Research Paper

Clinical Autonomic Research 2000, **10**:35–42

Fludrocortisone and sleeping in the head-up position limit the postural decrease in cardiac output in autonomic failure

Johannes J. van Lieshout, M.D., Ph.D.,[1,2] A. Derk Jan ten Harkel, M.D., Ph.D.,[2] and Wouter Wieling, M.D., Ph.D.[1,2]

[1]Cardiovascular Research Institute Amsterdam, The Netherlands; [2]Department of Internal Medicine, Academic Medical Centre, Amsterdam, The Netherlands

Please address all correspondence to Dr. Johannes J. van Lieshout, Academic Medical Centre, University of Amsterdam, Department of Internal Medicine, Room F4-264, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands.
Tel: 31-20-566 2371; Fax: 31-20-566 4440
E-Mail: j.j.vanlieshout@amc.uva.nl

Received July 7, 1999; accepted as revised October 26, 1999

Treatment with head-up tilt sleeping and low-dose fludrocortisone effectively minimizes orthostatic symptoms and increases orthostatic blood pressure in patients with neurogenic orthostatic hypotension. The aim of the present study was to examine whether the improvement in orthostatic blood pressure during combined treatment with low-dose fludrocortisone and nocturnal head-up tilt in patients with neurogenic orthostatic hypotension can be attributed to expansion of plasma volume or to increased total peripheral resistance.

The effects of a 3-week treatment with fludrocortisone and nocturnal head-up tilting on the postural changes in arterial pressure, heart rate, and cardiac output (pulse contour) were evaluated in eight consecutive patients with orthostatic hypotension.

The period during which the patients were able to remain in the standing position without orthostatic complaints increased minimally from 3 to 10 minutes. The decrease in arterial pressure after 1 minute of standing—(means with standard deviations in parentheses) systolic, 49 (20) mm Hg; diastolic, 18 (11) mm Hg—before treatment was produced by a greater than normal decrease in cardiac output: 37% (10%) in patients with neurogenic orthostatic hypotension versus -14% (8%) in control subjects. Treatment increased upright arterial pressure from 83 (19) mm Hg systolic and 55 (13) mm Hg diastolic to 114 (22) mm Hg systolic and 60 (16) mm Hg diastolic by limiting the decrease in cardiac output. Body weight increased but hematocrit did not change. Leg pressure–volume relationship decreased in the two patients studied. The responses of plasma renin activity and aldosterone to orthostatic stress prior to treatment were subnormal and became even lower after treatment.

The improvement in upright blood pressure in orthostatic hypotension during treatment with fludrocortisone and nocturnal head-up sleeping is the result of a reduction in the orthostatic decrease in cardiac output. Preliminary data suggest that the expanded body fluid volume is allocated to the perivascular space rather than to the intravascular space.

Key words: blood pressure, stroke volume, vascular resistance, body fluids, hormones, plethysmography.

Patients with autonomic disorders present most often with symptoms of orthostatic hypotension. There is no specific treatment for sympathetic vasomotor failure, and therapy is focused on alleviating the patient's orthostatic tolerance by increasing the magnitude of the circulating volume [1] with mineralocorticoid treatment and by sleeping in the head-up tilt position [2–4]. The presumed circulatory effect of fludrocortisone is an increase in plasma volume by enhanced renal preservation of sodium. An increase in systemic vascular resistance (SVR) by sensitization of alpha-adrenoreceptors has also been suggested [5–9]. Maintenance of the head-up position during the night is assumed to prevent renal sodium loss and development of hypovolemia by means of chronic hypotensive baroreceptor stimulation [7]. The combined treatment of fludrocortisone and head-up sleeping is commonly applied.

This study examined whether the improvement in orthostatic blood pressure (BP) during combined treatment with low-dose fludrocortisone and nocturnal head-up tilt in patients with neurogenic orthostatic hypotension (NOH) can be attributed to expansion of plasma volume or to an increase in SVR. We studied the hemodynamic and hormonal effects of combination treatment with fludrocortisone and nocturnal head-up tilting in consecutive patients with NOH.

Subjects and methods

Patients

Six women and two men with NOH (defined as an orthostatic decrease in arterial BP greater than or equal to 20 mm Hg systolic and/or 5 mm Hg after 1 minute of standing and an increment in plasma norepinephrine below 120 ng/L) [10] were observed. Patient characteristics are given in Table 1. Hypoadrenergic orthostatic hypotension was related to pure autonomic failure (PAF) in five patients. In another

Table 1. Characteristics of eight patients with orthostatic hypotension

Patient no.	Age/gender (y)	Diagnosis	Standing time (seconds)	BP supine (mm Hg)	BP* upright (mm Hg)	HR supine (bpm)	HR* upright (bpm)	Nor† supine (ng/L)	Nor*‡ upright (ng/L)	Protocol 1	2	3
1	55 f	PAF	150	165/90	82/54	87	95	115	145	x	x	x
2	23 f	Hodgkin	120	132/70	61/43	68	149	78	81	x		
3	38 f	sympathectomies	180	123/74	89/64	55	108	102	110	x		
4	65 m	PAF	600	145/82	94/62	64	82	35	45	x	x	x
5	53 f	poliomyelitis	600	149/76	112/72	69	101	210	340	x		
6	65 m	PAF	30	109/62	58/33	64	82	105	105	x		
7	34 f	PAF	25	120/48	76/38	73	78	13	39		x	
8	65 f	PAF	100	128/68	106/58	70	66	56	90		x	
Mean			50	134/71	85/53	69	95	89	119			
SD			16	18/13	19/14	9	26	61	96			

BP = blood pressure; HR = heart rate; bpm = beats per minute; Nor = norepinephrine; PAF = pure autonomic failure.
*10 minutes in sitting or standing position.
†Supine reference values for norepinephrine: 145–575 ng/L (95% confidence limits).
‡Lower limit of 95% confidence interval for the difference between standing and supine norepinephrine values: 120 ng/L.

three patients, orthostatic hypotension was subsequent to Hodgkin disease [11], extensive sympathectomies [12], and previous poliomyelitis [13], respectively. None of the patients had symptoms or signs of organic heart disease as indicated by history, electrocardiography, or echocardiography. Six control subjects (three women, three men; mean age, 42 y; age range, 30–58 y) served as age- and sex-matched controls. They were normotensive (average BP, 110/60 mm Hg; range, 92–124/46–72 mm Hg), had normal physical fitness without special sports training, were nonsmokers, and did not use medication. The investigation conforms with the principles outlined in the Declaration of Helsinki, and the study protocol was approved by the Academic Medical Centre ethical committee. All subjects gave their informed consent before participating.

Experimental protocols

Three protocols were used (Table 1). In protocol 1, the cardiovascular adjustment to active standing was studied in six patients (patients 1–6). The measurements were performed twice, once before and once after 3 weeks of treatment with nocturnal sleeping in the 12° head-up tilt position, and 0.1 to 0.2 mg fludrocortisone was administered at 10:00 PM. The daily sodium intake was 150 to 200 mmol and the minimal water intake was 2,000 ml. Body weight was measured twice a day (at 08:00 AM and 10:00 PM) after micturition, using the same scale while the patient was wearing the same clothes. At 8:00 AM after an overnight fast, a standing-up test was performed. After instruction and instrumentation, the patients rested for at least 10 minutes [14] prior to standing up. They were requested to stand and to remain motionless while upright. Standing was terminated at the onset of presyncopal symptoms such as weakness or dizziness or after a maximal period of 10 minutes in the upright position. In control subjects, the standing-up test was performed once. In protocol 2, BP, heart rate (HR), packed cell volume, plasma levels of renin activity (PRA), aldosterone level, antidiuretic hormone level, and atrial natriuretic peptide (ANP) level were measured before and after 3 weeks of treatment in four patients with PAF (Table 1, patients 1, 4, 7, and 8). In protocol 3, the capacity for venous pooling was assessed in two patients (patients 1 and 4).

Methods

Blood was sampled through an indwelling polyethylene antecubital or hand vein catheter after 20 minutes of rest in the supine position and after 10 minutes of standing or at impending syncope, whichever occurred first.

The change in hematocrit induced by orthostatic stress was assessed by sampling peripheral hematocrit early (less than 60 seconds after laying down). This was demonstrated early to reflect the true overall intravascular hemoconcentration that resulted from facilitation of proper mixing of blood between circulatory compartments [15]. The samples were drawn into chilled tubes containing appropriate enzyme inhibitors, placed on ice, and centrifuged at 2,000 rounds per minute and 4°C for 10 minutes. Plasma was then stored at -30°C until it was analyzed. PRA was measured by commercial radioimmunoassay for angiotensin I generation (ng angiotensin I generation/L/min), plasma aldosterone (Abbott, Amstelveen, The Netherlands), and ANP (Incstar, Amsterdam, The Netherlands). Changes in plasma volume were calculated from changes in packed cell volume [16].

Arterial pressure. BP was measured as a continuous noninvasive recording of finger BP by means of a TNO model 5 Finapres (Ohmeda Monitoring Systems, Englewood, CO, USA). The Finapres measurement is based on the volume clamp technique of Peñáz and the Physiocal criteria of Wesseling [17] and accurately reflects systolic, mean, and diastolic BP changes during complex maneuvers such as standing up [18] as well as during arterial hypotension [19–21]. The finger cuff was held at heart level to avoid hydrostatic level errors. HR was derived from the pulse pressure interval. The measured signals and an event marker were recorded simultaneously on a thermopaper writer (Sanborn) for direct inspection and on a four-channel FM instrumen-

tation tape-recorder (model TI; Bell and Howell) for off-line evaluation.

Stroke volume from BP. Changes in left ventricular stroke volume (SV) were obtained from BP with use of a pressure pulse contour method. This method is based on a hemodynamic model that relates BP to flow by means of an aortic characteristic impedance [22]. It computes changes in left ventricular SV from the pulsatile systolic area. SV is computed as

$$SV = \frac{A_{sys}}{Z_{ao}},$$

where SV is the pulse contour SV of the heart, A_{sys} is the area under the systolic portion of the pressure wave, and Z_{ao} is the characteristic impedance of the aorta. However, the characteristic properties of the aorta are pressure dependent and vary with age. In addition, the pulse wave velocity increases with age, causing peripheral reflections to return to the heart during systolic ejection, disturbing the model. Therefore, we used the improved method, correcting for pressure-dependent properties of the arterial impedance, and we used HR to correct for early reflections coming from the periphery, the degree of correction depending on the age of the subject [22]. Cardiac output (CO) was the product of SV and HR. SVR was mean BP divided by CO. A 5-second moving average was used to account for buffering effects of the aortic Windkessel between the heart and periphery. Aortic pressure is the preferred waveform for the computation of pulsatile systolic area. This pressure can be replaced with radial [23], brachial [21], or finger pressure [21,24]. The pulse contour method has been validated against thermodilution while patients were in the supine position [23] and against inert gas rebreathing during orthostatic stress [24]. Pulse contour SV from radial artery pressure correlates to thermodilution CO with a regression slope close to 1 (0.94) [23]. The standard deviation for the difference between the two methods is 11% (0.5 L × min^{-1}) under the adverse conditions of open-heart surgery. Pulse contour SV from noninvasive finger pressure was comparable with inert gas rebreathing CO in seated control subjects with a limited offset (linear regression coefficient between pulse contour and rebreathing, 0.96; standard deviation of the difference of the two methods, 0.5 L × min^{-1}) [24]. Also, SV as calculated by the pulse contour technique was similar to SV obtained from a validated model simulation of the human aortic input impedance [25–28]. SV was expressed as changes relative to control.

Capacity for venous pooling. The pressure–volume relationship, or compliance, of the calf as a measure of the capacity for venous pooling was assessed by quantifying the degree of increment of the calf circumference in two patients (patients 1 and 4), with venous outflow uninterrupted, but with arterial inflow unimpaired [29]. We used venous occlusion plethysmography with multiple proximal occlusion pressures on the lower leg. A cuff was placed around the thigh, and a double stranded mercury-in-rubber strain gauge was placed at the largest circumference of the calf. The leg was supported and elevated above heart level, with horizontal orientation of the calf and the heels approximately 20 cm above the horizontal plane to allow for emptying of the calf veins. Actual measurements started after a further resting period of at least 10 minutes. The occlusion cuff was inflated stepwise from 20 to 60 mm Hg; cuff pressure was increased by 20 mm Hg to the next level without deflation when calf circumference had reached a new plateau by visual inspection of the strip chart tracing. At this plateau level, venous pressure was equal to cuff pressure. Attainment of a steady pressure level required 2 to 3 minutes.

Data analysis

The BP, ECG, and marker signals were analyzed off-line. All signals were analogous/digital converted by computer at a sampling rate of 100 Hz. Beat-to-beat systolic, mean, and diastolic BP values corresponding to each RR-interval were derived. Mean BP was obtained as the integral of pressure over 1 beat divided by the corresponding interval. Instantaneous HR in beats per minute was computed as the inverse of the pulse pressure interval. The end of the last RR interval before the event marker was taken as t = 0. Beat-to-beat data were transformed to equidistantly sampled data at 2 Hz by polynomial interpolation [30], and group mean values were calculated. Supine control values were obtained by averaging data from the 30-second supine period prior to standing up, including BP and HR (absolute values) and SV, CO, and SVR (set at 100%). Values are given as differences from supine control as beats per minute (for HR), mm Hg (for BP), or relative changes (%) from the supine control period before treatment (SV, CO, and SVR). Early steady state responses and responses to prolonged standing of the derived parameters were quantified by averaging 10-second periods after 1, 2, and 10 minutes of standing (55–65, 115–125, 595–605 seconds). The inspiratory–expiratory difference in HR during forced breathing was calculated as the mean of the difference between maximal and minimal HR [31].

The influence of treatment on the neurohormonal condition was expressed in supine-position versus upright-position hormone plasma levels before and after treatment. The distensibility of the calf, assessed as the change in calf volume during stepwise venous occlusion, was expressed as the shift from control calf volume (in procentual change) of the curve relating cuff pressure to calf volume.

Values are expressed as means with standard deviations in parentheses. The results within and between the patients and control subjects were analyzed by the Wilcoxon rank sum test. A p value less than 0.05 was considered a statistically significant difference.

Results

Cardiovascular adjustment to standing (protocol 1, n = 8)

Standing up before treatment: patients with NOH versus control subjects. Supine BP increased in the patients ($p < 0.05$ for systolic, mean, and diastolic BP). Six of the eight patients

could not remain in the standing position for more than 3 minutes. The peripheral vasoconstriction that is usually subsequent to orthostasis was absent; the mean increase in SVR was 2% (standard deviation, 12%) in patients with NOH versus 30% (24%) in control subjects ($p < 0.05$; Fig. 1, Tables 2 and 3). SV and CO in the patients decreased after 1 minute in the upright position. As a result, instead of increasing, BP decreased excessively after 1 minute of standing: systolic, -49 (20) mm Hg; diastolic, -18 (11) mm Hg. In the patients with diagnoses other than PAF, there was a greater decrease in SV after 1 minute of standing: 64% (11%) in patients 2, 3, and 5 versus 49% (3%) in patients 1, 4, and 6. This was matched by a greater increase in HR (respectively 81, 53, and 32 beats per minute after 1 minute in the upright position); the result was a similar reduction in CO: 35% (14%) versus -38% (5%).

Standing up after treatment. After 3 weeks of treatment, the tolerated period of upright posture had increased minimally to 10 minutes in all patients. The increase in body weight was 1.3 kg (range, 0.5–2.4 kg; $p < 0.05$ for the difference before vs during treatment) with development of slight pitting ankle oedema in all patients. Supine control values for HR, BP, SV, CO, and SVR were not influenced by treatment (Table 3). Upright BP increased from 83 (standard deviation, 19)/55 (13) mm Hg to 114 (22)/60 (16) mm Hg after 1 minute of standing, and the magnitude of the postural decline in SV and CO was less (Fig. 2, Table 3). The decrease in systolic BP, SV, and CO from 1 to 10 minutes of standing was statistically significant (Table 3). In contrast, these values did not change in the control subjects (Table 2).

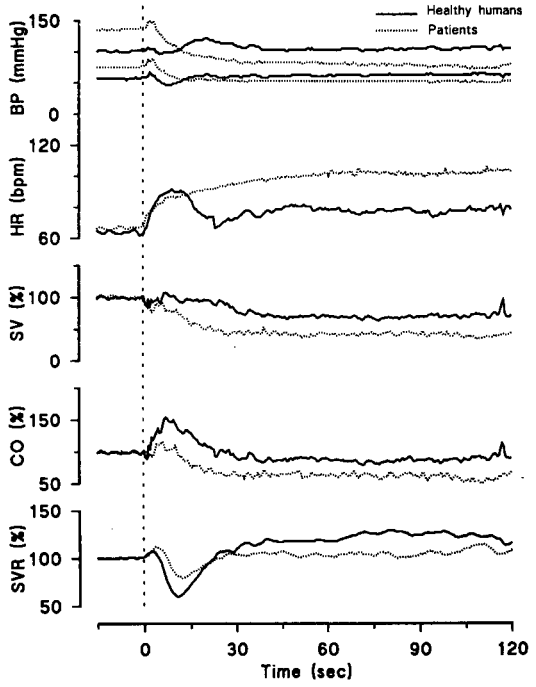

Figure 1. Cardiovascular adaptation to standing before treatment. Average systolic arterial pressure, diastolic arterial pressure, heart rate, stroke volume, cardiac output, and total peripheral resistance responses to standing in normal controls (continuous lines, N = 6) and patients before treatment (dotted lines, N = 6). The dotted line at time 0 marks the start of standing up. BP = blood pressure; HR = heart rate; SV = stroke volume; CO = cardiac output; SVR = systemic vascular resistance.

Neurohormonal measurements (protocol 2, n = 4)
Supine plasma renin activity decreased (<1.2 ng angiotensin I generation/L/min). During orthostatic stress, plasma renin activity increased in one patient (from 1.2 to 3.6 ng/L/min). After treatment, supine and upright plasma renin activity had become undetectable. Plasma aldosterone levels did not change during orthostatic stress: supine, 0.20 (0.14) nmol/L; upright, 0.22 (0.14); they tended to decrease further after treatment: supine, 0.10 (0.07) nmol/L; upright, 0.10 (0.07). Plasma ANP tended to increase after treatment: supine, from 70 (31) to 203 (189) ng/L; upright, from 56 (27) to 124 (98) ng/L; $p > 0.05$. Packed cell volume did not change by treatment: supine, 0.36 (0.02) versus 0.36 (0.04); upright, 0.37 (0.02) versus 0.37 (0.04).

Leg compliance (protocol 3, n = 2)
Calf circumference increased 2% to 3% at 20 mm Hg, occluding pressure, with a further 1% increment for each pressure step up to 60 mm Hg (Fig. 3). After treatment, the increase in calf circumference had decreased 1% to 2% for all levels of occlusion pressure.

Discussion

This study examined whether the improvement in orthostatic BP during combined treatment with low-dose fludrocortisone and nocturnal head-up tilt in patients with NOH can be attributed to expansion of plasma volume or to an increase in SVR. The main finding was that this treatment directly increases upright BP in patients with sympathetic failure by means of a lower decrease in upright SV and CO. The data suggest that this is accomplished principally by a reduction of the capacity for orthostatic venous pooling.

Orthostatic circulatory responses before treatment
In normal humans, standing up from the supine position causes a decrease of 30% to 40% in SV. The subsequent decrease in CO remains limited by a reflex increase in HR, and mean BP either does not change or increases slightly through reflex vasoconstriction (Fig. 1) [32,33].

Patients with sympathetic failure are at a disadvantage with respect to their adaptation to orthostatic stress. The key problem in these patients is the defective vasoconstriction mechanism with a decrease in BP, amplified further by the higher orthostatic decrease in CO (Fig. 1, Table 3) [34,35]. This reflects an excessive decrease in venous return as a result of enhanced venous pooling of blood. A considerable HR increase on standing (Fig. 1, Table 1) was observed in only those patients who had sympathetic failure but unaffected HR control (Table 1). Their normal initial and early steady state HR response was attributed to vagal

Table 2. Postural changes in arterial pressure, heart rate, stroke volume, cardiac output, and total peripheral resistance in six control subjects

	Supine	1 Minute standing	10 Minutes standing	p supine vs 1 minute standing
Heart rate (beats/minute)	67 ± 13	80 ± 11	82 ± 13	ns
Psystolic (mm Hg)	105 ± 7	114 ± 22	110 ± 14	<0.05
Pdiastolic (mm Hg)	58 ± 5	68 ± 13	68 ± 10	ns
Pmean (mm Hg)	74 ± 6	82 ± 16	82 ± 11	ns
Pulse pressure (mm Hg)	47 ± 6	46 ± 12	42 ± 8	ns
Stroke volume (%)	100	71 ± 5	68 ± 12	<0.05
Cardiac output (%)	100	86 ± 8	84 ± 13	<0.05
Peripheral resistance (%)	100	130 ± 24	135 ± 24	<0.05

ns = not significant.

withdrawal and intact efferent sympathetic HR control [11,12] and is in contrast to the generalized sympathetic defect in patients with PAF. The finding of a similar reduction in CO in these two patients suggests that an excessive decrease in venous return impairs the ability of the heart to limit the decrease in CO by increasing HR. Impaired myocardial contractility and/or slower ventricular filling and relaxation rate as reported in patients with defective sympathetic cardiac innervation [36,37] could play an additional role in the high decrease in SV. This possibility cannot be ruled out by the normal echocardiographic findings obtained in this study under static conditions.

Orthostatic circulatory and neurohumoral responses after treatment

The present study provides evidence that the main effect of combined treatment is restriction of the excessive orthostatic decrease in upright SV and CO (Fig. 2, Table 3). The lower decrease in CO was explained solely by the decrease in SV; the HR increase was less. In patients with autonomic failure who lack vasomotor control, the higher CO after treatment increases upright BP [38]. The following mechanism may have been operative in the increase in SV as induced by treatment. In control subjects who are treated with large doses of fludrocortisone (400–800 μg daily), plasma volume, defined as the intravascular technetium 99m albumin space, increases. This intravascular volume expansion is reflected by a 10% decrease in hematocrit [9]. On the basis of such data obtained in control subjects, the beneficial effects of mineralocorticoid treatment in patients with orthostatic hypotension have been ascribed so far mainly to expansion of the plasma volume [5,7,8].

The finding that supine plasma ANP levels increased after treatment with a decrease in PRA indicates that the body had sensed an expansion of the intravascular volume. The substantial increase in upright ANP levels after treatment (Fig. 2, Table 3), with a further decrease in PRA and plasma aldosterone, is compatible with an increase in mean upright circulatory filling volume and pressure [39]. These decreases in PRA and aldosterone plasma levels after treatment are of interest because they demonstrate that the higher plasma levels before treatment reflect remnant reflex neurohormonal control exposed by profound postural arterial hypotension. Therefore, these data indicate higher SV and filling volume after treatment in patients with sympathetic failure.

Several stimuli for the release of renin into the blood stream have been proposed, including a decrease in distending pressure in the afferent arterioles, referred to as a renal baroreflex [40], a decrease in the amount of sodium reaching the adjacent macula densa tubular cells, and an increase in efferent sympathetic renal nerve activity to β-adrenoreceptors on the juxtaglomerular cells [41].

The subnormal increase in renin in our patients (this

Table 3. Effects of therapy on upright arterial pressure, heart rate, stroke volume, cardiac output, and systemic vascular resistance in six patients with neurogenic orthostatic hypotension

	Before therapy				After therapy					
	Supine	1 Minute standing	p 1 minute standing patients vs controls	p supine vs 1 minute standing	Supine	1 Minute standing	10 Minutes standing	p supine vs 1 minute standing	p 1 vs 10 minutes standing	p 1 minute standing before vs after treatment
Heart rate (beats/minute)	67 ± 11	102 ± 23	ns	<0.05	63 ± 15	82 ± 18	88 ± 18	<0.05	ns	ns
Psystolic (mm Hg)	137 ± 18	83 ± 19	<0.01	<0.05	139 ± 27	114 ± 22	98 ± 19	ns	<0.05	<0.05
Pdiastolic (mm Hg)	76 ± 9	55 ± 13	<0.01	<0.05	71 ± 15	60 ± 16	60 ± 13	ns	ns	ns
Pmean (mm Hg)	98 ± 13	64 ± 16	<0.01	<0.05	95 ± 18	77 ± 18	72 ± 15	ns	ns	ns
Pulse pressure (mm Hg)	62 ± 10	28 ± 7	<0.01	<0.05	68 ± 14	53 ± 11	38 ± 9	ns	<0.05	<0.05
Stroke volume (%)	100	43 ± 11	<0.01	<0.05	100	76 ± 17	56 ± 13	<0.05	<0.05	<0.05
Cardiac output (%)	100	63 ± 10	<0.01	<0.05	100	92 ± 14	77 ± 16	ns	<0.05	<0.05
Peripheral resistance (%)	100	102 ± 12	<0.05	ns	100	90 ± 18	101 ± 9	ns	ns	ns

ns = not significant.

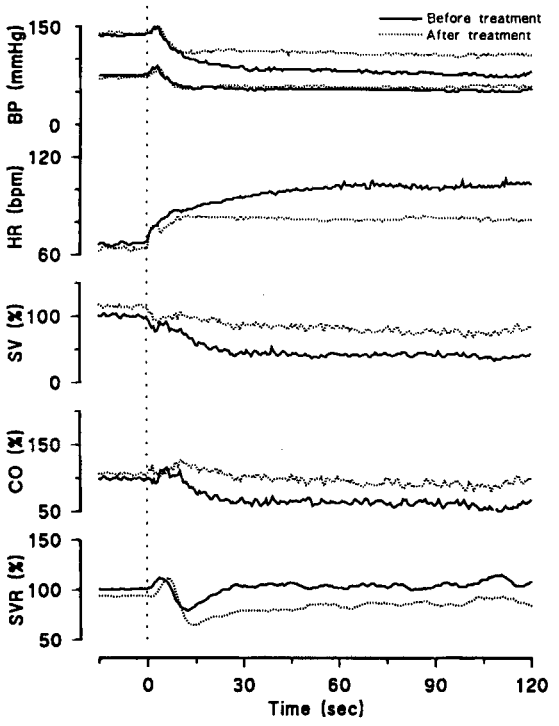

Figure 2. Cardiovascular adaptation to standing after treatment. Average systolic arterial pressure, diastolic arterial pressure, heart rate, stroke volume, cardiac output, and total peripheral resistance responses to standing before (continuous lines, N = 6) and after (dotted lines, N = 6) chronic volume expansion. The dotted line at time 0 marks the start of standing up. BP = blood pressure; HR = heart rate; SV = stroke volume; CO = cardiac output; SVR = systemic vascular resistance.

study) [42] is in contrast to a recent observation of increased renin release in a patient with PAF [43]. However, there is convincing evidence that, in the majority of patients, plasma renin activity decreases both in the recumbent position and in the upright position [41]. The upright levels are reported to be only approximately 50% of normal values, which indicates a subnormal renin release level because orthostatic hypotension should be a potent stimulus for renin release. Defective sympathetic innervation is thought to be the underlying mechanism [41].

Mechanisms underlying the rise in SV

When considering a patient who weighs 70 kg, with a total body water amount of 42 L (or 42 kg) of which 40% (approximately 17 L) is located in the extracellular space, a 1.5-kg increase in body weight would imply an increase in extracellular fluid volume from 17 to 18.5 L, with an estimated increase in plasma volume of only 300 ml [44]. We realize that there may be variable degrees of sludging of red blood cells, with trapping of blood cells in the peripheral circulation and a variable relationship between total body hematocrit and peripheral venous hematocrit. However, the blood sample was taken while the patient was in the recumbent position within the first minute after completion of standing, allowing the opportunity for proper mixing of blood between peripheral and central circulatory compartments [15]. We consider that the absence of a change in hematocrit after treatment argues against an important increase in intravascular volume. It suggests that intravascular volume expansion is not the principal mechanism involved in the larger SV (after treatment). Therefore, the substantial increase in upright SV and ANP levels after treatment (Fig. 2, Table 3) cannot be adequately explained by a small increase in intravascular volume. The average increase in body weight of 1.5 kg after full treatment in this study also implies that the increase in intravascular volume must have been small.

The anomaly in dynamic plasma volume regulation in patients with autonomic failure is complex and not well-understood [41,42]. The level of upright BP is closely related to the magnitude of the blood volume [37] and is presumably so because, in the absence of reflex adjustments, CO has become strictly dependent on venous return, which depends on effective blood volume [45,46]. Under conditions of low sodium intake, patients with progressive autonomic failure lose three times as much body weight as control subjects, and there are data that suggest that this extra fluid loss is derived primarily from the interstitial space [45]. This would imply that a decrease in BP could reset the balance of Starling forces in favor of reabsorption of fluid from the interstitium into the bloodstream [46]. This fluid

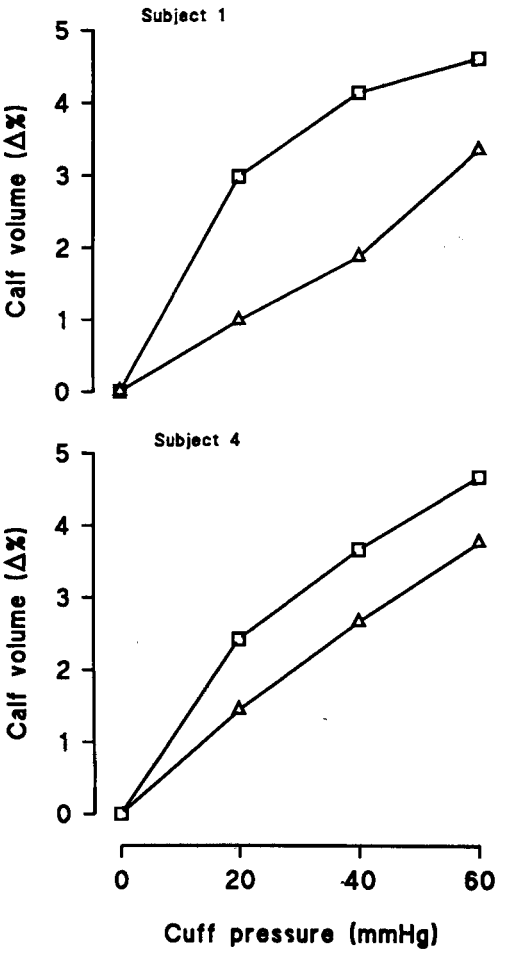

Figure 3. Percentage changes in calf volume during venous occlusion plethysmography before (squares, subjects 1 and 4) and after chronic volume expansion (triangles).

redistribution has been suggested as an important defense against severe hypotension in patients who lack cardiovascular reflex control because their BP levels are unusually dependent on plasma volume [45].

The development of ankle edema, and the observation in two patients for whom the compliance of the legs decreased in the post-treatment state (Fig. 3), suggest allocation of the expanded body fluid volume to the perivascular space rather than to the intravascular space. This mechanism is supported by the observation that head-up tilt sleeping becomes effective coincidentally with the appearance of slight edema of the lower legs and that the beneficial effects of head-up tilt sleeping are also observed in patients without renin release [42,47,48]. This perivascular "water jacket" in the legs limits the vascular volume available for orthostatic venous pooling and explains the reduction of the orthostatic decrease in CO. The contributory mechanism of upright (legdown) sleeping could be a partial conservation of this water jacket. During prolonged standing, SV declined slowly but progressively in patients with NOH but not in control subjects (Tables 2 and 3). The beneficial effects of an increased perivascular counterpressure might have been partially offset by an increase in capillary hydraulic pressure that is related to the higher level of orthostatic BP after treatment (Table 3) [41,45].

The cardiovascular effect of fludrocortisone in patients with orthostatic hypotension has also been attributed to amplified vascular sensitivity as a result of circulating catecholamines with a hypothesized but unproven increase in SVR [5–8]. We cannot exclude a contributory role of fludrocortisone on peripheral resistance, but this study suggests that the effects of treatment on CO are much stronger. Supine hypertension is common in patients with sympathetic failure and restricts the use of mineralocorticoid treatment [49,50]. The effect of head-up tilting on orthostatic BP enables a limiting of the dosage of fludrocortisone, avoiding aggravation of supine hypertension (Table 3) [42].

In summary, treatment with fludrocortisone and nocturnal head-up tilting effectively improves orthostatic tolerance in patients with NOH by restricting the orthostatic decrease in CO. Preliminary data suggest that the expanded body fluid volume is allocated to the perivascular space rather than to the intravascular space. This observation needs to be confirmed in a larger group of patients. The increase of 14 mm Hg in mean BP in the patients in this study is comparable in magnitude with the effects of erythropoietin (17 mm Hg) [8] and midodrine (16 mm Hg) [51]. It underscores that the combination of low-dose fludrocortisone and nocturnal head-up tilting is an effective and low-cost treatment in symptomatic orthostatic hypotension.

References

1. Robertson D, Davis TL. Recent advances in the treatment of orthostatic hypotension. *Neurology* 1995; 45(suppl 5):S26–S32.
2. Ten Harkel ADJ, van Lieshout JJ, Wieling W. Treatment of orthostatic hypotension with sleeping in the head-up tilt position, alone and in combination with fludrocortisone. *J Intern Med* 1992; 232: 139–145.
3. Wieling W, van Lieshout JJ. Investigation and treatment of autonomic circulatory failure. *Curr Opin Neurol Neurosurg* 1993; 6: 537–543.
4. Wieling W, Cortelli P, Mathias CJ. Treating neurogenic orthostatic hypotension. In: *The autonomic nervous system,* part II, *Dysfunction.* Appenzeller O, ed. *Handbook of clinical neurology;* vol 75. Elsevier Science, 1999.
5. Chobanian AV, Volicer L, Tifft CP, Gavras H, Liang CS, Faxon D. Mineralocorticoid-induced hypertension in patients with orthostatic hypotension. *N Engl J Med* 1979; 301:68–73.
6. Davies IB, Bannister RG, Sever PS, Wilcox CS. Fludrocortisone in the treatment of postural hypotension: altered sensitivity to pressor agents. *Br J Clin Pharmacol* 1978; 6:444P–445P.
7. Bannister R, Mathias CJ. The management of postural hypotension. In: *Autonomic failure. A textbook of clinical disorders of the autonomic nervous system.* Bannister R, Mathias CJ, eds. Oxford: Oxford University Press; 1992. pp. 622–646.
8. Hoeldtke RD, Streeten DHP. Treatment of orthostatic hypotension with erythropoietin. *N Engl J Med* 1993; 329:611–615.
9. Mion D, Jr., Rea RF, Anderson EA, Kahn D, Sinkey CA, Mark AL. Effects of fludrocortisone on sympathetic nerve activity in humans. *Hypertension* 1994; 23:123–130.
10. Wieling W, van Lieshout JJ. Maintenance of postural normotension in humans. In: *Clinical autonomic disorders.* 2nd ed. Low PA, ed. Boston: Little Brown and Co; 1997. pp. 73–82.
11. van Lieshout JJ, Wieling W, Van Montfrans GA, Settels JJ, Speelman JD, Endert E, *et al.* Acute dysautonomia associated with Hodgkin's disease. *J Neurol Neurosurg Psychiatry* 1986; 49:830–832.
12. van Lieshout JJ, Wieling W, Wesseling KH, Endert E, Karemaker JM. Orthostatic hypotension caused by sympathectomies performed for hyperhidrosis. *Neth J Med* 1990; 36:53–57.
13. Ten Harkel ADJ, van Lieshout JJ, Wieling W. Circulatory autonomic failure 50 years after acute poliomyelitis. *Clin Auton Res* 1991; 1:215–217.
14. Ten Harkel ADJ, van Lieshout JJ, van Lieshout EJ, Wieling W. Assessment of cardiovascular reflexes: influence of posture and period of preceding rest. *J Appl Physiol* 1990; 68:147–153.
15. Lundvall J, Bjerkhoel P. Failure of hemoconcentration during standing to reveal plasma volume decline induced in the erect posture. *J Appl Physiol* 1994; 77:2155–2162.
16. Van Beaumont W. Evaluation of haemoconcentration from haematocrit measurements. *J Appl Physiol* 1972; 3:712–713.
17. Wesseling KH. Finapres, continuous non-invasive finger arterial pressure based on the method of Peñáz. In: *Blood pressure measurements.* Meyer-Sabellek W, Anlauf M, Gotzen R, Steinfeld L, eds. Darmstadt: Steinkopf Verlag; 1991. pp. 161–172.
18. Imholz BPM, Settels JJ, Van der Meiracker AH, Wesseling KH, Wieling W. Non-invasive continuous finger blood pressure measurement during orthostatic stress compared to intra-arterial pressure. *Cardiovasc Res* 1990; 24:214–221.
19. Friedman DB, Jensen FB, Matzen S, Secher NH. Non-invasive blood pressure monitoring during head-up tilt using the Penaz principle. *Acta Anaesthesiol Scand* 1990; 34:519–522.
20. Petersen ME, Williams TR, Sutton R. A comparison of non-invasive continuous finger blood pressure measurement (Finapres) with intra-arterial pressure during prolonged head-up tilt. *Eur Heart J* 1995; 16:1641–1654.
21. Jellema WT, Imholz BPM, Van Goudoever J, Wesseling KH, van Lieshout JJ. Finger arterial versus intrabrachial pressure and continuous cardiac output during head-up tilt testing in healthy subjects. *Clin Sci (Colch)* 1996; 91:193–200.
22. Wesseling KH, De Wit B, Weber JAP, Smith NT. A simple device for the continuous measurement of cardiac output. *Adv Cardiovasc Physics* 1983; 5-II:16–52.
23. Jansen JRC, Wesseling KH, Settels JJ, Schreuder JJ. Continuous cardiac output monitoring by pulse contour during cardiac surgery. *Eur Heart J* 1990; 11(suppl I):26–32.
24. Stok WJ, Baisch F, Hillebrecht A, Schulz H, Meyer M, Karemaker JM. Noninvasive cardiac output measurement by arterial pulse analysis compared with inert gas rebreathing. *J Appl Physiol* 1993; 74:2687–2693.
25. Wesseling KH, Jansen JRC, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol* 1993; 74:2566–2573.
26. Jellema WT, Imholz BPM, Oosting H, Wesseling KH, van Lieshout JJ. Estimation of beat-to-beat changes in stroke volume from ar-

terial pressure: a comparison of two pressure wave analysis techniques during head-up tilt testing in young healthy males. *Clin Auton Res* 1999; 9:185–192.
27. Jellema WT, Wesseling KH, Groeneveld ABJ, Stoutenbeek CP, Thijs LG, van Lieshout JJ. Continuous cardiac output in septic shock by simulating a model of the aortic input impedance. A comparison with bolus injection thermodilution. *Anesthesiology* 1999; 90:1317–1328.
28. Harms MPM, Wesseling KH, Pott F, Jenstrup M, Van Goudoever J, Secher NH, van Lieshout JJ. Continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in humans under orthostatic stress. *Clin Sci* 1999; 97:291–301.
29. Buckey JC, Lane LD, Plath G, Gaffney FA, Baisch F, Blomqvist CG. Effect of head down tilt for 10 days on the compliance of the leg. *Acta Physiol Scand* 1992; 144(S604):53–60.
30. Bevington PR. *Data reduction and error analysis for the physical sciences.* New York: McGraw-Hill Book Co; 1969.
31. Wieling W. Non-invasive recording of heart rate and blood pressure in the evaluation of neurocardiovascular control. In: *Autonomic failure, a textbook of clinical disorders of the autonomic nervous system.* 3rd ed. Bannister R, Mathias CJ, eds. Oxford: Oxford University Press; 1992. pp. 291–311.
32. Tanaka H, Sjöberg BJ, Thulesius O. Cardiac output and blood pressure during active and passive standing. *Clin Physiol* 1996; 16:157–170.
33. Rowell LB. *Human cardiovascular control.* 2nd ed. New York: Oxford University Press; 1993; 441–483.
34. van Lieshout JJ, Secher NH. Orthostatic stress and autonomic dysfunction. In: *Exercise and circulation in health and disease.* Saltin B, Secher NH, Mitchell JH, Boushel R, eds. Champaign, IL: Human Kinetics; 1999. pp. 305–324.
35. Smit AAJ, Halliwill JR, Low PA, Wieling W. Pathophysiological basis of orthostatic hypotension in autonomic failure. Topical review. *J Physiol* 1999; 519:1–10.
36. Meredith IT, Esler MD, Lambert GW, Jennings GL, Eisenhofer G. Biochemical evidence of sympathetic denervation of the heart in pure autonomic failure. *Clin Auton Res* 1991; 1:187–194.
37. Ibrahim MM, Tarazi RC, Dustan HP, Bravo EL. Idiopathic orthostatic hypotension: circulatory dynamics in chronic autonomic insufficiency. *Am J Cardiol* 1974; 34:288–294.
38. van Lieshout JJ, Wieling W, Wesseling KH, Karemaker JM. Pitfalls in the assessment of cardiovascular reflexes in patients with sympathetic failure but intact vagal control. *Clin Sci* 1989; 76:523–528.
39. Sagnella GA, Markandu ND, Shore AC, Forsling ML, MacGregor GA. Plasma atrial natriuretic peptide: its relationship to changes in sodium intake, plasma renin activity and aldosterone in man. *Clin Sci* 1987; 72:25–30.
40. Wang BC, Sundet WD, Hakumaki MOK, Goetz KL. Vasopressin and renin responses to hemorrhage in conscious, cardiac-denervated dogs. *Am J Physiol* 1983; 245:H399–H405.
41. DiBona GF, Wilcox CS. The kidney and the sympathetic nervous system. In: *Autonomic failure.* 3rd ed. Bannister R, Mathias CJ, eds. Oxford: Oxford University Press; 1992. pp. 178–196.
42. van Lieshout JJ, Ten Harkel ADJ, Van Leeuwen AM, Wieling W. Contrasting effects of acute and chronic volume expansion on orthostatic blood pressure control in a patient with autonomic circulatory failure. *Neth J Med* 1991; 39:72–83.
43. Hohenbleicher H, Klosterman F, Schorr U, Seyfert S, Persson PB, Sharma AM. Identification of a renin threshold and its relationship to salt intake in a patient with pure autonomic failure. *Hypertension* 1997; 30:1068–1071.
44. Rose BD. *Clinical physiology of acid-base and electrolyte disorders.* 3rd ed. New York: McGraw-Hill; 1989; 589–600.
45. Wilcox CS, Puritz R, Lightman SL, Bannister R, Aminoff MJ. Plasma volume regulation in patients with progressive autonomic failure during changes in salt intake or posture. *J Lab Clin Med* 1984; 104:331–339.
46. Wilcox CS. Body fluids and renal function in autonomic failure. In: *Autonomic failure, a textbook of clinical disorders of the autonomic nervous system.* Bannister R, ed. Oxford: Oxford University Press, 1985:115–154.
47. MacLean AR, Allen EV. Orthostatic hypotension and orthostatic tachycardia; treatment with the "head-up" bed. *JAMA* 1940; 115: 2162–2167.
48. MacLean AR, Allen EV, Magath TB. Orthostatic tachycardia and orthostatic hypotension: defects in the return of venous blood to the heart. *Am Heart J* 1944; 27:145–163.
49. Mahar LJ, Frewin DB, Dunn DE. Idiopathic orthostatic hypotension controlled with a monoamine oxidase inhibitor and 9-alpha-fluorohydrocortisone. *Med J Aust* 1975; 2:940–943.
50. Jordan J, Shannon JR, Pohar B, Paranjape SY, Robertson D, Robertson RM, *et al.* Contrasting effects of vasodilators on blood pressure and sodium balance in the hypertension of autonomic failure. *J Am Soc Nephrol* 1999; 10:35–42.
51. Jankovic J, Gilden JL, Hiner BC, Kaufmann H, Brown DC, Coghlan CH, *et al.* Neurogenic orthostatic hypotension: a double-blind, placebo-controlled study with midodrine. *Am J Med Sci* 1993; 95:38–48.