Induction of Neurally Mediated Syncope With Adenosine

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Background—Tilt testing is used to establish the diagnosis of neurally mediated syncope. However, applicability of the tilt test is limited by test sensitivity and length of time required to perform the test. We hypothesized that adenosine could facilitate the induction of neurally mediated syncope through its sympathomimetic effects and therefore could be used as an alternative to routine tilt testing.

Methods and Results—In protocol 1, the yield of adenosine tilt testing (12 mg while upright, followed by 60° tilt for 5 minutes) and a 15-minute isoproterenol tilt test were compared in 84 patients with a negative 30-minute drug-free tilt test. In protocol 2, 100 patients underwent an initial adenosine tilt test followed by our routine tilt test (30-minute drug-free tilt followed by a 15-minute isoproterenol tilt). Six additional control patients underwent microneurography of the peroneal nerve to compare the sympathomimetic effects during bolus administration of adenosine and continuous infusion of isoproterenol. In protocol 1, the yields of adenosine (8 of 84, 10%) and isoproterenol (7 of 84, 8%) tilt testing were comparable (P=NS). In protocol 2, the yields of adenosine (19 of 100, 19%) and routine (22 of 100, 22%) tilt testing were also comparable (P=NS). Although the yield of adenosine tilt testing was comparable in both protocols, patients with a negative adenosine tilt test but a positive routine tilt test usually required isoproterenol to elicit the positive response. Microneurography confirmed discordant sympathetic activation after adenosine and isoproterenol administration.

Conclusions—Adenosine is effective for the induction of neurally mediated syncope, with a diagnostic yield comparable to routine tilt testing. However, the discordant results obtained with adenosine and the isoproterenol phase of routine tilt testing suggest that adenosine and isoproterenol tilt testing may have complementary roles in eliciting a positive response. Therefore, a tilt protocol that uses an initial adenosine tilt followed, if necessary, by an isoproterenol tilt would be expected to increase the overall yield and reduce the duration of tilt testing. (Circulation. 1999;99:1318-1324.)

Key Words: adenosine • syncope • tests

Over the past decade, tilt testing has become a widely accepted diagnostic tool for the evaluation of neurally mediated syncope.1–3 Syncope during orthostatic stress is thought to be initiated by venous pooling, with a subsequent reduction in central blood volume and stroke volume and a compensatory increase in sympathetic activity. In susceptible individuals, the increase in sympathetic activity may trigger the Bezold-Jarisch reflex,4 which results in bradycardia and/or hypotension.

Despite its clinical acceptance as a test to diagnose neurally mediated syncope, tilt testing continues to be limited in use partly because of (1) concerns over the sensitivity of the test, (2) the lack of a standardized test protocol, and (3) the lengthy duration of a complete study. In those patients with a negative drug-free tilt test who require pharmacological tilt testing, the total test duration may approach 2 hours.5

Recently, adenosine has been proposed to be an endogenous modulator of neurally mediated syncope.6 It is also possible that exogenous adenosine, like isoproterenol, is a facilitator of neurally mediated syncope through its sympathomimetic effects. In contrast to the well-characterized inhibitory cardiovascular actions of adenosine, including depression of sinoatrial and AV nodal activity, attenuation of the stimulatory effects of catecholamines, and inhibition of norepinephrine release from nerve terminals,7,8 it also has a sympathoexcitatory effect mediated via baroreflex and peripheral chemoreceptor activation.9–11

We hypothesized that adenosine could facilitate the induction of neurally mediated syncope through its sympathomimetic effects and therefore could be used as an alternative to routine tilt testing. The use of adenosine during tilt testing would offer several potential advantages over routine tilt testing: (1) ease of administration, (2) short drug half-life, and most importantly (3) a marked reduction in the time needed to perform tilt testing. Therefore, we sought to contrast the safety and diagnostic yield of adenosine tilt testing with routine tilt testing.

Methods

Patient Selection
We prospectively evaluated 255 consecutive patients referred for tilt testing between August 1996 and October 1997 to evaluate unex-
plained presyncope and/or syncope despite appropriate medical and/or neurological evaluation.

Fifty-four patients were excluded from the analysis, including 24 patients taking β-blockers at the time of the tilt test. Other reasons for exclusion included history of asthma (n=5), orthostatic hypotension (n=5), inability to administer isoproterenol because of concomitant angina (n=3) or aortic stenosis (n=2), patient refusal (n=1), and miscellaneous reasons that precluded completion of the entire protocol (n=14). Of the last group, 4 patients were excluded from analysis because carotid sinus massage subsequent to the tilt test reproduced their clinical symptoms.

Study Protocol

All patients were studied in the fasting state after informed written consent was obtained. Patients were monitored via a Passport recorder (Datascope Corp). The recorder permitted continuous heart rate monitoring and automatic noninvasive measurements of blood pressure at 60-second intervals.

We evaluated 3 protocols over the course of the study. The first 101 patients were enrolled in protocol 1, which compared the diagnostic yield of adenosine and isoproterenol tilt testing in patients with an initial negative drug-free tilt test (Figure 1). Resting supine blood pressure and heart rate measurements were obtained over 15 minutes. Patients were subsequently tilted upright at a 60° angle for 30 minutes on a tilt table with a footboard. If the patient’s clinical episodes of presyncope and/or syncope were reproduced, the patient was returned to the supine position and the test was terminated. The remaining patients with a negative drug-free tilt test received while remaining upright a bolus of 12 mg adenosine IV (Adenocard, Fujisawa) followed by a 10-cm³ flush of isotonic saline and were observed for up to 5 minutes. After development of initial bradycardia and/or AV block, all patients developed a reflex sinus tachycardia. Shortly thereafter, patient experienced typical presyncope prodrome followed by vasovagal syncope. This was characterized by marked cardioinhibitory response that reproduced clinical “seizures.” Routine tilt test, with and without isoproterenol, was normal.

The initial dose of adenosine was 150 μg/kg (≈12 mg). If an adenosine effect (a transient decrease in heart rate by ≥20% compared with baseline or transient AV block) was not demonstrated, the patient was returned to the supine position. After 5 minutes, the patient was retitled and given an incremental dose of adenosine (an additional 75 μg/kg). The process was repeated until an adenosine effect was observed.

Protocol 3 was designed to compare and contrast the patterns of muscle sympathetic nerve activity (MSNA) between adenosine and isoproterenol. Six control patients (2 men; age, 37±11 years) without significant cardiovascular history underwent microneurography while supine according to methods previously described. After a 20-minute rest period following identification of the peroneal nerve, 5 minutes of baseline recordings was obtained (Figure 4A). Subsequently, isoproterenol (1±1 μg/min) was infused to increase resting heart rate by 20%. After 5 minutes to reach a steady state at the desired isoproterenol dose, an additional 5 minutes of recordings was obtained (Figure 4B) and analyzed at 1-minute intervals. Isoproterenol infusion was then discontinued. After a 30-minute washout period and a 1-minute baseline recording period (Figure 4C), all patients received a bolus administration of 150 μg/kg (13±4 mg) adenosine and underwent an additional 3-minute recording.

Protocol 2: 100 patients

Weight-Adjusted Adenosine

Initial dose: 150 μg/kg, titrated to achieve sinus bradycardia of 20% or AV block

Figure 2. Induction of neurally mediated syncope with adenosine. Continuous single-lead ECG recording (surface lead II) from patient with lifelong history of “seizures” precipitated by emotional distress and accompanied by nausea and light-headedness. Patient received 12 mg adenosine while upright. Transient sinus tachycardia was followed by 2 seconds of AV block, which was followed by reflex sinus tachycardia. Shortly thereafter, patient experienced typical presyncope prodrome followed by vasovagal syncope. This was characterized by marked cardioinhibitory response that reproduced clinical "seizures." Routine tilt test, with and without isoproterenol, was normal.

Protocol 3 compared the efficacy of an adenosine tilt test with our routine tilt test, with and without isoproterenol, in 100 patients (Figure 3). Resting supine blood pressure and heart rate measurements were obtained over 5 minutes in protocol 2 patients. Patients were tilted upright at a 60° angle and immediately given adenosine as previously described. After 5 minutes of observation, patients were returned to the supine position, and our standard tilt test protocol was performed. Regardless of the response to adenosine, all patients underwent our routine tilt test. Resting supine blood pressure and heart rate measurements were obtained for 15 minutes. As previously described, this was followed by 30 minutes of drug-free tilt testing and, if necessary, 15 minutes of tilt testing during isoproterenol infusion.
period. These data were analyzed in 10-second intervals and then normalized to 1-minute intervals to allow comparison with the isoproterenol data. After adenosine administration, all patients developed initial transient AV block (Figure 4D) followed by sinus tachycardia (Figure 4E).

**Definitions**
Presyncope was defined as the induction of symptoms of imminent syncope. Presyncope was considered a positive end point only in patients being evaluated for clinical presyncope. Syncope was defined as the transient loss of consciousness. Our routine tilt test was a drug-free tilt test (60° for 30 minutes); if necessary, this was followed by an isoproterenol tilt test (60° for 15 minutes). A positive tilt test was defined as the reproduction of clinical presyncope or syncope, after either an adenosine or routine tilt test accompanied by relative bradycardia (≥20% decrease in heart rate compared with baseline) and/or hypotension (systolic blood pressure ≤80 mm Hg).

**Statistical Analysis**
All continuous variables are expressed as mean±SD. Group comparisons of continuous and dichotomous variables were calculated by use of Student’s t test and Fisher’s exact test, respectively. Comparisons of diagnostic yields in matched patients were made using McNemar’s χ² test. Comparison of repeated measures was performed by within-group ANOVA with the use of prespecified contrasts to compare results during or after adenosine or isoproterenol infusion with those obtained during multiple control intervals (Crunch 4.0, Crunch Software Corp). For all comparisons, P<0.05 was considered statistically significant.

**Results**

**Demographics**
The mean age of the 201 patients was 55±20 years. The study population consisted of 81 men (40%) and 120 women (60%). Patients were referred for the evaluation of syncope (66%), presyncope (19%), or both (15%). The first episode prompted evaluation in 50 patients (25%); 31 patients (15%) had 2 episodes, and 118 patients (60%) had ≥3 episodes. Left ventricular (LV) ejection fraction was known for 115 patients (57%) and was normal in 100 of these patients (88%). History of cardiac disease was noted in 36% of the patients. This included hypertension (21%), coronary artery disease (13%), congestive heart failure (3%), and cardiomyopathy (2%). In 5% of the patients, ventricular pacing was available via a permanent pacemaker or internal defibrillator.

Protocols 1 and 2 were performed in 101 and 100 patients, respectively. No significant differences were observed between patients in protocols 1 and 2 with respect to age, sex, number of clinical episodes before tilt testing, indication for tilt testing, and LV systolic function (the Table).

**ECG**
A baseline 12-lead ECG was available in all patients and was normal in 158 (79%). Abnormalities on the ECG included a rhythm other than sinus, including sinus bradycardia (heart rate <50 bpm) in 5%, atrial fibrillation or flutter in 3%, ventricular pacing in 4%, first-degree AV block in 4%, intraventricular conduction delay in 9%, ventricular hypertrophy in 3%, and/or evidence of prior Q-wave myocardial infarction in 5%.

**Adenosine Administration**
Adenosine was well tolerated. The most frequent symptoms associated with adenosine were flushing, diaphoresis, light-headedness, and shortness of breath. In 2 patients, syncope developed in the setting of prolonged AV block (>10 seconds) immediately after infusion of 12 mg adenosine. These patients were returned to the supine position before adenosine-mediated tachycardia developed and were among those patients excluded from analysis because of an uninterpretable adenosine tilt test. All effects of adenosine were self-limited; no patient required pharmacological intervention as a result of adenosine administration. In addition, no patient developed atrial fibrillation after adenosine infusion.
The most common ECG effect of adenosine, observed in 67% of patients, was development of transient AV block. The mean duration of AV block was $6_{\pm}3$ seconds (maximum, 14 seconds). Less common effects included sinus pauses in 18% and sinus bradycardia in 15%. The mean duration of sinus pause was $6_{\pm}2$ seconds (maximum, 10 seconds). In all patients with a positive adenosine tilt test, the vasovagal response occurred within 2 minutes of the resolution of AV block after adenosine administration.

Protocol 1
Seventeen (17%) patients developed a vasovagal response during the initial drug-free tilt test (Figure 5). The mean time to a vasovagal response was 16$_{\pm}$11 minutes. According to protocol, the remaining 84 patients underwent a pharmacological tilt test. After administration of adenosine, 8 patients (10%) developed a vasovagal response. A positive response was similarly observed in 7 patients (8%, $P=$NS) after administration of isoproterenol $2_{\pm}1$ mg/min. The mean time to a vasovagal response was 6$_{\pm}2$ minutes during isoproterenol infusion. Concordant positive responses to adenosine and isoproterenol were observed in 3 patients, and discordant responses were seen in 9 (Figure 6).

Protocol 2
Nineteen patients (19%) developed a vasovagal response after administration of adenosine (Figure 7). As described earlier, all patients then underwent a routine tilt test regardless of their response to adenosine. A drug-free tilt test was positive in 11 patients (11%). Of the 89 patients with a negative drug-free tilt test, an additional 11 (12%) had a positive response to tilt testing during infusion of isoproterenol $2_{\pm}1$ µg/min. The mean time to a vasovagal response was 16$_{\pm}$11 minutes for patients with a positive drug-free tilt test. During isoproterenol infusion, the mean time to a vasovagal response was 8$_{\pm}$4 minutes. There was no significant difference between the overall positive yields of an adenosine tilt test (19%) and the routine tilt test (22%) ($P=$NS).

A positive tilt test with adenosine or during the routine protocol was observed in 31 patients. Nine patients were adenosine positive only; 12 patients were positive only during the routine tilt test protocol; 10 patients had a concordant positive response. Therefore, the concordance and discordance rates were 79% (79 of 100) and 21% (21 of 100), respectively, between adenosine and routine tilt testing (Figure 8). An example of a discordant response is shown in Figure 2, which depicts an ECG recording during adenosine tilt testing from a patient with a lifelong history of “seizures” precipitated by emotional distress and accompanied by nausea and light-headedness. However, extensive neurological testing, including MRI and electroencephalography, was normal. The patient had been treated unsuccessfully with anticonvulsant medications for several years. Although a subsequent routine tilt test, with and without isoproterenol, was normal, the adenosine tilt test was markedly positive and reproduced her clinical “seizures.”

Demographics of Patients in Protocols 1 and 2

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Protocol 1</th>
<th>Protocol 2</th>
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<tr>
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<td>100</td>
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<td>54±20</td>
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<tr>
<td>Sex, n (%)</td>
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<td></td>
</tr>
<tr>
<td>M</td>
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<td>45 (45)</td>
</tr>
<tr>
<td>F</td>
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<td>55 (55)</td>
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<tr>
<td>Clinical indication, n (%)</td>
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<td></td>
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<td>Presyncope</td>
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<td>20 (20)</td>
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<tr>
<td>Syncope</td>
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<td>71 (71)</td>
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<td>Number of episodes, n (%)</td>
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<tr>
<td>LV ejection fraction, n (%)</td>
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</tr>
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</table>

*Normal ejection fraction was defined as ≥60%.

$P=$NS for all comparisons between protocol 1 and 2 patients.
Of the 10 patients who were positive during both the adenosine and routine tilt tests, 8 (80%) did not require isoproterenol for a positive response during the routine tilt test. In contrast, of the 12 patients who were positive during the routine tilt test protocol but negative during adenosine tilt testing, 9 (75%) required isoproterenol to produce a positive response ($P < 0.03$, Figure 8).

Adenosine Administration

The mean adenosine dose in these patients was $11.5 \pm 3.4$ mg (range, 6 to 24 mg). Only 6 patients required additional adenosine because the initial dose failed to result in an adenosine effect. Of these patients, 2 developed syncope in response to a larger dose of adenosine after an earlier dose failed to cause sinus slowing or AV block or to produce a vasovagal response. No patient who failed to demonstrate an initial negative chronotropic or dromotropic response with a given dose of adenosine developed a positive adenosine tilt test at that dose. Figure 9 is a recording from a patient who received sequential doses of adenosine. After doses of 12 and 18 mg adenosine, there was neither an adenosine effect nor a vasovagal response. However, after receiving 24 mg of adenosine, the patient developed transient AV block, consistent with an adenosine effect, which was followed by adenosine-mediated sinus tachycardia and a vasovagal response, which reproduced the patient’s clinical episode. According to protocol, the patient underwent a routine tilt test. After a negative drug-free tilt test, a vasovagal response was reproduced during the isoproterenol phase of the tilt protocol.

Predictors of a Positive Test

A positive tilt test could not be predicted from baseline demographic variables, including age, sex, indication for tilt testing, LV ejection fraction, and history of cardiac disease. In addition, baseline ECG abnormalities were not predictive of a positive tilt test. However, the likelihood of a positive tilt test increased with the number of clinical episodes. A positive routine tilt test was observed in 7%, 19%, and 31% ($P = 0.02$) of patients with 1, 2, and $\geq 3$ clinical episodes, respectively, before tilt testing. A similar trend, 8%, 14%, and 18%, was observed with adenosine tilt testing ($P = \text{NS}$).

Protocol 3 (Microneurography)

Adenosine was associated with transient AV block, which resulted in bradycardia and hypotension (Figure 10A and 10B). This period was characterized by marked sympathetic activation as reflected by an increase in MSNA by as much as 360% (19$\pm$3 to 52$\pm$17 bursts per minute; Figure 10C). On resolution of AV block, there was transient sinus tachycardia ($\sim 10$ seconds) followed by a return of heart rate and blood pressure to baseline. Concomitantly, MSNA decreased by as much as 67% compared with baseline (19$\pm$3 to 9$\pm$3 bursts per minute) and remained significantly depressed for an additional 90 seconds. No significant differences in root mean square successive differences were observed between baseline and the 3-minute period after resolution of adenosine-induced AV block. In contrast, isoproterenol infusion was associated with sinus tachycardia, a decrease in mean arterial pressure, and an $\sim 100\%$ sustained increase in MSNA (14$\pm$2 to 26$\pm$1 bursts per minute; Figure 10D through 10F).

Figure 8. Concordant and discordant responses between adenosine-based and routine tilt testing (protocol 2).

Figure 9. Adenosine dose-dependent vasovagal response. Continuous single-lead ECG recordings (surface lead II) from 47-year-old man with history of syncope referred for tilt testing. Blood pressure and sinus cycle length (ms) are denoted in C and D. See text for discussion. *Syncope.
The principal finding of this study is that adenosine is a safe and effective pharmacological agent for the provocation of neurally mediated syncope in susceptible individuals. The positive yield of adenosine tilt testing is similar to isoproterenol tilt testing in patients with a negative drug-free tilt test and, more importantly, is similar to the overall yield of routine tilt testing (drug-free tilt followed by an isoproterenol tilt). These findings have significant clinical implications because in a heterogeneous population referred for tilt testing, these pharmacological agents were administered at time 0. A. After administration of adenosine, there is initial bradycardia (during AV block), followed briefly (~10 seconds) by sinus tachycardia and then a return to baseline. B. Bradycardia associated with transient AV block is accompanied by hypotension; however, blood pressure quickly returns to baseline. C. Period of AV block is characterized by marked increase in MSNA; subsequently, there is rapid decrease in MSNA, which remains significantly depressed for ~90 seconds. Isoproterenol infusion is characterized by tachycardia (D), hypotension (E), and sustained increase in MSNA (F). *P<0.05; **P<0.01.

Discussion

The hemodynamic effects of bolus doses of adenosine, as performed in our study, are less well characterized than the effects during continuous infusion of adenosine. In a recent report, bolus doses of adenosine were associated with a triphasic hemodynamic response. There was an immediate hypertensive response, suggesting sympathetic activation, followed by hypotension (related to vasodilatation) and finally sinus tachycardia (likely caused by baroreceptor unloading). In susceptible individuals, vasovagal syncope occurred after this last response.

Although adenosine causes a dose-dependent decrease in blood pressure and heart rate when injected into the nucleus solitarius, it is unlikely that exogenous adenosine, at the doses given in our study (~150 μg/kg), crosses the blood-brain barrier. Therefore, a more likely explanation for the response to exogenous adenosine is that it increases sympathetic activation through unloading of baroreceptors and arterial chemoreceptor activation, which then triggers a vasovagal event in susceptible individuals. Thus, exogenous adenosine can be considered a means by which to increase sympathetic activation during orthostatic stress.

There are several possible explanations for the discordance between the results of adenosine and isoproterenol tilt testing in individual patients. In some patients, the discordance may be due to the delivery of a subdiagnostic adenosine dose. We believe that demonstrating an adenosine effect (transient sinus slowing or AV block) is required to confirm that an adequate dose was given. In most patients, a dose of 150 μg/kg (~12 mg) is sufficient. Higher doses of adenosine rarely are required. Failure to achieve an adenosine effect may result in a false-negative adenosine-based tilt test.

Additionally, discordance may reflect differential patient sensitivities related to the mechanisms of sympathetic activation by adenosine (chemoreceptor activation and unloading of baroreceptors) and isoproterenol (direct β-adrenergic stimulation and unloading of baroreceptors). To clarify this issue, we performed microneurography and examined the differences in the pattern of sympathetic activation after adenosine and isoproterenol infusion. In contrast to the effects of continuous adenosine infusion, the effects on MSNA after bolus doses of adenosine have not previously been reported.

In our study, bolus doses of adenosine were associated with initial sympathetic activation, as reflected by a marked increase in MSNA and effective pharmacological agent for the provocation of neurally mediated syncope. Adenosine and isoproterenol tilt testing may have complementary roles in the evaluation of patients with neurally mediated syncope.
increase in MSNA (as much as 360% relative to baseline), followed by prolonged (≈90 seconds) sympathetic withdrawal, as reflected by a decrease in MSNA (as much as 67% relative to baseline). The absence of a significant change in root mean square successive differences suggests that the decrease in MSNA reflects sympathetic withdrawal rather than augmented vagal tone. Presumably, in susceptible individuals, there is continued sympathetic withdrawal that results in vasovagal syncope. In contrast, continuous isoproterenol infusion was associated with a sustained increase in MSNA. However, the maximum increase in MSNA in response to isoproterenol was less than one third that associated with adenosine. Therefore, adenosine results in an initial rapid and large increase in sympathetic activation followed by a rapid decline, whereas isoproterenol produces a more modest but sustained increase in MSNA.

Finally, discordance may reflect a false-positive response to either adenosine or isoproterenol. In the absence of a true gold standard, it is not possible to determine the actual sensitivity and specificity of tilt testing with or without pharmacological provocation. The most applicable surrogate is the reproduction of the patient’s clinical episode with a concordant hemodynamic response. Because this was our end point for determination of a positive tilt test, we do not believe that discordance reflects a false-positive response.

**Study Limitations**

A possible limitation of our study is that we did not test the adenosine or routine tilt test protocol in a control population of subjects without a history of presyncope or syncope. However, the specificity of both adenosine and routine tilt testing with a protocol similar to ours has previously been reported. The 12-mg adenosine bolus dosing regimen during tilt testing has a specificity of 93%, similar to the specificity of low-dose isoproterenol tilt testing with a 60° protocol (88%). Because previous studies have already demonstrated an acceptable specificity for both adenosine and routine tilt testing, the primary aim of our study was to compare adenosine with isoproterenol and routine tilt testing. A second potential limitation is that the order in which the diagnostic tests were performed (eg, adenosine versus isoproterenol and adenosine versus routine tilt testing) was not systematically varied, so the possibility that the results of the adenosine stage may have affected the results of the subsequent stages cannot be excluded. Finally, the discordant effects of adenosine and isoproterenol on MSNA may reflect differences in their mode of administration and/or differences in the hemodynamic response induced by these drugs. Specifically, the greater increase in MSNA with adenosine may reflect the effect of bolus administration of adenosine (versus continuous isoproterenol infusion), which may result in a greater degree of hypotension and baroreceptor unloading.

**Implications**

Using our findings and bearing in mind the discordance between adenosine and routine tilt testing, we propose a simplified, more efficient tilt test protocol. Patients would initially undergo adenosine tilt testing (with a weight-adjusted dose of adenosine). A positive adenosine tilt test would obviate the need for further testing, providing a substantial time savings for the patient and physician. Patients with a negative adenosine tilt test would then undergo a 15-minute isoproterenol tilt phase. This recommendation is based on our observation that patients with a negative adenosine but a positive routine tilt test usually require isoproterenol to yield a positive response during tilt testing. Compared with current clinical tilt test protocols that use an initial drug-free tilt test followed by pharmacological provocation with isoproterenol, this protocol may offer a more efficient and sensitive means for diagnosing neurally mediated syncope.

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**References**

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