The response of arginine vasopressin and plasma renin to postural change in normal man, with observations on syncope

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Summary

1. Fourteen mildly hydropenic normal volunteers were slowly tilted at a constant rate from the horizontal to the 85° head-up position in order to study the interrelationship between plasma arginine vasopressin concentration, plasma renin activity and the change of plasma volume.

2. Nine subjects did not develop vaso-vagal symptoms and were studied for 45-60 min. Arginine vasopressin rose biphasically in all subjects: a small initial rise, which was seen at 3 min and persisted for 30 min, was followed by a striking rise between 30 and 45 min, when the fall of plasma volume had reached its maximum (17%).

3. Plasma renin activity reached a maximum at 30 min but fell by 45 min, as plasma concentration of arginine vasopressin rose.

4. Five subjects developed vaso-vagal symptoms 4-24 min after reaching 85° when the study was terminated. A striking increase of arginine vasopressin concentration was seen within 4 min of syncope, but there was no change of plasma osmolality, cortisol concentration or renin activity.

Key words: plasma volume, posture, renin, syncope, tilt, vasopressin.

Introduction

The mechanisms for preserving plasma volume during orthostasis are necessarily highly developed in man. The circulatory responses to the upright posture have been well documented (McMichael & Sharpey-Schafer, 1944; Tuckman & Shillingford, 1966) but less is known about the changes and interrelationship between the two major hormonal mechanisms concerned with the homeostasis of salt and water, namely the renin-aldosterone system and vasopressin. The object of our study was to relate orthostatic changes of plasma renin activity and plasma arginine vasopressin concentration both to each other and to the fall of plasma volume.

Despite attempts to minimize the incidence of syncope, a well-known hazard of head-up tilt (Brigden, Howarth & Sharpey-Schafer, 1950), we are able to report metabolic and hormonal changes occurring within 4 min of syncope in five normal young people.

Some of the data described in this paper were presented at the Society for Endocrinology, November 1974 (Davies & Forsling, 1975).

Materials and methods

Ten normal men and four normal women (aged 22-26 years) were studied at 10.00 hours. They were not receiving any medication and had been asked to abstain from drink and food for 12 h. The subjects wore light indoor clothing and the ambient temperature was maintained at 15-18°C. After 90 min of supine rest, the subjects were tilted to an angle of 85° on an electrically operated tilt bed (model 83000, Nesbit-Evans, Wednesbury, Staffs, U.K.) at a constant rate over 90 s. Each subject was familiarized with the procedure by a
preliminary 'dummy run'. No restraining straps were used and the subjects were encouraged to make such use of their antigravity muscles as to be consistent with comfort. An 18G cannula (Argyle, Medicut) was inserted into a left antecubital fossa vein at the beginning of the rest period. During blood sampling the subjects were made to avert their gaze. Blood was collected without stasis and samples for plasma renin activity and arginine vasopressin determination were taken into heparinized tubes and cooled at once to 4°C. The plasma was separated within 5 min and stored at -20°C. Blood sampling and arterial pressure determination were carried out with the arm at the level of the heart. Plasma renin activity was determined by radioimmunoassay (Ménard & Catt, 1972) of angiotensin I generated by incubation for 3 h at pH 5.5 in the presence of EDTA and 8-hydroxyquinoline. Arginine vasopressin was measured by bioassay in ethanol-anaesthetized, water-loaded rats, after extraction from plasma (Forsling, Jones & Lee, 1968; Forsling, 1974). Osmolality was measured by a freezing-point depression method (Osmometer model 3L, Advanced Instruments Inc., Massachusetts, U.S.A.). Peripheral venous packed cell volume was estimated from the haemoglobin concentration and mean corpuscular volume (Coulter-S model 1034, Coulter Electronics Ltd).

Results are expressed as the mean \( \pm \) SEM and analysed by Student's \( t \)-test for paired data, unless otherwise specified.

Results
Nine subjects did not develop vaso-vagal symptoms; four of them were studied for 45 min and five for 60 min. Five subjects developed presyncopal symptoms or actual syncope when the tilt was immediately terminated.

Subjects without syncope

Heart rate and arterial pressure. The heart rate rose from a mean supine value of 64 beats/min \( \pm 3 \) to 85 \( \pm 3 \) \( (P<0.001, t = 5.45, n = 9) \) within 2 min of reaching 85° and the increased rate was sustained throughout the study.

The arterial pressure stabilized within 4 min. The systolic pressure did not change significantly: e.g. the mean supine value was 109 mmHg \( \pm 6 \) and the value at 10 min was 109 \( \pm 3 \). Diastolic pressure rose consistently and significantly from a mean supine value of 71 \( \pm 7 \) to 83 \( \pm 3 \) \( (P<0.001, t = 3.9, n = 9) \). The systolic and diastolic pressures remained unchanged thereafter.

Change of plasma volume. The change of plasma volume was measured indirectly from the change of the peripheral venous packed cell volume in seven subjects according to the following formula:

\[
P = \frac{100}{100 - H_1} \times \frac{100(H_2 - H_1)}{H_2}
\]

where \( P = \% \) fall in plasma volume, \( H_1 = \) the initial, and \( H_2 = \) the final, packed cell volumes (modified from LeQuesne, Hobsley & Hand, 1960). The mean packed cell volumes were: supine, 41.0\% \( \pm \) 0.4; 15 min, 44.7\% \( \pm \) 0.5; 30 min, 45.5\% \( \pm \) 1.2; 45 min, 45.5\% \( \pm \) 1.3. From the formula above, the mean reduction of plasma volume was 13.9\% \( \pm \) 2.5, 16.6\% \( \pm \) 2.1 and 16.8\% \( \pm \) 1.5 at 15, 30 and 45 min respectively (Fig. 1c). The fall of plasma volume between 15 and 30 min was small but an increase of packed cell volume was observed in six of the seven subjects. However, the variance of the response was considerable so that the mean values are not significant when Student's \( t \)-test is applied, although it becomes significant \( (t = 2.7, P<0.025) \) when the single anomalous subject is omitted. With the \( \chi^2 \) distribution test, the difference between 15 and 30 min is significant at the 5\% level \( (\chi^2 = 14.09) \) when all the data are analysed.

Arginine vasopressin. The changes of plasma arginine vasopressin concentration are shown in Table 1 and summarized in Fig. 1(a). The mean arginine vasopressin concentration rose slightly within 3 min of reaching 85° from 0.97 \( \mu \)unit/ml \( \pm 0.2 \) to 1.9 \( \mu \)units/ml \( \pm 0.3 \). This only just reached significance at the 5\% level \( (P<0.05, t = 2.23, \)
Vasopressin and renin in tilt and syncope

FIG. 1. (a) Plasma arginine vasopressin (AVP) concentration, (b) plasma renin activity (PRA), and (c) the change of plasma volume after an 85° head-up tilt (7) in normal people. Note that between 30 and 45 min there is a considerable rise of arginine vasopressin concentration but a fall of plasma renin activity at a time when the plasma volume has reached its minimum. Mean values ± SEM are shown.

Plasma renin activity. The changes are summarized in Fig. 1(b). The mean supine value was 1.96 pmol h⁻¹ ml⁻¹ ± 0.12, and this rose to 3.14 pmol h⁻¹ ml⁻¹ ± 0.16 at 15 min and 3.33 pmol h⁻¹ ml⁻¹ ± 0.12 at 30 min. The values at 15 and 30 min were both very highly significantly greater than the supine value (t = 13.8 and 15.8 respectively, P < 0.001 for each). In eight of the nine subjects, renin activity fell between 30 and 45 min to a mean value of 2.89 pmol h⁻¹ ml⁻¹ ± 0.08, and this fall was significant (t = 5.5, 0.01 < P < 0.0125).

Plasma osmolality. Osmolality was measured in six of the subjects in whom arginine vasopressin had been determined and it remained unchanged; the mean supine value was 282 mosmol/l ± 2 and subsequent values at 15, 30 and 45 min were 281 ± 2, 281 ± 3 and 282 ± 2 respectively. These values are similar to those observed after 12–18 h of strict fluid deprivation in normal people, in another study from this group (Khokhar & Slater, 1976).

Plasma cortisol concentration. Cortisol was estimated in five subjects as a measure of possible

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<td>Mean ± SEM</td>
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Table 1. Plasma arginine vasopressin concentrations in subjects tilted for 45–60 min
Changes in adrenocorticotropic hormone. The mean supine value was 353 ± 76 mmol/l and subsequent values at 15, 30 and 45 min were 356 ± 78, 317 ± 69 and 320 ± 64 respectively. None of these values was significantly different from the others.

Subjects with syncope

Two subjects lost consciousness and three developed presyncopal symptoms necessitating termination of the study.

These episodes were accompanied by yawning, deep respiration, skin pallor and sweating. Syncopal signs developed 4-24 min after reaching 85°. The heart rate fell precipitously from 80-100 beats/min to 40-50 beats/min. When signs of impending syncope appeared the subjects were laid flat and the 'post-syncopal' blood samples were taken within 4 min when bradycardia was still present. Sufficient blood was available for the measurement of arginine vasopressin in five subjects and for the measurement of cortisol and plasma renin activity in three subjects. Arginine vasopressin rose dramatically after syncope; the mean supine concentration was 1.1 ± 0.1 μunits/ml, and the value 3 min after reaching 85° was 1.6 ± 0.5 (for subjects without syncope; supine and 3 min values were 0.97 ± 2 and 1.9 ± 0.3 respectively). After syncope the mean concentration of arginine vasopressin was 10.9 ± 1.8 μunits/ml. A five- to eight-fold rise was seen in each of the five subjects (Fig. 2). The mean value observed after syncope was very highly significantly greater than any of the mean values up to 30 min seen in those without syncope (P < 0.001, t = 5.31 to 5.99 at 3, 7, 15 and 30 min). Even when compared with the 45 min value in those without syncope, the value was highly significantly greater (P < 0.01, t = 3.39).

After syncope the plasma cortisol concentrations in the three subjects were 309, 408 and 215 mmol/l, which are not different from the supine values of 320, 340 and 232 mmol/l respectively. Plasma renin activity values after syncope were 2.76, 3.25 and 2.06 pmol h⁻¹ ml⁻¹ and did not differ from the expected values, relative to the time of syncope after reaching 85°, when compared with the values observed in non-syncopal subjects at a comparable interval after assuming the upright posture.

Discussion

Subjects without syncope

Changes of heart rate, arterial pressure and plasma volume. In this study we have minimized the use of invasive techniques, which, by causing discomfort and stress, might otherwise influence plasma renin activity and the plasma concentration of arginine

![Figure 2](image-url)
vasopressin and cortisol. The haemodynamic changes we have observed, as assessed by the change of heart rate and of arterial pressure, are very similar to those recorded in studies in which stroke volume and/or cardiac output were measured (McMichael & Sharpey-Schafer, 1944; Tuckman & Shillingford, 1966). Although different angles of tilt were used in these studies, the hydrostatic effect of tilt to angles of 60° or more is, for all practical purposes, the same as the effect of the erect position (Gauer & Thron, 1965).

In addition to the immediate effects of venous pooling, there is a gradual fall of plasma volume due to loss of protein-free fluid through dependent vascular beds. We have been impressed by the size of this loss, which occurred consistently in all our subjects. The fall of plasma volume is rapid initially and reaches a maximum of about 17% by 30 min. This confirms earlier studies (Thompson, Thompson & Daily, 1928; Waterfield, 1931a, b; Nielson & Møller, 1968). As indicated below, the careful delineation of the size and time-course of the fall of plasma volume may be critical for the release of vasopressin.

Changes of arginine vasopressin concentration and of plasma renin activity. We have demonstrated significant increases in concentration of arginine vasopressin after postural change. This rise appears to take place in two phases: there is an initial very small increase amounting to 1-6-1.9 times the supine value, which occurs within 3-7 min of reaching 85°. However, at 30-45 min, there is a striking rise to 3-15 times the supine value. This rise occurs at a time when heart rate and arterial pressure are constant, but it coincides with the maximum fall of plasma volume. Although the change of plasma volume between 15 and 30 min is small, we suggest that the fall of plasma volume may reach a critical value and trigger the second phase of the response of arginine vasopressin. Blood volume change provoked by haemorrhage is well known to lead to release of arginine vasopressin in animals (Weinstein, Berne & Sachs, 1960; Share, 1961; Gauer, Henry & Behn, 1970; Claybaugh & Share, 1973). Gauer et al. (1970) have reported a similar biphasic response after controlled haemorrhage in dogs; the initial increase of arginine vasopressin was small when up to 10% of the blood volume was removed, but beyond this critical point further bleeding provoked a striking rise in arginine vasopressin.

Studies of the effect of real (e.g. haemorrhage) or apparent (e.g. tilt) fall in blood volume in man are conflicting. Segar & Moore (1968), using a bioassay in mildly hydropenic normal volunteers (U/P osmolar ratio 1.9-3.7) reported mean plasma arginine vasopressin concentrations of 0.4, 1.4 and 3.1 μunits/ml in the lying, sitting and standing positions respectively. In addition, they reported a threefold rise in arginine vasopressin in normal subjects after vasodilatation induced by warmth. This group also reported similar results with centrifugation (Rogge, Moore, Segar & Pasola, 1967) and with application of negative pressure to the lower portion of the body in normal man (Rogge & Moore, 1968). In contrast Norton, Padfield & Forsling (1975), using a radioimmunoassay for arginine vasopressin, were unable to demonstrate any rise after the non-hypotensive haemorrhage over 10 min, nor after tilting to 85°. Furthermore Share, Claybaugh, Hatch, Johnson, Lee, Muirhead & Shaw (1972), Beardwell, Geelen, Palmer, Roberts & Salomonson (1975) and Kimura, Minai, Matsui, Mouri, Sato, Yoshinaga & Hoshi (1976) were all unable to demonstrate a rise of plasma arginine vasopressin concentration on standing. From our data and from those of Robertson (1974), who describes a small but significant fall of arginine vasopressin concentration when hydropenic people lie down but not when normally hydrated people do so, we suggest that the differences can be explained by differences of the state of hydration, the extent to which plasma volume falls and the timing of blood samples. Morton et al. (1975), Beardwell et al. (1975) and Kimura et al. (1976) used water-loaded or normally hydrated subjects. Share et al. (1972) did not sample until 4 h in ambulant subjects, and the fall of plasma volume described by Kimura et al. was only just over half that seen in the present study.

We suggest that the increase of plasma arginine vasopressin concentration is due to the isosmotic fall of plasma volume but it is possible that emotional factors may be relevant (Verney, 1947). However, we minimized discomfort and anxiety, the response at 30-45 min was consistent both in its extent and timing and there was no change in plasma cortisol concentration.

Renin release after postural change has been extensively studied in man, and in these studies there is considerable variation both in the magnitude of the change of renin activity or renin concentration in
response to orthostasis and in the variance of the change (Cohen, Rovner, Conn & Blough, 1964; Brown, Davis, Lever, MacPherson & Robertson, 1966; Nielsen & Møller, 1968; Molzahn, Dissman, Halim, Lohmann & Oelkers, 1972). The change varied from 5 to 500% above the recumbent value and this probably reflects different experimental protocols and different assay methods. In the present study we have shown that it is possible to reduce greatly this variability of response. For example, when the response was at its maximum at 30 min, the range of response was modest, from 46 to 118%.

From our results it is both clear and noteworthy that after 30 min of orthostasis plasma renin activity began to fall, an observation we have made in two previous studies (Davies, Payne & Slater, 1975; Khokhar, Slater, Jowett & Payne, 1976). The fall between 30 and 45 min is significant statistically and it occurred in all except one subject and at a time when haemodynamic factors were stable and when the fall of plasma volume had reached a maximum. Consideration of current physiological concepts is unfruitful but a possible explanation is that this fall of plasma renin activity resulted from the rapidly rising concentration of circulating arginine vasopressin which we observed between 30 and 45 min. In experimental animals infusions of arginine vasopressin in physiological amounts inhibit renin release (Bunag, Page & McCubbin, 1967), and in humans Khokhar, Slater, Forsling & Payne (1976) reported an inverse relationship between plasma renin activity and arginine vasopressin during very low rates of infusion of the latter to achieve concentrations within the physiological range.

In this study we have interpreted the rise of renin activity and arginine vasopressin after postural change as indicating an increase in the rate of secretion rather than a fall in clearance of these hormones. Certainly in dogs, hepatic extraction of renin is not diminished even by severe haemorrhage (Schneider, Johnson, Davis & Baumber, 1971), nor by an 80° tilt in man (Kotot, Kuska & Czekala, 1968). Furthermore, Culbertson, Wilkins, Ingelfinger & Bradley (1951) demonstrated that hepatic blood flow falls only in very severe circulatory embarrassment. Arginine vasopressin is cleared largely by the kidneys (Lauson, 1974) and postural change undoubtedly affects renal function; for example, Brun, Knudsen & Raaschou (1945) found a 20–25% fall of glomerular filtration rate in normal volunteers on 60° head-up tilt. Detailed studies of the effect of changes in renal function upon clearance of arginine vasopressin are lacking, but recent work in this laboratory (Khokhar & Slater, 1976) has shown a twofold increase in urinary arginine vasopressin in normal subjects tilted to 45°, a rise similar to that we have observed in plasma arginine vasopressin, suggesting that there is no change in the handling of the compound by the kidney after tilt. A minor increase of plasma protein concentration may contribute to the rise of plasma renin activity on tilt to a small extent, but the plasma protein concentration determined in five subjects, supine and at 30 min, increased only by a mean value of 17%, whereas the corresponding mean increase of renin activity was 73%.

Subjects with syncope

The symptoms experienced by our subjects and the accompanying signs corresponded closely with those described by Lewis (1932). Such attacks are a well-known hazard of tilting (McMichael & Sharpey-Schafer, 1944) and of venesection (Poles & Boycott, 1942). Brun et al. (1946) first reported an initial period of oliguria after syncope, after which a diuresis supervened, an observation commented upon earlier by Lewis (1932). Noble & Taylor (1953) subsequently reported the presence of an antidiuretic substance in the urine of subjects who had experienced vaso-vagal attack 2 h earlier, but they were unable to make any direct measurements of arginine vasopressin. In this study we have observed a striking rise in plasma arginine vasopressin concentration within 2–4 min of syncope.

Tilt mimics non-hypotensive haemorrhage and the incidence of syncope after such haemorrhage is proportional to the amount of blood removed. For example, Poles & Boycott (1942) found an incidence of 3.8% in blood donors who had lost 440 ml of blood, whereas the incidence of syncope was 8.5% when 540 ml of blood was removed.

To compensate for real or apparent fall of blood volume, vasoconstriction occurs to reduce the size of the vascular compartment. Occasionally, this compensatory mechanism fails and vasodilatation, particularly of muscle arterioles, occurs (Brigden et al., 1950), leading to a sudden increase of vascular capacity. This leads to a sharp hypovolaemic but isometric stimulus to release of arginine vasopressin. The exact trigger to this release in these circum-
stances is uncertain; it may be via intrathoracic volume receptors (Henry, Gauer & Reeves, 1956), or arterial baroreceptors (Robertson, Mahr, Athar & Sinha, 1973) or, alternatively, it may be a consequence of a brief period of hypoxia. Certainly, acute hypoxia can lead to an antidiuresis in conscious man (Granberg, 1962) and to vasopressin release in the sheep (Alexander, Forsling, Martin, Nixon, Ratcliffe, Redstone & Tunbridge, 1972).

Whatever the exact nature of the final stimulus for release of arginine vasopressin it may be specific to the syncopal response rather than a non-specific response to stress. Thus, in those subjects in whom measurements were possible, both plasma cortisol concentration and renin activity did not increase. It is possible, however, that the time course of release of renin and adrenocorticotropic hormone differs from that of arginine vasopressin. Nonetheless, the increase of plasma arginine vasopressin concentration within 4 min of syncope is striking and hitherto unrecorded. It seems to underline the sensitivity of the mechanisms for the preservation of the circulating volume which appear so well developed in man, as opposed to other animals. The upright posture is, after all, a specifically human attribute.

Acknowledgments

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