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CME

Syncope Without Prodromes in Patients With Normal Heart and Normal Electrocardiogram

A Distinct Entity

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A Distinct Entity

Objectives This study sought to investigate the clinical and laboratory findings of patients affected by sudden-onset syncope without prodromes who had a normal heart and normal electrocardiogram.

Background The pathophysiology of syncope in these patients is uncertain.

Methods We compared the clinical and laboratory findings of 15 patients with sudden-onset syncope without prodromes who had a normal heart and normal electrocardiogram (the study group) with those of 31 patients with established vasovagal syncope (VVS).

Results The patients in the study group were older than those with VVS (age 61 ± 12 years vs. 46 ± 17 years) and had a history of fewer episodes of syncope (median of 2 [interquartile range [IQR]: 1 to 2.5] vs. 9 [IQR: 4 to 15] years) that were of more recent onset (median of 1 [IQR: 0 to 1] vs. 10.5 [IQR: 3.3 to 27] years). The study group had lower median baseline adenosine plasmatic levels than the VVS group (0.25 μmol/l [95% confidence interval: 0.10 to 1.51] vs. 0.85 μmol/l [95% confidence interval: 0.32 to 2.80]). On receiver-operating characteristic curve analysis, the adenosine plasmatic level of ≤0.36 best discriminated between groups, displaying 73% sensitivity and 93% specificity. Tilt table testing was more frequently positive in patients with VVS than in the study group (74% vs. 33%). A similarly high positivity rate of adenosine/adenosine triphosphate testing was found in both groups.

Conclusions Common clinical features and a low adenosine plasmatic level define a distinct form of syncope, distinguish it from VVS, and suggest a causal role of the adenosine pathway. (J Am Coll Cardiol 2013;62:1075–80) © 2013 by the American College of Cardiology Foundation

In patients without structural heart disease and a normal electrocardiogram (ECG), once nonsyncopal causes of loss of consciousness are excluded, syncope is usually regarded as a manifestation of an abnormal vasovagal reflex (1). Vasovagal syncope (VVS) is typically preceded by prodromes due to autonomic activation and triggered by predisposing factors. Virtually all episodes of VVS induced during tilt table testing are preceded by prodromes, which start 30 to 60 s before the loss of consciousness (2,3). In rare cases, the absence of prodromes during spontaneous episodes of VVS is attributed to retrograde amnesia (1,4). Conversely, syncope occurring without prodromes in patients with structural heart disease is regarded as an ominous finding suggestive of a cardiac arrhythmia as the cause of syncope (Stokes-Adams attack) (1,5,6). In the absence of structural heart disease and conduction abnormalities on ECG, cardiac syncope is very unlikely and the results of an electrophysiological study are invariably negative (7,8). Therefore, in patients affected by syncope without prodromes who have a normal heart and normal ECG, the diagnosis of syncope remains unexplained (1).

In this study, we described the peculiar clinical characteristics of patients with this form of unexplained syncope and assessed the potential causal role of plasmatic adenosine.

Methods

The study group included 15 consecutive patients with sudden-onset syncope without prodromes who had a normal heart and normal electrocardiogram. 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 in establishing whether a definite syncope had occurred.

The control group included 31 consecutive patients with typical VVS (1), characterized by the presence of well-identifiable triggers (central [i.e., emotional distress] or peripheral [i.e., prolonged standing]) and preceded by symptoms of autonomic activation (i.e., feeling of warmth, an odd sensation in the abdomen, and lightheadedness or dizziness, nausea, and sweating). Atypical forms of VVS (e.g. those with short prodromes or without identifiable triggers) were excluded.

Once enrolled, patients in the study group and control group underwent a common protocol, which included assay of the baseline adenosine plasmatic level (APL), tilt table testing, and an adenosine or adenosine triphosphate (ATP) test. No patient dropped out of the study or was excluded at this stage.

The APL was determined as previously described (9). Baseline blood samples were collected (with the patients in a supine position) and processed using laboratory-prepared tubes containing 3 ml of cold-stop solution under vacuum. This method allows whole blood to mix quickly with the cold-stop solution, thus preventing degradation or adenosine uptake by red blood cells. After collection, samples were immediately placed and maintained on ice until

centrifugation. After deproteinization, adenosine was quantified using high-pressure liquid chromatography (ChromSystems, Munchen, Germany). The technicians who treated the samples and performed the assays were unaware of the patient's study group assignment. 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 81 control subjects without syncope (mean age, 59 ± 12 years; 43 male subjects), is 0.49 μmol/l (interquartile range: 0.38 to 0.68 μmol/l).

Adenosine and ATP tests were performed by means of rapid injection (<2 s) of 20 mg of ATP or 18 mg of adenosine via a brachial vein, followed by a 10 ml 5% glucose flush. Positivity was defined as complete atrioventricular (AV) block with ventricular asystole >6 s (10) or third-degree AV block >10 s (11).

Tilt table testing, both passive and potentiated with nitroglycerin, was performed according to the Italian protocol (12).

Statistical analysis. Continuous data are shown as averages ± SD or medians (25th to 75th percentile) as appropriate. The Shapiro-Wilks test was performed to check the skewness of distributions. Absolute and relative frequencies were used to show categorical data. The unpaired Student *t* test and the nonparametric Mann-Whitney *U* test were used to compare continuous variables as appropriate. Fisher exact test was used to compare proportions. The ability of the APL to distinguish patients in the study group from patients with VVS was evaluated using receiver-operating characteristic curve analysis. MedCalc Software (Mariakerke, Belgium) was used for statistical analysis.

Results

Patient characteristics and test results of the 15 patients in the study group and 31 patients with VVS are shown in Table 1. The patients in the study group were older than those with VVS and had a history of fewer episodes of syncope that were of more recent onset. In all patients in the study group, syncope was unpredictable and displayed no detectable trigger. The study group had a lower median baseline APL than the VVS group (Table 2). On receiver-operating characteristic curve analysis, the APL of ≤0.36 showed the highest accuracy (minimal false-negative and false-positive results), displaying 73% sensitivity and 93% specificity (Table 3). A similarly high positivity rate on adenosine/ATP testing was found in both groups. The tilt table testing was more frequently positive in patients with VVS than in the study group.

Discussion

Patients with unexplained sudden-onset syncope without prodromes who have a normal heart and normal electrocardiogram are typically >40 years of age and have a recent onset of history of syncope in middle/old age and low APL. The late onset of the syndrome suggests a pathological process or, more generally, an aging process. The clinical features described in the preceding text clearly distinguish these patients from those with VVS; syncope in patients with VVS should be regarded as an isolated manifestation of individual differences in the susceptibility of the autonomic nervous system that are probably present in all healthy subjects (13).

Abbreviations and Acronyms

APL = adenosine plasmatic level
ATP = adenosine triphosphate
AV = atrioventricular
ECG = electrocardiogram
VVS = vasovagal syncope

The lack of evidence of activation of a central or peripheral baroreflex (no signs or symptoms of autonomic activation or triggers) and the peculiar APL profile prompted us to hypothesize a pivotal role of biochemical or neurohumoral mechanisms. Patients with sudden-onset syncope without prodromes who have a normal heart and normal electrocardiogram are "low adenosine syncope" patients, as opposed to patients with VVS, who are "high adenosine" patients (14,15). Indeed, in the present study, "low adenosine syncope" patients had APLs that were lower not only than those of patients with VVS but also those of healthy subjects without syncope ($p = 0.01$ compared with 81 control subjects from the core laboratory; see Methods). Only 7% of patients with VVS and 21% of healthy subjects had an APL less than the cutoff of 0.36 μmol/l (Fig. 1). The difference in APLs between the study group and the VVS group was unrelated to an effect of different ages (Fig. 2); the control subjects and patients in the study group were of similar age. Involvement of the adenosine pathway is also suggested by the observed 60% rate of positive responses to adenosine/ATP testing, defined as an AV block with a pause ≥6 s, which was higher than the 28% rate observed in a general syncope population and the 5% rate observed in subjects without syncope (10). Because the results of adenosine/ATP testing were also frequently positive in patients with VVS, this tool was unable to distinguish between the 2 groups, unlike APL. Admittedly, although a role of the adenosine pathway in the genesis of syncope is possible, these data are insufficient to prove a causal relationship, because a low APL is only a marker or an associated condition of a more complex mechanism. Syncope due to extrinsic (or functional) mechanisms in patients with a normal heart probably involves a wide spectrum of pathogenic pathways in addition to adenosine. Several other alterations in neurohumoral mechanisms have been advocated: epinephrine, serotonin, tyrosine hydroxylase and norepinephrine transporter proteins, and so on (16,17). Finally, the observed different positivity rate of the tilt table test also supports a different mechanism in the 2 groups; the positivity rates observed in this study are consistent with the findings of another study that showed greater positivity in patients with clinical triggers (71% central and 75% peripheral) than in those without (36%) (18).

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Table 1 Patient Characteristics and Test Results of the 15 Patients in the Study Group and the 31 Patients With Vasovagal Syncope

Patient #	Age/Sex	Total No. With Syncope	No. of Syncopes in the Past 2 Yrs	Duration of Syncope (yrs)	Adenosine Plasmatic Level (μmol/l)	ATP Test: Pause >6 s (Duration [s])	ATP Test: Duration of Third-Degree Atrioventricular Block >10 s (Duration [s])	Tilt Table Testing
Patients in the study group								
1	68/F	1	1	0	0.13	No	No	Negative
2	44/M	1	0	0	0.36	Yes (10.6)	Yes (16)	Negative
3	69/F	12	4	9	0.25	No	Yes (13.2)	Positive (mixed)
4	68/F	1	1	1	0.10	No	No	Negative
5	56/M	1	1	1	0.31	Yes (6.9)	Yes (12)	Negative
6	46/F	3	3	1	0.25	No	No	Negative
7	41/M	5	5	1	0.10	Yes (6.3)	Yes (12.1)	Negative
8	64/F	2	2	0	1.20	No	No	Positive (mixed)
9	47/F	2	2	1	0.11	Yes (8.2)	No	Negative
10	62/M	2	2	1	0.50	Yes (7)	No	Positive (mixed)
11	63/F	1	1	0	0.18	Yes (6.2)	No	Negative
12	75/M	2	2	0	0.11	Yes (9)	No	Negative
13	55/F	3	1	12	0.12	Yes (6.4)	No	Positive (mixed)
14	68/F	1	1	0	2.00	Yes (10.4)	Yes (10.4)	Positive (mixed)
15	85/F	1	1	0	1.30	No	No	Negative
Patients with vasovagal syncope								
1	60/F	50	20	40	0.7	Yes (7.2)	Yes (25)	Positive (CI)
2	44/F	10	4	30	NA	No	Yes (12.9)	Positive (mixed)
3	17/F	10	6	5	0.26	No	No	Positive (CI)
4	31/M	3	2	15	1.67	No	No	Positive (CI)
5	37/F	3	2	3	0.9	No	No	Positive (mixed)
6	39/M	10	6	7	0.25	No	No	Positive (CI)
7	76/F	2	1	29	0.56	Yes (6.1)	No	Negative
8	50/F	1	0	0	0.8	No	Yes (22)	Negative
9	30/M	10	3	20	1.69	No	Yes (16.8)	Positive (CI)
10	32/M	4	1	16	1.8	No	No	Negative
11	42/F	15	3	32	0.5	Yes (11.5)	Yes (18)	Positive (CI)
12	37/F	100	NA	NA	3.2	NA	NA	Negative
13	24/F	20	4	16	1.7	No	No	Positive (mixed)
14	40/F	4	1	20	2.3	Yes (6.2)	No	Positive (mixed)
15	49/F	10	1	30	1.8	No	No	Positive (mixed)
16	21/F	15	6	11	0.45	Yes (6.4)	Yes (24)	Positive (mixed)
17	23/M	50	10	10	0.4	Yes (6.1)	No	Positive (mixed)
18	37/F	6	4	3	0.51	Yes (8.4)	Yes (21.6)	Positive (CI)
19	19/F	3	3	1	1.2	Yes (40)	Yes (30)	Positive (mixed)
20	42/F	30	15	10	0.7	Yes (14.2)	Yes (18.4)	Negative
21	62/M	5	5	0	0.7	No	No	Positive (CI)
22	55/M	5	2	20	0.69	No	No	Positive (mixed)
23	56/M	2	2	0	1.2	No	No	Positive (mixed)
24	67/F	4	2	5	0.8	Yes (9.4)	No	Positive (mixed)
25	62/F	15	1	45	0.7	Yes (11.2)	Yes (11.2)	Positive (CI)
26	49/M	2	2	0	1.5	No	No	Positive (mixed)
27	39/M	4	4	0	0.4	No	No	Negative
28	72/F	17	2	60	3.2	Yes (9.8)	No	Negative
29	71/M	6	2	10	0.9	No	No	Positive (mixed)
30	61/F	10	1	35	1.7	No	No	Positive (mixed)
31	79/M	9	4	4	0.96	Yes (12)	Yes (12)	Negative

ATP = adenosine triphosphate; CI = cardioinhibitory (pause >3 s); NA = not available.

The laboratory features of "low adenosine syncope" patients were fairly similar to those we previously observed in patients with idiopathic AV block (19). These latter patients had a median APL of 0.33 (interquartile range: 0.20 to 0.36) (Fig. 1); the adenosine/ATP test result was positive (i.e., pause >6 s) in 67%, and the tilt table test

Table 2 Comparison Between Study Group and Patients With VVS

	No Prodromes, Normal Heart, and Normal Electrocardiogram	Typical VVS	p Value
n	15	31	
Age (yrs)	61 ± 12	46 ± 17	0.005
Female	10 (71%)	19 (61%)	1.0
Total no. of syncopes	2 (1–2.5)	9 (4–15)	0.0001
No. of syncopes in the past 2 yrs	1 (1–2)	2.5 (2–4)	0.03
Duration of syncope (yrs)	1 (0–1)	10.5 (3.3–27)	0.0005
APL (μmol/l), median (95% confidence interval)	0.25 (0.10–1.51)	0.85 (0.32–2.80)	0.0004
APL ≤0.36 μmol/l (receiving-operating characteristic curve discriminant)	11 (73%)	2/30 (7%)	0.0001
Adenosine/ATP test, pause >6 s	9 (60%)	13/30 (43%)	0.35
Adenosine/ATP test, third-degree atrioventricular block >10 s	5 (33%)	11/30 (37%)	1.0
Positive tilt table test result	5 (33%)	23 (74%)	0.01

Values are n, mean ± SD, n (%), or median (interquartile range). The APL was not available for 1 patient with VVS because of technical problems, and the ATP test was not performed in 1 patient with VVS because of patient refusal.

APL = adenosine plasmatic level; ATP = adenosine triphosphate; IQR = interquartile range; VVS = vasovagal syncope.

result was positive in 41%. Moreover, most patients with idiopathic AV block also had sudden-onset syncope without prodromes or triggers, absence of structural heart disease, and a normal ECG. Patients with idiopathic AV block also had ECG documentation of a paroxysmal AV block with a long pause that was responsible for syncope. We therefore hypothesized that, in idiopathic paroxysmal AV block, the effect of adenosine on the AV node is mainly due to the stimulation of high-affinity A1 receptors, which are much more numerous in the AV node than in the sinoatrial node (20–22). Like many other cell surface receptors, the number of cardiac adenosine A1 receptors undergoes up-regulation and down-regulation when cardiac tissues are chronically exposed to low or elevated concentrations of adenosine receptor agonist (i.e., adenosine), respectively. A transient release of endogenous adenosine could be sufficient to block conduction in the AV node when a large number of free high-affinity A1 receptors in the AV node are available (patients with low APLs) but not when long-term exposure to high APLs desensitizes A1 receptors (patients with VVS who have high APLs) (14,19). The clinical characteristics and results of laboratory tests of the patients in the present study are in favor of a large overlap between these patients and patients with idiopathic AV block. If this is confirmed, the identification of patients with idiopathic AV block would become much easier, without need for ECG documentation of the syncope. A prospective study aimed at documenting spontaneous syncope in patients with sudden onset of low APL by means of an implantable loop recorder is ongoing.

Conclusions

Common clinical features and a low APL define a distinct form of syncope, distinguish it from VVS, and suggest a causal role of the adenosine pathway. "Low adenosine

Table 3 Criterion Values and Coordinates of the Receiver-Operating Characteristic Curve

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	−LR
<0.1	0.00	0.0–22.0	100.00	88.3–100.0		1.00
≤0.18	46.67	21.3–73.4	100.00	88.3–100.0		0.53
≤0.25	60.00	32.3–83.6	96.67	82.7–99.4	18.00	0.41
≤0.26	60.00	32.3–83.6	93.33	77.9–99.0	9.00	0.43
≤0.36*	73.33	44.9–92.0	93.33	77.9–99.0	11.00	0.29
≤0.45	73.33	44.9–92.0	83.33	65.3–94.3	4.40	0.32
≤0.5	80.00	51.9–95.4	80.00	61.4–92.2	4.00	0.25
≤0.96	80.00	51.9–95.4	40.00	22.7–59.4	1.33	0.50
≤1.2	86.67	59.5–98.0	33.33	17.3–52.8	1.30	0.40
≤1.3	93.33	68.0–98.9	33.33	17.3–52.8	1.40	0.20
≤1.8	93.33	68.0–98.9	10.00	2.2–26.6	1.04	0.67
≤2	100.00	78.0–100.0	10.00	2.2–26.6	1.11	0.00
≤3.2	100.00	78.0–100.0	0.00	0.0–11.7	1.00	

*The value corresponding to the highest accuracy (minimal false-negative and false-positive results).

CI = confidence interval; +LR = positive likelihood ratio; −LR = negative likelihood ratio.

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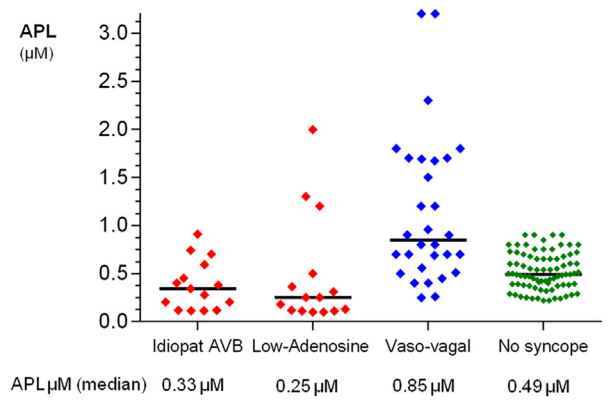

Figure 1 **Individual APLs in 15 "Low Adenosine Syncope" Patients, 30 Patients With VVS, 18 Patients With Idiopathic Paroxysmal Atrioventricular Block, and 81 Control Subjects Without Syncope**

The individual adenosine plasmatic levels (APLs) of the 4 groups of patients are plotted. The median APL of each group is also shown. The data regarding Idiopathic AV block and no syncope are reprinted from Brignole et al. (19). AVB = atrioventricular block; VVS = vasovagal syncope.

syncope" is characterized by age >40 years, recent onset in middle/old age, sudden onset without prodromes, and a normal heart and normal electrocardiogram.

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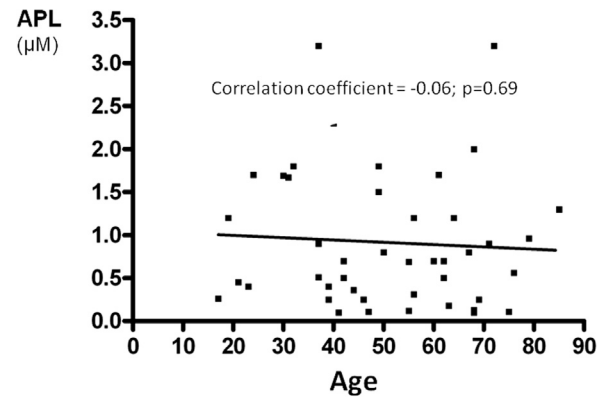

Figure 2 **Lack of Correlation Between APLs and Age in "Low Adenosine Syncope" Patients and Patients With VVS**

The linear regression line is superimposed. Abbreviations as in Figure 1.

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