Vasoactive neuroendocrine responses associated with tolerance to lower body negative pressure in humans

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Summary

The purpose of this investigation was to test the hypothesis that peripheral vasoconstriction and orthostatic tolerance are associated with increased circulating plasma concentrations of noradrenaline, vasopressin and renin–angiotensin. Sixteen men were categorized as having high (HT, $n = 9$) or low (LT, $n = 7$) tolerance to lower body negative pressure (LBNP) based on whether the endpoint of their pre-syncopal-limited LBNP (peak LBNP) exposure exceeded −60 mmHg. The two groups were matched for age, height, weight, leg volume, blood volume and maximal oxygen uptake, as well as baseline blood volume and plasma concentrations of vasoactive hormones. Peak LBNP induced similar reductions in mean arterial pressure in both groups. The reduction in leg arterial pulse volume (measured by impedance rheography), an index of peripheral vascular constriction, from baseline to peak LBNP was greater ($P<0{\cdot}05$) in the HT group ($-0{\cdot}041 \pm 0{\cdot}005$ ml 100 ml^{-1}) compared to the reduction in the LT group ($-0{\cdot}025 \pm 0{\cdot}003$ ml 100 ml^{-1}). Greater peak LBNP in the HT group was associated with higher ($P<0{\cdot}05$) average elevations in plasma concentrations of vasopressin (pVP, $\Delta = +7{\cdot}2 \pm 2{\cdot}0$ pg ml^{-1}) and plasma renin–angiotensin (PRA, $\Delta = +2{\cdot}9 \pm 1{\cdot}3$ ng Ang II ml^{-1} h^{-1}) compared to average elevations of pVP ($+2{\cdot}2 \pm 1{\cdot}0$ pg ml^{-1}) and PRA ($+0{\cdot}1 \pm 0{\cdot}1$ ng Ang II ml^{-1} h^{-1}) in the LT group. Plasma noradrenaline concentrations were increased ($P<0{\cdot}05$) from baseline to peak LBNP in both HT and LT groups, with no statistically distinguishable difference between groups. These data suggest that the renin–angiotensin and vasopressin systems may contribute to sustaining arterial pressure and orthostatic tolerance by their vasoconstrictive actions.

Keywords: blood pressure regulation, noradrenaline, orthostatic tolerance, peripheral vascular resistance, renin–angiotensin system, vasoconstriction, vasopressin.

Introduction

Orthostatic intolerance reported in subjects exposed to bed rest or space flight was associated with a reduced capacity for vasoconstriction (Buckey *et al.*, 1996; Engelke *et al.*, 1996). Noradrenaline, vasopressin and renin–angiotensin are known to cause contraction of vascular smooth muscle and are elevated during orthostasis (Rogge & Moore, 1968; Graboys *et al.*, 1974; Davies *et al.*, 1976; Baylis *et al.*, 1978; Goldsmith *et al.*, 1982; Leimbach *et al.*, 1984; Rasmussen *et al.*, 1986; Williams *et al.*, 1988; Engelke *et al.*, 1996; Fritsch-Yelle *et al.*, 1996; Convertino, 1998). Consistent with these relationships, it is not surprising that development of orthostatic hypotension and pre-syncopal symptoms has been associated with attenuated plasma noradrenaline compared to non-syncopal subjects in health and disease (Robert-

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son, 1992; Engelke *et al*., 1996; Fritsch-Yelle *et al*., 1996; Convertino, 1998). However, definition of the contributions of noradrenaline, vasopressin and renin–angiotensin to vascular resistance responses and orthostatic tolerance in healthy human subjects has been limited by failure to use tests designed specifically to induce pre-syncopal endpoints in all subjects (Murray *et al*., 1968; Davies *et al*., 1976; Montgomery *et al*., 1977; Fritsch-Yelle *et al*., 1996), to consider differences in confounding physiological status such as low blood volume (Montgomery *et al*., 1977; Engelke *et al*., 1996; Fritsch-Yelle *et al*., 1996; Convertino, 1998), or to investigate responses in subjects who have been compromised by the deconditioning effects of inactivity or low-gravity environments (Engelke *et al*., 1996; Fritsch-Yelle *et al*., 1996).

Orthostatic tolerance may be affected by height (Ludwig & Convertino, 1994), blood volume (Ludwig & Convertino, 1994), blood pooling in the lower extremities (Luft *et al*., 1976) and aerobic capacity (Convertino, 1987). Accordingly, we reasoned that the ability to demonstrate a meaningful relationship between pressor substances, vascular resistance and orthostatic tolerance in healthy subjects would require the comparison of subjects who are identified as having high and low orthostatic tolerance using pre-syncopal-limited tests and matched for age, height, weight, volaemic state, lower-extremity vasculature and maximal oxygen uptake. Using this approach, we designed this study to test the hypothesis that attenuated peripheral vasoconstriction is associated with low orthostatic tolerance and reduced plasma levels of noradrenaline, vasopressin and renin–angiotensin.

Subjects and methods

Eighteen asymptomatic, non-smoking, normotensive men gave their written consent to serve as subjects for this investigation after they had been informed of all procedures and risks. All procedures were approved by the Institutional Review Board at NASA-Ames Research Center. During an orientation session conducted prior to the study, all subjects were made familiar with the laboratory personnel, procedures and protocols. Data regarding haemodynamic responses associated with orthostatic tolerance in all 18 subjects have been reported previously (Sather *et al*., 1986). Data obtained in the present experiment were generated from a subset of 16 subjects since we were unable to obtain blood samples in two subjects.

Within an eight-day experimental period, each subject underwent tests to determine peak oxygen uptake (peak $\dot{V}O_2$), blood volume and tolerance to a graded protocol of lower body negative pressure (LBNP). Peak $\dot{V}O_2$ was determined from ventilation volume and expired gas measurements collected during the final minute of a standard graded treadmill protocol designed to induce volitional fatigue in all subjects. Within 48 h prior to LBNP testing, plasma volume was measured using a modified Evans blue dye dilution method and blood volume was calculated from microhaematocrit (Hct) measures (Greenleaf *et al*., 1979).

Orthostatic tolerance was determined by applying LBNP while the subject was in the supine posture according to procedures described by Sather *et al*. (1986). After a 5 min baseline period, pressure within the LBNP chamber was reduced by 30 mmHg for 3 min. Decompression was increased to −50 mmHg for 5 min followed by stepwise increments of –10 mmHg every 5 min until test termination (Sather *et al*., 1986). During LBNP, heart rate (ECG), and systolic, diastolic and mean arterial blood pressures (automated sphygmomanometer) were measured every 30 s. Impedance rheography was used to measure changes in fluid accumulation and arterial pulse volume in the legs (Nyboer, 1970). No subject completed 5 min at −100 mmHg, and all subjects expressed one or more subjective pre-syncopal symptoms that coincided with a reduction in systolic blood pressure to <90 mmHg. A cumulative stress index for LBNP tolerance was derived (Luft *et al*., 1976) and maximal decompression tolerated by each subject was denoted as peak LBNP. Nine subjects were categorized as the high LBNP tolerance (HT) group based upon entrance into the −70 mmHg pressure (or surpassing a cumulative stress index of 640 mmHg·min), and seven subjects were categorized as a low LBNP tolerance (LT) group based upon failure to complete −60 mmHg pressure (Sather *et al*., 1986; Convertino, 1993; Ludwig & Convertino, 1994).

A 21-gauge needle with polyethylene catheter was placed in an antecubital vein of the left arm for withdrawing blood samples during the final minute of baseline and immediately prior to LBNP termination. Changes in plasma volume during LBNP were calculated from changes in Hct between baseline and LBNP using the previously measured baseline plasma volume (Greenleaf *et al.*, 1979). After determination of Hct, blood samples were centrifuged at 4°C and plasma was removed and frozen at −60°C. Radioimmunoassay was used to measure plasma renin activity (PRA; Haber *et al.*, 1969) and plasma vasopressin (pVP; Keil & Severs, 1977). A technique which couples liquid chromatography and electrochemistry was used to measure plasma noradrenaline concentration (Goldstein *et al.*, 1981).

Values for all measurements are presented as mean ± 1 standard error of the mean (SE). Statistical comparisons were conducted on subject descriptive data and the changes (Δ) in mean arterial pressure, peripheral vascular response, plasma volume, noradrenaline, pVP and PRA from baseline to peak LBNP between HT and LT groups using an unpaired two-tailed *t* test. A paired two-tailed *t* test was used to determine changes in mean arterial pressure and leg arterial pulse volume from baseline to pre-syncopal LBNP within each group. The Mann–Whitney test (non-parametric equivalent to the *t* test) was performed to substantiate *t* test trends. The null hypothesis was rejected when $P<0{\cdot}05$.

Results

The HT and LT groups were statistically similar in terms of age, height, weight, leg volume, total blood volume, and peak $\dot{V}O_2$ (Table 1). However, maximal tolerance to LBNP was greater ($P<0{\cdot}05$) in

Table 1 Physical characteristics of the subjects.

	High LBNP tolerance group (n = 9)	Low LBNP tolerance group (n = 7)
Age (years)	37 ± 2	41 ± 3
Height (cm)	179 ± 1	176 ± 2
Weight (kg)	79·1 ± 3·7	75·0 ± 2·1
Leg volume (ml)	9471 ± 638	9631 ± 490
Total blood volume (ml)	5945 ± 196	5811 ± 168
Peak $\dot{V}O_2$ (ml kg^{-1} min^{-1})	49·3 ± 3·8	44·8 ± 3·8

Values are mean ± SE.

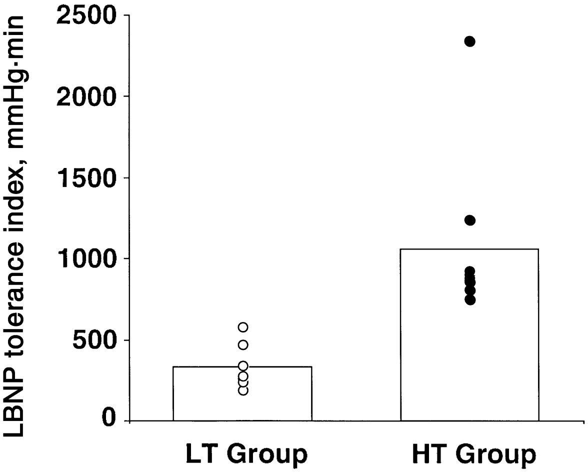

Figure 1 Individual and average cumulative index for lower body negative pressure (LBNP) tolerance in low tolerant (LT) and high tolerant (HT) subjects.

the HT (−74 ± 3 mmHg) compared to the LT subjects (−53 ± 2 mmHg). The peak LBNP tolerances corresponded to cumulative stress indices of 1062 ± 166 mmHg·min in the HT group, compared to 335 ± 53 mmHg·min in the LT group (Fig. 1). Mean arterial pressure was 73 ± 2 mmHg in both groups at baseline and was reduced to a similar degree at peak LBNP in the HT group (65 ± 4 mmHg) and LT group (60 ± 4 mmHg) (Fig. 2, top panel). Baseline leg arterial pulse volume was statistically similar in both groups, but the reduction in leg arterial pulse volumes from baseline to peak LBNP was greater ($P<0{\cdot}05$) in the HT group ($\Delta = -0.041 \pm 0{\cdot}005$ ml 100 ml^{-1}) compared to the reduction in the LT group ($\Delta = -0.025 \pm 0{\cdot}003$ ml 100 ml^{-1}) (Fig. 2, bottom panel).

No statistical inter-group differences were measured in plasma volume or any of the three vasoactive hormone concentrations during the baseline period prior to LBNP (Fig. 3). LBNP caused reductions ($P<0{\cdot}05$) in plasma volume, but both groups demonstrated statistically similar plasma volume reductions (i.e. changes in Hct) at peak LBNP (Fig. 3). However, at peak LBNP, average elevations in plasma concentrations of pVP ($\Delta = +7{\cdot}2 \pm 2{\cdot}0$ pg ml^{-1}) and PRA ($\Delta = +2{\cdot}9 \pm 1{\cdot}3$ ng Ang II ml^{-1} h^{-1}) in the HT group were greater ($P<0{\cdot}05$) compared to average elevations of pVP ($\Delta = +2{\cdot}2 \pm 1{\cdot}0$ pg ml^{-1}) and PRA ($\Delta = +0{\cdot}1$

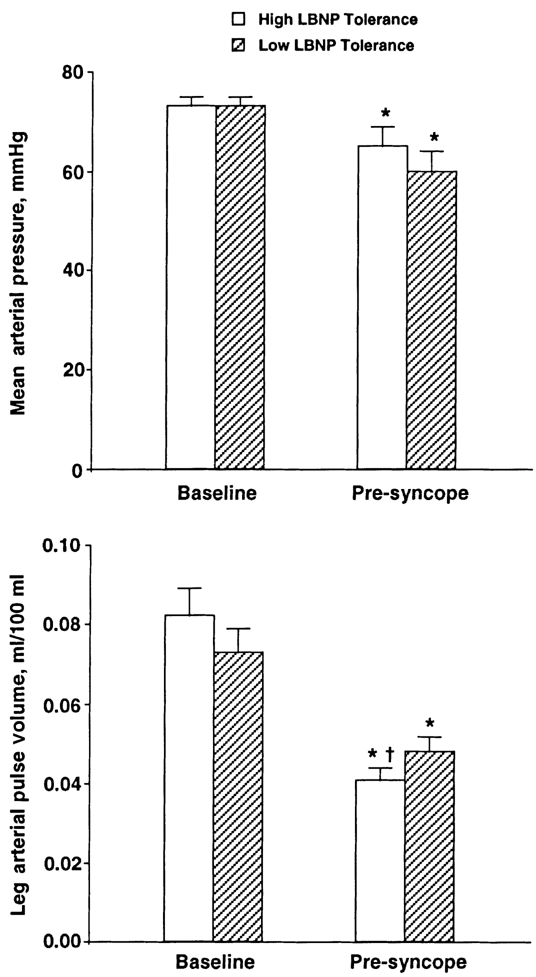

Figure 2 Mean arterial pressure (top panel) and leg arterial pulse volume (bottom panel) at baseline and pre-syncope (peak LBNP) in subject groups with high tolerance (open bars) and low tolerance (hatched bars) to LBNP. Bars represent mean ± 1 SE; *$P<0{\cdot}05$ versus baseline value; †$P<0{\cdot}05$ for change from baseline to peak LBNP versus the LT group.

± 0·1 ng Ang II ml^{-1} h^{-1}) in the LT group. Plasma noradrenaline concentrations were increased ($P<0{\cdot}05$) from baseline to peak LBNP in both HT ($\Delta = +504 \pm 203$ pg ml^{-1}) and LT ($\Delta = +264 \pm 86$ pg ml^{-1}) groups, with magnitudes that were not statistically distinguishable as a result of large inter-subject variability.

Discussion

Our experimental approach was unique in that it allowed for comparisons of vasoconstrictive hormones and vascular reactivity between two groups of healthy subjects with low and high orthostatic tolerance who were identified systematically by pre-syncopal-limited LBNP exposure. We measured responses of plasma noradrenaline, pVP, PRA, and an index of peripheral arterial vasoconstriction to a pre-syncopal-limited LBNP challenge to test the hypothesis that low orthostatic tolerance would be associated with attenuated peripheral vasoconstriction and reduced liberation of vasoconstrictor hormones. The results from this study support the notion that less peripheral vascular constriction observed in subjects with low LBNP tolerance was associated with significantly lower circulating levels of pVP and PRA than subjects with high LBNP tolerance.

The underlying cause for early onset of orthostatic hypotension and syncope is multi-factorial. Our results confirm those of previous studies that less capacity for vasoconstriction and adequate elevation of peripheral vascular resistance contribute to low orthostatic tolerance (Buckey *et al.*, 1996; Engelke *et al.*, 1996; Fritsch-Yelle *et al.*, 1996). HT subjects demonstrated greater reduction in arterial pulse volume than LT subjects at pre-syncope, suggesting greater peripheral vascular constriction and subsequent elevation of total systemic vascular resistance in the legs.

Low plasma noradrenaline concentrations have been associated with less elevation in total systemic peripheral resistance, orthostatic hypotension and syncope in astronauts and patients with Bradbury–Eggleston syndrome (Robertson, 1992; Fritsch-Yelle *et al.*, 1996). Therefore, we expected that greater vasoconstrictive responses at peak LBNP in HT subjects would be associated with a greater noradrenaline response compared to responses in the LT group. When compared to baseline measures, plasma concentrations of noradrenaline increased on average by 138% and 83% in the HT and LT groups, respectively. Large inter-subject variability may explain why the noradrenaline response to pre-syncope was not statistically distinguishable between groups. Since the HT group demonstrated greater vasoconstriction at pre-syncope, our results raise the possibility that high orthostatic tolerance is associated with greater α-adrenoreceptor responsiveness. However, if adrenoreceptor and noradrenaline responses

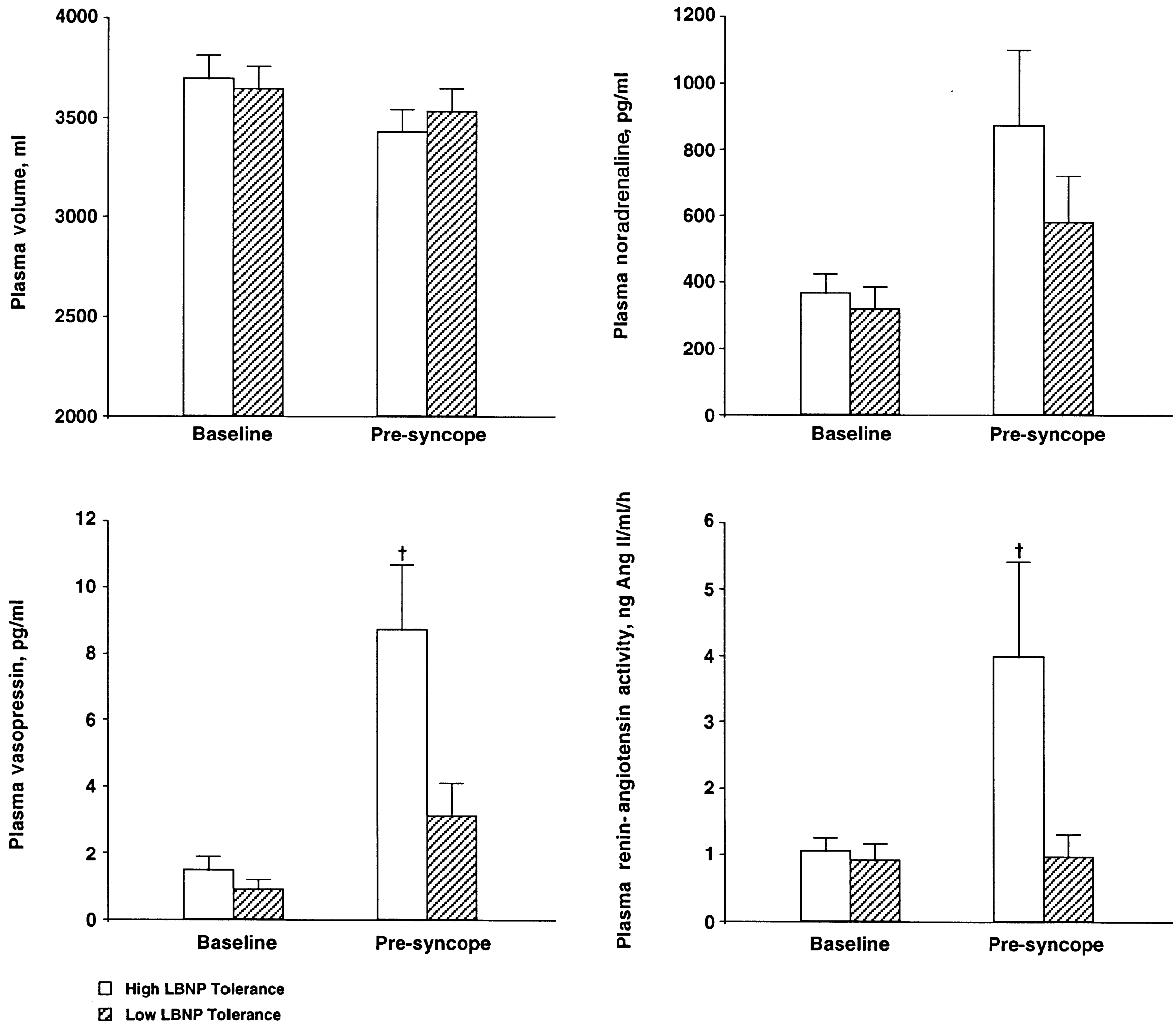

Figure 3 Plasma volume, noradrenaline, vasopressin and renin–angiotensin II at baseline and pre-syncope (peak LBNP) in subject groups with high tolerance (open bars) and low tolerance (hatched bars) to LBNP. Bars represent mean ± 1 SE; †P<0·05 for change from baseline to peak LBNP versus the LT group.

were not truly different between populations with high and low orthostatic tolerance, then other factors that stimulate vasoconstriction might explain the enhanced vasoconstrictive response observed in subjects with high LBNP tolerance.

Like noradrenaline, pVP and angiotensin II have potent vasopressor effects at physiological plasma concentrations (Cowley *et al.*, 1983; Altura & Altura, 1984; Share, 1996), and are released under conditions of orthostatic stress (Oparil *et al.*, 1970; Davies *et al.*, 1976; Davies *et al.*, 1977; Baylis *et al.*, 1978; Williams *et al.*, 1988; Convertino, 1993; Share, 1996; Convertino, 1998). Although evidence suggests that the sympathetic nervous system rather than pVP and angiotensin II is the primary system for blood pressure regulation during rest (Hasser & Bishop, 1988), pVP and angiotensin II appear necessary for normal maintenance of arterial blood pressure during hypotension (Brooks, 1989). The results of the present study are consistent with the notion that pVP and angiotensin II may have contributed to peripheral vasoconstriction and orthostatic tolerance since HT subjects demonstrated greater pVP and PRA than LT subjects.

Although angiotensin II is the vasopressor agent of the renin–angiotensin system, we chose PRA as a valid index of changes in angiotensin II since elimination of the elevation in angiotensin II during upright tilt can be induced by inhibition of PRA (Davies *et al*., 1977; Karlberg, 1983). LT subjects showed no elevation in PRA at peak LBNP compared to the fourfold increase observed in the HT group. Our observation is consistent with previous data which demonstrate a depressed PRA response in 25% of normal subjects who develop vasovagal syncope after upright tilting compared to non-syncopal subjects (Davies *et al*., 1976; Oparil *et al*., 1970). The primary mechanism for renin–angiotensin activation is increased renal sympathetic nerve activity (Karlberg, 1983; Reid *et al*., 1988). Since there was no statistically distinguishable difference in circulating noradrenaline between HT and LT groups, our results might suggest that healthy individuals with low orthostatic tolerance have less responsive or a decreased number of renal adrenergic receptors. These results also support the notion that angiotensin might serve as an important adjunct to sympathetically mediated vasoconstriction when sympathetic nerve activity can no longer maintain adequate peripheral vascular resistance and arterial blood pressure (Rowell, 1993). These hypotheses require further investigation.

HT subjects in the present investigation demonstrated greater peripheral vasoconstriction and elevation in pVP than the LT group at the point of peak LBNP. Although LBNP termination was not determined by loss of consciousness in either HT or LT groups, impending hypotension was demonstrated by similar reductions (approximately 20%) in mean arterial pressure. Since LBNP termination was based on pre-syncopal symptoms, a precipitous increase in pVP, which has been associated with vasodepressor syncope (Baylis *et al*., 1978; Goldsmith *et al*., 1982; Davies *et al*., 1976), was not observed. Since elevation in pVP was less than 10 pg ml^{-1} in the HT group, the contribution of pVP to the vasoconstrictive responses of our subjects may be small (Cowley *et al*., 1974). Nonetheless, elevation in pVP during LBNP in our HT subejcts was similar to that reported in pre-syncopal subjects (Rogge & Moore, 1968; Davies *et al*., 1976; Davies *et al*., 1977) and corroborates an association between pVP response and orthostatic tolerance.

The mechanism for the greater pVP response in HT compared to LT subjects is unclear. Differences in pVP responses to orthostatic challenges may be explained by differences in state of hydration (Davies *et al*., 1976; Schrier *et al*., 1979), osmolality (Schrier *et al*., 1979; Leimbach *et al*., 1984), and the extent to which plasma volume falls in response to the challenge (Davies *et al*., 1976). Both groups probably had similar hydration states and osmolality as indicated by similar baseline blood volumes and circulating levels of noradrenaline, pVP and PRA. Further, osmolality is not altered during orthostatic challenge (Davies *et al*., 1976; Davies *et al*., 1977). The reduction in plasma volume was similar between HT and LT groups (Fig. 3). Since angiotensin II can increase pVP under conditions of hypotension (Brooks *et al*., 1986), it is possible that higher angiotensin II in the HT group may be partly responsible for their greater pVP response to LBNP.

Baroreflex function may have contributed to the difference in secretion of vasopressor agents in the HT and LT groups. Stimulation of carotid baroreceptors increased pVP and renin secretion in hypotension (Schrier *et al*., 1979; Thames & Schmid, 1981; Bishop & Hasser, 1985). At peak LBNP, the elevation in heart rate in the HT subjects ($\Delta = +40 \pm 6$ bpm) was more than threefold greater than that in the LT subjects ($\Delta = +12 \pm 5$ bpm) at similar reductions in arterial blood pressures (Sather *et al*., 1986). These responses are consistent with a greater carotid–cardiac baroreflex response in the HT group (Convertino *et al*., 1990). If the carotid baroreceptors were more sensitive to hypotension in the HT group, a greater elevation in pVP and PRA would be expected in these subjects. The possible relationship between carotid baroreflex responsiveness and secretion of vasopressor agents may be a partial explanation for the consistent predictability of orthostatic tolerance by carotid–cardiac baroreflex response (Convertino *et al*., 1990; Ludwig & Convertino, 1994; Ludwig *et al*., 1998).

In the present study, subjects with relatively high orthostatic tolerance demonstrated elevations in pVP, PRA and noradrenaline associated with greater peripheral vasoconstriction during peak LBNP, whereas subjects with lower tolerance showed a trend for lower elevations in plasma noradrenaline. Since higher PRA and pVP responses were associated with greater peripheral vasoconstriction and tolerance to higher LBNP levels, our results suggest that the renin–angiotensin and vasopressin systems may contribute to sustaining arterial pressure and orthostatic tolerance by their vasoconstrictive actions. Data from this investigation suggest that vasopressin analogues devoid of anti-diuretic action, or angiotensin II may provide effective treatment for management of deficiencies in peripheral vasoconstriction.

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