Mechanism of syncope without prodromes with normal heart and normal electrocardiogram

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BACKGROUND "*Unexplained syncope, no prodromes, and normal heart*" has been described as a distinct clinical and biological entity.

OBJECTIVE The purpose of this study was to assess the mechanism of syncope.

METHODS In this prospective multicenter study, 58 patients presenting with unexplained syncope, no prodromes, and a normal heart received an implantable loop recorder (ILR) and were followed up until a diagnosis was established. Their outcomes were compared with those of 389 patients affected by reflex syncope with prodromes who received an ILR.

RESULTS During a mean observation period of 16 ± 13 months, a diagnostic event was documented by the ILR in 29 patients (50%); an asystolic pause of 11 ± 5 seconds (range 3.5–22 seconds) was present at the time of the diagnostic event in 19 patients (66%). Compared with patients affected by reflex syncope with prodromes, patients with unexplained syncope, no prodromes, and a normal heart more frequently had an asystolic syncope (66% vs 47%; $P = .001$), and this was more frequently due to idiopathic paroxysmal atrioventricular block (47% vs 21%; $P = .04$). Ten patients with asystolic pauses underwent cardiac pacing, and 8 patients underwent oral theophylline treatment. During the subsequent 17 ± 12 months of follow-up, syncope recurred in 1 patient on theophylline and presyncope occurred in 1 patient with pacemaker.

CONCLUSION A long asystolic pause, frequently due to idiopathic paroxysmal atrioventricular block, played a role in the mechanism of syncope in two-thirds of patients who had electrocardiographic documentation of a diagnostic event. When a specific therapy was administered in patients with asystolic syncope, the short outcome was favorable.

KEYWORDS Syncope; Adenosine; Implantable loop recorder; Cardiac pacing; Theophylline

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Introduction

Syncope of sudden onset, that is, without prodromes, in patients with a normal heart and a normal electrocardiogram (ECG) has recently been described as a distinct clinical and biological entity.[1] Patients with unexplained syncope, no prodromes, and a normal heart have been shown to differ from patients with vasovagal syncope.[1] Patients affected by this syndrome have an adenosine profile that is opposite to that observed in patients with vasovagal syncope and that is characterized by low plasma adenosine values, low expression of adenosine A2A receptors, and a high rate of transient complete heart block during exogenous injection of adenosine.[2] Unlike in patients with vasovagal syncope tilt testing is usually negative.[2] Clinical and biological characteristics are similar to those observed in patients affected by idiopathic paroxysmal atrioventricular (AV) block.[3] This form of syncope has been labeled "low adenosine syncope,"[1,4] and this terminology will be used throughout this article. The exact mechanism of syncope is unknown.

In this prospective multicenter study, we wanted to assess the mechanism of syncope by means of prolonged ECG monitoring. Taking into account the possible role of adenosine as a chemical mediator of no-prodrome syncopes, our study hypothesis was that the ECG mechanism of such syncopes may involve asystolic pauses.

Methods

This multicenter, prospective, observational study was conducted in 5 structured syncope units in Italy and France.

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Table 1 Characteristics of the study group and control group

Characteristic	No prodromes (n = 58)	Prodromes (n = 389)	*P*
Age (y)	63 ± 15	65 ± 13	.30
Sex: male	23 (38)	183 (47)	.26
Total syncopes during life	4 (3–7)	6 (4–10)	.0001
No. of syncopes in the last 2 y	3 (2–4)	4 (3–5)	.0001
Duration of syncopes (y)	2 (1–5)	7 (4–23)	.0001
Age on first syncope (y)	62 (45–71)	52 (33–69)	.004
Trauma	46 (79)	190 (49)	.0001
Mild	27 (47)	166 (43)	.57
Severe	19 (33)	24 (6)	.0001
Hypertension	26 (45)	179 (46)	.89

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

Patient recruitment started in January 2012 and ended in December 2015. Follow-up ended in June 2016. The study protocol was approved by the institutional review board of each unit.

Patient selection

The study included 58 consecutive patients affected by recurrent (≥2 episodes) unexplained syncope without, or with short (ie, ≤5 seconds), prodromes who had a normal heart and a normal ECG. The absence of prodromes was carefully investigated, and doubtful cases were excluded. Specifically, we excluded patients if retrograde amnesia could not be ruled out, especially in the context of unexplained falls in older adults. An eyewitness account was often the vital key to establishing whether a definite syncope had occurred. These patients received an implantable loop recorder (ILR) and were followed-up quarterly until a diagnosis was established or the study ended.

On enrollment, baseline adenosine plasma level (APL) was determined in all patients; APL assay was performed by means of high-pressure liquid chromatography, as described previously.[5,6] All APL assays were performed in the Laboratory of Biochemistry and Molecular Biology of Timone University Hospital (Marseille, France). The normal median laboratory APL, measured in 120 control patients without syncope (mean age 53 ± 14 years; 69 [57%] male patients), was 0.60 μM (5%–95% percentile 0.40–0.78 μM). The outcome of the study group patients was compared with that of a historical control group constituted by 389 patients with reflex syncope and prodromes >5 seconds who had been enrolled in the Second and Third International Study on Syncope of Uncertain Etiology (ISSUE-2 and ISSUE-3).[7,8]

In both the study and control groups, the primary study end point was a diagnosis established by the ILR according to the criteria of current guidelines[9] and defined as recurrence of any syncope (documented by ILR) or non-syncopal arrhythmias defined as non-syncopal pause >6 s, or rapid prolonged paroxysmal atrial or ventricular tachyarrhythmias (i.e. >160 bpm for >32 s).

Statistical analysis

The probability of diagnostic asystolic ECG documentation in ISSUE-2 and ISSUE-3 was 17% at 1 year.[7,8] In the absence of any data on the prevalence of asystolic pauses in patients with unexplained syncope, no prodromes, and a normal heart, we planned to enroll 60 patients. This number was chosen to give 80% power to detect a 2-fold increase in the rate of asystolic events in the study group with a probability of 95%.

Continuous data are presented as mean ± SD or median (interquartile range)), as appropriate, whereas categorical data are presented as absolute and relative frequencies. The Kolmogorov-Smirnov method was used to check the normality of distribution. Continuous variables were compared using the *t* test or a nonparametric Mann-Whitney test. The Fisher exact test was used to compare proportions. The time to the first asystolic event and the time to diagnosis were analyzed by means of Kaplan-Meier survival curves, which were compared using the log-rank test. Analyses were performed using the MedCalc version 15.8 (MedCalc Software, Mariakerke, Belgium).

Results

Patient characteristics

The clinical characteristics of the 58 patients with unexplained syncope, no prodromes, and a normal heart are presented in Table 1. Of these, 34 (59%) never had prodromes, whereas 24 (41%) sometimes had prodromes ≤5 seconds, mostly described as momentary lightheadedness or blurring of the vision. Evaluable APL values were

Table 2 Outcome

Outcome measure	No prodromes (n = 58)	Prodromes (n = 389)	*P*	Hazard ratio	95% CI
Duration (mo)	16 ± 13	13 ± 9			
End-point event (diagnosis)	29 (50)	139 (36)	.27	1.2	0.8–1.9
Asystolic pauses	19 (66)	66 (47)	.02	1.8	1.0–3.3
SB + SA	9 (47)	49 (74)	.001		
Sudden AVB	9 (47)	14 (21)	.04		
AF followed by a pause	1 (5)	3 (5)	.50		
Normal sinus rhythm	9 (31)	69 (50)	.85		
Tachyarrhythmias*	1 (3)	4 (3)	.50		

Values are presented as mean ± SD or n (%).

AF = atrial fibrillation; AVB = atrioventricular block; CI = confidence interval; SA = sinus arrest; SB = sinus bradycardia.

*Paroxysmal supraventricular tachycardia in 1 patient in each group and ventricular tachycardia in 2 patients in the prodrome group.

Table 3 Types of diagnoses and management in 29 patients with unexplained syncope, no prodromes, and a normal heart

Patient no.	Age (y)	Sex	Adenosine plasma level (μmol/L)	End-point event (diagnosis)	Maximum pause duration (s)	Remarks	Mechanism-specific therapy	Recurrence of syncope on therapy
1	72	M	0.09	Sudden AVB	6.1		Theophylline	No
2	78	F	Hemolysis	Sudden AVB	20		Pm	Presyncope
3	77	F	0.15	Sudden AVB	10		Pm	No
4	71	F	0.37	Sudden AVB	3.5 + 2.5 + 2.5		Pm	No
5	80	F	Hemolysis	Sudden AVB	13		Theophylline	No
6	78	F	0.60	Sudden AVB	22		Theophylline	No
7	71	F	0.10	Sudden AVB	7		Theophylline	No
8	71	F	0.14	Sudden AVB	10		Pm	No
9	73	F	0.40	Sudden AVB	10		Pm	No
10	38	M	0.12	Sudden SA	16		Pm	No
11	20	F	0.09	Progressive SB + SA	14		Theophylline	No
12	71	F	0.15	Progressive SB + SA	6.5		Pm	No
13	50	M	<0.01	Progressive SB + SA	14		Theophylline	No
14	58	M	0.15	Progressive SB + SA	4 + 2 + 2		Theophylline	Syncope
15	41	M	0.18	Progressive SB + SA	6		Theophylline	No
16	76	F	0.7	Progressive SB + SA	12		Pm	No
17	72	F	0.50	Progressive SB + SA	8		Pm	No
18	69	M	0.27	Progressive SB + SA	9		–	
19	83	F	0.12	Pause at the end of AF	6	Intrinsic cardiac cause	Pm	No
20	42	F	0.27	Progressive slight SB	–	Hypotension	–	
21	71	M	0.30	Progressive slight SB	–		–	
22	73	F	0.16	Progressive slight SB	–		–	
23	64	M	0.09	SVT 240 beats/min	–	Intrinsic cardiac cause	Catheter ablation	
24	84	F	0.12	No rhythm variation	–	Another episode of asymptomatic SA 5 s	–	
25	66	M	0.35	No rhythm variation	–	Suspected epilepsy	–	
26	50	M	0.30	No rhythm variation	–	Depressive mood	–	
27	60	F	0.20	No rhythm variation	–	Unknown mechanism	–	
28	81	F	0.44	No rhythm variation	–	Unknown mechanism	–	
29	56	F	0.15	No rhythm variation	–	Unknown mechanism	–	

AF = atrial fibrillation; AVB = atrioventricular block; F = female; Pm = pacemaker; M = male; SA = sinus arrest; SB = sinus bradycardia; SVT = supraventricular tachycardia.

available in 54 patients; their median APL value was 0.20 μM (interquartile range [IQR] 0.12–0.30 μM); 87% of patients had a value below the 5% percentile of the value recorded in normal individuals (0.40 μmol/L). Compared with control patients with prodromes, they were similar in age and sex but had had fewer syncopal episodes in their history, which was shorter and began later in life. Given the absence of prodromes, these patients were at higher risk of severe trauma (fracture, head concussion).

Outcome

During a mean observation period of 16 ± 13 months, a diagnosis was established by the ILR in 29 patients (50%); an asystolic pause of 11 ± 5 seconds was present at the time of the diagnostic event in 19 patients (66%) (Tables 2 and 3). No patient had adverse events related to syncopal relapse. Compared with patients with prodromes, patients without prodrome had more frequently an asystolic syncope (66% vs 47%; $P = .001$) that was more frequently due to sudden-onset AV block with constant P-P cycle, that is, so-called idiopathic paroxysmal AV block[3] (47% vs 21%; $P = .04$) (Figure 1). While the actuarial diagnostic rate was similar in the 2 groups (Figure 2), the actuarial estimate of asystolic events was higher in the no-prodrome group (27% vs 17% at 1 year and 38% vs 22% at 2 years; $P = .02$) (Figure 3).

There was no significant difference in APL value between patients with asystolic pauses and others (0.15 μM [IQR 0.12–0.37 μM] vs 0.24 μM [IQR 0.15–0.30 μM]; $P = .53$).

Treatment

Ten patients with asystolic pauses underwent dual-chamber cardiac pacing, and 8 patients underwent oral theophylline 400–600 mg twice daily treatment in order to maintain the therapeutic range of 12–18 μg/mL (Table 3). During the subsequent 17 ± 12 months of follow-up, syncope recurred in 1 patient on theophylline and presyncope occurred in

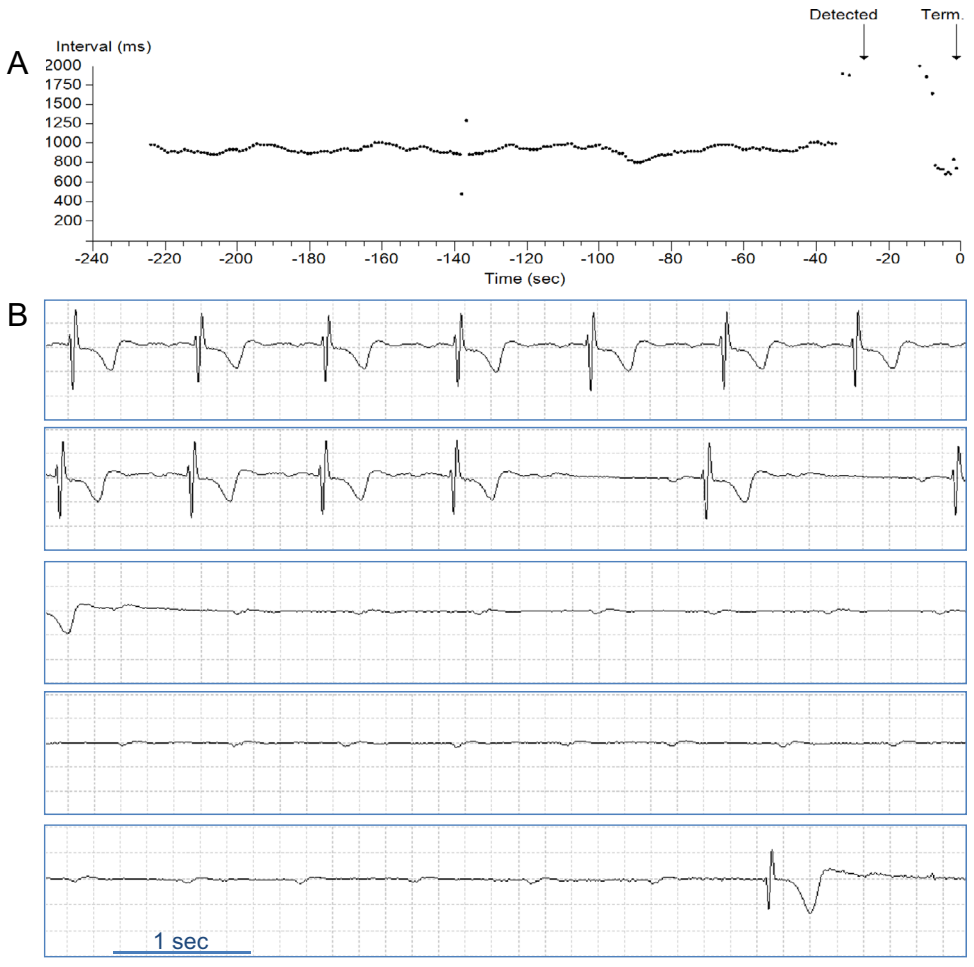

Figure 1 Case 2: Implantable loop recorder documentation of syncope due to idiopathic artioventricular (AV) block. **A:** Heart rate trend during 4-minute loop recording. Initially, the heart rate is stable at 60 beats/min and suddenly falls at the time of syncope. **B:** Expanded electrocardiogram. The 5 strips are continuous and show a blocked P wave followed by a complete AV block with an asystolic pause of 20 seconds. During AV block, the P-P cycle is initially constant and then progressively shortens, indicating compensatory reflex sympathetic activation. There is no apparent trigger of the onset of AV block. This finding distinguishes idiopathic AV block from intrinsic cardiac AV block, which is initiated by atrial, His, or ventricular premature extrasystole, increased heart rate (tachy-dependent AV block), or decreased heart rate (brady-dependent AV block), all characteristics that support a diagnosis of intrinsic AV block.[3,10,11]

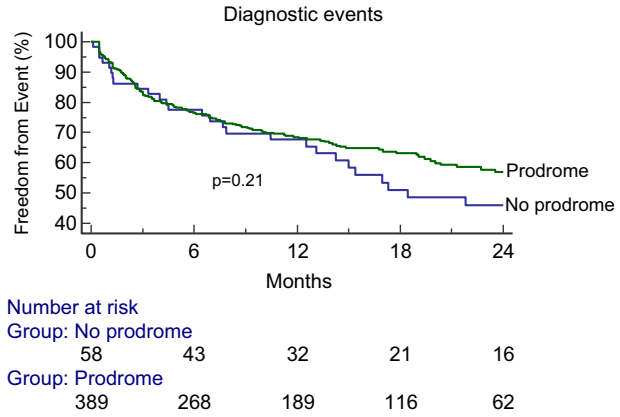

Figure 2 Estimated rates of diagnostic events in patients with unexplained syncope, no prodromes, and a normal heart and in control patients with reflex syncope and prodromes.

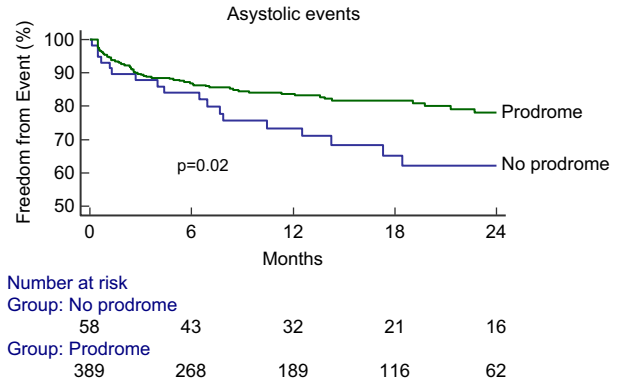

Figure 3 Estimated rates of asystolic events in patients with unexplained syncope, no prodromes, and a normal heart and in control patients with reflex syncope and prodromes.

1 patient with pacemaker no patients had progression toward persistent AV block or sinus node dysfunction.

Discussion

Patients presenting with unexplained syncope without or with short prodromes, a normal heart, and a normal ECG are frequently challenging from a diagnostic and therapeutic point of view.[9] Previous studies[1,2] have shown that these patients exhibit peculiar clinical and biological characteristics. The present study, focusing on the ECG mechanism of the syncope, showed that a long asystolic pause, frequently due to paroxysmal idiopathic AV block, was observed in two-thirds of these patients. When a specific therapy, either pacemaker or theophylline, was administered in patients with asystolic syncope, the short outcome was favorable.

In previous studies,[1–3] we showed that these patients have peculiar clinical characteristics that distinguish them from patients with vasovagal syncope. From a biological point of view, patients with no prodromes are patients with "low adenosine" whereas patients with prodromes are patients with "high adenosine". The low adenosine pattern is also confirmed in the present study and may explain the observed ECG mechanism: compared with patients with reflex syncope and long prodromes, patients without prodrome more frequently had asystolic pauses, and these were more frequently due to idiopathic AV block. This finding supports the study hypothesis that a low plasma adenosine level may be involved in the mechanism of syncope in such patients. When APL values are low, below the affinity constant value for high-affinity A1 adenosine receptors, which is 0.7 μM,[12] adenosine A1 receptors are upregulated and are highly susceptible to endogenous adenosine release; even a mild increase in APL may recruit these receptors, which are located within the sinus node and AV node, and precipitate sinus bradycardia and/or AV block.[1,2,13] The good response to therapy with theophylline, an antagonist of adenosine receptors, observed in the present study and in a previous study,[14] indirectly confirms this hypothesis.

Interestingly, sudden-onset AV block was a frequent mechanism observed during ECG documentation of syncopal recurrences in the no-prodrome group. In patients with a normal heart and a normal ECG, an intrinsic conduction disease is unlikely to explain such an ECG pattern. Furthermore, AV block was never initiated by atrial, His, or ventricular premature extrasystole, increased heart rate (tachycardia-dependent AV block), or decreased heart rate (bradycardia-dependent AV block), all characteristics that support a diagnosis of intrinsic AV block[10,11] (Figure 1). Therefore, our results support a close similarity between patients without prodrome and patients with idiopathic AV block.[3]

Mechanism-specific therapy was fairly effective in patients without prodrome with documented asystolic events, with the syncopal recurrence rate being 6% during a mean follow-up of 17 months. No patient with pacemaker had syncopal recurrence; moreover, during oral theophylline therapy, syncope recurred only in 1 of 8 patients (12%). This rate is similar to the 15% recurrence rate observed in a previous study.[14] In contrast, cardiac pacing is less effective in patients with reflex syncope. For example, a recurrence rate of 25% (95% confidence interval, 13%–45%) was reported in patients with ILR-documented asystolic events in the ISSUE-3 trial.[8] The likely explanation for this difference is the hypotensive component that is more present in patients with reflex syncope[15] than in low adenosine patients.[1,2] The decision between pacemaker and theophylline was individual patient's and physician's preference. No comparison can be inferred from this study. However, theophylline may be considered as an encouraging alternative to permanent pacing therapy in such patients. This study provides the rationale for planning future randomized trials.

Study limitations

Although consistently observed in the majority of no-prodrome patients with ECG documentation of syncopal recurrence, asystolic pauses were not observed in all of them: 2 patients had syncope due to intrinsic cardiac cause, that is,

atrial fibrillation followed by a long pause and paroxysmal supraventricular tachycardia; 6 patients had no rhythm variations at the time of syncope; and 3 patients showed only mild sinus rhythm. APL values were low in these patients as in those with asystolic pauses. Similar heterogeneity in the mechanism of syncope was also found in the control group of patients with reflex syncope. In ISSUE-3, the diagnosis of reflex syncope on initial evaluation was not confirmed by ILR findings in 13% of cases.[16] This is not too surprising, as inclusion criteria were based on the absence of prodromes or the presence of short prodromes. The duration of prodromes is largely subjective and imprecise. A value of ≤5 seconds has been found to be able to distinguish arrhythmic syncope from reflex syncope[17]; in patients without structural heart disease, a duration of prodromes of >10 seconds has proved to be able to distinguish arrhythmic syncope from reflex syncope.[18] It is well known that the perception of symptoms is variable from patient to patient and that a phenomenon of retrograde amnesia frequently occurs in patients with syncope.[9] Moreover, other causes of syncope, other than low adenosine, are likely to be able to present without prodromes. Indeed, tachyarrhythmias can also be asymptomatic before causing loss of consciousness.

No ECG finding was specific for low adenosine syncope: although less frequently, paroxysmal idiopathic AV block was also found in control patients with prodrome, and conversely, progressive sinus bradycardia that is considered a typical ECG pattern of vasovagal syncope was also present in a minority of patients with low adenosine. These observations suggest that "low adenosine" syncope and vasovagal syncope can coexist and overlap. This is consistent with the pathophysiological knowledge that despite differences in their receptors, adenosine and the neurotransmitter acetylcholine have remarkably similar effects on cardiac function and that the excitatory and inhibitory effects of the adrenergic, cholinergic, and purinergic outflows are integrated at the level of the receptor-effector coupling system, resulting in the final cardiac effect.[13]

Although any structural cardiac and ECG abnormalities were carefully ruled out, we cannot exclude the possibility that some patients had subtle sinus node impairment or AV conduction disease, which, by increasing cardiac susceptibility to adenosine, may have contributed to the development of asystolic events and clinical manifestations.

Finally, we achieved a diagnosis in half the population during the observation period. Therefore, we do not know whether the mechanism of syncope would have been the same in the other half who did not have events during follow-up. The actuarial rate of asystolic events in Figure 3 is almost rectilinear after month 3, thus suggesting a similar rate of asystolic events in the overall population. However, the low (32% [19 of 58]) rate of asystolic events and the 50% rate of total events during 16 months of observation, in the absence of adverse events, justifies a strategy of waiting and observing by means of ILR before starting any therapy.

Conclusion

Low adenosine syncope is a distinct clinical entity. A long asystolic pause is the cause of syncope in two-thirds of patients who have ECG documentation of a diagnostic event. The efficacy of pacemaker or theophylline therapy justifies extensive use of prolonged monitoring in patients with unexplained syncope, no prodromes, and a normal heart.

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