Mechanisms underlying the impairment in ortostatic tolerance after nocturnal recumbency in patients with autonomic failure

Stefano OMBONI*†, Adrianus A. J. SMIT*, Johannes J. van LIeSHOUT*, Jos J. SETTELS‡, Gerard J. LANGEWOUTERS‡ and Wouter WIELING*

Department of Internal Medicine, Meibergdreef 9, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands, †Department of Internal Medicine, S. Gerardo Hospital, Monza and Instituto Auxologico Italiano, Università di Milano-Bicocca, Milan, Italy, and ‡TNO Biomedical Instrumentation, Academic Medical Centrum, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

ABSTRACT

In the present study, we have assessed in patients with neurogenic orthostatic hypotension the haemodynamics underlying the reduced tolerance to standing after prolonged recumbency at night. In 10 patients with neurogenic orthostatic hypotension (age 33–68 years), of which seven were being treated with fludrocortisone and/or sleeping in the 12° head-up tilt position, 24 h continuous non-invasive finger blood pressure was recorded by a Portapres device. Beat-to-beat blood pressure, heart rate, stroke volume, cardiac output and total peripheral vascular resistance obtained by pulse contour analysis were assessed during 5 min of standing in the evening (at 22.30 hours) and in the morning (at 06.30 hours). On average, the inverse of the normal 24 h blood pressure profile was found, with a large diversity in blood pressure profiles among patients. Supine blood pressure values were similar, but standing blood pressure values were lower in the morning than in the evening ($P<0.01$). This resulted from larger falls in stroke volume and cardiac output upon standing in the morning compared with the evening, while total peripheral resistance did not change. There was no relationship between the decrease in body weight during the night (mean 0.9 kg; range 0.2–1.6 kg) and the evening–morning difference in standing blood pressure. We conclude that, in patients with neurogenic orthostatic hypotension, the impaired tolerance to standing in the morning is due to larger falls in stroke volume and cardiac output. Not only nocturnal polyuria, but also a redistribution of body fluid, are likely mechanisms underlying the pronounced decreases in stroke volume and cardiac output after prolonged recumbency at night.

INTRODUCTION

In patients with neurogenic orthostatic hypotension, symptoms such as light-headedness, visual disturbances and muscle ache frequently occur, limiting the patients’ activities in their daily life. In particular, after a night sleep, tolerance to standing and upright exercise is reduced, with a subsequent improvement in the course of the day [1–7]. In view of the dependence of orthostatic symptoms on blood pressure, these clinical observations have led to the study of diurnal blood pressure patterns in these patients.

During continuous intra-arterial monitoring of blood pressure in ambulant patients with neurogenic orthostatic hypotension, an inverse of the normal blood pressure pattern was observed in the hourly average plots, with

Key words: ambulatory blood pressure, autonomic failure, finger blood pressure, orthostatic tolerance, pulse contour analysis.

Correspondence: Dr Wouter Wieling (e-mail W.Wieling@amc.uva.nl).
the lowest blood pressures occurring in the morning, increasing pressure during the day and the highest pressures at night [8–10]. Interestingly, confinement to bed during the day did not substantially alter the inverse diurnal pattern [8–10]. This finding, suggesting a minor influence of posture and physical activity on the diurnal pattern, is difficult to explain, since orthostasis and exercise are the main conditions causing hypotension in patients with autonomic failure [1,3,6,11–13]. Thus at present the mechanisms underlying the diurnal patterns of orthostatic tolerance and blood pressure remain unknown.

We have addressed this issue and evaluated trends in blood pressure during the course of the day in patients with autonomic failure. Using non-invasive continuous ambulatory finger blood pressure monitoring [12,14] and a protocol with controlled activities, both the trends in hourly averages and the trends during common activities, such as standing and walking, were analysed. The underlying haemodynamic processes were studied using stroke volume monitoring by pulse contour analysis [15–17].

**METHODS**

**Subjects**

A total of 10 patients (age 33–68 years) with neurogenic orthostatic hypotension were included. At the time of the study, the mean supine oscillometric blood pressure in the morning was 160/98 mmHg (range 108–190/68–122 mmHg) and standing blood pressure after 2 min was 91/57 mmHg (range 70–115/41–78 mmHg). In all patients, supine plasma levels of noradrenaline and the increment in noradrenaline upon standing had been shown repeatedly to be abnormally low. Three patients with mild symptoms received no treatment. The other patients were being managed by sleeping in the 12° head-up tilt position, either alone (n = 2) or in combination with fludrocortisone (0.1–0.2 mg/day; n = 5) [18]. Therapy was continued during the study protocol, since we wanted to evaluate the patients during normal conditions. Written informed consent was obtained from each subject, and the study was approved by the local ethical committee.

**Measurements**

Continuous non-invasive finger blood pressure recording was performed using a Portapres™ Model-1 device (TNO; BMI, Amsterdam, The Netherlands) [14,19]. Appropriately sized cuffs were wrapped around the middle finger and around the ring finger of the non-dominant hand. Blood pressure measurement was switched from one finger to the other every 30 min throughout the 24 h recording period. The instrumented hand was supported by a sling and held at heart level. In addition, a height correction system was used to adjust for hydrostatic height differences between the hand and the heart. The blood pressure and hydrostatic height signals were stored in the built-in TEAC tape cassette recorder, along with a marker signal superimposed on the height signal channel. We had no problem obtaining finger arterial pressure due to Raynaud’s phenomenon in our patients, who were within the hospital setting with a relative high ambient temperature. In addition, the hand was covered at all times by the sling.

Adequate reflection of changes in intra-arterial blood pressure during daily activities and (hypotensive) orthostatic stress by the measurement of finger arterial pressure has been verified [14,21–23].

**Protocol**

The patients were housed in a private room in the institution’s research unit during the 24 h blood pressure recording. The actual protocol was started at 12.00 hours, and lasted until 12.00 hours the next day. During the 24 h period, several controlled activities were carried out. The times of lunch and dinner, and of going to bed in the evening and arising in the morning, were also controlled (Table 1) [14,24]. Sleep was not measured. The starting times of the activities were, for obvious reasons, not identical, but differed by no more than 30 min. In one patient (patient 10) the protocol was started in the afternoon for logistical reasons. When the patients were not subjected to a protocol, they were left free to perform non-fatiguing daily activities in the research unit, such as watching television.

<table>
<thead>
<tr>
<th>Time of day</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.00 hours</td>
<td>Starting of the recording, followed by lunch</td>
</tr>
<tr>
<td>14.00–15.30 hours</td>
<td>Siesta</td>
</tr>
<tr>
<td>16.00–16.05 hours</td>
<td>Sitting</td>
</tr>
<tr>
<td>16.05–16.20 hours</td>
<td>Walking in the hospital</td>
</tr>
<tr>
<td>16.35–16.55 hours</td>
<td>Cycling</td>
</tr>
<tr>
<td>18.00 hours</td>
<td>Dinner</td>
</tr>
<tr>
<td>22.00 hours</td>
<td>Micturition and assessment of body weight</td>
</tr>
<tr>
<td>22.40–22.50 hours</td>
<td>Supine</td>
</tr>
<tr>
<td>22.50–22.55 hours</td>
<td>Standing</td>
</tr>
<tr>
<td>23.00–06.30 hours</td>
<td>Night sleep</td>
</tr>
<tr>
<td>06.30–06.35 hours</td>
<td>Standing</td>
</tr>
<tr>
<td>08.00 hours</td>
<td>Micturition and assessment of body weight</td>
</tr>
<tr>
<td>08.30 hours</td>
<td>Breakfast</td>
</tr>
<tr>
<td>10.00–10.05 hours</td>
<td>Sitting</td>
</tr>
<tr>
<td>10.05–10.20 hours</td>
<td>Walking in the hospital</td>
</tr>
<tr>
<td>12.00 hours</td>
<td>End of the recording</td>
</tr>
</tbody>
</table>


**Tolerance to standing**

Assessment of tolerance to standing was studied just before going to sleep (22.30 hours) after 10 min of supine rest, and in the morning immediately after waking up (06.30 hours). The seven patients who were sleeping in the 12° head-up tilt position were studied in that position. Patients were asked to stand still in the erect posture for 5 min. The combination of the arterial blood pressure responses to standing and the severity of complaints of orthostatic light-headedness and (near) syncope were used to assess tolerance to standing. We did not use a questionnaire and a clinical rating scale to assess the symptoms of orthostatic hypotension in great detail, as has been suggested by Senard et al. [25]. Evidently orthostatic tolerance is related to cerebrovascular changes especially in these patients [26], but we did not gauge this parameter specifically in the present study.

In addition, body weight was measured after micturition at 22.30 hours and 08.00 hours, and urine was collected in the period between the two body weight measurements. On each occasion body weight was measured by S.O. and/or A.A.J.S., using the same calibrated scale and with the patient wearing the same clothes. Patients abstained from eating or drinking at night in the time period between the two body weight measurements.

**Tolerance to walking**

Walking at a comfortable speed for each patient was performed in the afternoon (16.00 hours) and in the morning (10.00 hours) for 15 min. Patients sat quietly for 5 min before walking.

**Siesta**

This activity comprised a supine period from 14.00 to 15.30 hours. The subjects rested on a bed, but did not sleep.

**Data analysis**

The recorded blood pressure signal was analysed off-line by means of a software program (FAST System; TNO). Stroke volume was obtained from arterial pressure by a modified and improved version of the pulse contour method developed by Wesseling and co-workers [15,16] that corrects for pressure-dependent properties of the arterial impedance and heart rate-dependent early reflections coming from the periphery, with the degree of correction depending on the age of the subject. Changes in left ventricular stroke volume were computed from the pulsatile systolic area [15,16]. To obtain absolute stroke volume values, calibration with a standard method is needed. In the absence of such calibration the relative changes in stroke volume track absolute stroke volume well [16,17,22,24,27]. The digitized blood pressure wave was displayed on a computer screen to allow identification and removal of artifacts (morphological aberrations of the signal and physiological calibrations). The total number of rejected beats represented on average 9% of the total available beats. These missing beats were linearly interpolated.

**Statistical analysis**

In order to show the time course of the haemodynamic changes that occurred upon standing or during exercise, 10 s averages from the beat-to-beat tracing were computed. This was done (1) for the last 2 min of supine rest preceding standing up and the last 2 min of sitting prior to walking, and (2) for the periods of standing and walking. Average values were also calculated for the entire duration of each period, i.e. supine, sitting, standing and walking. Comparison of average values of blood pressure, heart rate and haemodynamics at different time points was carried out using a non-parametric test for dependent samples (Wilcoxon’s test). The Pearson correlation coefficient (r) was computed to assess the relationship between evening–morning differences for the fall in blood pressure upon standing and changes in body weight overnight. Statistical analysis was performed using the SPSS/PC+ statistical package [28]. A value of $P < 0.05$ was considered statistically significant.

**RESULTS**

**Trends in 24 h blood pressure**

When assessing the subjects as a group an inverse of the

![Figure 1](image)
normal 24 h blood pressure pattern was present, but large inter-individual differences were observed (Figure 1). In some patients a flat or even normal blood pressure pattern was observed (patients 7 and 10 in Figure 2), while in others marked nocturnal hypertension occurred (patients 6 and 8 in Figure 2). No clear relationship was present between the severity of the patient’s condition and these patterns. It is also evident from Figure 1 that average systolic/diastolic blood pressure values during siesta (113 ± 13/58 ± 7 mmHg) were lower than those during night sleep (132 ± 28/72 ± 18 mmHg; *P < 0.05). No differences were found between the first (135 ± 29/73 ± 20 mmHg) and the last (130 ± 26/70 ± 16 mmHg) 90 min of sleep. In the individual hourly averaged tracings, the effects of posture and brief exercise periods are not clearly visible (Figure 2).

### Table 2  Cardiovascular haemodynamics before (supine) and during standing in the evening and in the morning in the 10 patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Evening</th>
<th>Morning</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>143 (112 to 188)</td>
<td>135 (101 to 187)</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td>76 (61 to 99)</td>
<td>70 (48 to 98)</td>
</tr>
<tr>
<td><strong>HR (beats/min)</strong></td>
<td>69 (55 to 85)</td>
<td>68 (60 to 79)</td>
</tr>
<tr>
<td><strong>ΔSV (%)</strong></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>ΔCO (%)</strong></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>ΔTPR (%)</strong></td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Supine blood pressure and heart rate did not change significantly after a night sleep. Standing blood pressure in the evening was higher than that on the next morning (*P < 0.01*) (Table 2 and Figure 3). In the morning, three patients experienced severe orthostatic light-headedness and could stand for only 1–3 min; their averaged standing finger blood pressure ranged from 57 to 62 mmHg (systolic) and from 28 to 36 mmHg (diastolic). In the evening these patients stood for 4–5 min, with an

© 2001 The Biochemical Society and the Medical Research Society
Figure 3  Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) profiles before (supine) and during standing in the evening (left panels) and in the morning (right panels)

Data are shown as 10 s averages for each of the 10 subjects included in the study (thin lines) and as the average for the whole group (thick line).

averaged standing blood pressure of 84–103 mmHg (systolic) and 45–51 mmHg (diastolic). For the whole group, averaged standing heart rate in the evening did not differ from that in the morning.

Upon standing, the decreases in stroke volume and cardiac output in the evening were less than those in the morning (both \( P < 0.01 \)) (Table 2 and Figure 4). No significant difference was observed between evening and morning with regard to total peripheral resistance.

Total urine output was 0.7 litres (range 0.5–1.0 litres) during the night and 0.7 litres (range 0.2–1.2 litres) during the day. Body weight decreased overnight by 0.9 kg (range 0.2–1.6 kg). The evening–morning differences in upright blood pressure showed no significant relationship with the change in body weight \( (r = -0.23 \) and \( -0.49 \) for systolic and diastolic blood pressure respectively.

Tolerance to walking

Two severely affected patients were not able to complete a 15 min walk in the morning due to the occurrence of light-headedness, but were able to walk in the afternoon without interruption. Figure 5 shows a continuous blood pressure and heart rate recording for one of these patients. Systolic blood pressure and cardiac output during walking were higher in the afternoon (66 compared with 47 mmHg, and +12 compared with −16% respectively). Similar results were obtained in the other patient (results not shown).

In the remaining eight patients, sitting blood pressures were not significantly different between the afternoon (systolic/diastolic blood pressure 115±19/99±18 mmHg; mean±S.D.) and the next morning (111±21/100±15 mmHg). During walking, blood pressure decreased and heart rate increased (Figure 6). The decreases in systolic and diastolic blood pressure during walking were on average slightly greater in the afternoon (−16±21/−18±11 mmHg) than in the morning (−12±20/−12±14 mmHg; \( P < 0.05 \) for diastolic blood pressure only). The decrease in total peripheral resistance during walking in the afternoon was greater (−43±8%) than on the next morning.
Figure 4  Stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) profiles before (supine) and during standing in the evening (left panels) and in the morning (right panels)
Data are shown as 10 s percentage average changes (Δ%) from supine for each of the 10 subjects included in the study (thin lines) and for the whole group (thick line).

Figure 5  Beat-to-beat systolic and diastolic blood pressure and heart rate values before and during walking (boxes) in the morning (10.00 hours) and in the afternoon (16.00 hours) in a representative patient
Note that, in the morning, walking was interrupted due to presyncopal symptoms.
Orthostatic tolerance in autonomic failure

Figure 6  Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) profiles before (supine) and during walking in the afternoon (left panels) and in the morning (right panels)

Data are shown as 10 s averages for each of the eight subjects who could perform the entire activity (thin lines), and as the average for the whole group (thick line). ($-34 \pm 10\% ; P < 0.05$). Stroke volume and cardiac output increased similarly (Figure 7).

DISCUSSION

The present study documents that the increases in hour-to-hour blood pressure over a 24 h period in patients with neurogenic orthostatic hypotension can be explained almost exclusively by an increase in upright blood pressure. The underlying mechanism is a better maintained stroke volume.

24 h blood pressure pattern

In the study by Mann et al. [8,9], only two out of the six patients studied were taking fludrocortisone, and sleeping in the head-up tilt position was discontinued 48 h before the study, in order to amplify the effects of orthostasis. In contrast, in the present study the patients were studied during their regular regimen based on volume expansion, i.e. in conditions simulating daily life. Despite these differences, almost identical results were obtained in the hourly average plots, i.e. on average an inverse of the normal 24 h blood pressure pattern was observed, with high blood pressures at night and low pressures in the morning (Figure 1), as well as substantial between-patient variability in the 24 h blood pressure pattern (Figure 2). Mann et al. [8,9] observed a flat blood pressure pattern in a young patient with relatively mild disease. We obtained a similar result (patient 10, Figure 2), but we also observed a flat pattern in a severely affected chair-bound patient (patient 7, Figure 2). At present these observations are hard to explain. Differences in ambulation during daytime, fluid shift during the night and endocrine aspects, such as the renin–angiotensin and the vasopressin systems, should be considered [29].

The hourly averaging technique (Figures 1 and 2) masked the marked short-term influences of posture and physical activity on blood pressure (Figures 3, 5 and 6). Thus strict synchronization of daily activities and a separate detailed analysis of these short periods is compulsory in order to analyse changes in blood pressure over a 24 h period in patients with neurogenic orthostatic hypotension. The ability to leave the bed and to sit upright during the ‘bed-confined’ condition, and inactivity in the hospital during the ‘ambulant’ condition, might explain the similarity in blood pressure profiles under ambulant and bed-confined conditions in the older studies, as was suggested by the authors themselves.
In addition, the blood pressure lowering effect of meals should be considered. Thus this activity should also be standardized and synchronized among patients, as was done in the present study.

**Effect of siesta**

We observed that blood pressure during siesta was lower than during sleep. Interestingly, during this period the subjects rested on the bed, but did not sleep, implying that recumbency alone seems to be a key factor. Food is known to have a hypotensive effect that lasts for several hours in patients with autonomic failure [30]. We attribute the lower blood pressure during daytime recumbency without sleep compared with that during recumbency at night to the fact that the siesta period immediately followed lunch.

**Tolerance to standing**

The impairment of standing blood pressure and orthostatic tolerance in the morning was explained solely by the larger fall in stroke volume; the increase in heart rate was actually greater in the morning. The changes in total peripheral resistance upon standing were very abnormal, with on average no increase, as is typical of patients with neurogenic orthostatic hypotension [31]. No consistent difference between the values for total peripheral resistance in the morning and evening was found.

The average fall in cardiac output during standing in our patients in the morning (approx. 35%) was greater than that observed in our previous studies in normal subjects (15–25%) [32], but almost identical with that obtained in previous studies in patients with neurogenic orthostatic hypotension [7,33–37]. Excessively lowered cardiopulmonary blood volume during orthostasis has been suggested to underlie this large fall in cardiac output [37,38].

The findings of impairment of orthostatic tolerance and a larger fall in cardiac output in the morning observed in the present study suggest that the cardiopulmonary blood volume decreased during the night and subsequently increased during the day. This postulated decrease in blood volume during the night is usually explained by the nocturnal polyuria observed in patients with autonomic failure [39,40]. The observation that desmopressin prevents nocturnal polyuria and improves orthostatic tolerance in the morning supports this view [39,40]. Nocturnal polyuria was observed in the present study.
study, but the evening–morning difference in body weight and the fall in blood pressure upon standing were not correlated. This finding suggests that loss of body fluid due to nocturnal polyuria is not the only mechanism involved, and supports the view that important shifts of fluid volume between the intravascular and extravascular compartments occur in patients with autonomic failure [41–43].

**Tolerance to walking**

Tolerance to walking is often reported to be decreased in patients with autonomic failure [1,3–6], but blood pressure readings during this type of activity have not been studied under daily life conditions. In two severely affected patients with symptomatic hypotension during walking in the morning, the improved tolerance to exercise later in the day was related to the greater values for systolic blood pressure and cardiac output during walking. In the afternoon the haemodynamics of these two patients were similar to those observed in the remaining eight patients for whom no difference was found in cardiac output during walking between the morning and the afternoon. Thus the main determinant of the improvement in tolerance to walking over the course of the day in severely afflicted patients with neurogenic orthostatic hypotension is again the ability to maintain cardiac output.

**Conclusions**

In patients with neurogenic orthostatic hypotension, the improvement in tolerance to standing during the course of the day is related to a decrease in the orthostatic falls in stroke volume and cardiac output, and not to an increase in total peripheral resistance. This observation was obtained using a non-invasive technique in conditions that simulated real daily life. The lack of a relationship between change in body weight and change in cardiac output suggests that intravascular venous filling is affected not only by loss, but also by redistribution, of body fluid.

**REFERENCES**


© 2001 The Biochemical Society and the Medical Research Society


38 MacLean, A. R. and Allen, E. V. (1940) Orthostatic hypotension and orthostatic tachycardia; treatment with the “head-up” bed. J. Am. Med. Assoc. 115, 2162–2167


Received 5 March 2001/8 June 2001; accepted 25 July 2001