

Cardiac vagal response to water ingestion in normal human subjects

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A B S T R A C T

In healthy young subjects there is direct evidence for sympathetic vasoconstrictor activation after drinking water, but this is not accompanied by an increase in arterial blood pressure. A marked pressor response to water ingestion has, however, been observed in elderly subjects and in patients with autonomic failure. We examined the effect of water ingestion on haemodynamic variables and heart rate variability (HRV) markers of cardiac vagal control in ten healthy young subjects and four cardiac transplant recipients with confirmed persistent cardiac vagal denervation. In a random order crossover protocol, changes in heart rate, blood pressure and measures of high frequency (HF) HRV were compared over time following the ingestion of 500 ml and 20 ml (control) of tap water. In healthy subjects, after drinking 500 ml of water the heart rate fell from 67.6 ± 2.0 (mean \pm S.E.M.) to 60.7 ± 2.4 beats/min ($P < 0.01$), and the bradycardic response peaked between 20 and 25 min. There were no significant changes in arterial blood pressure. Over the same time course, water ingestion caused increases in measurements of HF HRV: root-mean-square of successive RR interval differences (RMSSD) increased by 13 ± 2.7 ms after 500 ml versus 2 ± 3.1 ms after 20 ml ($P < 0.05$); HF power increased by 686 ± 400 versus -63 ± 322 ($P < 0.01$). In transplant recipients water ingestion was followed by a pressor response (range 13 to 29 mmHg). These results provide evidence that water ingestion in normal subjects is followed by an increase in cardiac vagal control that may counteract the pressor effects of sympathetic activation. We suggest that in the elderly, in transplant recipients and in autonomic failure, loss of this buffering mechanism explains the pressor response to drinking water.

INTRODUCTION

The essential daily activity of drinking water has recently been shown to have unexpected haemodynamic effects which may be of clinical importance [1–3]. Jordan and colleagues noted that in patients with autonomic failure, the severity of their symptoms of orthostatic hypotension were substantially decreased shortly after drinking water. They then demonstrated in these patients that drinking 0.5 litre of water caused an acute rise in blood pressure of between 30 and 100 mmHg [1,3]. A more modest pressor effect of approx. 10 mmHg was also demonstrated in

healthy middle-aged and elderly subjects, but was not seen in young adults [2]. There is now substantial evidence that this pressor response to water drinking, which is maximal at about 30 min is due to an increase in sympathetic output. In patients with autonomic failure the pressor response was accompanied by a rise in plasma noradrenaline [2]. Studies in healthy young volunteers using direct measurement of muscle sympathetic nerve activity from the peroneal nerve also showed a rise in sympathetic nerve traffic after water drinking [4]. Despite this, there was no change in arterial blood pressure and notably no change, or even a slight reduction in heart

Key words: autonomic nervous system, baroreceptors, blood pressure, heart rate.

Abbreviations: HF, high frequency; HRV, heart rate variability; LF, low frequency; pNN50, percentage of successive RR interval differences exceeding 50 ms; RMSSD, root-mean-square of successive RR interval differences.

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rate. Thus it appears that sympathetic activation is a normal response to water drinking but paradoxically, an associated pressor response is present only in those with autonomic dysfunction and in the elderly. This suggests that in young patients, an effective 'buffering' mechanism exists to counteract the pressor effect of sympathetic vasoconstrictor activation. It has been suggested that this may be due to a concomitant increase in cardiac vagal activation, which prevents a rise in arterial pressure by reducing cardiac output [2,4]. The present investigation was designed to determine whether this was the case, by examining the effect of water drinking in healthy young volunteers on haemodynamic variables and heart rate variability markers of cardiac vagal control. As a further test of the importance of autonomic control of the heart we also determined the haemodynamic response to water ingestion in cardiac transplant recipients in whom there is a specific loss of cardiac innervation, whilst sympathetic vasomotor pathways remain intact.

METHODS

Subjects

Ten subjects (6 males, 4 females) aged between 24 and 34 years were studied. All subjects were normotensive, non-smokers, on no medication and were screened by history and physical examination to exclude cardiovascular or neurological dysfunction. In addition four cardiac transplant recipients were recruited (2 males, 2 females) aged between 50 and 62 years and between 2 and 9 years post-transplant. In each patient persistent cardiac vagal denervation had been confirmed by power spectral analysis of ECG recordings and lack of measurable baroreflex sensitivity by the phenylephrine bolus method [5].

Protocol

The study was approved by the South Birmingham Regional Ethics Committee and all subjects provided written informed consent prior to taking part. Subjects attended an initial habituation and training visit to our dedicated clinical autonomic research laboratory. At this visit they were trained to breathe to an audio signal set close to the individual's resting respiratory frequency.

Subjects were studied in a random-order crossover design and all studies were commenced at 08.00 hours after a 12-h fast. Subjects were asked to avoid alcohol for at least 24 h before each study and to empty their bladder before starting the study. Transplant recipients withheld their regular medication on the morning of each study, with the exception of immunosuppressive therapy. The laboratory temperature was kept constant at 23 ± 1 °C and subjects rested in the semi-supine position throughout. A standard three-lead ECG signal was amplified, processed [high frequency (HF) signal noise filter > 500 Hz], and digitized at 500 Hz with the use of a National Instru-

ments NB/MIO/16XH/18 analog-to-digital converter board (National Instruments Corporation, Newbury, Berks., U.K.). A continuous arterial pressure signal was obtained with the Portapres device (TNO Biomedical Instrumentation, Amsterdam, The Netherlands) and was similarly digitized. Respiratory excursion was recorded from the amplified output of a standard strain gauge attached to an elastic strap around the subject's chest. All signals were displayed on the screen of a personal computer running Laboratory View 5.0 software (National Instruments Corporation). In addition, blood pressure was recorded throughout the protocol at 5 min intervals, taking the mean for three consecutive measurements using automated arm cuff sphygmomanometry.

Subjects were rested for 30 min, after which 5-min segments of the three digital signals were recorded during breathing at the predetermined frequency and stored to disk. Subjects were then asked to drink tap water at 18 °C as quickly as was comfortable. All subjects were randomly assigned to drinking 500 ml or 20 ml (control) of water during the first of two studies. The second volume was given during a separate study visit 7 to 14 days later. ECG and blood pressure monitoring continued for a further 45 min whilst 5 min recordings for analysis of heart rate variability were stored at 5, 20 and 35 min after drinking during fixed frequency respiration.

Data analysis

The ECG series for analysis were coded so that the investigator performing the analysis was blinded to the nature of the study. All ECG series were reviewed and if necessary edited to exclude ectopic and artifact signals. The RR intervals before and after any ectopic beats were replaced by interpolation from the previous and following sinus intervals. No signal containing > 1% of ectopic beats was used for analysis. R waves were detected by an individually adjusted threshold. Heart rate variability (HRV) was analysed off-line on data lengths of 256 RR intervals.

Time domain analysis

We used the standard time domain measures of root-mean-square of successive RR interval differences (RMSSD), and percentage of successive RR interval differences exceeding 50 ms (pNN50). These indices, based on successive differences in RR intervals, assess HF ('beat-to-beat') variation associated with respiratory sinus arrhythmia mediated principally by the vagus nerve [6].

Frequency domain analysis

Power spectral analysis was performed with the use of the Burg algorithm (autoregressive modelling), with a model order between 8 and 20 selected to minimize the Akaike information criterion. The power at each underlying frequency was quantified by decomposing the total

variability signal according to previously published methods [7,8]. Powers at low frequency (LF; centred at 0.1 Hz) and at HF (corresponding to the observed respiratory frequency) were thus determined.

Statistical analysis

Data for arterial blood pressure and RR interval in the water and control arms of the study were compared by a two-tailed paired Student's *t* test. Differences between groups for time and frequency domain indices of HRV were determined with the Wilcoxon signed rank test for paired data. Statistical significance was defined by a value of $P < 0.05$. Numerical values are expressed as mean \pm S.E.M.

Table 1 Baseline arterial blood pressure, RR interval and RR interval variability before the ingestion of 500 ml and 20 ml of water (paired data on separate study days)

Values are means \pm S.E.M.

Index	Water volume ...	Baseline	
		500 ml	20 ml
Systolic blood pressure (mmHg)		117 \pm 3	115 \pm 3
Diastolic blood pressure (mmHg)		79 \pm 3	79 \pm 3
Mean arterial pressure (mmHg)		92 \pm 3	91 \pm 3
RR interval (ms)		893 \pm 23	937 \pm 24
RMSSD (ms)		42 \pm 8	48 \pm 6
pNN50 (%)		21 \pm 5	29 \pm 5
HF absolute power (ms ²)		1870 \pm 998	2059 \pm 544
LF absolute power (ms ²)		278 \pm 79	600 \pm 164

Table 2 Changes from baseline values (Δ) in haemodynamic variables, time domain indices of HF HRV (RMSSD, pNN50) and frequency domain indices (HF and LF absolute power) at various intervals of time following water ingestion

Values are given as mean \pm S.E.M for the group comparing results after drinking 500 ml of water with results after drinking 20 ml of water as a control. ns, not significant ($P > 0.05$); vs, versus.

Index	Time ...	5 min		20 min		35 min	
		Water volume ...	500 ml vs 20 ml	500 ml vs 20 ml	500 ml vs 20 ml		
Δ Systolic blood pressure (mmHg)			3.1 \pm 0.8 vs -1.2 \pm 2.0 ns	1.0 \pm 1.4 vs -1.5 \pm 2.0 ns	-2.0 \pm 1.5 vs -2.0 \pm 1.5 ns		
Δ Diastolic blood pressure (mmHg)			2.4 \pm 1.3 vs -0.9 \pm 1.4 ns	2.7 \pm 1.4 vs -1.1 \pm 1.3 ns	2.1 \pm 1.4 vs -1.1 \pm 1.1 ns		
Δ RR interval (ms)			44 \pm 19 vs 16 \pm 21 ns	107.5 \pm 62.8 vs 39.3 \pm 63.6 $P < 0.001$	88 \pm 20 vs 45 \pm 15 ns		
Δ RMSSD (ms)			8.1 \pm 2 vs 4.1 \pm 2.7 ns	13 \pm 2.7 vs 2 \pm 3.1 $P < 0.05$	10.9 \pm 3.4 vs 8.8 \pm 4.8 ns		
Δ pNN50 (%)			6.7 \pm 2.4 vs 4.5 \pm 2 ns	9.7 \pm 2.9 vs 2.2 \pm 3.2 ns	9.9 \pm 2.4 vs 6.8 \pm 4.2 ns		
Δ HF absolute power (ms ²)			392 \pm 168 vs -288 \pm 287 ns	686 \pm 400 vs -63 \pm 322 $P < 0.01$	178 \pm 213 vs 61 \pm 450 ns		
Δ LF absolute power (ms ²)			197 \pm 90 vs 303 \pm 146 ns	245 \pm 111 vs -11 \pm 135 ns	499 \pm 199 vs 589 \pm 305 ns		

RESULTS

The frequency of metronomic breathing was within the range 0.18 to 0.22 Hz. Baseline values for mean arterial pressure, RR interval, and indices of HF HRV were not significantly different in the group before drinking 500 ml or 20 ml of water (Table 1). Drinking 500 ml of water did not result in any change in arterial blood pressure measured by Portapres or brachial sphygmomanometry (Table 2). After ingesting 500 ml of water there was, however, a fall in the heart rate in each of the ten subjects (Figure 1). This decrease was maximal at

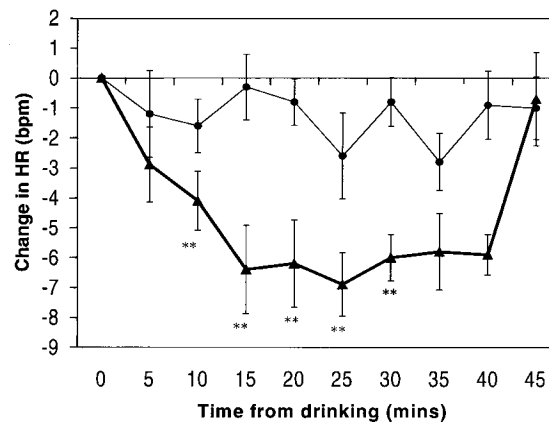


Figure 1 Magnitude of changes in heart rate (HR), in beats/min (bpm), over time after the ingestion of 500 ml (\blacktriangle) or 20 ml (\bullet ; control) of tap water

Values are mean \pm S.E.M. *** $P < 0.01$, 500 ml versus 20 ml of water (control).

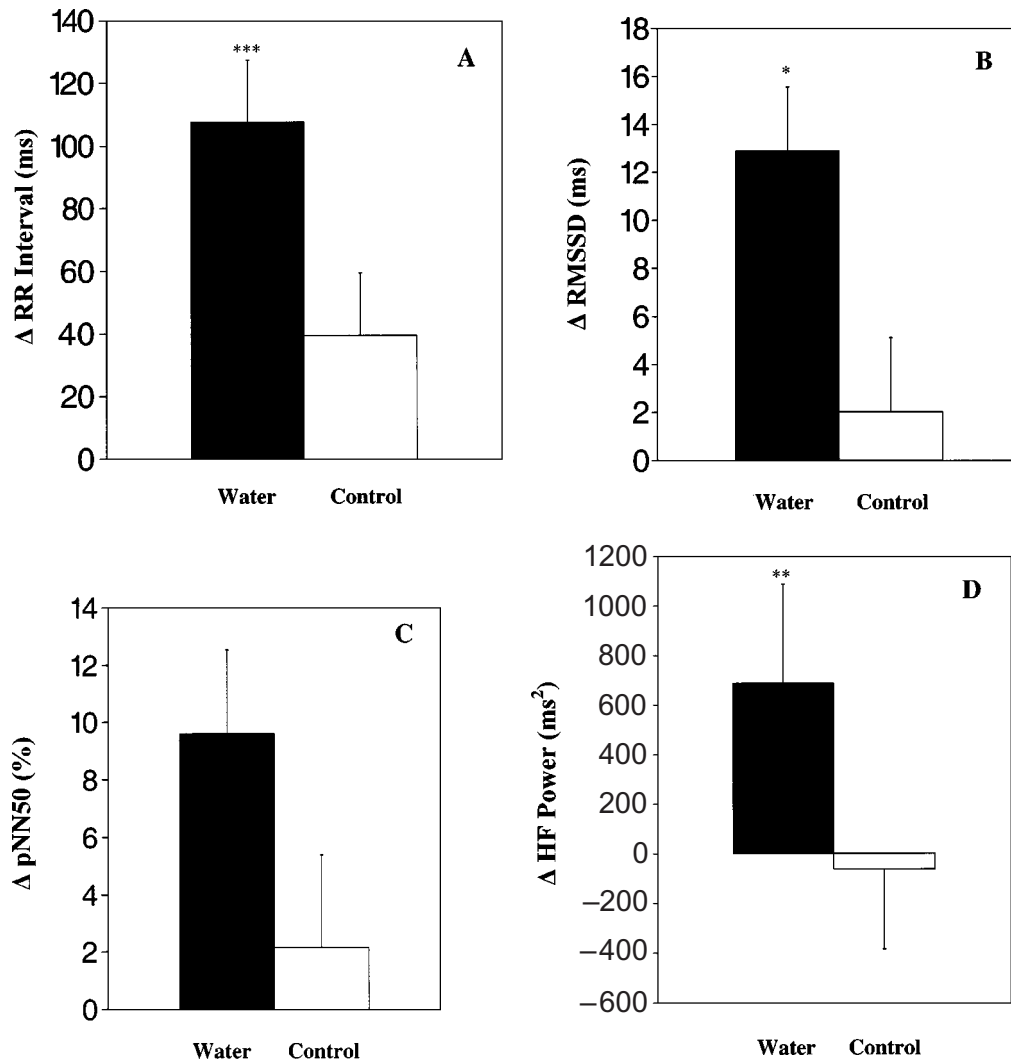


Figure 2 Change in the (A) RR interval, (B) RMSSD, (C) pNN50, and (D) absolute power of the HF peak (HF Power) from baseline, 20 min after drinking water

Values are means \pm S.E.M. Significance of differences for 500 ml versus 20 ml of water (control): * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Filled bars, 500 ml of water; open bars, 20 ml of water (control).

20 min after ingestion. The heart rate returned to a level not statistically different from baseline values at 40 min. In contrast, in the control arm of the study, with the same subjects drinking 20 ml of water, there was no significant change in the heart rate (Figure 1).

Measures of HF vagally mediated HRV in both time and frequency domains were significantly higher after the ingestion of 500 ml of water than after the ingestion of 20 ml (Table 2). A comparison of the magnitude of change at 20 min in RR interval, RMSSD and pNN50 from baseline values (Figure 2A, 2B and 2C) emphasizes the markedly discrepant responses between the two volumes ingested. There was also a significant increase in HF absolute power in response to water ingestion, which did not occur in the control arm (Figure 2D). Compared

with control, there was no significant increase in LF power.

In the cardiac transplant recipients the resting heart rate was 89 beats/min and the heart rate did not change significantly from baseline throughout the study period. Baseline systolic arterial blood pressure was 137 mmHg (range 124–144) and between 15 and 30 min following ingestion of 500 ml of water had increased in all four subjects, returning to baseline at 40–45 min. The changes in systolic pressure by automated brachial sphygmomanometry at 20 min after drinking 500 ml of water were +19 mmHg, +13 mmHg, +29 mmHg and +14 mmHg. Measures of HF HRV were extremely low or absent in all transplant patients and remained so throughout the study.

DISCUSSION

The main finding of the present study was that water drinking in normal subjects caused a bradycardia, which our HRV analysis indicated was due to an increase in cardiac vagal activity. The vagus nerve is inaccessible to direct recording in humans, but vagal modulation of heart rate can be assessed indirectly using HF ('beat-to-beat') variability. This is the only neural mechanism capable of mediating variability at this frequency and HF indices such as RMSSD, pNN50 and the power of the HF peak (derived from power spectral analysis) are widely held to reflect the degree of vagal modulation of heart rate [6].

In addition, our results have confirmed that in normal young subjects, compared with the elderly or those patients with autonomic failure, ingestion of a moderate volume of water does not lead to a rise in arterial blood pressure. This is in keeping with the results of previous investigators who, despite convincingly demonstrating a rise in sympathetic vasoconstrictor activity, found no rise in arterial blood pressure using a Finapres device [4,9].

Our results therefore suggest that the physiological response to water drinking in healthy subjects may be an integrated response, consisting of an increase in sympathetic vasoconstrictor activity coupled with a parallel increase in cardiac vagal activity. Thus the increase in total peripheral resistance is counteracted by a fall in cardiac output. Such an autonomic response is unusual, since under most circumstances sympathetic and parasympathetic outflows are inversely related. The response is similar in some respects to the 'diving reflex' in which trigeminal nerve stimulation by cold results in cardiac vagal activation and a profound bradycardia, as well as sympathetic activation and vasoconstriction [10,11]. The response to water drinking, however, differs in that it has a gradual onset, the consequent bradycardia is prolonged throughout 35–40 min and it occurs in response to water at room temperature. An integrated response of this nature would explain why, in these young volunteers and in those studied previously [2,4,9], despite increases in sympathetic vasoconstrictor discharge and peripheral resistance, blood pressure remains stable, as a result of a vagally mediated fall in cardiac output. The fall in cardiac output is likely to be mediated by reductions in both heart rate and stroke volume, since vagal stimulation has been demonstrated recently, in both humans and animal subjects, to have negative inotropic effects [12].

Whilst the present investigation was not designed to determine the nature of the afferent stimuli to such an integrated autonomic response, two mechanisms have been proposed to explain the activation of sympathetic pathways in normal subjects. Gastric distension with water or a balloon in both animal [13–16] and human [17] studies has been repeatedly demonstrated to cause an increase in sympathetic activity. Decreases in portal

osmolality have also been implicated in a reflex that results in sympathetic vasoconstriction, a diuresis and sweating [18,19]. Similar afferent stimuli might also lead to an increase in cardiac vagal efferent activity; however, it must be noted that the characteristics of the observed response are not those that would be expected from a conventional reflex. The bradycardic response we have observed following water ingestion has a slow increase in magnitude and a slow decay, a pattern more characteristic of a response driven by the generation of humoral factors. Factors such as angiotensin II and atrial natriuretic peptide can affect brain centres with a poor blood–brain barrier such as the area postrema and subcortical areas of the forebrain, either of which may be involved in the generation of the autonomic response to water ingestion.

Ageing is associated with marked reductions in cardiac vagal control even in healthy adults [20,21]. Similarly, baroreflex sensitivity is markedly reduced in elderly subjects [22,23]. We propose that a deficiency in the cardiac vagal component of this integrated response to water ingestion may explain the moderate rise in blood pressure that occurs in healthy elderly subjects after drinking water.

In patients with chronic autonomic failure, residual sympathetic activity may be responsible for the pressor response, whilst loss of cardiac vagal control of heart rate means that this rise in arterial blood pressure is not compensated for by a decrease in cardiac output. Some doubt remains regarding the mechanism of sympathetic activation, particularly in this group of patients who are often unable to mount an adequate pressor response to overcome disabling postural drops in blood pressure. This has been highlighted recently by Mathias and colleagues, who postulated that in patients with autonomic failure, the observed response may be due to restoration of intravascular volume [3]. The increase in cardiac vagal activity after water drinking that we have shown would also be consistent with an increase in circulating volume and the consequent low pressure baroreceptor response. This explanation is not, however, consistent with the previous reports of an increase in sympathetic nerve activity in response to water drinking in normal subjects. In addition, previous studies of plasma volume after drinking water have found no significant change [2,4]. We therefore favour a neurally mediated pressor effect.

The aim of our studies with the transplant patients was to document the haemodynamic response to water drinking in a group whose autonomic pathology could be more clearly defined than in those with the more diverse syndromes of chronic autonomic failure. This group of patients had been demonstrated to have complete persistent cardiac vagal denervation between 1–3 years after surgery. The finding in these individuals of a pressor response to water ingestion (of a magnitude between that of elderly subjects and patients with autonomic failure),

again suggests that cardiac vagal innervation is required to prevent this pressor response. The rise in arterial pressure was variable but modest considering the intact peripheral sympathetic innervation and lack of cardiac vagal innervation. This may be explained by the baseline hypertension of the transplant patients and their treatment with cyclosporin, which is well recognized to cause high basal levels of sympathetic activity [24].

The physiological response to water drinking in normal subjects appears to be complex, involving both limbs of the autonomic nervous system. Further investigations are required to define this response in detail. Only when the normal response to water drinking is clearly understood will we be able to explain the powerful and potentially useful effects of water ingestion on blood pressure in subjects with autonomic dysfunction.

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