Effect of standing on neurohumoral responses and plasma volume in healthy subjects

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JACOB, GIRIS, ANDREW C. ERTL, JOHN R. SHANNON, RAFFAELLO FURLAN, ROSE MARIE ROBERTSON, AND DAVID ROBERTSON. Effect of standing on neurohumoral responses and plasma volume in healthy subjects. J. Appl. Physiol. 84(3): 914–921, 1998.—Upright posture leads to rapid pooling of blood in the lower extremities and shifts plasma fluid into surrounding tissues. This results in a decrease in plasma volume (PV) and in hemocoagulation. There has been no integrative evaluation of concomitant neurohumoral and PV shifts with upright posture in normal subjects. We studied 10 healthy subjects after 3 days of stable Na⁺ and K⁺ intake. PV was assessed by the Evans blue dye method and by changes in hematocrit. Norepinephrine (NE), NE spillover, epinephrine (Epi), vasopressin, plasma renin activity, aldosterone, osmolarity, and kidney response expressed by urine osmolality and by Na⁺ and K⁺ excretion of the subjects in the supine and standing postures were all measured. We found that PV fell by 13% (375 ± 35 ml plasma) over ~14 min, after which time it remained relatively stable. There was a concomitant decrease in systolic blood pressure and an increase in heart rate that peaked at the time of maximal decrease in PV. Plasma Epi and NE increased rapidly to this point. Epi approached baseline by 20 min of standing. NE spillover increased 80% and clearance decreased 30% with 30 min of standing. The increase in plasma renin activity correlated with an increase in aldosterone. Vasopressin increased progressively, but there was no change in plasma osmolarity. The kidney response showed a significant decrease in Na⁺ and an increase in K⁺ excretion with upright posture. We conclude that a cascade of neurohumoral events occurs with upright posture, some of which particularly coincide with the decrease in PV. Plasma Epi levels may contribute to the increase in heart rate with maintained upright posture.

THE UPRIGHT POSTURE leads to rapid pooling of blood in the lower extremities, with a consequent movement of plasma water to the surrounding interstitium and microcirculation (18, 29). The intravascular shift of ~700 ml of fluid is derived from the central compartment, with 500 ml going to the lower extremities and 200 ml to the pelvic region (3). The decrease in central venous pressure reduces afferent baroreflex traffic to the brain stem (24) by unloading cardiopulmonary baroreceptors, which elicits an increase in sympathetic tone (4, 29) and subsequent increases in norepinephrine (NE). This causes a relative increase in total peripheral resistance and an increase in heart rate (HR) to blunt the potential decrease in mean arterial blood pressure (MAP) during the orthostatic stress. In addition, prolonged orthostasis activates the renin-angiotensin-aldosterone (Aldo) system (RAAS) (11) and releases epinephrine (Epi) (29) and arginine vasopressin (AVP) (31).

The net movement of fluid from the vascular compartment to the interstitial space is driven by increased hydrostatic pressure in the lower body during standing. Ten to 20 min elapse before an apparent dynamic equilibrium is attained (18). The resulting decrease in plasma volume (PV) causes hemocoagulation, including increases in hematocrit (Hct), hemoglobin (Hb), and plasma protein (PP). Changes in these components permit calculation of relative change from PV at baseline (19).

Neurohumoral systems have been widely studied; however, differences in study design, time courses, and subject population did not allow for an integrated analysis of their interrelationships (8, 23, 32), especially the relationship of PV shift to NE spillover (NSO) and clearance, Epi, RAAS, AVP, kidney response, blood pressure (BP), and HR. Furthermore, there has not been adequate attention paid to control of Na⁺ balance, which itself can significantly affect the various systems involved in volume regulation (RAAS, AVP, kidney response) and can also alter many other neurohumoral responses (28). Also, important questions remain with regard to the time course and the correlations of the magnitude of the dynamic PV changes and the amplitude of the consequent changes in neurohumoral systems and kidney responses as assessed by Na⁺ and K⁺ excretion and by urine osmolality during controlled quiet standing. Also, there has not been an integrated analysis of all these variables in a single study in the literature.

The present study was undertaken to establish in normal subjects under controlled Na⁺ intake the time course and the magnitude of the decrease in PV to assess the degree of the consequent neurohumoral counterregulators and the kidney responses during 1 h of quiet standing. The underlying hypothesis is that the magnitude of the counterregulation elicited will correlate with the physiological orthostatic hypovolemia (orthostatic PV decrease). This study might then serve as a prototype for future studies to address potential abnormalities in a well-standardized fashion in subjects with various autonomic disorders and other systemic illnesses.

METHODS

Subjects. Ten healthy subjects (8 women and 2 men) were enrolled in the study. Their mean age was 30 yr with a range of 22–46 yr. They had no history of alcohol or drug addiction

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and were within 10% of ideal body weight. After a detailed oral and written explanation of the experimental procedures, informed consent was obtained according to the Declaration of Helsinki. One week before the study, each subject underwent a physical examination, 12-lead electrocardiograph (ECG), and screening blood work evaluation. All investigative procedures were approved by the Vanderbilt Institutional Review Board.

Experimental design. Subjects were placed on a diet containing 150 meq Na\(^+\) and 70 meq K\(^+\) per day for the entire study. The diet was free of caffeine-containing beverages and was low in monoamine. No smoking or medications were allowed. After 3 days of controlled diet, the subjects were admitted for 2 nights and 2 days to the Elliot V. Newman Clinical Research Center at Vanderbilt University where confirmation of Na\(^+\) balance was achieved with urinary Na\(^+\), K\(^+\), and creatinine monitoring. After remaining supine overnight, they underwent PV determination and posture-induced dynamic changes in PV and catecholamines. The second day the humoral response [AVP, plasma renin activity (PRA), Aldo] to standing and simultaneous kidney responses were studied. The same day, systemic NSO was measured. All studies were conducted in the same quiet room, partially darkened, with an ambient temperature of 24°C, by the same investigators. The subjects sat for 30–60 s at the edge of the bed and then stood slowly to avoid transient unpleasant lightheadedness or dizziness. Once they stood (for 60 min) without any assistance, they were allowed a limited movement between the times of blood sampling. The allowed movement was limited to a 1-foot-square area on a towel placed on the floor.

PV and dynamic PV determinations. PV was determined after the subjects’ overnight supine and fasted condition with Evans blue dye (T-1824, New World Trading, DeBarry, FL) by using a modification of the technique of Campbell et al. (5) with Sephadex columns (PD-10, Pharmacia, Upplands, Sweden) used in place of hand-packed cellulose columns. An 18- or 20-gauge intravenous catheter (Flash-Cath, Baxter Healthcare, Deerfield, IL) was placed in a large antecubital vein to allow samples to be drawn without stasis. PV was determined from plasma obtained before and 10 min after injection of 2.5 meq of Evans blue dye in 2.5 ml normal saline. Total blood volume (TBV) was calculated from PV and the 10-min postinjection Hct (see below) (19). All Hct measurements were corrected for 4% trapped plasma (0.96) and for a venous-to-whole body Hct ratio of 0.91 (0.96 × 0.91 = 0.87)

\[
\text{TBV(ml)} = \frac{\text{PV(ml)} \times 100}{100 - (0.87 \times \text{Hct})}
\]

Subsequent relative dynamic percent changes (Δ) in PV were calculated from Hct from free-flowing blood samples, where Hct1 is the control and Hct2 is the test as follows (26)

\[
\text{Dynamic } \Delta \text{PV}(%) = \frac{100}{\text{Hct}_{1} - \text{Hct}_{2}} \times \frac{1}{\text{Hct}_{2}}
\]

Estimated blood volumes (BV) for each subject were calculated from the height (Ht, meters) and weight (Wt, kg) as follows (1)

\[
\text{Estimated BV(liter)} = 0.414 \times \text{Ht}^{3} + 0.0328 \times \text{Wt} - 0.03
\]

Hct was performed in quadruplicate by using microcapillary tubes centrifuged at 11,500 revolutions/min for 10 min on an International Equipment microhematocrit centrifuge (model MB, Needham Heights, MA). Values were read to 0.1% on an International Equipment microcapillary reader. Hb was measured in triplicate with an Hitachi model 100-20 spectrophotometer (Hitachi, Tokyo, Japan) by using the cyanomethemoglobin method. Total protein (TP) was measured in triplicate by refractionometry.

Supine and upright dynamic changes in catecholamines. At the times of the Hct sampling, we drew 6 ml of blood for determination of NE, Epi, dihydroxypyphenylglycol (DHPG), and dopamine (0, 2.5, 5, 7.5, 10, 15, 20, 30, 45, and 60 min of standing). The blood was collected in plastic syringes and immediately transferred to chilled, heparinized vacuum tubes and was placed on ice. The plasma was separated by refrigerated centrifugation at −4°C for 10 min at 3,000 g, stored at −70°C, and assayed within 4 wk. Analysis was performed on 1-ml aliquots of plasma. Samples were partially purified by batch alumina extraction followed by reverse-phase high-performance liquid chromatography (HPLC) for separation and electrochemical detection for quantification in a method modified from Goldstein et al. (16). Recovery through the alumina extraction is 70–75% for NE and Epi. Catecholamine concentrations in each sample were corrected for recovery of known concentration of the internal standard dihydroxybenzylamine. The limit of detection was 5–15 pg/ml for NE and Epi.

BP and HR. During the dynamic postural study BP and HR were measured with an automated sphygmomanometer (Dinamap, Critikon, Tampa, FL) on the contralateral arm immediately after each blood draw.

NSO. An antecubital vein was cannulated for drug infusion, and a contralateral antecubital vein was used for blood drawing. Systemic BP and HR were monitored by superficial four-lead ECG and plethysmographic finger probe, respectively. After complete instrumentation, the subject rested quietly for at least 30 min. \[\text{[3H]NE}\] was prepared for each subject just before use by diluting sterile pyrogen-free, [ring 2,5,6-\text{H}]NE (Dupont-NE, Boston, MA) of high specific activity (50–60 Ci/mmol) in 0.9% saline. The [\text{[3H]NE}] intravenous infusion was initiated with a loading dose of 25 μCi over 2 min, followed by a maintenance dose of 1 μCi·ml⁻¹·min⁻¹. After the initial 30 min of infusion, a steady-state concentration of plasma [\text{[3H]NE}] was achieved, and a baseline sample was drawn. The patient then stood quietly for 30 min, as blood samples were drawn in duplicate at 20 and 30 min of standing for the measurement of NE and [\text{[3H]NE}]. Because of a technical limitation, the need to achieve steady state to determine the NSO (13), we were able to learn about the late phase, but not about the early phase, of standing. The volume of blood drawn was replaced by equal amounts of saline. Three milliliters of [\text{[3H]NE}] infusate were collected and frozen at the end of each study for scintillation counting to calculate the systemic NSO and clearance. Catecholamine samples were treated as mentioned above and collected in duplicate. The amounts of [\text{[3H]NE}] in plasma and the infusate were measured in fractions of the column effluent corresponding in retention time to that of NE. The fractions were collected in scintillation vials, and the [\text{[3H]NE}] was assayed by liquid scintillation counting (LS 6000IC, Beckman Instruments, Fullerton, CA). Radioactivity (disintegrations/min (dpm)) was adjusted for background, and for the injected volume of the extracted plasma to the HPLC (75 μl from 100 μl) and for recovery through the alumina extraction step.

Whole body NE plasma clearance (systemic clearance) was determined as follows

\[
\text{Systemic clearance } = \frac{\text{[3H]NE infusion rate (dpm)}}{\text{Plasma [3H]NE (dpm/ml)}}
\]
The rate at which NE appears in plasma (systemic spillover) was determined as follows

Systemic spillover (µg/min) = systemic clearance (l/min) \times \text{plasma NE concentration (µg/l)}

PRA, Aldo, and AVP. PRA, Aldo, and AVP were assessed after the subjects rested overnight in the supine position and after they stood for 15 and 30 min. PRA was assayed by conversion of angiotensinogen to angiotensin I and expressed as nanograms of angiotensin I produced per milliliter per hour. Plasma Aldo was measured by radioimmunoassay (Coat-a-Count Diagnostic Products, Los Angeles, CA). For AVP, blood was collected in EDTA-containing tubes, and radioimmunoassay was used.

Kidney response. A 24-h urine was collected for Na\(^+\) and K\(^+\) measurement on the fourth day while subjects were in metabolic balance. Two hours before the postural study, an indwelling Foley catheter was placed in each subject. Urine was sampled every 30 min beginning 30 min before the subjects stood and for the next hour of standing. Na\(^+\) and K\(^+\) concentrations were determined by ion-selective flame photometer electrodes (model IL 943, Instrumentation Laboratories, Lexington, MA) on a fresh sample.

Statistical analysis. Results are presented as means ± SE and as confidence intervals (CI). The level selected for statistical significance was set at P < 0.05. A one-way analysis of variance (ANOVA) for repeated measurements was used to assess the effect of standing time on the different variables. Nonlinear regression analysis was used to assess dynamic changes in PV and the corresponding changes in NE. A correlation analysis between simultaneous changes in NE and dizziness at the first minute of standing in some subjects was performed. Paired or nonpaired t-tests were used to compare between single points. Data were analyzed with Quattro Pro (Borland International) and GraphPad Prism (GraphPad Software, version 2.0, Oct. 1995).

RESULTS

BV. The mean measured TBV of 4,080 ± 240 ml (CI 3,520–4,640 ml) was not statistically different from the estimated calculated TBV of 4,140 ± 210 ml (CI 3,650–4,620). The difference between predicted and calculated TBV was −1 ± 4% (CI −10 to +8%). Similarly, the PV and TBV per kilogram body weight were not significantly different from predicted values of 42 ± 2 ml/kg (CI 37–47 ml/kg) and 63 ± 3 ml/kg (CI 56–67 ml/kg), respectively.

Dynamic PV changes. All subjects tolerated standing without adverse reactions except mild lightheadedness and dizziness at the first minute of standing in some subjects. All measured variables (Hct, TP, and Hb) were linearly correlated to each other (r = 0.92–0.98) in the single experiments. The mean PV changes (calculated from the changes in the Hct) are depicted in Fig. 1B. These dynamic changes in PV fitted with exponential decay curves (r = 0.98 and P < 0.001) allowed calculation of t\(_{1/2}\) and plateau time (t\(_{1/2}\) = 0.69/k; plateau time = 5 × t\(_{1/2}\)). The mean decrease in PV with standing was 13% and reached a relative plateau after 14 min (t\(_{1/2}\) = 2.8 min). A further nonsignificant decrease in PV occurred during the subsequent 45 min of standing. The mean absolute decrease in effective circulating PV was 375 ± 35 ml (CI 290–445 ml).

Catecholamines and their dynamic change. The mean overnight supine NE was 195 ± 20 pg/ml (CI 150–241 pg/ml) and on standing increased significantly until it reached near-plateau levels of 590 ± 86 pg/ml (CI 400–790 pg/ml) after 7.5 min (t\(_{1/2}\) = 1.5 min). Further slow increases were not statistically significant (Fig. 1D). The mean supine Epi was 23 ± 4 pg/ml (CI 14–33 pg/ml) and after 8–10 min of standing attained the maximal level of 69 ± 12 pg/ml (CI 40–115 pg/ml) before declining almost to baseline value 35 ± 6 pg/ml (Fig. 1C). The mean supine DHPG was 1,100 ± 80 pg/ml (CI 940–1,290 pg/ml) and continued to rise in parallel with the NE with the same t\(_{1/2}\) of 1.5 min (Fig. 1E). There was also a significant positive correlation between the AUC of the postural dynamic changes in PV and the AUC of the parallel changes in NE (r = 0.68, P < 0.04). Also, there was a strong positive correlation between the means of NE and DHPG (r = 0.88, P < 0.006). Epi correlated with the change of PV only during the first 7.5 min of standing (r = 0.5, P < 0.03).

Systemic NE kinetics. The mean supine NSO and supine clearance were 1.8 ± 0.3 µg/min and 6.8 ± 0.9 l/min, respectively (CI 1–2.5 µg/min and 4.8–9 l/min, respectively). During upright posture the increase in NSO was associated with a parallel decrease in clearance. These changes were 80% and −30%, respectively, after 30 min in the upright posture (1-way ANOVA, P < 0.01; Fig. 1F).

Hormonal responses. The activation of RAAS occurred gradually (Fig. 2, B and C); PRA increased about threefold after 30 min of quiet standing from 0.7 ± 0.08 to 2 ± 0.3 ng·ml\(^{-1}\)·h\(^{-1}\). Simultaneously, Aldo increased in parallel fashion from 10 ± 2.5 to 32 ± 5 after 30 min of standing. Plasma levels of AVP increased gradually even though the plasma osmolality remained unchanged (Fig. 2A). Supine AVP and plasma osmolality were 1.0 ± 0.07 pg/ml and 290 ± 2.5 mosmol/l, respectively. Meanwhile, during quiet standing, AVP increased about threefold (3.2 ± 0.7 pg/ml) with a nonsignificant change in plasma osmolality (290 ± 2 to 292 ± 2 mosmol/l; Fig. 2D).

Kidney excretory patterns. After 3 days of controlled diet, the mean total 24-h Na\(^+\) and K\(^+\) excretion were 142 and 58 meq, respectively. During the last 0.5 h of supine posture the mean Na\(^+\) and K\(^+\) excretion were 1.6 ± 0.1 and 0.6 mmol, respectively. After 0.5 and 1 h of standing, the total amounts of Na\(^+\) and K\(^+\) excreted were 1 ± 0.2 mmol and 0.54 ± 0.1 mmol for Na\(^+\) and 0.73 ± 0.1 mmol and 0.75 ± 0.09 mmol for K\(^+\), respectively (Fig. 2, E and F). Thus the Na\(^+\) excretion decreased by 40% after 30 min standing and 63% after 1 h standing. Urine osmolality increased from 584 ± 50 mosmol/kg H\(_2\)O supine to 743 ± 40 mosmol/kg H\(_2\)O after 1 h in the upright posture (ANOVA, P < 0.01; Fig. 2G).

BP and HR. Supine systolic BP (SBP), diastolic BP (DBP), MAP and HR were 108 ± 2 mmHg, 63 ± 2 mmHg, 78 ± 2 mmHg, and 66 ± 2 beats/min, respectively. With standing, SBP decreased significantly by
7.5 min of quiet standing (in parallel to the increase of Epi, as shown in Fig. 1, A and C) and then increased gradually until almost reaching supine values. Immediately on the assumption of the upright posture by the subjects, DBP increased 5 ± 3 mmHg (P = 0.04) and was maintained. Hence, MAP was maintained or increased with standing. The mean HR increase was 15 ± 3 beats/min and remained almost constant during the 1 h of standing (Fig. 1A). There was a significant positive correlation between HR and plasma levels of Epi in the first 7.5 min of standing (r = 0.55, P < 0.03). After 45 min of quiet standing by the subjects, SBP, DBP, MAP, and HR showed further increases to 109 ± 3 mmHg, 74 ± 4 mmHg, 88 ± 4 mmHg, and 88 ± 5 beats/min, respectively (in parallel to the NE values).

Interaction between PV changes and the neurohumoral response. To test our hypotheses, we examined correlations between the changes in PV with standing and neurohumoral responses. As depicted in Table 1, the changes in PV during quiet orthostatic stress correlate significantly with the magnitude of the plasma NE increase and plasma Epi (during the first 7.5 min of standing), but no significant correlation was found between the changes in dynamic orthostatic PV and NSO (r = 0.38, P = 0.1). Furthermore, the increase in plasma AVP was related to the changes in PV but not with plasma osmolarity, which remains unchanged. Also, the kidney excretory pattern of K+ correlates significantly with the amount of increase of plasma Aldo, and, finally, the urine osmolality correlates significantly with the plasma levels of AVP.

**DISCUSSION**

After 3 days of controlled Na+ intake by the subjects, our main findings are as follows: 1) normal subjects in well-controlled Na+ balance during quiet standing decrease their PV (physiological orthostatic hypovolemia)
~13%, reaching a plateau after 14 min; 2) the neurohumoral response during standing is to some extent related to the extent of the physiological orthostatic hypovolemia, and PV correlates with the increase in plasma NE, Epi, and antidiuretic hormone but not with PRA; 3) the kidney excretory response to orthostatic stress is consistent with mediation by Aldo and antidiuretic hormone; and, finally, 4) as expected, plasma NE correlates with its main neuronal metabolite DHPG, and PRA correlates with plasma levels of Aldo.

Maintenance of appropriate blood flow to critical organs on assumption of upright posture is a major...
important modulator of HR change in the first few minutes of standing. In Fig. 1, it can be seen that there is a rapid loss of PV from the vasculature on assumption of upright posture. This adjustment occurs over a period of 14 min. Both plasma Epi and HR increase, reaching maxima at approximately the time the major shift in PV from the vasculature has occurred. The SBP in the upright posture reaches a nadir soon after the HR and plasma Epi peak.

The pattern of Epi levels over the 60 min of observation with the subjects in the upright posture deserves special attention. It is recognized that Epi can exert significant effects, particularly on \(\alpha_2\) and \(\beta_2\)-adrenoreceptors (humoral receptors) in the circulation, while also having effects on \(\alpha_1\) and \(\beta_1\)-adrenoreceptors (neuronal receptors) (20). The correlation between the HR and Epi level appears to be closer than that between HR and any other variable assessed in this study. One possible explanation for this is that Epi is a more important modulator of HR change in the first few minutes of standing than has previously been appreciated. Because hemorrhage in experimental animals and human subjects is such a potent stimulus for adrenomedullary secretion, it is possible that the dynamic orthostatic PV reduction in these subjects was eliciting the Epi response. After 15 min, however, the Epi level had returned toward baseline. By this time, AVP, PRA, and Aldo were all rising significantly and the compensatory effects of these hormones may be responsible for the gradual rise in SBP that occurs during the last 45 min of the 1-h period of standing. Of all the variables assessed in this study, only Epi appeared to return to near baseline, as standing continued.

Analysis of the role of NE in homeostatic adjustment is more complex than that of Epi because the plasma NE level represents spillover of the neurotransmitter from the synaptic cleft (21). It is likely that significant increments in NE concentration in the synaptic cleft occur rapidly, whereas washout of the NE into the plasma occurs with a much slower time frame. For this reason, it is especially valuable to use the concepts of spillover and clearance of NE to better interpret events occurring in the synaptic cleft. In our subjects, the plasma NE on standing showed the expected doubling after 20 min and remained unchanged at 30 min. The phase of most rapid rise in plasma NE corresponded to the period of the greatest loss of PV. This is clearly a large increase in sympathetic nervous system activation, possibly enhanced by the actions of the adrenomedullary-derived Epi on the presynaptic \(\beta_2\)-adrenoreceptors on noradrenergic neurons (22). However, not all the increase in plasma NE can be accounted for by spillover increases with upright posture. Along with the 80% increase in PRA, there was a 30% decrease in NE clearance after 30 min of standing (9). Thus the increased absolute NE level observed represented the combined effect of increased neurotransmitter spillover and reduced neurotransmitter clearance. Also, the strong correlation between DHPG (the neuronal NE metabolite) and NE suggests that the main source of NE in the plasma is more from spillover than from clearance.

It might be expected that a rise in PRA would be translated into a concomitant increase in plasma Aldo, and that is what was observed in our subjects (2). As expected, urinary Na\(^+\) and Aldo did not correlate significantly. This could be explained by the fact that multiple factors affect the renal Na\(^+\) excretion. During orthostatic stress, glomerular filtration rate (GFR) and atrial natriuretic factor are reduced, but, on the other hand, Aldo, renal sympathetic activity and consequently PRA and angiotensin II are increased. The net outcome of these neurohumoral events is the decrease in Na\(^+\) tubular excretion to maintain acceptable effective circulating BV during the orthostatic stress.

Any increase in angiotensin II levels resulting from the rise in PRA and Aldo release could exert numerous effects to maintain posture: increasing tubular Na\(^+\) reabsorption at the level of the kidney (7), direct vasoconstriction at the level of the vascular smooth muscle, and enhancement of NE release by actions on

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<td>(\text{Epi}<em>{7.5\text{min}}) vs. (\text{HR}</em>{7.5\text{min}})</td>
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PV, plasma volume; AUC, area under the curve; Epi, epinephrine; PRA, plasma renin activity; ADH, antidiuretic hormone; NE, norepinephrine; NSO, NE spillover; DHPG, dihydroxyphenylglycol; Aldo, aldosterone; HR, heart rate; U, urinary; \([K^+]\), potassium concentration; \([Na^+]\), sodium concentration; 7.5 min, first 7.5 min of standing; NS, not significant.
the presynaptic noradrenergic neurons (6) and possibly also at the level of the central nervous system (24). Aldo plays a major role in K⁺ homeostasis. It has been shown that Aldo has an early action that is not mediated by adenosinetriphosphatase-pump synthesis. This might explain the significant correlation between Aldo and urinary K⁺ excretion, but, because of the multiple factors affecting GFR, it may not explain the correlation between Aldo and urinary Na⁺ excretion.

The plasma AVP level rose with a time course similar to that of PRA, but significant changes in plasma osmolality were not observed. It is likely that the dynamic orthostatic BV reduction contributed to this response. It has been reported in animals and in humans that secretion of AVP is modulated not only by changes in plasma osmolality but also by changes in BV through baroreflex activation. We found a correlation between PV changes and AVP plasma levels that suggests the power of the volume in the modulation of the AVP secretion (15, 26). Also, there was a correlation between AVP and urinary osmolality, which is the main factor that determines urine concentration to save water on the assumption of the upright posture. The possibility that the raised AVP level during standing may have actions to vasoconstrict the vasculature or act through the area postrema of the brain stem to alter baroreflex function must be considered (2, 24). Within the framework of our investigation, definitive conclusions on this point cannot be made. There is considerable evidence from animal and human studies that increases in circulating vasopressin can enhance baroreflex function (10, 24).

In summary, this report highlights the importance of events between 1 and 10 min after the assumption by the subjects of the upright posture in the pattern of BP and HR changes observed. In particular, the rapid fall in PV and the rapid increase in plasma Epi over this time frame may have a hemodynamic importance that has heretofore been neglected.

This work was supported in part by National Institutes of Health Grants PO1 HL-56693, RR-00095, and NS-33460 and by National Aeronautics and Space Administration Grants NAG9-563, NAGW 3873. G. Jacob was the recipient of a Merck International Fellowship in Clinical Pharmacology. Present address of G. J. Jacob: Rambam Medical Center, Recanati Autonomic Dysfunction Center, Haifa, Israel 31096.

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