

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2001;104;2045-2050

DOI: 10.1161/hc4201.097837

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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Mechanism of Syncope in Patients With Bundle Branch Block and Negative Electrophysiological Test

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Background—In patients with syncope and bundle branch block (BBB), syncope is suspected to be attributable to a paroxysmal atrioventricular (AV) block, but little is known of its mechanism when electrophysiological study is negative.

Methods and Results—We applied an implantable loop recorder in 52 patients with BBB and negative conventional workup. During a follow-up of 3 to 15 months, syncope recurred in 22 patients (42%), the event being documented in 19 patients after a median of 48 days. The most frequent finding, recorded in 17 patients, was one or more prolonged asystolic pause mainly attributable to AV block; the remaining 2 patients had normal sinus rhythm or sinus tachycardia. The onset of the bradycardic episodes was always sudden but was sometimes preceded by ventricular premature beats. The median duration of the arrhythmic event was 47 seconds. An additional 3 patients developed nonsyncopal persistent III-degree AV block, and 2 patients had presyncope attributable to AV block with asystole. No patients suffered injury attributable to syncopal relapse.

Conclusions—In patients with BBB and negative electrophysiological study, most syncopal recurrences have a homogeneous mechanism that is characterized by prolonged asystolic pauses, mainly attributable to sudden-onset paroxysmal AV block. (*Circulation*. 2001;104:2045-2050.)

Key Words: syncope ■ electrophysiology ■ arrhythmia ■ heart block ■ electrocardiography

In patients with syncope and bundle branch block (BBB), syncope is likely to be attributable to a paroxysmal atrioventricular (AV) block when electrophysiological study shows definite abnormalities of the His-Purkinje conduction system. For example, in a study conducted by Gronda et al,¹ complete electrophysiological investigation, including drug stress, was able to predict the development of stable AV block in 87% of patients. However, little is known about the mechanism of syncope in patients with a negative electrophysiological investigation. In patients with negative electrophysiological studies, Link et al² observed development of stable AV block in 18% (after 30 months) and Gaggioli et al³ in 19% (after 62 months) of patients, thus suggesting that some results are false negatives; the syncope recurrence rate was 19% after 2.2 years in one study⁴ and ≈40% after 3 years in another²; mortality was generally low.^{2,4,5}

A significant problem in evaluating syncope and bifascicular block is the transient nature of high-degree AV block and the long interval sometimes required to document it electrocardiographically. An implantable event monitor has recently

become available and has been validated in patients with unexplained syncope.⁶ The implantable loop recorder (ILR) is placed subcutaneously under local anesthesia and has a battery life of 15 to 18 months. The device has a solid-state loop memory and, in the present version, the ECG of up to 40 minutes before and 2 minutes after activation can be stored.

In the present study, we implanted an ILR in patients with BBB and negative electrophysiological study to evaluate the natural history of these patients and obtain additional information on the mechanism of syncope.

Methods

The International Study of Syncope of Uncertain Etiology (ISSUE) is a multicenter international prospective study aimed at analyzing the diagnostic contribution of ILR in 4 predefined groups of patients with syncope of uncertain origin: (1) isolated syncope group; namely, patients without structural heart disease or with minor cardiac abnormalities that were considered to be without clinical relevance and not suggestive of a cardiac cause of syncope, absence of intraventricular conduction defects, and negative complete workup, including tilt testing; (2) tilt-positive group; namely, patients as above but who had a positive response to tilt testing;

Received June 5, 2001; revision received August 3, 2001; accepted August 15, 2001.

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*A complete list of investigators appears in the Appendix.

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(3) suspected bradycardia group; namely, patients with BBB and negative electrophysiological test; and (4) suspected tachycardia group; namely, patients with overt heart disease at risk of ventricular arrhythmia, because these were patients with previous myocardial infarction or cardiomyopathy with depressed ejection fraction or nonsustained ventricular tachycardia in whom an electrophysiological study did not induce sustained ventricular arrhythmias. The patients of the present study belong to the subgroup of BBB and negative electrophysiological test. The results of isolated syncope and tilt-positive groups are also published.⁷

Study Protocol

This group included all patients with any type of BBB with QRS >100 ms, no documentation of II- or III-degree AV block, and a negative electrophysiological study.

Patients were included in the study only if a careful history, physical examination, baseline ECG, carotid sinus massage, echo-

TABLE 1. Patient Characteristics

No. of patients	52
Age, y	71±8
Male sex, n (%)	43 (83)
History of syncope	
Duration of syncope, y	2 (1–3)
No. of syncopes during last 2 years	3 (2–4)
Patients with presyncopal episodes during the last 2 years, n (%)	27 (52)
Trauma (total), n (%)	34 (65)
Severe trauma (wounds, fractures), n (%)	10 (19)
No warnings, n (%)	38 (73)
Vasoactive therapy at the time of the index syncope, n (%)	30 (58)
Standard electrocardiogram	
Bundle branch block type, n (%)	
Right plus right axis deviation	22 (42)
Right, no axis deviation	9 (17)
Left	20 (38)
Intraventricular conduction defect	1 (2)
Associated PR prolongation ≥0.22 s, n (%)	10 (19)
Mean QRS duration, ms	134±18
Permanent atrial fibrillation, n (%)	5 (10)
Associated structural heart disease, n (%)	28 (54)
Ischemic	13
Dilated	3
Valvular	4
Hypertensive	8
Heart failure	0 (0)
Ejection fraction <40% (echocardiogram)	5 (10)
Nonsustained ventricular tachycardia on Holter recording	7 (13)
Electrophysiological study	
Baseline HV interval length, ms	55±9
Maximum HV interval after Ajmaline infusion, ms	79±19
Induction of polymorphic ventricular tachycardia or fibrillation, n (%)	4 (8)
Sinus node recovery time >1500 ms, n (%)	1 (2)
Tilt testing, positive response, n (%)	7/51 (14)

Values are mean±SD, median (range), or n (%).

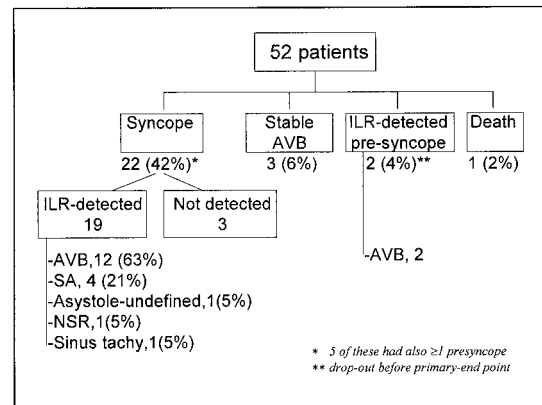


Figure 1. Events observed during the study period. AVB indicates AV block; SA, sinus arrest; and NSR, normal sinus rhythm.

cardiogram, 24-hour ambulatory monitoring, and complete electrophysiological study were not diagnostic of the etiology of syncope.

No patient with BBB was assigned to any of the other groups of the ISSUE study. The study group can therefore be considered representative of the patient population affected by BBB and unexplained syncope. Therefore, patients with both BBB and a positive response to tilt testing were included, because the specificity of a positive response to tilt testing has raised serious concern, and, in that, positivity cannot exclude a cardiac cause of syncope.^{8,9}

The electrophysiological study included measurement of the sinus node recovery time; measurement of the HV interval at the baseline and under stress by incremental atrial pacing and, if the baseline study was inconclusive, pharmacological provocation with slow infusion of ajmaline (1 mg/kg IV); assessment of the inducibility of ventricular arrhythmia by means of programmed ventricular stimulation; and assessment of the inducibility of supraventricular arrhythmia by any atrial stimulation protocol. In accordance with the literature,^{1,10–16} the electrophysiological study was considered diagnostic, and, therefore, the patients were excluded from the study in the following cases: (1) sinus bradycardia and abnormal sinus node recovery time; (2) baseline HV interval of ≥70 ms, 2nd or 3rd degree His-Purkinje block demonstrated during incremental atrial pacing, or high-degree His-Purkinje block elicited by intravenous administration of ajmaline; (3) induction of sustained monomorphic ventricular tachycardia; or (4) induction of rapid supraventricular arrhythmia, which reproduced hypotensive or spontaneous symptoms.

When patients were deemed eligible, an ILR (Reveal, Medtronic) was implanted subcutaneously. The recommended programmed mode was 1 event, 21 minute preactivation, and 1 minute postactivation. Patients were instructed to activate the device after every episode of syncope or presyncope. The records of all episodes were retrieved, printed, and analyzed by investigators in each center and reevaluated by the 3 members of the event committee.

End Points

The primary end point of this study was the analysis of the electrocardiographic tracing obtained during the first syncopal episode that was correctly recorded by the device.

Secondary end points were the study of the natural history of the patients with syncope and BBB, which included major clinical events, the development of stable AV block and total prevalence of syncopal recurrences, and the analysis of electrocardiographic recordings when the device was activated for nonsyncopal episodes.

Statistical Methods

For the secondary end points, comparison between continuous variables was carried out by means of Student's *t* test; comparison between proportions was made by Fisher's exact test; and the time to

TABLE 2. Primary End Point

ID	Time Since Enrollment, days	Event Description	Ventricular Pause, s	Total Duration, s
La9	7	Sudden 3° AVB followed by 2° AVB	19	36
La14	15	Sudden 3° AVB, triggered by one APB	48	55
Na1	2	Sudden 3° AVB	10+6+4	26
Re1	100	Sudden 3° AVB, triggered by one VPB	5+6	18
Re3	77	Sudden 3° AVB triggered by APB+VPBs	23+19	60
Re25	82	Sudden 3° AVB	10	30
Vs1	21	Sudden 3° AVB, sinus rhythm, 3° AVB	15+8	60
Xv1	4	Sudden 3° AVB triggered by VPBs	12	47
Xv2	212	Sudden 3° AVB	5+8+5	20
Do2	137	Sudden 3° AVB with prolonged asystole	Undefined	Undefined
Cp10	16	Sudden 3° AVB with prolonged asystole	Undefined	Undefined
Cp6	62	Sudden 3° AVB	12+11	>300
Vn5	10	Sudden undefined asystole triggered by VPBs, sinus rhythm, undefined asystole	10+14	105
Ch1	26	Progressive sinus bradycardia followed by SA	3+4+3	48
Fu1	33	Sudden SA followed by sinus bradycardia	25+9	45
Ms1	101	SA	22	Undefined
Co3	35	Sinus tachycardia followed by progressive sinus bradycardia followed by SA	6+6+5	60
Vr1	367	Normal sinus rhythm
Vr3	102	Progressive sinus tachycardia

AVB indicates atrioventricular block; SA, sinus arrest; APB, supraventricular premature beat; and VPB, ventricular premature beat.

the onset of the events was analyzed by means of Kaplan-Meier survival curves.

Results

Clinical Characteristics of Patients

From November 1997 to July 2000, 53 patients were included. Patients were seen at the outpatient clinic every 3 months and were followed up until the primary endpoint was reached, the battery of the ILR ran down, or the patient died. As one patient was lost to follow-up and was excluded from the analysis, 52 patients completed the study protocol. The patients' characteristics are shown in Table 1. The minimum follow-up was 3 months. Follow-up was completed in October, 2000.

Primary End Point

An ILR-documented syncopal event occurred in 19 patients (37%) after a median of 48 days (interquartile range, 16 to 100) (Figure 1). The most frequent finding, observed in 17 patients, was one or more prolonged asystolic pauses attributable to AV block or sinus arrest (Table 2 and Figures 2, 3, and 4); the remaining 2 patients had normal sinus rhythm or sinus tachycardia. The onset of the AV block was always sudden, but in 5 cases it was triggered by atrial or ventricular premature beats. In 2 patients who had sinus arrest, the pause was preceded by progressive bradycardia. The median duration of the arrhythmic event was 47 seconds (interquartile range, 31 to 60). No patients suffered injury attributable to syncopal relapse.

Secondary End Points

Another 9 patients had clinical events during the study period (Figure 1): 3 patients developed nonsyncopal persistent III-degree AV block; 3 patients had syncope but were unable to activate the ILR; 2 patients had ILR-detected presyncope, attributable in both cases to sudden AV block with asystole of 6 and 7 seconds, respectively; and 1 patient died suddenly. In this latter case, death occurred while the patient was undergoing a sigmoid-colonoscopy examination; the ILR was activated and revealed initial rapid atrial fibrillation (the

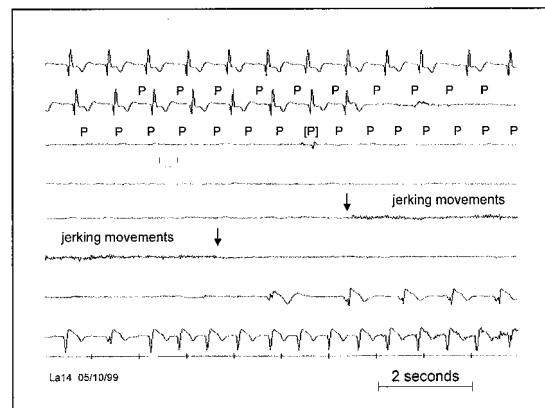


Figure 2. Continuous electrocardiographic recording of the syncopal event suffered by patient La14. Onset of AV block is sudden, without any change in the PP interval. The noise recorded from the 30th to the 37th second of asystole probably reflects jerking movements of the patient.

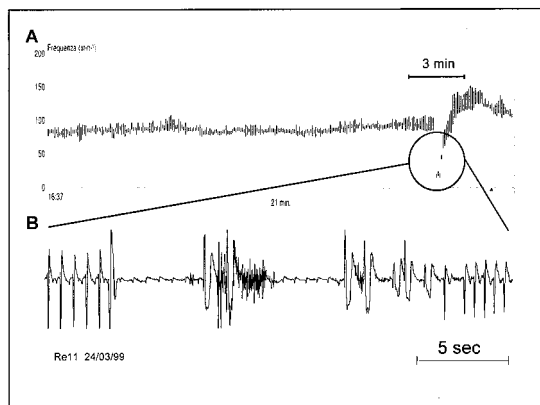


Figure 3. Syncope observed in patient Re11. A, Heart rate trend during the whole 21-minute loop recording. Initially, the heart rate is stable at ≈ 80 bpm and suddenly falls at the time of the syncope. B, Expanded ECG shows a blocked P wave with 2 main pauses of 5- and 6-second duration.

patient was affected by chronic atrial fibrillation) followed by bradycardia progressing to asystole; the episode lasted 5 minutes. Thus, a total of 28 patients (54%) had events; their actuarial estimates were 33%, 48%, and 56% at 3, 9, and 15 months, respectively (Figure 5). Most events were attributable to AV block. Indeed, an intermittent or stable AV block was observed in 17 patients (33%) and possibly in 1 additional patient in whom the cause of asystole remained undefined because of the low amplitude of the ILR-detected P waves. The actuarial estimates of AV block (calculated on 17 patients) were 24%, 34%, and 34% at 3, 9, and 15 months (Figure 5). No baseline clinical variable was able to predict the development of stable or intermittent AV block during follow-up, but patients with right BBB without axis deviation and those with a history of syncopal episodes lasting >2 years tended not to develop AV block (Table 3). Syncope recurred in a total of 22 patients (42%); the actuarial estimates were 26%, 40%, and 48% at 3, 9, and 15 months (Figure 5).

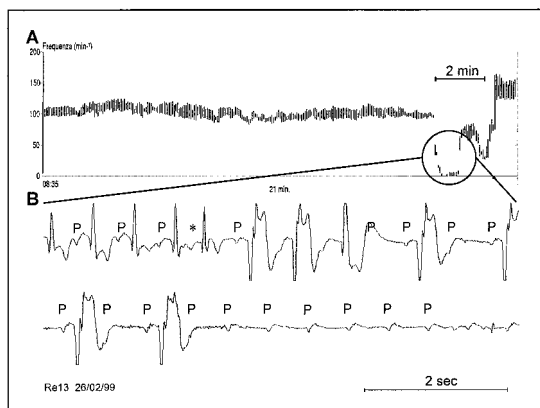


Figure 4. Syncope observed in patient Re13. A, Heart rate trend during the whole 21-minute loop recording. Initially, the heart rate is stable at ≈ 100 bpm and suddenly falls at the time of the syncope. B, Expanded ECG shows a premature atrial beat (*) that seems to trigger the AV block. Initially during the block, there are 7 idioventricular beats, then prolonged asystole occurs.

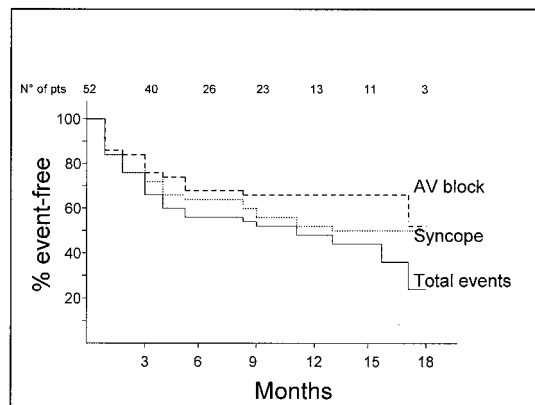


Figure 5. Kaplan-Meier estimates of the probability of remaining free of AV block, syncope, and total events.

Presyncopal events occurred in 7 patients. Of these, 2 patients had asystolic AV block and dropped out of the study before the primary end point was reached; 1 patient (La9) had a presyncopal event attributable to AV block 35 bpm without asystole and, later, a syncopal event attributable to AV block with prolonged asystole; 1 patient (Cp6) had 2 presyncopal episodes showing ventricular tachycardia and frequent ventricular premature beats, respectively, and subsequent syncope attributable to AV block; 1 patient (Xv2) had 2 presyncopal episodes showing normal sinus rhythm and sinus tachycardia, respectively, but syncope was attributable to AV block; and, finally, 2 patients had a normal sinus rhythm at the time of presyncope and, later, a syncopal event without activating the ILR.

A positive response during tilt testing was observed in 7 cases (14%); it was never asystolic. A positive response was present in 3 of 15 patients who had AV block (cases La9, Re11, and Do2) and in 1 of 4 patients who had sinus arrest (case Fu1).

As a consequence of the results of the study, 23 patients (44%) underwent implantation of a permanent pacemaker. No therapy was given to the other patients.

Discussion

The main finding of this study is that in patients with BBB and negative electrophysiological study, most syncopal recurrences have a homogeneous mechanism that is characterized by prolonged asystolic pauses mainly attributable to sudden-onset paroxysmal AV block. These findings are consistent with the clinical feature of Stokes-Adams attacks. However, approximately one half of the patients remained free of events for <1 year.

The finding that, with few exceptions, a prolonged asystole was the cause of syncope is at variance with that of Krahn et al,⁶ who found more heterogeneous results, with bradycardia being present in only a minority of patients. These different results can easily be explained by the different selection of patients in the two studies. Also in the other arms of the ISSUE study, namely in the patients with isolated unexplained syncope or tilt-positive syncope,⁷ there was a high incidence of bradycardic syncopes, but the mechanism was largely different; in these latter groups, the onset of the pauses

TABLE 3. Positive and Negative Predictive Factors of Paroxysmal or Stable AV Block During Follow-Up

Variable	AV Block (17 patients)	No AV Block (35 patients)	P
Age, y	72±10	70±7	NS
BBB type, n (%)			
Right+right axis deviation	8 (47)	14 (40)	NS
Left	7 (41)	13 (37)	NS
Right, no axis deviation	1 (6)	8 (23)	NS
Intraventricular conduction defect	1 (6)	...	
Baseline HV interval length, ms	58±8	53±9	NS
Maximum HV interval after ajmaline infusion, ms	78±9	80±13	NS
History of syncope without warning, n (%)	15 (88)	24 (69)	NS
History of syncopal episodes lasting >2 years, n (%)	3 (18)	14 (40)	NS
Structural heart disease, n (%)	8 (47)	20 (57)	NS
Ejection fraction <40%, n (%)	0 (0)	5 (14)	NS
Nonsustained VT on Holter monitoring, n (%)	2 (12)	5 (14)	NS
Induction of polymorphic ventricular tachycardia or fibrillation, n (%)	1 (6)	3 (9)	NS
Positive response on tilt testing, n (%)	3/15 (19)	4 (11)	NS

Values are mean±SD or n (%). BBB indicates bundle branch block.

was usually preceded by progressive bradycardia or tachycardia rather than being sudden and the arrhythmia was a sinus arrest instead of an AV block. These different findings are consistent with different etiologies: an intrinsic disease of the His-Purkinje system in the patients with BBB and an abnormal neurally mediated reflex in the other groups. The duration of bradycardia was longer in the BBB group (47 seconds) than in the other two (31 and 33 seconds). In the present study, the finding of progressive bradycardia followed by sinus arrest, as was recorded in the isolated syncope and tilt-positive syncope groups, was observed only in 2 patients; although these patients had a negative response to tilt testing, we cannot exclude the possibility that a reflex mechanism was responsible for the arrhythmia. Similarly, in the patients who had a positive response to tilt testing, we cannot exclude the possibility that the syncope was neurally mediated. Nevertheless, in 4 patients who had a documented relapse, the type of response during tilt testing was different from the spontaneous episode and the sudden onset of the spontaneous episode was in contrast with the modality of onset of the patients with neurally mediated syncope, as discussed above.⁷ Therefore, our results confirm the concern raised in previous studies^{8,9} regarding the low specificity of tilt testing in patients with BBB.

Owing to the small number of patients that could be evaluated, the value of presyncope recording as a surrogate for syncope in establishing the diagnosis remains uncertain. Although the finding of a paroxysmal AV block associated with presyncope suggests the same mechanism for syncope, some discordance is likely to exist when different rhythms are recorded. For example, 2 patients had multiple presyncopal episodes attributable to ventricular tachyarrhythmias or sinus tachycardia or during normal sinus rhythm but had syncope attributable to AV block.

Using the results of the present study as a reference standard for arrhythmic cause of syncope, we can shed new light on the diagnostic value of electrophysiological investi-

gation. In particular, this study shows that a negative electrophysiological investigation cannot rule out a paroxysmal AV block as the cause of syncope, because 33% of the patients with a negative study had a documented episode of AV block. Until now, this figure could be calculated only indirectly from the rate of development of stable AV block, which was approximately 5% per year in the literature^{2,3} and is confirmed in this study. The mechanism that triggers a sudden block of the atrioventricular conduction or the arrest of the sinus node automaticity remains largely uncertain. However, we observed that the onset of AV block was sometimes triggered by one or a few atrial or ventricular premature beats, as already reported in the literature.¹⁷

Finally, although no baseline clinical variable was able to predict the development of stable or intermittent AV block during follow-up, the patients with right BBB without axis deviation and those with a history of syncopal episodes lasting >2 years were at lower risk of development of AV block. We cannot exclude that with a larger series we would have been able to detect a significant difference in the 2 groups (type II error).

Practical Implications

The results of the present study cannot be generalized to all syncope patients with BBB but apply only to the minority of those with a negative conventional workup that includes electrophysiological study. Although screening logs were not maintained throughout the trial, data from 2 Syncope Units (Lavagna and Reggio Emilia) showed that 15% of the patients referred for syncope and BBB met the inclusion criteria for ILR implantation, because the diagnosis had remained unexplained at the end of the conventional workup. We can expect other causes of syncope to be found during conventional investigations in the general population of patients with BBB; for example, data from the above-mentioned Syncope Units showed that bradyarrhythmia was

diagnosed in only 40% of patients and a neurally mediated mechanism was diagnosed in an additional 40% of cases.

In patients with BBB and negative electrophysiological study, an ILR-guided strategy seems reasonable, with pacemaker implantation being safely delayed until symptomatic bradycardia is documented. In accordance with this approach, 44% of our patients received a pacemaker after their first documented syncope. Other patients would probably have had a documented syncopal recurrence if the monitoring phase had been prolonged additionally. The usefulness of a very prolonged monitoring phase and the efficacy of therapy in suppressing additional syncopal recurrences remain to be proved. Owing to the high rate of AV block observed, the only acceptable alternative strategy is to implant a pacemaker in all patients with BBB and unexplained syncope. Which of these two strategies is more cost-effective remains to be proved. The present study forms the background for programming research in this direction.

Conclusions

This study highlights the importance of paroxysmal AV block as a frequent cause of syncope in patients with BBB and recurrent syncope.

Appendix

The following centers and investigators participated in the study (number of patients in parentheses): Ospedale S. Maria Nuova, Reggio Emilia: C. Menozzi, N. Bottoni (8); Ospedali Riuniti, Lavagna: M. Brignole, P. Donato, G. Gaggioli (7); Hospital Clinico, Barcelona: L. Mont, J. Brugada (5); Hospital Virgen de las Nives, Granada: L. Tercedor, M. Alvarez (3); Hospital Virgen del Rocío, Sevilla: F. Errazquin (3); Hospital Xeral de Vigo, Vigo: J. Beiras (3); Hospital Clinico Universitario, Valencia: R. Garcia-Civera (2); Ospedale Civile, Bentivoglio: B. Sassone (2); Hospital de Basurto, Bilbao: J.M. Ormaetxe (2); Ospedale Civile, Piacenza: A. Capucci, G. Villani, F. Groppi (2); Hospital Ramon Y Cayal, Madrid: C. Moro, A.H. Madrid (2); Hospital Virgen de la Salud, Toledo: E. Castellanos (2); Hospital Complejo Hospitalario, Leon: M. Fidalgo (1); Ospedale S. Anna, Como: G. Botto, A. Sagone (1); Hospital 12 de Octubre, Madrid: F. Arrivas (1); Ospedale S. Pietro Igneo, Fucecchio: A. Del Rosso (1); Hospital Juan Ramon Jimenez, Huelva: R. Barba (1); Hospital General Universitario, Murcia: A. Garcia-Alberola (1); Ospedale Umberto I, Mestre: A. Raviele, F. Giada (1); Hospital Miguel Sevot, Zaragoza: A. Asso (1); Ospedale Policlinico, II Università degli Studi, Napoli: L. Santangelo (1); Ospedale S. Maria delle Croci, Ravenna: S. Silvani (1); Hospital Universitario, La Paz: J.L. Merino, R. Peinado (1).

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Event Committee: M. Brignole, C. Menozzi, A. Moya.

Study Managers: S. Cavaglia, R. Migliorini, X. Navarro, L. Rapallini.

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