The effects of water ingestion on orthostatic hypotension in two groups of chronic autonomic failure: multiple system atrophy and pure autonomic failure

T M Young, C J Mathias

Background: Oral ingestion of water increases seated blood pressure in patients with chronic autonomic failure by mechanisms that remain unclear. As orthostatic hypotension is common in chronic autonomic failure, and is not always adequately controlled by medication, the potential benefits of water ingestion on standing blood pressure were studied in two types of autonomic failure: multiple system atrophy (MSA), in which the lesion is central and pre-ganglionic, and pure autonomic failure (PAF), in which the lesion is post-ganglionic.

Methods: In 14 patients with autonomic failure (seven PAF and seven MSA) standing blood pressure and heart rate were measured before, and 15 and 35 minutes after ingestion of 480 ml distilled water. Patients remained seated for 15 minutes after water ingestion, with beat to beat cardiovascular indices measured with the Portapres II device with subsequent Modelflow analysis.

Results: Standing prior to water ingestion caused a significant fall in blood pressure in all patients. After water ingestion there was a rise in seated blood pressure. Seated and standing blood pressure at 15 and 35 minutes after water ingestion was significantly higher than before water, with an improvement in orthostatic symptoms. The time to first significant rise in seated blood pressure occurred at 5 minutes post water ingestion in PAF and at 13 minutes in MSA. These increases were accompanied by increases in total peripheral resistance, reaching significance by 5 minutes in PAF and 13 minutes in MSA. There were no significant changes in cardiac output, stroke volume, or ejection fraction.

Conclusions: Water is thus beneficial in improving standing BP in AF, acting within 15 minutes in both MSA and PAF. The earlier onset of the pressor effect in PAF may reflect the differing lesion site and underlying pathophysiology between these conditions.

Ingestion of water increases seated blood pressure (BP) in chronic autonomic failure. This pressor effect first occurs between 5 and 15 minutes after water ingestion, reaches a peak effect at about 30–35 minutes, and lasts for just under an hour. The volume of water ingested influences the pressor response, with 480 ml producing greater effect than 240 ml, but the temperature (9°C and 24°C) of ingested water does not seem to be an important factor. Although the underlying mechanisms of the pressor action of water in AF have not previously been determined, possible mechanisms include partial residual sympathetic activity, baroreflex dysfunction, gastric distension, or fluid redistribution. Multiple system atrophy (MSA) and pure autonomic failure (PAF) provide contrasting models of chronic autonomic failure. In MSA the underlying lesion site is central and pre-ganglionic, whilst in PAF it is distal and post-ganglionic. The detailed haemodynamic response to water ingestion while seated has been studied in PAF, but there have been no comparisons with MSA. We postulated that differences in the pressor response to water between the two groups would relate to the different lesion site in PAF and MSA, and might provide information on the mechanism of the pressor effect.

Orthostatic hypotension (OH) is common to both PAF and MSA, may cause substantial symptoms, and often is inadequately controlled by medication. We determined whether water ingestion would improve standing BP and also symptoms in these patients. Previous work has suggested that OH in chronic autonomic failure is improved 35 minutes after ingestion of 480 ml of water, although the effects on symptoms are not known. Water increases seated BP 5–15 minutes after ingestion, raising the possibility of an earlier improvement in OH. We therefore measured standing BP 15 and 35 minutes after water ingestion in our subjects.

SUBJECTS AND METHODS

A total of 14 patients with chronic autonomic failure (seven MSA, seven PAF) were studied. The mean (SD) age of the MSA patients was 62 (9.5) (four males, three females) and that of the PAF patients 59 (10) (three males and four females). MSA and PAF were diagnosed using existing criteria. All patients had documented sympathetic and parasympathetic dysfunction with severe orthostatic hypotension (table 1). PAF had greater supine BP than MSA. There were no differences in the vasoactive medication between the two groups: three in each were on fludrocortisone and two in each on ephedrine, one PAF took midodrine and two subjects in each group were on no medication. None of the subjects was on anti-parkinsonian medication. Vasoactive medication was withdrawn the night prior to the study. All patients gave informed consent to participate in the study. The study had ethical approval from the National Hospital for Neurology & Neurosurgery and St Mary's Hospital.

Study design

On the morning of the study the patients fasted after a light breakfast at 0800. The study took place in a dedicated...
autonomic laboratory between 1000 and 1300. The patients emptied their urinary bladders. They were then seated, and BP was recorded both intermittently and continuously. Intermittent brachial BP values were obtained every 3 minutes using an automated Dynamap (Critikon) sphygmomanometer on the left arm. Continuous measurement of beat to beat BP was obtained throughout the study with the Portapres II device on the middle finger of the right hand. Beat BP was obtained throughout the study with the meter on the left arm. Continuous measurement of beat to beat BP values were obtained every 3 minutes after standing up. The patient then returned to the seated position. Following standing the patient was questioned on the presence and severity of orthostatic symptoms. After baseline BP had been re-established, the patient drank 480 ml of distilled water at room temperature within a target time of 5 minutes (mean time taken by the MSA patients was 3 minutes 45 seconds; no significant difference between groups). On completion of water ingestion the patient remained seated for a further 15 minutes. The patient then stood in an identical manner to Stand 0; this was termed Stand 1, the first after water ingestion. On completion of Stand 1, the patient returned to the seated position for a further 15 minutes. After this time (now 35 minutes after water ingestion) the patient stood for 5 minutes (Stand 2). The three subjects (two MSA and one PAF) who experienced no symptoms during Stand 0 noted subjective improvement in their orthostatic symptoms during Stands 1 and 2. The three subjects (two MSA and one PAF) experienced no symptoms during Stand 0. All 11 of the subjects symptomatic on Stand 0 noted subjective improvement in their orthostatic symptoms during Stands 1 and 2. The three subjects (two MSA and one PAF) who experienced no symptoms during Stand 0 remained without symptoms during both subsequent standing periods.

Data analysis
Dynamap values for systolic and diastolic BP (SBP, DBP) were compared at 3 and 5 minutes to each stand before and after water. Patients acted as their own controls with BP's for stands 1 and 2 being compared with their own Stand 0 values. Paired Student’s t-test was used, with statistical significance being taken as p<0.05.

RESULTS
Pooled dynamap data for all 14 patients, before and during standing
The 14 AF subjects showed a significant fall in SBP and DBP (Dynamap data) on standing compared with seated values. There was no significant change in the drop on standing after water ingestion, but, as seated SBP and DBP rose significantly over this time, the net result was a significant increase in standing SBP and DBP at both 15 and 35 minutes after water ingestion compared with baseline. These results are shown in table 2.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Autonomic function testing on study patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MSA (n=7)</td>
</tr>
<tr>
<td>Supine SBP</td>
<td>139.4 (24.0)</td>
</tr>
<tr>
<td>Standing SBP</td>
<td>99.4 (16.9)</td>
</tr>
<tr>
<td>Change in SBP</td>
<td>-40.0 (28.0)</td>
</tr>
<tr>
<td>Hand grip</td>
<td>6.2 (5.2)</td>
</tr>
<tr>
<td>Cold pressor</td>
<td>8.7 (19.0)</td>
</tr>
<tr>
<td>Supine DBP</td>
<td>82.0 (11.2)</td>
</tr>
<tr>
<td>Standing DBP</td>
<td>6.2 (17.7)</td>
</tr>
<tr>
<td>Sinus arrhythmia ratio</td>
<td>1.11 (0.05)</td>
</tr>
</tbody>
</table>

Values are mean (SD) for MSA and PAF. SBP, systolic blood pressure; DBP, diastolic blood pressure.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Dynamap blood pressure and heart rate in 14 patients with AF (seven MSA, seven PAF) on standing, and before and after ingestion of 480 ml water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stand 0 (before water)</td>
<td>Stand 1 (15 min after water)</td>
</tr>
<tr>
<td>SBP 100.6 (25.1)</td>
<td>122.9 (29.0)</td>
</tr>
<tr>
<td>DBP 69.6 (12.9)</td>
<td>76.4 (13.9)*</td>
</tr>
<tr>
<td>HR 73.7 (11.2)</td>
<td>70.5 (8.6)</td>
</tr>
<tr>
<td>3 min of stand SBP 79.5 (21.5)</td>
<td>101.0 (23.3)</td>
</tr>
<tr>
<td>DBP 51.5 (15.0)*</td>
<td>63.1 (13.0)*</td>
</tr>
<tr>
<td>HR 82.9 (15.2)</td>
<td>75.8 (13.1)**</td>
</tr>
<tr>
<td>5 min of stand SBP 77.4 (25.6)**</td>
<td>95.3 (23.0)**</td>
</tr>
<tr>
<td>DBP 49.6 (16.3)*</td>
<td>63.4 (16.1)**</td>
</tr>
<tr>
<td>HR 81.9 (16.2)</td>
<td>76.6 (14.6)**</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

*Values are mmHg (SD) for BP and beats/min (SD) for HR: Stand 1 and 2 compared with Stand 0.

**p<0.05; ***p<0.01; ****p<0.001.

Symptoms experienced on standing
After standing on each occasion the subjects were questioned about the presence and severity of three common symptoms of OH: light headedness, visual disturbance, and “coat hanger” neck pain in the occipital and shoulder region. Of the 14 subjects, 11 reported one or more of these symptoms during Stand 0. All 11 of the subjects symptomatic on Stand 0 noted subjective improvement in their orthostatic symptoms during Stands 1 and 2. The three subjects (two MSA and one PAF) who experienced no symptoms during Stand 0 remained without symptoms during both subsequent standing periods.

Subset analysis (MSA and PAF data)
Dynamap data
Baseline seated BP did not differ significantly between MSA (117.3 (18.6)/73.0 (13.8) mmHg) and PAF (103.9 (30.1)/66.3 (11.9)), as shown in table 4. Stand 0 resulted in a significant drop in BP at 3 and 5 minutes in both MSA and PAF, with no significant difference between the groups. Subgroup analysis showed a similar increase in standing BP after water ingestion in both groups of patients (table 4), with no significant difference between the groups.

Beat to beat haemodynamic data
Beat to beat data was assessed before and during the 15 minutes immediately following water ingestion, during
which time the patients remained seated. In PAF an increase in seated SBP and DBP was recorded after water ingestion, which first reached significance 5 minutes post water ingestion (fig 1) and remained so until the end of the study. Seated HR increased, first reaching significance 5 minutes after ingestion (fig 1) and remained so until the end of the study. Seated TPR increased, first reaching significance 5 minutes after ingestion and remaining so until the end of the study. Seated CO, SV, and EF did not significantly change during the study. There was a non-significant reduction in seated HR (beats/min) over the first 15 minutes post water ingestion in both subsets (mean (SD) baseline 73.5 (10.1) and 78.2 (9.7); 15 minutes post water 67.8 (6.1) and 74.4 (8.6) for PAF and MSA respectively). Beat to beat data during each stand (table 3) showed no significant difference between MSA and PAF.

In MSA, an increase in seated SBP and DBP was recorded after water ingestion, which first reached significance 13 minutes after ingestion (fig 2) and remained so until the end of the study. Seated HR increased, first reaching significance 13 minutes after water ingestion and remaining so until the end of the study. Seated HR showed a reduction, which failed to reach statistical significance. Seated CO, SV, and EF did not significantly change during the study.

**DISCUSSION**

Our results have shown that oral ingestion of 480 ml of distilled water results in subjective and objective improvements in OH on standing in both MSA and PAF subjects when measurements were made at 15 and 35 minutes after water. In addition the detailed analysis, utilising continuous haemodynamic measurements pre and post water indicate that there are temporal differences in the pressor response between MSA and PAF. In previous studies1 2 there did not appear to be differences, and it may be that intermittent measurements every 3 or 5 minutes may have made comparisons difficult.

The haemodynamic differences between MSA and PAF while seated warrant discussion. In PAF the pressor effect occurred sooner (within 5 minutes) than in MSA (13 minutes after ingestion). This may shed further light on the mechanisms responsible for the pressor response, as in PAF.

**Table 3** Beat to beat haemodynamics in MSA and PAF on standing, before and after water

<table>
<thead>
<tr>
<th></th>
<th>Seated</th>
<th>Stand 0</th>
<th>Seated</th>
<th>Stand 1</th>
<th>Seated</th>
<th>Stand 2</th>
</tr>
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<tbody>
<tr>
<td>MSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>102.8 (28.9)</td>
<td>93.7 (32.2)</td>
<td>113.0 (28.5)</td>
<td>102.4 (24.6)</td>
<td>118.9 (28.2)</td>
<td>108.2* (33.7)</td>
</tr>
<tr>
<td>DBP</td>
<td>59.7 (17.4)</td>
<td>56.6 (21.4)</td>
<td>69.0 (19.5)</td>
<td>63.3* (17.6)</td>
<td>71.2 (19.1)</td>
<td>68.3* (22.4)</td>
</tr>
<tr>
<td>CO</td>
<td>5.2 (1.7)</td>
<td>4.4 (1.3)</td>
<td>4.7 (1.7)</td>
<td>4.4 (0.9)</td>
<td>4.8 (2.0)</td>
<td>3.5 (1.1)</td>
</tr>
<tr>
<td>TPR</td>
<td>1.0 (0.5)</td>
<td>1.1 (0.6)</td>
<td>1.3 (0.2)</td>
<td>1.1 (0.4)</td>
<td>1.1 (0.5)</td>
<td>1.4 (0.7)</td>
</tr>
<tr>
<td>SV</td>
<td>68.7 (20.4)</td>
<td>51.7 (17.1)</td>
<td>63.0 (16.8)</td>
<td>54.5 (8.7)</td>
<td>65.2 (19.6)</td>
<td>49.5 (11.1)</td>
</tr>
<tr>
<td>HR</td>
<td>76.1 (10.2)</td>
<td>87.2 (17.1)</td>
<td>74.4 (8.6)</td>
<td>81.3 (14.9)</td>
<td>72.6 (10.5)</td>
<td>82.0 (9.4)</td>
</tr>
<tr>
<td><strong>PAF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>102.8 (67.2)</td>
<td>67.2 (23.6)</td>
<td>130.3 (39.2)</td>
<td>95.6** (26.9)</td>
<td>131.6 (40.4)</td>
<td>98.4** (26.9)</td>
</tr>
<tr>
<td>DBP</td>
<td>62.1 (41.5)</td>
<td>41.5 (15.9)</td>
<td>77.3 (17.7)</td>
<td>58.6* (17.2)</td>
<td>80.0 (20.3)</td>
<td>61.5* (17.2)</td>
</tr>
<tr>
<td>CO</td>
<td>3.5 (1.5)</td>
<td>2.8 (0.9)</td>
<td>3.7 (1.9)</td>
<td>3.5 (1.5)</td>
<td>3.6 (2.2)</td>
<td>3.3 (1.5)</td>
</tr>
<tr>
<td>TPR</td>
<td>1.7 (1.1)</td>
<td>1.3 (0.9)</td>
<td>1.8 (0.8)</td>
<td>1.6 (0.8)</td>
<td>1.9 (1.2)</td>
<td>1.7 (1.0)</td>
</tr>
<tr>
<td>SV</td>
<td>47.9 (18.5)</td>
<td>38.4 (13.8)</td>
<td>53.6 (24.5)</td>
<td>49.1 (19.0)</td>
<td>52.2 (27.4)</td>
<td>45.6 (18.2)</td>
</tr>
<tr>
<td>HR</td>
<td>72.1 (11.2)</td>
<td>76.2 (13.3)</td>
<td>67.8 (6.1)</td>
<td>71.4 (8.0)</td>
<td>67.3 (7.3)</td>
<td>71.1 (9.4)</td>
</tr>
</tbody>
</table>

Values (SD): Stand 1 and 2 compared with Stand 0.

SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); CO, cardiac output (l/min); TPR, total peripheral resistance (MU); SV, stroke volume (ml); HR, heart rate (beats/min).

* p < 0.05; ** p < 0.01; *** p < 0.001.

**Table 4** Dynamap blood pressure and heart rate in patients with PAF and MSA on standing, before and after ingestion of 480 ml water

<table>
<thead>
<tr>
<th></th>
<th>PAF (n=7)</th>
<th></th>
<th>MSA (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stand 0 (before water)</td>
<td>Stand 1 (15 min after water)</td>
<td>Stand 2 (35 min after water)</td>
</tr>
<tr>
<td>SBP</td>
<td>103.3 (35.5)</td>
<td>79.4 (30.0)</td>
<td>121.7 (34.1)</td>
</tr>
<tr>
<td>DBP</td>
<td>60.9 (19.3)</td>
<td>48.5 (19.9)</td>
<td>73.1 (18.4)</td>
</tr>
<tr>
<td>CO</td>
<td>4.3 (1.8)</td>
<td>3.5 (1.3)</td>
<td>4.2 (1.8)</td>
</tr>
<tr>
<td>TPR</td>
<td>1.3 (0.9)</td>
<td>1.2 (0.8)</td>
<td>1.6 (0.8)</td>
</tr>
<tr>
<td>SV</td>
<td>58.3 (21.6)</td>
<td>44.6 (16.3)</td>
<td>58.3 (20.8)</td>
</tr>
<tr>
<td>HR</td>
<td>74.1 (10.5)</td>
<td>81.3 (15.8)</td>
<td>71.1 (7.9)</td>
</tr>
</tbody>
</table>

Values in mmHg (SD) and beats/min (SD): Stand 1 and 2 compared with Stand 0.

* p < 0.05; ** p < 0.01; *** p < 0.001.
all the subjects had clear evidence of substantial peripheral sympathetic denervation, whereas in MSA the predominant lesion was likely to be preganglionic. The pressor response to water is known to be dependant on the volume ingested, and may be the result of gastric distension increasing sympathetic nerve activity by reflex mechanisms, as has been described in normal subjects. This response is likely to be dependent on residual sympathetic activity, and is therefore expected to be minimal in PAF and greater in MSA. This would be consistent with the effects previously described of yohimbine, an $\alpha_2$ agonist that is dependent on sympathetic activity, and where the pressor response was related to the pressor response of water. However, this was not the case in our study, as the response was as great in PAF, and had a more rapid onset than in MSA. An alternative may be that the pressor response in PAF was related to denervation supersensitivity, which has been well documented in this group, and is greater than in MSA. It is possible that in PAF, even a small amount of NA released could have acted on supersensitive receptors, although this seems less plausible than the release of other vasoconstrictor substances, including factors such as endothelin, which may then exert the pressor response. These possibilities may explain the rise in peripheral resistance found in this study. A further substance to be considered is vasopressin, which is known to be released in PAF but not MSA during the head up position.
Another factor to be considered with water ingestion is the effect of fluid repletion, in patients who are known to be prone to salt and water loss, especially when they are recumbent. The study was supported by a grant from the Sarah Matheson Trust.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Sarah Matheson Trust Autonomic Disorders Association.

REFERENCES


Authors’ affiliations

T M Young, Neurovascular Medicine Unit, Faculty of Medicine, Imperial College London at St.Mary’s Hospital

C J Mathias, Autonomic Unit, Institute of Neurology, the National Hospital for Neurology and Neurosurgery, Queen Square, University College London, London, UK

Competing interests: none declared
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*J Neurol Neurosurg Psychiatry* 2004 75: 1737-1741
doi: 10.1136/jnnp.2004.038471