Predicting the cause of syncope from clinical history in patients undergoing prolonged monitoring

Sachin Sud, MD, George J. Klein, MD, Allan C. Skanes, MD, Lorne J. Gula, MD, Raymond Yee, MD, Andrew D. Krahn, MD

From the Division of Cardiology, University of Western Ontario, London, Ontario, Canada.

BACKGROUND Syncope may be the result of primary bradycardia or tachycardia, vasovagal syncope, or noncardiac syncope. Risk factors and outcome scores to predict prognosis in patients with syncope have been developed. Although these correlate with morbidity and mortality in patients with syncope, their relationship with the mechanism of syncope has not been investigated.

OBJECTIVE The purpose of this study was to identify clinical predictors of primary bradycardia in a cohort of patients undergoing prolonged monitoring for unexplained syncope.

METHODS One hundred nineteen patients underwent prolonged monitoring with an implantable or external loop recorder after assessment at a single-center, tertiary care arrhythmia service. Fifty-two patients with recurrent syncope during monitoring were classified according to the mechanism of syncope (International Study on Syncope of Uncertain Etiology [ISSUE] classification). Clinical predictors of primary arrhythmic syncope were identified.

RESULTS Twenty patients were classified with primary arrhythmia and 32 patients were classified with nonarrhythmic syncope. Five clinical variables were associated with primary arrhythmia: left bundle branch block, structural heart disease, and syncope without prodrome increased the likelihood of primary arrhythmia; a normal baseline ECG and history of syncope in childhood decreased the likelihood of primary arrhythmia. After multiple logistic regression, risk factors for the diagnosis of primary arrhythmia included syncope without warning symptoms and structural heart disease. The presence of left bundle branch block correlated perfectly with primary arrhythmia, whereas a normal ECG reduced the likelihood of primary arrhythmia.

CONCLUSION Clinical predictors of primary arrhythmia in patients with recurrent syncope include normal ECG and structural heart disease. Left bundle branch block is an important finding in patients with unexplained syncope.

KEYWORDS Syncope; Bradycardia; Pacemaker; Diagnosis; Monitoring

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Introduction

Syncope affects 12% to 48% of the population at some point in their lives.[1] However, the etiology is established in only 50% to 75% of patients who present to a physician's office or emergency department.[2–4] Use of an external or implanted loop recorder increases the diagnostic yield among patients in whom the etiology of syncope remains elusive.[5,6] Although several studies have linked clinical features to adverse outcomes and arrhythmic events, these studies enrolled heterogenous populations and lacked a uniform reference standard for the diagnosis of cardiac syncope.[1,7–17]

The primary aim of this study was to clarify which clinical features identify patients with recurrent syncope in whom a diagnosis of primary arrhythmia is likely. Clinical features from the syncope history, routine cardiovascular testing, and baseline ECG were compared with the eventual diagnosis of primary arrhythmia in patients undergoing prolonged monitoring using a diagnostic gold standard of symptom rhythm correlation.

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Methods

Patient selection

Patients who underwent prolonged monitoring for recurrent unexplained syncope or a single episode of unexplained syncope with injury and who had a left ventricular ejection fraction greater than 35% were screened for possible inclusion. All patients from the Randomized Assessment of Syncope Trial (RAST)[5] and Monitoring of asymptomatic arrhythmias in syncope trial (MAST)[6] were considered for this study. Patients were selected if they had recurrence of syncope or presyncope reproducing index symptoms during prolonged monitoring with an implantable loop recorder, with an external loop recorder, or during continuous ECG. A prodrome was considered present or absent based on the index event leading to referral. All patients underwent consultation with the Arrhythmia Service at the London Health Sciences Center, which arranged prolonged monitoring until recurrent syncope for up to 1 year with an external or implanted loop recorder, after a minimum of 48 hours of Holter or in-patient monitoring, and cardiac imaging. Tilt table testing and carotid sinus massage were performed in selected patients suspected of having neu-

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rally mediated syncope at the discretion of the treating physician or when protocol was mandated in RAST.[5]

Data collection

Hospital charts were reviewed to obtain relevant baseline clinical details, including baseline ECG, telemetry or Holter monitoring, tilt testing, electrophysiologic testing, and echocardiography. Syncope was established to be the result of a primary cardiac arrhythmia through rhythm correlation during prolonged monitoring with an implantable loop recorder, external loop recorder, or continuous ECG recording. At least two investigators, blinded to patient demographic and clinical data, reviewed printouts from all symptomatic events recorded during loop recorder follow-up. All events were classified according to the International Study on Syncope of Uncertain Etiology (ISSUE) classification of loop recorder events.[18] According to the ISSUE classification, the mechanism of syncope is classified as (1) vasovagal syncope, based on the presence of gradual-onset bradycardia and progressive sinus slowing, or minimal variations in heart rate; (2) primary bradycardia, based on the presence of abrupt onset of bradycardia, sinus node acceleration, or no change in sinus rate; (3) primary tachyarrhythmia; or (4) noncardiac syncope.[18] The ISSUE classification has been validated[18–22] and predicts response to therapy in patients with bradycardia and vasovagal syncope.[23,24] In cases where the features were inconclusive, at least two investigators not involved in the primary statistical analysis independently established the diagnosis and resolved differences by consensus.

A priori clinical and historical features associated with primary bradycardia or tachyarrhythmia were identified from the existing literature.[7,11,25] Patients in whom the etiology of syncope remained unclear were contacted in order to ascertain whether a diagnosis had been made after prolonged follow-up. Structural heart disease was defined as a known history of cardiomyopathy, ischemic heart disease, left ventricular hypertrophy, or valvular or aortic root disease. Baseline ECG was considered to be normal if it demonstrated sinus rhythm without evidence of previous infarction, ischemia, conduction abnormality, QT prolongation, or Brugada sign. Isolated q waves in lead III and first-degree AV block were considered normal variants.

Statistical analysis

Continuous data are expressed as mean ± SD. Student's t-test was used for comparison of continuous data, and Fisher exact test was used for comparison of categorical outcomes. Twenty-eight variables from a prespecified list (Table 1) were assessed in univariate analyses for association with syncope due to arrhythmia (i.e., ISSUE classification 1C, 4B, 4C, 4D).[18] Univariate and multiple logistic regression was performed to identify variables that were independently predictive of primary arrhythmia. Due to the modest number of endpoints, a more liberal level of significance ($P < .10$) in identifying univariate variables for multiple logistic regression was used. The model was further evaluated using the Hosmer-Lemeshow goodness of fit test and the R^2 statistic. Correlation between variables in the multivariate analysis was assessed using the Spearman rho and phi-squared statistic where appropriate. Tests of interaction were performed between variables in the regression analysis.

Table 1 Clinical variables used for univariate and multiple logistic regression analyses

Patient demographics
Age
Gender
Syncope history
Syncope in childhood or adolescence
Situational syncope (e.g., syncope with pain, medical procedure, sight of blood, extreme emotion)
No. of syncopal episodes in prior year
Nausea associated with syncope
Diaphoresis associated with syncope
Pallor associated with syncope
Episodes of presyncope without syncope
Prodrome of presyncope preceding syncope
Injury associated with syncope
Falls associated with syncope
Palpitations associated with syncope
Confusion after syncope
Fatigue after syncope
Physical examination
S4 on cardiac auscultation
Orthostatic hypotension
Positive carotid sinus massage
Cardiovascular history
Structural heart disease
History of coronary artery disease
History of transient ischemic attack or stroke
History of peripheral vascular disease
History of diabetes (type I or type II)
Ejection fraction
Baseline ECG characteristics
Presence of normal ECG
Left bundle branch block
Atrial fibrillation
Conduction system disease (bundle branch block *or* hemiblock *or* high-grade AV block)

In a post hoc analysis, the Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) risk score was computed for each patient, and then univariate and multiple logistic regression was performed using the OESIL score as the independent variable and syncope due to primary arrhythmia as the dependent variable.[7] The OESIL score predicts adverse events in patients presenting to an emergency department after syncope and is calculated by assigning one point for abnormal ECG, prior history of cardiovascular disease, age greater than 65, and syncope without prodromal symptoms. The age at the time of index event leading to referral was substituted for monitoring for age at presentation to the emergency department.[7] For all analyses $P < .05$ was considered significant. All analyses were performed in JMP 7.0 (SAS Institute, Cary, NC, USA).

Results

Fifty-two of 119 patients who underwent prolonged monitoring experienced recurrence of symptoms and were classified according to the ISSUE classification (Figure 1 and Table 2). Forty-six (88%) of 52 patients had a history of multiple unexplained syncopal episodes prior to prolonged

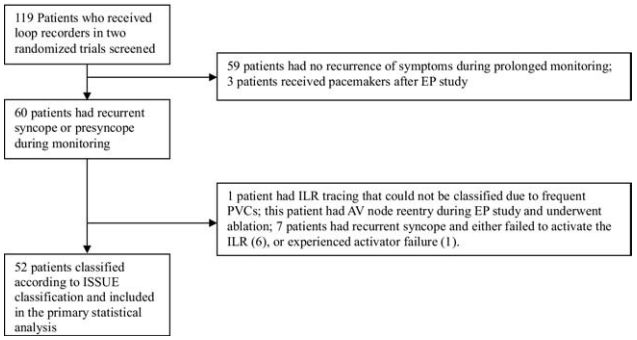

Figure 1 Patient flow in the study. AV = atrioventricular; EP = electrophysiologic; ILR = implantable loop recorder; ISSUE = International Study on Syncope of Uncertain Etiology (see Appendix 1 and Brignole et al[18]); PVC = premature ventricular complex.

monitoring. Eight patients with recurrent symptoms during monitoring could not be classified and were excluded: one had recurrence of symptoms with multiple premature ventricular complexes and subsequently underwent electrophysiology study, which demonstrated AV nodal reentrant tachycardia; and seven patients had recurrent symptoms but either did not activate the implantable loop recorder (n = 6) or experienced device activation failure (n = 1). The remaining 59 patients did not experience recurrent symptoms during monitoring. The baseline characteristics of patients included in the study are listed in Table 3.

Twenty patients were classified as primary arrhythmia (ISSUE 1C, 4B, 4C, 4D) and 23 patients as vasovagal syncope (type 1A, 1B, 2A, 2B, 3A, or 3B). The diagnosis remained unclear in nine patients (ISSUE 3A or 4A). The diagnosis eventually was considered seizure disorder in two of these patients, and an Arnold-Chiari malformation was found in one patient. Five of the 20 patients with primary arrhythmia had left bundle branch block on baseline ECG versus none in the nonarrhythmia group (Table 2, $P = .006$). Of these five patients, four developed complete heart block with asystolic pauses (ISSUE class 1C), and one patient developed symptomatic ventricular tachycardia (ISSUE 4C). No patient with primary arrhythmia reported syncope during childhood or teenage years, versus 6 of 32 in the nonarrhythmia group ($P = .071$). Ischemic heart disease was more common in the primary arrhythmia group (40% vs 13%, $P = .04$), as was the overall prevalence of structural heart disease (55% vs 25%, $P = .04$). There were no significant differences in age, gender. or ejection fraction.

Clinical variables associated with syncope due to arrhythmia

Results of the univariate analysis are given in Table 4. Four variables increased the likelihood of syncope due to primary arrhythmia: ischemic heart disease, structural heart disease, syncope without prodrome, and left bundle branch block. Two

Table 2 Classification of loop recorder events

Loop recorder characteristics		All patients (n = 52)
Recurrence symptoms		
Syncope		46
Presyncope reminiscent of index syncope		6
Monitoring characteristics		
Implantable loop recorder		50
External loop recorder		2
Heart rate <40 bpm		20
Ventricular asystole >3 seconds		24
Ventricular Asystole >5 seconds		18
AV block		16
ISSUE classification of loop recorder events		
Asystole (RR >3 seconds)		
1A (vasovagal)	Progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest	9
1B (vasovagal)	Progressive sinus bradycardia followed by AV block (and ventricular pause/s) with concomitant decrease in sinus rate *or* sudden-onset AV block (and ventricular pause/s) with concomitant decrease in sinus rate	4
1C (arrhythmia)	Sudden-onset AV block (and ventricular pause/s) with concomitant increase in sinus rate	12
Bradycardia		
2A (vasovagal)	Decrease of heart rate >30%	2
2B (vasovagal)	Heart rate to <40 bpm for >10 seconds	4
No or slight variation		
3A (noncardiac)*	No variation or <10% variation in heart rate	11
3B (vasovagal)	Increase in heart rate >10% but <30% and <120 bpm; or decrease >10% but <30% and >40 bpm	1
Tachycardia		
4A (arrhythmia)	Progressive sinus tachycardia	1
4B (arrhythmia)	Atrial fibrillation	4
4C (arrhythmia)	Supraventricular tachycardia (except sinus)	3
4D (arrhythmia)	Ventricular tachycardia	1

ISSUE = International Study on Syncope of Uncertain Etiology.

*In cases where the loop recorder tracing was classified as 3A but tilt testing was positive, the diagnosis was considered vasovagal. Assuming all patients classified as 3A syncope have noncardiac syncope did not affect the results of the analysis.

Table 3 Patient characteristics

	All patients with recurrent syncope or presyncope during monitoring (n = 52)	Primary arrhythmic (n = 20)	Nonarrhythmia (n = 32)	*P* value
Age (years)	67 ± 14	69 ± 14	66 ± 15	.44
Male (%)	28 (54%)	60%	50%	.57
Structural heart disease				
Coronary artery disease (%)	12 (23%)	40%	13%	.04
Any structural heart disease	19 (37%)	55%	25%	.04
Ejection fraction (%)	55 ± 8	54 ± 8%	55 ± 7	.56
Syncope in previous year	3.7 ± 6.9	5.6 ± 10.7	2.65 ± 2.1	.24
Syncope during childhood or adolescence (%)	6 (12%)	0%	19%	.07
Normal ECG (%)	29 (56%)	30%	72%	.02
Electrophysiologic study	16 (31%)	5 (25%)	11 (34.4%)	.55
Left bundle branch block	5 (10%)	25%	0%	.006
Positive HUT	5	1/10	4/17	.62
Beta-blocker	12	25%	22%	1.00

variables, a history of syncope before age of 20 years and a normal baseline ECG, decreased the likelihood of primary arrhythmia.

After multiple logistic regression, a history of structural heart disease ($P = .037$) and abnormal baseline ECG ($P = .012$) were independently associated with primary cardiac arrhythmia (Table 4 and Figure 2). An additional variable, syncope without warning, was associated with primary arrhythmia but was of borderline statistical significance ($P = .051$). Tests of interaction were not significant (P range .27–.74). The multiple logistic regression model was statistically significant for syncope due to primary arrhythmia ($P = .012$) but explained 23% of the observed variation in the etiology of syncope. The test for lack of fit was not significant ($P = .48$). The relationship between the number of predictors present in the study population and the underlying risk for primary arrhythmia prior to implantable loop recorder (pretest risk) is given in Table 5.

OESIL score and prediction of syncope due to cardiac arrhythmia

The OESIL score was derived for all patients with symptomatic events during prolonged monitoring and was statistically significant for primary arrhythmia in a univariate analysis (unadjusted odds ratio 3.68 per one-point increase in OESIL score [95% confidence interval 1.63–8.27, $P = .0016$]).[7] After adjusting for age, baseline ejection fraction, and gender, the OESIL score remained an independent predictor of primary arrhythmia (adjusted odds ratio 4.63 per one-point increase in OESIL score [95% confidence interval 1.84–11.65, $P = .001$]).

Discussion

The current study found that a history of syncope without prodrome, abnormal resting ECG, and structural heart disease is associated with spontaneous primary arrhythmia (predominantly bradycardia) in patients with unexplained syncope. Unlike existing prediction models,[7,9,11] these associations were derived from a "gold standard" symptom rhythm correlation. Predictors of primary arrhythmia resembled predictors of mortality in the OESIL study[7] despite heterogeneity in study populations, clinical setting, and primary outcomes in these two studies. Our study included prespecified variables and took steps to reduce bias.

Our study displays a relationship between clinical features that are prognostically important in patients with syncope and clinical features that are indicative of undiagnosed primary arrhythmias. Colivicchi et al[7] described predictors of mortality in a large cohort of patients who presented to the emergency room with syncope, but their study did not specifically address the mechanism of syncope. The OESIL

Table 4 Variables associated with syncope due to primary arrhythmia (ISSUE class 1C, 4B, 4C, or 4D). Predictors were structural heart disease, syncope without prodrome and absence of a normal ECG

	Univariate analysis			Multiple logistic regression*	
Risk factor	Arrhythmia group (n = 20)	Nonarrhythmia group (n = 32)	*P* value (Fisher exact test)	Odds ratio (95% confidence interval)	*P* value (Wald test)
Ischemic heart disease	8	4	.040	Dropped†	—
Syncope without warning symptoms	11	9	.079	4.10 (0.99–16.90)	.051
Structural heart disease	11	8	.040	4.90 (1.11–21.76)	.036
Normal ECG	6	23	.023	0.16 (0.04–0.67)	.012
Syncope in childhood	0	6	.071	Dropped‡	—
Left bundle branch block	5	0	.006	Dropped‡	—

ISSUE = International Study on Syncope of Uncertain Etiology.

*Multiple logistic regression analysis performed with variables with $P < .10$ for primary arrhythmia and other potentially clinically or physiologically important variables including baseline age, ejection fraction, and gender.

†Ischemic heart disease and structural heart disease were highly correlated (phi = 0.72); thus, only structural heart disease was retained in the multivariate model. No other variables included in the multiple logistic regression were correlated (phi = 0.048–0.14).

‡Variables that perfectly predict outcomes are dropped because they lead to unstable parameters without improving the predictive accuracy of multivariate models.

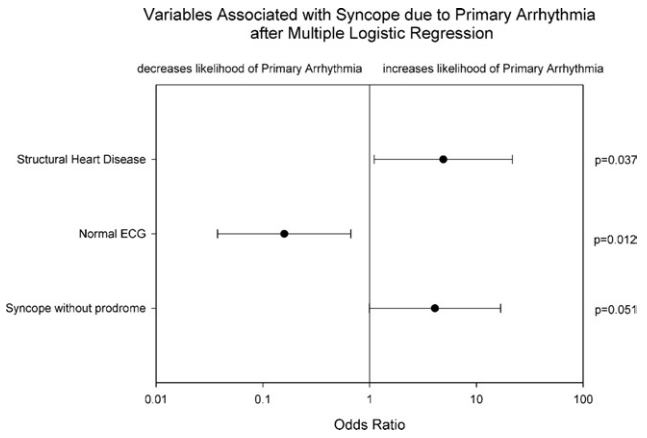

Figure 2 Multiple logistic regression model for clinical variables associated with primary arrhythmia in patients with syncope.

predictors of mortality in patients with syncope resemble variables we identified by multiple logistic regression as risk factors for primary arrhythmia in patients undergoing prolonged monitoring. We found that a modified OESIL score was associated with underlying primary arrhythmia, even after adjusting for differences in age, gender, and ejection fraction in the arrhythmia and nonarrhythmia groups. The prospectively derived San Francisco Syncope Score identified patients with syncope in an emergency setting who were at risk for adverse outcomes and found that abnormal ECG and history of congestive heart failure predicted adverse outcomes.[11] Both of these studies focused on the use of baseline variables to predict morbidity and mortality but not on the mechanism of recurrent syncope.

An abnormal ECG has been shown to be an independent predictor of adverse outcomes,[7,11] a predictor of arrhythmic events during follow-up in patients referred for electrophysiologic study,[8] and a predictor of cardiac syncope in patients undergoing an extensive diagnostic workup for unexplained syncope.[9] Prospective studies have also found an independent association between structural heart disease and mortality[7] and between structural heart disease and cardiac syncope.[9] None of these studies uniformly applied a reference standard of symptom rhythm correlation to diagnose cardiac syncope. Conversely, Sheldon et al[25] showed that age ≤35 years and the presence of prodromal symptoms were independent predictors of tilt positive vasovagal syncope. Although a normal ECG was not itself independently predictive of vasovagal syncope, the authors found that any one of bifascicular block, asystole, supraventricular tachycardia, or diabetes decreased the likelihood of vasovagal syncope. The fact that age was not an independent predictor of primary arrhythmia in our study may reflect selection bias because patients in our study were generally older.

Our study was not sufficiently powered to demonstrate which ECG features were most specific for primary arrhythmia. Nonetheless, left bundle branch block on baseline ECG was highly suggestive of primary arrhythmia but could not be included in the multiple logistic regression analysis because it perfectly predicted the occurrence of primary bradycardia and occurred infrequently. In a study of 52 patients with bundle branch block who received an implantable loop recorder, 17 patients developed prolonged asystolic pauses attributable to AV block.[19] This finding is consistent with our study, in which all patients with left bundle branch block developed either complete heart block or ventricular tachycardia. Thus, suspicion of primary arrhythmia is low when the baseline ECG is normal and high when left bundle branch block is present.

Predictors of primary arrhythmia may be useful in risk-stratifying patients, particularly elderly patients with unexplained syncope for whom the clinical question is empiric pacing or prolonged monitoring (Table 5). Although the presence of one or two predictors argues modestly for primary arrhythmia, the absence of any risk factor strongly suggests an etiology other than primary arrhythmia. Furthermore, the presence of left bundle branch block may be strong evidence for empiric pacing in elderly patients. Given the small numbers of patients in our study and the retrospective design, prospective studies are needed to validate this hypothesis.[11]

Study limitations

The study has several limitations. Certain variables could not be included because they were not routinely recorded at baseline, such as family history of syncope or a history of mood disorder.[26,27] The study was underpowered to determine which baseline ECG features were specific for primary arrhythmia. Furthermore, only patients who experienced recurrent symptoms were included in the study, a potential source of selection bias that might limit the generalizability of the findings. Nonetheless, this study included a prespecified list of variables chosen for their clinical and physiological significance, the use

Table 5 Relationship between number of predictors of primary arrhythmia present and pretest risk (prior to implantable loop recorder monitoring) of primary arrhythmia*

No. of predictors of primary arrhythmia present	Primary arrhythmia (n = 20)	Nonarrhythmia (n = 32)	Pretest risk of primary arrhythmia (95% confidence interval)	Likelihood ratio for primary arrhythmia (95% confidence interval)
0	1	12	7.7% (1.3–33.3)	0.13 (0.02–0.95)
1	6	13	31.6% (15.4–54.0)	0.74 (0.34–1.63)
2	10	7	58.8% (36.0–78.4)	2.29 (1.04–5.03)
3	3	0	100% (43.9–100)	10.67 (0.60–202)†

*Predictors were structural heart disease, syncope without prodrome and absence of a normal ECG.
†When calculating this likelihood ratio, 0.5 was added to each cell of a 4×4 table to obtain a noninfinite likelihood ratio.

of a "gold" standard of symptom rhythm correlation in the identification of the mechanism of syncope, and methods for reducing bias. Although the results are drawn from a selected patient population, they are consistent with the results of other larger studies looking at prognostic factors in patients with syncope and provide a potential mechanistic basis for the findings of these studies.[26,27]

Conclusion

In patients with unexplained syncope undergoing prolonged monitoring, risk factors for the diagnosis of primary arrhythmia include syncope without warning symptoms and structural heart disease. The presence of left bundle branch block strongly suggests primary arrhythmia, whereas a normal ECG reduces the likelihood of primary arrhythmia.

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Appendix 1

ISSUE classification of detected rhythm from the implantable loop recorder

Classification	Sinus rate	AV node	Comment
Asystole (RR >3 seconds)			
1A	Arrest	Normal	Progressive sinus bradycardia until sinus arrest probably vasovagal
1B	Bradycardia	AV block	AV block with associated sinus bradycardia probably vasovagal
1C	Normal or tachycardia	AV block	Abrupt AV block without sinus slowing suggests intrinsic AV nodal disease
Bradycardia			
2A	Decrease >30%	Normal	Probably vasovagal
2B	HR <40 bmp for >10 seconds	Normal	Probably vasovagal
Minimal HR change			
3A	<10% variation	Normal	Suggests noncardiac cause, unlikely vasovagal
3B	HR increase or decrease 10%–30%, not <40 bpm or >120 bpm	Normal	Suggests vasovagal
Tachycardia			
4A	Progressive tachycardia	Normal	Sinus acceleration suggests orthostatic intolerance or noncardiac cause
4B	NA	Normal	Atrial fibrillation
4C	NA	Normal	Supraventricular tachycardia
4D	NA	Normal	Ventricular tachycardia

HR = heart rate; ISSUE = International Study on Syncope of Uncertain Etiology; NA = not applicable.
Adapted from Quinn et al.[17]