Haemodynamics of the pressor effect of oral water in human sympathetic denervation due to autonomic failure

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ABSTRACT

Oral water ingestion increases blood pressure in normal elderly subjects and in patients suffering from autonomic failure, but the time course of the haemodynamic changes is not known. We therefore studied 14 subjects with documented sympathetic denervation due to pure autonomic failure, with continuous haemodynamic recordings obtained before and after ingestion of 500 ml of distilled water at room temperature. The time course of changes in values of systolic and diastolic beat-by-beat finger blood pressure, heart rate, stroke volume, cardiac output, ejection fraction and total peripheral resistance were analysed. Systolic blood pressure rose from $115 \pm 8$ mmHg (mean $\pm$ S.E.M.) to $133 \pm 8$ mmHg ($P < 0.001$), and diastolic blood pressure from $64 \pm 4$ to $73 \pm 4$ mmHg ($P < 0.001$), with the pressor response beginning a few minutes after water ingestion, plateauing between 10 and 35 min (peak at 14 min), and returning to baseline at 50 min. Heart rate fell from $71 \pm 2.5$ to $67 \pm 2$ beats/min ($P < 0.001$), and total peripheral resistance increased from $1.31 \pm 0.19$ to $1.61 \pm 0.24$ m-units ($P < 0.001$). There were no significant changes in ejection fraction, stroke volume or cardiac output. This study confirmed a pressor response to oral water in subjects with sympathetic denervation. The temporal profile of the response did not favour reflexly mediated sympathetic activation. As subjects with autonomic failure are prone to salt and water depletion, and since blood pressure is exquisitely sensitive to such changes, it may be that the observed response is due to repletion or restoration of intravascular and extravascular fluid volume.

INTRODUCTION

In 1999, Jordan et al. [1] reported that oral ingestion of tap water increased systolic blood pressure (SBP) in elderly normal subjects, with an even greater increase (33 mmHg) observed in subjects with autonomic failure (AF) who had sympathetic denervation. In a later paper they extended these observations and, using mainly a combination of pharmacological approaches and neurohormonal measurements, concluded that water drinking raises sympathetic neural activity significantly and rapidly [2]. In both of these studies, the composition of tap water was not provided, and limitations in the latter study included the degree of sympathetic denervation of

Key words: arterial blood pressure, autonomic failure, distilled water.

Abbreviations: AF, autonomic failure; BP, blood pressure; CO, cardiac output; DBP, diastolic blood pressure; EF, ejection fraction; HR, heart rate; MSA, multiple-system atrophy; SBP, systolic blood pressure; SV, stroke volume; TPR, total peripheral resistance.

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the AF subjects, as some had pressor responses to physiological stimuli; no details of haemodynamic changes were provided. Furthermore, in a subsequent study utilizing a similar protocol in subjects with AF associated with Parkinson’s disease, the pressor responses to oral water were not reproduced [3].

The objectives of our present study included the following; to confirm in subjects with clearly defined sympathetic denervation as a result of AF that a similar amount of water had a pressor effect; to exclude the possible contribution of chemicals and electrolytes by using distilled water; and to characterize the haemodynamic factors responsible for the pressor response by using continuous recording of cardiovascular variables.

METHODS

A total of 14 subjects (four male and ten female; age range 39–78 years; average 64 years) with sympathetic denervation due to pure AF took part in the study. All gave written informed consent to participate in the study, which had local Ethics Committee approval and was conducted in accordance with the Declaration of Helsinki (1989) of the World Medical Association. Each had a long history (> 5 years) of chronic orthostatic hypotension (a fall in SBP of 30 mmHg or more when changing from a supine to an upstanding position) and documentation of severe sympathetic denervation. A series of physiological tests of autonomic function [4] confirmed a fall in BP of > 30 mmHg in response to head-up tilt, abnormal BP and heart rate (HR) responses to the Valsalva manoeuvre, and a lack of a rise in BP following various pressor tests (mental arithmetic, cutaneous cold and isometric exercise; Table 1). All had low levels of plasma noradrenaline at rest; levels were 148 ± 30 pg/ml (mean ± S.E.M.), compared with values of 392 ± 39 pg/ml in 59 age-matched normal controls; there were minimal or no changes on head-up tilt (161 ± 29 pg/ml). No subjects had additional neurological features (to favour multiple system atrophy or other Parkinsonian syndromes) or other medical conditions, such as diabetes [5].

All medications (including fludrocortisone and the sympathomimetic drugs ephedrine and midodrine) were withdrawn on the day before the study. All subjects abstained from food or fluids (including water) from 09.00 hours on the morning of the study. All subjects emptied their bladder before starting the study.

The investigation was performed at 12.00 hours. This maximized the effect of withdrawal of medication (over five half-lives) and in part prevented dehydration, which may be substantial (because of nocturnal polyuria) [6] if water abstinence overnight was enforced. Subjects were made to sit in a chair in a relaxed position, and were supervised continuously to avoid any actions or manoeuvres, such as crossing of the legs or calf contraction, that may modify BP levels [7]. Continuous BP was recorded with the Portapres II® (TNO-TPD Biomedical Instruments*), with the sensor on the middle finger of the left hand. In addition, an automated sphygmomanometer (Dinamap®; Critikon*) intermittently measured brachial SBP, diastolic blood pressure (DBP) and HR from the contralateral arm at 5 min intervals.

A baseline recording over at least 30 min was obtained after the subjects had been familiarized with the machines and felt comfortable. They then drank 500 ml of distilled water at room temperature (23–24 °C) within 3–4 min. Recordings were continued for 1 h following water ingestion. Calculations of SBP, DBP, HR, total peripheral resistance (TPR), stroke volume (SV), ejection fraction (EF) and cardiac output (CO) were made using a pressure wave analysis method, Modelflow®. There is one report [8] suggesting that this technique might not be accurate in estimating CO during exercise. In that report CO did not correlate with the corroboratory method.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pure AF</th>
<th>Normal subjects</th>
</tr>
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<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>174 ± 8</td>
<td>124 ± 6</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>92 ± 3</td>
<td>77 ± 2</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>72 ± 3</td>
<td>71 ± 3</td>
</tr>
<tr>
<td>∆SBP (mmHg)</td>
<td>-93 ± 13</td>
<td>2 ± 3</td>
</tr>
<tr>
<td>∆DBP (mmHg)</td>
<td>-36 ± 5</td>
<td>5 ± 3</td>
</tr>
<tr>
<td>∆HR (beats/min)</td>
<td>0 ± 3</td>
<td>0 ± 2</td>
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<tr>
<td>Head-up tilt (2 min)</td>
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<tr>
<td>∆SBP (mmHg)</td>
<td>-70 ± 10</td>
<td>-8 ± 2</td>
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<tr>
<td>∆DBP (mmHg)</td>
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<td>3 ± 1</td>
</tr>
<tr>
<td>∆HR (beats/min)</td>
<td>5 ± 2</td>
<td>2 ± 2</td>
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<tr>
<td>Cutaneous cold</td>
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<tr>
<td>∆SBP (mmHg)</td>
<td>-2 ± 3</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>∆DBP (mmHg)</td>
<td>-7 ± 2</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>∆HR (beats/min)</td>
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<td>1 ± 1</td>
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<tr>
<td>Mental arithmetic</td>
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<tr>
<td>∆SBP (mmHg)</td>
<td>2 ± 2</td>
<td>13 ± 3</td>
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<tr>
<td>∆DBP (mmHg)</td>
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<td>9 ± 2</td>
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<td>∆HR (beats/min)</td>
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<tr>
<td>Handgrip</td>
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<tr>
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<td>1 ± 3</td>
<td>17 ± 3</td>
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<td>∆DBP (mmHg)</td>
<td>-5 ± 3</td>
<td>11 ± 2</td>
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<tr>
<td>∆HR (beats/min)</td>
<td>2 ± 1</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>Response to Valsalva</td>
<td>0.98 ± 0.04</td>
<td>1.62 ± 0.06</td>
</tr>
</tbody>
</table>

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but this occurred during exercise, and does not apply to our present study. This non-invasive technique has been validated in the resting state with stimulation (but non-exercising) by several groups [9–16], in terms of both correlation with brachial blood pressure and reliability of calculation of haemodynamic parameters, especially CO in comparison with the thermodilution method [13]. The Modelflow* method calculates the haemodynamic parameters using a non-linear, time-varying three-element Windkessel model. The model elements include aortic characteristic impedance, arterial compliance and systemic vascular resistance. The aortic characteristic impedance and arterial compliance depend on the aortic cross-sectional area; this is estimated by taking into account the subject’s parameters, including mean arterial pressure, age, gender, height and body weight [10,15,16].

One-way repeated-measures ANOVA, followed by post-hoc comparisons (Bonferroni’s t-test against baseline), were used for statistical analysis of the responses. A more sensitive approach, based on the cumulative sum (CUSUM) derivative of the peri-stimulus time histogram [17,18], was employed to determine the onset of increases/decreases in BP or other haemodynamic parameters. All results are expressed as means ± S.E.M.

RESULTS

BP responses

Pre-ingestion basal BP levels were 115 ± 8 mmHg for SBP and 64 ± 4 mmHg for DBP (Figure 1). Following water ingestion, both SBP and DBP rose after a few minutes. Values remained elevated between 10 and 35 min post-ingestion [SBP, 133 ± 8 mmHg (+15.6%), P < 0.001; DBP, 73 ± 4 mmHg (+14 %), P < 0.001], with a peak value at 14 min, and had returned to basal levels at 50 min after ingestion (SBP, 117 ± 8 mmHg; DBP 65 ± 4 mmHg; Figure 2). The first value that was significantly higher than baseline levels was recorded after 2 min. The greatest increases above baseline were 64 mmHg for SBP and 37 mmHg for DBP; the smallest were 7 mmHg and 5 mmHg respectively.

Similar values and trends were obtained with automated intermittent brachial BP recordings (Figure 3): SBP rose from 114 ± 9 to 132 ± 8 mmHg by 15 min after water ingestion, and had returned to the basal level (112 ± 8 mmHg) at 45 min; DBP rose from 71 ± 5 to 80 ± 4 mmHg at 15 min (P < 0.001), and had returned to basal (72 ± 5 mmHg) at 45 min.

Figure 1 Mean values of SBP and DBP before and after ingestion of 500 ml of distilled water in 14 subjects with pure AF

The observed increases were significant (P < 0.001), as assessed by repeated-measures ANOVA. The first value that is significantly different from that at time 0 is denoted by *.

Figure 2 Continuous finger BP recording in a subject with pure AF before and after water ingestion

Figure 3 Mean values of brachial SBP and DBP before and after ingestion of 500 ml of distilled water

HR

Pre-ingestion HR was 71 ± 2.5 beats/min; this fell to 67 ± 2 beats/min (−5.6%; P < 0.001) between 10 and
Figure 4  Mean HR before and after ingestion of 500 ml of distilled water in 14 subjects with pure AF
The observed increases were significant ($P < 0.001$), as assessed by repeated-measures ANOVA. The first value that is significantly different from that at time 0 is denoted by *.

Figure 5  Mean TPR before and after ingestion of 500 ml of distilled water in 14 subjects with pure AF
TPR is given in m-units. The observed increases were significant ($P < 0.001$), as assessed by repeated-measures ANOVA. The first value that is significantly different from that at time 0 is denoted by *.

35 min after water ingestion, before returning to 69±2 beats/min at 50 min (Figure 4). The first value that was significantly higher than baseline levels was recorded after 3 min. Similar values were obtained with the automated brachial measurements: 70±3 beats/min at time 0, 66±2 beats/min at time 15 min ($P < 0.001$) and 69±2 beats/min at 50 min after water ingestion.

SV
Pre-ingestion SV was 62.7±8.4 ml; mean values were 64±8.4 ml (+2.1%) between 10 and 35 min after water ingestion, and 62±8.5 ml at 50 min after ingestion. The changes were not significant ($P > 0.05$).

CO
Pre-ingestion CO was 4.3±0.5 litres/min; mean values were 4.2±0.5 litres/min (−2.3%) between 10 and 35 min after water ingestion, and 4.4±0.5 litres/min at 50 min after ingestion. These changes were not significant ($P > 0.05$).

EF
Pre-ingestion EF (ratio) was 0.318±0.009; levels were 0.331±0.01 (+4%) between 10 and 35 min after water ingestion, and had returned to baseline at 50 min after ingestion. These changes were not significant ($P > 0.05$).

TPR
Pre-ingestion TPR (Figure 5) was 1.31±0.19 m-units. Levels rose to 1.61±0.24 m-units (+22.9%; $P < 0.001$) between 10 and 35 min after water ingestion, and had returned to 1.31±0.19 m-units at 50 min. The first value that was significantly higher than baseline was recorded after 3 min, and the time course of the increase was delayed compared with the rise in BP.

DISCUSSION
These data unequivocally confirm the results of Jordan et al. [1] with regard to the pressor effect of the oral ingestion of water in subjects with severe sympathetic denervation due to pure AF. Our observations were made in carefully selected subjects, in whom a series of physiological tests excluded their ability to raise BP in response to a variety of stimuli designed to reflexly activate sympathetic nerves. Their basal supine plasma noradrenaline levels were below normal, and did not rise with head-up postural change; this is consistent with observations in this group of subjects, where sympathetic denervation is post-ganglionic [19]. This contrasts with the situation in another group of patients with chronic primary AF, multiple-system atrophy (MSA; synonymous with the Shy–Drager syndrome), where the lesion is pre-ganglionic, predominantly central and often associated with a basal level of plasma noradrenaline within the normal range [20].

Previous studies have suggested that the electrolytic and mineral composition of water may influence BP. This was raised originally in relation to hypertension in both children and adults, although it was thought to be unlikely, even in areas where a higher sodium content of drinking water was observed [21–23]. Subjects with AF can be extremely sensitive to the effects of pressor substances or electrolytes, which was the basis of the successful use of sea water (albeit with a considerably higher sodium content) to reduce orthostatic hypotension in one such subject [24]. In our present study
distilled water was used, and a definite pressor response was observed, thus excluding a contribution of either electrolytes or pressor substances to this response.

After oral water ingestion, there was a rise in both SBP and DBP, which began after a few minutes, peaked around 10 min and plateaued for about 30 min with further waning, so that by 50 min the levels had returned to baseline. In the previous study by Jordan et al. [2], the pressor response in four AF subjects was not temperature-dependent, as a similar rise in BP occurred with identical volumes of water at 9°C and 24°C; we used water at room temperature (23–24°C). In their study, the volume ingested did, however, influence the pressor response; in four AF subjects, ingestion of 240 ml of water raised SBP (as derived from their figure) by approx. 33 mmHg, while after a volume of 480 ml the SBP rose by 47 mmHg. It was suggested [2] that gastric distension may have been responsible for the rise in BP, with a reflex mediated via the sympathetic nerves. However, the time course of the pressor response after water was over minutes rather than seconds, and thus not as rapid as would be expected if it was reflexly induced, as in an analogous situation during reflex sympathetic activation in tetraplegics [25]. Furthermore, in our study there was a pressor response to water in subjects in whom a variety of stimuli were unable to elicit a pressor response dependent on reflex sympathetic activation. It may be argued that, in the face of a muted or absent sympathetic reflex response, there was a secondary release of pressor substances, possibly from the gut or elsewhere, which caused a late elevation in BP. In AF subjects, as in normal subjects, various vasoactive peptides are released in response to food ingestion, except that these are likely to result in vasodilation, thus accounting for post-prandial hypotension in AF [26]. These observations were mainly in response to liquid or solid meals of varying compositions; water ingestion, however, is reported in normal subjects to cause secretion of the vaso dilator vasoactive intestinal peptide [27], which would be expected to lower BP. Therefore both the temporal sequence and the previous observations in subjects with AF of the responses to food ingestion militate against either a sympathetic reflex or neurohormones from the gastrointestinal tract accounting for the pressor responses to oral water ingestion.

The possibility that other humoral substances and neurohormones may contribute to the pressor response was evaluated by Jordan et al. [2] who, on the basis of their data, excluded a humoral explanation. Previous observations in subjects with AF indicate low levels of renin and aldosterone, possibly due to sympathetic denervation of the kidney. Plasma levels of renin activity did not change in their study, and nor did vasopressin levels [2]. In pure AF (but not in MSA with central lesions), vasopressin release in response to osmotic stimuli is preserved [28,29], but water ingestion would be expected to decrease rather than increase vasopressin levels. Whether the release of other vasopressor substances, including endothelial-derived factors such as endothelin (not studied by either group), may have contributed to the pressor response and to the rise in TPR is not known, and warrants further study.

The pressor response to oral water was not associated with a rise in SV, CO or EF. In tetraplegics with physiologically complete spinal cord transection, increased isolated spinal cord reflex sympathetic activity (as part of autonomic dysreflexia) can be induced by visceral stimulation [25]. This results in rapid rises in BP, SV and CO, accompanied by a transient rise in HR followed later by bradycardia, because the baroreceptor afferents and vagus nerves are intact and respond to the rise in BP [30]. Continuous recordings in our subjects did not indicate an initial transient tachycardia. There was a small fall in HR corresponding to the rise in BP, suggesting minimal baroreflex activation in response to the latter; the changes, however, were small in relation to the rise in pressure, as expected in subjects with AF. There was a significant rise in calculated TPR, with a temporal profile similar to that of the pressor response, and a time curve which followed the rise in BP. It may be that a transient elevation of noradrenaline levels, in the presence of a-adrenoceptor pressor supersensitivity or even adrenaline release due to splanchnic activation, raised BP. However, the time course of the pressor response argues against the former. Furthermore, subjects with pure AF are unlikely to release adrenaline from the adrenal medulla, as demonstrated with considerably stronger stimuli such as hypoglycaemia [31].

Jordan et al. [2], on the basis of their pharmacological evidence, favoured a sympathetic reflex as being the cause of the pressor rise; they reported that ganglionic blockade lowered pre-ingestion BP in two subjects with AF and in seven younger normal subjects, following which there was no pressor response to oral water. Their two AF subjects had MSA, a disorder in which post-ganglionic sympathetic pathways are known to be preserved; therefore they were dissimilar to our subjects with pure AF, who had severe peripheral sympathetic denervation. Furthermore, during ganglionic blockade a different protocol to the other studies was used [2], with baseline values measured in the supine (and not the seated) position, followed by raising the head of the bed to allow for water drinking. Whether this itself lowered BP in the two MSA subjects with known orthostatic hypotension remains a possibility. Importantly, in their study Jordan et al. [2] clearly stated that younger normal subjects do not have a pressor response to oral water; thus the conclusion that ganglionic blockade abolished the pressor response does not apply to them.

A feature of subjects with AF is their exquisite sensitivity to changes in fluid balance; volume depletion can lower BP rapidly, while infusion of small volumes of
saline can raise BP markedly [30]. In AF, despite orthostatic hypotension, supine hypertension often can be induced if subjects lie in a horizontal position. This recumbency-induced reversal of hypotension is postulated to be due in part to the movement of fluid (initially pooled in the periphery) into the central compartment, especially in the presence of baroreceptor denervation. During recumbency, substantial diuresis (as observed overnight) often occurs, presumably because of better renal perfusion, resulting in weight loss and more severe orthostatic symptoms in the morning. The lack of sympathetic innervation of the renal tubules may enhance the tendency to sodium loss and contribute further to water depletion [32]. These possible mechanisms are the basis for the use of nocturnal head-up tilt and desmopressin to reverse nocturnal polyuria and improve morning hypotension [6,33]. A speculative explanation for the pressor response to oral water over the time scale observed may be an attempt to replete a negative fluid balance and elevation or restoration of intra- and extra-vascular fluid volume. Jordan et al. [2] measured plasma volume by an indirect method based on the haematocrit, which may have caused a reduction in sensitivity, especially in non-arterialized venous blood samples. After oral water, repletion may have been mainly in the central fluid vasculature, thus reducing precision in the derivation of plasma volume in peripheral samples. Furthermore, their derivations of plasma volume were carried out 30 and 60 min after water ingestion, when the pressor response had peaked and begun to wane, and when redistribution into the extravascular spaces may have occurred.

In conclusion, our studies in subjects with severe sympathetic denervation due to pure AF confirm the pressor response to oral water ingestion; this begins after a few minutes and lasts for approx. 30 min. The response occurred with distilled water, thus excluding a role for electrolytes or chemicals. Continuous recording of haemodynamic responses excluded a rise in SV or CO. The responses observed in our lesion deficit human haemodynamic responses excluded a rise in SV or CO. Furthermore, their derivations of plasma volume were carried out 30 and 60 min after water ingestion, when the pressor response had peaked and begun to wane, and when redistribution into the extravascular spaces may have occurred.

REFERENCES


ACKNOWLEDGMENTS

We thank Ms Katharine Bleasdale-Barr and Ms Lydia Thornley for their help in this study, and the International Spinal Research Trust for their support.


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