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Effect of Two Hours Head-down Bedrest on Orthostatic Tolerance

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=ABSTRACT=

This study was carried out to determine the effect of -6° head-down bedrest on the cardiovascular and hormonal responses to orthostasis and to evaluate the mechanism of orthostatic intolerance. Ten healthy young men were changed the body position from -6° head-down or supine bedrest for 2 hr to 70° head-up tilt for 20 min.

During the bedrest, there were no differences in hemodynamic and hormonal changes between the head-down and the supine positions. However, the tendency of decreased end-diastolic volume and increased cardiac contractility during the later period of 2 hr showed that the cardiovascular adaptation could be accelerated within a relatively short period in the head-down bedrest.

During the head-up tilt, presyncopal signs were developed in five subjects of the supine bedrest, and one of the same subjects of the head-down bedrest.

In the tolerant subjects, the increase in cardiac contractility and plasma epinephrine level during the head-up tilt was greater following the head-down bedrest than that following the supine bedrest to compensate for reduced venous return.

The intolerant subjects showed the greater decrease in end-diastolic and stroke volume, and the greater increase in heart rate during the head-up tilt than the tolerant subjects. Cardiac contractility and plasma epinephrine level were remarkably increased. However, arterial pressure was not maintained at the level for the appropriate compensation of the reduced venous return.

It seems that the tolerance to orthostasis is more effective after the short-term head-down bedrest than after the supine bedrest, and the secretion of epinephrine induces the higher cardiac performance as a compensatory mechanism for the reduced venous return during the orthostasis following the head-down bedrest than the supine bedrest.

Key Words: Cardiovascular adaptation, Epinephrine, Orthostatic intolerance

INTRODUCTION

The cardiovascular system adapts to the requirement of the new stress level: weightlessness in space. For a person returning to the earth from space travel, however, this adaptation may result in the loss of appropriate cardiovascular responses to orthostatic challenge, defined as orthostatic intolerance. This is a component of cardiovascular deconditioning which could be a serious physiological consequence of the exposure to microgravity for long duration of spaceflight(Nicogossian & Parker, 1982; Blomqvist & Stone, 1983; Lollgen et al,

1986). The etiologic mechanism and possible preventive countermeasures have been widely studied. Investigators have commonly used -6° head-down bedrest to simulate cardiovascular changes during the spaceflight(London et al, 1983; Katkov et al, 1985; Lollgen et al, 1986; Guell et al, 1991), and passive head-up tilt for the simulation of the environment on return to the earth after the spaceflight(Butler et al, 1990; Williamson et al, 1992).

Vasoactive hormones including catecholamines, arginine vasopressin and renin-angiotensin as well as the neural reflexes, have been reported to play major role in determining the orthostatic tolerance(Sprangers et al, 1991; Williamson et al, 1993). These neuro-endocrine responses may be induced by an unloading of baroreceptors when thoracic blood volume is shifted toward the lower extremities during the orthostasis. However, it has not been known which was the major mechanism of the orthostatic intolerance evoked after spaceflight.

The purpose of this study was to observe the cardiovascular and endocrinological effects of -6° head-down bedrest of 2 hr on the response to passive head-up tilt and to evaluate the mechanism of the orthostatic intolerance comparing the differences between tolerant and intolerant subjects to the passive head-up tilt.

METHODS

Subjects

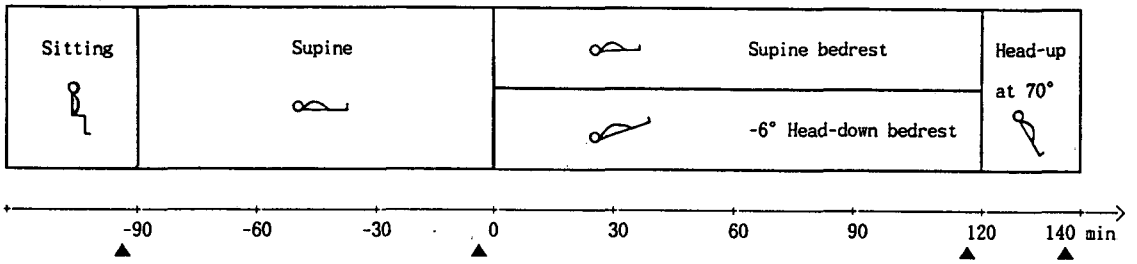
Ten healthy young male medical students participated in the experiment as volunteers. Their physical characteristics are as follows: age, $24.7 \pm 5,70$ yr(mean $\pm$ SD); weight, 65.4 ± 5.78 kg; height, 174.9 ± 6.98 cm. No one had any history of drug abuse, alcoholism, cardiovascular and endocrinological diseases, and experience of regular physical exercise. Subjects were informed a detail about the experimental principle and procedures, and signed on written informed consent. They also viewed and experienced the equipments of head-up tilt once.

Experimental protocol

They were recommended to abstain from alcoholic beverages, any drugs, and a vigorous exercise for 24 hr preceding the experiment. They were also asked to take no meal and no drink at home in the morning of the experimental day. The subjects arrived at the laboratory in 9:00 a.m. and were asked to empty their bladder immediately before the experiment. They took 200 ml milk to hydrate and to prevent the gastric soreness during the experiment. While the resting in a sitting position, they were equipped for determination of hemodynamic parameters and hormones. The subjects lay on a tilting table and took a supine position for 90 min to eliminate the effect of body tilt from the sitting to the supine on the cardiovascular system(Park et al, 1994). Baseline data were collected during last 5 min of the supine position. Each subject participated in two separate protocols; -6° head-down position for 2 hr(HD bedrest) and continuing the supine position for 2 hr(SUP bedrest). Two protocols were carried out at least 1 week interval in random order to rule out the possible influence of the previous protocol. After collection of control data at the end stage of the HD or the SUP bedrest, they were passively tilted to 70° head-up tilt(HUT) for 20 min by a tilting table(Fig. 1). In spite of some subjects successfully completed the HUT test for 20 min(tolerant subjects), the others terminated the test because of the appearance of presyncopal signs (intolerant subjects). The criteria of presyncopal signs included a decrease in arterial pressure or in heart rate below the value of pre-HUT. The signs were usually accompanied with one or more significant subjective symptoms: nausea, clammy skin, paleness, chest discomfort, cold sweating and blurred vision.

Hemodynamic Measurements

Cardiac output(CO), heart rate(HR), stroke volume(SV), thoracic fluid volume(TFV), end-diastolic volume(EDV) and systolic time ratio(STR) were



Hemodynamic measurements: Systemic arterial pressure, Cardiac output, Heart rate, Stroke volume End-diastolic volume, Thoracic fluid volume, Systolic time ratio Total peripheral resistance

Hormonal measurements(▲): Blood sampling for measurements of plasma concentration of norepinephrine, epinephrien, arginine vasopressin and renin activity.

Fig. 1. Protocol of the experiment. Two seperate protocols of 2 hr head-down bedrest and 2 hr supine bedrest were applied to the same subject with at least 1 week interval. Data collections of hemodynamic parameters were obtained every 10 min during the bedrests and every 2 min during the head-up tilt.

continuously recorded before and during the HUT by a impedance cardiograph(NCCOOM$_3$-R7, BoMed, USA). Arterial blood pressure(AP) was determined by a noninvasive automatic blood pressure monitor (DE-70, Nissei, Japan). Total peripheral resistance (TPR) was calculated by mean AP and CO. The AP was represented the mean value of three determinations in every 10 min before the HUT, and of two determinations in every 2 min during the HUT. Other hemodynamic parameters were represented the average value of last 5 min in every 10 min before the HUT, and of last 1 min in every 2 min during the HUT.

Hormonal measurements

A catheter was inserted in left median cubital vein at least 30 min before the baseline measurement, and physiological saline solution was kept in dripping to prevent blood clotting in the catheter. The following hormones and enzyme activities were measured: epinephrine(E) and norepinephrine(NE), arginine vasopressin(AVP) and plasma renin activity(PRA). For the measurement of plasma AVP, 4 ml of blood was transferred into the tube containing EDTA and aprotinin(Sigma, USA), mixed and centrifuged for 20 min at 3,000 rpm. Plasma was stored at −20 °C until AVP was extracted with Sep-Pak C18 cartridge(Waters, USA). The component containing AVP was collected by perfusion with solution of 90% ethanol − 4% acetic acid, dried with 100% nitrogen gas, and stored at −70°C. The plasma for PRA was sampled from 1 ml of blood and stored at −70°C. Plasma concentration of AVP and PRA were determined with the radioimmunoassay determined by Lee et al(1987), and Cho et al(1985), respectively. The plasma for catecholamines was sampled with the solution of EGTA and reduced glutathione(Sigma, USA) from 1 ml of blood and stored at −70°C. The plasma concentrations of catecholamines were measured by radioenzymatic method(Cat A kit, Amersham, UK).

Statistical analysis

All data were processed with SAS in a personal computer. The hemodynamic and hormonal data were presented in mean and standard error(SE). The comparison between the HD and the SUP bedrests or paired comparison were made with Student's t-test. Statistical significance was accepted at 95% and 99% reliability.

RESULTS

On application of the HUT to subjects, five of ten subjects were tolerable to the orthostasis(tolerant subjects), but the others developed presyncopal signs

during the HUT following the SUP bedrest and terminated the experiment(intolerant subjects). The average termination time was 11 min; two subjects at 6 min, two at 11 min, one at 20 min. Following the HD bedrest, only one of the same intolerant subjects developed the syncopal signs at 4 min of the HUT.

Hemodynamic changes during 2 hr HD or SUP bedrest are shown in Table 1 and Fig. 2. MAP, CO, TPR, EDV and SV did not significantly change during the earlier period of 2 hr in the both bedrests. During the later period, EDV and SV decreased in the HD bedrest, whereas there were no changes in the SUP bedrest. TFV exhibited significant increase ($p<0.05$) during the earlier period in the HD bedrest comparing to the SUP bedrest, and slightly decreased in the later period. HR did not change in the earlier period, then tended to increase in the HD bedrest, whereas HR increased significantly($p<0.05$) at 30 min and 2 hr during the SUP bedrest. STR decreased($p<0.05$) during the earlier 60 min in the both bedrests. During the later period, STR tended to increase in the SUP bedrest but decreased in the HD bedrest.

During the HUT for 20 min, hemodynamic changes are shown in Fig. 3 to 5. The changes in hemodynamic parameters were very dramatic with the occurrence of presyncopal signs. It might be related to the different hemodynamic responses that could occur between tolerant and intolerant subjects to orthostasis. In tolerant subjects, the increase of DBP was more prominent than SBP. There were no significant differences of the changes in AP, CO, HR, TPR and SV during the HUT between post-SUP and post-HD bedrests, except of TPR at 16 min. However, EDV more decreased($p<0.05$) and STR less increased($p<0.05$) during the HUT in the post-HD bedrest than in the post-SUP bedrest. In intolerant subjects of the both bedrests, MAP did not increase as remarkable as tolerant subjects, but SBP decreased. HR further increased($p<0.05$), whereas EDV and SV further decreased in the intolerant subjects than in the tolerant subjects. STR showed the tendency to less increase in the intolerant subjects.

After HD or SUP bedrests for 2 hr, plasma NE decreased($p<0.05$) in the HD bedrest, but not in the SUP bedrest. PRA decreased($p<0.01$) but E and AVP did not change in the both bedrests(Fig. 6 & 7).

During the HUT, plasma NE, E and PRA remarkably increased 2 or 3 times in the both bedrests,

Table 1. Hemodynamic values before and after 2 hours supine and head-down bedrests

Parameter	Unit	Supine bedrest		Head-down bedrest	
		Before	After	Before	After
Arterial pressure	mmHg				
Systolic		99.4±3.28	105.7±2.60	98.7±2.78	104.7±3.10
Mean		77.1±2.21	81.2±1.34	75.6±1.68	78.5±1.99
Diastolic		65.8±2.05	69.0±1.97	64.0±1.76	65.4±2.29
Cardiac output	L/min	5.5±0.37	5.3±0.37	5.2±0.39	5.1±0.36
Heart rate	beats/min	64.8±3.23	69.1±4.47	65.4±3.82	67.3±4.65
Total peripheral resistance	PRU	0.89±0.079	0.98±0.090	0.92±0.069	0.98±0.093
Stroke volume	ml	84.9±7.39	80.2±7.96	80.1±7.67	77.0±7.71
End-diastolic volume	ml	137±10.4	129±10.3	132±10.2	124±10.8
Thoracic fluid volume	ml	6190±241	6200±254	6140±230	6190±238
Systolic time ratio	%	34.3±1.63	35.1±2.50	37.0±2.23	34.7±2.18

Note: Values are presented mean±standard error. PRU=peripheral resistance unit.

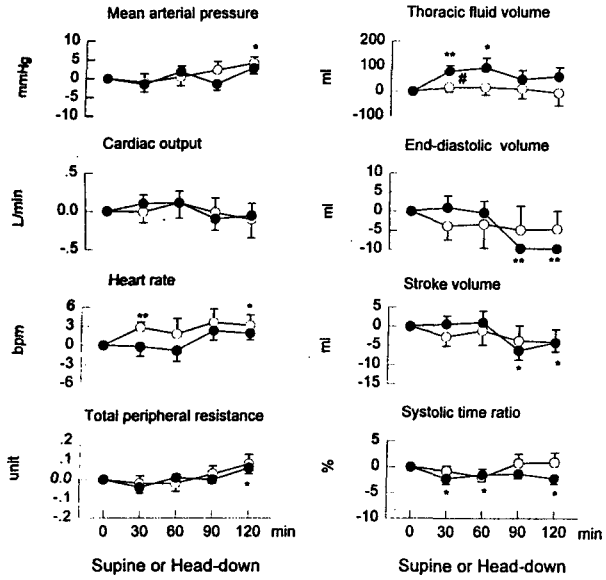


*Fig. 2. Hemodynamic changes during supine(○) or −6° head-down(●) bedrests for 2 hours. Significance of the change before vs during each bedrest: * p<0.05, ** p<0.01; between supine and head-down bedrests: # p<0.05.*

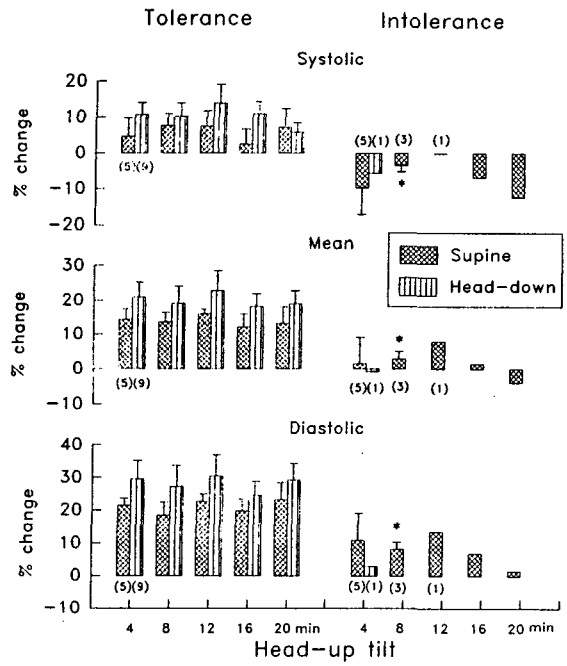


*Fig. 3. Comparison of changes in arterial blood pressures between tolerant and intolerant subjects during the head-up tilt. Number in parenthesis indicates the subjects continuing the experiment at the corresponding time. Comparison of the changes between intolerant and tolerant subjects: * p<0.05*

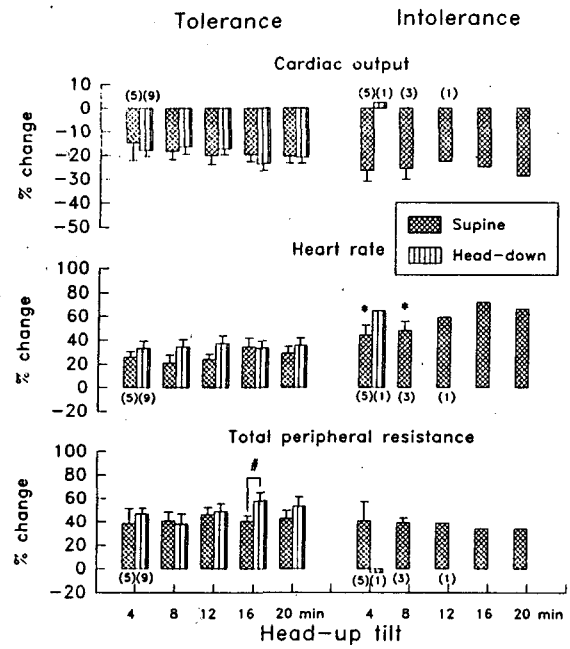


*Fig. 4. Comparison of change in hemodynamics between tolerant and intolerant subjects. Number in parenthesis indicates the subjects continuing the experiment at the corresponding time. Comparison of the changes between intolerant and tolerant subjects: * p<0.05; between supine and head-down bedrests: # p<0.05.*

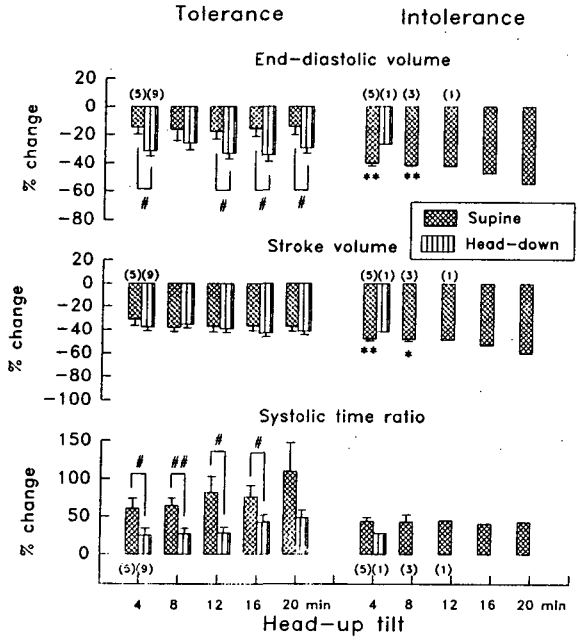


*Fig. 5. Comparison of change in hemodynamics between tolerant and intolerant subjects. Number in parenthesis indicates the subjects continuing the experiment at the corresponding time. Comparison of the changes between intolerant and tolerant subjects: * p<0.05, ** p<0.01; between supine and head-down bedrests: # p<0.05, ## p<0.01.*

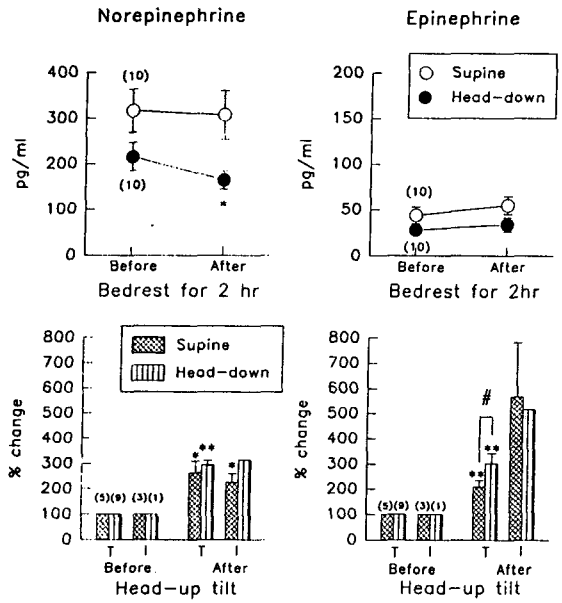


*Fig. 6. Comparison of changes in plasma catrcholamine concentration. T = tolerant subjects; I = intolerant subjects. Number in parenthesis indicates the subjects continuing the experiment at the corresponding time. Comparison of the change before vs after each position change: * p<0.05, ** p<0.01; between supine and head-down bedrests: # p<0.05.*

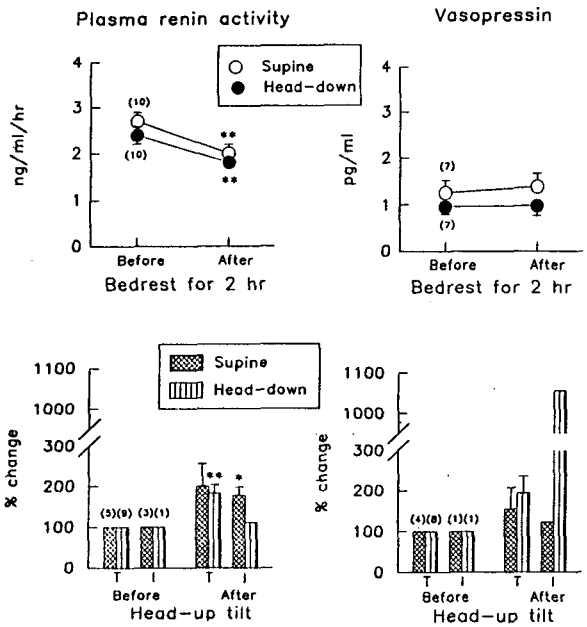


*Fig. 7. Comparison of changes in plasma renin activity and arginine vasopressin. T = tolerant subjects; I = intolerant subjects. Number in parenthesis indicates the subjects continuing the experiment at the corresponding time. Comparison of the change after vs before each position change: * p<0.05, ** p<0.01.*

whereas AVP did not show the significant change except in intolerant subject of the post-HD bedrest which showed increase more than 10 times comparing to the pre-HUT value, it was not verified statistically, however. The amount of increase in plasma E was more prominent in tolerant subjects of the post-HD bedrest than in those of post-SUP. In comparison between tolerant and intolerant subjects during the HUT, plasma E in intolerant subjects tended to further increase.

DISCUSSION

We did not observe significant differences in hemodynamic and hormonal changes between the HD and the SUP bedrests throughout the 2 hr period. Both SUP and HD bedrests induce the headward fluid shift which stimulates volume receptors in the low-pressure systems. The activation of these receptors inhibits sympathetic neural activity, plasma AVP and renin-angiotensin-aldosterone system (Sekiguchi et al, 1993). In the later period of 2 hr bedrests, however, a process of cardiovascular adaptation to the central blood pooling tended to be more rapidly accelerated in the HD bedrest than in the SUP bedrest. The lower tendency of STR and EDV in the HD bedrest seems to be related with the accelerated adaptation which may influence the cardiovascular tolerance during orthostasis(Bae & Park, 1995).

Orthostasis induces fluid shifts toward the legs, as indicated by the increased leg volume(Butler et al, 1991). The fluid shift leads to decrease in venous return and CO, which elicits the increase of HR, TPR and AP for a compensatory response of baroreceptors in order to maintain the adequate blood flow to the vital organs(Lollgen et al, 1986; Frey et al, 1987). Vasoactive hormones such as plasma NE and PRA also increase in this stage(Butler et al, 1991; Sekiguchi et al, 1993). We observed the same trends in the cardiovascular and hormonal responses to the HUT mentioned above, regardless of the post-HD or the post-SUP bedrest, but they were not exactly same in all parameters. In the post-HD bedrest, lower EDV was compensated by increased cardiac contractility, and SV was maintained. Butler et al(1991) also reported higher TPR and lower STR during HUT in the HD group than in 5 min supine group in which lower STR indicates the higher myocardial contractility.

The adaptation of cardiovascular system to the HD bedrest has been proved to induce the inappropriate orthostatic responses. The 2 hr exposure to HD bedrest in the present study was quite short-term compared with the current spaceflight, lasting several days to months. However, orthostatic intolerance was observed after the spaceflight of about 5 hr duration(Nicogossian & Parker, 1982). Five subjects after the 2 hr SUP bedrest, experienced presyncopal signs during the orthostasis, and only one of the same subjects after the 2 hr HD bedrest. This means that the 2 hr HD bedrest is more tolerable to orthostasis than the 2 hr SUP bedrest, which was an unexpected result. We postulate that this result was a transient phenomenon of the cardiovascular deconditioning occurring in the early stage of HD bedrest, and might suggest a clue for the countermeasure to orthostatic intolerance which could occur following a spaceflight as the consequence of cardiovascular deconditioning.

Though the etiology responsible for orthostatic intolerance remains unresolved, one or more possible mechanisms including the reduction of blood volume, the failure of appropriate autonomic reflexes, and the changes of venous compliance in the lower limbs, would be involved(Butler et al, 1991; Sekiguchi et al, 1993).

Several investigators have suggested the role of reduced blood volume during the bedrest for the cause of orthostasis intolerance(Nixon et al, 1979; Gaffney et al, 1985). However, others reported the negative results that the replacement of fluid volume failed to counteract the orthostatic intolerance(Bungo et al, 1985); the orthostatic intolerance could be found under the constant plasma volume(Buttler et al, 1990). Though we did not measure the changes

in plasma volume, there was no hemodynamic evidence that the orthostatic intolerant subjects have had the relatively decreased blood volume prior to the HUT.

In autonomic control on the vascular system, Convertino et al(1990) reported that prolonged HD bedrest could impair the vagal reflex as indicated by bradycardia, and Sekiguchi et al(1993) reported that the primary event of presyncope seemed to be the failure of response of heart rate to the reduced venous return. However, we did not observe the direct relationship between reduced SV and bradycardia to support such result. In the intolerant subjects, HR rather increased, and plasma NE and PRA maintained at the similar level as that of the tolerant subjects. Cardiac contractility was more efficient in compensatory response to lower SV and EDV in the intolerant subjects, which was indicated by the responses of plasma E and STR.

The cause of orthostatic intolerance may be related to the decreased tone in venous capacitance vessels, adapted by a stress relaxation with time to the increased stress of the fluid shift(Buttler et al, 1991). Cardiovascular deconditioning disturbed the hemodynamic adjustment by the reduced constrictive ability of peripheral vessels(Convertino et al, 1990). The time course for the change in venous capacitance might be indicated by the changes in the cardiovascular responses to the HD bedrest. It would be correlated with the lower EDV and SV in the intolerant subjects in this study.

Guezennec et al(1990) reported that circulating catecholamines increased during orthostasis. Marked increase of plasma E during the HUT in the intolerant subjects and in the HD bedrest, comparing to the tolerant subjects and the SUP bedrest respectively, suggest a rapid secretion from the adrenal medulla to compensate the reduced venous return. In the intolerant subjects, however, the decrements of EDV and SV were not adequately compensated by the sympathoadrenal activation, consequently arterial pressure was not maintained and cerebral blood flow diminished, which occurred the presyncope.

The increased activity of renin-angiotensin-aldosterone system and AVP could be attributed to stimulation of arterial baroreceptors and central volume receptors due to the decrease in thoracic blood volume during the orthostasis(Robertson et al, 1976; Johnson et al, 1977). However, it seems that PRA and AVP did not play the role as the primary mechanism of orthostatic intolerance.

The present study represents the evidence that the blood pooling in the venous capacitance system is a primary cause of orthostatic intolerance. Comparing cardiovascular and hormonal responses during the orthostasis, distinct differences were found in EDV, STR and plasma E between the post-HD and the post-SUP bedrests, and also found in HR, EDV, SV and plasma E in the intolerant subject just before presyncope. From these results, the mechanism of orthostatic intolerance can be explained as follows. While blood shifting to the lower body to the orthostasis, the greater venous pooling by greater venous compliance reduces further the venous return. Generally, the decreased venous return is compensated by increased HR and TPR resulted from the adjustment of autonomic nervous and vasoactive hormonal reflexes. In the HUT following the HD bedrest, the sympathetic nervous activation can not maintain arterial pressure and CO properly, which induces a higher secretion of E from the adrenal medulla and raises the cardiac contractility as an additional hormonal compensation. In the case of orthostatic intolerance, however, arterial pressure and CO are still reduced inspite of the compensation by the increased secretion of E, and presyncope develops finally. Therefore, it seems that plasma level of E may play a role in determination whether to initiate the mechanism of the orthostatic intolerance, and it is possible that long lasting HD bedrest would be more susceptible to the orthostasis than the supine bedrest. Further study will be necessary to understand the mechanisms of susceptibility to cardiovascular deconditioning.

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