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RESEARCH ARTICLE

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Comparison of the active standing test and head-up tilt test for diagnosis of syncope in childhood and adolescence

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Abstract We examined 51 children and adolescents with orthostatic symptoms using two orthostatic tests, the active standing test (the AS test) and head-up tilt test (HUT), and compared circulatory responses, autonomic function in addition to the induction rate of syncope during short-time orthostasis. Syncope was induced in eight patients with both tests, in only six patients with the AS test and in only one patient with HUT. The induction rate was significantly higher with the AS test ($p < 0.0001$). In addition, the AS test is common and daily postural motion and does not require a tilt table. We calculated percent changes in systolic blood pressure at the initial drop (ΔID-SBP), in systolic blood pressure (ΔSBP), in diastolic blood pressure (ΔDBP), in heart rate (ΔHR), component coefficient variation LF/HF (ΔLF/HF) from supine to upright. ΔHR were significantly larger in fainters than in non-fainters with both tests, although there was no difference in ΔSBP and in ΔDBP. In six fainters only with the AS test, ΔHR was significantly larger with the AS test than with HUT. With the AS test ΔID-SBP were correlative with ΔLF/HF, and ΔLF/HF were correlative with ΔHR, whereas these relations were not clear in HUT. These results indicated the AS test caused cardiac sympathetic activation associated with an initial pressure drop, and was more prone to induce syncope with a greater HR increase in some patients. We conclude the AS test is as potential as HUT as a diagnostic test for syncope.

Key words orthostatic intolerance · syncope · orthostatic test · active standing test · child

Introduction

Syncope, the transient loss of consciousness and postural tone, is not an uncommon medical symptom in childhood or adolescence [1, 14]. It has been estimated that 15–47 % of children will have syncopal episodes before reaching adulthood [17, 20]. Etiology varies, and symptoms can be cardiogenic, hematogenic, neurogenic, endocrinogenic and so on, but it is rather rare to find abnormalities based on physical examinations. Recent studies indicated that the majority of syncopal episodes might be caused by neurally mediated mechanisms associated with orthostatic intolerance [20].

For the diagnosis of syncope without organic abnormalities (so-called unexplained syncope), passive head-up tilt test (HUT) has emerged in clinical practice because of the high rate of induction of neurally mediated syncope (NMS). Mechanisms responsible for NMS during HUT are thought to be associated with insufficient venous return to the heart and exaggerated ventricular contraction in combination with tachycardia. Previous reports that isoproterenol infusion during HUT increased the induction rate of NMS [5] may support the

evidence. In order to increase positive response to HUT, invasive procedure (e. g. isoproterenol infusion) and long-time-load (60-minute HUT) are now applied in adults and children. Alehan reported that sensitivity of 10min-HUT for children with unexplained syncope increased to 76.6 % by infusion of isoproterenol while that of 45min-HUT was 48.5 % [3].

According to previous literature, orthostatic tests using gravity include two methods: HUT and the active standing (AS) test. The AS test does not require a tilt table and can be performed by the bedside. Wieling reported that the AS test, taking more common and daily postural motion than HUT, caused dramatic changes in blood pressure and heart rate in the initial phase of standing which clearly explains patient's complaints of orthostatic intolerance [31]. We also found the AS test caused more potent cardioacceleration than HUT in healthy adults [25].

The comparison of induction rate of syncope with the AS test and HUT has not been reported. We set out to determine which test is the more appropriate and efficient method for inducing syncope. We examined children and adolescents with orthostatic symptoms including syncope using both the AS test and HUT and compared the induction rates of syncope/pre-syncope to evaluate which method is adequate for the diagnosis of orthostatic intolerance in children and adolescents. In this comparative study we chose a short-time load because of the clinical usefulness in pediatric practice. Moreover, it is difficult to keep children standing still during the AS test without a body support.

Materials and methods

Materials

Subjects were 51 children and adolescents, comprising 21 boys and 30 girls, ages 6–16 years (mean age, 12.7 ± 2 years) were referred to Osaka Medical College Hospital for further examination of suspected syncope or near-syncope. They also had three or more symptoms of orthostatic intolerance including more than one episode of syncope or near-syncope, dizziness, headache, vertigo, and/or general fatigue for more than one month. History was unremarkable for all subjects. All underwent general physical examinations including neurologic examination, chest X-ray, 12-lead ECG, and blood tests including hematologic analysis, serum electrolytes, serum cortisol and serum thyroxine. No abnormalities were found.

Methods

Finger arterial blood pressure was determined by Finapres (Ohmeda, 2300), based on the volume clamp technique, which provides a continuous arterial pressure curve with analogue signals as well as a beat-to-beat digital display of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) and heart rate (HR). Finger cuff (small, medium or large) was selected according to finger size. Subjects were first laid on a tilt-table, the finger cuff was placed on third right finger, and leads were attached for three-lead ECG. For the AS test, SBP, DBP, MBP and HR were determined for 10 minutes with the patients in the supine posture. Thereafter, subjects actively stood up, maintaining upright posture quietly for 7 minutes. Prior to the AS test subjects were instructed to stand quickly and independently without using the right hand so as not to affect the Finapres recording. All subjects stood within 3–4 seconds. Recordings were made for 7 minutes during active standing, and patients were then returned to the supine position. In cases that syncope or pre-syncope was induced within 7 minutes subjects were immediately returned to the supine position. After subjects lay quietly on the tilt-table for more than 10 minutes, SBP, DBP, MBP and HR were measured again for 10 minutes. The table was then tilted upward 60 degrees within 3–4 seconds, and SBP, DBP, MBP and HR were measured in the upright posture for 7 minutes. As with the AS test in cases that syncope or pre-syncope was induced, subjects were immediately returned to the supine posture. The AS test and HUT were performed in the morning in a soundproof room with the temperature between 23 °C and 25 °C, and subjects did not eat or drink for 2 hours prior to testing. During upright posture, the cuffed finger was always kept at the level of the right atrium by an assistant. All subjects were required to remain quiet without bodily movement in both the supine and upright postures. None had taken medication. In this study we used seven-minutes upright in the orthostatic test according to our previous studies in healthy school children and children with orthostatic intolerance [27, 32].

The research protocol was approved by the Ethical Committee of Osaka Medical College Hospital.

Data analysis

Finger arterial blood pressure and ECG signals were subjected to analogue-to-digital conversion at a sampling frequency of 250 Hz, and the data were on a personal computer (Hewlett Packard ES/12). A signal analysis program [11] was used to provide data automatically on beat-to-beat R-R intervals of the ECG, SBP and DBP. Mean values of SBP, DBP and HR in the supine posture were calculated based on the latter half of the 10-minute recording period and mean values of SBP, DBP and HR per every minute in the upright posture were calculated based on the full 7-minute recording period. Then we calculated percent changes in systolic (ΔSBP), diastolic (ΔDBP) blood pressure and heart rate (ΔHR) every minute from the supine to the upright posture for both tests and percent changes in SBP of initial drop (ΔID-SBP). In the cases of syncope or pre-syncope induction, we only used measurements up to 30 seconds before the onset of syncope or pre-syncope.

In addition we calculated heart rate variability using power spectral analysis during supine and upright posture. R-R interval spectra for the latter half in the supine posture and for 1–4 min in the upright posture were calculated using auto-regressive analysis [11]. Spectral power was partitioned into LF (0.04–0.15 Hz) and HF (0.15–0.49 Hz) power bands. We integrated LF and HF bands and calculated component coefficient variation LF/HF and component coefficient variation HF by using Hayano's method [13]. We also calculated percent changes in component coefficient variation LF/HF (ΔLF/HF) and in component coefficient variation HF (ΔHF) from the supine to the upright posture. This analysis system was completely set up during the study. Thereafter, we applied this and determined heart rate variability in 39 consecutive patients out of 51 patients.

Statistics

The significance of differences was determined with ANOVA. Correlations were determined by linear regression analysis (least square methods). Chi-square analysis was for contingency table data. A p-value of less than 0.05 was considered to indicate significance.

Results

Syncope or pre-syncope induction rate

Syncope or pre-syncope was induced by the AS test in 14 of the 51 patients (27 %, eight boys and six girls). Among these, two patients fainted at min 3 of standing, one at min 4, three at min 5, one at min 6 and seven at min 7. On the other hand, nine patients fainted in HUT (18 %, five boys and four girls). Among these, one patient fainted at min 2 in HUT, two at min 3, two at min 5, one at min 6 and three at min 7 (Table 1). Six patients fainted only in the AS test, but not in HUT as shown in Fig. 1. The induction rate of fainting was significantly higher with the AS test ($p < 0.0001$). The difference between the sexes within each group was not significant. Subjects in whom syncope/pre-syncope was induced in the AS test or HUT were determined as "AS-fainters" or "HUT-fainters," respectively.

Table 1 Fainters and non-fainters with the active standing test and heat-up tilt test

	HUT		
	Fainters	Non-fainters	Total
AS			
Fainters	8	6	14*
Non-fainters	1	36	37
Total	9	42	51

AS the active standing test; *HUT* head-up tilt test
* $p < 0.0001$ (AS vs. HUT)

Comparison of circulatory responses between fainters and non-fainters

Blood pressure and heart rate

In the supine posture there was no significant difference in SBP, DBP and HR between AS-fainters and AS-non-fainters (104 ± 17 vs. 106 ± 17 mmHg for SBP, 53 ± 9 vs. 55 ± 9 mmHg for DBP and 72 ± 13 vs. 78 ± 14 for HR, respectively), and between HUT-fainters and HUT-non-fainters (108 ± 19 vs. 105 ± 12 mmHg for SBP, 55 ± 11 vs. 55 ± 9 mmHg for DBP and 72 ± 15 vs. 77 ± 13 for HR, respectively).

Heart rate variability

The data were available for calculation of heart rate variability with autoregressive analysis in thirty-nine patients. In the supine position, AS-fainters had significantly higher HF of heart rate variability than

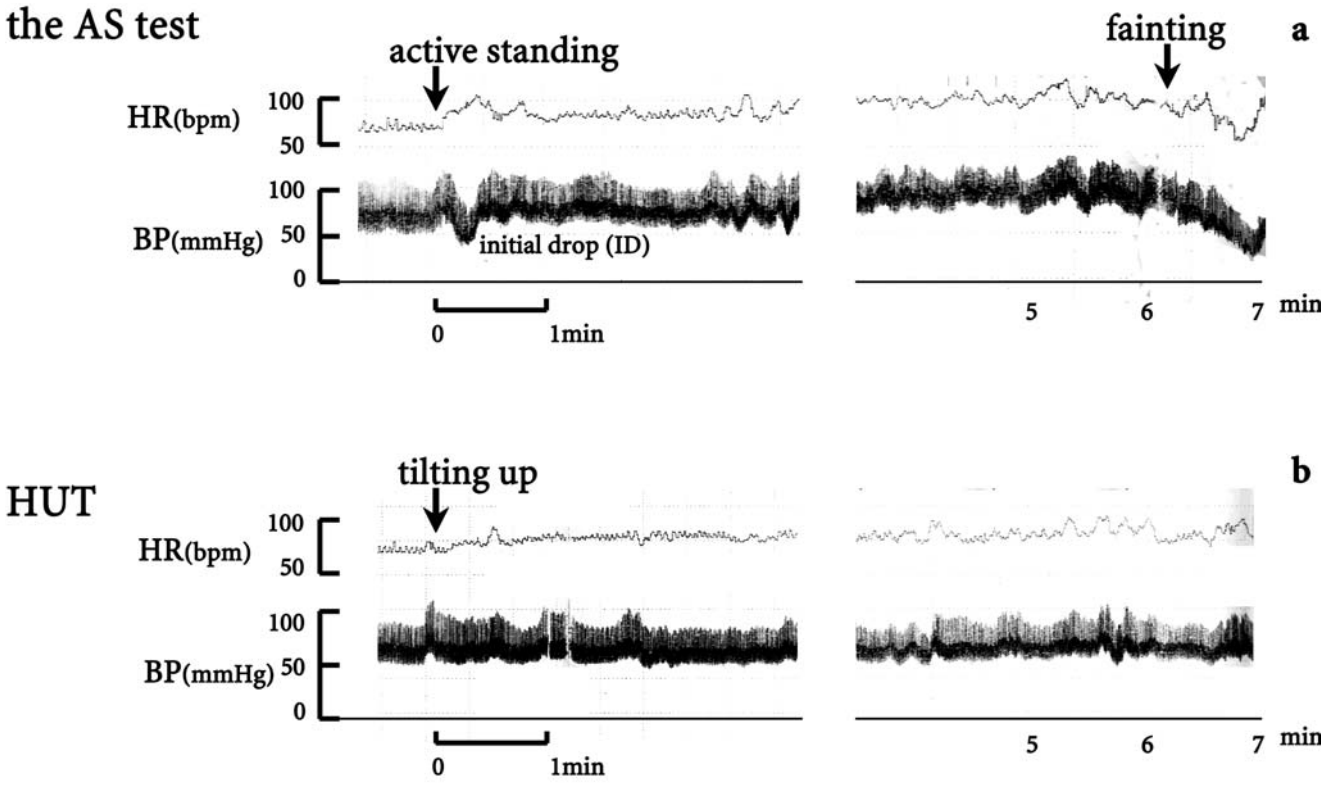

Fig. 1 An original recording of an 11-year-old boy who fainted at min 6 in the active standing test (**a**), and did not faint in head-up tilt (**b**)

AS-non-fainters. LF/HF ratio did not differ between groups (Table 2). There was no significant tendency for LF/HF, ΔLF/HF and ΔHF between fainters and non-fainters in both tests.

Table 2 Component coefficient heart rate variability (%) determined by autoregressive analysis in fainters and non-fainters in the active standing (AS) test

	AS-fainter (n = 9)	AS-non fainter (n = 30)
Supine position		
HF	4.092 ± 1.8*	2.857 ± 1.4
LF/HF	0.909 ± 0.4	1.051 ± 0.4
During standing		
ΔHF	−45.6 ± 25	−32.7 ± 23
ΔLF/HF	133.0 ± 83	103.0 ± 70

HF the power of high frequency band in the supine position; *LF/HF* the power ratio of low frequency/high frequency band in the supine position; *ΔHF* percent change of HF from the supine to the standing position; *ΔLF/HF* percent change of LF/HF from the supine to the standing position
* $p < 0.05$ (AS-fainter vs. AS-non-fainter)

Comparison of circulatory responses during the AS test and HUT

At the onset of posture change a marked transient drop was found during the AS test both in the AS fainters and AS-non-fainters, but not in the HUT test (Figs. 1 and 2).

ΔSBP and ΔDBP between fainters and non-fainters did not differ significantly during the later stage of both orthostatic tests as in Fig. 2. On the other hand, ΔHR was significantly higher in fainters than in non-fainters during both tests. This trend was more marked in the AS test. Six patients who fainted in the AS test but not in HUT had significantly higher ΔHR in the AS test than in HUT (Fig. 3).

In all subjects the AS test caused a significantly larger pressure drop at the initial phase of postural change than HUT did (ΔSBP/ΔDBP, −40 ± 13/−44 ± 17 mmHg vs. −7 ± 15/−2 ± 21 mmHg for the AS test vs. HUT test, respectively, $p < 0.0001$). The average ΔHR in the AS test was significantly higher than that in HUT (ΔHR averaged from min 1 to 7, 37 ± 19 vs. 31 ± 21 beats/min for the AS test vs. HUT test, respectively $p < 0.001$). The average

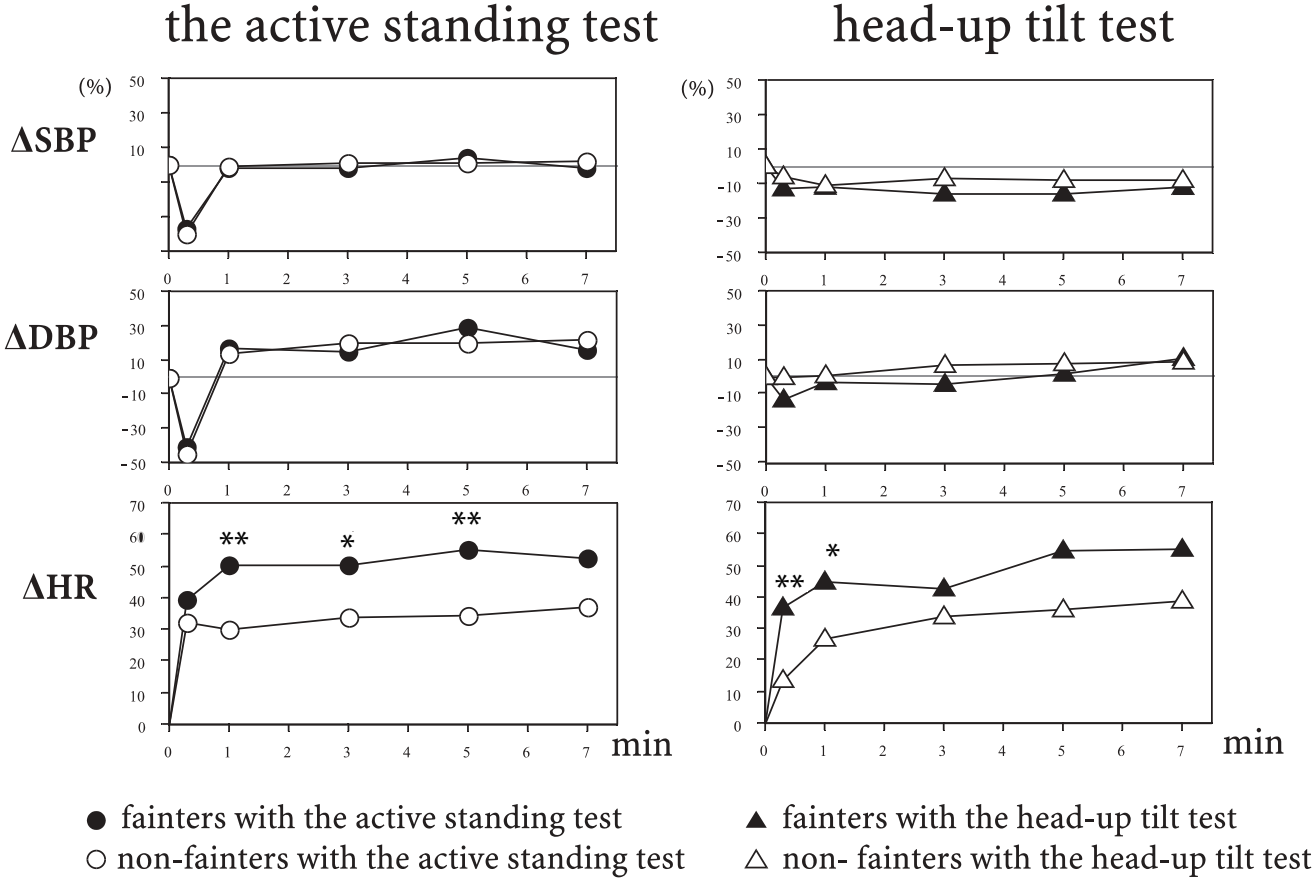

Fig. 2 Percent changes in blood pressure and heart rate after the active standing/tilt up (the comparison of fainters and non fainters). *ΔSBP* percent changes in systolic blood pressure; *ΔDBP* percent changes in diastolic blood pressure; *ΔHR* percent changes in heart rate. Significant differences between fainters and non-fainters are denoted by * ($p < 0.05$) and ** ($p < 0.01$)

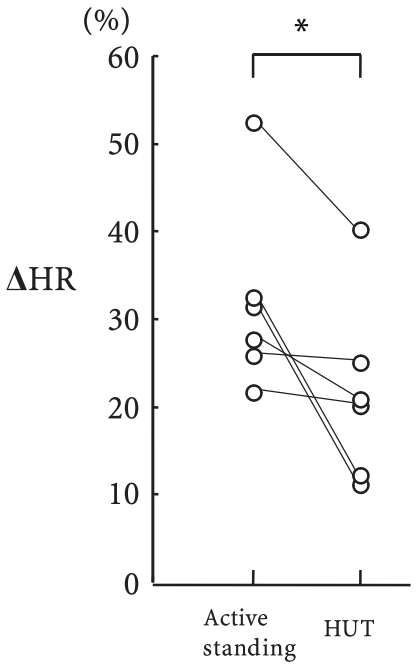

Fig. 3 Heart rate increase by active standing and by head-up tilt (HUT). Increment of heart rate was averaged at every minute until orthostatic maneuvers were over in each patient. Significant differences between the active standing test and head-up tilt test are denoted by * ($p < 0.05$)

ΔSBP in the AS test was significantly higher than that in HUT (averaged ΔSBP/ΔDBP from min 1 to 7, 0 ± 11/18 ± 16 mmHg vs. –7 ± 12/6 ± 16 mmHg for the AS test vs. HUT test, respectively, $p < 0.0001$).

In the AS test ΔHR was significantly correlative with ΔLF/HF and ΔLF/HF was correlative with ΔID-SBP ($p < 0.05$, Fig. 4). However, the relation between heart rate increases, heart rate variability and blood pressure was not observed in HUT.

Discussion

Which is a better orthostatic test, the AS test or HUT?

Two types of orthostatic maneuvers, the AS test and HUT, have been used for the investigation of circulatory control in patients with orthostatic intolerance. HUT has recently been widely accepted for the evaluation of neurally mediated syncope [7] in adult patients probably because of larger blood pooling in the dependent areas caused by a lack of sustained contraction of the leg muscles during HUT. Guidelines on management of syncope presented by the European Society of Cardiology recommend HUT as a diagnostic method [7]. It is also widely used in pediatric practice on the basis of adult studies. As Alehan reported, the average time for development of symptoms of syncope with HUT was about 20 minutes [2–4] and, therefore, 45min-HUT was recommended in syncopal children when isoproterenol is not used.

However, there is no evidence that HUT is a better maneuver than active standing. Ross et al. reported that syncope was induced within 11 minutes of the AS test with 44 % sensitivity [19]. Balaji reported 61 % (100/161) sensitivity by the 20 min AS test [6]. We have summarized the recent studies on HUT and the AS test in childen with syncope (Tables 3 and 4). The positive rate of the AS test and HUT does not seem to be different (mean: 43 % and 47 %, respectively). In the present study, comparing HUT and the AS test, we first reported that the AS test is as potential as HUT as a diagnostic test for syncope. The induction rate of the AS test and HUT was 27 % (14/51) and 18 % (9/51), respectively. The rate is rather low compared with previous studies. This was probably due to a short-time orthostatic load (for 7 minutes) in addition to absence of intravascular catheterization. Sung et al. reported the similar positive rate of active standing (15 min) without catheterization [24]. We understand the longer the tilting, the better the method. Seven-minutes standing in our protocol is rather short, but this does not reduce the importance of this study

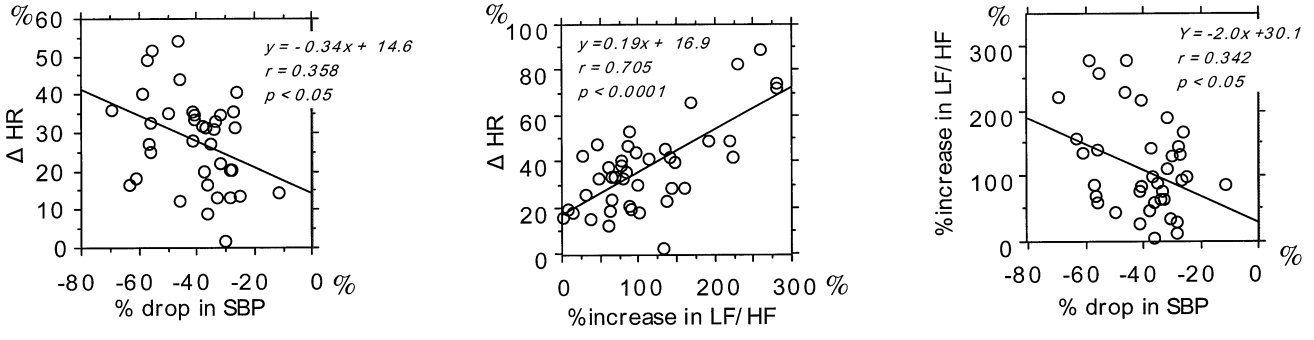

Fig. 4 Correlation of percent changes in component coefficient variation LF/HF from the supine to the upright posture (ΔLF/HF), percent changes in systolic blood pressure at the initial drop with the active standing test (ΔID-SBP) and percent changes in heart rate in the active standing test (ΔHR)

Table 3 Sensitivity and specificity of the active standing test

Investigator	Year	Standing time (min)	Patient (n)	Control (n)	Isoproterenol infusion	Sensitivity (%)	Specificity (%)
Pongiglione, G.	1990	10	20	–	– +	20 60	– –
Ross, B. A.	1991	12	104	–	–	44	–
Perry, J. C.	1991	10	22	–	–	64	–
Balaji, S.	1994	20	162	–	–	61	–
Tanaka, H.	1997	10	54	–	–	30	–
R. Y. Sung	2000	15	32	23	–	31	100
R. Y. Sung	2001	15	23	35	–	35	100

Table 4 Sensitivity and specificity of HUT

Investigator	Year	Tilting angle	Tilting time (min)	Patient (n)	Control (n)	Isoproterenol infusion	Sensitivity (%)	Specificity (%)
Thilenius, O. G.	1991	60	60	35	–	– +	37 43	–
Lerman-Sagie, T.	1991	60	60	14	–	–	43	–
Grubb, B. P.	1992	80	30	30	18	– +	20 50	83 –
Fouad, F. M.	1993	60	20	44	–	–	57	–
O'Marcaigh, A. S.	1994	65	15	27	–	– +	15 55	–
Stewart, J. M.	1996	80	30	29	–	–	59	–
Alehan, D.	1996	60	25 10	20	10	– +	75	90
Alehan, D.	1997	60 60	25 45	30 35	15 15	+ –	77 49	87 93
Brembilla-Perrot, B.	1997	70–80	40	105	–	–	44	–
de Jong de Vos van Steenwijk, C. C.	1997	70–80	5	–	68	–	–	57
Kouakan, C.	1997	60	45	79	–	+	57	–
Rodriguez-Nunez, A.	1997	80	30	25	–	–	76	–
Lewis, D. A.	1997	60–80	30	–	69	–	–	65
Stewart, J. A.	1998	80	40	26	13	–	62	70
Pollono, I.	1998	60	45	243	–	–	11	–
Tercedor, L.	1999	70	30	31	–	–	92	–
R. Y. T. Sung	2000	80	30	32	23	–	41	100
R. Y. T. Sung	2001	80	30	23	35	–	57	100
Moak, J. P.	2002	80	30	23	–	–	52	–

that emphasizes the potential of the AS test. In pediatric practice, a long-time orthostatic test is too stressful for most children to keep quiet on the tilt bed. Moreover, a more than 20-min standing is not realistic in daily life in children. Pediatric researchers, therefore, should make an effort to develop a short, less invasive and less stressful test for syncope. In this respect the AS test, a simpler method (just as a daily motion) without a need for a tilt table, should be verified for its efficacy.

Heart rate increase and syncope

The onset of NMS seems to be associated with a pronounced increase in heart rate during upright posture whereas blood pressure did not differ between fainters and non-fainters in this study. This finding is in line with a number of previous studies reporting greater increases in heart rate in fainters [10, 29]. This is also consistent with the notion that the isoproterenol infusion is used to increase positive rate of syncope during HUT.

Fainters had higher power of HF band of heart rate variability than non-fainters in the supine position

(Table 2). This difference was cancelled and thus causing a higher increase of heart rate while upright. This might be explained by basal predominance of vagal modulation in the fainters.

As shown in Fig. 3, heart rate increase was heightened in the AS test than in HUT (by six beats/min) in six patients who fainted only in the AS test. Compared with HUT, the AS test might have more potent effects on cardioacceleration. We previously reported that the AS test causes higher heart rate increases than HUT in healthy young adults [25]. Sprangers et al. also showed a similar observation [22].

There may be controversy that HUT with the angle of 60 degree was less intensely upright than the AS test. However, the former can logically generate 87 % of 1G, that is, only 13 % less hydrostatic pressure than that in the AS test. This small difference can not totally explain the enhanced increase in heart rate during the AS test mediated through the low pressure baroreflex pathway, because narrowing of pulse pressure, an indicator of blood shift to the lower part of the body, did not differ between the AS test and HUT.

Hemodynamic changes in the initial phase of active standing

Wieling's group and our group separately reported that active standing causes a large initial pressure drop at the onset of standing [22, 28, 31, 32] and this is a large difference compared to passive head-up tilt. Tanaka et al. reported that an initial pressure drop was larger in active standing than in HUT (41 vs. 17 %, respectively), which was caused by a more marked decrease in total peripheral resistance (–58 vs. –16 %) [25]. A precipitous rise in intra-abdominal pressure (43 mm Hg) was observed on uprising only in active standing. These results suggest that active standing causes systemic vasodilatation mediated through cardiopulmonary baroreflexes due to a rapid shift of blood from the splanchnic vessels and calf muscles. Moreover, it is suggested that non-autonomically mediated vasodilatation, i. e., local mechanisms might also be involved [30].

An initial pressure drop is usually found in active standing, and also sometimes in HUT in the severe orthostatic intolerance in adolescents. Recently, Stewart reported initial orthostatic hypotension during HUT (–40 % reduction of SBP). We also observe 30 % initial reduction of SBP by HUT in patients with severe instantaneous orthostatic hypotension. However, this reduction is milder in degree compared with that by active standing (60 %) [21].

Higher heart rate increase in the AS test and its mechanism

We hypothesize that an initial pressure drop at the onset of active standing is a possible mechanism of higher heart rate increase in the AS test. As shown in Fig. 4, heart rate increase in the AS test (ΔHR) was significantly correlative with an initial pressure drop (% drop in SBP), and an initial pressure drop related with component coefficient variation LF/HF increase (% increase in LF/HF). These relations were not found in HUT. This is consistent with our previous study that heart rate increase of active standing was significantly correlated with a change in SBP at initial drop ($r = 0.36$) [26]. These data support the notion that active standing causes a large initial pressure drop at the onset of standing, and this induces rapid vagal withdrawal and sympathetic activation mediated through the baroreflex pathway, resulting in a heart rate rise.

An additional possible mechanism of a heart rate rise during active standing might be a continuing positive chronotropic drive triggered by sustained muscle contraction of the legs, which is less involved during tilting [25].

Why do adolescents faint?

In some adolescents an initial pressure drop is abnormally large, prolonged, and consequently impairs cerebral circulation severely. Dambrink reported two teenagers with a postural dizziness [9] and Tanaka reported 44 cases with instantaneous orthostatic hypotension (INOH) [28]. Surprisingly, 68 % of patients with INOH had a syncopal episode. The episode usually disappeared with growth [9, 32]. This is consistent with the description by Ganzeboom that the peak of syncopal episode is seen around 15 years of age. They found that the triggers of syncope in young adults were warm environment (31 %), prolonged standing (27 %) and pain (25 %), but did not emphasize initial orthostatic dizziness (often associated with a large initial pressure drop). We, therefore, propose the importance of dramatic reduction of blood pressure at the onset of active standing which is associated with the mechanism of syncope.

In this study, adolescent fainters had a higher increase in heart rate during upright posture. This was enhanced by active standing probably due to an abnormally large initial pressure drop associated with the standing motion frequently seen in adolescents. This sequence of circulatory response hardly occurred in HUT with fewer events of syncope. Even in adolescents being in the growth period, however, it is doubtful that the formerly held view of a Bezold-Jarish type reflex is still valid, because the evidence against it is now accumulating. Finally, Kaufmann and Hainsworth properly de-

scribed that "the trigger mechanism for converting vasoconstriction and tachycardia to vasodilation and bradycardia remains elusive but it does seem often to involve central mechanisms, peripheral reflex, or possibly both" [15].

Limitation of the study

In our routine orthostatic test, the AS test is usually first performed, because instantaneous orthostatic hypotension (INOH) [28], a major subset of orthostatic intolerance, is much more easily diagnosed by the AS test than HUT. There is a problem that the crossover design was not taken to compare HUT and the AS test. However, this does not totally reduce the importance of this study. A possible confounding factor influencing the outcome of the repeated tests might be habituation. However, previous studies reported that immediate reproducibility of orthostatic tests (within about 30 minutes from the first test) was 87 % by Chen [8], 82 % by Morillo [16], 91 % by Nakagawa [18]. Repeated orthostatic tests hardly cause habituation. Our results might be valid to some extent, although the crossover design of the AS test and HUT will be needed in the future.

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