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DOI

[10.1046/j.1365-201X.1997.00203.x](https://doi.org/10.1046/j.1365-201X.1997.00203.x)

Publication date

1997

Published in

Acta physiologica Scandinavica

[Link to publication](#)

Citation for published version (APA):

Voogel, A. J., Stok, W. J., Pretorius, P. J., van Montfrans, G. A., Langewouters, G. J., & Karemaker, J. M. (1997). Circadian blood pressure and systemic haemodynamics during 42 days of 60 head-down tilt. *Acta physiologica Scandinavica*, 161, 71-80.
<https://doi.org/10.1046/j.1365-201X.1997.00203.x>

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Circadian blood pressure and systemic haemodynamics during 42 days of 6° head-down tilt

A. J. VOOGEL,¹ W. J. STOK,² P. J. PRETORIUS,³ G. A. VAN MONTFRANS,¹
G. J. LANGEWOUTERS⁴ and J. M. KAREMAKER²

¹ Department of Internal Medicine, University of Amsterdam, Amsterdam, the Netherlands

² Department of Physiology, University of Amsterdam, Amsterdam, the Netherlands

³ Department of Physiology, University of Potchefstroom, South Africa

⁴ TNO BioMedical Instrumentation, Amsterdam, the Netherlands

ABSTRACT

Head-down tilted bedrest is a ground-based microgravity simulation model. Since in this position the influence of chief external determinants of circadian blood pressure variation, i.e. activity and posture, are reduced, it may reveal endogenous oscillatory factors. The effects of 42 days of 6° head-down tilt on the circadian profiles of continuous finger blood pressure, heart rate, stroke volume, cardiac output and total peripheral resistance were analysed. In seven healthy volunteers (25–31 years) twelve 22 h Portapres registrations were performed: two in an ambulatory baseline period, eight during 42 days of head-down tilt, and two during recovery. Stroke volume was estimated by a pulse contour method ('Modelflow') from the finger arterial blood pressure tracing. Head-down tilt rapidly reduced circadian BP variation, especially for diastolic blood pressure. No effect of long-term head-down tilt on blood pressure level was observed. The day-night difference in heart rate was essentially unaffected. Cardiac output was maintained through an increase of heart rate and simultaneous decline of stroke volume. Our observations confirm the overriding importance of physical activity and orthostatic load on the diurnal variation of BP. The time-frame of the changes in stroke volume and heart rate during head-down tilt might point to a contribution of other factors besides a reduction of circulating blood volume affecting cardiovascular performance under these conditions.

Keywords blood pressure, cardiac output, circadian, fingers, head-down tilted bedrest, haemodynamics, human, total peripheral resistance.

Received 23 September 1996, accepted 1 April 1997

Six degrees head-down tilted bedrest (HDT), which is commonly accepted as a ground-based simulation model for microgravity (Blomqvist & Stone 1983, Baisch *et al.* 1992), has pronounced effects on the cardiovascular system. In this body position, the net hydrostatic forces on the vascular tree are minimized, and redistribution of blood volume occurs towards the thoracocephalic region, activating the arterial and cardiopulmonary pressure receptors. This leads to diuresis and a decrease in total blood volume. These effects on fluid balance are established within 6 h (Blomqvist *et al.* 1980). The physical inactivity associated with bedrest leads to muscular atrophy and possibly to an impairment of cardiovascular control (Covertino *et al.* 1990, Hughson *et al.* 1994a, 1994b).

The concurring action of these changes leads to orthostatic intolerance at reassumption of the upright position, resembling the deconditioning syndrome after long-term spaceflights.

The circadian variation of blood pressure is closely related to differences in physical activity and posture accompanying the sleep wake cycle (Athanassiadis *et al.* 1969, Mann *et al.* 1979, Clark *et al.* 1987, Degaute *et al.* 1991). In HDT the influence of these determinants is diminished, and therefore an immediate attenuation of the circadian blood pressure profile is expected. Besides an acute effect on circadian blood pressure variation, prolonged HDT might have some effects on cardiovascular regulation with a longer time constant. The influence of HDT on humoral factors like angiotensin

and possibly catecholamines (Leach *et al.* 1983, Davydova *et al.* 1986, Robertson *et al.* 1994), which act as cardiovascular growth factors, may continue to affect cardiovascular performance long after start of microgravity.

The collaborative 42 day HDT study organized by the European Space Agency (ESA) and the Centre National des Etudes Spatiales (CNES) offered a unique opportunity to study the effects of long-term HDT on circadian blood pressure regulation. During this protocol, no countermeasures were planned in order to reduce the postural hypotension at the end of HDT. Our aim was to study circadian blood pressure variation under conditions in which the influence of overriding external oscillators is diminished. We did this by performing 12 circadian registrations of continuous finger BP by Portapres before, during and following a 42 day HDT period. With the use of Modelflow, a computing program to estimate beat-to-beat stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) from continuous pressure tracings, changes in underlying haemodynamics could also be determined without interfering daily activities. Our protocol was part of a collaborative ESA-CNES long-term bedrest study, which took place from September to December 1994 at Toulouse, France. The purpose of the bedrest study was to assess the effect of long-term simulated microgravity on cardiovascular function, musculature, bone metabolism, immunology, energetic balance and equilibrium.

METHODS

Subjects

After extensive physical and psychological screening, 10 healthy, male volunteers were recruited. All were non-smokers. Two subjects were planned as back-ups to be included in case of a drop-out during the baseline data collection period (BDC). Eight volunteers entered the HDT phase. One subject resigned after 27 days of HDT because of irradiating pains from the shoulder and the cervical region. The data of this subject are not included in the results. The mean age of the remaining seven subjects was 28 years (range 25–31).

The protocol consisted of 12 circadian recordings with Portapres in each volunteer: two in BDC, eight during the HDT phase and two during the recovery period (REC). Our aim was to investigate the effects of long-term HDT on circadian blood pressure.

All volunteers signed the informed consent form approved by French law. The overall experiment protocol had been submitted to the 'Comité Consultative de Protection des Personnes dans la Recherche Biomédicale – Région Midi-Pyrénées'.

Equipment and measurements

The finger arterial blood pressure signal was recorded continuously and non-invasively, alternating every 30 min between the third and fourth fingers. Portapres Model 2, the portable version of TNO-BMI's Finapres, was used (Imholz *et al.* 1993, Parati *et al.* 1989). Portapres is based on Finapres technology, and allows the study of changes in systemic haemodynamics under various conditions, with almost no interference with daily routine, including sleep (Parati *et al.* 1989). The device measures finger arterial BP by means of Peñáz's (1973) volume clamp method and Wesseling's (1990) physiological calibration criteria. Portapres is provided with a height-correcting system which measures the position of the finger relative to heart level and corrects the blood pressure signal for hydrostatic changes. In daytime during the ambulatory recordings, volunteers kept their arm most of the time suspended in a sling to prevent movement artifacts.

Portapres M2 is able to store 28 h of continuous finger BP waveform in a digital flash-memory after data compression. The data stored inside Portapres were read out once a day, after which the memory was erased. This procedure took about half an hour. The machine was then ready for reuse in the next test subject. During HDT, the quality of the signal was constantly monitored by connecting to the RS232 communication port of a computer monitor; this was not possible during the ambulatory phases. Off-line artifact rejection of the finger arterial pressure tracing was performed both visually and digitally, rejecting spikes differing more than 15% from the average of 10 adjacent beats.

From the continuous Portapres BP waveform, several parameters were derived with the signal processing program 'Beatfast' (TNO BioMedical Instrumentation, Amsterdam, The Netherlands). Beat-to-beat values of SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were computed for each blood pressure signal using the Beatfast program (Wesseling 1993). This pattern-recognition program identifies beat-to-beat values of the haemodynamic parameters; SBP is defined as the maximum pressure during ejection, MAP as the true integrated mean and DBP as the end-diastolic pressure just preceding the upstroke. SV was computed with the Modelflow method (Wesseling *et al.* 1993), which computes aortic flow using a three-element model, representing the major properties of the arterial tree: aortic characteristic impedance (Z_0), aortic compliance (C_w) and peripheral resistance (Toorop *et al.* 1987). In this model, in contrast to the pulse contour method, the elements Z_0 and C_w are non-linearly dependent on pressure, as derived from arctangent pressure–area relationships of

the human aorta obtained in *in vitro* measurements of human thoracic aortas (Langewouters *et al.* 1984). Modelflow has been shown to reliably measure SV from radial intra-arterial pressure readings compared with thermodilution in a group of open heart surgical patients, in which haemodynamics parameters were varied by pharmacological intervention (Wesseling *et al.* 1993b).

In a separate study we assessed the reproducibility of haemodynamic 24 h profiles obtained by Portapres with an intervening period of 1 week. In six healthy volunteers, the 24 h averages differed on average ($\pm$ SD) by 2.0 ± 2.6 mmHg for SBP and 0.9 ± 2.9 mmHg for DBP. We also found that the reproducibility of circadian variations of Modelflow SV (day- and night-time expressed as a percentage of the corresponding 24 h average levels) was excellent, and amounted to $-0.3 \pm 5.5\%$ and $-0.7 \pm 12.2\%$, respectively. Stok *et al.* (1993) showed that relative CO, measured with pulse contour analysis, can be reliably measured from a peripheral pulse wave obtained by Finapres compared with inert gas rebreathing, with a good reproducibility during several weeks.

Protocol

The volunteers entered pairwise into the protocol, which consisted of a 2 week ambulatory baseline data collection (BDC) period, 42 days of HDT, and a 2 week ambulatory recovery period (REC). During the HDT period, all activities were completed in this position, including personal hygiene.

In each of the seven volunteers who completed the protocol, 12 Portapres recordings during 22 h were performed. The measurements were made in two volunteers simultaneously sharing the same room. The first measurement was used for habituation of the volunteers to the equipment, and these results are therefore not included in this analysis. The second baseline measurement was used as a reference value (coded as C2), against which the changes observed during HDT (codes

T1 to T8) and the recovery period REC (coded as R1 and R2) were compared. An outline of the protocol is given in Figure 1. The circadian profile was monitored over 22 h (from 09.00 h to 07.00 h the following morning) due to the read-out and re-preparing interval between two registration days. The first recording in the recovery period was an exception to this: measurements were between 19.30 h and 15.30 h.

Research settings

Our protocol was part of the 1994 ESA-CNES long-term bedrest study, held in Toulouse (France) from September to December 1994. It was a collaborative study planned in order to assess the effects of long-term simulated microgravity on cardiovascular and pulmonary function, musculature, bone metabolism, immunology, energetic balance and equilibrium. The protocol was performed in a research ward of the Centre Hôpitalier Universitaire Purpan. No countermeasures to reduce the physiological effects of bedrest, such as physical exercise or an increased salt intake, were planned during the HDT period. Efforts were made to avoid any effect on our measurements by interfering protocols of other research groups, and when this was expected the Portapres measurements were planned in the days preceding this experiment. The majority of the experiments were performed in the control periods; during the 6 weeks of HDT, hardly any protocols besides our own were active. Since we could not exclude an effect of the saline infusion experiment performed by a French research group on day HDT28 on the following Portapres measurements, the time of this specific procedure in relation to our protocol has been indicated explicitly in the results.

The eight volunteers were housed in four separate rooms, each with two beds. During the ambulatory periods the volunteers were allowed to walk within the premises of the research ward. Each morning of the Portapres registration days, cardiovascular function tests were performed, which obliged the volunteers to

Figure 1 Outline of the protocol. Indicated are the codes of the 22 h finger arterial blood pressure measurements with Portapres in relation to the start of the 42 days of head-down tilted bedrest period.

lie motionless for several hours. During HDT the volunteers were at liberty to watch television, to read books and to talk with their room-mate and the nursing staff. Lunch was from 13.00 h to 13.30 h and dinner from 19.00 h to 19.30 h. Before dinner and supper, the volunteers rested for 30 min. No attempts were made to control the volunteers' sleep–wake cycle, e.g. by modifying the ambient light intensity.

Pressure differences between two fingers

Portapres M2 is able to measure and store the continuous finger BP waveform. To avoid patient discomfort, the measurements were taken alternately from two adjacent fingers, using a 30 min switch time. Finger arterial pressure of the third and fourth fingers are not necessarily identical, although the difference is usually small (Imholz *et al.* 1993). Larger differences, during the course of a registration, may come and go. Before the start of each measurement, the finger BP levels of both fingers were checked to be equal. However, in some instances differences were encountered when Portapres switched from one finger to the other. In the case of persisting finger differences, we rejected the complete highest half-hour period if two succeeding 30 min averaged levels in the recorded diastolic finger BP differed by more than 10 mmHg, since repositioning of the cuffs under those circumstances without exception tended to decrease the BP level, and never to increase it. During the recordings we were able to monitor the volunteers by closed-circuit television, which allowed discrimination between physiological variations of BP and artifacts due to vasoconstriction or displacement of the finger cuff.

Data reduction and statistics

The circadian variation of the haemodynamic parameters was assessed by comparing average day- and night-time values. Night-time was defined as the time-period in which the volunteers claimed to have actually slept. The information regarding the sleeping times of each individual night was collected from the volunteers' diaries and the notes from our team member on night duty. Daytime was defined as the average level during the complete 22 h registration minus the sleeping period. This implies that the daytime measurements in C2, R1 and R2 were mainly performed during sitting and ambulation and, to a limited extent, in the supine position. During the 6 weeks of HDT, the volunteers were continuously in the head-down tilt position during both day and night.

In all comparisons, each subject served as his own control. Since no repeated individual calibrations of Modelflow with a reference method of CO determi-

nation were available, only relative measures were used for SV, CO and TPR; these parameters were presented as percentage changes from the 24 h average of baseline C2 values. Variability of BP and HR was assessed by calculating the coefficients of variation (standard deviation weighted for the average level BP or HR).

Values of separate measurements and average levels of the three test conditions (C2, HDT, REC) were compared. Values of separate measurements were compared using Wilcoxon's matched signed rank test. The changes of the haemodynamic parameters during the control period, HDT and recovery were analysed using a repeated measurements ANOVA (*F*-test from general multivariate model) after averaging the eight measurements during HDT and the two measurements during recovery. The consistency of the observed trends of the haemodynamic parameters during the 6 weeks of HDT was tested using an *F*-test from compound symmetry model for within-subject covariance matrix. Mean differences and 95% confidence intervals (CI) of the three test conditions, C2, HDT and REC, were computed. Correction was made for multiple comparisons, and therefore a value of $P \leq 0.01$ was considered to indicate a significant difference.

RESULTS

Of a total of 84 registrations, one complete registration was rejected due to many episodes of digital vasoconstriction, movement artifacts and unacceptable pressure differences between two fingers (C2 of subject F). For this subject, the first measurement C1 in BDC was used as a reference. On average, $7.0 \pm 5.7\%$ of the data was rejected for various reasons.

Effects on haemodynamics

Figures 2 and 3 show the course of the haemodynamic variables during the three test conditions. Figure 4 shows the group-averaged profiles of the haemodynamic parameters during the ambulatory C2 measurement and after 26 days of HDT (registration T6). We chose registration T6 since it was the last registration before the acute salt and water loading infusion experiment on day HDT28. This experiment was performed by another research group and was not part of our protocol. Since this procedure theoretically could interfere with our measurements, the time of this procedure is also explicitly indicated in Figures 3 and 4. The transient increases in blood pressure at approximately 13.00 and 19.00 h coincide with the lunch and dinner times. The results of the repeated measurement ANOVA analyses are summarized in the Table 1. The attenuation of the circadian profile was more pronounced for DBP than for SBP. This was caused by

Figure 2 The influence of 6 weeks of head-down tilted bedrest on systolic and diastolic blood pressure (SBP and DBP) in seven healthy subjects. During the control periods (C2 and R1 to R2), the volunteers were ambulatory in the daytime. The timing of the volume expansion, which was performed by another research group as part of the collaborative protocol, is indicated. Open circles, daytime group average; solid circles, night-time group average ($n = 7$). Small data points represent individual day- and night-time averages. See Figure 1 for time axis.

a drop of daytime DBP and a slight, though significant, increase of night-time DBP compared with C2 (3.7 mmHg; 95% CI 0.5–6.9). In 29% of the registrations in HDT, the circadian rhythm was reversed, i.e. having an average night-time DBP exceeding daytime levels. For SBP this was only observed in 11%. The effects of HDT on circadian blood pressure were already maximal at T2, and no obvious changes were observed in the course of the 6 week period.

In contrast to BP, the day- to night-time difference of HR was essentially unaffected by HDT. After 2 weeks of HDT there was a gradual increase of mean day- and night-time HR levels. Surprisingly, HR returned to the baseline level at T8. Both day- and night-time HR were significantly elevated during REC, and had not returned to pre-tilt values at measurement R2, which was performed 8 days after reassumption of the upright posture. The condition of bedrest was not reflected in a reduced overall variability of SBP, DBP and HR in the daytime (Table 2). The variability of HR was significantly increased during sleep in HDT as compared to C2 ($P < 0.01$). In the ambulatory C2 period, SV was highest during the night; in HDT and recovery, day- and night-time SV were similar. In the course from T1 to T7, a gradual and consistent reduction of SV was

observed, which amounted maximally to -16% at T7 compared with T1 ($P < 0.01$). As for HR, the level of SV at T8 had returned to a pre-tilt level.

CO was unaffected during the whole experiment, both the levels in day- and night-time relative to C2, and the amount of day–night variation.

No circadian variation of TPR was observed in the ambulatory periods C2 and REC. In HDT there was a significant pattern, with the highest values of TPR at night and the lowest during the day. Compared to pre-tilt conditions, daytime TPR decreased by -13.0% , and night-time TPR increased by 7.6% .

DISCUSSION

This study shows that the circadian profiles of SBP and DBP are attenuated during long-term head-down tilted bedrest. The effect was already maximally present in the first week of HDT, and did not obviously change during the succeeding 5 weeks of HDT. The circadian profile was almost completely blunted for DBP, whereas for SBP a fair amount of day–night variation remained. CO was unaffected by HDT, as a result of counteracting changes in HR and SV. While in the ambulatory periods daytime TPR was similar to night-

Figure 3 Daytime and night-time values of heart rate (HR), stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) in the course of the experiment. Open circles, daytime group average; solid circles, night-time group average ($n = 7$). Small data points represent individual averages. The timing of the volume expansion is indicated. See Figure 1 for time axis.

time levels, the highest levels were reached during the night in HDT.

Extensive research has been conducted on the background of circadian blood pressure variability. We acknowledge that describing circadian rhythmicity by merely comparing day- and night-time average levels is a simplification of the total circadian variability. Averaged over a group, circadian blood pressure describes a sinusoidal profile, with more or less gradual increases and declines in the early morning and late evening. However, this so called S-shaped profile is artificial, and correction for actual sleep–wake cycles results in two more or less stable levels of blood pressure (Floras *et al.*

1978). In the present study, we defined day- and night-time on the basis of actual waking and sleeping periods. The state of physical inactivity and the absence of orthostatic loading associated with HDT bedrest was expected to cause an immediate attenuation of the circadian BP variability. The residual day–night variation of BP can be explained by other sources of BP variability still present when confined to bed, such as mental stress (James *et al.* 1986), talking (Lynch *et al.* 1981), micturition and defecation (Littler *et al.* 1974) and the effect of ingested food and drink (Kelbaek *et al.* 1989). A striking rise of BP was observed during the meals in the HDT period, which were taken while lying

Table 1 *P* values of the repeated measurements ANOVAs performed to determine the changes in average levels between C2, HDT and REC (left panel), and the consistency of the trends of the haemodynamic variables observed during 6 weeks of HDT (right panel)

Variable	Changes from C2 to REC			Analysis of trend in 6 weeks of HDT		
	Day	Night	Profile	Day	Night	Profile
SBP	0.01	NS	0.002	<0.0001	NS	0.007
DBP	0.007	NS	0.0004	<0.0001	NS	0.005
HR	0.002	0.003	0.001	0.001	0.0009	NS
SV	NS	<0.0001	NS	0.007	NS	NS
CO	NS	NS	NS	NS	NS	NS
TPR	NS	NS	0.004	NS	NS	NS

$P \leq 0.01$ was considered significant; NS, not significant.

Profile: ratio of average night/day values.

For explanation of acronyms C2 and REC, see Figure 1.

with the face downward and the head protruding out of the bed. It is probable that compression of the splanchnic region in this body position and isometric contractions of the neck muscles were responsible for this transient increase of BP. The elevation of night-time DBP during HDT is consistent with earlier observations of the effect of bedrest on blood pressure (Bevan *et al.* 1969, Mann *et al.* 1979). These authors hypothe-

sized that sleeping problems were responsible for this phenomenon. The logistics of the collaborative protocol in which we participated did not allow us to measure sleep quality by electroencephalographic monitoring. However, the test subjects reported to have slept well once they were accustomed to the HDT position.

Whereas the state of physical inactivity clearly influenced the day-to-night variation of BP, the effect on

Table 2 Coefficients of variation during day- and night-time during the ambulatory C2 recording, during HDT, and during recovery (R1 and R2)

Variable	Daytime				Night-time			
	C2	HDT	R1	R2	C2	HDT	R1	R2
SBP (%)	9.5	8.7	8.7*	9.6	7.8	8.3	8.5	8.6*
DBP (%)	10.3	9.9	9.7	10.3	8.4	8.4	9.6	8.8
HR (%)	11.9	11.4	10.4	11.3	10.0	11.7*	10.0	10.2

*, $P < 0.05$ compared with pre-tilt C2 value (Wilcoxon's matched signed rank test). For acronyms C2, R1 and R2, see Figure 1.

HR in this respect was far less pronounced. This demonstrates that circadian variations in HR are less closely linked to variations in activity and posture compared to blood pressure. Sundberg *et al.* (1988) suggested that HR might be partly endogenously mediated in contrast to blood pressure, since an abrupt reversal in the sleep–wake cycle resulted in a total reversal of the blood pressure profile, and not of HR.

The reduction in SV observed from T1 to T7, amounting to -16% , was in close agreement with the reduction in SV during HDT reported by the team of Arbeille in this same study, who used ultrasound echography (ESA-CNES preliminary report). Several authors reported a reduction of SV after simulated or real microgravity (Pottier *et al.* 1988, Arbeille *et al.* 1992, Beck *et al.* 1992). Since the effect of microgravity on the circulating blood volume seems to be present within hours (Blomqvist *et al.* 1980), the gradual changes observed in our present study occurring in the course of 6 weeks of HDT suggest that a reduction of cardiac contractility might also have contributed. However, previous studies have failed to pinpoint firm indications of cardiac deconditioning after spaceflight (Arbeille *et al.* 1992, Hung *et al.* 1983), while some even reported an increase in cardiac contractility (Atkov *et al.* 1987, Bungo *et al.* 1987).

In the ambulatory periods, day- and night-time levels of TPR were similar; in HDT a clear pattern was observed with daytime levels lower than those during the night-time. A previous study by Veerman *et al.* (1995) suggested that variations of TPR were closely linked to variations in physical activity. Whereas TPR was lowest during walking, the highest levels were reached at night. The nightly drop in BP was therefore mainly CO-mediated. In the ambulatory periods of our study, TPR was similar in both the day- and night-time. This may be explained by the fact that, in the present study, the amount of physical activity in the daytime was relatively limited compared with the protocol of Veerman *et al.* which included a 90 min outdoor walking period and bicycle exercise.

Although a number of different research protocols were carried out simultaneously, we do not expect that these interfered with our results. Most importantly the amount of physical and psychological stress preceding

and during the successive Portapres recordings was highly comparable. The majority of the research protocols had been planned in the pre- and post-tilt periods. Experiments with a possible influence on cardiovascular performance (saline infusions, $\dot{V}O_{2\max}$ determinations) were scheduled for the day directly following a Portapres registration, on average 4 days before the next Portapres registration. On HDT28, the effects of acute volume expansion (18 mL kg^{-1} isotonic saline infused in 30 min, followed by 100 mL h^{-1} over the day to a total of 30 mL kg^{-1}) were investigated by another research group. Since saline loading may act as a countermeasure to reduce the amount of orthostatic intolerance after long-term spaceflight and bedrest, we could not exclude beforehand that our results might have been affected by this experiment. Figures 2 and 3 show the timing of the salt infusion experiment in relation to the Portapres measurements. Apparently, the pattern of changes in haemodynamic parameters in the course of HDT was not altered by this experiment. Therefore, we consider it unlikely that the return of HR and SV to pre-tilt levels observed at T8 are spurious. Possibly, they may partly be explained by the aroused state of the volunteers who anticipated the end of the bedrest period, and the increased presence of staff and experimenters on the ward.

Summarizing, the following conclusions can be drawn from this study:

(1) HDT causes a rapid attenuation of the circadian BP profile, which confirms the overriding importance of physical activity and orthostatic loading on the diurnal variation of BP, suggesting that the circadian BP rhythm is predominantly externally mediated.

(2) The state of physical inactivity of being confined to bed had little effect on the circadian variation of HR, indicating that the circadian variability of HR is less externally mediated in comparison with BP.

(3) Although CO remained unaffected during 6 weeks of HDT, a gradual reduction in SV with an increase of HR was observed. The time-frame of these changes might point to a contribution of other factors besides a reduction of circulating blood volume.

We are indebted to the MEDES medical and nursing staff, as well to the CNES- and ESA-science and project management. Our participation was supported by grant MG-020 from the Space Research

Organization Netherlands. We thank K. H. Wesseling of TNO BioMedical Instrumentation for critical review of the manuscript.

REFERENCES

- Arbeille, Ph., Gauquelin, G., Pottier, J.M., Pourcelot, L., Güell, A. & Gharib, C. 1992. Results of a 4-week head-down tilt with and without LBNP countermeasure: II. Cardiac and peripheral hemodynamics – Comparison with a 25-day spaceflight. *Aviat Space Environ Med* **63**, 9–13.
- Athanassiadis, D., Draper, G.J., Honour, A.J. & Cranston, W.I. 1969. Variation of automatic blood pressure measurements over 24-hour periods. *Clin Sci* **36**, 147–156.
- Atkov, O.Y., Bednenko, V.S. & Fomina, G.A. 1987. Ultrasound techniques in space medicine. *Aviat Space Environ Med*, **58** (suppl. 9), A69–A73.
- Baisch, F., Beck, L., Karemaker, J.M., Arbeille, Ph., Gaffney, F.A. & Blomqvist, C.G. 1992. Head-down-tilt bedrest HDT⁸⁸ – an international collaborative effort in integrated systems physiology. *Acta Physiol Scand* **144** (suppl. 604), 1–12.
- Beck, L., Baisch, F., Gaffney, F.A., Buckley, J.C., Arbeille, Ph., Patat, F., Ten Harkel, A.D.J., Hillebrecht, A., Schultz, H., Karemaker, J.M., Meyer, M. & Blomqvist, C.G. 1992. Cardiovascular response to lower body negative pressure before, during, and after ten days head-down tilted bedrest. *Acta Physiol Scand*, **144** (suppl. 604), 43–52.
- Bevan, A., Honour, A.J. & Stott, F.D. 1969. Direct intraarterial pressure recording in unrestricted man. *Clin Sci* **36**, 329–344.
- Blomqvist, C.G., Nixon, J.V., Johnson, R.L., Jr & Mitchell, J.H. 1980. Early cardiovascular adaptation to zero gravity simulated by head-down tilt. *Acta Astronautica* **7**, 534–553.
- Blomqvist, C.G. & Stone, H.L. Cardiovascular adjustments to gravitational stress. 1983. In: J.T. Shepherd & F.M. Abboud (eds) *Handbook of Physiology, Vol. III, Sec. 2 The Cardiovascular System*, pp. 1025–1063. American Physiological Society, Bethesda, MD.
- Bungo, M.W., Goldwater, D.J., Popp, R.L. & Sandler, H. 1987. Echographic evaluation of space shuttle crewmembers. *J Appl Physiol* **62**, 278–283.
- Clark, L.A., Denby, L., Pregibon, G.A., Pickering, T.G., Blank, S. & Laragh, J.H. 1987. A quantitative analysis of the effects of activity and time of day on the diurnal variations of blood pressure. *J Chron Dis* **40**, 671–681.
- Covertino, V.A., Doerr, D.F., Eckberg, D.L., Fritsch, J.M. & Vernikos-Danellis, J. 1990. Head-down bed-rest impairs vagal baroreflex responses and provokes orthostatic hypotension. *J Appl Physiol* **68**, 1458–1464.
- Davydova, N.A., Shishkina, S.K., Korneyeva, N.V., Suprunova, Y.V. & Ushakov, A.S. 1986. Biochemical aspects of some neurohumoral system functions during long-term anti-orthostatic hypokinesia. *Kosm Biol Aviakosm Med* **20**, 91–95.
- Degaute, J.P., van de Borne, P., Linkowski, P. & van Cauter, E. 1991. Quantitative analysis of the 24-hour blood pressure and heart rate patterns in young men. *Hypertension* **18**, 199–210.
- Floras, J.S., Jones, J.V., Johnston, J.A., Brooks, D.E., Hassan, M.O. & Sleight, P. 1978. Arousal and the circadian rhythm of blood pressure. *Clin Sci Mol Med* **55**, 395s–397s.
- Hughson, R.L., Maillet, A., Gharib, C., Fortrat, J.O., Yamamoto, Y., Pavy-Le Traon, A., Rivièrè, D. & Güell, A. 1994a. Reduced spontaneous baroreflex slope during lower body negative pressure after 28 days of head-down bed rest. *J Appl Physiol* **77**, 69–77.
- Hughson, R.L., Yamamoto, Y., Maillet, A., Fortrat, J.O., Pavy-Le Traon, A., Butler, G.C., Güell, A. & Gharib, C. 1994b. Altered autonomic regulation of cardiac function during head-up tilt after 28-day head-down bed-rest with counter measures. *Clin Physiol* **14**, 291–304.
- Hung, J., Goldwater, D., Convertino, V., McKillop, J.H., Goris, M. & DeBusk, R. 1983. Mechanisms for decreased exercise capacity after bedrest in normal middle-aged men. *Am J Cardiol* **51**, 344–348.
- Imholz, B.P.M., Langewouters, G.J., van Montfrans, G.A., Parati, G., van Goudoever, J., Wesseling, K.H., Wieling, W. & Mancia, G. 1993. Feasibility of ambulatory, continuous 24-hour finger arterial pressure recording. *Hypertension* **21**, 65–73.
- James, G.D., Yee, L.S., Harshfield, G.A., Blank, S.G. & Pickering, T.G. 1986. The influence of happiness, anger, and anxiety on the blood pressure of borderline hypertensives. *Psychosom Med* **48**, 502–508.
- Kelback, H., Munck, O., Christensen, N.J. & Godtfredsen, J. 1989. Central haemodynamic changes after a meal. *Br Heart J* **61**, 506–509.
- Langewouters, G.J., Wesseling, K.H. & Goedhard, W.J.A. 1984. The static elastic properties of 45 human thoracic and 20 abdominal aortas in vitro and the parameters of a new model. *J Biomech* **17**, 425–433.
- Leach, C.S., Altchuler, S.I. & Cintron-Trevino, N.M. 1983. The endocrine and metabolic response to space flight. *Med Sci Sport Exerc* **15**, 432–440.
- Littler, W.A., Honour, A.J. & Sleight, P. 1974. Direct arterial pressure, pulse rate, and electrocardiogram during micturition and defecation in unrestricted man. *Am Heart J* **88**, 205–210.
- Lynch, J.J., Long, J.M., Thomas, S.A., Malinow, K.L. & Katcher, A.H. 1981. The effects of talking on the blood pressure of hypertensive and normotensive individuals. *Psychosom Med* **43**, 25–33.
- Mann, S., Millar Craig, M.W., Mellville, D.I., Balasubramanian, V. & Raftery, E.B. 1979. Physical activity and the circadian rhythm of blood pressure. *Clin Sci* **57**, 291s–294s.
- Parati, G., Casadei, R., Gropelli, A., Di Rienzo, M. & Mancia, G. 1989. Comparison of finger and intraarterial blood pressure monitoring in rest and during laboratory tests. *Hypertension* **13**, 647–655.
- Peñáz, J. 1973. Photoelectric measurement of blood pressure, volume and flow in the finger. In: R. Albert, W. Vigt & W. Helbig (eds) *Digest 10th Int Conf Med Biol Eng*, P.104. Dresden, Germany
- Pottier, J.M., Arbeille, Ph. & Patat, F. 1988. Comparative study of the early cardiovascular adaptation to zero-G during 7 days space flights. *Physiologist* **31**, 14–5.

- Robertson, D., Convertino, V.A. & Vernikos, J. 1994. The sympathetic nervous system and the physiologic consequences of spaceflight: a hypothesis. *Am J Med Sci* **308**, 126–132.
- Stok, W.J., Baisch, F., Hillebrecht, A., Schultz, H., Meyer, M. & Karemaker, J.M. 1993. Noninvasive cardiac output measurement by arterial pulse analysis compared with inert gas rebreathing. *J Appl Physiol* **74**, 2687–2693.
- Sundberg, S., Kohvakka, A. & Gordin, A. 1988. Rapid reversal of circadian blood pressure rhythm in shift workers. *J Hypertens* **6**, 393–396.
- Toorop, G.R., Westerhof, N. & Elzinga, G. 1987. Beat-to-beat estimation of peripheral resistance and arterial compliance during pressure transients. *Am J Physiol* **5**, 495–507.
- Veerman, D.P., Imholz, B.P.M., Wieling, W., Wesseling, K.H. & G.A. van Montfrans, G.A. 1995. The circadian profile of systemic hemodynamics. *Hypertension* **26**, 55–59.
- Wesseling, K.H. 1990. Finapres, continuous non-invasive finger arterial pressure based on the method of Peñáz. In: W. Meyer-Sabellek, M. Anlauf, R. Gotzen & L. Steinfeld (eds) *Blood Pressure Measurement*, pp. 161–172. Steinkopff Verlag, Darmstadt.
- Wesseling, K.H. 1993. *The BMI-FAST-mf/-cZ system user manual*. TNO-Biomedical Instrumentation, Academic Medical Center, Amsterdam, the Netherlands.
- Wesseling, K.H., Jansen, J.R.C., Settels, J.J. & Schreuder, J.J. 1993. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol* **74**, 2566–2573.