Syncope : an integrative physiological approach

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Is orthostatic hypotension in autonomic failure associated with an increase in venous pooling in the lower limbs?

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Submitted

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Chapter 5

Abstract

Background: In autonomic failure (AF) blood pressure (BP) falls upon standing which is commonly ascribed to defective vasoconstriction and excessive pooling. Observations on the amount of pooling in AF are contradictory.

Methods: We evaluated pooling using strain gauge plethysmography (SGP) during head-up tilt (HUT) with a parachute harness fixed to the tilt table to avoid muscle tension in the lower limbs and thus to maximise pooling. 23 Healthy subjects and 12 patients with AF were tilted for 5 minutes. Heart rate, continuous BP and calf volume changes as measured by SGP were measured continuously. Multiple regression analysis was used to examine the effect of AF on orthostatic fluid shifts after adjustment for potential confounders.

Results: Patients did not differ from controls with respect to the increase of calf volume after 5 min HUT. The acute (0-1 min) and the prolonged (1-5 min) phases of calf volume responses to HUT were also similar between patients and controls. No correlation was found between the degree of orthostatic hypotension and the orthostatic calf volume change in AF. In one patient an additional measurement was made before rising from bed in the early morning demonstrating a greater albeit small increase of calf volume upon HUT.

Conclusion: Orthostatic fluid shifts at the level of the calf in AF are not augmented during the course of the day despite marked hypotension. However, a small increase of pooling may be expected when the patient first gets out of bed in the morning probably due to the absence of edema.

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Introduction

Upon standing, 300 to 1000 ml of blood may shift to the lower parts of the body.[91,168,230,257] The time course of orthostatic fluid shifts is characterised by a first fast increase due to filling of veins caused by a rise in hydrostatic pressure and a second slow phase due to fluid filtration through capillary walls.[7,31,230,244] The gravitationally induced fluid shifts contribute to the marked differences in pressure in the body upon standing, with a substantial increase in arterial pressure below the heart and a decrease above it.[98] Despite such pressure changes, mean arterial pressure at level of the neck is maintained in healthy humans mainly through rapidly acting neural reflex mechanisms causing constriction of the capacitance vessels.[272] In autonomic failure (AF) these systems fail and orthostatic hypotension (OH) occurs upon standing. Accordingly, once the gravitational forces are counteracted in AF by standing in water up to the level of the heart or by the inflation of 'antigravity suits', the upright position does not evoke hypotension anymore.[67,121,234] OH is commonly ascribed to defective arteriolar vasoconstriction and excessive venous pooling.[230] As increased orthostatic fluid shifts reduce the venous return to the heart and hence may lower blood pressure, a relationship between the degree of OH and the degree of pooling seems plausible. However, several studies suggested that the orthostatic fluid shifts to the lower limbs in AF are negligible.[10,32,234,260] In contrast, a modest increase of orthostatic pooling to the lower limbs was found in healthy controls after ganglionic blockade.[33,158,189]

Recently, we described a new method to assess orthostatic fluid shifts with strain gauge plethysmography (SGP) in the free hanging position,[244] and reported a significant gender effect on the amount of pooling to the lower limbs: calf volume upon head-up tilt increased more in men than in women. As previous studies on pooling in AF did not control for sex, gender differences may have confounded these results. In addition, it is conceivable that findings were complicated by the time of measurement, i.e., diurnal variation in venous pooling. Leg veins in AF are exposed to higher than normal intravenous pressure,[33] causing the development of edema during the course of the day.[24] Edema may function as a ”water jacket” around the veins hereby preventing further pooling.[161,256] Orthostatic fluid shifts are therefore expected to be larger when there is no edema, i.e., when the patient first gets out of bed and less during the course of the day.

In the present study we examined whether OH in AF is associated with excessive orthostatic fluid shifts at the level of the calf. In addition, we evaluated both the acute and the prolonged phase of orthostatic fluid shifts and in one hospitalised patient we explored the diurnal variation in venous pooling.

Methods

Subjects

13 Patients with AF were recruited from the outpatient clinic of our tertiary referral centre. Patients were included if they had a history of primary AF and symptomatic orthostatic hypotension, and excluded if they had cardiac disease, varicosities or used antihypertensive medication. One patient with Parkinson's disease was excluded from analysis because of severe dyskinesias causing problems with SGP measurements. Causes of AF in the remaining 12 patients included multiple system atrophy (MSA) (n=5), pure autonomic failure (n=3), Parkinson's disease (n=1), anti-Hu neuropathy (n=1), vincistrine-induced polyneuropathy (n=1) and Sjögren's disease (n=1). One patient used medication for AF (midodrine 30 mg daily) and slept in the 12° head-up tilt position. The other patients were without medication for AF.

23 Healthy volunteers without orthostatic hypotension, recurrent syncope, cardiac disease, varicosities or the use of antihypertensive medication were recruited through an advertisement. The study protocol was approved by the Leiden University Medical Centre ethics review committee. All participants gave written informed consent. All studies were performed in the late morning or the early afternoon. In one hospitalised patient an additional measurement in the early morning was performed to assess the diurnal variation in orthostatic fluid shifts.

Study protocol

The temperature of the room was maintained at 23±1°C. Subjects lay on a motor-driven tilt table (Dewert tilt-table, GmbH). For this experiment the foot board was removed from the table. Tilting time, from 0º to 60º head up, was 12 seconds. While supine, subjects were fitted with a parachute harness fixed to the tilt table to avoid muscle tension in the lower limbs upon tilting. A cushion was placed under the buttocks and a net was attached to the tilt table in order to form a seat. The seat was added to prevent the subject from sliding downwards during HUT and to avoid constriction of the thighs by the leg straps of the harness during

HUT. All subjects were tilted with a parachute harness to 60° head up for 5 minutes after at least 5 minutes of supine rest.

Measurements

Both calves were instrumented with mercury-in-silastic strain gauges, placed 10 cm distally from the tibial tuberosity.[244] The strain gauges were fitted to the measured circumference and connected to a custom built plethysmograph based on the principles of the Hokanson EC-2 plethysmograph. To avoid direct contact of the strain gauges with the tilt table, the heel was kept away from the table with a small cushion. Beat-to-beat finger blood pressure (BP) was measured by finger volume-clamp method (Finometer, Finapres Medical Systems, Arnhem, the Netherlands). Heart rate (HR) was derived from ECG. All signals were routed to a computer (sampling rate 120 Hz) for off-line analysis using custom-written software. Volume changes were averaged for both calves. In four patients calf volume measurements of one side were excluded from analysis: two because of previous surgery in that limb and two because of failure to obtain a valid calibration signal.

Data analysis and statistics

Our main outcome measure was the average relative change in calf volume of both legs after 5 minutes of tilt. Our secondary outcome measures included the calf volume response to the acute phase of tilting (0-1 minute HUT), mainly reflecting filling of veins caused by a rise in hydrostatic pressure, and the prolonged phase of tilting (1-5 min HUT), mainly reflecting the degree of fluid filtration through capillary walls.[230] The independent sample t-test was used to compare the baseline characteristics and the hemodynamic responses to HUT between patients and controls. Significantly different baseline characteristics were considered potential confounders. Multiple linear regression was used to analyse the effect of AF on orthostatic calf volume changes both before and after adjustment for sex and potential confounders. The association between orthostatic calf volume changes and orthostatic BP changes was assessed using Pearson's correlation. Data analysis was performed with SPSS software, version 12.0. All tests were performed two-sided. Significance threshold was set at 5%.

Results

As shown in Table 1, patients were significantly older, weighed more and had a greater BMI than controls. Patients and controls were similar with respect to length, baseline calf circum-

Figure 1 Time course of calf volume changes in patients (black line) and controls (grey line) as measured by strain-gauge plethysmography during head-up tilt with a parachute harness. Because of a significant influence of sex on calf volume changes, males (left panel) and females (right panel) are depicted separately. Data are presented as mean ± SEM.

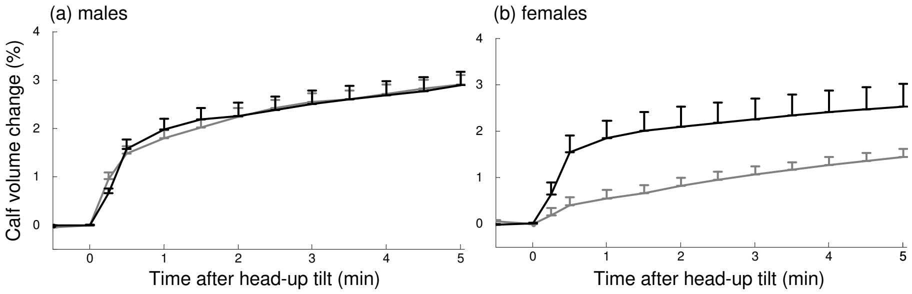


Table 1 Baseline characteristics and hemodynamic responses to head-up tilt with a parachute harness for patients with autonomic failure (*n*= 12) and healthy controls (*n*=23). Values are presented as means ± SD. * Significance p<0.05; independent samples T-test.

		Patients (*n* = 12)	Controls (*n* = 23)
Age (years)		60 ± 16*	33 ± 13*
Length (cm)		175 ± 10	177 ± 10
Weight (kg)		78 ± 11*	70 ± 9*
BMI (kg/m^2)		25 ± 4*	22 ± 2*
Baseline calf circumference (cm)		36 ± 3	36 ± 2
Systolic blood pressure (mmHg)	supine	129 ± 21	127 ± 17
	tilted	101 ± 20*	125 ± 18*
Diastolic blood pressure (mmHg)	supine	65 ± 16	68 ± 13
	tilted	56 ± 11*	75 ± 13*
Heart rate (bpm)	supine	76 ± 8	69 ± 11
	tilted	85 ± 11	77 ± 14

ference and supine and tilted heart rate. As expected, BP was significantly lower in the HUT position (Table 1). However, patients did not differ from controls with respect to calf volume changes after 5 min HUT both before and after adjustment for age, sex, weight and BMI (crude 95% CI for the effect of AF: -0.2 to 1.1%, p=0.2; adjusted 95% CI: -0.8% to 0.7%, p=0.9; Figure 1). Calf volume changes in the acute (0-1 min) and the prolonged (1-5 min)

Figure 2 Relationship between orthostatic fluid shifts at the level of the calf and the orthostatic fall of BP in 12 patients with autonomic failure. No significant correlation was found between the degree of orthostatic hypotension and calf volume changes after 5 minutes of head-up tilt (r=0.14, p=0.7). Females (open circles) and males (closed circles).

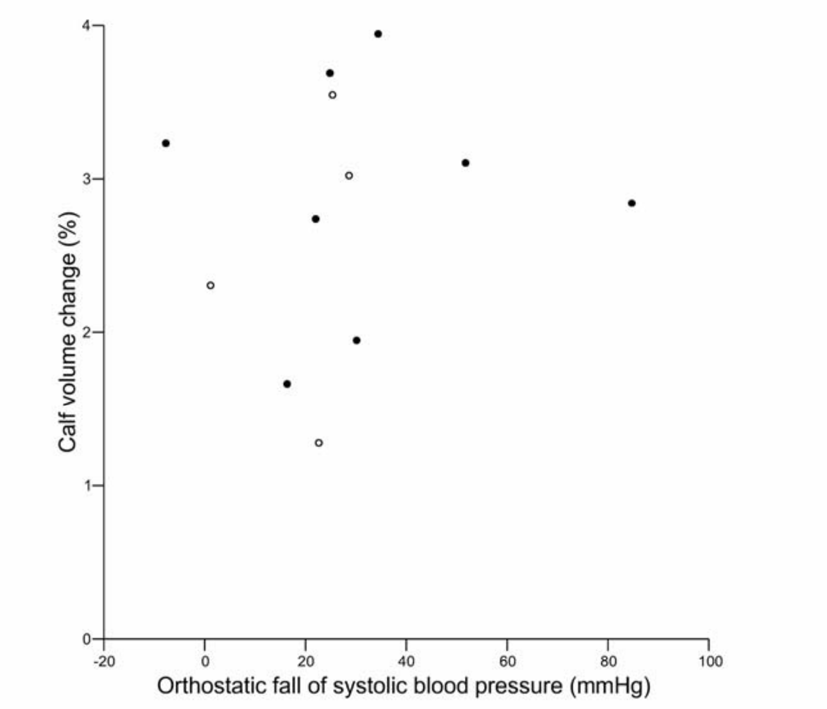


Table 2 Change of calf volume during head-up tilt (HUT) with a parachute harness in patients with autonomic failure (*n*=12) and healthy controls (*n*=23). Data for males and females are shown separately because of gender differences in orthostatic pooling. Values are presented as means ± SEM.

	Autonomic Failure		Healthy controls	
	men (*n*=8)	women (*n*=4)	men (*n*=14)	women (*n*=9)
Change of calf volume during 5 min HUT (%)	2.9 ±0.3	2.5 ±0.5	2.9 ±0.2	1.5 ±0.2
-acute phase (0-1 min HUT)	2.0 ±0.2	1.9 ±0.4	1.8 ±0.2	0.6 ±0.2
-prolonged phase (1-5 min HUT)	0.9 ±0.2	0.7 ±0.2	1.2 ± 0.1	0.9 ±0.1

pahse of tilting were also similar between patients and controls both before and after adjustment for age, sex, weight and BMI (Table 2). No correlation was found between the degree of orthostatic hypotension and the orthostatic calf volume change in the patients with AF (r=0.14, p=0.7, Figure 2).
Of all variables entered in the regression model only gender significantly affected the calf volume changes induced by 5 min HUT: a greater increase of calf volume upon tilting was seen in men compared to women (95% CI for the difference: 0.4 to 2.2%, p=0.005).

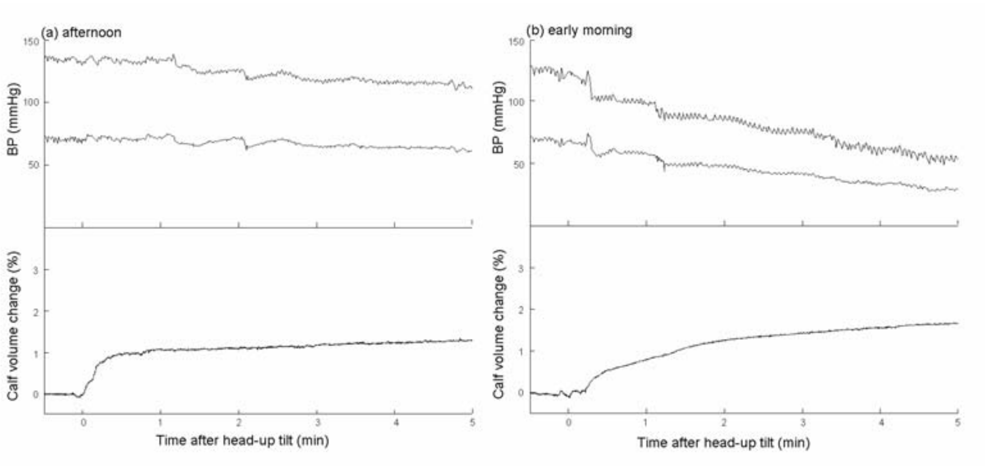
Diurnal variation in orthostatic fluid shifts

A 28 year-old patient with young onset Parkinson’s disease was admitted to our hospital because of frequent syncope owing to severe orthostatic hypotension. 24-Hour BP recording demonstrated marked diurnal BP variations with lowest values in the early morning. Nocturnal weight loss averaged 2 kg. During the course of the day she habitually developed ankle edema. After an afternoon measurement an additional measurement was performed in the early morning. The patient had not stood upright that morning prior to the experiment except for micturition during the night. She had slept with elastic stockings to limit the effect of standing on the amount of pooling. As shown in Figure 3, BP fall induced by HUT was greatest in the early morning (systolic BP fall: 69 mmHg vs. afternoon: 23 mmHg). Calf volume increased more in the early morning (1.7%) than in the afternoon (1.3%). The increase seen in the acute phase of HUT was comparable in both measurements (early morning: 0.7%; afternoon: 1.0%), whereas the increase during the prolonged phase of HUT was markedly reduced in afternoon (early morning 1.0% vs 0.3% afternoon).

Discussion

We found no evidence for excessive pooling at the level of the calf in AF during the course of the day despite marked hypotension. However, the additional measurement in our hospitalised patient suggests that a small increase in orthostatic fluid shifts to the calves may be expected when the patient first gets out of bed in the morning. Since edema may function as a ”water jacket” around the veins,[161,256] the observed diurnal variations in pooling are best explained by the development of edema during the course of the day preventing fluid filtration.

Figure 3 Orthostatic fluid shifts at the level of the calf during 5 minutes of head-up tilt with a parachute harness in a 28 year-old patient with young onset Parkinson's disease. Upon tilting in the afternoon (panel a) only a small fall of blood pressure (BP) was found (systolic BP fall: 23 mmHg). This orthostatic fall was accompanied by a 1.3% increase of calf volume. By contrast, head up tilt in the early morning (panel b) caused severe orthostatic hypotension (systolic BP fall: 69 mmHg), but only a small increase of calf volume (1.7%) was seen compared to the afternoon measurements. The observed diurnal variations in pooling are best explained by the development of edema during the course of the day preventing fluid filtration.



Before discussing the clinical implications of our findings, several limitations to this study deserve mention. First, the degree of AF varied considerably between our patients, as three patients did not meet criteria of OH at the day of the study (Figure 2).[242] One might assume that this explains the lack of venous pooling in AF. However, contrary to expectation no association was found between the degree of OH and the amount of orthostatic pooling, a matter further discussed below. Second, both patients with central and peripheral AF were included. Although both conditions cause OH, preganglionic (central) and postganglionic (peripheral) lesions of the autonomic nervous system cause different types of autonomic dysfunction.[44,275,276] The previous finding of a decreased calf compliance, i.e. stiffer veins, in patients with MSA may indicate that pooling is reduced in central AF,[153] whereas in peripheral AF the amount of pooling proved to be normal in patients with familial dysautonomia[32] and increased in subjects after ganglionic blockade.[33,158,189] Thus, while our study suggests that OH per se does not cause increased orthostatic fluid shifts to the calves, pooling might differ between central and peripheral AF, but this should be subject of further study. Third, one patient was studied while using α adrenergic medication, midodrine. Although this decreases calf venous compliance and may thus reduce orthostatic calf volume changes in healthy subjects, the administration of midodrine did not alter venous compliance in patients with MSA.[153] It is therefore not likely that the inclusion of this patient affected our results. Finally, measurements were performed at various times during the day ranging from the late morning to the early afternoon. Given the observed diurnal variation in pooling in our patient with PD, it is conceivable that owing to the development of edema during the course of the day a lower amount of pooling to the calves may be found at measurements in the afternoon. Nevertheless, given the relatively small difference between pooling in the early morning and the late afternoon in our patient with PD, the effects of differences in the development of edema our results are probably minimal once the patient has risen in the morning.

Calf volume during HUT increased more in men than in women. Gender differences in venous pooling are best explained by a higher venous compliance in men, i.e. more flexible veins, together with an increased hydrostatic pressure due to greater height in men.[172,179,244] Surprisingly, as seen in Figure 2 the difference between both sexes was less in our patients than in healthy subjects. We cannot provide a sufficient explanation for this discrepancy. One could assume that gender differences in healthy subjects are sympathetically mediated, and are thus reduced in case of sympathetic denervation. However, the gender difference in calf venous compliance was greater during rest compared to sympathetic activation, thus pleading against a sympathetically-mediated cause.[179] Alternatively, this discrepancy may be confounded by differences in the amount of OH within the patients. However, as seen in Figure 3, the orthostatic BP fall was not greater but lower in female patients.

Although we did not directly assess absolute volume shifts, we can roughly estimate the amount of pooling for the lower leg. Given an average calf volume of 2077 ml in men,[54] a 3% increase would equal an increase of 62 ml per calf. In confirmation of previous studies we found no evidence for excessive pooling at the level of the calf in AF. The lack of increased venous pooling at the level of the calf in patients with AF may be explained by the scarce sympathetic innervation of the veins in the lower leg in healthy humans.[158] In contrast, the splanchnic vascular bed is richly innervated and orthostatic pooling in the splanchnic region is probably increased in AF through impaired arterial vasoconstriction.[46,230,231] Accordingly, compression of the abdomen proved to be more effective to prevent OH compared to compression of the lower limbs suggesting that orthostatic fluid shifts to the splanchnic vascular bed are of greater importance to OH in AF.[67,121,234] However, the importance of active capacitance responses in the splanchnic bed is difficult to assess in humans and remains debated.[100,203,230] Diurnal variations in orthostatic fluid shifts have not been noted previously and should be taken into account in further studies on pooling. The greater amount of pooling when patients rise in the morning may contribute to circadian BP changes in AF, as patients with AF have their lowest BP recordings in the early morning.[162,191] Nevertheless, it should be stressed that the circadian variation of BP in AF cannot be explained by pooling and consequent edema alone, as confinement to bed did not abolish the daytime BP changes.[162]

In conclusion, in AF there is no evidence for increased orthostatic fluid shifts at the level of the calf during the course of the day. However, a small increase of venous pooling may be expected in the early morning upon first rising from bed, probably due to the absence of edema. These findings suggest that OH should not be ascribed to excessive pooling at the level of the calf. Venous pooling in other vascular beds such as the splanchnic region might be of greater importance to OH in AF.

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