CLINICAL STUDY

Diagnostic yield of adenosine and nitroglycerine stimulated tilt test in patients with unexplained syncope

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Abstract

Objectives: **We aimed to compare diagnostic yield of adenosine tilt test (A-HUT) with nitroglycerine tilt test (NTG-HUT) in patients with unexplained syncope and to assess the use of adenosine tilt test as an alternative to routine tilt testing.**
Background: **Adenosine could provoke a vasovagal response in susceptible patients. Adenosine stimulated tilt testing is less time consuming than conventional tilt testing.**
Methods: **Forty-one consecutive patients with unexplained syncope were tested (29 females /12 males; mean age 44±20 years). As a part of standard diagnostic testing they undewent both adenosine and nitroglycerin stimulated tilt testing in random fashion.**
Results: **NTG-HUT was positive in 28 patients (68 %). Six patients (14.6 %) developed a vasovagal response after adenosine stimulated head-up tilt test (A-HUT). All patiens with positive A-HUT showed also the positivity of NTG-HUT. No patient from with negative NTG-HUT developed a vasovagal response after adenosine induction. The diagnostic yield of NTG-HUT was significantly higher than yield of A-HUT (p<0.001). The diagnostic yield of A-HUT was significantly affected by age. Subjects with a positive adenosine tilt test were younger than those with a negative tilt (29±10 vs 46±20 years, p=0.016). Five of six positive patients were <30 years of age. Diagnostic yield in those patients was 31 %, whereas in patients >30 years of age was significantly lower (4 %, p=0.007).**
Conclusion: **Diagnostic yield of the adenosine stimulated tilt testing is significantly lower than diagnostic yield of nitroglycerine stimulated tilt testing. Given the very short time needed for performing adenosine stimulated HUT, it may be useful in patiens <30 years of age. In this group of patiens positive adenosine-stimulated HUT may obviate need for the time consuming nitroglycerine-stimulated HUT *(Tab. 1, Fig. 3, Ref. 17).* Full Text (Free, PDF) *www.bmj.sk*.**
Key words: vasovagal syncope, adenosine, nitroglycerine, head-up tilt test.

Syncope is defined as a transient self-limited loss of consciousness and posture with complete recovery, caused by transient cerebral hypoperfusion (1, 2). The most common (approximately 60 %) is vasovagal syncope as a type of neurally mediated syncope. It can occur at any age; typically it begins in the teenage years and there may be a long period of life without recurrences (3). In general, it doesn't threaten a life of patient. Nevertheless, it can compromise quality of life and lead to significant morbidity (2).

Pathophysiology of vasovagal syncope is connected with sudden withdrawal of sympathetic activity and parasympathetic dominance with corresponding hypotension and bradycardia which can be provoked by prolonged standing, extreme emotion, severe pain or instrumentation (2). Details of pathogenesis are not known besides autonomic tone changes also humoral factors may play an important role (4).

Diagnostics of vasovagal syncope may be accurately made by history and clinical features alone, but it must be often proved by a head-up tilt test (HUT), widely accepted diagnostic tool for the evaluation of neurally mediated syncope. Although a gold standard does not exist, HUT's specificity and sensitivity were estimated from pooled data to be 85 % and 87 % (2). Several different protocols are in use, the Italian protocol becoming one of the most popular. It consists of 20 minute drug free tilt test with another 15 minutes tilt after nitroglycerine (NTG) adminis-

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tration (5). Another widely accepted type of pharmacological stimulation is isoproterenol.

Adenosine stimulated tilt test 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) a marked reduction in the time needed to perform tilt testing, (2) short drug half-life, (3) ease and responsibility of administration (6). The injection of a bolus of adenosine during tilt testing has been seen to provoke a vasovagal response in susceptible patients with syncope with a positivity rate comparable with that of isoprenaline (7).

Adenosine, a purine nucleotide, is a ubiquitous natural metabolic substance with effects on heart rate and contractility, smooth muscle tone, sedation, release of neurotransmitters, glycolysis, lipolysis, and renal, platelet, leukocyte, and endothelial cell function (8). It is present in all human cells. 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, it also has a sympathoexcitatory effect. Sympathetic activation by adenosine can be direct (i.e., cardiac excitatory afferent nerves) and indirect (i.e., vasodilation and reflex sympathetic activation) (9).

Attending in the induction of vasovagal mechanism, adenosine could be an endogenous trigger of neurally mediated syncope (6). Recent studies have demonstrated, that adenosine plasma levels 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 (10). Both endogenous and exogenous adenosine may induce vasovagal syncope. Adenosine is able to oppose the stimulatory action of norepinephrine on adenylat cyclase and decreases sympathetic efferent nerve activity. It also promotes vasodilation and inhibits rennin release (11).

Adenosine has a wide range of applicability in cardiologic diagnostics. It is also used as adenosine triphosphate (ATP), which is rapidly metabolized to adenosine and acts at purinergic adenosine A1 myocardial receptor. ATP and adenosine have similar effects in humans. Thus adenosine can be used in place of ATP (7).

ATP test was suggested for the in diagnosis of myocardial ischemia (12), sick sinus syndrome (13) and dual AV node physiology (14), ATP test has also been proposed as an investigative tool in patients with unexplained syncope. Interpretation of the result of the test is exclusively based on the duration of the cardiac pause. The test is considered positive if ATP produces a ventricular asystole due to complete AV block pause longer than 6 seconds (7) or complete AV block /SA block lasting at least 10 seconds (11).

Only a minority of patients with unexplained syncope has an increased susceptibility to adenosine triphosphate. This test is able to identify patients with syncope due to transient (paroxysmal) AV block. As shown in studies using implantable loop recorder it has a high rate of false positive results which makes this test of little value in selecting treatment (11).

ATP test is distinct from adenosine stimulated HUT, the latter is used for identifying patients susceptible to vasovagal reaction. It was documented that ATP-positive patients have clinical features and mechanisms of syncope which are different from tilt-positive patients (5).

The aim of the present study was to compare diagnostic yield of adenosine tilt test with nitroglycerine tilt test in patients with unexplained syncope and to assess its use and safety as an alternative to routine tilt testing.

Methods

Forty-one consecutive patients (29 females/12 males; mean age 44±20 years) with unexplined syncope were tested by standardized diagnostic algorhithm consisting of history, physical examination, carotid sinus massage, 12 lead ECG, 24 hour ambulatory ECG monitoring, echocardiography and neurological examination. In addition, transoesophageal stimulation, invasive electrophysiology and electroencephalography were performed if indicated. In all patients HUT was performed both during nitroglycerine and adenosine stimulation in random order during one session.

13 another patients were excluded from the analysis, including 2 patients taking ß-blockers or theophyllines at the time of the tilt test. Other reasons for exclusion included history of asthma (n=2), orthostatic hypotension (n=1), patient refusal (n=2), and miscellaneous reasons that precluded completion of the entire protocol (n=3).

Mean number of syncopal episodes was 4±7 (2–20 episodes). Coronary artery disease was documented in 8 patients (20 %) and hypertension in 13 patients (32 %). Baseline ECG was normal 38 patients (93 %). 2 patients had ventricular bigeminy, 1 patient had incomplete RBBB.

Head up tilt test

A tilt table with footboard support located in a quiet room was used. The tests were done between 9:00 a.m. and 12:00 a.m. and the subjects had been fasting overnight having a small breakfast. All cardioactive drugs were excluded for at least 3 days. Venous cannulation of cubital vein was performed before 20 min supine pre-tilt phase. Patients were tilted upright at a 60° angle. Second test was performed after 30 min supine pause after previous drug administration.

The electrocardiogram was recorded by ECG monitor and simultaneously stored using a Holter monitor. Blood pressure was mesured by mercury sphygmomanometer at 5 minute interval during asymptomatic phase of NTG-HUT and in 1 minute interval during A-HUT and symptoms occurrence.

HUT was defined as positive at the onset of syncope or presyncope when hypotension (systolic blood pressure <80 mmHg) and/or bradycardia (HR blow 50/min) and was terminated immediately. For the classification of positive responses to tilt testing ESC Task force report classification was used : type 1 (mixed type), type 2A (cardioinhibition without asystole), type 2B (cardioinhibition with asystole) and type 3 (vasodepressor response) (12).

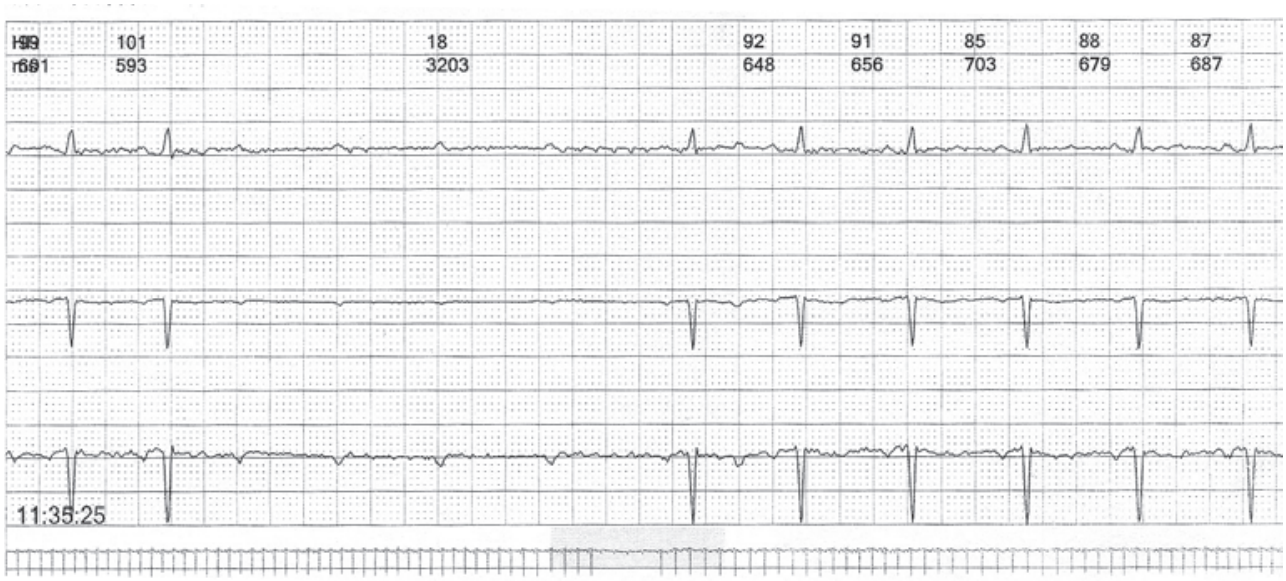

Fig. 1. Adenosine induced high degree atrioventricular block.

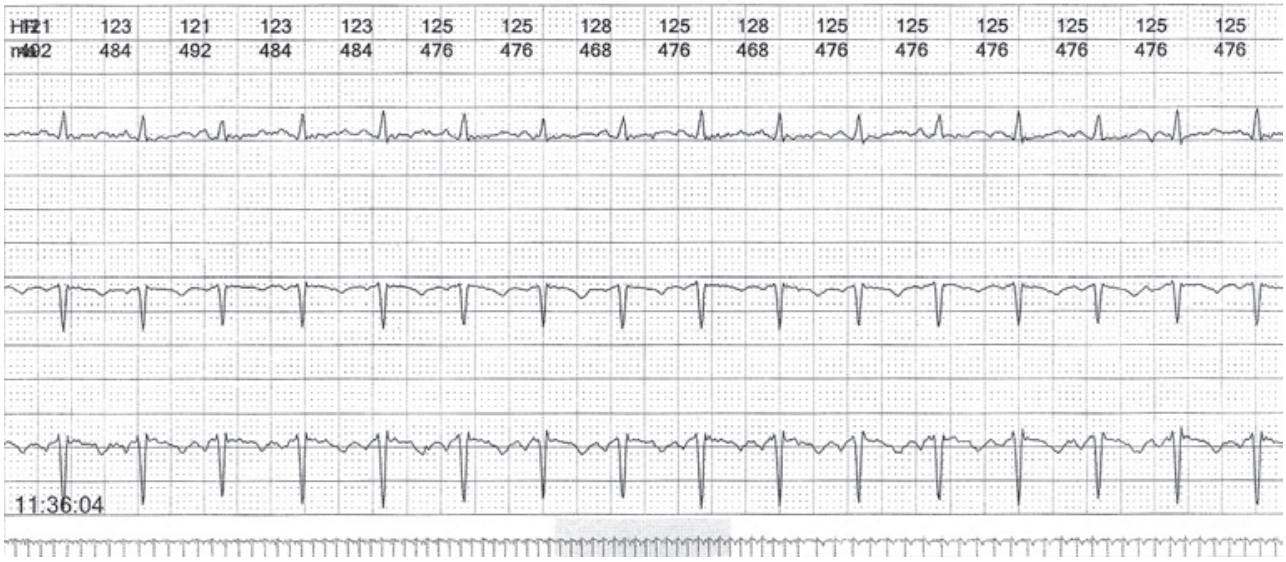

Fig. 2. Reflex sinus tachycardia after adenosine induced atrioventricular block.

Nitroglycerin HUT protocol (Italian protocol)

Protocol consisted of drug-free (passive) phase and NTG stimulated phase. If passive test was negative 400 µg of glyceryl trinitrate spray was administered sublingually at 20 minute and patient was observed for up to 15 min without lowering to supine position We considered orthostatic hypotension to be present when systolic blood pressure decreased by >20 mmHg or diastolic blood pressure decreased by >10 mmHg during the first 3 minutes of orthostasis, patients were excluded from the study.

Adenosine HUT protocol

Adenosine was administred immediately after assuming o upright position. A bolus of adenosine was given IV followed by a 10 cm^3 flush of isotonic saline. The initial dose of adenosine was 150 µg/kg.

An appropriate adenosine effect was defined as a transient decrease in heart rate of at least 20 % compared with baseline or transient AV block (Fig. 1). Patient was observed for up to 5 minutes. If an adenosine effect was not demonstrated, the patient was returned to the supine position. After 5 minutes, the patient was retilted and given an incremental dose of adenosine (an additional 75 µg/kg). The process was repeated until an adenosine effect was observed.

After development of initial bradycardia and/or AV block, patients developed a reflex sinus tachycardia (Fig. 2). In susceptible patients, this was followed by a vasovagal response (Fig. 3).

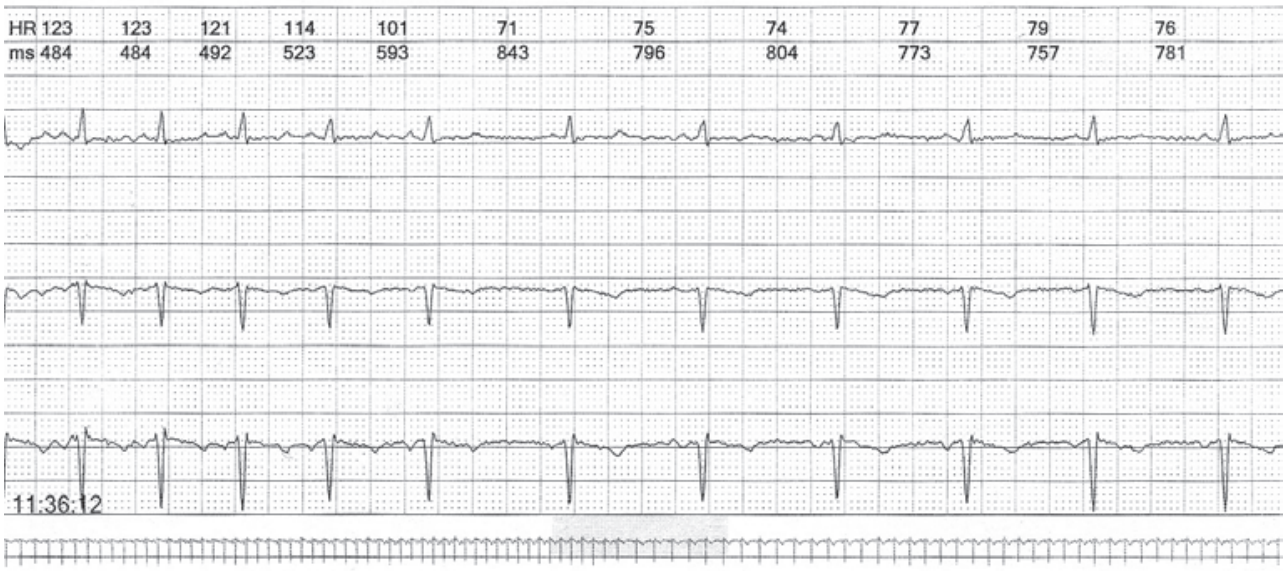

Fig. 3. Mixed type of adenosine induced vasovagal reaction – after reflex sinus tachycardia an onset of mixed type vasovagal reaction can be seen. Simultaneously drop in blood pressure was recorded.

These patients were classified as having a positive adenosine tilt test.

NTG and adenosine administration were in random order. If hypotension was present after NTG-HUT, adenosine tilting was not performed untill systolic pressure in upright position reached pretest values or at least 100 mmHg.

Statistics

Comparison between diagnostic yield of NTG-HUT and adenosine HUT was carried out by means of chí square test. Comparison of the lenght of AV block was was made by Student t test and ANOVA $p<0.05$ was considered statistically significant.

Results

Nitroglycerine stimulated head-up tilt test (NTG-HUT) was positive in 28 patients – 68 % (20 females/8 males, mean age was 44±21 years) and negative in 13 patients (9 females/4 males, mean age was 43±18 years). Six patients (14.6 %) developed a vasovagal response after adenosine stimulated head-up tilt test (A-HUT). All patiens with positive A-HUT showed also the positivity of NTG-HUT. No patient from with negative NTG-HUT developed a vasovagal response after adenosine induction. Diagnostic yield of NTG-HUT was significantly higher than yield of A-HUT ($p<0.001$)

Nitroglycerine HUT

28 patients had a positive NTG-HUTT (68 %). In all patients symptoms developed in NTG stimulated phase of the test. Seven patients (25 %) had mixed vasovagal reaction (VASIS 1), 2 patients (7 %) had cardioinhibitory vasovagal reaction with asystolic pause (VASIS 2A) and 19 patients (68 %) had vasodepressor vasovagal reaction (VASIS 3). Mean duration of asystole was 6.5±3.5 seconds. Most frequent symptoms during presyncopal episodes were dizziness, blurred vision, pallor and sweaing.

Adenosine HUT

Mean dose of adenosine needed for obtaining adenosine effect was 12.1±2.5 mg (6 to 18 mg). Incremental dose of adenosine was required only in one patient. He underwent one repeated tilt with increased dose of adenosine (from 12 mg to 18 mg) with adequate response.

Adenosine was well tolerated. No patient required pharmacological intervention to counteract effect of adenosine administration. The most frequent symptoms associated with adenosine aplication were flushing (18 patients), diaphoresis (8 patients), light-headedness (8 patients), chest pain or oppressions (29 patients) and shortness of breath (5 patients). They were self-limited and benign.

The most common ECG effect of adenosine observed in 29 patients (71 %) was development of transient AV block. The mean duration of maximal R-R interval during AV block was 3.3±2.5 seconds (minimum 1.2 seconds, maximum 8.1 seconds). Mean duration of an episode of AVB block was 8.2±1.8 seconds (minimum 1.5 seconds, maximum 29.7 seconds).

Less common effect was sinus slowing in 18 patients (44 %). Maximal P-P interval was 2140 ms, mean percentage of heart rate decrease was 17.9±14.4. Combination of sinus slowing and AV block occurrence was present in 6 patients (14.6 %).

No patient has a syncopal or presyncopal symptoms episode due to adenosine effect in the early phase of adenosine stimulated HUT. Symptoms occurred only in later phase of HUT after development of sinus tachycardia and were not temporally associated with the preceding sinus slowing or AV block.

Tab. 1. Negative chronotropic and dromotropic effect of adenosine in various groups of patients.

	NTG posit	NTG negat	AD posit	AD negat	p
Number of patients	28	13	6	35	
Age (years)	44±21	43±18	29±10	46±20	0.19
Maximal R-R interval during AVB (sec)	3.1±2.4	3.7±2.6	3.5±3.0	3.2±2.4	0.9
AVB total duration (sec)	7.1±6.8	10.6±8.5	7.1±7.0	8.4±7.6	0.57
SA slowing (%)	17.5±13.4	17.0±15.9	21.7±8.4	16.6±15.0	0.88

Legend: AVB – atrioventricular block, SA – sinoatrial, NTG – nitroglycerine, AD – adenosine

During A-HUT 5 patients (83 %) had mixed vasovagal reaction and 1 patient (17 %) had vasodepressor vasovagal reaction. There was no cardioinhibitory type of response during A-HUT. Presyncope occurred in 4 patients, syncope in 2 patients. Mean time interval between adenosine application and vasovagal reaction was 160±75 seconds, all reactions occured within 4 minutes of the resolution of AV block after adenosine administration. Normal sinus rhytm was documented in all six patients during vasovagal reaction. Mean systolic pressure decrease was 50±20 mmHg.

In total six patients (14.6 % 3 males/3 females) developed a vasovagal response after adenosine stimulated head-up tilt test. All patiens with positive A-HUT showed also the positivity of N-HUT. No patient from with negative N-HUTT developed a vasovagal response after adenosine induction.

Concordant vasovagal reactions triggered by adenosine and NTG were observed in 4 patients (66 %, 3 mixed and 1 vasodepressor type of vasovagal response). Discordant reactions were seen in 2 patients (33 %, vasopressor during N-HUT and mixed during A-HUT cardioinhibitory during N-HUT and mixed during A-HUT).

The diagnostic yield of A-HUT was significantly affected by age. Subjects with a positive adenosine tilt test were younger than those with a negative tilt (29±10 years vs 46±20 years, p=0.016). Five of six positive patients were <30 years of age. Diagnostic yield in those patients was 31 % (5 patients from 16 patients), whereas in patients >30 years of age was significantly lower (4 %, 1 patient from 25 patients), (p=0.007).

Sex of the patients did not affect the yield of A-HUT (10 % female vs 25 % male p=0.33).

The degree of sinus slowing, maximal R-R interval during complete AV block, total duration of AV block episode during adenosine reaction did not differ between A-HUT positive and A-HUT negative patients nor between NTG-HUT positive and NTG-HUT negative patients (Tab. 1).

Discussion

Adenosine has properties that make it a alternative pharmacologic agent in provocation of vasovagal syncope in susceptible individuals and can be used in diagnostics of syncope of unexplained origin. A diagnostic yield similar to isoproterenol stimulated HUT was reported (6) and it was suggested as a good alternative to routine tilt testing.

Our results do not support this finding. In our study was the diagnostic yield of adenosine-stimulated HUT significantly lower than diagnostic yield of nitroglycerine-stimulated HUT.

Mittal et al (16) showed that diagnostic yield of adenosine tilt testing is age-dependent – 41 % for subjects younger than 40 years, 15 % for subjects between the ages of 41 and 64 years, and 5 % for those at least 65 years old. Overal diagnostic yield was 18 %. Using a group of volunteers with no history of syncope they were able to determine specificity of adenosine tilt testing. A-HUT was negative in all subjects form healthy control group, thus the specificity of the test was 100 %. Our results are also comparable with these results showing diagnostic yield about 12 %.

These findings have significant clinical implications because in a heterogeneous population referred for tilt testing to evaluate unexplained presyncope and/or syncope, a single bolus dose of adenosine can provide a positive yield in <5 minutes.

In association with NTG-HUT, it can make a efficient tilt test protocol. It was shown that nitrate stimulated tilt testing, without a preceding passive tilt phase, and limited to a test duration of 15 minutes, provides an equally accurate, sensitive, and specific method to provoke vasovagal reactions than conventional tilt testing with passive phase prior to pharamocologic stimulation (17). Patients can initially undergo carotid sinus massage in supine and upright position, folowing with adenosine tilt testing (with a weight-adjusted dose of adenosine). A positive adenosine tilt test would obviate further testing, providing a substantial time savings for the physician and patient. Patients with a negative adenosine tilt test would then undergo a 15-minute NTG tilt phase. Compared with current clinical tilt test protocols that use an initial drug-free tilt test followed by pharmacological provocation with NTG, this protocol may offer a more efficient method for diagnosing neurally mediated syncope.

Occurrence of AV block and degree of SA slowing showed no differences between A-HUT positive and negative patients. This result is comparable with shown report, that in patients with adenosine-sensitive syncope (by ATP test), the mechanism of syncope is heterogeneous (11). The lenght of the asystolic pause caused by adenosine seems not to be helpful in diagnostics of neurally mediated syncope. They fulfilled positivity criteria also for ATP (taking into account that instead of ATP adenosine was used in our study). In these patients vasodepressor reaction was observed in the later phase of tilt testing. They could be classified as patients with adenosine-sensitive syncope (based on po-

sivitiy of ATP test) or vasovagal syncope (based on posivity of HUT). They probably represent an overlap between two diagnostic entities. Although clinical characteristics of adenosine sensitive and vasovagal syncope are different they share good prognosis even without any therapy. Thus, from the practical point of view is the exact classification of the syncope in these "overlap" patients of little value. We classified them as vasoval because symptoms identical with spontaneous syncope were associated with neurally nediated syncope.

Adenosine tilt test is a safe procedure and the rate of complications is very low. The presence of prolonged asystole during a positive response cannot be considered a complication, since this is an endpoint of the test.

Study limitations

In neuraly mediated syncope there is no diagnostic gold standard against which other diagnostic tests may be compared; therefore, it is not possible to determine the actual sensitivity and specificity of adenosine test.

The results of the study can be influences by the relatively small number of patients, larger studies are needed.

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Abbreviations: HUT – head-up tilt test, NTG – nitroglycerine, NTG-HUT – Nitroglycerin stimulated head-up tilt test, A-HUT – Adenosine stimulated head-up tilt test, HR – heart rate, AV – atrioventricular, AVB – atrioventricular block, SA – sinoatrial, IV – intravenous, ATP – adenosine triphosphate, RBBB – right bundle brunch block, ESC – European Society of Cardiology.