



Thirst response to acute hypovolaemia in healthy women and women prone to vasovagal syncope[☆]



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HIGHLIGHTS

- Self-perceived thirst score increased three-fold when LBNP of 40 mm Hg was applied.
- Thirst increase in women prone to vasovagal syncope was doubled compared to controls.
- Plasma concentrations of angiotensin II increased in response to hypovolaemia, but did not correlate to thirst.
- Angiotensin II increase was positively correlated to hypovolaemia-induced increased heart rate.

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ABSTRACT

The present study measured self-perceived thirst and plasma angiotensin II (ATII) concentrations during graded hypovolaemic stress, induced by lower body negative pressure (LBNP), to elucidate the dependence of thirst on haemodynamics. A total of 24 women aged between 20 and 36 (mean age, 23) years rated their thirst on a visual analogue scale, graded from 0 to 100, when LBNP of 20, 30 and 40 mm Hg was applied. Half of the women had a history of vasovagal syncope (VVS). The results showed that the thirst score increased three-fold when LBNP was applied, from 11 (median; 25th–75th percentiles, 9–25) to 34 (27–53; $P < 0.001$). The women in the VVS group had twice as great an increase as those without a history of VVS ($P < 0.02$). The plasma ATII concentration increased significantly in response to LBNP, both in the VVS group and in the control group, but the changes did not correlate with thirst. Application of LBNP decreased systolic and mean arterial pressures, cardiac output and pulse pressure ($P < 0.001$ for all), but thirst correlated only with increase in heart rate and, independently, with reduction of mean arterial pressure. In conclusion, thirst and ATII increase in response to hypovolaemic stress, but are not statistically related. The haemodynamic parameter that was most strongly related to thirst was tachycardia.

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1. Introduction

Thirst is a sensation that is aroused by a need for water, which is crucial for maintaining homeostasis of the body fluids [1,2]. High osmolality is a known signal for thirst, and additional factors include hypovolaemia and release of angiotensin II (ATII). Knowledge of the aetiology of thirst is important for our understanding of how body fluid homeostasis is maintained and also enables us to treat the

excessive thirst that is a feature of certain disease states, such as heart failure [3–5]. The current view of the relationship between ATII and thirst is primarily based on animal studies [1,6,7], while human thirst trials reveal a less clear picture [8]. Previous findings about the role of AT II on the regulation of thirst are difficult to generalize for thirst in humans [7,9,10].

One situation in which increased thirst occurs is hypovolaemia, in which blood volume is reduced, due to events such as bleeding, pooling or dehydration. Hypovolaemia has profound effects on venous filling, venous return, and cardiac output [11,12] and the responses may reveal different characteristics in individuals suffering from vasovagal syncope (VVS) attacks [13]. Lower body negative pressure (LBNP) is an excellent model for hypovolaemic circulatory stress, as it induces central hypovolaemia and unloading of

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baroreceptors with activation of the sympathetic autonomic system [12]. Orthostatic tolerance to LBNP is decreased in individuals with induced hypovolaemia as well as in young women [14,29]. Low blood volume might also play a role in the pathophysiology of VVS [15]. The ATII response to LBNP has not been studied in patients suffering from VVS.

We therefore chose to study the sensation of thirst during hypovolaemia in women suffering from recurrent VVS as well as in women without a history of syncope. Our aim was to examine whether thirst increases during acute hypovolaemic stress and whether ATII, haemodynamic parameters or a history of VVS can be statistically related to any inferred change.

2. Materials and methods

2.1. Volunteers

A total of 24 women, age between 20 and 36 (mean age 23) years volunteered and participated in the study. Their mean (SD) body height was 165 (6) cm, mean body weight was 63 (11) kg and mean BMI was 23.0 (3.5) kg/m². Three additional volunteers were excluded, due to missing data ($n = 1$) or to both objective and subjective signs of presyncope during the protocol ($n = 2$). The participants had declared themselves to be non-smokers and free from cardiopulmonary disease, and were not taking medications that affect the cardiovascular system.

The volunteers were selected from two different cohorts; those who had a history of VVS (VVS group) and those who had never experienced syncope (control group). Eleven volunteers had previously been investigated due to clinically relevant syncope in daily life, and had all been diagnosed with VVS during a positive tilt table test. Moreover, they all had a negative cardiovascular examination and were found otherwise healthy, ruling out cardiac syncope. The women with VVS were recruited from a database in the Department of Clinical Physiology in Link ping. The healthy controls were recruited from the general population; they had never experienced syncope and were matched regarding age and fitness level.

All women were scheduled in the follicular phase (days 2–10) of the menstrual cycle. Five women in the VVS group, but none in the control group, were on oral contraceptives; similar studies conducted in our laboratory have not detected any significant impact of oral contraceptive use on cardiovascular findings [16]. All volunteers gave written, informed consent to the experiments, which were approved by the regional ethical review board in Link ping, in accordance with the Declaration of Helsinki.

2.2. Procedure

The participants arrived at the Department of Clinical Physiology at random, either in the morning or the afternoon, having had a light meal 1 h prior to arrival. They had been instructed to abstain from vigorous-intensity activity and beverages containing caffeine for the 24 h preceding the experiments. To ensure optimal fluid balance typical for each volunteer, they were all instructed to drink 1 L of water on the evening prior to the experiments, allowing the night time for excretion of excess fluid.

The participants were not permitted to drink for 45 min prior to, as well as during, the experiments, which were performed at a stable room temperature of 25  C. The study began after the participants had rested in the supine position for 30 min to reach haemodynamic steady-state. Immediately after the participant was placed in the supine position, an indwelling catheter was inserted in the left antecubital vein.

2.2.1. Lower body negative pressure

In the supine position, the lower part of the body up to the level of the iliac crest, was enclosed in an airtight box with a seal fitted

hermetically around the waist [11]. The box was connected to a vacuum source that permitted a stable negative pressure to be produced within 5 s and to be continuously measured with a rheostat. Experiments were performed at LBNP of 0, 20, 30 and 40 mm Hg, which were maintained for 4–5 min each. To assure return to the basal state in blood pooled to the lower part of the body, blood pressure and peripheral resistance, a break of 3–4 min between each LBNP step was permitted.

2.3. Measurements

The measurements included assessment of thirst, blood sampling of ATII and central haemodynamics at baseline and after application of LBNP. Heart rate variability (HRV) was analysed from electrocardiogram (SphygmoCor , AtCor Medical Pty Ltd, West Ryde, Australia) recordings of heart rate.

2.3.1. Thirst

Perceived thirst intensity was assessed using a visual analogue scale (VAS), which has previously been used to evaluate thirst in patients with cancer, renal failure and heart failure, as well as during trauma resuscitation [3–5,10]. The volunteers were informed just before the experiments started that they would be asked to rate their thirst sensation. They did not receive any information prior to or during the experiments about thirst or that thirst intensity might change.

The participants were asked to grade their thirst from ‘none’ (0 mm) to ‘worst possible’ (100 mm), by marking a cross at the appropriate point on a 100 mm line. The volunteers were in the supine position in the LBNP chamber and strapped down with equipment, which meant that they were unable to move their arms. Therefore, the researcher moved a pencil along the line and the volunteers stated where on the line they wanted the cross to be placed. The researcher who performed the thirst assessments during the experiments had no preconceived stance on thirst or on the impact of LBNP on thirst.

2.3.2. Angiotensin II

A venous blood sample for measurement of ATII was withdrawn from each participant, at baseline and at the end of each 4-min period of LBNP, in a cold anticoagulated tube. These samples were immediately placed in an ice bath and cold centrifuged within 20 min of being taken. The plasma samples were then stored at –70 C until analysed (Study Centre, Clinical Chemistry, Karolinska University Laboratory, Stockholm, Sweden). The plasma concentration of ATII was measured with a radio-immunological method after separation with Sep-Pak C-18 and incubation for approximately 24 h with antibodies from rabbit directed against ATII. A trace amount of ¹²⁵I-ATII was then added, and the incubation continued for an additional 6 h. The bound and free ATII were then separated using a second antibody directed against the rabbit antibodies. After centrifugation and decanting, the ¹²⁵I activity was taken as the measure of the plasma concentration of ATII. The coefficient of variation was 8.6% in the studied range.

2.3.3. Haemodynamics

Heart rate and arterial pressure were monitored non-invasively, beat-by-beat (Finometer  Midi, Finapres Medical Systems, Amsterdam, the Netherlands). A Vivid E-9 ultrasound scanner (GE Healthcare, Wauwatosa, WI, USA) with a transthoracic 4 MHz probe and a non-imaging 2.5 MHz Doppler probe was used to measure stroke volume. Prior to arrival at the laboratory, the participants had a routine echo to rule out structural cardiac disease and to measure left ventricular (LV) size, ejection fraction, cardiac output and stroke volume, based on the volume measurement according to Teichholz formula (Table 1). During the experiments, each participant was in the supine position flat on her back, and it was not always possible to obtain acceptable Doppler

Table 1

Demographic and echocardiographic characteristics of the study participants at baseline.

Measure	Controls (n = 13)	Vasovagal syncope (n = 11)
Age (years)	22.3 (2.3)	24.2 (5.3)
Length (cm)	167 (5)	164 (7)
Weight (kg)	64.4 (11.8)	61.5 (10.0)
BMI (kg/m ²)	23.0 (4.0)	22.9 (3.0)
Cardiac output (L/min)	4.87 (0.98)	4.52 (1.2)
Stroke volume (mL/min)	74.8 (12.5)	67.4 (13.2)
Peripheral resistance (mm Hg min/L)	19.7 (4.2)	22.0 (6.9)
LVEDV	120 (18)	103 (21)
LVESV	45.1 (10.6)	38.5 (9.3)
Ejection fraction (%)	62.5 (5.7)	62.5 (3.6)
LV FS	0.34 (0.04)	0.34 (0.03)

Data are the mean (SD). None of the differences between the groups are statistically significant.

LVEDV: left ventricle end-diastolic volume; LVESV: left ventricle end-systolic volume; LV FS: left ventricle fractional shortening.

recordings from the apical 4-chamber view. Therefore, aortic outflow was measured from the suprasternal view (jugulum) using a non-imaging probe. All measurements were conducted at the same phase in the respiratory cycle (expiration). The recordings were carried out at baseline, just prior to the start of each LBNP level and just prior to LBNP termination. Two subsequent aortic outflow measurements, whereby the probe was displaced in between, were conducted at each point of measure to optimise the detection of the peak velocity integral. The same individual conducted all measurements for both the VVS group and the control group. During both subsequent aortic flow measurements, the valvular velocity time integral (VTI) was analysed during three consecutive heart beats, and SV was calculated as the sub-valvular area \times VTI. Cardiac output was measured as the product of heart rate and SV.

2.3.4. HRV analysis

HRV analysis is a tool for use in the investigation of the sympathetic and parasympathetic function of the autonomic nervous system [17,18]. In the present study, the HRV analyses (frequency domains) were conducted from continuous ECG recordings, using commercial HRV software (SphygmoCor®, AtCor Medical Pty Ltd, West Ryde, Australia), which assessed low frequency (LF), high frequency (HF), LF/HF ratio, LF power normalised and HF power normalised, as well as total power. At each LBNP step, the analysis included a division of the power spectrum into LF (0.04–0.15 Hz) and HF (0.15–0.40 Hz) bands. The reported parameters are the maximum low and high frequencies (LF_{max} and HF_{max}), the normalised low and high frequency power (LF_{power} and HF_{power}), the LF/HF ratio, and the total power.

2.4. Statistical analyses

Data having a normal distribution were reported as the mean and standard deviation (SD), and differences between groups and over time were measured by two-way repeated-measures analysis of variance (ANOVA). Data showing a skewed distribution were given as the median and 25th–75th percentile range. Changes over several LBNP levels were compared by Friedman's test and over two levels by the Wilcoxon matched-pair test, while differences between study groups were measured with the Mann–Whitney *U* test. Stepwise multiple regressions were used to scan correlations between the key outcome measures and study parameters. Final evaluation of correlations was made by simple and multiple linear regressions, after logarithm-transformation of data showing a skewed distribution. *P* < 0.05 was considered to be statistically significant.

3. Results

There were no statistically significant demographic differences or haemodynamic differences at baseline between the VVS group and the control group (Table 1). All volunteers presented with normal echocardiography and cardiac function at rest (Table 1).

3.1. Thirst

The median (25th and 75th percentiles) thirst ratings at baseline was similar in VVS and controls (10 (8–30) vs. 20 (9–27; *P* = 0.40)). Thirst increased gradually in response to LBNP (*P* < 0.001 for all volunteers; Fig. 1, top), both in the control group (*P* < 0.001) and in the VVS group (*P* < 0.01). Women with VVS had a greater increase of thirst (median 20, 18–41) than the controls (median 10; 8–23; *P* < 0.02).

3.2. Angiotensin II

No group difference in plasma AT II concentration was seen at baseline (Fig. 1, bottom). No difference was seen in baseline AT II concentration in VVS group on oral contraceptives (*n* = 5) compared to VVS women not using oral contraceptives (*n* = 6; *P* = 0.29). The plasma AT II concentration increased in response to LBNP (*P* < 0.001 for all volunteers) and was generally higher among volunteers in the VVS group than in the control group (median 11.5 pmol/L, 7.5–18.5 vs. 7.5, 5.9–11.5; *P* < 0.001). The final AT II concentration was significantly higher in the VVS group than in the control group (*P* < 0.02).

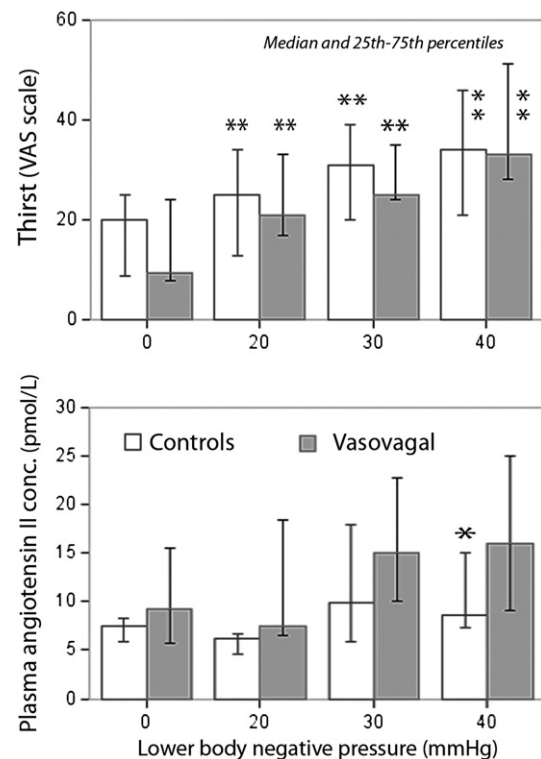


Fig. 1. Self-reported thirst (top) and plasma angiotensin II concentration (bottom) before and after lower body negative pressure had been applied. Top: No group difference was seen at thirst level at baseline (*P* = 0.40). Thirst increased in both groups with increasing LBNP (*P* < 0.001) and thirst increase was twice as high in VVS during LBNP of 40 mm Hg (*P* < 0.02). Bottom: Plasma AT II concentrations increased with increasing LBNP in both groups (*P* < 0.001) and were greater in VVS during LBNP of 40 mm Hg (*P* < 0.02). *Denotes comparisons between baseline values and LBNP (Wilcoxon matched-pair test). **P* < 0.05; ***P* < 0.01.

The increase in plasma ATII primarily occurred in a non-linear fashion after application of LBNP of 30 mm Hg; the pooled plasma AT II concentration at 0–20 mm Hg was median 6.9 (6.2–11.2) pmol/L, compared to 10.0 (7.5–16.3) pmol/L at 30–40 mm Hg ($P < 0.01$).

No correlation between thirst and the ATII concentration was found.

3.3. Haemodynamics

The arterial systolic, mean and pulse pressures and cardiac output all decreased with increasing LBNP level ($P < 0.001$), with no systematic differences between the study groups. A trend towards a greater decrease in pulse pressure with increasing LBNP level was seen in VVS ($P = 0.06$). Compared to rest, pulse pressure decreased already at application of LBNP of 20 mm Hg in VVS ($P = 0.05$), while it did not decrease until LBNP of 30 mm Hg in controls ($P = 0.60$ in controls at LBNP 20 mm Hg; Fig. 2). Furthermore, pulse pressure was lower at LBNP of 40 mm Hg in VVS compared to controls ($P = 0.03$; Fig. 2). Heart rate increased gradually with increasing LBNP in both groups ($P < 0.001$; Fig. 2). Compared to rest, heart rate was significantly increased already during LBNP of 20 mm Hg in VVS ($P = 0.006$), while heart rate was not significantly increased in controls until LBNP of 30 mm Hg was applied (Fig. 2).

Analyses based on all four points in time showed that thirst correlated most positively with heart rate (Fig. 3A). A multiple linear regression showed an inversely and independent correlation with thirst and mean arterial pressure ($r = 0.47$, $P < 0.001$). In these regression analyses, VVS did not serve as a statistically significant co-factor.

3.4. HRV analysis

LF_{power} and the LF/HF ratio increased, while HF_{max} and HF_{power} decreased in response to LBNP ($P < 0.001$) (Table 2). There were no statistically significant differences in HRV parameters between the study groups, but the rise in LF/HF ratio was observed first at greater hypovolaemic stress in the VVS group (Fig. 3B).

Heart rate correlated positively with LF/HF ratio ($r = 0.50$, $P < 0.001$; Fig. 3C). Of the components of this ratio, heart rate correlated positively with LF power ($r = 0.44$, $P < 0.001$).

4. Discussion

Hyperosmolality caused by water deprivation is the most well-established stimulus for thirst in humans, but there is abundant evidence to suggest that other mechanisms also are involved. The present study used induced short bouts of hypovolaemic stress to investigate possible relationships between thirst, ATII and haemodynamic factors in this setting. We also included volunteers with a history of VVS, with the aim of improving understanding of the interplay between the thirst signal and haemodynamics.

Self-perceived thirst score increased three-fold for all volunteers when LBNP of 40 mm Hg was applied and was doubled in women prone to VVS compared to the controls. The results also show that the plasma concentration of ATII almost doubled when hypovolaemia was induced by LBNP. Group trends show that thirst gradually increased when LBNP was raised, while ATII rose first during LBNP levels of 30 mm Hg and above (Fig. 1), which is in agreement with the findings of Tidgren et al. [19]. At this time, heart rate increased in both groups, while arterial pressures and cardiac output remained virtually unchanged (Fig. 2). This is consistent with the role that the renin–angiotensin system plays in maintaining haemodynamics in hypovolaemic states. A modulating role for ATII in haemodynamics is further suggested by the generally higher plasma concentrations that were observed in the participants with a history of VVS, seemingly with greater decrease in pulse pressure as well as increased heart rate already at a lower LBNP level (Fig. 2).

Multiple regression analysis identified two haemodynamic factors that correlated with thirst. The most important of these was the heart rate, which acts to maintain cardiac output during hypovolaemia. However, tachycardia does not always occur in response to haemorrhage [20], and is a poor index of hypovolaemia during surgery [21]. The increase of LH/HF ratio with heart rate supports the theory that the tachycardia was due to sympatheticovagal imbalance [17,18].

Thirst increased with reduced mean arterial pressure, which supports evidence suggesting that arterial baroreceptors arouse the thirst

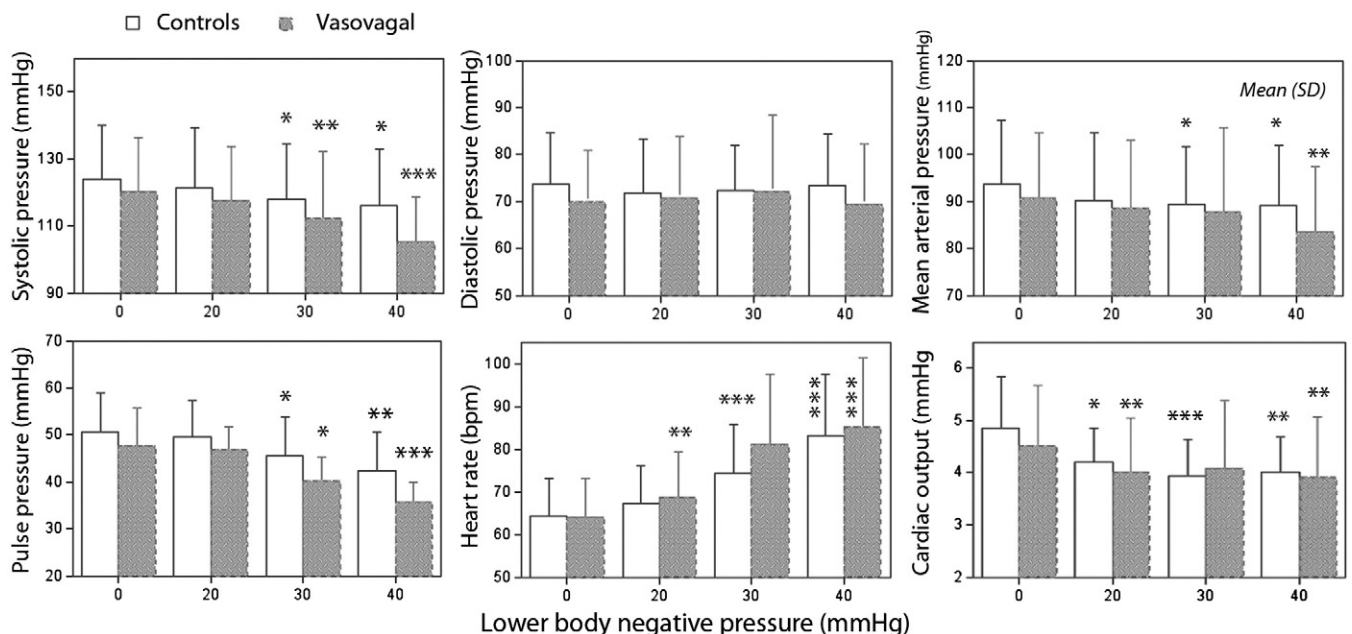


Fig. 2. Arterial pressure, heart rate and cardiac output before and during LBNP. Comparisons are made with repeated measures ANOVA followed by Dunnett's test. *Denotes comparisons between baseline values and LBNP. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Pulse pressure was lower in VVS compared to controls during LBNP of 40 mm Hg ($P < 0.05$).

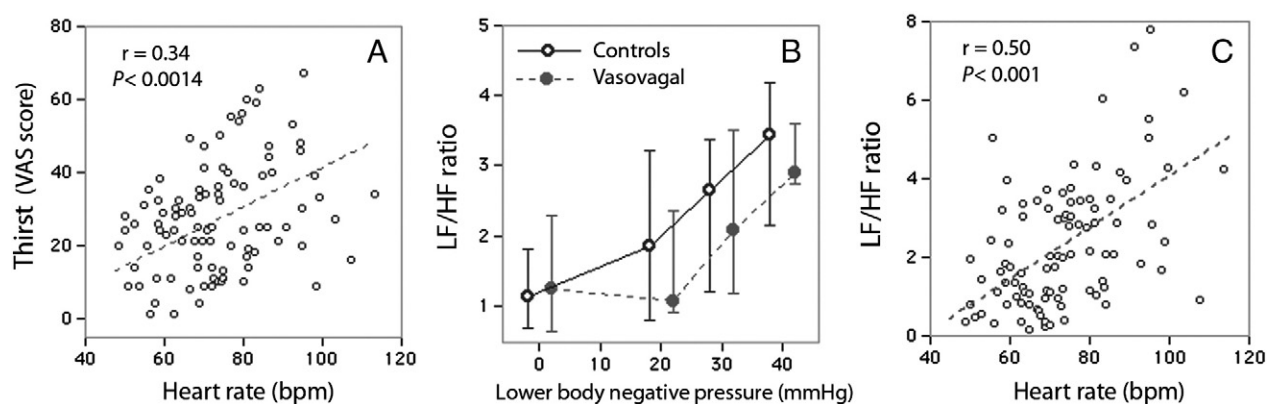


Fig. 3. Selected correlations between thirst, heart rate and heart rate variability were tested with linear regression analysis. LF/HF ratio = low frequency power divided by high frequency power.

centre in the brain [22]. We also detected greater increase in thirst in women with VVS with seemingly greater hypovolaemia than the controls, at least at LBNP of 40 mm Hg (Figs. 1 and 2). Interestingly, there was a poor overall correlation, or none at all, between thirst and more direct indices of hypovolaemia, such as pulse pressure and cardiac output. Furthermore, the overall linear correlations between thirst and haemodynamics were not very strong, indicating that factors other than those identified here are of importance to perceived thirst. Besides the effects of hypovolaemia, the most important stimulation for thirst is an increase of the osmotic pressure in plasma that affects the thirst centre in the brain. The intracellular decrease of body fluid might also cause dry mouth that can be associated with pronounced thirst.

The view that ATII increases thirst has often been proposed in medical textbooks, but remains poorly supported in humans. AT II is the physiological response to a decrease in blood volume and water and salt are needed to restore the volume. Because of this interaction, it can be difficult to comprehend the role of hypovolaemia and AT II on thirst. In acute trauma, evidence for mechanistic interplay between thirst and ATII was recently sought by a linear regression analysis that was based on individual participants, rather than on group mean values [10]. These analyses did not disclose any inter-correlation. However, both the thirst sensation and ATII concentration gradually increased with hypovolaemia. One study in male volunteers reported that thirst increased in a similar way on infusion of ATII or saline; nevertheless, there was a statistically significant linear correlation between changes in thirst and plasma ATII in a subgroup of four volunteers who drank more water than the other study participants after the infusion [8]. Drinking water was shown to decrease ATII in another study in humans [23].

The method we used for inducing circulatory stress (LBNP) creates central hypovolaemia which unloads low- and high-pressure baroreceptors, and overall hypovolaemic circulatory stress is increased in a linear fashion with increasing LBNP levels [12]. In the present study

it is of interest that LBNP of 10–20 mm Hg displaces 400–550 mL of blood to the lower part of the body [24,25], while LBNP of 30–40 mm Hg concomitantly displaces 500–1000 mL [12,26], equivalent to mild and moderate haemorrhage, respectively [12]. Low levels of LBNP (up to 15–20 mm Hg) activate mainly cardiopulmonary low-pressure receptors in healthy subjects, leading to increased peripheral sympathetic nervous system outflow, even in the absence of changes in arterial blood pressure or heart rate (Fig. 2), while higher levels of LBNP decreased arterial blood pressure and affected high-pressure arterial baroreceptors (Fig. 2) [27,28]. Thus, thirst seems to increase even before high-pressure arterial baroreceptors are deactivated (Fig. 1).

The participants in the present study were included on the basis of two different criteria; absence or presence of VVS. It has been stipulated that low blood volume could play a role in the pathophysiology behind VVS, at least to some extent [15]. LBNP tolerance is markedly reduced in individuals with hypovolaemia, induced either by furosemide [14] or controlled venesection of 500 mL of blood before onset of LBNP [29]. Therefore, we found it intriguing to study the effects of hypovolaemia on ATII and thirst in both healthy individuals and women suffering from recurrent syncope. Women with VVS had a greater increase in thirst sensation when LBNP of 40 mm Hg was applied, primarily because of lesser thirst at baseline, with no difference observed in thirst level at LBNP of 40 mm Hg (Fig. 1). No group differences were observed in any blood pressure parameters at rest. However, the VVS group experienced greater central hypovolaemia and an earlier deactivation of arterial baroreceptors in response to LBNP, as pulse pressure decreased to a larger extent in VVS (Fig. 2), further corroborated by the fact that two women with VVS did not complete the protocol due to subjective and/or objective signs of presyncope (not included in the study due to missing data). Furthermore, heart rate increased significantly in VVS at lower hypovolaemic stress than controls which is in line with the greater increase in thirst during LBNP in VVS (Figs. 1 and 2).

Table 2

Heart rate variability analysis before lower body negative pressure was applied and when negative pressure had been raised to 40 mm Hg.

	Controls		Vasovagal syncope	
	0 mm Hg	40 mm Hg	0 mm Hg	40 mm Hg
LF _{max} (Hz)	0.09 (0.08–0.11)	0.06 (0.05–0.10)*	0.08 (0.05–0.11)	0.07 (0.06–0.09)
HF _{max} (Hz)	0.26 (0.21–0.31)	0.19 (0.16–0.22)*	0.24 (0.18–0.28)	0.18 (0.16–0.19)
LF/HF ratio	1.14 (0.69–1.82)	3.44 (2.16–4.19)**	1.25 (0.65–2.31)	2.85 (2.41–3.59)*
LF _{power} (Hz)	53 (39–64)	78 (68–81)**	56 (39–69)	74 (70–78)*
HF _{power} (Hz)	47 (36–61)	23 (19–32)**	44 (31–61)	26 (22–30)*
Total power (kHz)	5.3 (1.9–7.0)	2.9 (1.7–6.2)	3.8 (1.8–6.0)	2.6 (1.2–3.1)

Data are the median and 25th–75th percentiles. LF_{max} and HF_{max} = maximum low and high frequencies, respectively.

LF_{power} and HF_{power} = normalised low and high frequency power, respectively.

Significance levels are *P < 0.05 and **P < 0.01.

Limitations of the present study include the fact that serum osmolality was not measured. However, the study period was fairly short and, in the absence of manipulations of fluid balance in addition to evaporation and blood sampling, there is little reason to believe that the gradually increasing thirst was due to hyperosmolality. Our study focused on thirst during hypovolaemic stress when LBNP was applied. We tried to ensure sufficient hydration with water intake the evening before the experiments. A second issue is that LBNP levels were not randomised. Although ATII has a very short half-life, only one measurement was made at each LBNP level, making it unclear as to whether the maximum concentration had been reached.

5. Conclusion

hypovolaemic stress increased thirst and plasma ATII concentrations in a non-linear fashion. Thirst correlated with tachycardia, LF/HF ratio and reduction of mean arterial pressure. Volunteers with a history of vasovagal syncope showed pronounced thirst and ATII responses than participants without a history of syncope.

Conflict of interest

The authors have no conflicts of interest to declare.

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