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Left Ventricular Dimensions and Autonomic Balance During Head-Up Tilt Differ Between Patients With Isoproterenol-Dependent and Isoproterenol-Independent Neurally Mediated Syncope

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Objectives. **This study sought to elucidate differences in mechanisms of neurally mediated syncope between patients with syncope induced by head-up tilt alone and those requiring isoproterenol infusion to induce syncope during head-up tilt.**

Background. **Some patients with neurally mediated syncope require isoproterenol to induce syncope during head-up tilt (isoproterenol dependent), and others do not (isoproterenol independent). Differences in mechanisms between these two groups have not been well elucidated.**

Methods. **A 60° head-up tilt test was performed in 13 patients with isoproterenol-independent syncope (Group I, mean [±SD] age 28 ± 12 years), 14 patients with isoproterenol-dependent syncope (Group II, mean age 34 ± 14 years) and 20 control subjects without syncope (Group III, mean age 32 ± 12 years). Left ventricular size and contractility were determined by echocardiography, and sympathovagal balance was determined with power spectral analysis of heart rate variability using a maximal entropy method.**

Results. **Group I patients had smaller left ventricular dimensions than Groups II and III during baseline tilt. During head-up tilt with isoproterenol infusion (0.01 to 0.04 μg/kg body weight per min), left ventricular dimensions decreased to the same extent in Groups II and III, but fractional shortening was greater in Group II than in Group III at the end of the tilt. The ratio of low (0.05 to 0.15 Hz) to high frequency (0.15 to 1.0 Hz) component became greater in Group I than in Groups II and III during the last period of baseline tilt. However, the ratio was greater in Group II than in Group III during the last period of the tilt with isoproterenol.**

Conclusions. **Patients with isoproterenol-independent syncope had an exaggerated decrease in left ventricular size and sympathetic predominance preceding syncope during head-up tilt. In contrast, in patients with isoproterenol-dependent syncope, similar changes in autonomic nervous balance were evident only during isoproterenol infusion in addition to head-up tilt.**

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Syncope due to neurally mediated hypotension and bradycardia (i.e., vasovagal syncope) is believed to account for the mechanism of unexplained syncope, especially in patients without apparent structural cardiovascular disease (1,2). Recently, the head-up tilt test has been shown to be a useful tool for the diagnosis of unexplained syncope during the tilt test (1–9). Several observations (2,3,5,6,9) suggest that the hypotension and bradycardia induced by head-up tilt are essentially equivalent to the spontaneous episodes of neurally mediated syncope. However, the exact mechanism of hypotension and bradycardia induced by head-up tilt is not yet well understood, and why the vasovagal reflex occurs during head-up tilt only in susceptible patients is still obscure. Some patients with neurally mediated syncope require isoproterenol infusion to induce syncope (isoproterenol dependent) (1–3,5), whereas others do not (isoproterenol independent) (3,10,11). Differences in the mechanisms of syncope between these two patient groups are still not well understood. Therefore, the present study sought to determine changes in left ventricular size and contractility and in sympathovagal balance in these two groups of patients with neurally mediated syncope and in a group of control subjects.

Methods

Patient selection. Patients who had been referred for diagnosis of unexplained syncope were included in the study if they met the following criteria: 1) at least one syncopal episode, the cause of which remained uncertain despite a careful history, comprehensive physical examination, neurologic evaluation, 12-lead electrocardiogram (ECG), 24-h ambulatory Holter monitoring and echocardiography; 2) no history of drug use known to cause orthostatic hypotension; 3) technically optimal echocardiographic images; 4) normal left ventricular wall motion evaluated by echocardiography; 5) no evidence of

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Table 1. Clinical Characteristics of Study Subjects

	Group I (n = 13)	Group II (n = 14)	Group III (n = 20)
Age (yr)	28 ± 12	34 ± 14	32 ± 12
Gender (M/F)	11/2	10/4	11/9
Syncopal episodes	15 ± 10*	5 ± 9	
Duration of symptoms (mo)	106 ± 77†	22 ± 44	
Associated cardiac disease			
VPC	3	3	3
2nd-degree AV block	2	2	4
PAF, PSVT	2		3
MVP	2	1	
HT		1	3
Head-up tilt test			
Duration (min)	9.6 ± 4.0	8.4 ± 4.2	
IP dose (ng/kg per min)		19 ± 7	21 ± 8
Response type			
Vasodepressor	4	5	
Mixed	9	9	

*$p < 0.05$, †$p < 0.01$ versus Group II. Data presented are mean value ± SD or number of patients. AV = atrioventricular; F = female; Group I = positive response during baseline head-up tilt; Group II = positive response only during isoproterenol infusion in addition to head-up tilt; Group III = control subjects; HT = hypertension; IP = isoproterenol; M = male; MVP = mitral valve prolapse; PAF = paroxysmal atrial fibrillation; PSVT = paroxysmal supraventricular tachycardia; VPC = ventricular premature contraction.

diabetes mellitus or neuropathy; 6) absence of frequent (≥5 beats/15 min) atrial or ventricular premature beats and atrioventricular (AV) conduction block during the study protocol (Table 1).

Of 35 consecutive patients with unexplained syncope, 27 met these criteria (21 men, 6 women; mean [±SD] age 31 ± 13 years, range 14 to 60). Eight patients were excluded from the study because of suboptimal quality of echocardiographic images in four, frequent atrial premature beats in two and Wenckebach AV block during the study protocol in two. The 27 patients were classified into two groups: 13 with a positive response during baseline tilt alone (Group I) and 14 with a positive response only with the addition of intravenous isoproterenol infusion (Group II). The day after the first head-up tilt test, the tilt test was repeated in 8 of 13 patients in Group I and 7 of 14 patients in Group II. The control group (Group III) included 20 subjects with no syncopal episodes and normal cardiac structure and function by conventional echocardiographic criteria with technically optimal images (11 men, 9 women; mean age 32 ± 12 years, range 13 to 67) (Table 1). Associated cardiovascular abnormalities for Group III patients are presented in Table 1.

Head-up tilt test. Written informed consent was obtained from each subject. Head-up tilt test was performed in the fasting state (≥4 h) after withdrawal of all cardioactive medications at least 5 half-lives before the study. After 30-min rest in the supine position, each subject was tilted to a 60° upright position for 15 min, with a footboard used for weight bearing (5,10–13). Blood pressure was determined by a cuff sphygmomanometer before and every 1 min after initiation of the tilt test. Mean blood pressure was calculated by adding one third of the pulse pressure to the diastolic pressure. If the results of the baseline head-up tilt test were negative (see later), the patient was returned to the supine position, and isoproterenol was infused intravenously at a rate of 0.01 to 0.04 μg/kg body weight per min in Groups II and III. The infusion rate was gradually increased until a 20% increase in heart rate was achieved, as in the previous study by Sra et al. (14). The head-up tilt was then repeated. A response was considered positive if significant arterial hypotension (decrease in mean blood pressure ≥20 mm Hg) in association with syncope or presyncope was encountered.

Electrocardiographic lead II was monitored throughout the study and recorded on a magnetic frequency modulation tape for later analysis.

Echocardiographic evaluation. Two-dimensional targeted echocardiograms of the left ventricular cavity were recorded using a 3.75-MHz transducer (Toshiba SSH-140A). Two-dimensional echocardiography can provide reliable estimates of left ventricular volume using the short-axis Simpson rule or area-length method (15). However, during the head-up tilt, multiple cross-sectional areas between the apex and base of the left ventricular cavity could not be determined sufficiently, and optimal echocardiographic images of the apical view were difficult to obtain. Therefore, left ventricular dimensions from the parasternal long-axis view were used to estimate changes in left ventricular volume because left ventricular wall motion abnormalities were not present, and global left ventricular function appeared normal in the study groups. Two-dimensional echocardiograms were recorded, along with a phonocardiogram in the supine position, within 1 min after the initiation of head-up tilt and every 1 or 2 min thereafter until the end of head-up tilt or the onset of a positive response. Left ventricular end-diastolic and end-systolic dimensions were determined using M-mode echocardiography at the peak of the R wave of the QRS complex and at the initial component of the second heart sound, respectively. Ventricular dimensions were determined independently by two observers without knowledge of the result of the tilt test. Mean values of two observers were determined to represent each subject. Percent left ventricular fractional shortening was calculated as follows: Fractional shortening (%) = [(End-diastolic dimension − End-systolic dimension)/End-diastolic dimension] × 100.

Heart rate spectral analysis. Assessment of heart rate variability provides a simple noninvasive means for quantitative analysis of cardiac sympathovagal tone (16–18). Heart rate variability was determined in the supine position and during the last 200 beats until 1 min before the end of tilt in 10 Group I patients (mean age 30 ± 15 years), 11 Group II patients (mean age 31 ± 13 years) and 14 Group III subjects (mean age 30 ± 14 years). Off-line analysis was performed on a microcomputer (NEC PC-9801 RX). The ECG recordings were played back from the frequency modulation tape and input into the R wave detection differentiator to convert the R wave to the R wave trigger pulse. Then, RR intervals were measured

Table 2. Blood Pressure and Heart Rate During Head-Up Tilt Alone and Head-Up Tilt With Isoproterenol Infusion (mean ± SD)

	Baseline HUT				HUT With Isoproterenol			
	Supine Position	1 min After Start of HUT	1 or 2 min Before End of HUT	End of HUT	Supine Position	1 min After Start of HUT	1 or 2 min Before End of HUT	End of HUT
BP (mm Hg)								
Group I	75 ± 6	72 ± 7	58 ± 10*†	45 ± 12*†				
Group II	82 ± 12	84 ± 13	83 ± 13	83 ± 12	83 ± 10	83 ± 10	70 ± 16‡§	54 ± 11†‡
Group III	80 ± 15	78 ± 15	77 ± 12	79 ± 13	76 ± 13	78 ± 11	79 ± 14	79 ± 13
HR (beats/min)								
Group I	58 ± 5	81 ± 12*	83 ± 20*	71 ± 23				
Group II	66 ± 8‖	80 ± 16*	85 ± 15*	86 ± 15†	106 ± 20	112 ± 19	109 ± 20	94 ± 24§
Group III	66 ± 12‖	79 ± 16*	83 ± 16*	85 ± 20†	108 ± 22	115 ± 23	128 ± 24*†	129 ± 27*†

*$p < 0.001$, ‡$p < 0.05$ versus supine position. †$p < 0.001$, §$p < 0.05$ versus 1 min. ‖$p < 0.05$ versus Group I. BP = blood pressure; HR = heart rate; HUT = head-up tilt.

by counting the number of 40-μs clocks between each consecutive pulse and sampled at 2 Hz after the spline interpolation. All ECG recordings were reviewed on the computer display by two cardiologists, and a time series of 200 consecutive RR intervals comprising only normal sinus rhythms and in a stationary state were selected. Spectral indexes of heart rate variability were computed by a maximal entropy method using the Burg algorithm on 200 consecutive RR intervals. The direct current component was excluded from the power spectra. Power spectra were quantified by measuring the area in two frequency bandwidths: low frequency component (0.05 to 0.15 Hz), a measure of sympathetic tone mediated by the parasympathetic nervous system, and high frequency component (0.15 to 1.0 Hz) reflecting parasympathetic activity. The ratio of low frequency to high frequency component was derived as a measure of sympathovagal balance (12,16–21).

Statistical analysis. Results are presented as mean value ± SD. The nonparametric Mann-Whitney *U* test was used for statistical comparison between two groups. Analysis of variance was used to determine differences among the three groups. Analysis of variance for repeated measures was used for intragroup comparisons of hemodynamic, echocardiographic and heart rate spectral changes. Multiple comparisons were made using the Scheffe test; $p < 0.05$ was considered significant.

Results

Clinical characteristics. Pertinent data of the subjects are summarized in Table 1. There was no significant difference in age among the three groups. Group I patients had had more frequent episodes of syncope and had had a longer history of syncope than Group II patients. Baseline left ventricular size and wall motion evaluated by echocardiography were within normal ranges. The duration of the control tilt in Group I did not differ from that with isoproterenol infusion in Group II. The maximal isoproterenol dosage did not differ between Groups II and III (Table 1).

Cardiovascular responses. Two distinct response patterns of heart rate and blood pressure characterized as vasodepressor and mixed response (6,22) were identified. In Group I, four patients had a vasodepressor response in which symptoms were associated with hypotension alone, and another nine had a mixed response in which symptoms were associated with both hypotension and bradycardia. In Group II, five patients had a vasodepressor response, and another nine had a mixed response. Eight Group I patients and seven Group II patients repeated the head-up tilt test on the second day and had the same response as that on the first day. This result indicates that the response to the head-up tilt was reproducible in these patients. The data obtained on the first day were used for the following analyses: Changes in mean blood pressure and heart rate during the head-up tilt are shown in Table 2. Baseline mean blood pressure did not differ among the three groups. There was no significant change in mean blood pressure during the baseline tilt in both Groups II and III. However, it decreased significantly at 1 to 2 min before and at the end of the baseline tilt when syncopal or presyncopal symptoms developed in Group I patients. Baseline heart rate was significantly lower in Group I than in Groups II and III. During the baseline tilt, heart rate increased significantly from the baseline value in the three groups. At the end of the baseline tilt, heart rate tended to decrease in Group I, but the difference did not reach the significance level, possibly because of the vasodepressor response without bradycardia that occurred in four patients.

During the tilt with isoproterenol infusion, mean blood pressure decreased significantly 1 to 2 min before and at the end of the tilt in Group II. However, it did not change significantly in Group III. Heart rate decreased significantly at the end of the tilt with isoproterenol infusion in Group II, but it increased significantly in Group III.

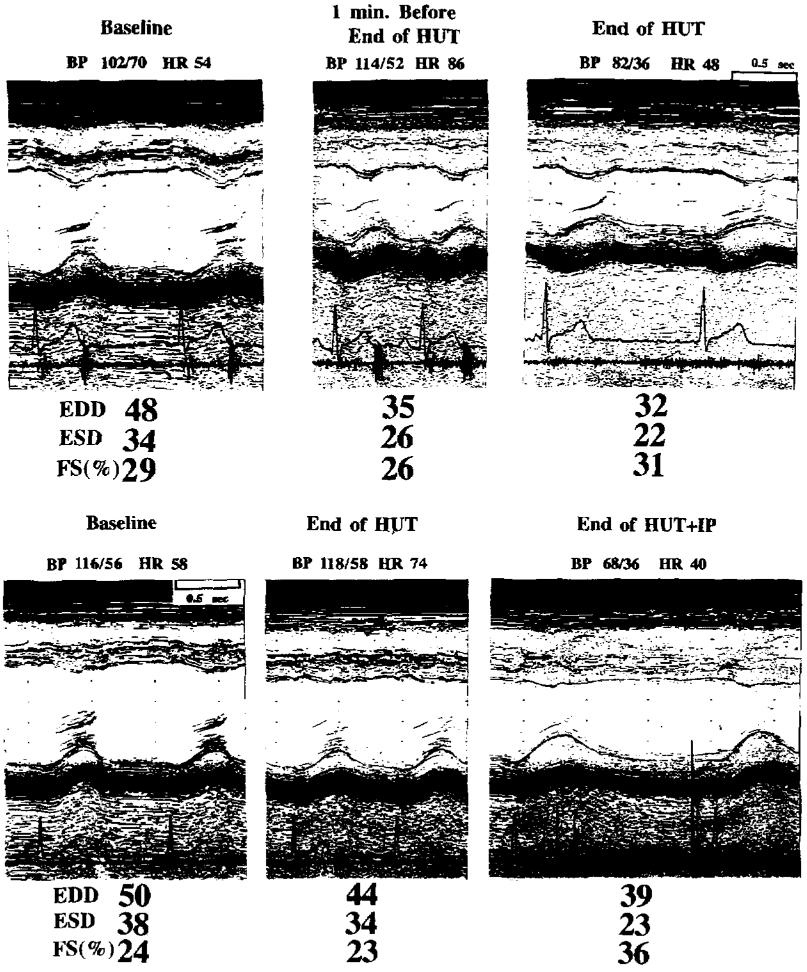

Figure 1. Top, Representative tracings of left ventricular M-mode echocardiogram from a 29-year old man in Group I during supine rest **(left)**, at 1 min before the end of head-up tilt (HUT) **(middle)** and at the end of head-up tilt **(right)**. At 1 min before the end of head-up tilt, end-diastolic (EDD) and end-systolic dimensions (ESD) decreased from 48 to 35 mm and from 34 to 26 mm, respectively. At the end of 8-min tilt, end-diastolic and end-systolic dimensions decreased further (32 and 22 mm, respectively), and blood pressure (BP) and heart rate (HR) decreased when the patient had presyncopal symptoms. Fractional shortening (FS) remained fairly stable throughout the study protocol. **Bottom,** Representative tracings of left ventricular M-mode echocardiogram from a 15-year old boy in Group II during supine rest **(left)**, at the end of head-up tilt (HUT) **(middle)** and at the end of head-up tilt with isoproterenol infusion (HUT+IP) **(right)**. At the end of head-up tilt, end-diastolic and end-systolic dimensions decreased to a smaller extent (from 50 to 44 and from 38 to 34 mm, respectively) than in the patient in Group I **(top)**, and fractional shortening did not change. At the end of 6-min head-up tilt with isoproterenol infusion, end-diastolic and end-systolic dimensions decreased (39 and 23 mm, respectively), and fractional shortening increased (36%) when compared with the values at the end of control head-up tilt. Blood pressure and heart rate decreased when the patient had a presyncopal symptom.

Changes in echocardiographic variables. Representative examples of echocardiographic changes during the tilt are shown in Figure 1, and echocardiographic variables are summarized in Figures 2 to 4. Baseline end-diastolic dimension was significantly greater in Group I than in Group III (49 ± 3 vs. 43 ± 5 mm, $p < 0.01$) but did not differ between Group II (46 ± 4 mm) and Group I or Group III. Baseline end-systolic dimension was not different among the study groups (Group I, 32 ± 3 mm; Group II, 31 ± 6 mm; Group III, 30 ± 5 mm). After starting the baseline tilt, end-diastolic and end-systolic dimensions decreased in all three groups but became smaller in Group I than in Groups II and III throughout the baseline tilt (Fig. 2 and 3, top). Fractional shortening did not change significantly in the three groups (Fig. 4, top).

During the supine position with isoproterenol infusion, end-diastolic dimension decreased to 90 ± 9% and 91 ± 9% of the baseline value in Groups II and III, respectively. During the tilt with isoproterenol infusion, end-diastolic dimension decreased to the same extent in both groups and to the same level as in Group I during the baseline tilt (Fig. 1 and 2). End-systolic dimension also decreased to 80 ± 13% and 76 ± 11% of the baseline value during the supine position with isoproterenol infusion in Groups II and III, respectively. End-systolic dimension also decreased to the same extent in both Groups II and III (Fig. 1 and 3). The percent decrease in end-systolic dimension was greater than that in end-diastolic dimension at the last 1 or 2 min of the tilt, both in Group II (35 ± 8% vs. 25 ± 7%, $p < 0.0005$) and Group III (33 ± 8% vs. 26 ± 10%, $p < 0.0005$). Fractional shortening in the supine position therefore increased significantly after starting isoproterenol infusion both in Group II (33 ± 8% to 41 ± 8%, $p < 0.001$) and Group III (31 ± 6% to 42 ± 8%, $p < 0.0001$). Fractional shortening did not differ between these two groups throughout the tilt, except at the end of the tilt when it was greater in Group II than in Group III (Fig. 3, bottom).

Heart rate variability. Representative changes in the power spectra of a Group I patient are shown in Figure 5. Among the three groups, the mean RR interval was not different during the supine position and during the last 200 beats until 1 min before the end of the tilt.

Changes in spectral components are summarized in Figures 6 and 7. The low frequency power did not differ among the three groups during the supine period and throughout baseline tilt, although it tended to be greater in Group I than in the other groups (Fig. 6). The high frequency power tended to be greater in Groups I and II during the supine position, but the

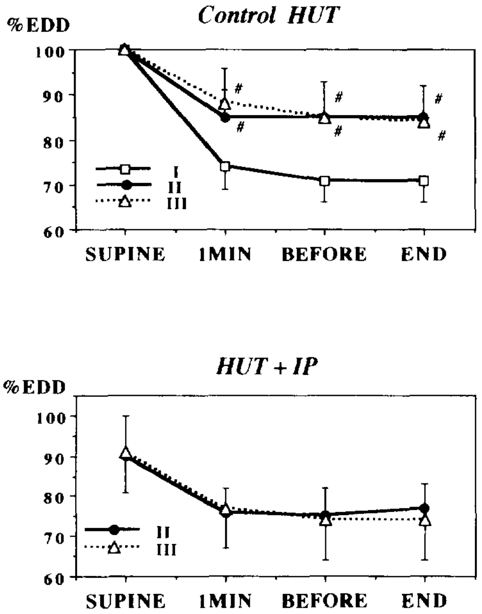

Figure 2. Percent changes in end-diastolic dimension (%EDD) during control head-up tilt (Control HUT) (**top**) and head-up tilt with isoproterenol infusion (HUT+IP) (**bottom**). In both panels, the baseline end-diastolic dimension value during the supine position without isoproterenol infusion was expressed as 100%. Throughout the control head-up tilt, percent changes in end-diastolic dimension were lower in Group I (**squares**) than in Groups II (**circles**) and III (**triangles**). During tilt with isoproterenol infusion, percent changes in end-diastolic dimension in Groups II and III decreased to the level of that in Group I during the control tilt but did not differ between Groups II and III during the tilt with isoproterenol infusion. SUPINE = during supine position; 1 MIN = 1 min after starting head-up tilt; BEFORE = 1 or 2 min before end of head-up tilt; END = end of head-up tilt. #p < 0.001 versus Group I. Results are mean value ± SD.

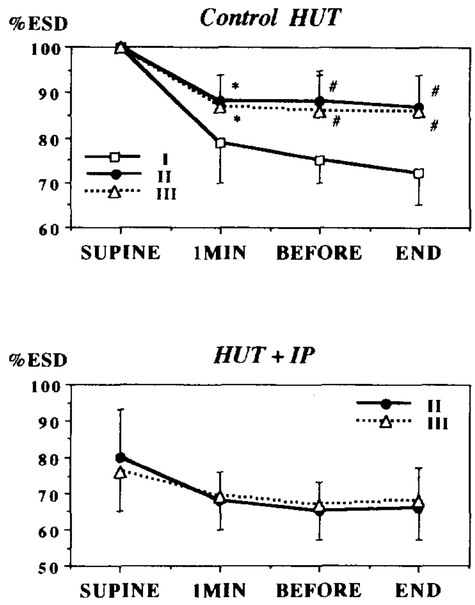

Figure 3. Changes in percent end-systolic dimension (%ESD) of the baseline value during control head-up tilt (HUT) (**top**) and head-up tilt with isoproterenol infusion (HUT+IP) (**bottom**). Throughout the control head-up tilt, changes in percent end-systolic dimension were smaller in Group I than in Groups II and III. During tilt with isoproterenol infusion in Groups II and III, changes in percent end-systolic dimension decreased to the level of that in Group I at the end of the control tilt but did not differ between Groups II and III during tilt with isoproterenol infusion. *p < 0.005, #p < 0.001 versus Group I. Format and other abbreviations as in Figure 2.

difference was not significant. During the last period of the head-up tilt, that is, the last 200 beats until 1 min before the end of the tilt, the high frequency power decreased to the same level in the three groups, but the decrease was not statistically significant in Group II. The low frequency/high frequency ratio was not different among the three groups at the supine position. During the last period of the tilt, the low frequency/high frequency ratio increased significantly in all three groups, and became greater in Group I (5.1 ± 2.4) than in Groups II and III (2.3 ± 1.7 and 2.2 ± 1.1, respectively, p < 0.001) (Fig. 6). This finding indicates that sympathetic activity became predominant in Group I compared with the other groups during the head-up tilt. During the supine position with isoproterenol infusion, low and high frequency power tended to be smaller than the baseline values obtained before isoproterenol infusion both in Groups II and III and did not differ between the two groups (Fig. 7). The low frequency/high frequency ratio increased in both groups because high frequency power decreased more than the low frequency power after the start of isoproterenol infusion. During the last period of the head-up tilt with isoproterenol infusion, the low frequency/high frequency ratio became greater in Group II (3.2 ± 1.1) than in Group III (1.8 ± 0.9, p < 0.01) (Fig. 7). The dosage of isoproterenol infusion was similar in the two groups (Table 1).

Discussion

The major findings of the present study are as follows: 1) Patients with isoproterenol-independent syncope (Group I) had an exaggerated decrease in left ventricular size during head-up tilt alone. In these patients, the low frequency/high frequency ratio increased markedly, indicating alteration in sympathovagal balance leading to sympathetic predominance before the development of syncope. 2) In contrast, patients with isoproterenol-dependent syncope (Group II) had sympathetic predominance during the tilt plus isoproterenol infusion compared with the control subjects (Group III), although left ventricular size decreased to the same extent in the other two groups. Contractility, expressed by fractional shortening, increased more in Group II than in Group III before the end of tilt with isoproterenol infusion.

Changes in echocardiographic variables. In an earlier study by Shalev et al. (10), a progressive decrease in left ventricular size was demonstrated during head-up tilt alone in patients with isoproterenol-independent neurally mediated syncope, and a decrease in size became significantly greater in these patients than in patients with isoproterenol-dependent syncope and subjects with negative head-up tilt responses. However, left ventricular end-systolic size was smaller in patients with isoproterenol-dependent syncope than in tilt-negative subjects at the end of tilt. Fractional shortening therefore increased both in patients with isoproterenol-

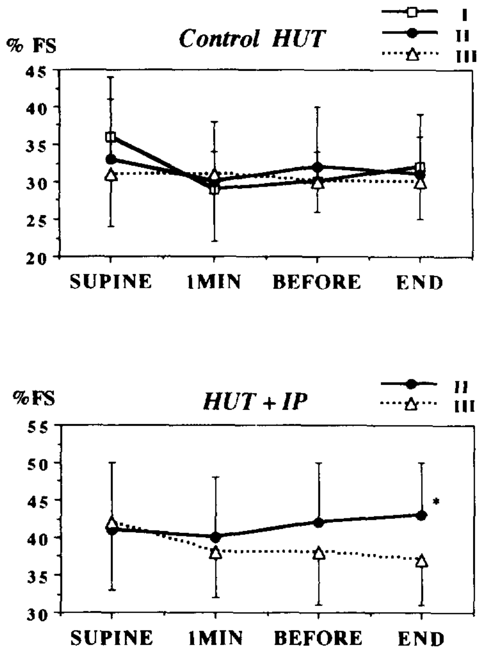

Figure 4. Changes in fractional shortening (%FS) during control head-up tilt (HUT) (**top**) and head-up tilt with isoproterenol infusion (HUT+IP) (**bottom**). Control fractional shortening did not differ among the three groups and did not change significantly throughout control tilt. During the supine position with isoproterenol infusion, fractional shortening increased significantly in Groups II and III. It did not differ between these two groups throughout the tilt with isoproterenol except for the end of the tilt when it was significantly greater in Group II than in Group III. *$p < 0.05$ versus Group III. Format and other abbreviations as in Figure 2.

dependent and isoproterenol-independent syncope at the end of tilt (10). Their study suggested that left ventricular size decreased markedly during head-up tilt in patients with isoproterenol-independent neurally mediated syncope, a finding in accordance with our result. However, an initial decrease in left ventricular size at the beginning of tilt did not differ among the groups in the study of Shalev et al. (10). In contrast, in the present study, it decreased more at 1 min after starting the tilt in patients with isoproterenol-independent syncope than in other groups.

Patients in whom syncope was induced during head-up tilt had less variable venous tone and a larger increase in their calf blood volume during the tilt (23). The increase in calf blood volume was greater throughout the tilt in these patients than in those without symptoms (23). Other investigators (24) have also suggested that impaired early vasoconstricting responses to head-up tilt, leading to excessive venous pooling, might be a primary phenomenon responsible for increased susceptibility to tilt-induced vasovagal reactions. A decrease in the left ventricular size might therefore be greater in patients with tilt-induced syncope than in subjects without symptom, as shown in the present study. Vasoconstricting responses to tilt might be preserved both in patients with isoproterenol-dependent syncope and in control subjects because an exaggerated decrease in left ventricular size was not demonstrated during head-up tilt alone in these subjects in the present study. Normally, the decrease in venous return during head-up tilt leads to a diminution of baroreceptor inhibitory impulses, which enhances adrenergic sympathetic tone and reduces parasympathetic tone (4,25–28), as observed in the present study (Fig. 6). Consequently, augmented adrenergic tone increases myocardial contractile force and heart rate to compensate for the reduced stroke volume (29–31). As previously reported in animal studies (26,32) and during echocardiographic evaluation (10), increased contractility in the small left ventricle might cause vasovagal reflex through stimulating left ventricular mechanoreceptors. However, fractional shortening, as an index of left ventricular contractility, did not increase in the present study because of variable changes of this variable in patients with isoproterenol-independent syncope during head-up tilt, whereas an exaggerated decrease in left ventricular size was a consistent finding. Shalev et al. (10) reported that the increase in percent fractional shortening became significantly greater in patients with isoproterenol-dependent syncope than in control subjects during the tilt with isoproterenol infusion. However, ventricular size was not described in their study (10). In the present study, a further decrease in left ventricular size, along with an increase in percent fractional shortening, was noted during the head-up tilt with isoproterenol infusion both in patients with isoproterenol-dependent syncope and in control subjects compared with the baseline tilt. However, left ventricular size and percent fractional shortening did not differ between these two groups except for percent fractional shortening at the end of the tilt. These results suggest that a small difference in percent fractional shortening might be critical to induce syncope (Fig. 4), although hypersensitivity of the mechanoreceptor might play some role in the initiation of vasovagal reflex during head-up tilt (33) because vasovagal reflex could not be induced in the control subjects with a similarly reduced left ventricular size.

Changes in heart rate spectral characteristics during head-up tilt. Assessment of heart rate variability provides a simple noninvasive means for quantitative analysis of cardiac sympathovagal tone (16–18). By changing from supine to head-up tilt, low frequency power increased, whereas high frequency power decreased, resulting in an increase in the low frequency/high frequency ratio in normal subjects (16,17,19,20). In affected patients the increase in low frequency power and low frequency/high frequency ratio was greater before syncope than that in normal subjects (19,21). These findings indicate that the sympathovagal balance was altered, resulting in sympathetic predominance, and are in accordance with previous results (34) in which plasma catecholamine levels were elevated just before vasovagal symptoms. However, to our knowledge heart rate spectral characteristics have not been compared in patients with isoproterenol-dependent and isoproterenol-independent neurally mediated syncope. In the present study, the low frequency/high frequency ratio did not increase in patients with isoproterenol-dependent syncope as much as in patients with isoproterenol-independent syncope

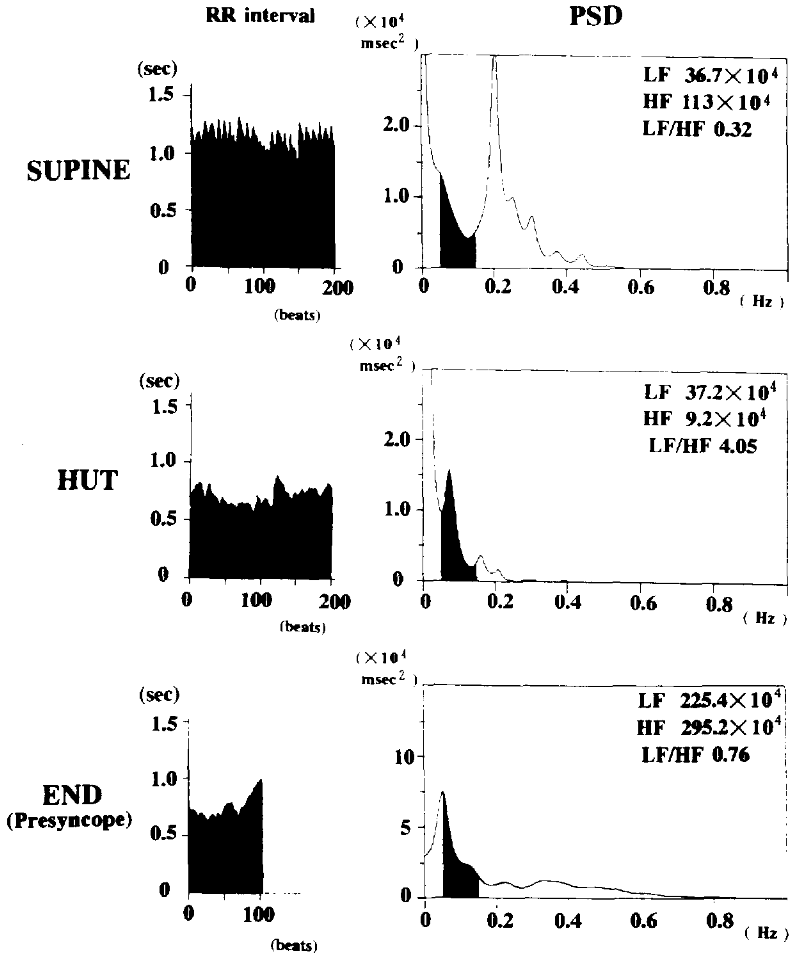

Figure 5. Representative changes in the tachogram of RR interval **(left)** and power spectra of heart rate variability **(right)** from a 15-year old boy in Group I during supine position **(top)** and head-up tilt (HUT) **(middle)** and at the end of head-up tilt with presyncope (END) **(bottom)**. **Right,** Abscissa indicates frequency (Hz), and **ordinate** indicates power spectral density (PSD) (ms^2). During head-up tilt, the high frequency (HF) component decreased, and the low frequency (LF) component (shown in **black**) became predominant, resulting in an increase in the low frequency/high frequency component ratio. At the end of head-up tilt, the high frequency component became predominant as the patient had a presyncopal symptom. It should be noted that scales of the ordinate are different.

during the baseline tilt. Changes in the power spectral components of heart rate variability did not differ between patients with isoproterenol-dependent syncope and control subjects during the baseline tilt. After administration of isoproterenol, the low frequency/high frequency ratio became greater before the end of the tilt in patients with isoproterenol-dependent syncope than in control subjects.

Recently, Bloomfield et al. (35) indicated that head-up tilt at 60° decreased high frequency power more than an infusion of low dose isoproterenol (1 μg/min) in the supine position despite the finding that similar heart rates were attained (35). However, the effects of sympathomimetic drugs, including isoproterenol, on heart rate spectral components have not yet been fully understood, and the effect of tilt plus isoproterenol infusion on the autonomic nervous system balance has not been thoroughly analyzed. Contrary to expectations from previous results using beta-blockade (17), the administration of isoproterenol decreased not only high frequency power, but low frequency power during the supine position in the present study. However, as expected, isoproterenol increased baseline low frequency/high frequency ratio during the supine position and increased it more during tilt in the present study. The increase in low frequency/high frequency ratio during tilt was greater in patients with isoproterenol-dependent syncope than in control subjects. It was reported (36) that an increased beta-adrenergic sensitivity determined by graded isoproterenol infusion was associated with susceptibility to syncope in children and adolescents. Beta-adrenergic hypersensitivity, reflected as an increase in percent fractional shortening and in the low frequency/high frequency ratio during head-up tilt with isoproterenol infusion, might be responsible for syncopal attack in our patients with isoproterenol-dependent syncope.

Methodologic considerations. There is a potential limitation regarding the spectral analysis technique for evaluation of the response to physiologic perturbations such as postural tilt (i.e., nonstationary conditions might increase noises in the data). The consecutive 200 beats were analyzed to assess the changes in sympathovagal balance in the present study. This time period seemed too long to determine the dynamic, serial changes in autonomic nervous activities. Therefore, our interpretation would be hampered in this context. Some investigators (37) suggested that the autoregression method might be more sensitive to physiologic stress, such as head-up tilt. Care was taken in the present study to include heart rate data during supine and head-up tilt while subjects were asymptomatic and to exclude subjects with frequent

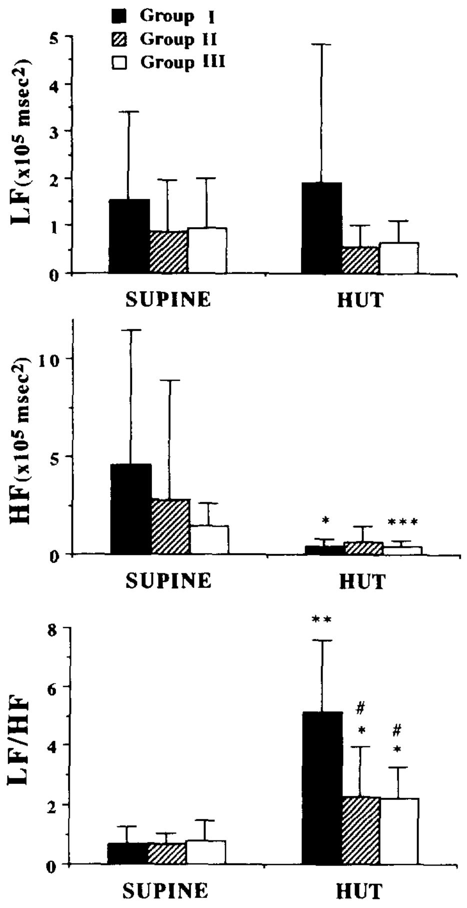

Figure 6. Power spectral components during the supine period and the last period of control head-up tilt (HUT) are summarized. **Top,** Low frequency (LF) component did not differ among the three groups during the supine period and during the last period of the control tilt, although it tended to be greater in Group I than in the other groups during tilt. **Middle,** High frequency (HF) component tended to be greater in Groups I and II during the supine period, but the difference was not significant. During head-up tilt, the high frequency component decreased to the same level in the three groups, but the decrease was not statistically significant in Group II. **Bottom,** The low frequency/high frequency component ratio (LF/HF) was not different among the three groups during the supine period. During head-up tilt, the low frequency/high frequency component ratio increased significantly in all three groups because of a marked decrease in the high frequency component without appreciable changes in the low frequency component. The low frequency/high frequency component ratio in Group I became greater than that in the other two groups. *$p < 0.05$, **$p < 0.005$, ***$p < 0.001$ versus the supine position, #$p < 0.001$ versus Group I.

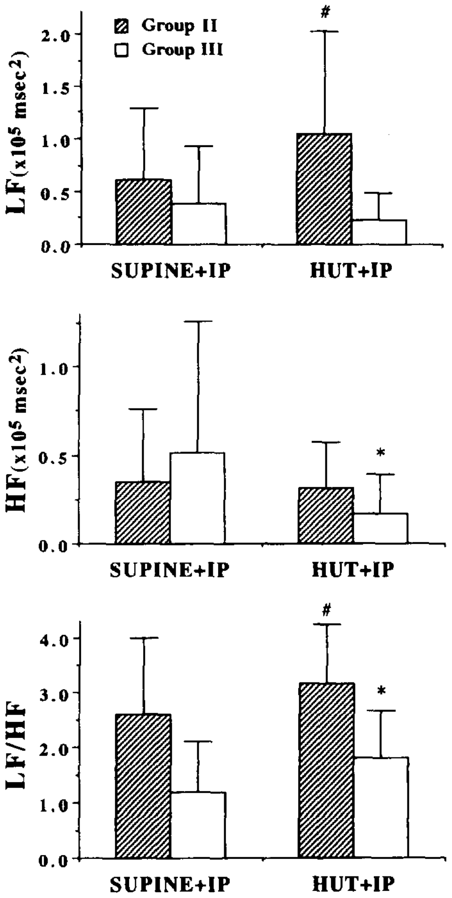

Figure 7. Power spectral components during the supine position and head-up tilt (HUT) after start of the isoproterenol (IP) infusion. During the supine position with isoproterenol infusion, low (LF) (**top**) and high frequency (HF) (**middle**) components tended to be smaller and the low frequency/high frequency component ratio (LF/HF) (**bottom**) greater as a result of a greater decrease in the high frequency than in the low frequency component in both Groups II and III compared with baseline values without isoproterenol shown in Figure 6. However, these variables did not differ between the two groups. During head-up tilt with isoproterenol infusion, the low frequency component became greater in Group II than in Group III, and the high frequency component decreased significantly only in Group III. Consequently, the low frequency/high frequency component ratio became greater in Group II than in Group III. #$p < 0.01$ versus Group III. *$p < 0.05$ versus the supine position and isoproterenol infusion.

arrhythmias during the test. The very low frequency component (<0.05 Hz) was not analyzed in the present study because the significance of this component is still not clear. If the nonharmonic 1/f component (38) is completely eliminated, this very low frequency component might reflect a function of some cardiovascular factors that include involvement of the renin-angiotensin system in heart rate changes (18). Although the groups were matched for age in the present study, it was not possible to match them for daily physical activities, which might have influenced the autonomic activities. Patients without optimal echocardiograms were excluded from the study, as mentioned in Methods. However, it seems unlikely that exclusion of these patients from the analysis affected the present results significantly because the number of patients excluded for this reason was small. The patients were classified into two groups: those who required isoproterenol infusion to induce syncope (isoproterenol dependent) and those who did not (isoproterenol independent). This division was not complete because there were patients with positive tilt test results during infusion of nitroglycerin (39) or other substances (40,41). These patients would show a different response to echocardiographic measures and in heart rate variability during the head-up tilt test. Finally, the infusion rate of isoproterenol was determined according to a previous report (14), even though the impact of isoproterenol might differ at the level of the sinus node compared with that at the level of the vascular system (42).

Conclusions. The present findings indicate that responses to head-up tilt differ between patients with isoproterenol-independent neurally mediated syncope and those with isoproterenol-dependent syncope. The former have an exaggerated decrease in left ventricular size and sympathetic predominance preceding syncope during head-up tilt alone. In contrast, the latter have a significant decrease in left ventricular size and sympathetic predominance only during tilt with isoproterenol infusion. The different responses of fractional shortening and sympathovagal balance to isoproterenol infusion between patients with isoproterenol-dependent syncope and control subjects suggest that different responses in peripheral vasoconstriction or hypersensitivity of the mechanoreceptor function, or both, could play some role in the genesis of neurally mediated syncope.

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