Salt Supplementation Improves Orthostatic Cerebral and Peripheral Vascular Control in Patients With Syncope

Victoria E. Claydon, Roger Hainsworth

Abstract—Salt supplementation improves orthostatic tolerance in many patients with posturally related syncope (PRS). This study aimed to examine whether in those patients who responded to salt loading there was also evidence of improved cerebral autoregulation and more powerful peripheral vasoconstriction during orthostasis. Eleven PRS patients were studied before and after ingestion of 100 mmol/d slow sodium for 2 months. Subjects underwent an orthostatic stress test of combined head-up tilting and lower body suction. We continuously monitored heart rate (ECG), blood pressure (Finapres), forearm and cerebral blood flow velocities (Doppler ultrasound), and end-tidal carbon dioxide (CO₂). Forearm vascular resistance was calculated from pressure divided by velocity. Cerebral autoregulation was assessed from the correlation coefficient of the relationship between cerebral blood pressure and velocity. Salt loading had no effect on resting heart rate or blood pressure. Symptoms and orthostatic tolerance significantly improved in 10 of the patients. This was associated with a significant increase in the maximal forearm vasoconstriction from 64.4%±13.7% (SEM) to 135.2%±23.9% (P<0.005). The relationship between cerebral velocity and pressure was less strong (before salt: r=0.74±0.8; after salt: r=0.41±0.1; P<0.02), indicating improved autoregulation. End-tidal CO₂ levels were not different between the 2 tests. Salt loading in PRS patients increases orthostatic tolerance and improves cerebrovascular and peripheral vascular control without affecting blood pressures. These changes are likely to contribute to the beneficial effects of salt loading in these patients. (Hypertension. 2004;43:809-813.)

Key Words: sodium ■ vascular resistance

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Previous work from our laboratory, including a double-blind placebo-controlled trial, has demonstrated that salt supplementation improves orthostatic tolerance in patients with posturally related syncope (PRS). This increase in tolerance to orthostatic stress was attributed partly to increases in plasma volume and partly to increased baroreceptor sensitivity.

We have also shown that the increase in vascular resistance in response to an orthostatic stress is significantly smaller in patients with poor orthostatic control than in healthy volunteers. Impaired responses were seen in patients with PRS and in those with the postural tachycardia syndrome. Because subjects with better orthostatic tolerance show larger responses of forearm vascular resistance to postural changes, the first aim of the present study was to examine whether an improvement in orthostatic tolerance induced by salt loading might be associated with larger vascular resistance responses.

We have also recently reported evidence of impaired cerebral autoregulation in patients with PRS. In another study, we demonstrated that water ingestion improved orthostatic tolerance in healthy control subjects and that this improvement in tolerance was associated with an improvement in cerebral autoregulation. Thus, the second aim of this study was to determine whether cerebral autoregulation in this group of PRS patients was improved after salt supplementation.

Methods

Subjects

Subjects for this study were recruited from patients referred to the laboratory for orthostatic stress testing because of recurrent attacks of syncope or near syncope. To be considered suitable for salt loading, patients needed to satisfy the following criteria: (1) a clinical history suggestive of posturally related hypotension; (2) no other clinical disorder, excluded by appropriate clinical investigations; and, in particular, no evidence of autonomic dysfunction or cardiac disease; (3) normal supine blood pressure (<140/90 mm Hg); (4) no prescribed medication; (5) orthostatic tolerance less than that predicted on the basis of previous studies; and (6) urinary salt excretion in the period before the study <170 mmol sodium per 24 hours (the average 24-hour sodium excretion was 132.5±16.9 mmol [SEM]).

On the basis of the aforementioned criteria, 11 consecutive patients (aged 20 to 53 years, mean age 34.6±3.7 years, 5 male) agreed to enter the study. All subjects gave informed consent. The study had received approval from the Research Ethics Committee of the United Leeds Teaching Hospitals and was performed in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Orthostatic Stress Test

The orthostatic stress test was performed using a combination of head-up tilt and graded lower body negative pressure. This test is...
Individual Responses of Orthostatic Tolerance, Heart Rate, and Blood Pressure Before and After Salt Supplementation

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Values are provided for heart rate (HR), orthostatic tolerance (OT) expressed as the time in minutes from the start of head-up tilt, mean arterial pressure (MAP), and symptom frequency reported as the number of episodes of syncope and presyncope per month. Patient 10 was the only subject not to improve after salt loading.

sensitive and specific and highly reproducible in terms of the time required to induce presyncope. Subjects were rested supine on the tilt table and were fitted with ECG leads and an auto-inflating sphygmomanometer (Hewlett Packard 78325C; Boehringer, Germany). A photoplethysmograph device (Finapres, Ohmeda, Wis) was fitted to the middle finger of the right hand to enable continuous blood pressure monitoring. A Doppler probe was positioned over the brachial artery to record forearm blood flow velocity, and a second Doppler recorded blood flow velocity in the middle cerebral artery as described previously. Cerebral blood pressure was calculated from systemic arterial blood pressure at heart level by adjusting for the height difference between head and heart imposed by standing. Paired nasal cannulae were positioned at the nasal septum to monitor end-tidal carbon dioxide levels using an infrared analyser (Binos-1; Leybold-Heraeus Limited, Köln, Germany). Forearm vascular resistance was expressed as mean blood pressure divided by mean brachial blood flow velocity.

Subjects then remained supine for 20 minutes while baseline readings were made. They were then tilted head-up at an angle of 60° for 20 minutes. After the head-up tilt period, they were subjected to head-up tilting to when the test was terminated. Tolerance was defined as the time in minutes from the start of head-up tilt to when the test was terminated.

Procedure
All experiments were performed in the mornings in a temperature-controlled laboratory (22°C to 24°C). Subjects were asked to abstain from caffeine-containing drinks and to consume only a light breakfast. Patients were asked to provide a 24-hour urine collection on their first visit. The orthostatic stress test was then performed to determine the subjects’ orthostatic tolerance and the cardiovascular and cerebrovascular responses to the stress. Values were compared at 2-minute intervals throughout the orthostatic stress test. After the orthostatic stress test, patients who satisfied the aforementioned criteria were administered 100 mmol/d (6 g) slow-release sodium chloride tablets (HK Pharma) and were reassessed after 2 months.

Statistical Analysis
Statistical analyses were performed using GraphPad InStat version 3.00 for Windows 95 (GraphPad Software, San Diego, Calif). Values reported are means±SEM. Data were tested for normality using the Kolmogorov and Smirnov assumptions. Comparisons between studies were performed using paired Student t tests. Correlations between variables were examined using the Spearman rank correlation coefficient.

Results
Symptomatic Changes
The frequency of occurrence of loss of consciousness reduced from a mean of 5 episodes every 2 months (range 1 per year to 3 per week) before salt to 3 episodes in the 2 months after starting salt (range none to 2 per week). The incidence of near-syncope also reduced from a mean of 2 episodes per day (range 1 per month to 11 per day) to 1 episode per week (range none to 1 per month). This reduction in symptoms was highly significant (P<0.0001; Fisher exact test). Of the 11 patients, most were symptom-free (n=4) or thought they were much improved (n=6). Only 1 subject, who showed no improvement in the results of the orthostatic stress test, did not improve. Individual data can be seen in the Table.

Orthostatic Tolerance
Salt supplementation caused an increase in orthostatic tolerance in 10 of the 11 subjects. The mean change in the improvers was from 19.9±2.9 to 31.8±1.3 minutes. One subject did not show an improved orthostatic tolerance (orthostatic tolerance decreased from 22 to 19 minutes). On the basis of previously published data, the mean orthostatic tolerance after salt loading increased to within the normal range in 8 subjects compared with clearly poor tolerance in all subjects before treatment. Individual data are shown in the Table. Group data are represented in Figure 1.

Heart Rate and Blood Pressure
As shown in Figure 2, the resting supine levels of heart rate and systolic, diastolic, and mean blood pressures were unaffected by the salt supplementation. The resting heart rate was 64.5±2.6 bpm before and 66.5±3.2 bpm after salt (not
significant [NS]). Resting mean arterial blood pressures were 86.2±2.4 mm Hg before and 85.2±2.4 mm Hg after salt supplementation. The subject who did not respond to salt also showed no change in resting blood pressure (from 130/67 to 129/67).

Tilting caused initial increases in heart rate and blood pressures in baseline and salt studies \((P<0.5)\). However, this increase in heart rate and blood pressure was not affected by salt supplementation. The increase in heart rate was 17.8±2.1 bpm before and 15.0±4.1 bpm after salt (NS). The assumption of the upright posture caused an increase in mean arterial pressure of 5.2±3.2 before and 5.6±2.1 mm Hg after salt (NS).

The blood pressures at which the test was terminated and the subject returned to supine were not significantly different after salt. It merely took longer to evoke the same blood pressure decrease (end of test systolic pressure 79.3±7.8 before and 107.7±9.0 bpm after salt, \(P<0.001\)).

**Forearm Vascular Resistance**

Forearm vascular resistance was calculated from mean arterial pressure divided by mean brachial blood flow velocity every 2 minutes throughout testing. Figure 3 shows the maximum vasoconstriction evoked during the tilt test on both days using data from patients who showed improved orthostatic tolerance. After salt supplementation, the maximum response of forearm vascular resistance (expressed as a percentage change from the supine level) was significantly greater \((135.2±23.9\%\) compared with \(64.4±13.7\%\) during the baseline study, \(P<0.005\)). In the subject who did not respond to salt maximum, forearm vascular resistance decreased from \(+67.0\%\) to \(+45.0\%\).

**Cerebral Autoregulation**

Figure 4 shows an example of cerebral autoregulatory control during the 2 studies in 1 representative subject. Cerebral blood pressure and cerebral flow velocity were plotted for each subject at 2-minute intervals throughout the testing
procedure. Values obtained when pressure decreased to <50 mm Hg toward the end of the test were excluded to ensure that all data points would be within the expected autoregulatory range. During the baseline study (white circles), changes in cerebral blood pressure were associated with changes in cerebral blood velocity. There was a significant linear relationship between the 2 variables ($R=0.71; P<0.05$). After salt loading, cerebral blood velocity was no longer seen to follow changes in cerebral blood pressure. There was no significant correlation observed between the 2 variables.

We took the correlation coefficient between cerebral blood flow velocity and pressure as a measure of the efficiency of autoregulation of cerebral flow. A low $R$ value indicates good autoregulation. Figure 5 shows the group cerebral autoregulation data. The autoregulation index was significantly reduced after salt supplementation from $0.761\pm0.06$ to $0.413\pm0.10$ ($P<0.02$). Before salt, there was a significant relationship between cerebral velocity and pressure in 9 subjects. After salt, it was statistically significant only in 3 subjects.

End-tidal carbon dioxide levels were monitored throughout testing and were not significantly different between the 2 tests. They tended to decrease (by the same amount on both days) as the test progressed reaching a minimal level at termination of the test of $4.2\pm0.15\%$ during the baseline study and $3.9\pm0.20\%$ after salt supplementation (NS).

There was a significant negative correlation between the maximum response of forearm vascular resistance to orthostatic stress and the autoregulation index, whereby a large response of forearm vascular resistance was associated with a small autoregulation index ($R=-0.59, P<0.02$).

**Discussion**

This study has confirmed previous findings from our laboratory that salt supplementation causes a significant improvement in the tolerance to orthostatic stress in patients with initially poor orthostatic tolerance.\(^1\)\(^-\)\(^3\) We feel confident that this represents a real improvement in tolerance, because the blood pressure at which the test was terminated was almost identical before and after salt. In this study, the mean improvement in tolerance after salt loading was 12 minutes, which actually represents a large change. Eight of 11 subjects had normal test results after salt, whereas by selection, all were abnormal before. The increased time of 12 minutes should be seen in relation to the reproducibility of the test in the absence of intervention, which is $\pm2$ minutes.\(^8\) The increased time that subjects tolerated the orthostatic stress after salt loading is actually greater than was seen in previous studies from our laboratory. In previous studies, we reported that salt loading increased the time to presyncope by 9 minutes,\(^1\) 5 minutes,\(^2\) and 4.5 minutes.\(^3\)

In the present study, we did not include a control group that was administered placebo instead of salt. This was because we had already established from a previous study in our laboratory using a randomized crossover design and with placebo control that salt supplementation does significantly improve orthostatic tolerance.\(^1\) In this earlier study, 71% of the subjects who received salt tablets had an improvement in orthostatic tolerance, whereas only 3 of 10 subjects who received placebo showed an improvement in orthostatic tolerance. Also, in those who improved on placebo, it became apparent from urine sodium analysis that they had voluntarily increased their sodium intake during the course of the trial. Thus, we considered that we had already established that salt loading improves orthostatic tolerance in the majority of subjects.\(^1\)\(^-\)\(^3\) Therefore, the aim of this study was not to test whether salt improves orthostatic tolerance, but rather to explore the mechanisms by which salt supplementation exerts its effects.

The results of the present study, in addition to confirming the previous findings of increased orthostatic tolerance after salt loading, provided additional novel findings. We demonstrated that the improvement in tolerance to orthostatic stress mediated by salt loading not only is linked to increases in plasma volume\(^1\)\(^,\)\(^2\) but also is associated with evidence of enhanced sympathetic control of the vasculature (as shown by the greater forearm vasoconstriction after salt supplementation) and improvements in the control of cerebral autoregulation, as shown by the loss of pressure dependency of blood flow in the cerebral circulation.

The finding of enhanced responses of forearm vascular resistance during orthostasis could be explained by previous findings whereby salt supplementation caused enhanced carotid baroreceptor sensitivity in upright individuals.\(^3\) This is supported by experimental studies performed in rats,\(^10\) cats,\(^11\) and dogs\(^12\) whereby a reduction in sodium intake was shown to be associated with impaired baroreceptor function (increased threshold and decreased pressure sensitivity). However, there may also be a direct action of salt on the resistance vessels themselves because in addition to effects on reflex control, in animals salt loading enhances the vascular response of isolated vessels to the application of noradrenaline.\(^13\)\(^,\)\(^14\)

Another interesting observation for which we have no clear explanation was that after salt, the heart rate at the point at which the test was terminated was greater. This was not a reflex effect caused by the blood pressures being lower, because pressures were actually found to be similar at this time. However, previous studies have shown that greater tolerance to orthostatic stress is associated with faster heart
rates⁵ and a greater sympathetic drive to the heart. This is likely to be a result of the greater stress tolerated rather than a result of improved tolerance.⁶ Thus, the faster heart rates provide another indicator of enhanced sympathetic activation.

The improvement in the control of the cerebral circulation is also difficult to explain. The pressure range over which measurements were taken was the same in both studies; yet after salt loading, cerebral blood flow velocity became less dependent on pressure. The pressure dependency of cerebral blood flow in PRS patients has been noted in a previous study.⁶ Also, in normal volunteers, we have shown that improvements in orthostatic tolerance (in that case through drinking water) were associated with evidence of improved cerebral flow autoregulation.⁷ This study has extended the finding that better orthostatic tolerance was associated with improved autoregulation in patients with PRS.

In this study, we have seen only the beneficial effects of salt supplementation on orthostatic tolerance; we have not seen the deleterious effect of salt on blood pressure that has been reported in previous epidemiological studies.¹⁵,¹⁶ However, it is important to note that all patients were normotensive and had baseline 24-hour sodium excretions < 170 mmol per day. It is also relevant to point out that we were only examining the effects of moderate salt loading for a short period, and that it is with increasing age and prolonged salt loading that hypertensive effects have been reported.¹⁷ We would advocate, therefore, that if salt loading is to be prolonged, then frequent checks of blood pressure should be made.

The results of this study have demonstrated, using previously established techniques, that salt supplementation is beneficial for normotensive patients with PRS, in the absence of coexisting hypertension, and in those with 24-hour urinary excretion of sodium of < 170 mmol/d. The improvement in orthostatic tolerance seen (and subjective improvement reported by the patients) was associated with an enhancement of the sympathetic control of the vasculature (and possibly to the heart), improved cerebral autoregulation, and (at least over the period during which observations were made) no change in the resting blood pressure. We suggest that in patients who fulfil the criteria for this study that salt supplementation be considered as a first-line treatment for postural syncope. However, we feel that because of the epidemiological link between high-salt intake and elevated blood pressure, the blood pressure status of all patients receiving salt therapy should regularly be monitored.

Perspectives
Postural syncope in otherwise completely healthy people is a common problem; yet despite the large number of people who have this, relatively little is known regarding the most appropriate management. A simple therapy such as the use of additional dietary sodium (in normotensive individuals) could help minimize the physical and psychological stress caused by frequent episodes of loss of consciousness. In this study, we have confirmed that salt supplementation is a highly effective therapy in most patients for the treatment of postural syncope. We have also provided some insight as to the mechanisms of action of this intervention. Salt supplementation is, in our experience, well tolerated. We have now shown that in addition to its known effect of expanding plasma volume, it also increases the vascular resistance responses to standing (and hence improves postural blood pressure control). It also improves cerebral perfusion by enhancing control of cerebral autoregulation. Perhaps equally as important, we have also demonstrated that in the patients studied, salt supplementation had no adverse effect on resting supine blood pressures, although careful monitoring of blood pressure is advisable. We advocate that medical practitioners should use these findings to enable appropriate and effective treatment of patients who fulfil the criteria applied in this study.

References
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