

Role of Endogenous Adenosine as a Modulator of Syncope Induced During Tilt Testing

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Background—Previous reports that used head-up tilt testing and adenosine administration have suggested that adenosine may be an important endogenous mediator that may trigger a vasovagal response in susceptible patients. However, little is known regarding endogenous adenosine plasma levels (APLs) during vasovagal syncope provoked by tilt testing. The aim of this study was to determine whether APLs differ in patients with a positive head-up tilt test compared with those with a negative test and whether APLs are modified during tilt-induced vasovagal syncope.

Methods and Results—APLs (mean±SEM) were measured during head-up tilt test in 26 patients who presented with unexplained syncope. In the 15 patients with a negative test, APLs were 0.39 ± 0.03 $\mu\text{mol/L}$ at baseline, 0.22 ± 0.03 $\mu\text{mol/L}$ immediately after tilting, and 0.44 ± 0.03 $\mu\text{mol/L}$ after 45 minutes. APLs were significantly higher in the 11 patients with a positive test (2.66 ± 0.67 $\mu\text{mol/L}$ at baseline and 3.22 ± 0.85 $\mu\text{mol/L}$ immediately after tilting) than in those with a negative test. During tilt testing–induced syncope, APLs increased to reach 4.03 ± 0.66 $\mu\text{mol/L}$ (ie, a 52% increase compared with baseline levels; $P<0.02$). Furthermore, we observed that the higher the APL during syncope, the shorter the time to appearance of symptoms.

Conclusions—This study showed that APLs were higher in patients with a positive tilt test than in patients with a negative test and that they increased during tilt testing–induced syncope. These observations suggest that adenosine release may be involved in the triggering mechanism of syncope induced during tilt testing. (*Circulation*. 2002;106:569-574.)

Key Words: adenosine ■ syncope ■ tests

Neurally mediated syncope is a common clinical problem that may alter the quality of life of affected patients. The syndrome is characterized by arterial vasodilatation associated with relative or absolute bradycardia. The pathophysiological mechanisms responsible for the genesis of neurally mediated syncope have not been elucidated. Defective baroreflex response to an increase in sympathetic activity in a setting of ventricular hypovolemia has been advocated. Other mechanisms such as alterations in neurohumoral mechanisms may play a role.¹

Tilt testing is an established tool for the evaluation of patients with unexplained syncope.² Several reports³⁻⁵ have shown that exogenous adenosine or ATP is an effective agent for the provocation of neurally mediated syncope in susceptible patients, with a diagnostic yield comparable to that of tilt testing. Therefore, it appeared likely that adenosine might be an endogenous modulator that may play a role in triggering vasovagal syncope in predisposed patients. However, to the best of our knowledge, there is no information regarding endogenous adenosine plasma level changes during neurally mediated syncope induced by tilt testing. We evaluated endogenous adenosine plasma levels in patients with unex-

plained syncope and compared patients with a positive head-up tilt test to those with a negative test at baseline and during vasovagal syncope or presyncope.

Methods

Patient Selection

In this prospective study, we measured adenosine plasma levels during head-up tilt testing in 26 patients referred to our institution for unexplained syncope who fulfilled the inclusion criteria. Patients had to experience at least 2 episodes of syncope within the year preceding inclusion in the study. The cause of syncope was unexplained in all patients despite complete medical and neurological evaluation, including routine laboratory tests, 12-lead ECG, 24-hour ECG ambulatory monitoring, chest radiograph, M-mode and 2D echocardiography, carotid sinus massage, and further evaluation of any clinical or historical findings indicative of a possible cause of the syncope. Patients thought to have vasovagal syncope and with a noncontributory above-mentioned workup were included in the study. All patients underwent head-up tilt testing for the first time. Patients with orthostatic hypotension, anemia, and endocrine abnormalities such as diabetes, hypoglycemia, or thyroid dysfunction were excluded from the study. The following patients were also excluded from the study: those with ECG abnormalities (sinus bradycardia <50 bpm or bundle-branch block) or with an abnormal electrophysiological study that showed sinus node dysfunction, altered AV

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TABLE 1. Clinical Characteristics of the Patients

| Variables | Population (26 Patients) | Negative Tilt Tests (15 Patients) | Positive Tilt Tests (11 Patients) | <i>P</i> |
|--|-----------------------------|--------------------------------------|--------------------------------------|----------|
| Age, y | 52±3.3 | 56.9±3.4 | 45.3±5.9 | NS |
| Sex, M/F | 15/11 | 9/6 | 6/5 | |
| Weight, kg | 65±3.1 | 68.5±4.5 | 60.3±3.8 | NS |
| Height, cm | 166±2 | 168±3 | 165±3 | NS |
| No. patients with heart disease | 2 | 2 | 0 | |
| Hypertension | 1 | 1 | 0 | |
| Mild mitral regurgitation | 1 | 1 | 0 | |
| None | 24 | 13 | 11 | |
| History of syncopal episodes | | | | |
| Time since first episode, mo | 4 (2–6) | 4 (3–7.5) | 3 (2–4.75) | NS |
| Syncope and presyncope per month | 1.2 (0.5–2) | 0.7 (0.4–1.2) | 2 (1.6–2.2) | <0.05 |
| Syncopal episodes per patient | 3 (2–4) | 2 (2–3) | 4 (3–6) | <0.05 |
| Presyncopal episodes per patient | 1.5 (0–3) | 0 (0–2) | 3 (0.25–3.75) | <0.05 |
| No. patients with presyncopal episodes | 14 | 6 | 8 | |
| No. patients with vasovagal symptoms | 11 | 3 | 8 | |

Values are given as number of patients, mean±SEM, or median (interquartile range). NS indicates not significant.

conduction, or significant ventricular arrhythmias during programmed ventricular stimulation; patients with implanted pacemakers or with syncope related to aortic stenosis, hypertrophic cardiomyopathy, pulmonary hypertension, or subclavian steal syndrome; and those with drug-induced syncope. No patient in the present study had an adenosine or ATP test before inclusion in the study. Patients included in the study were drug free and were instructed to avoid coffee and tea for the 24 hours preceding the study. None of them was a regular tea or cola consumer. Usual daily consumption of coffee was low or moderate (≤ 3 cups of coffee), with an estimated consumption of caffeine $< 3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ in all patients. No patient was treated with adenosine antagonists. Patients were studied in a fasting state after informed written consent was obtained. Clinical characteristics of patients are summarized in Table 1.

Study Protocol

Head-Up Tilt Test

Tilt testing was performed in a quiet and comfortable room maintained at 21°C with dimmed lights and equipped for cardiopulmonary resuscitation. Patients were allowed to lie on an electrically controlled tilt table (Siemens) for 30 minutes. During this time, an intravenous line containing 5% dextrose was inserted into one arm and an intravenous catheter was inserted into the other arm to facilitate blood sampling. A 6-lead ECG and an external blood pressure recorder were attached and regularly activated to familiarize the patient with their operation. The footboard support and chest and knee belts were adjusted and secured. The table was then smoothly tilted within 20 seconds to the 60° position for 45 minutes. The heart rate was monitored continuously and blood pressure measured manually by the same operator every 2 minutes. The table was returned quickly to the supine position when symptoms occurred or the test ended. Three blood samples were collected during every tilt test: (1) just before the table was tilted, (2) immediately after the table was tilted, and (3) either during syncope, immediately after the table was reset in the horizontal position (positive test), or after 45 minutes of tilting (negative test).

Definitions

Presyncope was defined as the induction of symptoms of imminent syncope, and syncope was defined as complete and transient loss of consciousness. A positive test was defined by the development of syncope or presyncope in association with relative bradycardia

($\geq 20\%$ decrease in heart rate compared with baseline) or hypotension (systolic blood pressure $< 80 \text{ mm Hg}$).

Adenosine Plasma Levels

Samples were collected and treated as described previously.^{6,7} Venous blood (3 mL) was withdrawn under vacuum together with a stop solution in Vacutainer tubes (Becton Dickinson). This method allowed blood samples to be mixed rapidly with 4 mL of stop solution, which prevents adenosine degradation and uptake. The stop solution was composed of dipyridamole 0.2 mmol/L, 4.2 mmol/L ethylene-diamine-tetraacetic acid disodium (Na_2 EDTA), erythro-9-(2-hydroxy-3-nonyl)-adenine (EHNA) 5 mmol/L, α, β -methyleneadenosine-5'-diphosphate (AMPCP) 79 mmol/L, heparin sulfate 1 IU/mL, deoxycoformycin 1 $\mu\text{g}/\text{mL}$, and 0.9% NaCl. The sample with the stop solution was centrifuged at 2500g for 10 minutes, and the supernatant was deproteinized by addition of 2 mL of 70% perchloric acid before a second centrifugation. The supernatant was lyophilized and redissolved in 1 mL of 50 mmol/L sodium phosphate buffer (pH 4).

Samples were analyzed by high-performance liquid chromatography (Waters) as described previously.^{6,7} Briefly, a modular system with a UV detector was used. Lyophilized samples were dissolved in 1 mL of phosphate buffer (pH 4) and eluted with a methanol gradient on a Merck LiChrospher C18 column. Adenosine was identified by its elution time and after incubation with adenosine deaminase, which increases the inosine peak and decreases the adenosine peak. Adenosine was quantified by comparison of these peak areas with those given by predefined quantities of adenosine. In these conditions, the sensitivity threshold was 10 pmol/L injected in 1 mL of plasma matrix. The intra-assay and interassay coefficients of variation for nucleosides ranged from 1% to 3%. The absence of xanthine derivatives was checked on each chromatogram. Sample treatment and adenosine assay were performed by a technician who was blinded to the study.

Reagents and Other Agents

Adenosine (crystallized, 99% pure), adenosine deaminase, and dipyridamole were obtained from Boehringer Mannheim; inosine (99% pure), AMPCP, EDTA, and deoxycoformycin from Sigma; and EHNA from Burroughs Wellcome.

Statistical Methods

Age, weight, height, left ventricular ejection fraction, heart rate, blood pressure, adenosine levels, and time to tilt symptoms are

TABLE 2. Patients With Negative Test: Individual Parameters and Mean Values

| Patients | Sex, M/F | Age, y | Heart Rate, bpm | | | Arterial Pressure, mm Hg | | | Adenosine, $\mu\text{mol/L}$ | | |
|----------|-------------|-----------|-----------------|------|----------|--------------------------|---------|----------|------------------------------|------|----------|
| | | | Baseline | Tilt | 45th min | Baseline | Tilt | 45th min | Baseline | Tilt | 45th min |
| 1 | M | 60 | 58 | 68 | 82 | 120/60 | 140/70 | 130/80 | 0.40 | 0.30 | 0.50 |
| 2 | F | 60 | 84 | 88 | 92 | 120/70 | 130/70 | 120/80 | 0.40 | 0.45 | 0.50 |
| 3 | M | 64 | 68 | 74 | 62 | 140/70 | 150/80 | 150/80 | 0.35 | 0.14 | 0.50 |
| 4 | F | 64 | 62 | 64 | 65 | 125/65 | 120/65 | 115/70 | 0.60 | 0.35 | 0.65 |
| 5 | M | 37 | 64 | 70 | 84 | 115/70 | 110/70 | 110/70 | 0.45 | 0.10 | 0.30 |
| 6 | M | 70 | 67 | 76 | 80 | 140/75 | 130/70 | 110/75 | 0.55 | 0.20 | 0.50 |
| 7 | M | 66 | 63 | 73 | 64 | 130/70 | 130/60 | 130/60 | 0.35 | 0.15 | 0.70 |
| 8 | F | 73 | 78 | 86 | 85 | 150/80 | 145/80 | 120/80 | 0.20 | 0.30 | 0.45 |
| 9 | M | 62 | 87 | 97 | 98 | 155/80 | 190/95 | 175/95 | 0.45 | 0.25 | 0.25 |
| 10 | M | 36 | 56 | 67 | 60 | 120/70 | 130/80 | 130/80 | 0.30 | 0.15 | 0.35 |
| 11 | F | 70 | 80 | 89 | 96 | 145/85 | 160/80 | 165/90 | 0.30 | 0.07 | 0.40 |
| 12 | M | 45 | 60 | 66 | 70 | 140/75 | 130/70 | 140/70 | 0.35 | 0.20 | 0.40 |
| 13 | F | 51 | 80 | 84 | 76 | 140/80 | 140/90 | 130/85 | 0.25 | 0.20 | 0.40 |
| 14 | M | 62 | 65 | 88 | 100 | 140/80 | 130/80 | 145/90 | 0.50 | 0.25 | 0.40 |
| 15 | F | 33 | 62 | 96 | 98 | 110/65 | 105/75 | 110/80 | 0.45 | 0.15 | 0.25 |
| Mean | | | 68.9 | 79.1 | 80.8 | 137/73 | 136/76 | 133/79 | 0.39 | 0.22 | 0.44 |
| SEM | | | 2.6 | 2.9 | 3.7 | 3.5/2.0 | 5.3/2.5 | 5.0/2.4 | 0.03 | 0.03 | 0.03 |

Tilt indicates immediately after tilting; 45th min, 45th minute of tilting, ie, the end of the test.

reported as mean \pm SEM. Number of syncope and presyncope episodes and time since first episode are expressed as median and interquartile range, with comparisons made by Mann-Whitney *U* test.

Intragroup and intergroup variations were compared by 1- and 2-way ANOVA followed by a paired bilateral *t* test. We used the Wilcoxon test for intragroup comparison with each patient as his or her own control. A probability value <0.05 was considered significant.

Results

Demographics and Symptoms

Twenty-six patients referred for evaluation of syncope fulfilled the inclusion criteria. The mean age was 52 ± 3.3 years (range, 15 to 73 years), as shown in Table 1. In all patients, syncope was unexplained on the basis of the clinical workup and was suspected to be vasovagal in nature, and a head-up tilt test was indicated. No significant difference was observed between the group of patients with a positive tilt test and the group with a negative tilt test with respect to sex, age, weight, height, baseline heart rate, and blood pressure. All had a normal left ventricular ejection fraction ($68\pm 6\%$). Regarding the history of syncopal episodes, the time since first episode was comparable between the 2 groups, but the frequency of syncope and presyncope events per month was significantly higher in the patients whose test was positive (2.4 ± 0.6 versus 0.9 ± 0.2 in those whose test was negative; $P<0.05$; Table 1).

Head-Up Tilt Test

The head-up tilt test was positive in 11 patients and negative in 15. In patients with a negative test, no significant modification of blood pressure was noted during the test. The heart rate increased significantly ($P<0.005$) immediately after tilting and 45 minutes later (15% and 17%, respectively; Table 2). Two patients with a negative tilt test underwent a

diagnostic electrophysiological study that was noncontributory. In the 11 patients with a positive test, syncope occurred in 9 and presyncope in 2 (Table 3). Heart rate increased significantly immediately after tilting (18%; $P<0.0001$). Symptoms occurred after 22.4 ± 3 minutes (range, 2 to 38 minutes). On syncope, systolic blood pressure dropped by an average of 59% ($P<0.0001$) and heart rate by 38% ($P<0.0001$). All patients recovered rapidly from their symptoms as soon as the table was reset to the horizontal position.

Adenosine Plasma Levels

In patients with a negative tilt test, adenosine plasma levels were 0.39 ± 0.03 $\mu\text{mol/L}$ at baseline, 0.22 ± 0.03 $\mu\text{mol/L}$ immediately after tilting, and 0.44 ± 0.03 $\mu\text{mol/L}$ after 45 minutes (Table 2). In contrast, patients with a positive test exhibited significantly higher ($P<0.0001$) adenosine plasma levels (2.66 ± 0.67 $\mu\text{mol/L}$) in the supine position (ie, 7 times greater than in the negative group), 3.22 ± 0.85 $\mu\text{mol/L}$ immediately after tilting (ie, ≈ 14 times greater than in the negative group), and 4.03 ± 0.66 $\mu\text{mol/L}$ during syncope, which was $\approx 52\%$ higher on average ($P<0.005$) than baseline values (Figure 1). There was no overlap between the 2 groups. None of the 15 patients with a negative tilt test had a baseline adenosine plasma level >0.6 $\mu\text{mol/L}$, and none of the 11 patients with a positive test had a level <0.9 $\mu\text{mol/L}$ (Tables 2 and 3). Linear relationships have been established at the moment of syncope between adenosine plasma levels and (1) time to tilt-induced symptoms and (2) heart rate; the higher the adenosine plasma level, the shorter the time to tilt symptoms and the lower the heart rate (Figure 2).

Discussion

The main findings of this study were 2-fold. (1) Patients with a positive tilt test had much higher baseline adenosine plasma

TABLE 3. Patients With Positive Test: Individual Parameters and Mean Values

| Patients | Sex, M/F | Age, y | Symptoms | Time to Symptoms, min | Heart Rate, bpm | | | Arterial Pressure, mm Hg | | | Adenosine, $\mu\text{mol/L}$ | | |
|----------|----------|--------|------------|-----------------------|-----------------|------|---------|--------------------------|--------|---------|------------------------------|------|---------|
| | | | | | Baseline | Tilt | Syncope | Baseline | Tilt | Syncope | Baseline | Tilt | Syncope |
| 1 | M | 70 | Syncope | 20 | 78 | 98 | 52 | 120/70 | 120/80 | 50 | 3 | 6.5 | 5 |
| 2 | M | 65 | Syncope | 2 | 70 | 80 | 38 | 130/80 | 140/80 | <50 | 9 | 9.19 | 8.74 |
| 3 | F | 16 | Syncope | 15 | 82 | 91 | 41 | 110/60 | 115/80 | <50 | 3 | 2 | 5 |
| 4 | F | 33 | Syncope | 19 | 75 | 80 | 40 | 120/60 | 120/60 | <50 | 2.45 | 5.5 | 5.25 |
| 5 | M | 68 | Syncope | 20 | 96 | 100 | 49 | 140/70 | 130/70 | <50 | 1.85 | 0.94 | 5.85 |
| 6 | F | 45 | Syncope | 38 | 74 | 80 | 58 | 120/80 | 110/80 | 60 | 0.9 | 0.5 | 1.2 |
| 7 | M | 52 | Presyncope | 25 | 60 | 75 | 48 | 115/60 | 105/70 | 60 | 0.9 | 1.3 | 2 |
| 8 | F | 66 | Presyncope | 34 | 80 | 100 | 55 | 120/80 | 125/70 | 60 | 2 | 1 | 2.2 |
| 9 | F | 42 | Syncope | 31 | 55 | 55 | 45 | 140/65 | 135/70 | 50 | 1.5 | 1.25 | 2.5 |
| 10 | M | 58 | Syncope | 22 | 66 | 74 | 53 | 110/60 | 105/60 | 65 | 2.9 | 4.2 | 3.14 |
| 11 | M | 15 | Syncope | 20 | 55 | 85 | 40 | 120/70 | 100/70 | <50 | 1.75 | 3 | 3.5 |
| Mean | | | | 22.4 | 71.9 | 85.3 | 44.9 | 122/69 | 119/72 | 49.5 | 2.66 | 3.22 | 4.03 |
| SEM | | | | 3.0 | 2.9 | 3.1 | 2.3 | 3.1/2.5 | 4/2.6 | 3.05 | 0.67 | 0.85 | 0.66 |

Tilt indicates immediately after tilting.

levels than patients with a negative tilt test, with no overlap between the 2 groups. Patients with a negative head-up tilt test had baseline adenosine plasma levels that were in the same range as those reported in the venous blood of normal healthy volunteers.^{6,8} (2) During syncope, adenosine levels increased by an average of 52% compared with baseline levels. The higher the adenosine plasma level, the earlier the symptoms appeared and the greater the slowing of heart rate.

Several investigators have hypothesized that adenosine is an important modulator that can trigger vasovagal syncope in susceptible patients.^{3-5,9} Indeed, the injection of exogenous adenosine or ATP during head-up tilt testing provoked a vasovagal response in those patients with syncope, with a yield comparable to that of isoproterenol.^{3-5,10} Adenosine-sensitive syncope has been identified as a cause of syncope in some patients with an abnormal response to an ATP test.⁹ More recently, Brignole et al¹⁰ suggested that ATP and head-up tilt tests may identify different patient populations with syncope. They also noted that the 2 syndromes do overlap. The clinical features of their patients with both a positive head-up tilt test and a positive ATP test differed from those of patients with tilt-induced syncope alone or with adenosine-sensitive syncope alone. They concluded that nu-

merous mechanisms may be responsible for neurally mediated syncope and that syncopal attacks may be caused by a vasovagal mechanism and/or by an adenosine-mediated mechanism.¹⁰ One may argue that the high adenosine levels observed in patients with a positive tilt test could be explained by the circulatory disorders associated with vasovagal symptoms (severe bradycardia, hypotension, and low blood flow). This is unlikely, because high adenosine levels were present at baseline, before tilting, in patients with a positive test. Our results support the hypothesis that endogenous adenosine is involved in the mechanisms that trigger a vasovagal response during tilt testing in susceptible patients, as suggested by Shen et al.³ Although several mechanisms may be implicated in the pathogenesis of neurally mediated syncope in these patients, the end result could be an increase in adenosine plasma levels.

Endogenous Adenosine and Syncope

Adenosine acts on blood vessel tone and on the sinoatrial node via activation of 4 subtypes of P1 purinergic receptors: A1, A2A, A2B, and A3.¹¹ The activation of A1 receptors mediates cardiac depression through negative chronotropic, dromotropic, and inotropic effects¹² and diminishes blood vessel tone via the prejunctional inhibition of neurotransmitter release on the perivascular sympathetic¹³ and capsaicin-

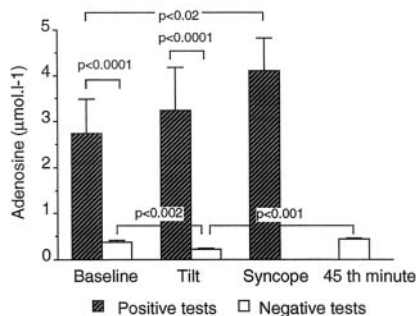


Figure 1. Adenosine plasma levels: intergroup and intragroup comparisons. Tilt indicates immediately after tilting; 45th min, 45th minute of tilting, ie, end of test in nonresponders.

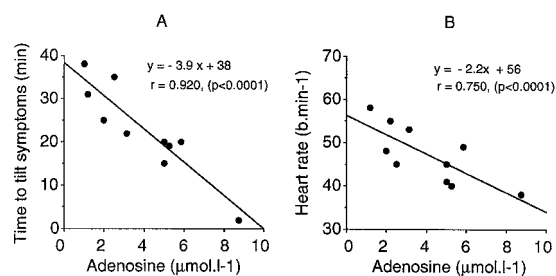


Figure 2. Relationship at moment of syncope between adenosine plasma levels and time to tilt-induced symptoms (A) and heart rate (B).

sensitive sensory afferents.¹⁴ A2 receptors are subdivided into A2A (high affinity) and A2B (low affinity) subtypes.¹⁵ The activation of these 2 subtypes mediates artery relaxation.^{16,17} The affinity of these receptors for adenosine depends on the receptor subtype in the following rank order: A1>A2A>A2B. Therefore, the tissue repartition of adenosine receptor subtypes, which is submitted to interindividual variations, and local adenosine concentrations have crucial biological effects. At high concentrations ($\approx 1 \mu\text{mol/L}$ and more), all receptors are activated, inducing synergistic effects on cardiac depression and vasodilatation.⁸ Thus, the high adenosine plasma levels observed in patients who developed symptoms during the head-up tilt test may have intervened in the triggering of a vasovagal syncope in these susceptible patients. The fact that the time to symptoms was shorter and the heart rate lower in patients with high adenosine plasma levels also supports this hypothesis. These findings may also explain why adenosine receptor antagonists are effective in the treatment of patients with vasovagal syncope.¹⁸

Desensitization and Downregulation

In the present study, syncope burden was higher in patients with a positive head-up tilt test and with high adenosine levels. However, these patients had no repeated syncopal episodes. This observation suggests receptor desensitization in patients with high adenosine plasma levels. For example, the number of A1 receptors in the AV node decreased by nearly 50% during chronic administration of agonists.^{19,20} These 2 mechanisms (desensitization and downregulation) may differ from one patient to another because of their individual sensitivity. Furthermore, expression and function of purinergic receptors can differ from one receptor subtype to the other.¹¹

On the other hand, nonspecific adenosine antagonists, such as xanthine derivatives, upregulate adenosine receptors²¹ and increase adenosine plasma levels.²² Consequently, subjects with heavy consumption of methylxanthines may have a potential compensatory increase in adenosine levels. Attention was paid to not include in the present study any patients with heavy caffeine consumption. Caffeine withdrawal, with resultant changes, may increase susceptibility to syncope development and a positive response to tilt testing or an increase in adenosine plasma levels. This is unlikely to have occurred in the present study, because caffeine consumption was low, and no xanthine derivatives were detected on the chromatograms during adenosine assay. The observation of high adenosine levels in patients with a positive head-up tilt test suggests that none of them was in a recent caffeine withdrawal period.²²

During syncope, adenosine plasma concentration showed an additional increase in 10 of 11 patients. This observation may be explained by the recruitment of a greater number of receptors ("spare receptors"), as has been reported in the coronary circulation.²³ Such increments in adenosine plasma levels, even small ones (as in patient 8, who developed a delayed presyncope), may be sufficient to induce symptoms in patients with high receptor sensitivity. In a single patient (patient 2), adenosine plasma levels did not increase at the time of syncope. This patient had very high adenosine plasma

levels and developed syncope quickly, within 2 minutes after tilting. The rapid circulating hypovolemia that results from venous pooling could have been the combined factor that precipitated syncope in this patient.

Adenosine and Baroreflex Function

Defective baroreflex function has been advocated as a potential mechanism to account for the development of neurally mediated syncope.¹ It was also reported that adenosine and its antagonists could modulate baroreflex activation²⁴ and that acute administration of caffeine could inhibit baroreflex sensitivity in humans.²⁵ Thus, it is possible that high adenosine plasma levels could contribute to the baroreflex dysfunction that occurs in some patients with neurally mediated syncope.

Source of Adenosine Release

One may speculate on the possible mechanism responsible for high adenosine plasma levels in patients with a positive tilt test. Adenosine is released by endothelial cells and vascular myocytes, particularly during ischemia.⁸ Nevertheless, ATP and adenosine are also released by sympathetic fibers^{26,27} and by poorly myelinated or nonmyelinated fibers, including C fibers.²⁸ The activation of myocardial mechanoreceptors, which are C fibers, is thought to be one of the mechanisms underlying vasodilatation and hypotension-induced syncope.^{1,28,29} Thus, we hypothesize that the activation of these fibers and increased sympathetic tone may be involved in adenosine release into the extracellular space. Even if there is no objective evidence for an increased sympathetic activation in patients with higher adenosine baseline levels (eg, similar heart rate and blood pressure), it can be hypothesized that sympathetic activation could be counterbalanced and masked by the effects of high adenosine concentration, which decreased heart rate and blood pressure. This hypothesis is supported by the observation that the lower the heart rate, the higher the adenosine plasma levels.

Our results suggest that adenosine plasma levels may allow pretest identification of patients who will have a positive head-up tilt test. However, additional studies in patients with neurally mediated syncope are needed to extend these initial observations.

Study Limitations

Although the present study included enough patients to reach statistical significance and to draw meaningful conclusions, additional studies including a larger group of patients are desirable. It is well known that neurally mediated syncope is not a uniform syndrome, and neurohumoral mechanisms are not the only mechanisms at play. In the present series, we mainly observed patients with a mixed response, ie, with both vasodepressive and cardioinhibitory properties. This obviously does not represent all varieties of patients with neurally mediated syncope.

The suggestion that adenosine may be a mediator of vasovagal syncope finds support in studies that showed that exogenous adenosine infusion was able to induce syncope in susceptible patients and in those demonstrating that adenosine antagonists are able to prevent tilt-induced syncope.^{3-5,10}

Furthermore, the present study suggests that these patients can be identified, and if further studies could show that syncope is reproduced by exogenous adenosine infusion in these patients, this will favor a causal mechanism of elevated adenosine plasma levels.

Conclusions

The present study evaluated adenosine plasma levels at baseline and during tilt testing in patients with unexplained syncope and showed that baseline levels of adenosine plasma were higher in patients with a positive tilt test than in patients with a negative tilt test, with no overlap between the 2 groups. A further increase in adenosine plasma levels was noted in most patients during tilt-induced syncope. The higher the adenosine plasma level, the earlier is the occurrence of syncope and the greater the decrease in heart rate.

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