Eur J Appl Physiol (1991) 62:26-30

European Journal of Applied Physiology and Occupational Physiology

Reduced orthostatic tolerance following 4 h head-down tilt

Gary C. Butler, Huacheng Xing, David R. Northey, and Richard L. Hughson

Department of Kinesiology, University of Waterloo, Waterloo, Ontario, Canada, N2L 3G1

Accepted July 4, 1990

Summary. The cardiovascular responses to a 10-min 1.22 rad (70°) head-up tilt orthostatic tolerance test (OST) was observed in eight healthy men following each of a 5-min supine baseline (control), 4 h of 0.1 rad (6°) head-down tilt (HDT), or 4 h 0.52 rad (30°) head-up tilt (HUT). An important clinical observation was presyncopal symptoms in six of eight subjects following 4 h HDT, but in no subjects following 4 h HUT. Immediately prior to the OST, there were no differences in heart rate, stroke volume, cardiac output, mean arterial pressure and total peripheral resistance for HDT and HUT. However, stroke volume and cardiac output were greater for the control group. Mean arterial pressure for the control group was less than HDT but not HUT. Over the full 10-min period of OST, the mean arterial pressure was not different between groups. Heart rate increased to the same level for all three treatments. Stroke volume decreased across the full time period for control and HDT, but only at 3 and 9 min for HUT. There was a higher total peripheral resistance in the HDT group than control or HUT. The pre-ejection period to left ventricular ejection time ratio was less in HDT than for control or HUT groups. These data indicate a rapid adaptation of the cardiovascular system to 4 h HDT that appears to be inappropriate on reapplication of a head to foot gravity vector. We speculate that the cause of the impaired orthostatic tolerance is decreased tone in venous capacitance vessels so that venous return is inadequate.

Key words: Microgravity simulation - Bedrest - Plasma volume - Blood pressure - Venous capacitance

Introduction

On earth, the circulatory system has adapted to counter the stress of the head to foot gravitational gradient. This includes a requirement to pump blood to the brain against the hydrostatic gradient, and prevention of blood pooling in the dependent capacitance vessels. On exposure to microgravity, or to earth-based analogs such as head-down tilt bed rest (HDT), the need to counter the effects of gravity is removed. The cardiovascular system adapts to the requirements of the new stress level (Blomqvist and Stone 1983; Gaffney et al. 1985). The consequence of this on return to earth from space travel, or after periods of supine on HDT bed rest, is the loss of appropriate cardiovascular reflexes to adequately meet the orthostatic challenge (Lollgen et al. 1986; Blomqvist and Stone 1983; Nicogossian and Parker 1982). This is a component of "cardiovascular deconditioning" (Levy and Talbot 1983).

The mechanisms responsible for cardiovascular deconditioning remain unresolved. It has been suggested that the reduction in blood volume, or a failure of appropriate autonomic reflexes to maintain adequate perfusion of the brain results in syncope or presyncopal symptoms (Blomqvist and Stone 1983). In this study, we report on the cardiovascular responses to head-up tilt (HUT 1.22 rad or 70°) orthostatic tolerance test (OST) following either 4 h HDT (0.1 rad or 6°) or 4 h of HUT (0.52 rad or 30°). It has been observed that within the first 30-60 min of HDT that cardiac output (Butler et al. 1990) and central venous pressure (Gaffney et al. 1985; Nixon et al. 1979) have significantly increased then returned to baseline values. Further, with relevance to the present investigation, it is known that blood volume is not significantly different from the control value after 4 h HDT (Butler et al. 1990). Therefore, it is possible to examine orthostatic tolerance where altered blood volume is not a potential mechanism for reduced cardiovascular function.

Methods

Subjects. Eight healthy male volunteers (ages 19-34 years) took part in this study. Subject characteristics and descriptive statistics (mean, SD) included the following: age 24.2, 6.3 years; height, 1·78, 0.068 m; mass, 76.7, 5.6 kg; and maximum oxygen consumption ($\dot{V}O_{2max}$), 45.5, 5.5 $ml \cdot kg^{-1} \cdot min^{-1}$. Each subject signed a consent form approved by the Office of Human Research

Offprint requests to: R. L. Hughson

after receiving a complete description of the procedures and the potential risks involved. All subjects were asked to refrain from heavy exercise and from caffeinated or alcoholic beverages for 24 h prior to the study. Subjects were asked to empty their bladders immediately on rising on the morning of the study, then to drink two large glasses of water or fruit juice.

Experimental procedure. Subjects completed the OST test (1.22 rad) on three separate occasions. The first was part of a preliminary testing session. The subjects rested in the supine position for 5 min immediately prior to being moved to the OST for 10 min. The second and third tests were presented in random order after two different experimental manipulations (Butler et al. 1990). The tests consisted of a 1-h baseline period of HUT (0.52 rad) followed by 4 h of HDT (0.1 rad), or 1 h of HUT (0.52 rad) followed by an additional 4 h of HUT (0.52 rad). Immediately on completion of the 4-h tilt, the subjects were rapidly moved into the OST position. The bed was constructed to permit easy movement between these desired tilt angles. Foot support was provided, and the subjects were instructed to remain as motionless as possible during the 10 min OST. Subjects were constantly observed for signs of presyncope.

Heart rate was monitored prior to the OST, then at 1, 3, 5, 7 and 9 min of tilt. Blood pressure was measured at the same time by sphygmomanometry. Stroke volume and cardiac output were obtained by impedance plethysmography (Model 304B, Surcom, Minneapolis, Minn.) at the same sample time. Four pairs of Ag/AgCl electrodes were placed on the lateral midlines at the same levels typically described for band electrode placement (Kubicek et al. 1966). A constant current of 4 mA at a frequency of 100 kHz was introduced into the outer electrode pairs with voltage recorded from the inner electrode pairs. The resultant values of basal impedance (Z_0), the rate of change of impedance (dZ/dt), and the electrocardiogram (ECG) were digitally recorded at a frequency of 100 Hz. All complexes recorded over a 15-s period were ensemble-averaged to yield a single complex for calculating of the stroke volume according to the equation of Bernstein (1986). The systolic time interval, pre-ejection period (PEP), and left ventricular ejection time (LVET), were obtained from the ECG and impedance signals corrected for heart rate (Venitz and Lucker 1984). PEP was taken from the Q wave of the ECG to the start of the rapid upslope of the dZ/dt signal. LVET was the time from the rapid upslope to the X point on the dZ/dt signal at the second heart sound.

Blood samples were obtained from a dorsal hand vein at the 1-h point of the baseline HUT (0.52 rad), and after 4 h of HDT (0.1 rad) or HUT (0.52 rad) (Butler et al. 1990). Hematocrit and hemoglobin concentrations were determined to permit calculation of change in plasma volume (Greenleaf et al. 1981).

Statistical analysis. A two-way analysis of variance was used to compare between experimental treatment (control, HDT and HUT), and time effects on each variable. Post-hoc analysis was with Student-Neuman-Keuls test when a significant main effect was found. A one-way analysis of variance was used to test for significant time effects with respect to the baseline measurement for the experimental treatment group. Post-hoc analysis was with Duncan's Multiple Range test. Statistics were performed on data from five subjects who completed 9 min of the OST.

Only those subjects who completed all data collection periods to 9 min were included in the statistical analysis presented here. Of the eight subjects, five completed the final data collection period after HDT. Presyncopal signs were seen in the 10th min of observation in three more subjects.

Results

Changes in plasma volume were followed from the 1 h HUT (0.52 rad) baseline position through 4 h of HDT (0.1 rad) or HUT (0.52 radians). In neither case was the plasma volume significantly different from baseline. Changes in plasma volume were not determined for the control experiments.

There were no differences between the HDT and HUT positions at the baseline measurement obtained following the 4-h period for each of heart rate, stroke volume, cardiac output, mean arterial pressure, and total peripheral resistance (Table 1). Likewise, the control baseline heart rate was not different from either HDT or HUT (Table 1). In contrast, after the 5-min supine baseline for the control tests, stroke volume and cardiac output were greater than HDT and HUT, mean arterial pressure was less than HDT but not HUT, and total peripheral resistance was significantly less than HDT and HUT (Table 1). The baseline value of PEP/LVET was smaller for both control and HDT than HUT (Table 2).

Most of the variables showed significant time-dependent effects. The notable exception was mean arterial pressure. It remained relatively constant across the observation period. However, it must be noted that during the control test, one subject experienced presyncopal symptoms just after the 9-min sample point. In the OST following HDT, three subjects were unable to complete 5 min of tilt (symptoms at 2.6, 4.5, and 4.7 min) and three more were unable to complete the full 10 min of tilt because of presyncopal symptoms (symptoms at 9.25, 9.25, and 9.90 min). Therefore, while three subjects (not included in the statistical analysis) exhibited similar responses to other subjects at the completed sample points, their blood pressure and other responses changed very dramatically with presyncope.

Heart rate increased significantly immediately on tilt to the OST position following HDT and control but not HUT (Table 1). There were no differences between groups during the tilt. Stroke volume significantly decreased across the whole time period in both the control and HDT groups, but only at 3 and 9 min in the HUT group during the tilt. Cardiac output decreased significantly only in the control group; both the HDT and HUT groups showed relative contstancy over the 10-min tilt test. Total peripheral resistance increased in the control group, but not in the HDT or HUT groups. There was, however, a trend towards greater total peripheral resistance at most sample points in the HDT group than the HUT or control groups. The PEP index increased, LVET index decreased and PEP/LVET increased significantly on going to the OST position for all three groups (Table 2).

Discussion

The adaptation of the cardiovascular system to HDT proved to be inappropriate for return to HUT (1.22 rad). This was evident as six of eight subjects experienced signs of presyncope and had to be returned to the horizontal position before the completion of the OST. Yet, these same subjects were all able to finish the OST following 4 h HUT (0.52 rad), and only one had

Table 1. Cardiovascular variables during 10 min of head-up tilt (1.22 rad) following control (Con), head down tilt (HDT) and head-up tilt (HUT) periods

		Time (min)					
		B	1	3	5	7	9
HR	Con	61	82*	89*	91*	89*	91*
(beats·min^{-1})		(11)	(12)	(15)	(14)	(13)	(10)
	HDT	60	81*	87*	87*	88*	89*
		(15)	(17)	(21)	(17)	(16)	(17)
	HUT	68	83	82	82	84	88
		(12)	(16)	(16)	(16)	(16)	(16)
SV	Con	123	74*	67*	65*	65*	68*
(ml)		(29)	(22)	(17)	(17)	(19)	(18)
	HDT	94	70*	69*	68*	62*	62*
		(30)	(19)	(19)	(16)	(14)	(17)
	HUT	90	82	74*	78	76	72*
		(29)	(24)	(27)	(23)	(19)	(22)
$\dot{Q}$	Con	7.4	5.9*	5.8*	5.8*	5.6*	6.1*
(l·min^{-1})		(1.8)	(1.5)	(1.3)	(1.3)	(1.2)	(1.3)
	HDT	5.0	5.4	5.7	5.8	5.3	5.3
		(0.9)	(0.9)	(0.9)	(0.87)	(0.76)	(0.79)
	HUT	5.9	6.4	6.2	5.9	6.4	6.2
		(1.0)	(0.6)	(0.9)	(1.3)	(0.4)	(1.1)
MAP	Con	11.2	12.2	12.0	12.1	12.1	12.3
(kPa)		(0.6)	1.5	1.2	(1.0)	(1.0)	(1.0)
	HDT	12.9	13.1	13.2	13.0	12.8	12.3
		(1.4)	1.4	1.6	(1.5)	(1.8)	(1.7)
	HUT	12.0	12.6	12.4	11.9	12.5	12.6
		(1.2)	(1.7)	(1.4)	(1.0)	(1.6)	(1.6)
TPR	Con	1.64	2.13*	2.13*	2.18*	2.25*	2.10*
(kPa·l^{-1}·min)		(0.35)	(0.50)	(0.49)	(0.54)	(0.52)	(0.52)
	HDT	2.50	2.50	2.32	2.32	2.42	2.36
		(0.47)	(0.50)	(0.43)	(0.37)	(0.32)	(0.54)
	HUT	2.10	2.01	2.11	2.05	2.00	2.10
		(0.38)	(0.29)	(0.39)	(0.30)	(0.19)	(0.49)

HR, heart rate; SV, stroke volume; $\dot{Q}$, cardiac output; MAP, mean arterial pressure; TPR, total peripheral resistance.
* $P<0.05$ for comparison with baseline (B) values.
] $P<0.05$ for comparison between treatment groups.
Values are mean (SD) of the five subjects who completed the 9-min sample point after HDT

signs of presyncope during the control test that followed 5-min supine rest. Evidence of impaired orthostatic tolerance following HDT or space flight has been noted before (Nicogossian and Parker 1982; Blomqvist and Stone 1983; Gaffney et al. 1985; Nixon et al. 1979; Lollgen et al. 1986). In the present study, impaired orthostatic tolerance was found in spite of (1) the short exposure to HDT, (2) the constancy of total plasma volume immediately prior to tilt, and (3) the directionally appropriate responses of the cardiovascular system. The mechanism for this altered function of the cardiovascular system is unknown, but several factors will be considered.

The 4-h exposure to HDT or HUT in the present study was quite short-term with respect to current manned space flight lasting several days to months. However, reduced orthostatic tolerance has been reported after space flight of greater than 5-h duration (Nicogossian and Parker 1982). Lollgen et al. (1986) observed that some subjects were unable to tolerate 18 min exposure to rather severe challenge of −50 mm Hg lower body negative pressure (LBNP) after 2 h HDT (0.1 rad) while all subjects were tested without problem some days prior to the test. The mechanism responsible for this impaired orthostatic tolerance was not resolved by Lollgen et al. (1986); however, these investigators speculated that a decrease in total blood volume might account for the smaller stroke volume and cardiac output. Other investigators who have studied orthostatic tolerance following longer periods of HDT or 6 h of water immersion also suggested a role for reduced total blood volume in the impairment (Gaffney et al. 1985; Nixon et al. 1979). While this remained an attractive explanation, it has been recognized that the degree of impairment is greater than can be accounted for solely by the loss of plasma volume (Blomqvist and Stone 1983). In fact, replacement of fluid volume to original levels fails to counter orthostatic intolerance (Bungo et al. 1985; Hyatt and West 1977). The current results go one step further in investigating the role of total plasma volume in orthostatic intolerance. We found that the plasma volume was not significantly different from either the

Table 2. The pre-ejection time:ejection time (PEP/ET) ratio, pre-ejection period and left ventricular ejection time during 10 min of head-up tilt (1.22 rad) following control (Con), head-down tilt (HDT) and head-up tilt (HUT) periods

		Time (min)					
		B	1	3	5	7	9
PEPI	Con	99	128*	137*	136*	140*	140*
(ms)		(19)	(15)	(14)	(15)	(11)	(10)
	HDT	103	122*	127*	129*	133*	133*
		(16)	(17)	(20)	(16)	(14)	(12)
	HUT	120	128	134	133	134	137
		(18)	(14)	(11)	(15)	(15)	(12)
LVETI	Con	398	360*	360*	362*	358*	364*
(ms)		(09)	(12)	(07)	(06)	(04)	(07)
	HDT	394	367*	370*	368*	364*	363*
		(08)	(8)	(15)	(11)	(15)	(16)
	HUT	356	353	357	352	353	356
		(17)	(18)	(11)	(13)	(12)	(14)
PEP/LVET	Con	0.25	0.35*	0.37*	0.38*	0.39*	0.38*
		(0.05)	(80.04)	(0.03)	(80.04)	(0.03)	(0.03)
	HDT	0.26	0.33*	0.34*	0.35*	0.36*	0.37*
		(0.04)	(0.04)	(0.05)	(0.04)	(0.03)	(0.03)
	HUT	0.34	0.36	0.37	0.37	0.38	0.38
		(0.06)	(0.03)	(0.03)	(0.04)	(0.04)	(0.03)

PEPI, Pre-ejection period index; LVETI, left ventricular ejection time index.
* $P<0.05$ for comparison with baseline (B) values.
] $P<0.05$ for comparison between treatment groups.
Values are mean (SD) of the five subjects who completed the 9-min sample point after HDT

baseline pre-tilt, or the HUT values (0.52 rad) (Butler et al. 1990), i.e., impaired orthostatic tolerance was found in the face of constant total plasma volume.

It could be argued that hemoconcentration may take place on going from HDT to the OST position as hydrostatic pressure changed in the lower limbs. We did not measure plasma volume changes in this period. Future studies might do this to determine if there is any contribution of postural hemoconcentration to orthostatic intolerance. In support of our results, Greenleaf et al. (1989) have indicated that the magnitude of resting hypovolemia is not a major factor in determining the orthostatic intolerance following HDT.

Another possible mechanism that could account for the reduced tolerance to orthostatic stress is an impairment of the autonomic control of the vascular system (Levy and Talbot 1983; Blomqvist and Stone 1983). If such a mechanism were to be operative, it might be attributed to reduced sympathetic neural activity. There is no evidence in the present study to support such an idea. Mean arterial blood pressure was maintained at a similar level in each of the control, HDT and HUT treatments. To accomplish this, there were slight differences in the mechanism between the treatments. There was no significant difference between each of control, HDT or HUT in the heart rate response to the OST. Although significant only at specific time points, the stroke volume and cardiac output were generally lower following HDT than in the control or HUT studies. There was a trend towards a greater increase in the total peripheral resistance calculated for the HDT treatment versus the control and HUT treatments. Blood pressure was maintained by both increased heart rate and greater peripheral vasoconstriction. The conclusion that autonomic regulatory mechanisms appear to be intact is in agreement with the reports of unchanged responsiveness to norepinephrine infusion (Chobanian et al. 1974) and the change in arterial pulse volume with LBNP (Blamick et al. 1988).

The apparent similarity of autonomic responses between treatment groups is also shown by the systolic time intervals. Pre-ejection period increased in all groups and left ventricular ejection time decreased. These responses are quantitatively similar to those observed by Stafford et al. (1970).

Because the total plasma volume was maintained, and the autonomic control appeared to be appropriate, at least in the early stages of the OST, additional mechanisms must be considered for the orthostatic intolerance following HDT. It is possible that the effective central venous blood volume was reduced on movement from HDT to the OST position. We speculate that during 4 h of HDT, the venous capacitance vessels adapted with time to the increased stress of the fluid shift by a relaxation or "creep" of the smooth muscle (Rothe 1983). This would reduce venous return as is suggested by the lower stroke volume during the OST following HDT. The time course for a change in venous capacitance might be indicated by the changes in the cardiovascular responses on assuming HDT. The increase in central venous pressure on going to HDT is maintained for less than 1 h (Nixon et al. 1979; Gaffney et al. 1985). Further, the increase in stroke volume and cardiac output in the same situation is also transient with

no significant difference from a HUT baseline after 30 min (Butler et al. 1990). Therefore, it appears that the venous capacitance vessels adapt and that about 30–60 min are required to see the full response. Recently, Monos et al. (1989) observed a dilation and hyperpolarization of saphenous vein smooth muscle in rats resulting from a 2-week exposure to HUT (0.78 rad). During the 10 min OST following HDT, the large central veins might have been unable to constrict to adequate levels to maintain venous return. In contrast, when the OST followed HUT, there had been some degree of pooling in the lower extremities over the previous 4 h such that the central veins were already constricted. The additional reflex response that occurred on going to OST (1.22 rad) might be added on to a baseline level of central venous passive tone that provided for adequate venous return over the full 10 min of the test.

The results of this study show the qualitative and quantitative differences in orthostatic tolerance following 4 h of HDT (0.1 rad) or HUT (0.52 rad). The 4-h tilt provided a period of time for major cardiovascular adaptations. We can conclude, as did Gaffney et al. (1985) for 20 h HDT, that the response to 4 h HDT is a successful adaptation to the new level of circulatory demand. Unfortunately, this adaptation is inappropriate when the challenge of the normal gravity vector is reintroduced. The present study has shown the rapidity of this adaptation. Further, we believe the data represent evidence of pooling of blood in the venous capacitance system.

Acknowledgement. This research was supported by a grant from the Natural Sciences and Engineering Research Council of Canada.

References

Bernstein DP (1986) A new stroke volume equation for thoracic electrical bioimpedance: theory and rationale. Crit Care Med 14:904–909

Blamick CA, Goldwater DJ, Convertino VA (1988) Leg vascular responsiveness during acute orthostasis following similated weightlessness. Aviat Space Environ Med 59:40–43

Blomqvist CG, Stone HL (1983) Cardiovascular adjustments to gravitational stress. In: Shepherd JT, Abboud FM, Geiger SR (eds) Handbook of physiology. The Cardiovascular system. Peripheral circulation and organ blood flow. American Physiological Society, Bethesda, MD, pp 1025–1063

Bungo MW, Charles JB, Johnson PC (1985) Cardiovascular deconditioning during space flight and the use of saline as a countermeasure to orthostatic intolerance. Aviat Space Environ Med 56:985–990

Butler GC, Xing HC, Hughson RL (1990) Cardiovascular response to 4 hours of 6° head-down tilt or 30° head-up tilt bed rest. Aviat Space Environ Med 61:240–246

Chobanian AV, Lille RD, Tercyak A, Blevins P (1974) The metabolic and hemodynamic effects of prolonged bed rest in normal subjects. Circulation 49:551–559

Gaffney FA, Nixon JV, Karlsson ES, Campbell W, Dowdey ABC, Blomqvist CG (1985) Cardiovascular deconditioning produced by 20 hours of bedrest with head-down tilt (−5°) in middle-aged healthy men. Am J Cardiol 56:634–638

Greenleaf JE, Sciaraffa D, Shvartz E, Keil LC, Brock PJ (1981) Exercise training hypotension: implications for plasma volume, renin, and vasopressin. J Appl Physiol 51:298–305

Greenleaf JE, Bernauer EM, Ertl AC, Trowbridge TS, Wade CE (1989) Work capacity during 30 days of bed rest with isotonic and isokinetic exercise training. J Appl Physiol 67:1820–1826

Hyatt KH, West DA (1977) Reversal of bedrest-induced orthostatic intolerance by lower body negative pressure and saline. Aviat Space Environ Med 48:120–124

Kubicek WG, Karnegis JM, Patterson RP, Witsoe DA, Mattson RW (1966) Development and evaluation of an impedance cardiac output system. Aerosp Med 37:1208–1212

Levy MN, Talbot JL (1983) Cardiovascular deconditioning of space flight. Physiologist 26:297–303

Lollgen H, Klein KE, Gebhardt U, Beier J, Hordinski J, Sarrasch V, Borger H, Just H (1986) Hemodynamic response to LBNP following 2 hours HDT (−6°). Aviat Space Environ Med 57:406–412

Monos E, Contney SJ, Cowley AW, Stekiel WJ (1989) Effect of long-term tilt on mechanical and electrical properties of rat sphenous vein. Am J Physiol 256:H1185–H1191

Nicogossian AE, Parker JF (1982) Space physiology and medicine. National Aeronautics and Space Administration, Washington, D.C.

Nixon JV, Murray RG, Bryant C, Johnson Jr RL, Mitchell JH, Holland OH, Gomez-Sanchex C, Vergne-Marini P, Blomqvist CG (1979) Early cardiovascular adaptation to simulated zero gravity. J Appl Physiol 46:541–548

Rothe CF (1983) Venous system: physiology of the capacitance vessels. In: Shepherd JT, Abboud FM, Geiger SR (eds) Handbook of physiology. The cardiovascular system III. American Physiological Society, Bethesda, pp 397–452

Stafford RW, Harris WS, Weissler AM (1970) Left ventricular systolic time intervals as indices of postural circulatory stress in man. Circulation 41:485–491

Venitz J, Lucker PW (1984) Impedance cardiography – a reliable method for measuring cardiac function noninvasively. Methods Find Exp Clin Pharmacol 6:339–346