
Mean age at diagnosis (years)	44 ± 14	45 ± 13	44 ± 15	.50
Type 1 BrS ECG†	50 (15%)	17 (12%)	33 (16%)	.26
Family history of sudden death at age <45 years	100 (30%)	43 (31%)	57 (29%)	.61
Familial SCN5A mutation‡	107 (34%)	44 (34%)	63 (34%)	.91
Initial presentation				
ACA	20 (5.8%)	20 (14%)	NA	
Syncope	39 (11%)	39 (27%)	NA	
Family screening	182 (53%)	61 (43%)	121 (60%)	<.01
Other causes	101 (30%)	21 (15%)	80 (40%)	<.01
ICD placement	85 (26%)	60 (43%)	25 (13%)	<.01

Values are given as no. (%) or mean ± SD.

ACA = aborted cardiac arrest; BrS = Brugada syndrome; ICD = implantable cardioverter-defibrillator; NA = not applicable.

*Symptomatic vs asymptomatic patients.

†Type 1 BrS ECG in the absence of provoking drugs.

‡Percentage displayed of patients with known presence or absence of familial mutations.

prodromes and triggers of ACA were used for analysis. The probability of recurrence of events by category was described by Kaplan–Meier cumulative estimates with comparison of probability of events by the log-rank test. $P < .05$ was considered significant.

Results

Patient characteristics

The total cohort comprised 342 patients. The mean age at diagnosis was 44 ± 14 years, and 205 (60%) were male. About half of the patients (n = 182/342 [53%]) were identified during family screening. Twenty patients (5.8%) initially presented with ACA and 11% (39/343) with syncope. The clinical characteristics of all patients are listed in Table 1.

Sudden cardiac arrest and syncope

By the time of diagnosis, 23 of 342 patients (23/123 families) had experienced ACA (7%; Figure 1), including 20 with an out-of-hospital-cardiac-arrest, 2 with polymorphic VT during exercise testing, and 1 with AV block with hemodynamic compromise.

Syncope was reported by 118 patients (34%; mean age at first syncope 29 ± 18 years), with 67% having experienced multiple syncope events (median 2 [quartiles 1–4]). The most prevalent cause of syncope was suspected nonarrhythmic syncope, which occurred in 57% of patients with (67/118) syncope and 20% of the total cohort (67/342 patients, 55/123 families). Suspected arrhythmic syncope was diagnosed in 28% of patients with syncope (33/118) and 10% of the total cohort (33/342 patients; 29/123 families). In 15% of patients (18/118), the cause remained unknown. Six of the 23 patients (26%) with ACA and 14 of the 33 patients (42%) with suspected arrhythmic syncope had additional nonarrhythmic syncope events, which increased the total proportion of patients with a lifetime history of suspected nonarrhythmic syncope in the total cohort to 87 of 343 (25%).

Clinical characteristics of ACA vs suspected nonarrhythmic syncope

Patients with ACA were older when they experienced the first event than those with suspected nonarrhythmic syncope

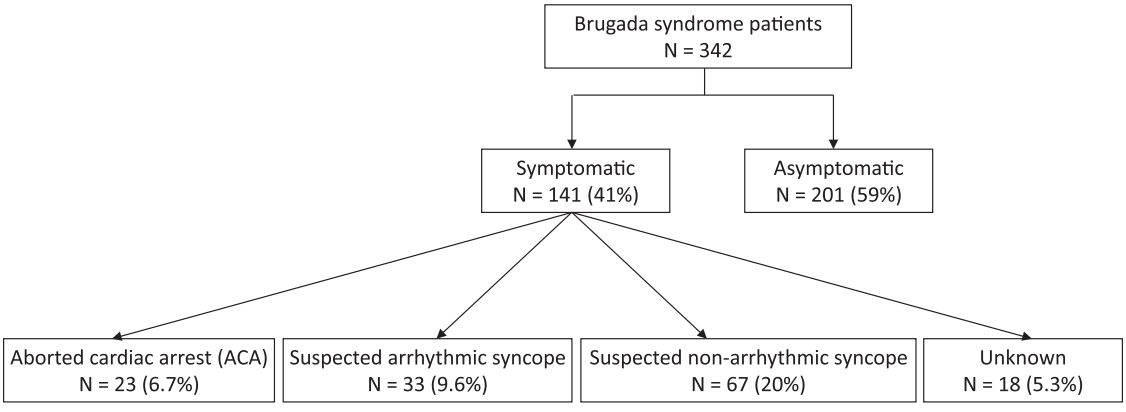

Figure 1 Flow chart.

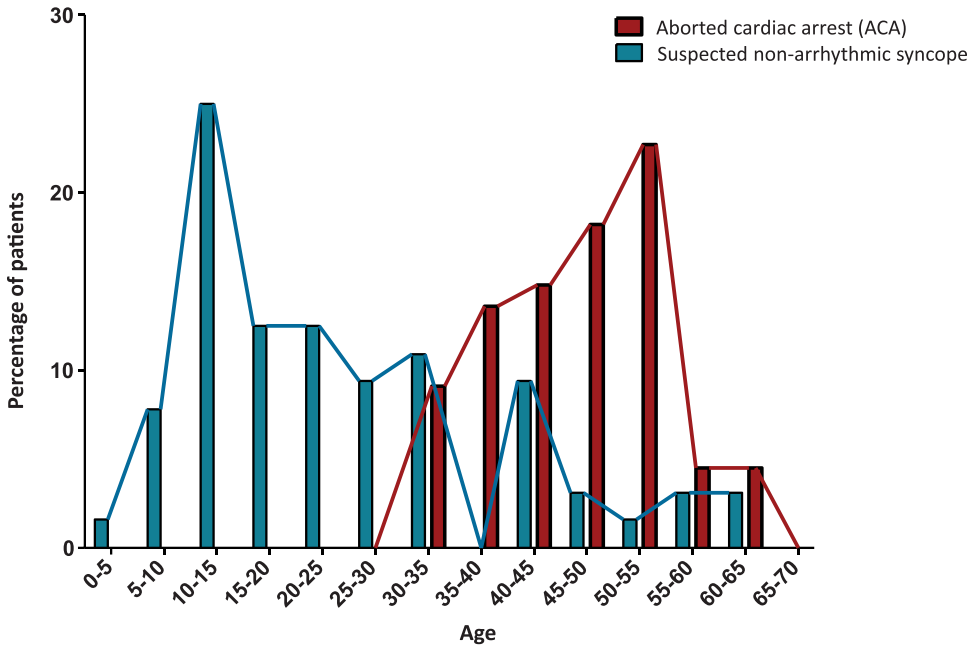

Figure 2 Age distribution at first event.

(45 vs 20 years, $P<.01$; Figure 2), more likely to be male (96% vs 45%, relative risk [RR] 2.1, $P<.01$), and to have urinary incontinence (45% vs 10%, RR 4.6, $P<.01$) (Table 2). There were no significant differences in the number of events or the occurrence of severe injury from the event between both groups. Also, there was no difference in the inducibility of VF during electrophysiologic study between patients with arrhythmic and those with nonarrhythmic syncope.

Table 3 lists the prodromes and triggers preceding ACA or syncope. Patients with ACA reported prodromes significantly less often than did patients with suspected nonarrhythmic syncope, such as nausea/vomiting (0% vs 40%), sweating (5% vs 71%, RR 0.1), facial pallor (20% vs 77%, RR 0.3) and lightheadedness (29% vs 78%, RR 0.4). Also, the events in patients with ACA were less often preceded by blurred vision (10% vs 47%, RR 0.2) or the feeling of wanting to lie down (10% vs 61%, RR 0.2). Palpitations were reported both in patients with ACA and those with suspected nonarrhythmic syncope (10% vs 31%).

ACA occurred more frequently with patients in the supine position (50% vs 13%, RR 3.9), whereas suspected nonarrhythmic syncope occurred more often with patients in the standing position (14% vs 75%, RR 0.2). Both ACA and suspected nonarrhythmic syncope occurred at night ($P = .13$). ACA at night always occurred while the patient was asleep, whereas suspected nonarrhythmic syncope at night always occurred while the patients was awake. In 4 of 6 patients with suspected nonarrhythmic syncope at night, the events occurred during or shortly after micturition, and in 2

Table 2 Clinical characteristics of patients with aborted cardiac arrest and suspected nonarrhythmic syncope

	ACA	Suspected nonarrhythmic syncope		
	(N = 23)	(N = 67)	*P* value	RR (95% CI)
Male	22 (96%)	30 (45%)	<.01	2.1 (1.6–2.8)
Age at first event [median (IQR)]	45 (39-52)	20 (12-31)	<.01	NA
Number of events [median (IQR)]	1 (1-6)	2 (1-5)	.32	NA
Duration of syncope event				
<1 minute	NA	28 (55%)	NA	NA
1–5 minutes	NA	17 (33%)	NA	NA
>5 minutes	NA	5 (9.8%)	NA	NA
Muscle jerking	3 (18%)	9 (17%)	1*	1.1 (0.3–3.3)
Urinary incontinence	9 (45%)	6 (9.8%)	<0.01	4.6 (1.7–10.9)
Severe injury after event	3 (14%)	5 (8.2%)	.43	1.7 (0.5–6.7)
HUT positive	1/1 (100%)	12/17 (71%)	1*	1.4 (0.5–2.5)
EEG abnormalities	0/2 (0%)	0/4 (0%)	1*	NA

ACA = aborted cardiac arrest; CI = confidence interval; EEG = electroencephalogram; HUT = head-up tilt test; IQR = interquartile range; NA = not applicable; RR = relative risk.

*Fisher exact test.

Table 3 Prodromes and triggers of aborted cardiac arrest or suspected nonarrhythmic syncope

	ACA	Suspected nonarrhythmic syncope		
	(N = 23)	(N = 67)	*P* value	RR (95% CI)
Prodromes[†]				
Nausea/vomiting	0/21 (0%)	23/58 (40%)	<.01	NA
Sweating	1/20 (5.0%)	41/58 (71%)	<.01	0.1 (0.01–0.5)
Facial pallor	3/15 (20%)	36/47 (77%)	<.01	0.3 (0.1–0.7)
Dizziness/lightheadedness	6/21 (29%)	45/58 (78%)	<.01	0.4 (0.2–0.7)
Blurred vision	2/20 (10%)	24/51 (47%)	<.01	0.2 (0.1–0.8)
Feeling of wanting to lie down	2/21 (9.5%)	34/56 (61%)	<.01	0.2 (0.04–0.6)
Palpitations	2/20 (10%)	16/52 (31%)	.07	0.3 (0.1–1.3)
Triggers[†]				
Position				
Standing	3/21 (14%)	47/63 (75%)	<.01	0.2 (0.1–0.6)
Sitting	12/21 (57%)	28/61 (46%)	.38	1.2 (0.8–2.0)
Supine	11/22 (50%)	8/62 (13%)	<.01	3.9 (1.8–8.4)
During exertion	3/22 (14%)	1/65 (1.5%)	.05	8.9 (1.0–80.9)
After exertion	0/22 (0%)	4/65 (6.2%)	.57[*]	NA
Prolonged standing	0/18 (0%)	18/63 (29%)	.01[*]	NA
Hot or crowded surroundings	0/18 (0%)	19/63 (30%)	.01[*]	NA
Postural changes	0/21 (0%)	10/64 (16%)	.05	NA
During micturition	0/17 (0%)	8/61 (13%)	.12[*]	NA
During night	5/19 (26%)	7/64 (11%)	.13[*]	2.4 (0.9–6.7)
Pain or emotional stress	0/22 (0%)	30/65 (46%)	<.01	NA
After blood donation/seeing blood	0/22 (0%)	18/66 (27%)	.01	NA

Values are given as no. (%).

ACA = aborted cardiac arrest; CI = confidence interval; NA = not applicable; RR = relative risk.

[*] Fisher exact test.

[†] Some subjects mentioned more than 1 prodrome or trigger for their event. The percentage displayed is for patients who recalled the presence or absence of a specific prodrome.

of 6 patients the events were preceded by pain. ACA was never triggered by hot/crowded surroundings, pain or other emotional stress, seeing blood, or prolonged standing, in contrast to suspected nonarrhythmic syncope (30%, 46%, 27%, and 29%, respectively).

Sudden cardiac arrest and suspected nonarrhythmic syncope during follow-up

During median follow-up of 54 months (quartiles 31–91), syncope or ACA occurred in 24% of the symptomatic patients (34/141) and in 4% of the asymptomatic patients (7/201). The events during follow-up were ACA in 5% (17/342) and suspected nonarrhythmic syncope in 7% (24/342).

ACA during follow-up occurred in 43% (10/23) ACA patients (8.7% per year) and in 12% (4/33) suspected arrhythmic syncope patients (2.2% per year). ACA did not occur in suspected nonarrhythmic syncope patients. ACA occurred in 1.5% of patients (3/201) who were asymptomatic at diagnosis (0.3% per year). One of these patients (baseline type 1 BrS ECG) had a suspected arrhythmic syncope during follow-up, for which he received ICD placement and multiple appropriate ICD shocks 5 years later. The 2 other patients (no baseline type 1 BrS ECG) had suspected arrhythmic syncope and underwent implantable loop recorder placement, which recorded sustained VT in 1 (followed by ICD placement), and symptomatic AV block and sinus node dysfunction in the other (followed by pacemaker implantation). Kaplan–Meier estimates of occurrence of ACA by baseline diagnosis are shown in Figure 3. The probability of occurrence at 9 years was 53% in ACA patients, 15% in suspected arrhythmic syncope patients, 0% in suspected nonarrhythmic syncope patients, and 3% in asymptomatic patients ($P < .01$).

Suspected nonarrhythmic syncope during follow-up occurred in 21% (14/67) suspected nonarrhythmic syncope patients (4.5% per year), 4% (1/24) ACA patients (0.5% per year), and 2.0% (4/201) asymptomatic patients (0.4% per year). Over 9 years of follow-up, there was no difference in the occurrence/recurrence of suspected nonarrhythmic syncope between groups ($P = .09$).

Discussion

Main findings

As many as 34% of patients with BrS had a history of ≥1 event of syncope at the time of diagnosis, of whom 57% had suspected nonarrhythmic syncope. Features suggesting ACA were male gender, older age, presence of urinary incontinence, absence of typical prodromes, and, most specifically, absence of typical triggers. The ACA rate during follow-up was 8.7% per year in ACA patients and 0%–0.3% per year in asymptomatic or suspected nonarrhythmic syncope patients. The absence of ACA in patients with nonarrhythmic syncope during long-term follow-up confirms that this diagnosis, which was based on the ESC guidelines, was correct.

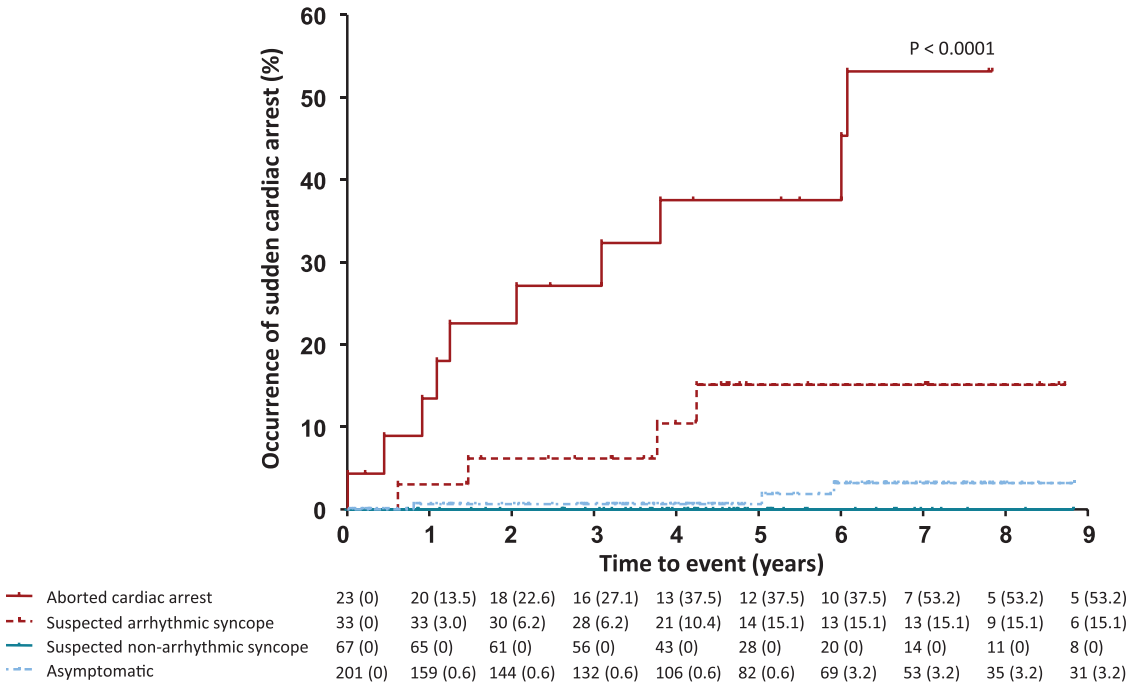

Figure 3 Occurrence of aborted cardiac arrest during follow-up by baseline category.

Prevalence of nonarrhythmic syncope

The high prevalence of syncope in our study is in line with previous studies of BrS patients.[10,11] However, our study confirms data from other smaller studies that almost half of patients with syncope have suffered from suspected nonarrhythmic syncope, which also explains the relatively high number of symptomatic female patients.[4,12] The 25% prevalence of suspected nonarrhythmic syncope in this total BrS cohort is comparable to the prevalence of nonarrhythmic syncope in the general population.[13] This high prevalence of nonarrhythmic syncope must be taken into account during risk stratification in BrS patients. This finding is supported by other studies, which demonstrated that BrS patients can suffer from both ACA/suspected arrhythmic syncope and nonarrhythmic syncope.[4,14] The presence of 1 type of syncope does not exclude another type, as 26% of patients with ACA also experienced suspected nonarrhythmic syncope. On the other hand, patients with multiple typical nonarrhythmic syncope events can also suffer from a suspected arrhythmic event, placing them at higher risk for sudden death.

Evidence from history taking

Distinguishing arrhythmic syncope from nonarrhythmic syncope remains a challenge, especially in patients with a high pretest likelihood of nonarrhythmic syncope because of age[15] or a high pretest likelihood of arrhythmia because of underlying disease.[2] The clinical history is the cornerstone in the diagnostic workup of patients with syncope.[5,8] Here we demonstrate that the ESC guidelines[5] can be used reliably to diagnose nonarrhythmic syncope because there were no occurrences of ACA during long-term follow-up in patients with this diagnosis. A treatment policy without ICD placement therefore is appropriate in these patients. The difficulty lies in the diagnosis of suspected arrhythmic syncope in which a variety of prodromes and triggers are present (Online Supplementary Appendix 2), without fulfilling the diagnosis of nonarrhythmic syncope according to the ESC guidelines. Here we assumed that the presentation of *true* arrhythmic syncope is similar to that of ACA, and therefore the syncope characteristics found in ACA patients are likely to apply to all patients with arrhythmic events. We found that patients with ACA were older at first event and were more likely to be male compared to patients with suspected nonarrhythmic syncope. Prodromes, especially nausea/vomiting, sweating, and the feeling of wanting to lie down, usually were associated with suspected nonarrhythmic syncope. These data confirm earlier findings from a smaller study by Take et al,[12] who also found that the absence of prodromes is related to VF in BrS patients. However, about 20% of ACA patients also experienced prodromes before the onset of VF. On the other hand, palpitations, which have previously been reported as a predictor for ACA/arrhythmic syncope in patients without suspected or diagnosed heart disease,[16] are very common in patients with suspected nonarrhythmic syncope, likely because of the pronounced postural tachycardia occurring before an actual faint.[17] Also, although urinary incontinence was more prevalent in patients with ACA, urinary incontinence and severe injury were also present in approximately 10% of the patients with suspected nonarrhythmic syncope.[18] Taken together, these data suggest that prodromes and these clinical features are not specific enough to distinguish arrhythmic from nonarrhythmic events, and physicians should not be deceived by the presence of these symptoms.

Syncope in specific situations, such as during prolonged standing, while being in hot or crowded surroundings, during pain or emotional stress, and after blood donation or seeing blood, was more specific for nonarrhythmic syncope because they were frequently present in patients with suspected nonarrhythmic syncope (27%–46%) but never in those with ACA. Interestingly, events at night were associated with both ACA and suspected nonarrhythmic syncope, although events during supine position had a 3.9 RR for ACA compared to suspected nonarrhythmic syncope. These data suggest that syncope at night is not specific because patients may suffer from typical nocturnal micturition syncope (4/6 patients with suspected nonarrhythmic syncope at night had events during/shortly after micturition).[19] Yet, loss of consciousness during sleep at night without any trigger is highly specific for ACA, which is supported by the literature.[20] Overall, our data suggest that triggers are important clues to distinguish arrhythmic events from nonarrhythmic syncope in BrS patients. Hence, it must be stressed that no single feature from the history is sufficient to diagnose the cause of syncope, and that a diagnosis can be made only by combining various features. Point scores combining several items have been demonstrated to be helpful in increasing the accuracy of diagnosing arrhythmic syncope in a general cardiology/syncope outpatient clinic and hospital wards.[21,22] However, especially in BrS patients who often have aberrant ECGs and a high pretest likelihood of ventricular arrhythmias, subtle clues can direct physicians with greater accuracy in diagnosing arrhythmic syncope with possible therapeutic consequences such as ICD placement. Therefore, patients with suspected arrhythmic syncope should be referred to a dedicated syncope unit for expert history taking.

Risk of future ACA

There is no doubt that BrS patients who have survived ACA are at high risk for recurrent ACA.[6] This was confirmed by our data showing that the annual ACA rate in patients with previous ACA was 8.7%. Additionally, in patients with suspected arrhythmic syncope, the annual ACA rate was 2.2%, in accordance with a study by Sacher et al,[4] who analyzed the outcome of arrhythmic syncope in BrS patients. This study also demonstrated that the absence of prodromes (or their presence for <10 seconds), absence of a particular circumstance, and short duration of loss of consciousness had a 100% negative predictive value for predicting the absence of arrhythmic syncope over the next 5 years. However, the risk of future ACA in suspected arrhythmic syncope patients was not as high as in ACA patients, probably because the suspected arrhythmic syncope group also falsely contained nonarrhythmic syncope patients (with lower ACA risk during follow-up) due to the highly sensitive diagnostic definition. This approach resembles clinical care in which a strategy of "better safe than sorry" prevails. Further analysis should be performed to diagnose the underlying cause in these extremely difficult cases. On the other hand, compared to the presumed arrhythmic syncope patients, almost twice as much patients have correctly been diagnosed as having nonarrhythmic syncope. Suspected nonarrhythmic syncope patients had a very low ACA risk during follow-up (0% per year), indicating that our methods for diagnosing suspected nonarrhythmic syncope were valid. Hence, the decision-making process in these patients was successful. However, the risk is not zero, as demonstrated in the asymptomatic patients (ACA risk 0.3% per year), which shows that even low-risk patients need to be reviewed carefully, especially because the majority of patients are asymptomatic before a lethal event.[23] Moreover, genetic variants in BrS have also been associated with sudden death in epilepsy, and BrS patients also might suffer from neurologically triggered sudden death.[24]

On the other hand, the pathophysiology of BrS is still under investigation, and VF and ACA in BrS mainly occur in the resting state, predominantly during sleep.[20] The clinical characteristics and ECG fluctuations under autonomic modulation indicate the potential role of the cardiac autonomic nervous system in the pathogenesis of arrhythmias in BrS.[25] ST-segment elevation during head-up tilt test[14] has been reported, and acetylcholine infusion to the coronary artery also induced ST-elevation and VF in BrS patients.[26] On the other hand, deep vagal stimulation with phenylephrine injection failed to provoke modification of ST-segment elevation or ventricular arrhythmias.[27] Additionally, there is no literature showing that nonarrhythmic syncope causes arrhythmic events in BrS patients. Therefore, the exact risk of a vagal reflex remains unclear, and vigilance is needed in BrS patients with nonarrhythmic syncope.

Study limitations

We compared the clinical characteristics (including prodromes and triggers) of suspected nonarrhythmic syncope and ACA, but one would also like to compare nonarrhythmic syncope and (suspected) arrhythmic syncope. However, the diagnosis of suspected arrhythmic syncope was mainly based on the absence of prodromes and typical triggers and therefore was not suitable for this comparison. This notwithstanding, we assume that the clinical presentation of arrhythmic syncope (nonsustained arrhythmia) probably is similar to the presentation of ACA (sustained arrhythmia), and our data can be cautiously extrapolated to distinguish arrhythmic from nonarrhythmic syncope. Moreover, the finding that ACA did not occur during follow-up in the suspected nonarrhythmic syncope group provided support that this diagnosis and our methods for group classification were correct. The accuracy of diagnoses made is critical in diagnostic research.[28] In the absence of a "reference standard," we considered the use of long-term follow-up to be a more meaningful method for verification than use of strict diagnostic criteria in a cross-sectional manner.

Furthermore, because next-generation sequencing was not performed systematically in this patient cohort, we were not able to study all genes associated with BrS. Therefore, we were

not able to determine whether pathogenic variants could predict the presence of arrhythmic and/or nonarrhythmic syncope.

Finally, the incidence of syncope was based on self-reported data and therefore is vulnerable to recall bias, especially data about syncope at an early age. This could have resulted in an underestimation of the lifetime history of syncope. Additionally, because some patients had the interview years after their first event, recall bias with regard to the circumstances of the events might have occurred, especially regarding prodromes (triggers might be remembered better).

Conclusion

As many as 34% of BrS patients have a lifetime history of syncope at initial presentation, of whom 57% have suspected nonarrhythmic syncope. Clinical features, including absence of prodromes and, particularly, absence of specific triggers, are different between nonarrhythmic syncope and ACA and may be used to distinguish arrhythmic from nonarrhythmic syncope. Therefore, history taking of BrS patients with syncope should be particularly directed to the search for such triggers. The high prevalence of nonarrhythmic syncope must be taken into account during risk stratification in BrS because the risk for future ACA is 0% to 3% after 9 years in asymptomatic patients or suspected nonarrhythmic syncope patients but is substantial (53% after 9 years) in ACA patients.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2014.10.014.

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CLINICAL PERSPECTIVES

In patients with Brugada syndrome (BrS), syncope is generally considered a sign of increased risk for sudden death. However, in the general population, nonarrhythmic syncope is the most frequent cause of syncope. It is difficult to establish whether syncope in BrS patients stems from arrhythmia or nonarrhythmic causes. Yet, it is important for clinical management to distinguish these types of syncope because arrhythmic syncope requires ICD placement, whereas ICDs are not beneficial in patients with nonarrhythmic syncope and only is disadvantageous (ICD complications, costs). This study reports the prevalence, clinical characteristics, and clinical significance of syncope episodes in almost 350 patients with BrS. As many as 34% of patients with BrS had a history of ≥ 1 episode of syncope at initial presentation, of whom 28% had suspected arrhythmic syncope and 57% had suspected nonarrhythmic syncope. In addition, clinical criteria may be used to distinguish arrhythmic events from nonarrhythmic syncope, including sex, age, presence of urinary incontinence, absence of prodromes, and, in particular, absence of specific triggers. These criteria were obtained from systematic history taking, highlighting the importance of history taking. Taking these criteria into account, the risk for future arrhythmic events was zero during a 9-year follow-up period in patients with nonarrhythmic syncope. With the increasing awareness and diagnosis of patients with a genetic predisposition for sudden cardiac death and subsequent ICD placement in high-risk patients, this knowledge on syncope risk stratification is critically important to prevent device overutilization in the future.