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Original Article

Two types of orthostatic dysregulation assessed by diameter of inferior vena cava

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Abstract

Aims: Orthostatic dysregulation (OD) is common in adolescents. This study was conducted to evaluate the usefulness of the measurement of the diameter of the inferior vena cava (IVC) for objective assessment of patients with OD.
Methods: Twenty children with OD (median 14 years, range 9–15 years) and 23 age-matched healthy children (median 12 years, range 10–15 years) were enrolled. A diameter of IVC was measured by an abdominal echogram before and after a head-up tilt table testing (HUT). Changes in IVC was assessed by an arbitrary parameter, collapse index (CI) as the following equation: [(maximal IVC diameter in the supine position − maximal IVC diameter in the standing position)/(maximal IVC diameter in the supine position)] × 100. CI was evaluated 4 weeks after treatment with an adrenergic agent.
Results: Children with OD demonstrated either higher CI or lower CI compared to that in control children: CI was more than 50 (range 50–71) in 12 patients with OD while that was equal to or less than 0 (range –225 to 0) in eight out of 20 patients. In contrast, CI was between 0 and 50 (range 1–26) in 23 healthy children. Pharmacological treatment induced the normalization in the CI in both higher and lower CI group.
Conclusion: OD can be classified into two subtypes: by HUT, one is characterized by an increase of IVC diameter while another is characterized by its decrease. Measurement of IVC diameter by HUT is useful to understand the pathophysiology and to assess the efficacy of treatment.

Key words abdominal echogram, head-up tilt table testing, inferior vena cava, orthostatic dysregulation, orthostatic intolerance.

Introduction

Orthostatic dysregulation (OD) or orthostatic intolerance is a common problem among Japanese children and adolescents.[1,2] Although prevalence of OD is estimated to be much higher in Japanese children than in Caucasian children,[3] this condition has increased in young Americans[4,5] due to changes of their lifestyle, such as lack of physical exercise and prolonged time in bed-rested pastime watching television.[6] Patients with OD have a variety of symptoms, such as recurrent dizziness,[7] chronic fatigue, headache and syncope,[8] resulting in impairment of quality of life in proportion to the severity of the illness. It is therefore necessary to study the underlying condition of OD for effective treatment.

The Task Force of Clinical Guidelines for Child Orthostatic Dysregulation of Japan has recently issued the clinical guidelines for juvenile OD (version 1)[9] which advocates new diagnostic criteria including a modified Schellong test, to classify the subtype of OD for a general pediatrician. In that guideline, four subsets of OD based on the hemodynamic change during active standing were demonstrated as follows: (i) instantaneous orthostatic hypotension (INOH);[10] (ii) postural tachycardia syndrome (POTS);[11] (iii) neurally mediated syncope; and (iv) delayed orthostatic hypotension. While this diagnotistic criteria is quite useful to speculate the pathophysiology, a more simple way is to evaluate the hemodynamics, in particular, the flow of the central venous return by an objective manner is desirable. An ultrasound determination of the diameter of the inferior vena cava (IVC) has been reported to be useful for the estimation of intravascular circulating blood volume.[12–14] The diameter of the IVC in a small number of patients with OD was markedly changed on a standing test compared to age-matched healthy children using an abdominal echogram.[15,16] Based on these findings, this study was conducted to evaluate the usefulness of the measurement of IVC diameter for objective assessment of patients with OD and of efficacy of pharmacological treatment with an alpha-1 agonist, midodrine hydrochloride.

Subjects and methods

Subjects

Twenty children with OD aged 9–15 years (median age 14 years, range 9–15 years; 10 males and 10 females) were enrolled in this study. The diagnosis of OD was based on the criteria of the Research Group on Orthostatic hypotension granted by the Ministry of Health and Welfare of Japan.[2] Twenty-three age-matched

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healthy volunteers who matched the age and sex (median age 12 years, range 10–15 years; 10 males and 13 females) were recruited for this study. This study was performed during March 2003 and November 2009. The number of patients and control children studied by season did not change.

Standing test

Head-up tilt table testing (HUT) has become the 'gold standard' among clinical laboratory diagnosis of vasovagal syncope and other neutrally mediated syncopal syndromes.[17] After an abdominal echogram was examined, patients quietly became supine and took a rest for 20–30 min in a waiting room until HUT, which was conducted in the morning in a quiet room before breakfast.

HUT was performed as described previously:[17] an upright tilt angle of 70° was calibrated and the transition from supine to upright position was achieved smoothly but swiftly in 10–15 s. The table permitted the patient to be gently secured to prevent falling and was sufficiently sturdy to avoid wavering or losing position during the test. The table was able to be reset quickly to the supine position in 10–15 s when the test was completed or symptoms, such as fainting, dizziness, nausea, sweating, or pallor developed. Although it is known that an active standing test is more prone to induce syncope than HUT,[18] we prefer HUT to assess precise IVC diameter as an index of change of venous return under standing position from supine position. During HUT, systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate were recorded serially by an automated sphygmomanometer (JENTOW-7700; Omron-Colin Co., Tokyo, Japan) using upper arms in addition to intermittent manual measurement of SBP, DBP and pulse rate by arterial Korotkoff sounds superimposed on the cuff pressure on the left arm of the subject.

To assess the clinical signs due to OD objectively, feeling of discomfort under HUT was scored: score 3, near-fainting and unable to keep on standing; score 2, nausea or palpitation; score 1, mild discomfort, score 0, no discomfort. Children with OD were re-examined under HUT as mentioned above after 4 weeks of treatment with oral midodrine hydrochloride (4 mg, twice times daily), an alpha-1 agonist known to be effective in patients with OD.

Data collection

Beat-to-beat digital signals of SBP, DBP and pulse rate were recorded into a personal computer. Maximal diameter of IVC (max IVC) was measured by an abdominal echogram: the subject was scanned in the supine position and both IVC and portal vein were visualized by a subcostal approach using a real time scanner (Pro-Sound SSD-5000; Aloka Co., Tokyo, Japan) and a sector probe of 5 MHz. To reduce the inter-assay and intra-assay variations in measurement of max IVC, the site for evaluation was fixed at retrohepatic location and at cranial site against the portal vein: the accuracy and validity for measuring max IVC by this method were reported previously to be highly reliable.[15,19]

In order to evaluate the hemodynamic change under HUT, a collapse index (CI) was used according to the following formula:[15,16] CI (%) = (max IVC in the supine position − max IVC at 1 min or 5 min after standing)/(max IVC in the supine position) × 100. Findings of an abdominal echogram including max IVC were recorded by a video tape recorder.

Statistics

Because the numerical data in the current study distributed non-parametrically, they were expressed in median and range. For statistical analysis, Wilcoxon *T*-test, Mann-Whitney *U*-test, Kruskal-Wallis *H*-test and Chi-square test were used for paired numerical data, unpaired numerical data and categorical data, respectively.

To analyze the relationship between the two groups of data, Spearman rank correlation test was applied. *P*-value less than 0.05 was considered significant.

Ethics

The purpose and procedure of the study was explained in advance to all subjects and their guardians and written informed consent was obtained from them. This study was approved by the ethical committee of Kansai Medical University (approval number: 0303).

Results

Clinical profile of the subjects

There were no significant differences in median age and male to female ratio between children with OD and control (OD: median 14, range 9–15; control: median 12, range 9–15, $P > 0.05$).

Median pulse pressure in children with OD, however, was significantly smaller than those in the control ($P = 0.002$) (Fig. 1).

Beat-to-beat digital signals of SBP, DBP, and max IVC under HUT

Figures 2 and 3 show the representative recordings in beat-to-beat digital signals and ultrasound findings both before (upper chart) and under (lower chart) HUT, respectively, in two children with OD and one control child. One with OD is characterized by

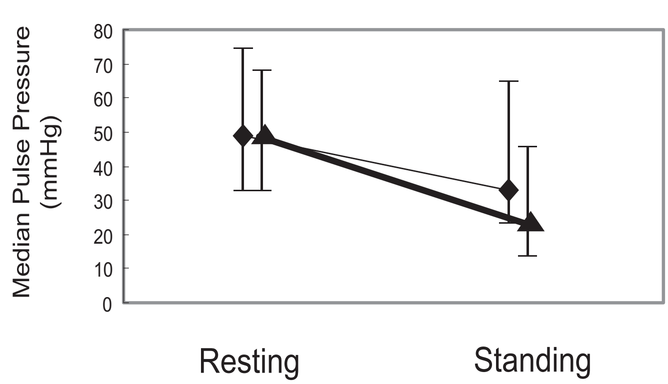

Fig. 1 Changes in pulse pressure under head-up tilt table testing (HUT) in children with and without orthostatic dysregulation (OD). *Minimum pulse pressure in children with OD (▲) after standing was significantly ($P = 0.002$) smaller than those in children without OD (◆). Data are shown as median and range.

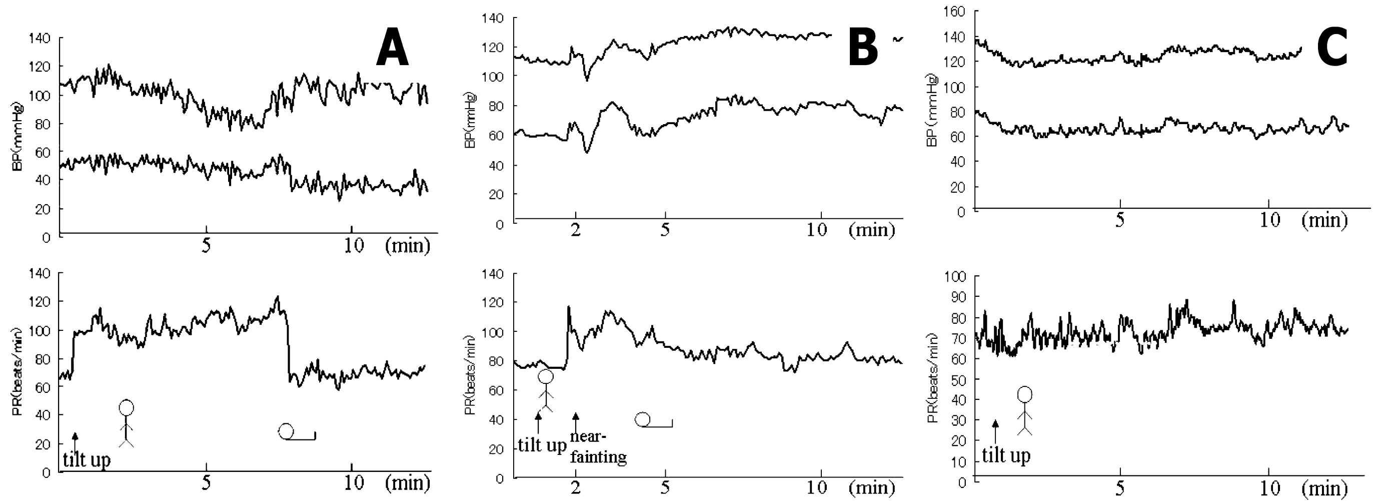

Fig. 2 Representative data of serial changes in blood pressure and pulse rate during head-up tilt table testing (HUT) in children with and without orthostatic dysregulation (OD). (a) Gradual reduction in pulse pressure and steep increase in pulse rates during 5 min of HUT. (b) Drastic changes in systolic blood pressure and pulse rates during 5 min of HUT. (c) Blood pressure and pulse rate were stable during HUT in a healthy control child. Upper chart showing the serial changes in blood pressure during head-up tilt table testing (HUT) and lower chart showing those in pulse rate during HUT.

a gradual decline in SBP and an abrupt increase in pulse rate (Fig. 2a) and marked decrease in max IVC (Fig. 3a) under HUT (CI: +69%). The other with OD is characterized by a fluctuant increase of pulse rate (Fig. 2b) and marked increase in max IVC (Fig. 3b; CI: –225%); Figures 2c and 3c was from the control child. She is characterized by stable BP and pulse rate under HUT (Fig. 2c) and no remarkable change in max IVC (Fig. 3c; CI: +13%).

Comparison among children with OD

As shown in Figure 4, the median of max IVC and CI were different among children with OD and showed higher CI (CI > +50), lower CI (CI ≦ 0), and control (CI 0–50). Children with OD therefore were classified into two subgroups: higher CI group of children with OD having more than 50 of CI and those showing equal to or less than 0 (lower CI group). There were no

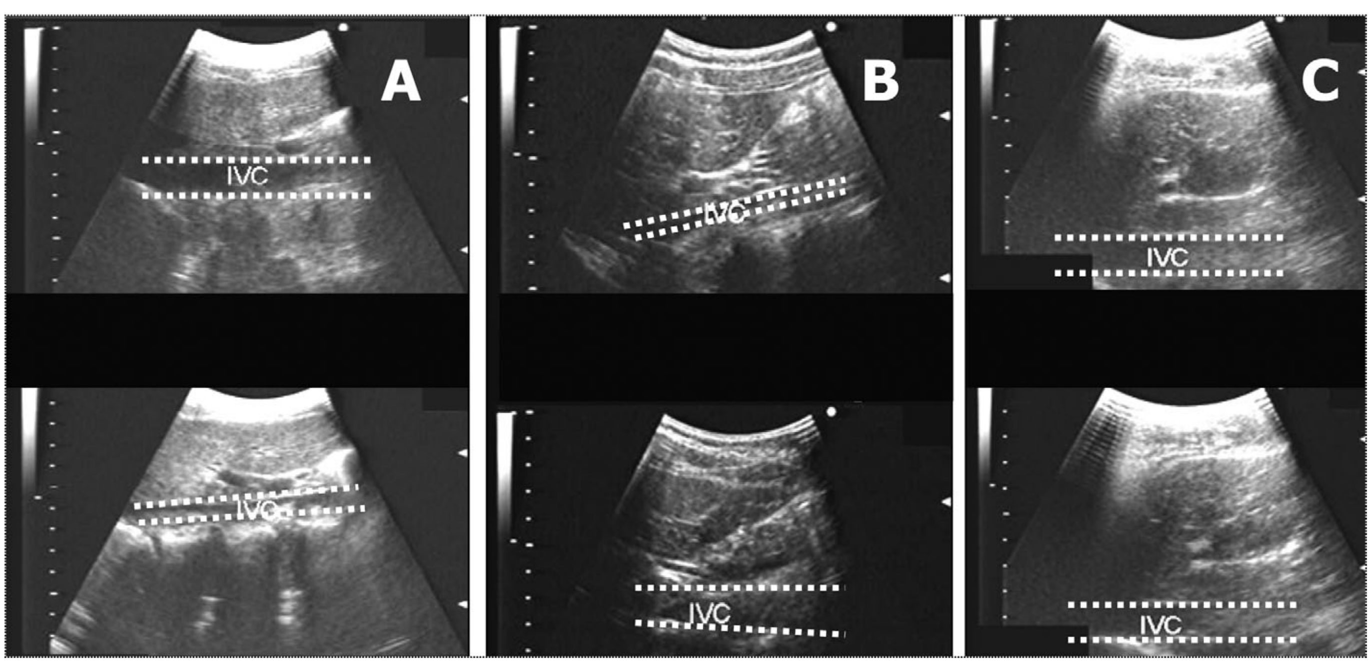

Fig. 3 Representative data of changes in inferior vena cava (IVC) diameter by postural change in children with and without orthostatic dysregulation (OD). Upper figure showing inferior vena cava (IVC) at resting; bottom figure showing IVC at standing for 5 min. Dotted lines denote the outlines of IVC. (a) Marked decrease in IVC diameter after standing in the child with orthostatic dysregulation (OD) corresponding to Figure 2a. (b) Marked increase in IVC diameter after standing in the child with OD corresponding to Figure 2b. (c) No remarkable change in IVC diameter even after standing was noted in a healthy child corresponding to Figure 2c.

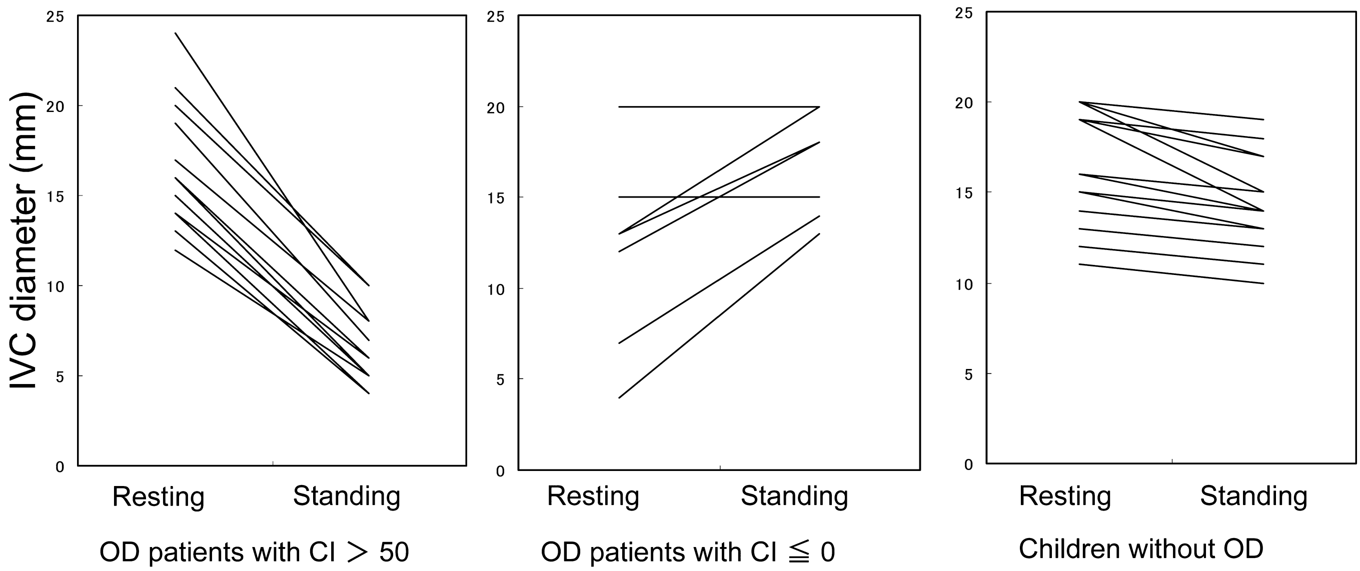

Fig. 4 Changes in inferior vena cava (IVC) diameter by posture. Significant changes in median values of max inferior vena cava (IVC) induced by standing were only found in children with orthostatic dysregulation (OD) showing either higher collapse index (CI) (CI > +50) or lower CI (CI ≦ 0) while healthy control children without OD (CI 0–50) demonstrated no remarkable changes.

significant differences in median age, male to female ratio, and changes in pulse pressure under HUT between the higher CI group and the lower CI group.

Effect of treatment on clinical symptoms and CI

After 4 weeks of treatment with oral midodrine hydrochloride (4 mg, twice daily), children with OD were re-examined under HUT as described above. CI of each subject with OD revealed significant changes after treatment both in the higher CI group and the lower CI group as shown in Figure 5. Furthermore, there was a significant correlation between absolute values in change of symptom score and those in CI. ($r_s = 0.57$, $P = 0.008$ by Spearman rank correlation test).

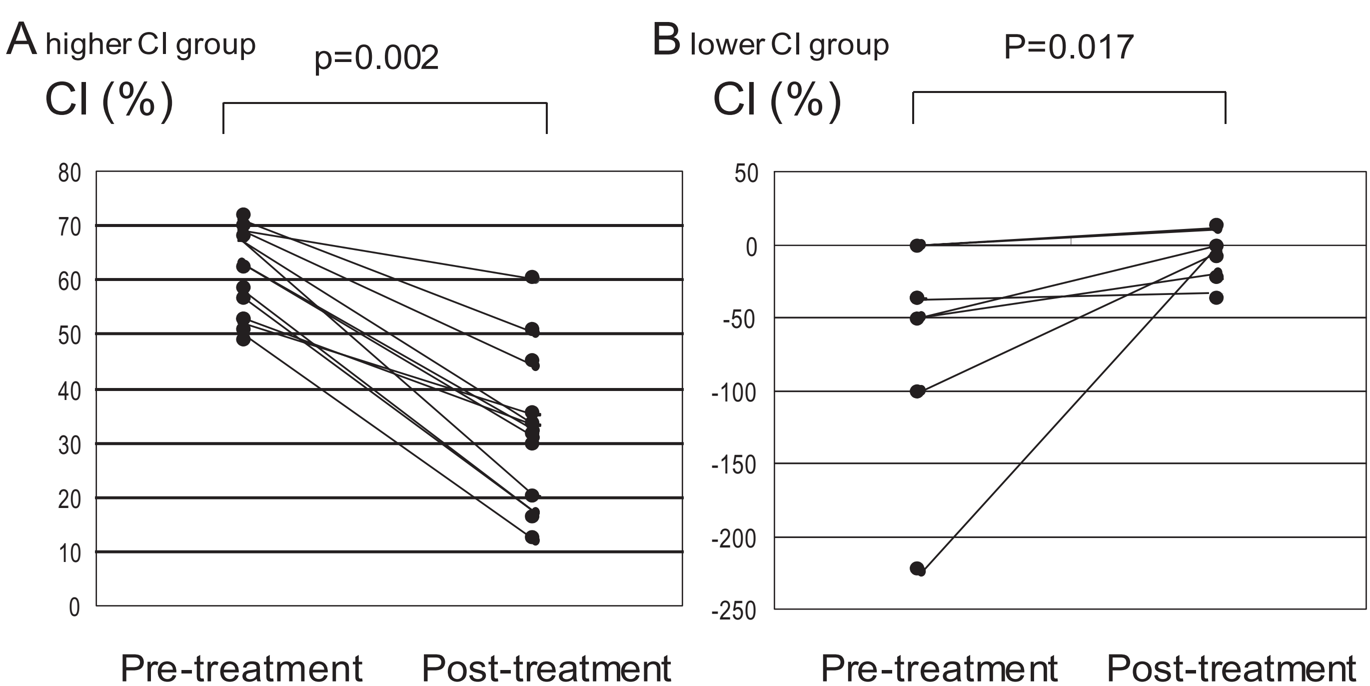

Fig. 5 Changes of collapse index (CI) in patients with orthostatic dysregulation (OD) between pre- and post-treatment by an adrenergic agent. Collapse index (CI) of patients with OD revealed significant changes after treatment both higher CI group (a: CI > 50, $N = 12$; $P < 0.002$) and lower CI group (b: CI ≦ 0, $N = 8$; $P < 0.017$).

Discussion

The current study suggests that OD can be classified into two subtypes: one is characterized by CI > 50 (higher CI group) and another is characterized by CI ≦ 0 (lower CI group). In 12 patients with OD demonstrating CI > 50, there was a marginal decrease in pulse pressure after standing with or without tachycardia. On the contrary, eight patients with OD showing CI ≦ 0 are characterized by a fluctuant increase of pulse rate and marked decrease in CI.

The higher CI group of children seems to correspond to INOH[10] or delayed orthostatic hypotension and the reductions in stroke volume and peripheral vascular resistance with venous pooling in the lower extremities result in the inability to maintain arterial blood pressure and reduce abdominal venous return on upright position.[20–22] Interestingly, it has been reported that increases in norepinephrine in response to standing are suppressed in INOH.[10] However, the lower CI group appears to be categorized into POTS[11] or neurally mediated syncope. As the former is reported to be due to thoracic hypovolemia with inadequate venous return during orthostasis[20] and the latter is induced by specific venous pooling within the splanchnic vascular bed,[23] underlying pathophysiology of this group of OD is speculated to be an increased splanchnic pooling without pooling in the lower extremities.[24]

We have explored more simple and easy ways to evaluate the patients with OD in regard to its hemodynamic change. Kino and Kobayashi[15] first reported that IVC diameter of children with OD on standing position was reduced and that CI was more than 50 in those children while mean CI in healthy adolescents was 10.5 in a relatively small number of subjects. Ishizaki *et al*.[19] later concluded that young adults with OD caused by a simulated microgravity experiment could be classified into subtypes based on the CI values. Although it is currently uncertain what affects the abnormal CI value in patients with OD, it should be noted that all of 20 patients with OD reveal abnormal CI (>50 or ≦0) while 23 healthy children demonstrated CI between 0 and 50 (diagnostic specificity 100% and sensitivity 100%).

In this study, it should be noted that a degree of improvement in symptoms under HUT after pharmacological treatment correlates well with that of change in CI value. This finding seems to be valuable because it is difficult to assess the efficacy of treatment in OD objectively at the outpatient clinic. Midodrine hydrochloride known to be effective in improving symptoms in POTS[25] is characterized by raising blood pressure without direct action on the heart or central nervous system.[26] The finding in normalization in CI by this drug in the present study suggests that the actions of the agent are not only via changes in arterial vascular tone but also via an increase in abdominal venous return.

We should note limitations of this study. The sample size was too small to analyze changes of blood pressure and pulse rate statistically. In order to establish the measurement of IVC of abdominal echography as a specific diagnostic tool of OD, it is obviously necessary to study the relationship between changes in IVC diameters on standing test and the other factors (i.e. peripheral vascular resistance, circulating catecholamine, and nitric oxide in a larger number of patients).

In conclusion, we postulate that the measurement of IVC diameter using an abdominal echogram is useful for diagnosis and simple classification of OD and for objective assessment of the efficacy of midodrine hydrochloride for the general pediatrician, though it is clearly needed to study larger number of patients. From the view point of clinical practice, we concluded that the measurement of IVC diameters was beneficial to examine the effect of pharmacological treatment more objectively and visually.

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