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Extracellular fluid volume expansion in patients with posturally related syncope

Introduction

This review will focus on the management of patients with orthostatic disorders by chronic expansion of the extracellular fluid volume. Studies in two main groups of patients will be discussed. First, we will consider effects in patients with chronic primary autonomic failure, who have structural disorders with permanent failure of circulatory control and severe symptomatic orthostatic hypotension. The majority of reports of this rare disorder refer to fewer than 10 patients studied. However, by careful evaluation of this small number of patients, valuable information has been obtained about the pathophysiology of orthostatic dysregulation and its treatment [1, 2].

Management strategies developed in patients with primary autonomic failure have been important for the second group of patients that we will discuss, i. e., patients with functional disorders with occasional failure of orthostatic blood pressure control and episodic posturally related syncope. In contrast to chronic primary autonomic failure this condition is very common [3]. It includes disorders like vasovagal fainting, situational syncope, and postural tachycardia. The first section of this review is concerned with the shifts in extracellular volume induced by orthostatic stress, the second section with sodium intake and orthostatic tolerance, and the remaining sections with the effects of exercise training and the effects of head-up tilt sleeping.

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Shifts in extracellular volume induced by orthostatic stress

The extracellular volume accounts for about 20 % of the body weight of an adult human, and includes both the circulating blood plasma and the interstitial fluid in the spaces between the cells. The extracellular fluid is in constant flux throughout the body. Plasma is transported by the blood and mixed with the tissue fluids by diffusion through the capillary walls. However, the hydraulic conductivity of the interstitium is very low due to its gel-like state and it does not behave as a continuous fluid column. Volume partitioning between the plasma volume and the interstitium fluid volume is complex and influenced by local mechanisms that oppose volume changes [4]. Maintenance of the plasma volume and the effective circulating blood volume, which is essential for tissue perfusion, is closely related to the regulation of sodium balance [5, 6].

The change from supine to the erect posture results in a decrease in the effective circulating blood volume and in important schifts of the extracellular fluid volume. One half to one liter of blood contained in the thorax is transferred rapidly to the legs and abdomen. In addition to this rapid downward transfer, the blood volume also decreases due to increased transcapillary filtration of fluid into the interstitial spaces in the dependent parts. This filtration is the effect of a high intracapillary pressure with little interstitial counterpressure on the Starling forces for filtration, and can result in significant hemoconcentration and reduced

plasma volume. Plasma volume decreases by about 10 % (500 ml) after 5 min and by 15–20 % (750 ml) after standing 10 min [7, 8]. Frank edema during prolonged standing is prevented by arterial vasoconstriction and a reduced capillary surface area, by colloid osmotic hydrostatic counterforces in plasma and interstitium, and by increased lymph drainage [9, 10].

In healthy humans, arterial pressure is maintained during orthostatic stress at an appropriate level through rapid reflex adjustments mediated by the neural regulatory systems. In patients with autonomic failure these systems fail and orthostatic hypotension occurs upon standing (for review see Smit et al. [8]). The fluctuating course of orthostatic hypotension in patients with autonomic failure has been shown to be closely related to the changes in blood- and extracellular fluid volume (Fig. 1) [11].

This is presumably so because, in the absence of reflex adjustments of the peripheral circulation, arterial blood pressure has become strictly dependent on cardiac output, which, itself, depends on the effective blood volume [11–14]. Consequently, therapeutic measures designed to stabilize or expand the extracellular fluid volume may be helpful in alleviating orthostatic hypotension. These will now be addressed.

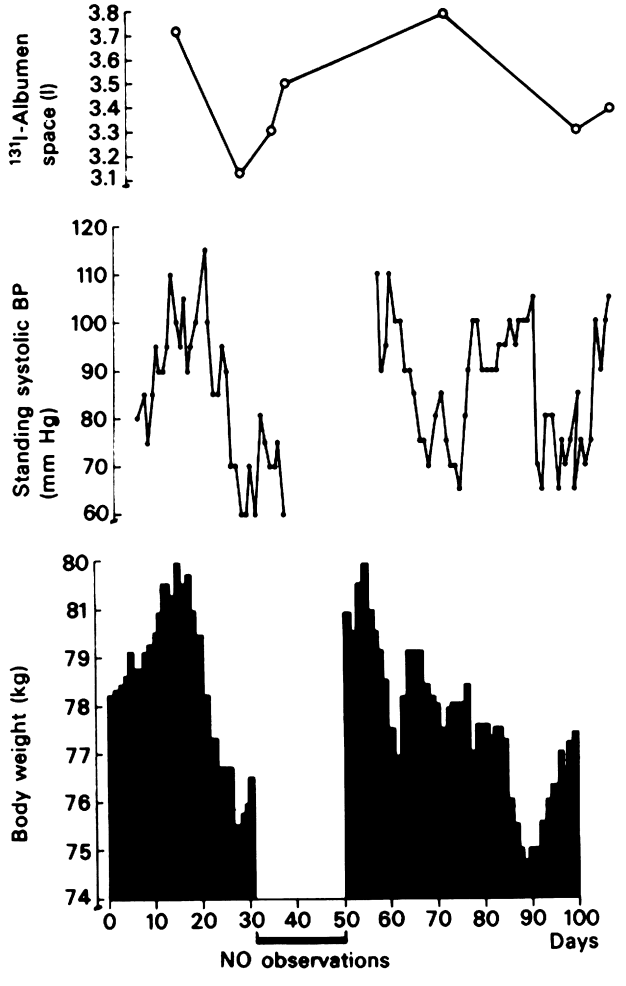

Fig. 1 Records of plasma volume (131 I-albumin space), standing systolic blood pressure measured in the morning and body weight in a patient with multiple system atrophy over a 100-day period. Note the close relation between bodyweight and orthostatic tolerance (from [11] with permission).

Salt intake and orthostatic tolerance

Healthy humans given a reduced dietary sodium intake reduce their sodium excretion rapidly over 2–5 days to achieve a sodium balance at the lower level of intake (Fig. 2). The level of blood pressure and its adjustment to the upright posture during daily orthostatic stresses is usually maintained [15–17].

During salt depletion, activation of both the renin-angiotensin system and the vasopressin system is necessary in normal humans to maintain postural normotension by reinforcing the vasoconstrictor action of the cardiovascular reflexes and by minimizing the loss of body water through activation of the renal blood volume controlling systems [6, 8, 18].

Postural stress, as explained above, leads to a progressive loss of effective circulating blood volume, partly due to distension of dependent veins and partly due to capillary fluid loss. It seems likely, therefore, that individuals, whose plasma volume in relation to body size is relatively large, would tolerate this stress well. This was found to be the case in that there was a significant positive correlation between time to presyncope during a graded orthostatic stress and plasma volume normalized for lean body mass (Fig. 3) [19].

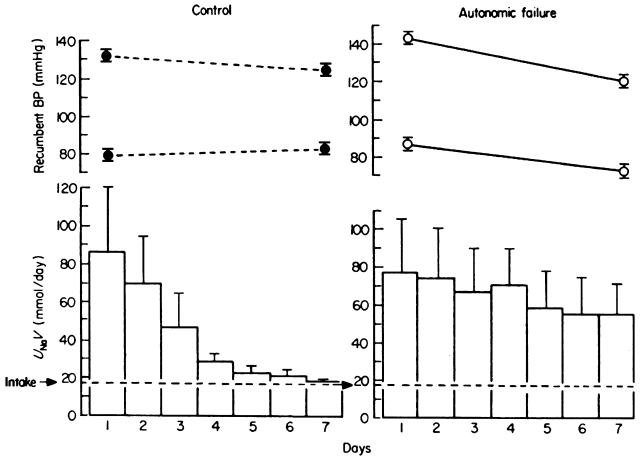

Fig. 2 Mean values ± SEM for systolic and diastolic blood pressure (BP) while recumbent and urinary sodium in five healthy subjects (left panel, closed circles) and five patients with autonomic failure due to pure autonomic failure and multiple system atrophy (right panel, open circles) during 7 days of reduced dietary sodium intake (17 mmol/24 h). Note the failure of the patients with autonomic failure to achieve sodium balance and their decrease in BP (from [16] with permission).

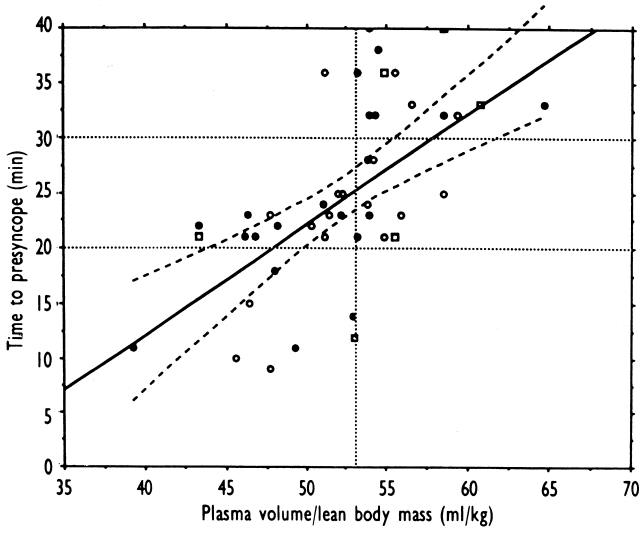

Fig. 3 Dependence of orthostatic tolerance on plasma volume. Orthostatic tolerance is expressed as time to presyncope in a test of combined head-up tilt and lower body suction. Plasma volume, estimated by Evans blue dilution, is divided by calculated lean body mass. The regression line with 95 % confidence bands is shown. Results are from 49 subjects, $r = 0.60$, $P < 0.0001$ (from [19]).

Effects of salt loading in patients with chronic autonomic failure

In contrast to normal subjects, patients with primary autonomic failure are unable to reduce renal sodium excretion appropriately during salt restriction (Fig. 2) [16, 20]. The resulting negative sodium balance is accompanied by a loss of body weight and worsening of the orthostatic hypotension. Failure to achieve sodium conservation may be ascribed in part to subnormal aldosterone secretion, but a reduced action of angiotensin and noradrenaline to enhance renal tubular sodium is also involved (for review see [21]).

Renal salt wasting provides a rational basis for provision of a high sodium intake and administration of salt supplements has been shown to be beneficial to patients with orthostatic intolerance due to autonomic failure [16, 22–29].

Patients should have a daily dietary intake of at least 150 mmol of sodium by the liberal addition of salt at meals or salt tablets. Some patients report better tolerance of buffered salt tablets. We monitor 24 hour urinary sodium excretion and add one or more 10 mmol salt tablets three times a day if needed. We ask the patient to measure early morning body weight after micturition. Symptoms and urinary sodium are then rechecked 1–2 weeks later. In adults, a fluid intake of 2–2.5 liter of fluid per day is to be encouraged and the majority is advised to be taken early in the day.

Expansion of the extravascular body fluid volume can be furthered by the administration of the synthetic mineralocorticosteroid fludrocortisone. The starting dose of fludrocortisone of 0.1 mg once a day can be increased by 0.1 mg increments at 1- to 2-week intervals up to 0.3 mg daily, if needed. A weight gain of 2–3 kg is a reasonable clue for adequate extracellular fluid volume expansion [21, 28, 30]. Slight leg edema is then usually present. The pressor action of fludrocortisone develops over days and doctors and patients should be aware of this. The full benefit of fludrocortisone on expanding body fluids and vascular volume requires a high dietary salt intake [25, 28]. Patients on fludrocortisone may develop hypokalemia within 2 weeks, and foods high in potassium (fruits, vegetables) should be advised. Potassium supplementation may be needed. High doses of fludrocortisone can result in fluid overload and congestive heart failure, severe supine hypertension and hypokalemia. It has been shown that, after a few weeks or months of treatment with fludrocortisone, the plasma volume and body weight return to baseline yet some improvement in orthostatic tolerance persists [31]. This suggests that the steroid-induced extracellular fluid volume expansion is only one of several mechanisms of fludrocortisone, which correct the orthostatic hypotension [21, 30]. This will not be further discussed here.

The rise in upright blood pressure induced by salt loading in patients with autonomic failure is relatively small. Mean arterial pressure in upright posture increases only 10–15 mmHg [28]. This apparent discrepancy between markedly improved orthostatic tolerance and the small increase in upright blood pressure can be explained by the fact that treatment shifts mean arterial pressure from just below to just above the critical level for perfusion of the brain [32].

Effects of salt loading in patients with episodic posturally related syncope

Since salt loading may increase plasma volume [33–36], this would also be a logical approach for the management of patients with episodic posturally related syncope. El-Sayed and Hainsworth [37] undertook a double blind trial of salt capsules (120 mmol/day) versus placebo in 20 patients aged 40–60.

The results indicate that 8 out of 10 patients given salt showed a significant increase in plasma volume (100–500 ml) and all had improved orthostatic tolerance (Fig. 4). Three out of 10 patients given placebo also increased both plasma volume and orthostatic tolerance. In these, however, spontaneous salt intake also increased as seen from 24-hour urine analyses. These results also indicate that patients whose initial salt intake was relatively low (24 hour excretion < 170 mmol/day) were more likely to show responses.

Effects of salt loading on orthostatic tolerance can be assessed quickly as an improvement is evident after as few as 3 days [38]. Further analyses of the relation be-

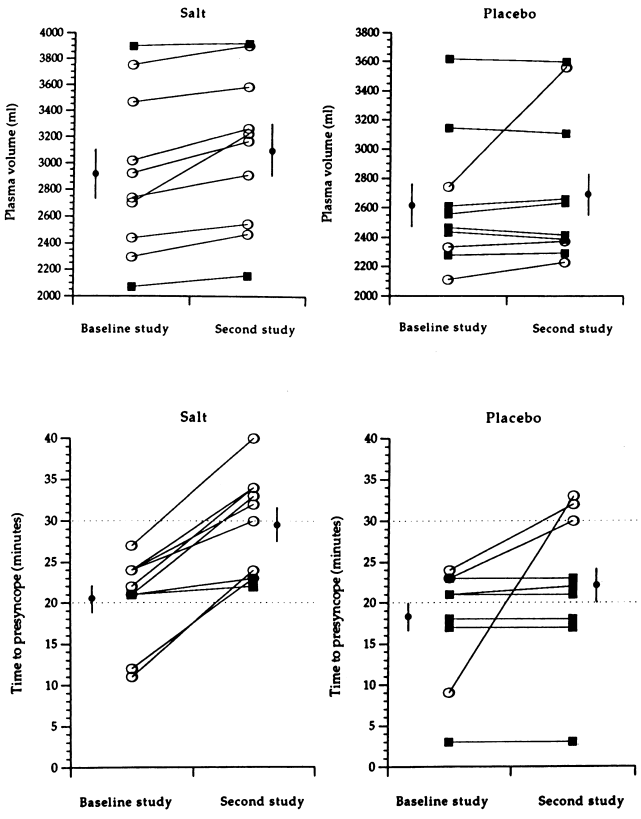

Fig. 4 Effects of salt loading and placebo on plasma volume (top) and orthostatic tolerance (bottom). Plasma volume (Evans blue dilution) and orthostatic tolerance (time to presyncope in test of head-up tilt and lower body suction) were determined before and after 2 months of either salt loading (120 mmol/day) or placebo, given as randomized double-blind trial to patients with posturally related syncope. Note that 8 patients given salt and 3 given placebo show increases in plasma volume and these patients also had increased orthostatic tolerance. The patients who improved on placebo showed evidence from urine collection of increased salt intake. o indicates patients showing significant increases in plasma volume (from [37]).

tween dietary salt intake and orthostatic tolerance has revealed that there is a significant positive correlation between salt intake and orthostatic tolerance, and that salt loading is effective in 70% of patients in whom it was used, with any effect, at least in the short term, on resting blood pressure being small and variable. Nocturnal hypertension is a potential side effect, but this was not observed in a recent study [39]. Nonrandomized studies suggest that extra fluid and supplemental salt are effective in children and the elderly subjects as well [40, 41]. We, therefore, regard salt loading as one of the first interventions to institute in patients with posturally related syncope and no other disorder, particularly no hypertension, cardiac disease or renal disease, and where initial salt excretion is < 170 mmol/day.

If prescription of a high salt diet alone is not effective, fludrocortisone is often added. In two nonrandomized studies fludrocortisone was reported to be effective in children and adolescents with episodic posturally related syncope [42, 43]. In adults, beneficial effects on orthostatic intolerance induced by bed rest have been described [44, 45]. In the elderly, side effects of fludrocortisone in the long term are a major problem [46]. No randomized clinical trials are available regarding the efficacy of fludrocortisone in patients with episodic posturally related syncope and this remains to be assessed.

Exercise training

In healthy humans, endurance exercise training results in increases in plasma and blood volumes whereas bed rest has the opposite effects [47–49]. The effects of training on a subject's tolerance to orthostatic stress is, however, controversial with some reports indicating no change or improvement [50, 51] or deterioration [52]. It has been suggested that there is an optimal level of fitness for maximal orthostatic tolerance and levels both above and below this are associated with reduced tolerance [53]. In practice, it seems that only extreme levels of aerobic fitness are associated with orthostatic intolerance. This is the level likely to be achieved only by elite military personnel or exceptional athletes such as marathon runners or fell walkers. Improving the aerobic capacity of moderately fit individuals is usually associated with improved orthostatic tolerance [54, 55]. In addition to the effects of increasing aerobic capacity, resistance training (weight lifting) may reduce venous pooling by increasing muscle tone [56, 57]. The opposite effects may be seen following prolonged inactivity [58, 59].

The beneficial effects of exercise training may be used to improve orthostatic tolerance in patients with autonomic failure, provided that they are able to maintain an adequate blood pressure to train. This approach has also been applied to patients with episodic syncope and poor orthostatic tolerance. Provided that they were able and willing to train to the extent that they showed a reduction in the elevation of the heart rate-oxygen uptake relationship, there was always an improvement in symptoms and an increase in plasma volume and a measured increase in tolerance to orthostatic stress [60]. As for the effects of salt loading, the improved orthostatic tolerance following exercise was related to the increase in plasma volume.

Head-up at night

Bradbury and Eggleston already noted that patients with autonomic failure appeared to improve symptomatically and objectively during the day and that this improvement had disappeared in the morning after sleep in bed at night [61].

Similar observations led MacLean and Allen to the

suggestion that patients with orthostatic hypotension should not sleep in a flat bed but should lie in a semi-inclined or head-up position [22]. MacLean and Allen accomplished the head-up position by placing the posts of the head of a bed on ordinary kitchen chairs, i. e., 40–45 cm high. Sleeping in a sitting position has been applied by Bannister et al. [62]. Clear evidence is available that head-up sleeping increases the extracellular fluid volume by decreasing sodium and water excretion during the night and improves orthostatic tolerance in patients with autonomic failure (Fig. 5) [23, 28, 62].

A steep head-up tilt sleeping position is likely to be the most effective, but is difficult to tolerate by the majority of patients and their partners. We instruct our patients to put the head-end of their bed on 20–30 cm blocks. A hard pillow under the mattress at the level of the thighs has been found useful to prevent sliding down. A footboard is another helpful measure [28]. Some patients with autonomic failure have been maintained satisfactorily for years solely by this form of treatment [63]. Head-up tilting also reduces supine hypertension in patients with autonomic failure and a reduction in cerebral arterial pressure due to a hydrostatic effect also occurs. A 20–25 cm elevation of the head of the bed lowers cerebral arterial pressure by about 15 mmHg.

In patients with primary autonomic failure in whom the combination of a high salt diet and a low dose of fludrocortisone is not effective, head-up sleeping is an effective expedient to expand the extracellular fluid volume [28, 64, 65].

It has been suggested that head-up sleeping operates by reducing renal arterial pressure and promoting renin release with consequent angiotensin II formation, leading to aldosterone release, and thus increasing the extracellular fluid volume and the volume of circulating blood for patients with autonomic failure, who can still release renin [62, 63].

A reduced nocturnal polyuria and natriuresis during head-up sleeping is also observed in patients without renin and aldosterone release (Figs. 6 and 7) [28]. Other sodium retaining mechanisms like pressure natriuresis [31] need to be considered in these patients. The administration of the vasopressin analogue desmopressin (DDAVP), which acts on renal tubular vasopressin–2 receptors, is another approach to diminish nocturnal polyuria and reduce overnight weight loss in patients with autonomic failure [66, 67], but this will not further be discussed here.

Although nocturnal polyuria is a typical feature of patients with autonomic failure, the degree of impair-

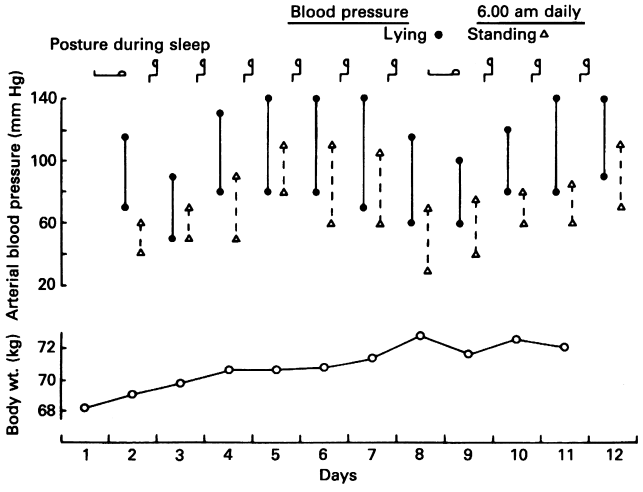

Fig. 5 The change in early-morning blood pressure (lying and standing) in a patient with primary autonomic failure and orthostatic hypotension when he slept in the sitting position for 10 days with one interruption. Note increase in body weight and standing blood pressure during sleeping in the sitting position (from [62] with permission).

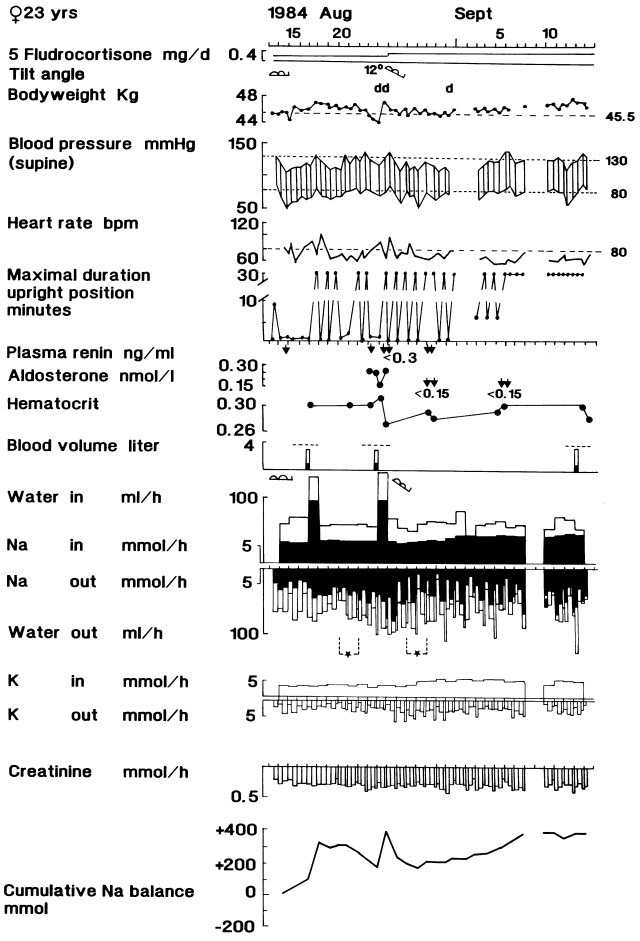

Fig. 6 Diurnal pattern of water and sodium excretion, body weight and orthostatic tolerance over an almost 5 week period in a 22 year old female patient with primary autonomic failure. Orthostatic tolerance in the early morning improved at a sodium balance of about +230 mmol during the combination of a high salt intake and 0.2 mg fludrocortisone and reached an acceptable level at + 300 mol after institution of head-up sleeping. Body weight increased by 2.2 kg. Note the absence of plasma renin activity (from [64]).

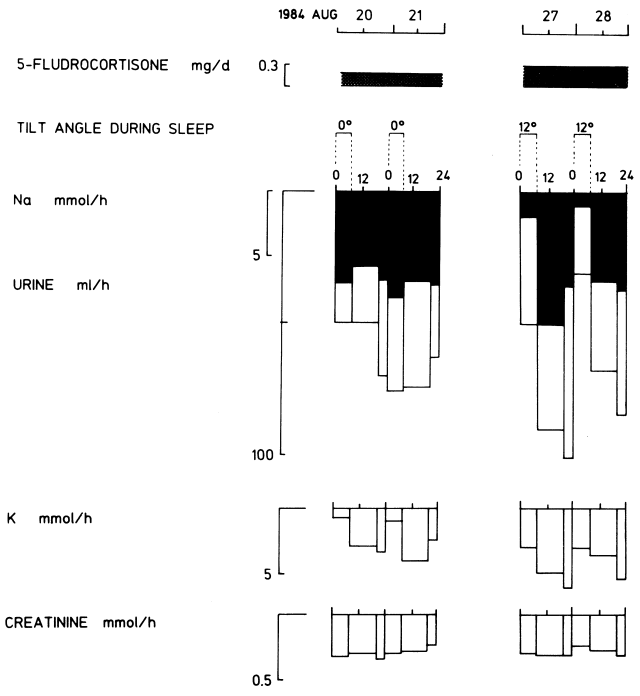

Fig. 7 Detail of Fig. 6. The nocturnal loss of sodium and water diminishes by sleeping in the head-up position at night (24 pm–8 am) (from [64]).

ment in orthostatic tolerance after a night's sleep cannot be explained only by the nocturnal polyuria. Marked diurnal variation in orthostatic tolerance can be found in patients with small diurnal differences in body weight. Transcapillary fluid shifts are thought to play an important role in these patients [28, 68]. The observation that head-up sleeping becomes effective coincidental with the appearance of slight edema of the lower legs suggests that the increased extracellular fluid volume in the lower extremities may play a crucial role in the beneficial effects of this intervention [22, 29].

Head-up sleeping has also been applied on apparently healthy subjects with episodic posturally related syncope and a recent report documents beneficial effects in these patients as well [69].

Conclusion

We consider that an important aim in the treatment of patients with posturally related syncope is to increase extracellular fluid and plasma volumes. This can be achieved by a high dietary salt intake, exercise training and head-up sleeping. Administration of fludrocortisone will further the effect. Plasma volume expansion, however achieved, will result in an increase in orthostatic tolerance (Fig. 8). Introduction of these simple measures are a logical approach to the management of patients with posturally related syncope.

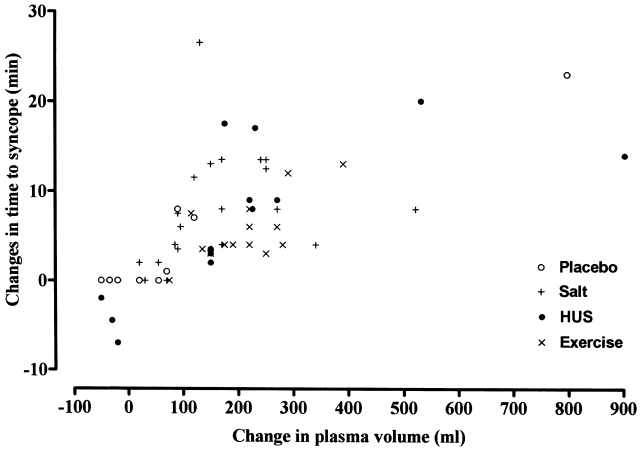

Fig. 8 Summary of effects of various interventions on plasma volume (Evans blue dilution) and orthostatic tolerance (time to presyncope in test of head-up tilt and lower body suction). Changes shown in response to following interventions: salt loading, placebo, exercise training and head-up sleeping. (Data compiled from [37, 38, 69].)

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