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## Assessment of orthostatic fluid shifts with strain gauge plethysmography

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## Abstract

We evaluated the use of strain gauge plethysmography (SGP) for the assessment of orthostatic fluid shifts during head up tilt (HUT). Subjects wore a parachute harness fixed to the tilt table to avoid muscle tension in the lower limbs during HUT. 22 Healthy subjects (9 women) were tilted for 5 minutes. Calf volume changes as measured by SGP, surface EMG, heart rate and blood pressure were measured continuously. Ten subjects underwent a second tilt test during which circulation in one leg was occluded with a pressure cuff at 250 mmHg. During HUT with occlusion, calf volume increased in the non-occluded leg by  $1.9 \pm 0.3\%$  (mean  $\pm$  SEM) and  $0.2 \pm 0.2\%$  in the occluded leg ( $p < 0.001$ ). During HUT without occlusion a significant correlation ( $r = 0.9$ ) was found between measurements of the left and right leg with a mean difference of  $0.03 \pm 0.1\%$ . HUT did not cause significant changes of surface EMG.

An unexpected gender effect was found: calf volume increased significantly more in men than in women. Men were significantly taller, but the hemodynamic response to HUT did not differ between both sexes. The gender effect on orthostatic increases of calf volume remained significant after adjustment for heart-to-calf distance.

SGP during HUT with a parachute harness is a new, promising method to assess orthostatic fluid shifts. The gender differences in orthostatic pooling in the calf may be explained by a higher calf compliance in men together with a greater hydrostatic pressure due to a greater height in men.

## Introduction

Upon standing, approximately 300-1000 ml of blood is pooled to the lower parts of the body [1-4]. Estimates of the amount of venous pooling depend on several factors, including the vessel beds investigated and the duration and type of orthostatic stress. The amount of venous pooling differs markedly between the areas of the body. For example, approximately 80% of the blood pooled in the legs is contained in the thigh and buttocks [2]. The estimate of the amount of pooling therefore depends on the regions studied. The time course of orthostatic fluid shifts is characterized 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 [5;6]. Thus, the duration of standing affects the amount of orthostatic venous pooling due to capillary filtration [7]. Finally, the type of orthostatic stress (lower body negative pressure (LBNP), passive tilting or active standing) affects the amount of fluid shifts as muscle tensing reduces venous pooling: a single contraction of the calf muscles may eject 60% of the blood entered upon standing [8].

Venous pooling is crucial to the pathophysiology of orthostatic hypotension in autonomic failure [1;2]. A non-invasive device with continuous measurements of orthostatic fluid shifts could provide more insight into the pathophysiology of autonomic failure. Impedance plethysmography has been used to this end, and a significant correlation was found with the estimated loss of plasma volume using the Evans dye method [6]. However, despite the strong correlation impedance plethysmography systematically underestimated the amount of fluid loss in the capillary filtration phase compared to the Evans dye method. It is unclear which method is more reliable as both methods rely on a number of assumptions [6].

Strain gauge plethysmography (SGP) has been used extensively to assess limb blood flow and venous compliance following orthostatic stress [9;10]. However, continuous measurements of orthostatic pooling have not been performed as muscle tensing affects limb volume and thus SGP measurements. A tilt-table with a parachute harness can be used to avoid muscle tension upon tilting [11]. This method may hereby allow the assessment of orthostatic fluid shifts with SGP. Therefore we evaluated the use of SGP for the assessment of the time course of orthostatic fluid shifts during HUT with a parachute harness.

## Methods

### *Subjects*

22 healthy volunteers were recruited by means of an advertisement (13 men; mean age 32 years; range 18-56 years). All 9 women used oral contraceptives and were premenopausal. The study protocol was approved by the Leiden University Medical Centre ethics review committee. All participants gave written informed consent. Subjects were excluded if they had a history of recurrent (more than 5 times) syncope, a known cardiac or neurological disease, or used any medication other than analgetics or oral contraceptives.

### *Study protocol*

The temperature of the room was maintained at  $23\pm 1^{\circ}\text{C}$ . Subjects lay on a motor-driven tilt table (Dewert tilt-table, GmbH). For this experiment the footboard was removed from the table. Tilting time (from  $0^{\circ}$  to  $60^{\circ}$  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 22 subjects were tilted with a parachute harness to  $60^{\circ}$  head up for 5 minutes after 5 minutes of supine rest. In 10 subjects (8 men) an additional tilt with a parachute harness was performed for four minutes. In these subjects, the upper thigh in one upper leg (randomly assigned) was instrumented with a pressure cuff (Hokanson EC-10 rapid cuff inflator) to 250 mmHg [12] to prove the absence of volume changes during arterial occlusion. The cuff was inflated 1 minute prior to tilting and pressure was released after 3 minutes of HUT.

### *Measurements*

Both calves were instrumented with mercury-in-silastic strain gauges, placed 10 cm distally from the tibial tuberosity. The strain gauges were fitted to the measured circumference and connected to a custom built plethymograph based on the principles of the Hokanson EC-2 plethymographs. To avoid direct contact of the strain gauges with the tilt table, the heel was raised with a small cushion. HUT without occlusion was repeated in 2 subjects on a separate occasion as the strain gauge in one calf moved downwards directly upon HUT causing a negative SGP measurement. Skin surface temperature of both calves was measured 1 minute before HUT and after 5 minutes HUT with an infrared pistol thermometer (Testo 825-T4, Testo, Almere, the Netherlands). Beat-to-beat finger blood pressure (BP) was measured by finger volume-clamp method (Finometer, Finapres Medical Systems, Arnhem, the Netherlands). Heart rate was derived by ECG. Muscle activity of the gastrocnemius muscle and the anterior tibial muscle was measured with surface electrodes. All signals were routed to a computer (sampling rate 120 Hz) for off-line analysis using custom-written software. Self-reported body weight was recorded and body height was measured including the heart-to-calf distance to estimate the height of the hydrostatic column.

### *Data analysis and statistics*

Data are presented mean  $\pm$  SEM or median (interquartile range). Our primary outcome measure was the change in calf volume after 5 minutes tilting. We divided the response to HUT in two phases: the acute phase (0-1 minute HUT), mainly reflecting filling of veins caused by a rise in hydrostatic pressure, and the prolonged phase (1-5 min HUT), mainly reflecting the degree of fluid filtration through capillary walls. The degree of agreement between the SGP measurements of the left and right leg was assessed with the method of Bland and Altman and Pearson's correlation coefficient [13]. The paired or unpaired t-test was used for comparisons between or within subjects for normally distributed continuous variables and the Mann-Whitney *U* test or Wilcoxon signed rank test for continuous variables without a normal distribution. Secondary analysis was performed for unexpected gender differences in calf volume during HUT using multiple linear regression. Data analysis was performed with SPSS software, version 12.0. All tests were performed two-sided. Significance threshold was set at 5%.

## Results

### *Occlusion test*

Figure 1 shows the time course of calf volume change during the occlusion test. Prior to HUT, inflation of the pressure cuff in the supine position caused a significant increase of calf volume ( $0.5 \pm 0.1\%$ ,  $p < 0.01$ ), presumably due to the fact that veins close at a lower pressure than arteries, so there is a temporary influx without outflux. During HUT the change of calf volume in the non-occluded leg vs. occluded leg was larger ( $1.9 \pm 0.3\%$  non-occluded leg,  $p < 0.001$ ).

### *Head up tilt with a parachute harness without occlusion*

After 5 minutes of HUT without occlusion, calf volume increased by  $2.3 \pm 0.2\%$  in the right leg and by  $2.3 \pm 0.2\%$  for the left leg. Measurements of both legs showed a significant correlation (Pearson  $r = 0.9$ ,  $p < 0.001$ ) and a satisfactorily small mean difference (left leg minus right leg  $0.03 \pm 0.1\%$ , 95% CI -0.2 to 0.2%). After 5 minutes of HUT, the skin temperature of both calves had significantly decreased by  $0.4 \pm 0.1^\circ\text{C}$  (supine:  $31.2^\circ\text{C}$ , tilted:  $30.8^\circ\text{C}$ ,  $p = 0.001$ ). Muscle tension as measured with EMG activity did not differ significantly between the supine and the tilted position (supine:  $0.3$  (0.1-0.8)  $\mu\text{V}^2/\text{s}$ , tilted:  $0.2$  (0.1-0.5)  $\mu\text{V}^2/\text{s}$ ;  $p = 0.1$ ).

A significant gender effect was found in the calf volume changes to HUT: men had a greater increase of volume during HUT than women (Table 1, Figure 2). The changes were only significant for the acute phase of HUT (0-1 min). No significant differences were found between both sexes for prolonged phase of HUT (1-5 min). Male subjects were significantly taller and weighed more than the female subjects, but body mass index, baseline calf volume, age, surface EMG activity and the hemodynamic response to HUT did not differ significantly between both sexes (Table 2). Calf volume significantly increased with heart-to-calf distance but this significance was lost once the contribution of gender was taken into account (95% CI for the coefficient: -0.04 to 1.0 (volume (%) per cm), adjusted  $R^2$  0.56,  $p = 0.4$ ). The gender effect on orthostatic increases of calf volume remained significant after adjustment for heart-to-calf distance (95% CI for the difference between both sexes 0.6 to 2.4%, adjusted  $R^2$  0.56,  $p = 0.008$ ).

## Discussion

We evaluated the use of SGP to estimate the time course of orthostatic fluid shifts in the free hanging position. Our method provided stable results, given the good agreement and significant correlation between the measurements of both legs. However, we cannot formally assess the validity of our method since there is no gold standard for the assessment of orthostatic fluid shifts. Nevertheless, the occlusion test provided evidence that the changes during HUT with a parachute harness were predominantly caused by orthostatic fluid shifts, except for a small (0.2%) increase during HUT in the occluded leg, which should ideally remain completely unaltered. This small increase may have resulted from congestion, as the inflation of the cuff prior to HUT induced a significant increase of calf volume. It is also possible that hydrostatic effects were not completely eliminated in the occluded leg, as there still was a column of blood from the foot to the site of occlusion in the thigh. Alternatively, the increase resulted from drift of the plethysmograph signal.

Muscle activity as measured with surface EMG did not increase during HUT with a parachute harness. It is therefore unlikely that muscle activity confounded the SGP measurements in the free hanging position. During HUT skin temperature significantly decreased by 0.4°C. A decrease of temperature causes a decrease of electrical resistance of the mercury-in-silastic strain gauge and thus an underestimation of the volume changes. However, we consider this effect to be negligible, since a decrease of temperature by 0.4°C would cause a similar change of electrical resistance as would be produced by a 0.02% decrease of calf volume [14].

We found an unexpected gender difference in orthostatic pooling: calf volume during HUT increased more in men than in women. This difference was only apparent during the acute phase of tilting. In the prolonged phase a similar slope of volume changes was obtained in both sexes. Venous pooling in the first minute of standing is mainly due to an acute increase of hydrostatic pressure [2]. Venous pressure at the level of the calf increases from the horizontal to the tilted position by 45 to 60 mmHg [7;9]. The gender differences in this phase may be explained by differences in venous compliance, as men have a higher venous compliance i.e., more flexible veins [15;16]. Calf venous compliance has been assessed in the supine position by inflating a thigh cuff to 60 mmHg with subsequent gradual reduction to 0 mmHg. However, venous occlusion plethysmography does not equal the pressure increase



induced by orthostasis as venous outflow is obstructed in occlusion plethysmography whereas venous outflow is unhindered in the upright posture. Besides this intrinsic difference in venous compliance, men were in our study on average 13 cm taller than women and therefore had a greater hydrostatic pressure at the level of the calf, thereby subjecting their more flaccid veins to larger pressures. The mean gender difference of 7 cm in the heart-to-calf distance equals a hydrostatic pressure difference of  $\sim 4$  mmHg [sinus  $60^\circ$  (tilt angle)\*  $0.735$ \* 7 cm blood]. The amount of orthostatic change of calf volume increased with heart-to-calf distance but the association lost significance after adjustment for sex. This finding does not rule out an effect of height on orthostatic pooling, since men were taller than women and height may thus partly add to the gender effect. We hypothesize that gender may affect venous pooling both through intrinsic differences in compliance and through differences in height. However, the present study was not designed to address the mechanisms of gender differences in orthostatic fluid shifts and further studies are required to resolve this issue.

The mechanism for the sex difference in venous compliance has yet to be identified. Volume changes during orthostatic stress or venous occlusion are caused by expansion of the deep intramuscular veins [7;17]. These are intrinsically passive tubes with little sympathetic innervation [7]. Meendering et. al hypothesized that the gender differences in calf compliance were caused by female sex hormones [16]. However, the authors found no significant influence of menstrual cycle and the use of oral contraceptives on calf venous compliance. Nevertheless, these findings do not exclude a long term effect of female sex hormones on the structure of the venous wall [16]. Alternatively, the sex difference in venous compliance may be explained by differences in training status, as more fit subjects have greater venous compliance than their unfit peers [18;19].

The observed gender differences in venous pooling and venous compliance contrast with the finding that women have a poorer orthostatic tolerance: a low compliance, i.e., stiffer veins, in women should reduce venous pooling and thereby improve orthostatic tolerance [20]. This discrepancy suggests either that venous pooling is less important than other factors for orthostatic tolerance, or that pooling is important, but not in the calf. Other regions, such as the upper thigh or the abdomen may be of greater importance to trigger syncope. An observation favouring the latter argument is that during lower body negative pressure (LBNP) men had a greater increase in calf circumference but women had greater increases in thoracic

impedance [21]. These results may indicate that in women fluid shifts preferentially towards the abdomen rather than towards the legs.

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 [22], a 3% increase would equal an increase of 62 ml per calf.

In conclusion, the use of SGP in the free hanging position is a new, promising method to assess orthostatic fluid shifts and can be used in patients with syncope or orthostatic intolerance. The gender differences in orthostatic pooling in the calf may be explained by a higher calf venous compliance in men than in women, together with a greater hydrostatic pressure at the level of the calf in men.

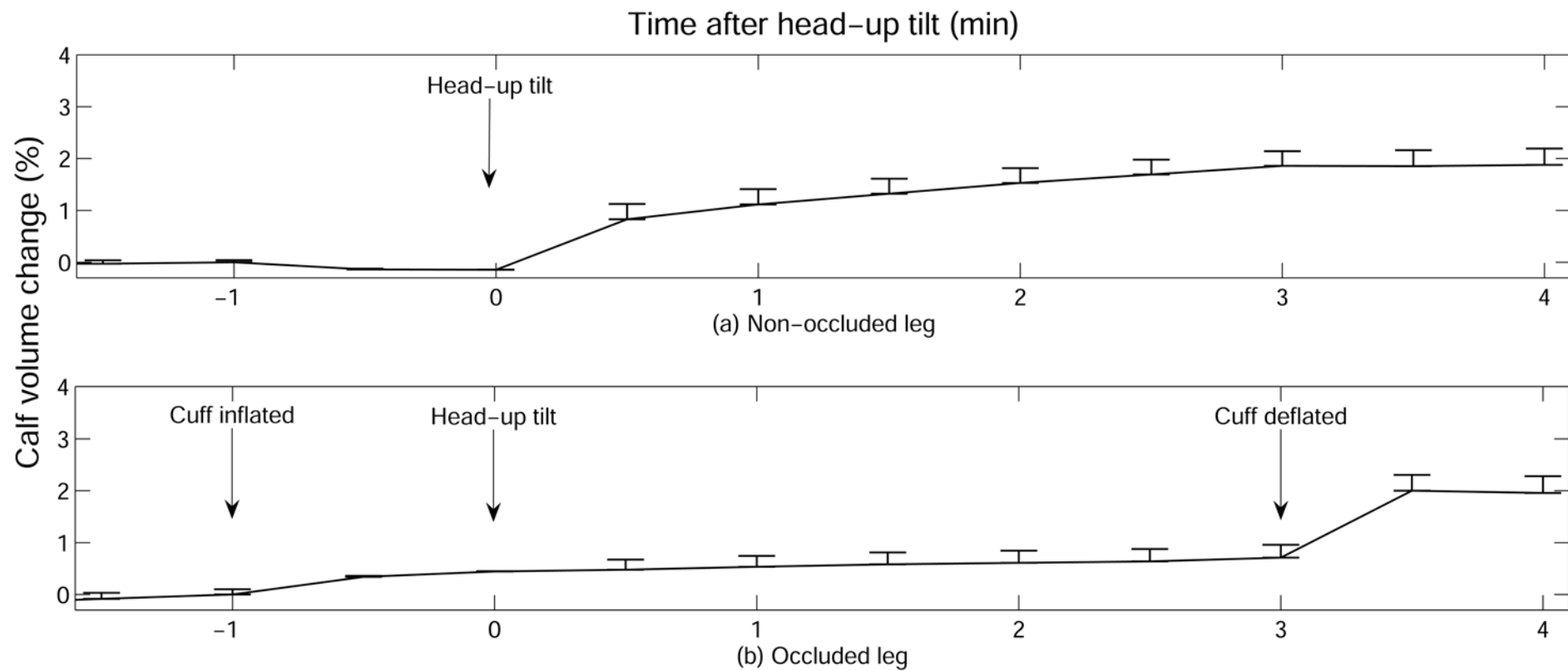
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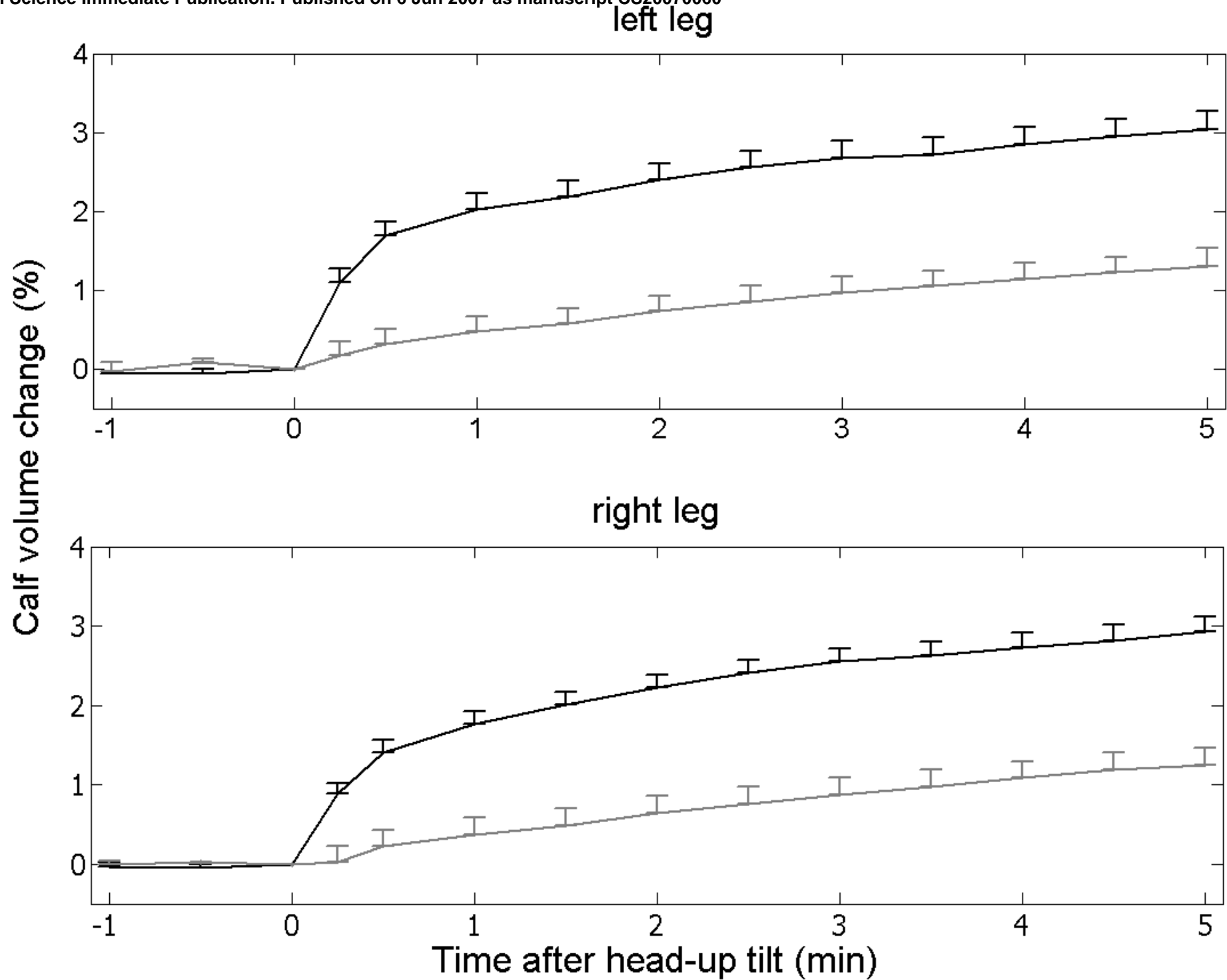
We sincerely thank Saskia le Cessie for her help with statistical analysis.

**Figure 1.** Volume changes in the calf as measured by strain-gauge plethysmography during head-up tilt with a parachute harness. One minute prior to head up tilt one leg was occluded with a pressure cuff at the upper thigh to 250 mmHg. The cuff was deflated after 3 minutes of tilting. Data are presented as mean  $\pm$  SEM.

**Figure 2**

Time course of calf volume changes in men (black line) and women (grey line) as measured by strain-gauge plethysmography during head-up tilt with a parachute harness. Data are presented as mean  $\pm$  SEM.





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**Table 1.** Change of calf volume during head-up tilt (HUT) with a parachute harness without occlusion in men ( $n=13$ ) and women ( $n=9$ ).

	Calf volume change (%)			Calf volume change (%)		
	right leg			left leg		
	Men	Women	<i>P</i> value	Men	Women	<i>P</i> value
Response to 5 min HUT	2.9 ±0.2	1.4 ±0.2	<0.001*	3.0 ±0.2	1.4 ±0.2	<0.001*
-acute phase (0-1 min HUT)	1.8 ±0.2	0.5 ±0.2	<0.001*	1.9 ±0.2	0.5 ±0.2	<0.001*
-prolonged phase (1-5 min HUT)	1.1 ±0.1	0.9 ±0.1	0.2	1.1 ±0.1	0.9 ±0.1	0.2

*Values are expressed as mean ± SEM*

*P-values: independent samples T-test*

**Table 2** Baseline characteristics and hemodynamic responses to head-up tilt with a parachute harness for men and women. Values are presented as means  $\pm$  SD or median (interquartile range). *P*-values: independent samples T-test or Mann-Whitney *U* test. \* Significance  $p < 0.05$ .

		Men (n = 13)	Women (n = 9)	<i>P</i> value
SBP (mmHg)	supine	129 $\pm$ 15	125 $\pm$ 14	0.6
	tilted	133 $\pm$ 16	127 $\pm$ 13	0.4
DBP (mmHg)	supine	71 $\pm$ 11	66 $\pm$ 11	0.3
	tilted	78 $\pm$ 11	73 $\pm$ 9	0.2
Heart Rate (bpm)	supine	64 $\pm$ 10	71 $\pm$ 10	0.1
	tilted	74 $\pm$ 12	80 $\pm$ 13	0.3
Baseline calf circumference (cm)	right leg	36 $\pm$ 2	36 $\pm$ 3	0.6
	left leg	36 $\pm$ 2	36 $\pm$ 3	0.8
Surface EMG activity ( $\mu\text{V}^2/\text{s}$ )	supine	0.4 (0.1-0.7)	0.1(0.1-1.6)	0.5
	tilted	0.2 (0.1-1.0)	0.2(0.1-0.3)	0.5
Age (years)		35 $\pm$ 13	26 $\pm$ 10	0.1
Length (m)		1.8 $\pm$ 0.1*	1.7 $\pm$ 0.1*	<0.001
Heart-to-calf distance (cm)		96 $\pm$ 6*	88 $\pm$ 5*	<0.01
Body weight (kg)		74 $\pm$ 5*	61 $\pm$ 7*	<0.001
Body Mass Index ( $\text{kg}/\text{m}^2$ )		22 $\pm$ 2	23 $\pm$ 2	0.3