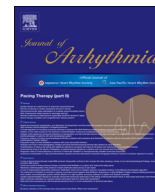




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## Original Article

# Characteristics of head-up tilt testing with additional adenosine compared with head-up tilt testing with isoproterenol and isosorbide dinitrate



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## ABSTRACT

**Background:** Head-up tilt (HUT) testing is used to establish the diagnosis of neurally mediated syncope (NMS). Adenosine administration during HUT testing is useful for inducing NMS. However, no comparison between adenosine HUT testing and HUT testing using other drugs has been reported. The purpose of this study was to investigate the clinical usefulness of adenosine compared with isoproterenol (ISP) and isosorbide (ISDN) during HUT testing.

**Methods:** The subjects comprised 103 consecutive patients with unexplained syncope who underwent adenosine and isoproterenol (ISP) HUT tests following a negative response in a drug-free HUT test. Subjects were first tilted upright at an 80° angle for 30 min and shown to have a negative response in drug-free HUT test. Subsequently, a continuous bolus of 0.1- or 0.2-mg/kg adenosine was administered while the subjects remained upright and were observed for 5 min (adenosine HUT test). Next, they were tilted upright for 15 min during a continuous infusion of 0.01–0.02 mg/kg min ISP (ISP HUT test). Lastly, they were tilted upright for 15 min after 1.25-mg ISDN infusion (ISDN HUT test).

**Results:** The diagnostic yield of the adenosine HUT test was 18.1% (18/99) and that of the ISP HUT test was 6.0% (6/99;  $p = \text{N.S.}$ ). Sixty-one of 99 patients underwent ISDN HUT testing, and 17 patients had a positive response. The diagnostic yield of the adenosine HUT test was 14.7% (9/61) and that of ISDN HUT test was 27.8% ( $p < 0.05$ ). Five patients had positive responses in both adenosine and ISDN HUT tests. Conversely, 4 patients had a positive response in the adenosine HUT test and a negative response in the ISDN HUT test.

**Conclusion:** The adenosine HUT test was effective in the diagnosis of NMS and is useful as the ISP HUT test for inducing NMS. The diagnostic yield of the adenosine HUT test was not higher than that of the ISDN HUT test. However, the adenosine HUT test took only a few minutes and induced NMS in some of the patients in whom NMS was not induced by the ISDN HUT test. Therefore, performing adenosine HUT testing is worthwhile.

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## 1. Introduction

Head-up tilt (HUT) testing has become a widely accepted diagnostic tool for the evaluation of neurally mediated syncope (NMS), which is a major cause of unexplained syncope [1–4]. However, a drug-free HUT test has a low diagnostic yield. HUT testing using isoproterenol (ISP) and isosorbide dinitrate (ISDN) has higher diagnostic yields than drug-free HUT testing but requires more time. ISP HUT testing requires continuous infusion

of ISP and titration to heart rate before HUT testing. However, this protocol is hampered by suboptimal specificity [5]. In addition, ISDN has been the most popular provocation agent for HUT testing. A common protocol of ISDN HUT testing consists of a 15-min HUT test after administration of ISDN. However, there is some discrepancy within the literature regarding the specificity of the ISDN HUT test [6–12]. The administration of exogenous adenosine triphosphate has various effects such as a vasodilatory effect, a depressive effect of atrioventricular (AV) node activity, and a sympathoexcitatory effect via baroreflex and peripheral chemoreceptor activation. Adenosine has been proposed to be an endogenous modulator of NMS [13]. Recently, it has been reported that adenosine is useful in eliciting NMS [13,14]. The purpose of

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this study was to investigate the clinical usefulness of adenosine compared to ISP and ISDN during HUT testing in a Japanese population.

## 2. Materials and methods

### 2.1. Subjects

From January 2006 to March 2010, we prospectively evaluated 103 consecutive patients who underwent adenosine HUT and ISP HUT tests following a negative drug-free HUT to evaluate unexplained presyncope or syncope.

### 2.2. Study protocol

All the patients were evaluated in the fasting state after informed written consent for HUT testing and participation in the study was obtained. An intravenous line and an arterial line were placed in one arm. The patients were monitored via the CardioLab electrophysiology system (GE Healthcare, Milwaukee, Wisconsin, USA), which permitted continuous heart rate and blood pressure monitoring. Measurements of baseline heart rate and blood pressure were obtained during a 5-min period in the supine position. All HUT tests were performed at a tilt angle of 80° on a tilt table with footboard support for 30 min (HUT test alone). If patients had a negative response in the HUT test alone, they were continuously and immediately administered a 0.1- to 0.2-mg/kg bolus of adenosine while being maintained in an upright position under observation for up to 5 min (adenosine HUT). An appropriate adenosine effect was defined by a decrease in sinus heart rate (< 20%) compared with baseline or transient AV block. Following resolution of sinus bradycardia and/or AV block, all the subjects developed a reflex sinus tachycardia. A positive response in adenosine HUT was defined as an NMS response occurring after sinus bradycardia and/or AV block. In this study, an NMS response that occurred during sinus bradycardia and/or AV block was excluded (15). Second, if HUT alone was negative, HUT with ISP infusion was performed for 15 min after a rest period of 15 min (ISP HUT test). ISP (0.1–0.2 µg/min) was infused to increase the resting heart rate by 20%. The patient was in an upright position with continuous ISP infusion for 15 min. Third, if the ISP HUT test result was negative, HUT testing with ISDN administration was performed for 15 min after a second rest period of 15 min (ISDN HUT test). The patient was administered a bolus of 1.25-mg ISDN while in a supine position. After blood pressure and heart rate were continuously monitored for 5 min, the patients were returned to the upright position for 15 min (Fig. 1).

### 2.3. Definitions

The positive end point of HUT was presyncope and syncope accompanied by relative bradycardia ( $\leq 40$  bpm) and/or hypotension (systolic blood pressure  $\leq 70$  mmHg) following an observation period in the upright position. In patients undergoing additional adenosine HUT test, the test was considered positive only when syncope occurred after the onset of temporal sinus tachycardia. The patients in whom syncope occurred during the initial period of adenosine-induced sinus slowing and/or AV block (indeterminate) were excluded. All other results were considered negative (Fig. 2).

### 2.4. Statistical analysis

All continuous variables were expressed as mean  $\pm$  SD. Group comparisons of dichotomous variables were evaluated by the use

of chi-square test. Group comparisons of continuous variables were evaluated by the use of Student's *t* test and one-way analysis of variance. Where there was a difference in the means, post hoc analysis using Scheffe's test was used to determine which means differed. For all the comparisons,  $p < 0.05$  was considered statistically significant.

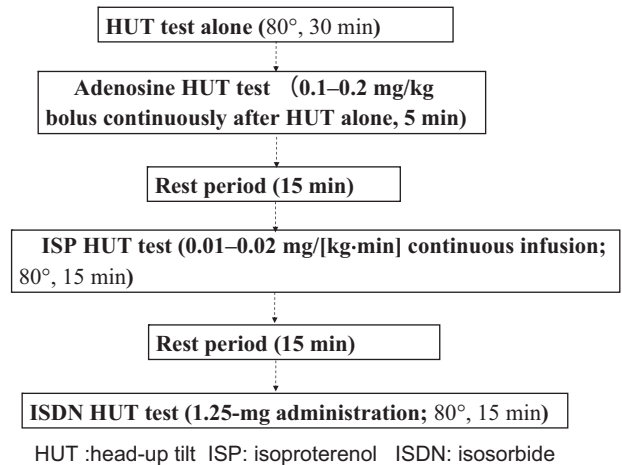


Fig. 1. Study protocol.

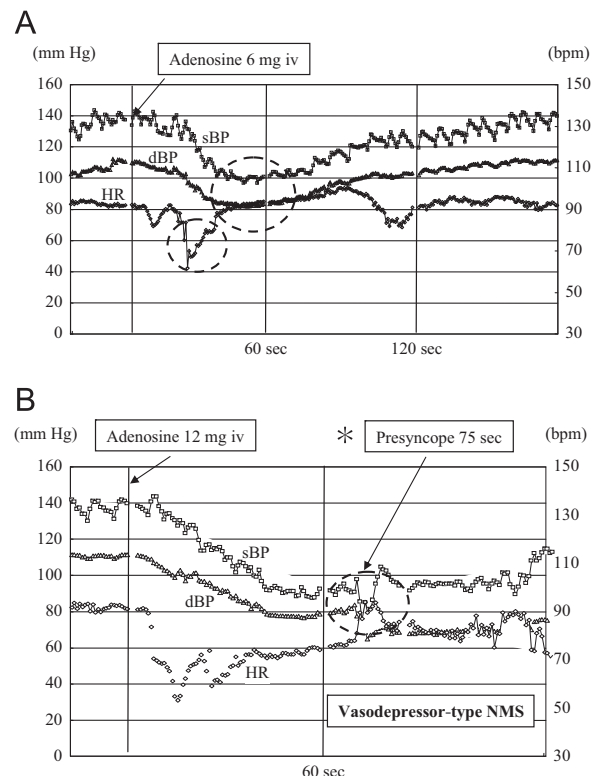


Fig. 2. (A) Negative adenosine tilt test result (normal response). (B) Positive adenosine tilt test result. Shown in each panel on the top, middle, and bottom are systolic pressure (sBP), diastolic pressure (dBP), and heart rate (HR), respectively. (A) After a 6-mg adenosine infusion, the patient developed transient atrioventricular block, which was associated with hypotension. The atrioventricular block resolved in 60 s, and the blood pressure returned to baseline. No subsequent syncope developed. (B) After the temporal atrioventricular block and hypotension developed and was subsequently resolved, the patient experienced progressive sinus slowing and HR hypotension that resulted in presyncope (\*).

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