Original Article

Autonomic Function in Adolescents with Orthostatic Dysregulation Measured by Heart Rate Variability

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We evaluated the responses of autonomic nervous system to transient positional changes and daily changes in orthostatic dysregulation (OD) patients in order to clarify the mechanisms underlying the appearance of symptoms. The control group consisted of 16 healthy adolescents (8 males and 8 females), and the OD group consisted of 25 adolescents (13 males and 12 females). Each subject underwent continuous electrocardiographic monitoring during the head-up tilt test, followed by electrocardiographic monitoring for 24 h. Low frequency power (LF) and high frequency power (HF) were calculated as indices of autonomic function. During 0–5 min in the standing position in the tilt test, HF was higher in the OD group than in the control group (180±110 ms^2 *vs.* 42.6±54.1 ms^2; $p<0.05$). The LF/HF ratio during standing for 15–20 min was higher in OD patients than in the controls (4.75±3.45 *vs.* 1.67±1.21; $p<0.05$). The 24 h analysis showed that HF during sleep was significantly lower in the OD patients than in the controls (516±290 ms^2 *vs.* 1,290±429 ms^2; $p<0.05$); the LF/HF ratios were consistently higher in the OD patients than in the controls (4.13±3.41 and 2.92±2.00 *vs.* 2.46±0.89 and 1.35±1.54 in waking and sleeping states, respectively; $p<0.05$). This study showed that OD patients have less variability of the parasympathetic nervous system as well as hyperactivity of the sympathetic nervous system. This autonomic dysfunction is responsible for the symptoms of OD. (*Hypertens Res* 2007; 30: 601–605)

***Key Words*: orthostatic dysregulation, adolescent, heart rate variability, autonomic function, head-up tilt test**

Introduction

Many Japanese adolescents suffer from orthostatic dysregulation (OD) (*1–4*), characterized by dizziness on standing, malaise, palpitation, headaches, abdominal pain, and syncope. Students with this disease sometimes cannot attend school, and this becomes a social problem. However, there is no clinical concept of this disease, there have been few reports of OD in other countries, and the mechanism of it is unclear.

Clinical diagnostic criteria have been established by a dedicated working group in Japan (*5*). These criteria are largely dependent on symptomatology and no objective diagnostic indicators are available for diagnosis (*1*).

A previous study analyzed heart rate variability (HRV) by Holter monitoring and found that OD is correlated with abnormalities in daily HRV changes due to autonomic dysfunction (*6*).

The head-up tilt test, in which changes in blood pressure and heart rate are measured as a patient changes position from lying to standing, is an established method of evaluating the function of autonomic nervous system (*7*, *8*). We predicted that the system's response to positional change in OD patients would be abnormal.

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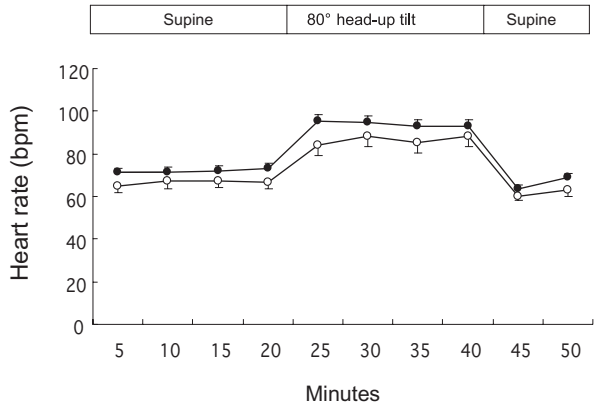

Fig. 1. *Heart rates during tilt test.* ¡, *control group;* ●, *OD group. bpm, beats per minute. Bar shows SEM.*

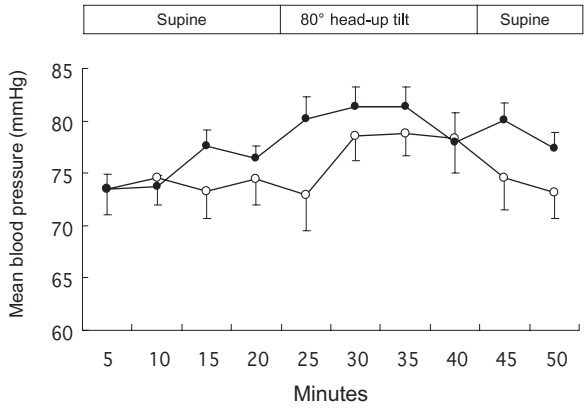

Fig. 2. *Mean blood pressure during tilt test.* ¡, *control group;* ●, *OD group. Bar shows SEM.*

In this study, we evaluated the responses of autonomic nervous system to transient positional changes and its daily changes in OD patients.

Methods

The control group consisted of 16 healthy adolescents comprised of 8 males and 8 females ranging from 13 to 14 years of age (mean 13.4). The OD group consisted of 25 adolescents diagnosed according to the criteria for OD (*5*): 13 males and 12 females ranging from 13 to 15 years of age (mean 13.9). Written informed consent was obtained from all subjects and their parents prior to participation in this study. The study protocol was approved by the Ethics Committee of Jichi Medical University School of Medicine.

Each subject underwent continuous electrocardiographic monitoring during the tilt test; data were recorded on a Holter recorder. The subjects remained in a supine position for 20 min before being moved to an 80° standing position on a tilt table (passive tilt test) (*9*). They then remained in a passive standing position for 20 min. Subsequently, the subjects were returned to a supine position for 10 min. The subjects were asked to breathe at a rate of 15 breaths per minute to exclude data fluctuation due to respiration. All the tilt tests were carried out in the afternoon without any restrictions placed on food intake or activity prior to the test.

Heart rate and systolic and diastolic blood pressures were monitored intermittently with a noninvasive Life Scope (Nihon Kohden, Tokyo, Japan) and recorded every 5 min. Mean pressure was calculated as follows:

$$\text{Mean pressure} = \text{diastolic pressure} + 1/3(\text{systolic pressure} - \text{diastolic pressure}).$$

After the tilt test, each subject underwent electrocardiographic monitoring for 24 h during their normal activities of daily living; data were recorded on a Holter recorder.

The Holter tapes were evaluated using a MARS 8000 analyzer (Marquette Electronics, Milwaukee, USA). After arrhythmia analysis, heart rate variability was measured as an indicator of autonomic function. In frequency domain analysis, we calculated the low frequency power (LF) from 0.04 Hz to 0.15 Hz, and the high frequency power (HF) from 0.15 Hz to 0.4 Hz. We then calculated the LF/HF ratio. HF is vagally mediated, but LF originates from a variety of sympathetic and vagal mechanisms (*10*). The LF/HF ratio is considered to represent sympathetic function (*11*). Heart rate variability was assessed every 5 min during the tilt test. LF and HF values showed marked individual differences. The LF and HF values were expressed in relation to supine 0–5, which was assigned a baseline value of 100.

After a 24 h analysis, we divided autonomic function between periods of sleep and wakefulness. Sleep was defined as the time between retiring and awakening.

We used two-way analysis of variance (ANOVA) for statistical analysis of the data in the tilt test and Fisher's protected least significant difference (PLSD) test for 24 h analysis. All data are expressed as mean±SD. Significance was established at the 0.05 level.

Results

Compared to baseline values, there were no significant differences in heart rate during the tilt test in controls or OD patients (Fig. 1). There were no significant differences in blood pressure between the two groups in either the supine or standing position (Fig. 2). LF did not change significantly in the standing position for either group and there was no significant difference between the controls and OD patients (Fig. 3).

HF in the controls decreased immediately after the change to the standing position, while HF in the OD patients decreased slowly. HF values while the subjects stood from 0 to 5 min differed significantly between the two groups (Fig. 4). LF/HF in the controls increased immediately after the

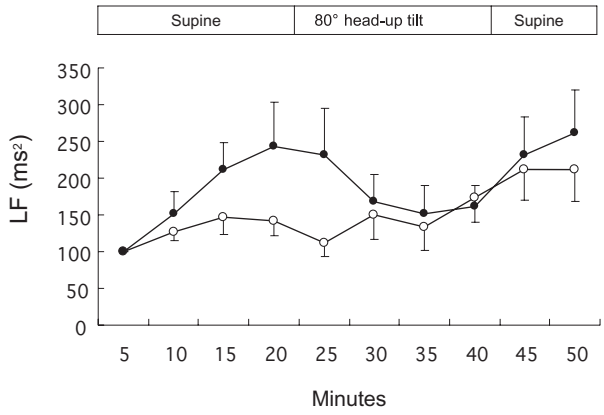

Fig. 3. *LF during tilt test.* ¡ *, control group;* ●*, OD group. Bar shows SEM.*

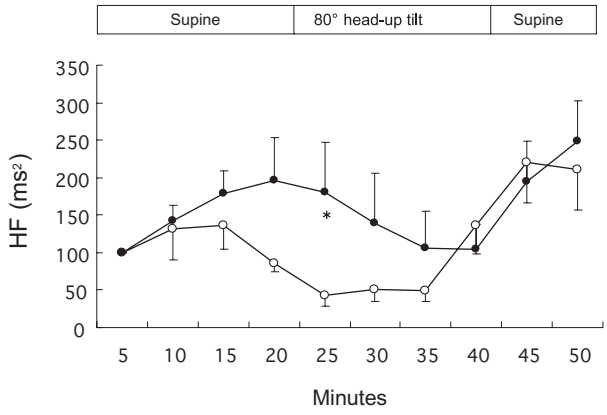

Fig. 4. *HF during tilt test.* ¡ *, control group;* ●*, OD group. Bar shows SEM. *p < 0.05 vs. control group in same period.*

change to standing, while LF/HF in OD patients increased more slowly. LF/HF during standing for 15 to 20 min was higher in the OD patients than in the controls (Fig. 5).

In Holter monitoring, HF in the OD patients was 516±290 ms^2 during sleep and 492±329 ms^2 when awake (Table 1). In the controls, HF was 1,290±429 ms^2 during sleep and 578±229 ms^2 when awake. HF during sleep was significantly lower in the OD patients than in the controls. In OD patients, HF did not vary during sleeping or waking states, whereas in the controls HF during sleep was higher than that when awake.

In OD patients, the LF/HF ratio was 2.92±2.00 during sleep and 4.13±3.41 when awake. In the controls, the LF/HF ratio was 1.35±1.54 during sleep and 2.46±0.89 when awake. The LF/HF ratio was consistently higher in OD patients than in controls.

Discussion

There are two kinds of standing tests, active and passive. Active standing test, in which the subject stands unassisted, is used as one of the clinical diagnostic criteria for OD. Head-up tilt test is a passive standing test. There is voluntary muscle tone in an active standing test and the effect of standing on autonomic nervous system is weaker in an active standing test than in a passive standing test. It has been suggested that a passive standing test should be performed to determine autonomic function. In this study, we performed the tilt test to evaluate the autonomic response to positional change in OD patients.

Since there is no cutoff value of blood pressure to differentiate OD patients from healthy subjects, blood pressure should be thoroughly evaluated to identify an indicator of decreasing blood pressure after the subject moves to a standing position, such as absolute value or changing value, or systolic pressure or diastolic pressure. Tanaka reported that mean pressure was a good indicator of decreasing blood pressure in children with instantaneous orthostatic hypotension (INOH), which is a subtype of OD (*12*). Therefore, we also used mean blood pressure as an indicator of decreasing blood pressure in this study.

Compared to baseline values, there were no significant differences in heart rate or blood pressure during the tilt test in either controls or OD patients. Decreased blood pressure and increased heart rate are not major criteria, but minor criteria. In the present study, it is thought that many OD patients were diagnosed by major criteria, and few showed significant differences in heart rate and blood pressure during the tilt test compared to values obtained before the test.

The tilt test in the present study showed that immediately after the subjects changed to a standing position, HF in the controls decreased significantly compared with that in OD patients. These observations suggested that OD patients exhibited less suppression of parasympathetic nerve activity upon a rapid change to a standing position. The symptoms of OD, such as headache, nausea, and abdominal pain, are thought to be due to parasympathetic nerve hyperactivity. The findings of the tilt test here confirmed the relation between symptoms and parasympathetic activity in OD patients.

In normal subjects, sympathetic function increases immediately after changing to a standing position (*13*). In OD patients in the present study, a longer period of standing is needed for an increase in sympathetic function during the head-up tilt test. Stewart performed tilt tests in patients with chronic fatigue syndrome (CFS) or posture tachycardia syndrome (POTS), the latter of which is one of the subtypes of orthostatic syncope (*13*). The changes in HF and LF/HF in their patients were similar to those observed in the present study. It is controversial whether OD in Japan represents the same disease entity as CFS and POTS in other countries. However, it is clear that all of these diseases occur due to an imbalance in the autonomic nervous function, and they may share the same pathology.

The Holter recording in the controls revealed that HF was

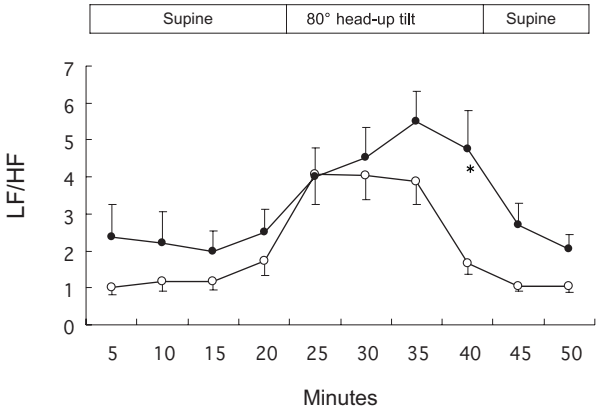

Fig. 5. *LF/HF during tilt test.* ¡, *control group;* ●, *OD group. Bar shows SEM.* **p*<0.05 *vs. control group in same period.*

Table 1. Diurnal Variation in Heart Rate Variability in the Control and OD Groups

	Control group (n=16)	OD group (n=25)
24 h		
LF (ms^2)	961±492	792±367
HF (ms^2)	522±302	424±264
LF/HF	2.04±0.63	1.91±0.48
Awake		
LF (ms^2)	1,318±567	1,920±683
HF (ms^2)	578±229	492±329
LF/HF	2.46±0.89	4.13±3.41
Sleep		
LF (ms^2)	1,710±730	1,450±494
HF (ms^2)	1,290±429$^{\#}$	516±290*
LF/HF	1.35±1.54	2.92±2.00
Awake/Sleep ratio		
LF (ms^2)	0.782±0.360	1.338±0.625
HF (ms^2)	0.460±0.233	0.942±0.234
LF/HF	1.822±0.586	1.450±0.664

Values are shown as mean±SD. $^{\#}p<0.05$ *vs*. awake period. **p*<0.05 *vs*. Control group. OD, orthostatic dysregulation; LF, low frequency component; HF, high frequency component.

higher during sleep than when awake, whereas in the OD patients there was no difference between sleeping and waking periods. HF during sleep was lower in the OD patients than in the controls. These findings of HF demonstrated a loss of daily variability in parasympathetic nervous function because of a decrease in parasympathetic nervous function during sleep. LF/HF was higher during sleeping and waking periods in the OD patients than in the controls, indicating hyperactivity of the sympathetic nervous system in the former. It is not clear whether LF/HF during sleep was high in OD patients because of hyperactivity of the sympathetic nervous system or simply because of a decrease in parasympathetic nervous function (lower HF). Insufficient rest during sleep and high tension when awake may promote malaise in OD patients. Kazuma *et al*. reported that OD patients have less variability in parasympathetic nervous function and are always in a highly catatonic state, consistent with the findings of the present study (*3*). In contrast to our findings, Fujiwara *et al*. reported that OD patients are parasympathetic dominant when sleeping and sympathetic dominant when awake (*6*). These differences may be due to differences in the subjects between the two studies; those in the Fujiwara study were entirely OD patients who could not attend school.

It is interesting to examine changes in autonomic function after OD patients awaken in the morning. Kazuma *et al*. reported that sympathetic nervous activity on waking in the morning increased more slowly and reached a lower peak value in the OD group than in normal controls (*14*). In the present study, we did not examine changes in HRV on waking. However, we found that a longer period of standing is needed for an increase in sympathetic function in OD patients in the tilt test. It is interesting that responses of autonomic nervous system to the transition from lying to standing are similar to the responses to the daily change from sleeping to waking.

OD patients have no variability in parasympathetic nervous function, and the sympathetic nervous system is dominant in daily life. These autonomic nervous conditions appear clearly with positional changes that are made many times per day. The findings of the present study suggest one possible cause of the varied symptoms of OD.

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