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Cardiovascular and Hormonal Changes with Different Angles of Head-up Tilt in Men

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Summary

The purpose of this study was to assess the endocrine status, thoracic impedance, blood concentration, and hemodynamic dose-responses using different angles of passive head-up tilt (HUT) ranging from 12° to 70° in the same subjects. Measurements were performed during 20 min supine position (pre-HUT), 30 min upright (HUT12, HUT30, HUT53, or HUT70), and 20 min supine (post-HUT); subjects 70 min in the supine position only (HUT0) served as resting controls. Norepinephrine increased above resting control values by 19, 44, 80, and 102 %; epinephrine by 30, 41, 64, and 68 %; aldosterone by 29, 62, 139, and 165 %; plasma renin activity n. s., 41, 91, and 89 %; vasopressin n.s., 27, 47, and 59 %; thoracic bioimpedance n. s., 8, 13, and 16 %; heart rate n. s., 5, 26, and 45 %, and mean arterial pressure n. s., 5, 7, and 10 %; at min 27 of HUT12, HUT30, HUT53, and HUT70, respectively. Pulse pressure decreased with HUT53 and HUT70 by 4 and 10 %. Hematocrit increased by 0.2, 1.7, 6.3, and 7.2 %, respectively. Blood density increased by 2.3 and 3.0 g/l, plasma density by 1.7 and 1.8 g/l with HUT53 and HUT70. After finishing HUT, heart rate fell to values which stayed below pre-HUT, and also below resting control levels for ≥ 5 min ("post-orthostatic bradycardia") even after the lowest orthostatic load (HUT12). Thoracic impedance and arterial pressure remained increased after terminating HUT30, HUT53, and HUT70. In conclusion, passive orthostatic loading of different extent produces specific dose-responses of different magnitude in the endocrine system, blood composition, thoracic impedance, and hemodynamic variables. The heart rate is depressed even after HUT12, while arterial blood pressure and thoracic impedance exceed pre-stimulus levels after greater head-up tilt, indicating altered cardiovascular response after passive orthostasis.

Key words

Cardiopulmonary baroreceptors • Thoracic electrical bioimpedance • Blood volume • Catecholamines • Arginine vasopressin (AVP)

Introduction

Gravitational stress causes a large number of physiological effects as can be seen during passive orthostasis. Such phenomena, individual or in

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combination, have been investigated in numerous studies. Cardiovascular and endocrine resetting, which continues to be operative after the orthostatic challenge, have attracted less attention. We hypothesized that hormonal and blood volume alterations together with possibly decreased post-tilt central venous pressure (Norsk *et al.* 1986) might alter other cardiovascular parameters after orthostatic stimulus, as well. Therefore, we investigated the full spectrum of variables not only during but also after application of passive orthostasis.

Furthermore, the quantitative relation between various amounts of receptor unloading by different degrees of head-up positioning (i.e. the tilt angle) and hormonal parameters, filtration-dependent blood changes, biophysical and neuro-dynamic variables do not appear to have been studied in the same experiment yet.

In the present study, hemodynamic, volume sensitive, and hormonal variables, as determined during as well as after head-up tilt, indicated elevated blood pressure and decreased heart rate at still reduced plasma volume and elevated hormone levels following 30 min orthostatic loading of different magnitude.

Methods

Subjects

Seven healthy male non-smokers (24-38 years old, 62-75 kg, 170-180 cm, 1.72-1.93 m^2 body surface area) were studied (with 13.6-17.6 % body fat mass estimated by BIA single-frequency bioimpedance measurement). They abstained from any medication, were fully informed about the purpose and the nature of the experiments and gave their informed consent. Medical clearance to participate was required from all subjects and was based on their medical history, physical examination and resting 12-lead electrocardiogram (ECG).

Experimental protocol

Each test day started with a light breakfast (100 g bread with butter and jam, 200 g orange juice) 60 min before the investigations which were performed between 09:00 and 11:00. Each experimental session began with a 40 min supine rest period during which impedance and ECG electrodes, a phonocardiograph microphone, and blood pressure cuff were put in place. The left antecubital vein was cannulated, using a 17-gauge 1.4 x 40 mm three-way stopcock Teflon catheter (TriCath In, Codan Steritex, Denmark). The arm was held in a position where the lower arm remained near the hydrostatic indifference point at all tilting position (Lukaski *et al.* 1986). Variables were measured before (20 min, designated as –20 to 0 min), during (30 min, designated as 0 to 30 min), and after (20 min, designated as 30 to +20 min) head-up tilting maneuver. For analyzing dose-response features and post-tilting states, values were obtained at min 27 (during HUT), min +2 (early post-HUT), and min +50 (late post-HUT), for hormones, from min 25 to 30 (during HUT) and from min 30 to +5 (post-HUT), for thoracic impedance, at min 30 (during HUT) and min +1 to +5 (post-HUT), for blood or plasma densitometry. All data were compared as treatment *vs.* rest control (HUT0) at the same protocol times. The tilt table provided a footboard and chest harness; tilting lasted 30 min.

All test persons underwent five experimental sessions (4 head-up tilt, 1 without tilting = rest control), in randomized order on different test days. No presyncopal symptoms occurred.

Venous blood was taken from an uncongested cannulated antecubital vein into heparinized polyethylene syringes. Plasma samples prepared by immediate centrifugation were deep-frozen for hormone determinations, or for density measurements within 30 min. Blood samples were taken for densitometry and hematocrit measurements at min –10, 0, 30, +2, and +50; hormones were measured in samples from min –10, 3, 27, +2, and +50.

Measurements

Body fat mass (% of total body weight) was estimated in test subjects lying in the supine position by a computerized single-frequency bioelectrical analyzer system (model BIA-103, RJL Systems, Detroit, MI, USA), with 0.8 mA current at 50 kHz, using a 4-electrode system (Lukaski *et al.* 1986).

Thoracic impedance (Z_0) measurements were performed by a computerized Noninvasive Hemodynamic Monitoring System (model ICG-M401, ASK Ltd., Budapest, Hungary). The method was described in detail elsewhere (Bernstein 1986, Mehlsen *et al.* 1991). Briefly, a constant sinusoidal alternating current of 4.0 mA and 100 kHz is applied between electrode pairs placed on the lateral part of the lower chest and on the root of the neck. The voltage is detected by an electrode pair placed 5 cm apart from the current electrodes parallel to the current path. We used self-adhesive Ag/AgCl electrodes (Red Dot monitoring electrodes, 3M Medical-Surgical

Division, St. Paul, MN, USA). Impedance was indicated at 12 s intervals.

Similar electrodes were used for continuous ECG monitoring (standard leads). Heart rate (HR; bpm) was continuously computed from the R-R intervals.

A Dinamap automatic oscillometer monitor (model 1846 SX, Critikon, Tampa, FL, USA) was employed for continuous blood pressure determination. Systolic, mean, and diastolic arterial blood pressure (SBP, MAP, DBP, mm Hg) were measured approximately every 20 s.

Microhematocrit (Hct) was determined in quadruplicate (10 min at 10 000 rpm). Blood density (BD) and plasma density (PD) were measured with a high-precision mass densitometry device (model 602 M, Paar KG, Graz, Austria) on 0.2 ml samples employing the mechanical oscillator technique, described in detail elsewhere (Hinghofer-Szalkay 1986). The resonant frequency of a U-shaped glass tube is determined and converted to corresponding density values. Density determinations were performed at 37.00±0.02 °C controlled by an ultrathermostat (Hetofrig, Heto, Denmark).

Hormone measurements

Cortisol was measured by enzymoimmunoassay (EIA), catecholamines using high-pressure liquid chromatography (HPLC) and all other hormones by radioimmunoassay (RIA).

Plasma renin activity (PRA) was determined by RIA of angiotensin-I (RENCTK, Sorin Biomedica, Italy) (Freedlender and Goodfrien 1979) and expressed as nanograms of angiotensin-II formed per ml of plasma per hour of incubation (ng/ml/h). The sensitivity, i.e. the amount of analyzed samples able to lower the binding ability of 2 S.D., was 0.13 ng/ml; the coefficient of variation for the within- and between-assay variability was 7.6 and 9.1 %, respectively.

Aldosterone was measured by a modified RIA method (Abraham *et al.* 1977) (AldoCTK-2, Sorin Biomedica, Italy). Sensitivity, defined as the apparent concentration of analyte that can be distinguished from the zero standard, was < 20 pg/ml at 95 % confidence limit. The coefficient of variation for the within- and between-assay variability was 9.7 and 11.5 %, respectively.

Cortisol was directly measured by EIA (KBF2145, Medix Biotech Inc., CA, USA) based on the competition between analyte and a standard amount of labelled derivative. The sensitivity defined as the detectable concentration equivalent to 2 S.D. of the zero-binding value was better than 3.5 nmol/l; inter-assay precision and intra-assay precision were 4.1 and 4.2 %, respectively.

Catecholamines were measured with HPLC using electrochemical detection after prior alumina (Al_2O_3) extraction (Pluto and Bürger 1988) (Chromsystems, FRG).

Statistics

Tables 1-3 present absolute values from the last 5 min pre-HUT, the last 5 min intra-HUT, and the first 5 min post-HUT. The average of every variable (except density data) within the last 5 min pre-HUT was taken as 100 % for each test subject and all other data were then converted to relative figures, i.e. percentages. These relative values were then used for presentation in the figures, and to test if there were differences between HUT and the resting controls at min 25 to 30 (late HUT), and 30 to +5 (early post-HUT), respectively. The homogeneity of all groups of raw variables was tested by Shapiro-Wilk´s W test. Repeated ANOVA measures were used to determine differences between the test conditions. For hypothesis testing, we used Student´s paired t-test, comparing HUT and resting control data from identical protocol times. Differences were considered significant if $p < 0.05$. Hypothesis testing was performed using the Statistica software set (version 5.0, StatSoft, Inc., Tulsa, OK, USA).

Results

Absolute values are given in Tables 1 to 3. Figures 1 to 3 present dose-response features and post-tilting states. In the following text, all differences refer to HUT *vs.* rest control (HUT0) at identical protocol times, all indicated changes significant for $p<0.05$.

Changes during HUT (last 5 min)

Hormone data (min 27)

Norepinephrine increased by 19, 44, 80, and 102 % above rest values at min 27 of HUT12, HUT30, HUT53, and HUT70, while epinephrine and aldosterone increased by 30, 41, 64, 68 % and by 29, 62, 139, and 165 %, respectively. PRA was elevated with 41, 91, and 89 %, AVP with 27, 47, and 59 % at the same time with HUT30, HUT53, and HUT70 (Fig. 1, Table 1).

Hemodynamic and impedance data (min 25 to 30)

HR, MAP, and Z_0 were unchanged with HUT12 but increased above HUT0 at the end of HUT30, HUT53, and HUT70 by 5, 26, and 45 % (HR), by 5, 7, and 10 % (MAP), and by 8, 13, and 16 % (Z_0). PP decreased with HUT53 and HUT70 by 4 and 10 % (Fig. 2, Table 2).

Density data (min 30)

Hematocrit increased above resting control values at the end of HUT12, HUT30, HUT53, and HUT70 by 0.2, 1.7, 6.3, and 7.2 %. BD and PD increased by 2.3 and 3.0 g/l and by 1.7 and 1.8 g/l with HUT53 and HUT70 (Fig. 3, Table 3).

Table 1. Hormone values before, during, and after HUT: variables (absolute values) at different angles of head-up tilt: 0º (rest, control study), 12º, 30º, 53º, and 70º.

	HUT (°)	**pre-HUT min –10**	**during HUT min 27**	**post-HUT min +2**
Cortisol (nmol/l)	0	378 ± 46	301 ± 41	295 ± 40
	12	362 ± 58	291 ± 52	279 ± 51
	30	344 ± 51	282 ± 44	268 ± 43
	53	343 ± 45	301 ± 39	276 ± 37
	70	326 ± 52	303 ± 57	295 ± 54
Aldosterone (pg/ml)	0	101 ± 15	93 ± 14	97 ± 15
	12	117 ± 22	142 ± 23	148 ± 24
	30	81 ± 10	136 ± 36	138 ± 36
	53	121 ± 20	262 ± 41	249 ± 36
	70	129 ± 18	371 ± 55	369 ± 73
PRA (ng/ml/h)	0	0.74 ± 0.14	0.70 ± 0.13	0.68 ± 0.11
	12	0.91 ± 0.16	0.92 ± 0.19	0.96 ± 0.19
	30	0.65 ± 0.08	0.90 ± 0.19	0.90 ± 0.15
	53	0.79 ± 0.18	1.43 ± 0.32	1.33 ± 0.31
	70	0.78 ± 0.13	1.70 ± 0.31	1.75 ± 0.33
AVP (pg/ml)	0	2.55 ± 0.37	2.37 ± 0.39	2.51 ± 0.36
	12	2.67 ± 0.27	3.00 ± 0.27	3.00 ± 0.30
	30	3.16 ± 0.41	4.06 ± 0.58	3.79 ± 0.50
	53	2.93 ± 0.26	4.29 ± 0.38	4.01 ± 0.42
	70	2.41 ± 0.31	3.59 ± 0.41	3.48 ± 0.38
Norepinephrine (pg/ml)	0	244 ± 19	247 ± 15	260 ± 13
	12	264 ± 38	315 ± 38	274 ± 32
	30	227 ± 15	325 ± 12	263 ± 16
	53	261 ± 39	482 ± 96	351 ± 48
	70	212 ± 20	421 ± 32	320 ± 27
Epinephrine (pg/ml)	0	51.0 ± 5.4	49.6 ± 6.6	50.7 ± 5.7
	12	46.4 ± 3.8	56.4 ± 3.2	50.3 ± 3.2
	30	47.9 ± 4.2	65.1 ± 8.7	55.4 ± 8.7
	53	44.2 ± 8.9	68.1 ±11.1	49.9 ± 6.4
	70	39.3 ± 3.9	65.1 ± 9.7	52.0 ± 5.3

Values are means ± S.E.M. of 7 test subjects; pre-HUT = min (–10) before starting HUT; during HUT = min 27 during HUT; post-HUT = min (+2) after finishing HUT; PRA, plasma renin activity; AVP, arginine vasopressin.

Dose-response relationships

Hormone data

Norepinephrine, epinephrine, PRA, and AVP increases showed roughly linear fit with sine of tilt angle,

while the best fit for aldosterone increase was exponential (Fig. 1). Extrapolation to standing (sin = 1.0) resulted in the following increases: aldosterone +180 %, norepinephrine and PRA +100 %, epinephrine +75 %, and vasopressin +60 %.

Hemodynamic and impedance data

Relative variables of min 25 to 30 (last 5 min during HUT) were compared within identical experiments to pre-HUT levels (last 5 min before HUT), which were regarded as 100 %. With HUT larger than 12°, HR increased exponentially with sine of tilt angle, MAP and Z_0 increased with a linear best fit (Fig. 2).

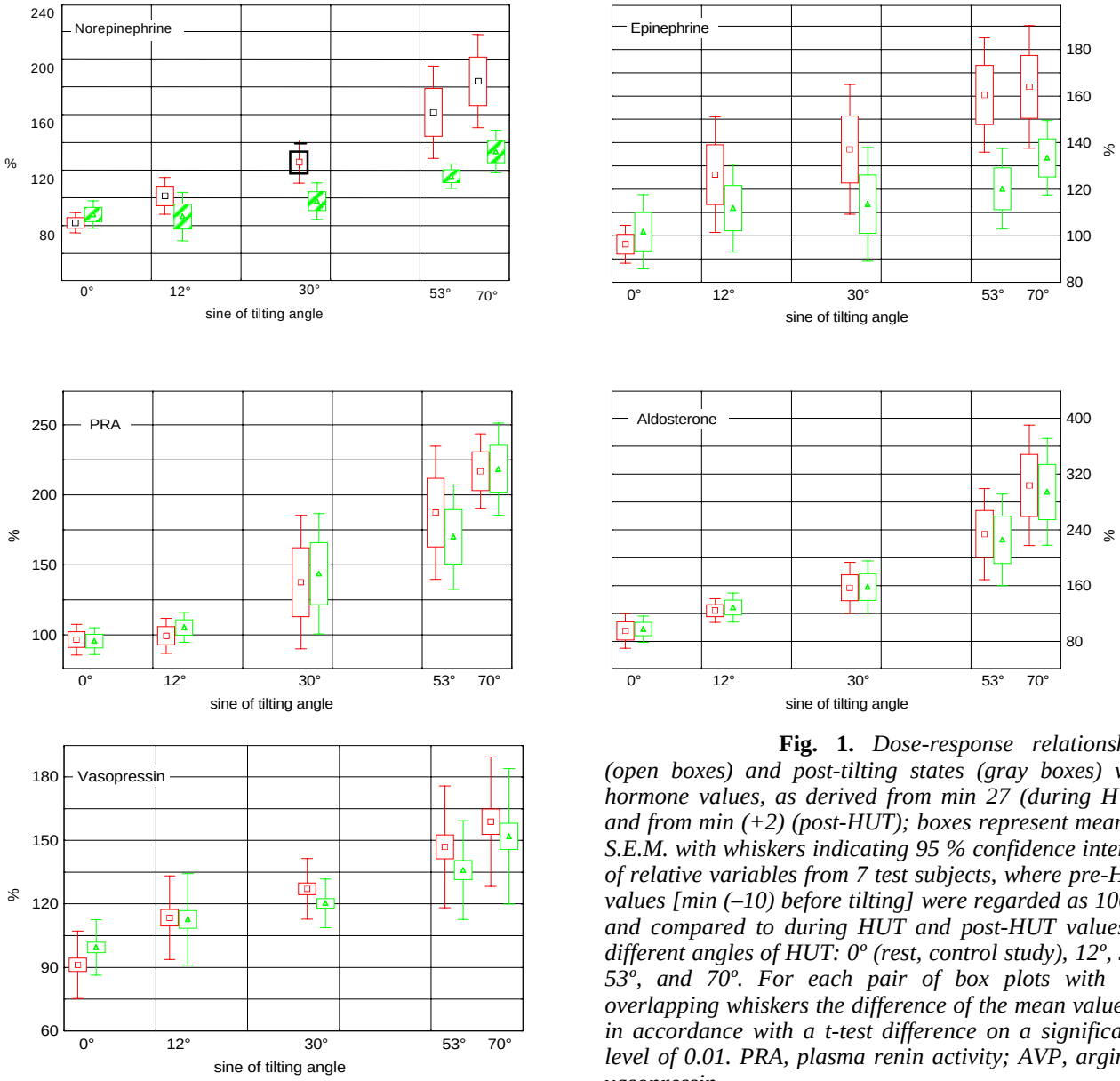


Fig. 1. *Dose-response relationships (open boxes) and post-tilting states (gray boxes) with hormone values, as derived from min 27 (during HUT) and from min (+2) (post-HUT); boxes represent means ± S.E.M. with whiskers indicating 95 % confidence interval of relative variables from 7 test subjects, where pre-HUT values [min (–10) before tilting] were regarded as 100 % and compared to during HUT and post-HUT values at different angles of HUT: 0º (rest, control study), 12º, 30º, 53º, and 70º. For each pair of box plots with non overlapping whiskers the difference of the mean values is in accordance with a t-test difference on a significance level of 0.01. PRA, plasma renin activity; AVP, arginine vasopressin.*

Density data

The best fit for Hct, BD, and PD increases with sine of the tilt angle, was the exponential fit (Fig. 3).

Changes in early post-HUT (first 5 min)

Hormone data (min +2)

Norepinephrine, epinephrine, PRA, AVP, and aldosterone were elevated above HUT0 after HUT12, HUT30, HUT53, and HUT70 (Fig. 1).

Hemodynamic and impedance data (min 30 to +5)

HR was lower than during the same protocol time of HUT0 after any tilt, whereas MAP and Z_0 were

higher than HUT0 after HUT30, HUT53, and HUT70 (Fig. 2).

Density data (min +2)

Hematocrit, BD, and PD were elevated above HUT0 values at identical protocol times after HUT30, HUT53, and HUT70 (Fig. 3).

Changes in late post-HUT (20-50 min after HUT)

Hormone data (min +50)

Norepinephrine, epinephrine, PRA, and AVP were unchanged, while aldosterone was elevated above HUT0 by 26, 53, 55, and 90 % after HUT12, HUT30, HUT53, and HUT70.

Hemodynamic and impedance data (min +20)

HR, MAP, and Z_0 did not differ significantly from variables at identical protocol times of HUT0.

Density data (min +50)

Hematocrit, BD, and PD, compared to HUT0 values at identical protocol times were unchanged after any tilt.

Table 2. Hemodynamic values before, during, and after head-up tilt: variables (absolute values) at different angles of HUT: 0º (rest, control study), 12º, 30º, 53º, and 70º.

	HUT (°)	pre-HUT min –5 to 0	during HUT min 25 to 30	post-HUT min 30 to +5
HR (bpm)	0	65.4 ± 0.5	66.8 ± 0.6	67.2 ± 0.5
	12	66.3 ± 0.5	65.6 ± 0.5	65.4 ± 0.3
	30	66.9 ± 0.6	71.6 ± 0.6	64.8 ± 0.5
	53	68.2 ± 0.6	87.1 ± 0.8	67.3 ± 0.5
	70	67.4 ± 0.6	98.8 ± 0.8	65.3 ± 0.7
MAP (mm Hg)	0	71.9 ± 0.7	70.6 ± 0.7	71.1 ± 0.7
	12	66.9 ± 0.6	67.1 ± 0.6	66.4 ± 0.6
	30	67.0 ± 0.5	69.1 ± 0.6	67.9 ± 0.6
	53	69.4 ± 0.7	73.3 ± 0.9	70.5 ± 0.7
	70	67.6 ± 0.6	72.9 ± 0.8	71.1 ± 0.6
PP (mm Hg)	0	51.6 ± 0.4	51.9 ± 0.5	52.3 ± 0.6
	12	50.3 ± 0.4	50.0 ± 0.4	50.8 ± 0.5
	30	52.1 ± 0.5	52.1 ± 0.5	51.6 ± 0.5
	53	53.7 ± 0.4	52.1 ± 0.6	55.5 ± 0.5
	70	53.1 ± 0.5	47.9 ± 0.7	52.8 ± 0.5
Z_0 (Ohm)	0	23.4 ± 0.2	23.3 ± 0.2	23.4 ± 0.2
	12	23.1 ± 0.1	23.6 ± 0.1	23.3 ± 0.2
	30	22.7 ± 0.1	24.4 ± 0.1	23.1 ± 0.1
	53	22.8 ± 0.1	25.6 ± 0.1	23.8 ± 0.1
	70	23.8 ± 0.1	27.6 ± 0.1	24.9 ± 0.1

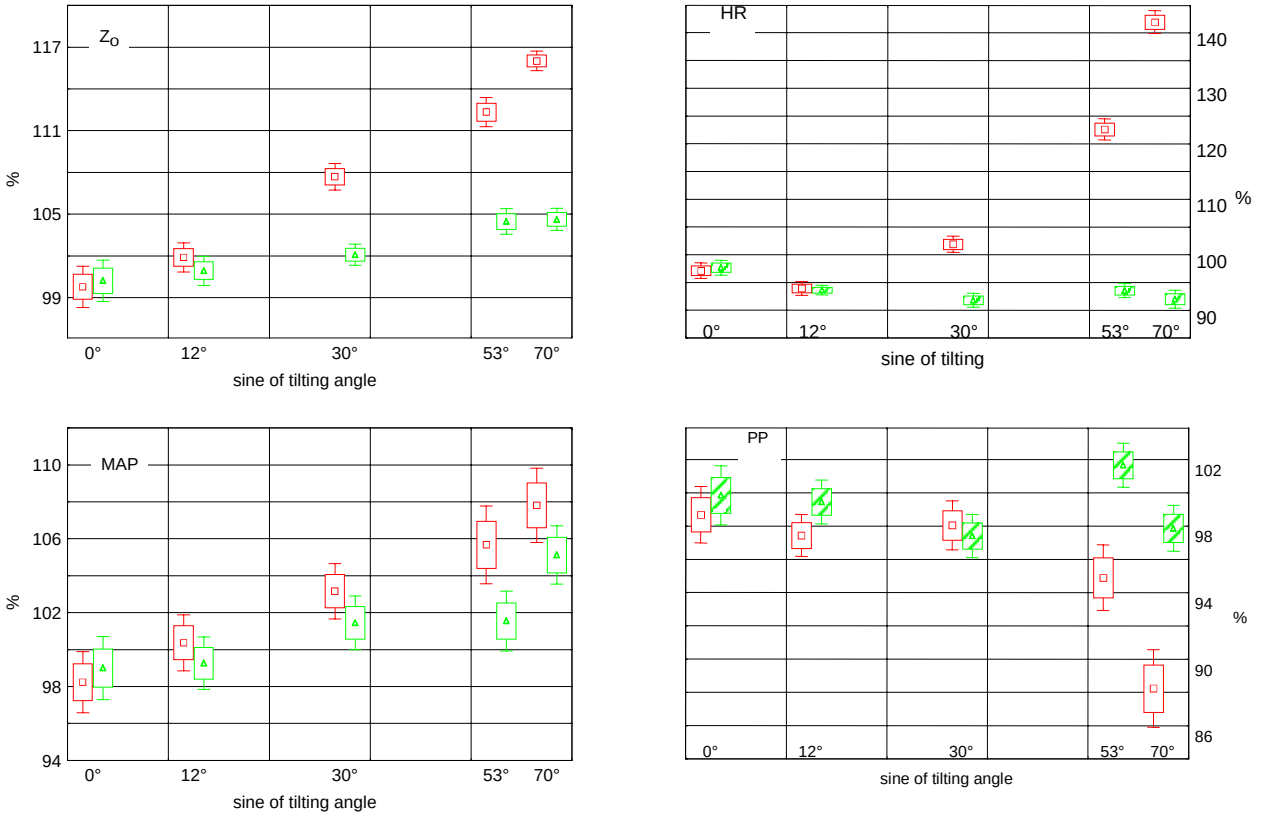
Values are means ± S.E.M. (N = 7) of 5 min averages from 7 test subjects; pre-HUT = last 5 min average before starting HUT; during HUT = 25-30 min average during HUT; post-HUT = first 5 min average after finishing HUT; HR, heart rate; MAP, mean arterial blood pressure; PP, pulse pressure; Z_0, basic thoracic bioimpedance.

Discussion

Orthostasis, centrifugation (hyper-G), and lower body negative pressure all induce similar orthostatic stress, cause blood redistribution from the thorax into the lower extremities and central hypovolemia with baroreceptor unloading (Hinghofer-Szalkay *et al.* 1995), albeit of different magnitude and possibly different quality, as well. Unloading of cardiopulmonary (low-pressure) baroreceptors raises peripheral vascular resistance and reduces forearm and splanchnic blood flow (Ebert *et al.* 1982, Mark and Mancia 1983, Hirsch *et al.*

1989), while unloading arterial (high-pressure) baroreceptors primarily increases heart rate (Abboud *et al.* 1979, Blomqvist and Stone 1983). Head-up tilt up to 10-30° and lower body negative pressure up to 10-15 mm Hg suction have been reported to decrease central venous pressure and cardiac preload without significantly

Fig. 2. *Dose-response relationships (open boxes) and post-tilting states (gray boxes) with impedance and hemodynamic variables, as derived from min 25 to 30 (during HUT) and from min 30 to +5 (post-HUT); boxes represent means ± S.E.M. with whiskers indicating 95 % confidence interval of raw relative variables from 7 test subjects, where pre-HUT values (last 5 min before tilting) were regarded as 100 % and compared to values during HUT and post-HUT values at different angles of HUT: 0º (rest, control study), 12º, 30º, 53º, and 70º. For each pair of box plots with non-overlapping whiskers the difference of the mean values is in accordance with a t-test difference at a significance level of 0.01. Z_0, basic thoracic bioimpedance; HR, heart rate; MAP, mean arterial blood pressure; PP, pulse pressure.*



altering heart rate and arterial blood pressure (Blomqvist and Stone 1983, Julius *et al.* 1983, Lacolley *et al.* 1992). However, we were able to demonstrate significant heart rate and blood pressure effects with HUT30, as well. Higher stimulus levels generally cause tachycardia and can be hypotensive (Musgrave *et al.* 1971).

Passive head-up positioning (usually to 70°) was reported to increase the heart rate by 26-43 %, decrease stroke volume by 30-45 % and cardiac output by 16-27 % (Tuckman and Schillingford 1966, Smith *et al.* 1970, Loeppky *et al.* 1981). Total peripheral resistance increased by 30-40 %, diastolic pressure by 12-17 %, and mean arterial pressure by 2-10 %. Systolic pressure was usually unchanged, whereas pulse pressure was found to be always reduced (Tuckman and Schillingford 1966, Smith *et al.* 1970, Loeppky *et al.* 1981, Hainsworth and Al-Shamma 1988). Our results of increased HR by 45 %, MAP by 10 %, and PP reduced by 10 % fit well into this framework. An almost linear correlation exists between the tilting/suction level and the decrease of thoracic blood volume, atrial diameters, and central venous pressure in healthy young people (Ebert *et al.* 1982, Norsk *et al.* 1993), the proportions of which depends on the time of treatment and the degree of orthostatic loading (Musgrave *et al.* 1971).

To partly separate the unloading effects on low- and high-pressure baroreceptor systems, and to quantitatively compare various dose-response traits in identical subjects, we employed 12° as "non-tachycardic", 30° and 53° as "intermediate", and 70° as "high-degree" tilting (sin 70° = 0.94); the sine of the respective angle of positioning is proportional to the

corresponding hydrostatic load (Musgrave *et al.* 1971, Blomqvist and Stone 1983, Julius *et al.* 1983).

It is conceivable to assume activation of several "lines of defense" in a consecutive and partly non-linear manner, including elevated volume guarding hormone levels (Rowell 1974, Norsk *et al.* 1993), and/or decreased compliance of capacitance vessels (Samueloff *et al.* 1966), thus resulting in augmented venous return. Such resetting would modify cardiopulmonary and arterial baroreflex mechanisms. An enhanced response to carotid baroreceptor activation or deactivation during head down-tilting or lower body suction indicates resetting of arterial pressure regulation by (un)loading of central "volume" sensors (Pawelczyk and Raven 1989, Nagaya *et al*. 1995).

Table 3. Hematocrit, blood, and plasma density values before, during, and after HUT: variables (absolute values) at different angles of HUT: 0 (rest, control study), 12, 30, 53, and 70º.

	HUT (°)	pre-HUT min 0	during HUT min 30	post-HUT min +2
Hct (%)	0	40.2 ± 0.6	40.5 ± 0.8	40.5 ± 0.4
	12	39.1 ± 0.6	39.4 ± 0.8	39.2 ± 0.4
	30	37.4 ± 0.8	38.3 ± 1.2	38.5 ± 0.6
	53	39.3 ± 0.9	42.0 ± 1.1	41.5 ± 0.6
	70	40.7 ± 0.7	43.9 ± 1.1	43.7 ± 0.5
BD (g/l)	0	1046.73 ± 0.45	1046.87 ± 0.60	1046.87 ± 0.29
	12	1045.94 ± 0.45	1046.22 ± 0.70	1045.90 ± 0.30
	30	1044.51 ± 0.61	1045.26 ± 0.95	1045.19 ± 0.41
	53	1046.13 ± 0.69	1048.46 ± 0.70	1048.14 ± 0.43
	70	1047.20 ± 0.47	1050.22 ± 0.74	1050.06 ± 0.27
PD (g/l)	0	1019.00 ± 0.22	1019.08 ± 0.27	1019.06 ± 0.12
	12	1018.35 ± 0.19	1018.33 ± 0.26	1018.14 ± 0.12
	30	1017.71 ± 0.24	1018.26 ± 0.28	1018.14 ± 0.12
	53	1018.15 ± 0.21	1019.81 ± 0.33	1019.37 ± 0.14
	70	1018.19 ± 0.23	1019.96 ± 0.32	1020.03 ± 0.17

Values are means ± S.E.M. from 7 test subjects; pre-HUT = min 0 before starting HUT; during HUT = min 30 during HUT; post-HUT = min (+2) after finishing HUT; Hct, hematocrit; BD, blood density; PD, plasma density.

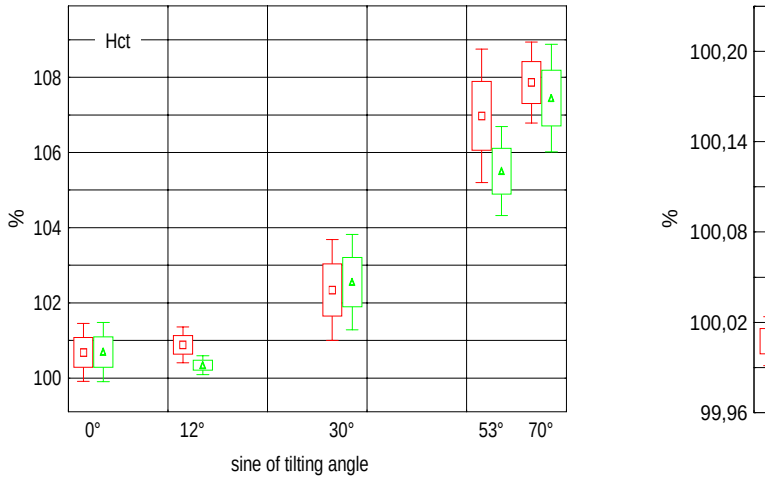
Postural changes to an upright position decrease central venous and arterial baroreceptor pressures and cause plasma catecholamines, renin-angiotensin-aldosterone, and occasionally vasopressin to rise (Rowell 1974, Norsk *et al.* 1986, 1993). This minimizes body water loss, promotes vasoconstriction, and stabilizes blood pressure in the upright position. Circulatory norepinephrine is derived primarily from sympathetic nerve endings, epinephrine from adrenal medullary secretion. We have also demonstrated an early significant norepinephrine increase with moderate head-up tilt (HUT12: +19 %, HUT30: +44 %), presumably triggered by cardiopulmonary baroreceptor unloading, which elicits reflex sympathoexcitation (Jacobs *et al.* 1996). Greater degrees of head-up tilt (HUT53, HUT70) elicit more pronounced sympathetic activation and norepinephrine values increase (+80 %, +102 %). Plasma epinephrine responded less intensively, as expected, with higher HUT levels (+68 % with HUT70), but its concentration was raised significantly with lower-level HUT as well.

In contrast to norepinephrine, renin levels need about 20 min to rise with orthostatic stress (Julius *et al.* 1983), and low levels of HUT or LBNP did not elicit significant renin/aldosterone changes in the present study. We are now also able to demonstrate significant responses with low level HUT, suggesting a contribution of cardiopulmonary baroreceptors in the neural regulation of the renin-angiotensin-aldosterone system.

Arginine vasopressin is one of the most potent vasoconstrictor agents known, but its participation in the regulation of arterial blood pressure during head-up posture is considered low or absent (Norsk *et al.* 1986, 1993). However, we found intensity-dependent elevations in arginine vasopressin levels with HUT30, HUT53, and HUT70. The fact that no significant changes in plasma

levels of cortisol occurred indicates the absence of emotional stress factors during our experiments.

Thoracic impedance (Z_0) values reflect intrathoracic hydration, comprising both intra- and extravascular fluid volumes (Matzen *et al.* 1991). Immediately after tilting, thoracic impedance changes rapidly, indicating intravascular fluid redistribution, followed by a slower phase, mainly due to transvascular fluid exchange. Variations in hematocrit and blood density are caused by filtration at the whole-body level, and possibly by redistribution of blood to or from microvascular beds, as well (Lee 1994). On the other hand, transcapillary fluid shifts must also influence plasma density due to a low protein concentration of filtered fluid (Hinghofer-Szalkay *et al.* 1995). In this study, blood and plasma density were increased in parallel 30 min after passive orthostasis, similarly to the increase of thoracic impedance. There was a linear correlation between thoracic impedance change and the sine of tilt angle. Both impedance and density changes showed an immediate rapid phase after starting and finishing passive orthostasis (first 2-3 min), followed by a slower exponential time course until the stimulus was discontinued.



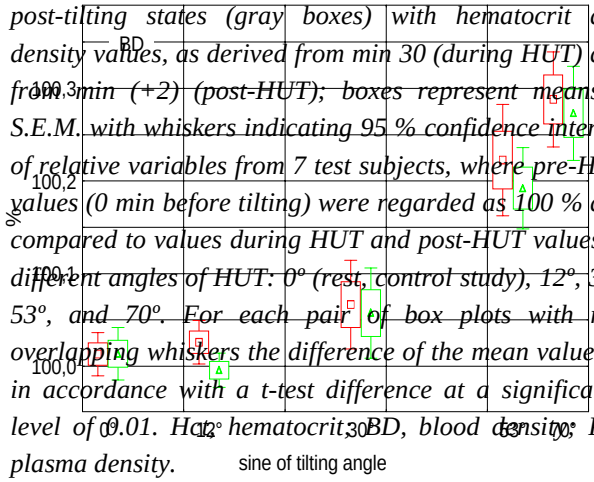


Fig. 3. *Dose-response relationships (open boxes) and post-tilting states (gray boxes) with hematocrit and density values, as derived from min 30 (during HUT) and from min (+2) (post-HUT); boxes represent means ± S.E.M. with whiskers indicating 95 % confidence interval of relative variables from 7 test subjects, where pre-HUT values (0 min before tilting) were regarded as 100 % and compared to values during HUT and post-HUT values at different angles of HUT: 0° (rest, control study), 12°, 30°, 53°, and 70°. For each pair of box plots with non overlapping whiskers the difference of the mean values is in accordance with a t-test difference at a significance level of 0.01. Hct, hematocrit; BD, blood density; PD, plasma density.*

The results show large linear increases in all hormone concentrations, thoracic bioimpedance, and mean arterial pressure with the sine of applied tilting angle. Surprisingly, however, the linear increases of the filtration parameters, blood density, plasma density, and hematocrit all started at the tilt angle of approximately 20° (Fig. 3). We suspect that an early hemodilution effect as observed with the onset of LBNP (Hinghofer-Szalkay *et al.* 1992) compensates weak hemoconcentration at low tilt angles, whereas the hemoconcentration effect prevails with higher tilt intensity. As was expected, high orthostatic load resulted in a non-linear increase in heart rate.

The second goal of this study was to investigate hormonal and hemodynamic variables after adaptation to

head-up tilt. We observed "post-tilting bradycardia" and significantly increased mean arterial blood pressure after finishing HUT. Z_0 stayed above pre-HUT levels, conceivably indicating relative thoracic tissue fluid loss in the early post-tilt period (Matzen *et al.* 1991, Nagaya *et al.* 1995). Data from the "zero" runs (supine rest, HUT0) served as comparison for detecting time-dependent changes due to head-up tilt. In an earlier study (Matzen *et al.* 1991), reduced plasma and central blood volume were observed in the post-tilt period, as measured with arterial hematocrit and distribution of $^{99}Tc^{m}$ labelled erythrocytes; thoracic bioimpedance stayed above pre-tilt levels for 30 min following head-up tilt (50° for 60 min). We observed similar changes of Z_0, indicating that interstitial thoracic fluid content remained low during recovery after orthostatic loading.

Furthermore, we observed reduced post-tilt heart rate after 30 min head-up tilt of only 12°, suggesting that cardiovascular resetting occurred even with slight unloading of cardiopulmonary baroreceptors which *per se* did not produce tachycardia.

Many factors may participate in post-tilting shifts of hemodynamic variables. Small alterations in the diameter of venous capacitance vessels might play a significant homeostatic role in the control of cardiac preload and therefore can alter cardiac afterload and arterial blood pressure (Epstein *et al.* 1968, Henriksen 1976, Henriksen and Sejrsen 1977). Upright tilt and lower body negative pressure produce slight but instantaneous venoconstriction (Epstein *et al.* 1968). Hormonal changes due to central hypovolemia also play an important role not only during but also after orthostatic stress. Longer-acting hormones, particularly of the renin-angiotensin-aldosterone system, which return to pre-stimulus levels with considerable delay (Norsk *et al.* 1993), may create post-tilting heart rate depression and vascular resistance shifts as found in this study.

In conclusion, different levels of passive orthostasis induce specific time course and dose-response patterns within hormonal, thoracic impedance, blood/plasma density, and hemodynamic variables. Changes in thoracic bioimpedance, hormone concentrations, and mean arterial pressure are linearly related to the sine of the applied tilt angle. Blood volume indicators and heart rate start to rise from a threshold angle of about 20°. Hormonal responses can be demonstrated for catecholamines and aldosterone even for the lowest (12°) tilt angle. Heart rate is depressed for several minutes even after HUT12, and arterial blood pressure exceeds control levels with ≥ HUT30. The cardiovascular control systems are reset after 30 min passive orthostasis of different intensity.

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