Usefulness of Head-up Tilt Test in the Evaluation and Management of Unexplained Syncope or Pre-syncope

Ber-Ren Fang, MD, and Li-Tang Kuo, MD

SUMMARY

This study included 87 consecutive patients with unexplained syncope or pre-syncope who had undergone the head-up tilt (HUT) test with concomitant isoproterenol infusion. A positive response was defined as development of syncope or pre-syncope in association with substantial hypotension (decline of systolic blood pressure ≥ 20 mmHg). Coronary artery spasm was suggested from the clinical symptoms and electrocardiographic findings in 1 patient (1 / 87 = 1.1%). Intolerance to isoproterenol infusion was noted in 8 cases (8 / 87 = 9%). Of the 78 patients who completed the study, 73 showed positive responses (73 / 78 = 94%). (baseline systolic blood pressure = 125 ± 23 mmHg vs endpoint systolic blood pressure = 76 ± 11 mmHg, \( p < 0.05 \); baseline heart rate = 73 ± 14 beats per minute vs endpoint HR = 80 ± 24 beats per minute, \( p < 0.05 \)). In 73 patients who showed positive responses, the systolic blood pressure (SBP) and heart rate (HR) returned to a safe level at 2 minutes when the patients were returned to a supine position (post-study 2 minutes SBP = 124 ± 18 mmHg vs baseline SBP = 125 ± 23 mmHg, \( p = \text{NS} \); post-study 2 minutes HR = 82 ± 18 beats per minute vs baseline HR = 73 ± 14 beats per minute, \( p < 0.05 \)). All 73 patients with a positive HUT test received Atenolol therapy (50 mg daily). Only 35 of these 73 patients took Atenolol regularly and had a repeat HUT test. After atenolol therapy, persistent positive responses were observed in 19 cases (19 / 35 = 54%) and negative responses were noted in 16 cases (16 / 35 = 46%). The mean dosage of isoproterenol needed to provoke a positive HUT test in 19 patients who had received Atenolol therapy and had a positive repeat HUT test was 2.3 ± 1.2 \( \mu \)g / min at baseline and 3.5 ± 0.9 \( \mu \)g / min for post-Atenolol therapy (\( p < 0.001 \)). Sixteen patients with a negative repeat HUT test were treated continuously with Atenolol and followed for a mean period of 13 ± 11 months (range, 1-34 months). All 16 patients were free of syncope or pre-syncope during the period of follow up. In conclusion, the HUT test is mostly well tolerated and safe, even though the test has a low rate of adverse effects. Atenolol is effective for the prevention of provoked or spontaneous recurrent syncope or pre-syncope. (Jpn Heart J 2000; 41: 623-631)

Key words: Head-up tilt test, Unexplained syncope, Atenolol
SYNCOPE is a common medical problem, accounting for 3% of emergency department visits and 6% of general medical admissions. The cause of syncope remains undetermined in about 25% of patients despite extensive diagnostic work-up. In 1986 Kenny, et al. first described the clinical usefulness of the head-up tilt (HUT) test for the diagnosis of neurally-mediated (N-M) syncope. Since then, the HUT test has been used extensively to diagnose N-M syncope and to assess the efficacy of therapeutic interventions. The cause of hypotension-bradycardia in patients with N-M syncope is not fully understood, but may be triggered by increased activity of ventricular mechanoreceptors secondary to enhanced sympathetic tone and empty left ventricular cavity. Thus, we postulate that beta-blockers may be effective at preventing the occurrence of N-M syncope. Accordingly, we conducted this study to assess the efficacy of Atenolol (a beta-blocker) for the treatment of N-M syncope by repeating the HUT test in patients with unexplained syncope or pre-syncope who had a positive HUT test. We also evaluated the possible adverse effects and safety of the HUT test as well as the patients' tolerance to the test.

MATERIALS AND METHODS

This study included 87 consecutive patients with unexplained syncope or pre-syncope who had undergone the HUT test with concomitant isoproterenol infusion. There were 37 males and 50 females. Their ages ranged from 12 to 82 (mean: 48 ± 18). Informed consent was obtained from each patient after they were given a full explanation of the procedure. The study was approved by the institutional review committee.

Definition of terms: Syncope is defined as a transient loss of consciousness and postural tone. Pre-syncope is defined as a transient loss of postural tone without a loss of consciousness. Unexplained syncope (presumably diagnosed as neurally-mediated syncope) is diagnosed in such patients on clinical grounds if there is no evidence of structural heart disease, arrhythmia or neurologic disease by clinical cardiac and neurologic evaluation, including 12-lead electrocardiography, 24 hour Holter monitoring, two-dimensional echocardiogram and electroencephalogram (if suggested). Intolerance to isoproterenol infusion is recognized when severe headache, nausea, or precordial chest pain develops during isoproterenol infusion and the participants request termination of the test.

Head-up tilt test protocol: All cardioactive drugs were withdrawn for at least 5 half-lives prior to the study. The HUT test was performed after 6 to 8 hours of fasting. The patient was positioned on a motorized tilt table with a foot board for weight bearing and supported by a loose belt across
the torso. The blood pressure (BP) was recorded every 2 minutes from the brachial artery with an automatic sphygomanometer and a continuous electrocardiographic rhythm monitor was performed throughout the test. At first, the patient was positioned in the supine position for 5 minutes for baseline measurement of both BP and HR. The patient was then tilted at an angle of 80 degrees for 10 minutes. If no syncope or pre-syncope occurred, the patient was lowered to the supine position and an intravenous isoproterenol infusion initiated at successive incremental dosages of 1 µg / minute, 2 µg / minute and 4 µg / minute. During each step, the patient was lowered to the supine position for 5 minutes, then tilted for a period of 10 minutes. If a positive response occurred during any step of the protocol, the patient was lowered to the supine position for a period of 10 minutes of post study data acquisition.

**Definition of positive response:** A positive response was defined as the development of syncope or pre-syncope in association with substantial hypotension (decline of systolic BP ≥ 20 mmHg) with or without brady-cardia.

**Patterns of positive response:** Vasodepressor type: only hypotension was noted at the moment of syncope or pre-syncope. Mixed type: both hypotension and bradycardia (< 35 sinus beats per minute) or junctional rhythm were noted at the moment of syncope or pre-syncope.

**Statistical methods:** Data are expressed as the mean ± SD. Continuous variables were compared by Student's *t* test. Comparison among three or more groups of variables was analyzed by one-way analysis of variance. Time to a positive response and the isoproterenol dosage needed to provoke a positive HUT test in baseline and after Atenolol therapy were compared by Wilcoxon’s signed rank test. A *p* value < 0.05 was considered statistically significant.

**RESULTS**

Of 87 patients who had undergone the HUT test, coronary artery spasm was suggested from the clinical symptoms and electrocardiographic findings in 1 patient (1.1%, 1 / 87), and intolerance to isoproterenol infusion was observed in 8 patients (9%, 8 / 87). Of the 78 patients who completed the study, 73 (73 / 78 = 94%) showed a positive response (vasodepressor type, *n* = 46; mixed type, *n* = 27). The BP and HR at baseline, endpoint, and post-study 1 minute, 2 minutes, and 4 minutes are shown in Figure 1 (left upper and lower panels).

**Isoproterenol dosage needed to provoke a positive HUT test:** Of 73 patients
who showed a positive response, 1 patient did not need isoproterenol, 8 needed 1 µg / min isoproterenol, 34 needed 2 µg / min isoproterenol, and 30 needed 4 µg / min isoproterenol to provoke a positive HUT test (Figure 2).

**Treatment with Atenolol and repeat HUT test:** Of the 73 patients with a positive HUT test, all received Atenolol 50 mg / day, but only 35 patients received medication regularly and had a repeat HUT test at least 10 days after treatment. Of these 35 patients, 19 showed a positive response during the repeat HUT test, while 16 had a negative response. The BP and HR during the repeat HUT test in these 16 patients are shown in the right upper and lower panels in Figure 1 (endpoint = at equivalent situation that causes a positive response in baseline study). In contrast to the depressed SBP (Figure 1 left upper panel) and only slightly increased HR (Figure 1 left lower panel) of positive HUT patients at endpoint compared to the baseline, in successfully treated patients, the SBP remained unchanged (Figure 1, right upper panel), and HR markedly increased (Figure 1, right lower panel) at the endpoint compared to the baseline, indicating the beneficial effects of sympathetic nerve blockade on the hemodynamics of the patients.

**Isoproterenol dosage needed to provoke positive HUT test in 19 patients who had received Atenolol therapy and had positive repeat HUT test:** The mean dosage of isoproterenol needed to provoke a positive HUT test in these 19 patients was 2.3 ± 1.2 µg / min at baseline and 3.5 ± 0.9 µg / min post-Atenolol therapy (p < 0.001) (Figure 3).

**Time to develop a positive HUT test in 73 patients and in 19 patients who had received Atenolol therapy and had a positive repeat HUT test:** The mean time to develop a positive HUT test in 73 patients was 4.3 ± 2.9 minutes. The mean time to develop a positive HUT test in the 19 patients who had received Atenolol therapy and had a positive repeat HUT test was 5.5 ± 3.4 minutes at baseline and 4.1 ± 3.0 minutes for post-Atenolol therapy (p = NS).

**Follow-up data:** Of the 35 patients who received Atenolol therapy and had a repeat HUT test, 16 showed a negative response during the repeat HUT test. These 16 patients were followed for a mean period of 13 ± 11 months (range, 1-34 months). All 16 patients were free of syncope or pre-syncope during the follow-up period. Each of the 19 patients with a persistent HUT positive test after Atenolol therapy was treated with disopyramide instead of Atenolol after the repeat HUT test.
DISCUSSION

Recurrent unexplained syncope is a challenging clinical problem, and the cause remains elusive in many patients despite extensive diagnostic evaluations. In recent years, the HUT test has been widely used to evaluate the susceptibility to hypotension and/or bradycardia in these patients. Two types of protocol have been used, one is a passive HUT test, the other is the addition of isoproterenol infusion in the HUT test. Studies of the passive tilt test show a positive response rate of 26% to 75%. The rate of positive response for the passive tilt test was 1.3% (1/78) in the present study. The discrepancy between the positive response rates of the present study and above mentioned studies may be related to the different protocols used. In the above mentioned studies, HUT to 60 degrees for a
Figure 2. Isoproterenol dosage needed to provoke positive HUT test in 73 patients with unexplained syncope or pre-syncope.

Figure 3. Isoproterenol dosage needed to provoke positive baseline HUT test (before Atenolol therapy) and to provoke positive repeat HUT test (after Atenolol therapy) in 19 patients who had received Atenolol therapy and showed a positive repeat HUT test.
duration of 60 minutes was used, while in our protocol, HUT to 80 degrees for a duration of 10 minutes was used. Some studies have observed that sympathetic activity increased markedly before the onset of hypotension and/or bradycardia during the passive HUT test. Thus, the concept that the addition of isoproterenol infusion during the HUT test might help increase the sensitivity of the test emerged. In 1989 Almquist, et al. first used isoproterenol during the HUT test. In their study, only 5 of 24 patients with idiopathic syncope had a positive response during a passive HUT test. However, after a retilt with a concomitant isoproterenol infusion, an additional 9 patients experienced a positive response. Subsequently, many reports showed similar findings. Some HUT protocols using isoproterenol show a positive rate of 75% to 87%. The rate of positive response increased to 94% with the addition of isoproterenol in the tilt test in the present study. However, the addition of isoproterenol in the tilt test may entail a risk of inducing coronary artery spasm in some participants. Our study showed a 1.1% (1/87) incidence of inducing suspected coronary artery spasm manifested as chest pain and ST segment elevation. This finding is similar to that reported by other investigators (1.1% incidence, 3/273). Thus, the HUT test with isoproterenol may be dangerous to undiagnosed coronary artery disease and it should be performed cautiously in patients with a history of coronary artery disease. Furthermore, some participants may exhibit intolerance to isoproterenol infusion during a HUT test. The symptoms of intolerance to isoproterenol infusion include severe headache, nausea and precordial chest pain. Our study showed 9% (8/87) of participants exhibited intolerance to isoproterenol infusion, and these participants requested termination of the test. This observation is similar to that reported by Kapoor, et al (10% incidence, 2/20).

The angle of tilt and the duration of the tilt portion of the HUT may both influence the rate of positive response. Some studies reporting the time to the development of a positive response found the average time was 30 minutes for a 60-degree tilt and 10 minutes for an 80-degree tilt. Our data showed that the average time to the development of a positive response was 4.3 ± 2.9 min for an 80-degree tilt in 73 patients. The pathophysiologic mechanism of N-M syncope is not fully understood. The postulated mechanism of N-M syncope is as follows: an upright posture leads to pooling of blood in the lower limbs, resulting in decreased venous return. A normal compensatory response increases sympathetic tone presenting as reflex tachycardia, and more forceful contraction of the heart and peripheral vasoconstriction occur. In individuals susceptible to
N-M syncope, however, this forceful contraction, in the setting of a relatively empty ventricle, may stimulate the cardiac mechanoreceptor, with subsequent increased vagal tone and withdrawal of sympathetic tone, resulting in hypotension or bradycardia (or both). Beta-blockers were commonly used in the prevention of recurrence of N-M syncope. The mechanism of action of beta-blockers is not fully understood, but they may diminish cardiac contractility, inhibiting the activation of cardiac mechanoreceptors.

A repeat HUT test after drug treatment has proved to be useful in the evaluation of drug efficacy. A review of recently published data evaluating beta-blockers for the treatment of N-M syncope has shown oral beta-blockers to be effective in 72% of patients with N-M syncope as tested by the repeat HUT test. Our data showed that the efficacy of Atenolol in the prevention of inducible syncope or pre-syncope is 46% (16/35). In addition, our data showed that the mean dosage of isoproterenol needed to provoke a positive HUT test in 19 patients who had received Atenolol and had a positive repeat HUT test was higher after Atenolol therapy than at baseline (3.5 ± 0.9 µg/min, after Atenolol therapy vs 2.3 ± 1.2 µg/min, baseline p < 0.001). Thus, Atenolol still may attenuate the susceptibility to the development of syncope or pre-syncope even though the repeat HUT test still showed a positive response.

Once hypotension and/or bradycardia occur during the HUT test, is it dangerous to the participant? Fortunately, the phenomenon is almost always self-limited when symptoms occur during the HUT test, and resumption of the supine position alone was sufficient to reverse hypotension and bradycardia. Our data have shown that the procedure is safe when hypotension and / or bradycardia occur during the HUT test, and that BP and HR return to a safe level (near baseline level) at 2 minutes when the participants were returned to a supine position.

In conclusion, the HUT test is mostly well tolerated and safe, even though the test has a low rate of adverse effects. Atenolol is effective for the prevention of provoked or spontaneous recurrent syncope or pre-syncope.

References
1. Abi-Samra F, Maloney JD, Fonad-Tarazi FM, Castle LW. The usefulness of head-up tilt testing and hemodynamic investigations in the work-up of syncope of unknown origin. PACE 1988; 11: 1202-14.