Hormonal, renal, and autonomic nerve factors involved in the excretion of sodium and water during dynamic salt and water loading in hypoxaemic chronic obstructive pulmonary disease

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Abstract

Background – Some patients with hypoxaemic chronic obstructive pulmonary disease (COPD) develop sodium and water retention and a subclinical autonomic neuropathy. The possibility that these might be associated has been investigated. **Methods** – The ability of 24 patients with COPD to excrete a 6 ml/kg 2.7% intravenous saline or 15 ml/kg oral water load was studied and changes in plasma electrolyte levels, osmolality, plasma aldosterone and vasopressin levels, urinary volume and sodium content, glomerular filtration rate, renal blood flow, and cardiovascular autonomic nerve function were measured. Patients were divided into groups of eight: those in group A (controls) had mild COPD with a PaO_2 of >9 kPa and no oedema, patients in group B were more hypoxaemic but had never been oedematous, whilst those in group C were hypoxaemic and mildly oedematous at the time of the study. **Results** – Patients in groups B and C excreted less sodium and water during saline loading and a lesser proportion of the water load. Patients in group C had a reduction in renal blood flow and glomerular filtration rate and all had a subclinical autonomic neuropathy, which was also found in three patients in group B. Their plasma aldosterone level was raised but did suppress appropriately on saline loading. Vasopressin levels were abnormally raised for the osmolality in patients in group C and in those with autonomic dysfunction throughout the water load and at 240 minutes after the salt load. Sodium and urine excretion was highly correlated with autonomic dysfunction, aldosterone levels at time zero, and renal blood flow. The 11 patients with autonomic dysfunction were more likely to be oedematous, more hypoxaemic, excreted much less urine and sodium, had lower glomerular filtration rate and renal blood flow, and higher aldosterone and vasopressin levels than the remaining patients.

Conclusions – In patients with COPD the inability to excrete sodium and water is multifactorial. This is the first study to

show that autonomic dysfunction is at least associated and might play an important part in the impaired sodium and water homeostasis seen in patients with severe COPD.

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Keywords: autonomic neuropathy, chronic obstructive pulmonary disease, sodium and water excretion.

The development of sodium and water retention in hypoxaemic patients with chronic obstructive pulmonary disease (COPD) implies a poor prognosis.¹ The cause of this retention is unclear, but it is not due to cardiac failure since cardiac output is maintained or even increased.^{2,3}

Abnormalities in vasopressin secretion and activation of the renin angiotensin aldosterone system have been identified in oedematous hypercapnic patients with COPD.⁴⁻⁶ The raised aldosterone levels may contribute to sodium retention and the increased levels of vasopressin may cause hyponatraemia and water retention. However, we have recently shown that inhibition of angiotensin converting enzyme, which reduces aldosterone levels to normal, does not improve sodium excretion in these patients.⁷ It is possible that the raised hormone levels, rather than being the cause of oedema in cor pulmonale, are an effect of disease processes such as reduction in renal blood flow, increased sympathetic stimulation, or even the effect of diuretics used to treat the oedema.

Sodium and water homeostasis is a complex interaction of many factors. The autonomic nervous system is important. Alterations in autonomic tone affects hormonal levels,⁸ renal blood flow,⁹ and is associated with oedema formation in patients with alcoholic cirrhosis.¹⁰

We have recently shown that patients with COPD have a subclinical autonomic neuropathy,^{11,12} the severity of which correlates with their degree of hypoxaemia. We hypothesised that such a neuropathy might be associated with the development of oedema and sodium and water retention in these patients. We therefore investigated the ability of 24 patients with varying severities of COPD to excrete both saline and water loads whilst measuring their hormonal responses, glomerular filtration rate, renal blood flow, and cardiovascular autonomic nerve function.

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Methods

SUBJECTS

Twenty four consenting patients with stable COPD were chosen from the chest clinic. Patients with known ischaemic or valvular heart disease, hypertension, liver disease, renal disease, hormonal disorder, or diabetes were excluded.

All patients were stable at the time of assessment. No patient had had an infective exacerbation in the preceding month. Diuretics were stopped for three days in the five patients who were receiving them, and oxygen therapy (five patients) was discontinued on the day of testing. Patients used their β_2 agonists as required only on awakening and then did not use them until the end of the test. No patient was on oral prednisolone or an angiotensin converting enzyme inhibitor.

Eight patients with COPD who had never suffered from peripheral oedema or documented hypoxaemia of <9 kPa were used as controls (group A). Eight patients with more severe COPD with more severe hypoxaemia who had never suffered from oedema or raised jugular venous pulse made up group B, and group C consisted of eight further patients with severe COPD who had stable oedema at the time of assessment.

The study was approved by the ethical committee of the Sheffield Health Authority. Patients gave consent freely after the aims and requirements of the study had been explained.

STUDY DETAILS

Each of the 24 consenting volunteers received at one week intervals the water load, DTPA renogram/autonomic function tests, and then the salt load. Before the experiment the patients ate a normal diet.

Hypertonic saline load

On the day of the salt or water load the patients were fasted overnight and brought by taxi to the laboratory at 09.00 hours. They were weighed, spirometric tests were performed (Vitalograph Compact) and urine was collected for measurement of osmolality and electrolyte levels. Throughout the experiment blood pressure (sphygmomanometer), pulse, and oxygen saturation were recorded by a Ohmeda Biox 3700 pulse oximeter.

Patients remained seated throughout the salt load test. Blood samples for measurement of urea electrolytes (Technicon SMAC analyser) and osmolality (Advance osmometer 2WII) were collected into serum tubes and plasma hormone levels collected into EDTA tubes. The EDTA tubes were immediately centrifuged and the plasma removed and frozen at -20°C until assayed. Samples were taken at -30 , 0 , 60 , 120 , 180 , and 240 minutes after the saline infusion. Between time 0 and 60 minutes each subject received an intravenous infusion of 2.7% saline (450 mmol/l) at a rate of 0.1 ml/kg/min. After four hours arterial blood gas estimations were made and the patients emp-

tied their bladders, the urine volume was noted, and urine sodium and creatinine levels and osmolality were measured.

Oral water load

The same procedure was used on the water load day, the only exception being that the patients drank 15 ml/kg body weight over the 60 minute period. Wherever possible the patients remained seated. This involved transfer to a commode or use of a urinary bottle where appropriate. Micturition was encouraged after venesection rather than before.

Creatinine clearance was calculated over the 4.5 hours of the test and used as a measure of the glomerular filtration rate. Filtered sodium (mmol/min) was calculated by multiplying the glomerular filtration rate by the plasma sodium concentration. Fractional sodium reabsorption was calculated by dividing excreted sodium (mmol/min) by the filtered sodium and subtracting from 1 ; the fraction was expressed as a percentage. Free water clearance ($= U_v - (U_{osm} \times U_v / P_{osm})$) was calculated using an average of the plasma osmolalities during the test (P_{osm}) and the end urine osmolality (U_{osm}) and the minute urine volume (U_v), negative values being the renal reabsorption of water (ml/min).

Hormone analysis

Plasma aldosterone levels were measured by SB-ALDO radioimmunoassay kits (CIS Bio International, Cedex, France) according to the manufacturers' instructions. The normal ranges quoted for the kits are 15 – 150 pg/ml when supine and 35 – 300 pg/ml when upright. The kit sensitivity is 15 pg/ml. Vasopressin was measured by a recognised radioimmunoassay method¹³ which had an interassay coefficient of variation of 15.3 and an intra-assay coefficient of variation of 9.7% with a limit of detection of 0.3 – 0.8 pmol/l depending on sample size.

Renal blood flow and glomerular filtration rate

Glomerular filtration rate was also measured during the technetium- 99m labelled diethylene triamine pentaacetate (99mTc -DTPA) renogram by venous plasma sampling at 120 , 180 , and 240 minutes after the injection. Renal blood flow was measured by the method described by Peters *et al.*¹⁴ This technique allows organ blood flow to be calculated by the principle of fractionation of the cardiac output and is applicable with any recirculating gamma emitting tracer. Results were expressed as a percentage of cardiac output.

Cardiovascular autonomic function testing

Cardiovascular autonomic nervous system function was measured on the day of the renogram as previously described.^{11 12 15} Briefly, this included the heart rate response to a valsalva manoeuvre where the maximum heart rate

Table 1 Patient characteristics, renal function and autonomic function (mean (SD))

	Group A (control) (n=8)	Group B (hypoxic) (n=8)	Group C (oedema) (n=8)
Age (years)	66.6 (6.3)	64.8 (4.2)	71.2 (3.8)
Height (cm)	167.7 (6.8)	158.1 (5.7)	155.4 (5.8)**
Weight (kg)	77.0 (8.7)	81.4 (8.0)	69.2 (17.3)
On diuretics	0	1	4
FEV ₁ (% predicted)	41.6 (14)	37.3 (10.8)	27 (5)*
FVC (l)	3.4 (0.8)	2.2 (0.8)	1.8 (0.6)*
Pao ₂ (kPa)	9.5 (0.6)	7.5 (0.7)	6.9 (0.7)***
Paco ₂ (kPa)	5.4 (0.9)	6.4 (1.0)	6.1 (0.9)
GFR (by DTPA renogram) ml/min	80 (15)	77 (13)	62 (12)*
RBF (as % cardiac output)	17.4 (3.3)	16.2 (5.8)	12.1 (3.5)*
Autonomic function			
Valsalva ratio	1.34 (0.17)	1.25 (0.18)	1.11 (0.03)**
I-E heart rate difference	12.6 (5.5)	9.5 (2.1)	5.7 (2.2)**
30:15 ratio	1.09 (0.05)	1.05 (0.02)	1.00 (0.02)***
Postural BP fall (mm Hg)	12.4 (11.2)	10.4 (8.9)	15.0 (8.7)
Autonomic score	1.4 (1.1)	2.9 (2.0)	5.6 (0.7)***
Comparison of groups during 2.7% saline loading:			
Volume of urine excreted (ml)	379 (100)	324 (90)	216 (67)**
Sodium excretion (mmol)	78.8 (19.8)	56.8 (19.1)	34.1 (10)***
% sodium load excreted	37.9 (8.9)	26 (8.9)	18 (5.6)***
Fractional sodium reabsorbed	97.5 (0.8)	98.3 (0.5)	98.6 (0.5)*
Free water clearance (ml/min)	-1.8 (0.5)	-1.2 (0.4)	-0.8 (0.2)***
Urine (sodium) start (mmol/l)	130 (57)	129 (47)	113 (32)
Comparison of groups during 15 ml/kg oral water loading:			
Volume urine excreted (ml)	1003 (324)	679 (111)	503 (190)**
% water load excreted	88 (30)	60 (16)	52 (24)*
Free water clearance (ml/min)	0.5 (0.9)	0.4 (0.5)	-0.3 (0.3)*
Urine osmolality at end (mosmol)	251 (73)	226 (62)	356 (82)*

FEV₁=forced expiratory volume in one second; FVC=forced vital capacity; Pao₂, Paco₂=arterial oxygen and carbon dioxide tensions; GFR=glomerular filtration rate; RBF=renal blood flow.

*p<0.05, **p<0.01, ***p<0.001 comparing all three groups by analysis of variance.

during the valsalva is divided by the minimum heart rate on valsalva release (normal >1.20, abnormal <1.11), heart rate difference between inspiration and expiration during deep breathing (I-E difference, normal >11 beats/min, abnormal <8), and the heart rate response to standing from a supine position (the ratio of the RR interval at beat 30 compared with that at beat 15 after standing (30:15 ratio) which is normal if >1.03 and abnormal if <1.01). Postural systolic blood pressure fall was also recorded during this last test (normal <10 mm Hg, abnormal >30 mm Hg). All four tests were scored 0 if normal, 1 if borderline, and 2 if abnormal to give a combined autonomic score out of 8.¹² Scores of >3 suggest an autonomic neuropathy.

REPEATABILITY OF THE TESTS

Repeatability of the DTPA renograms and the saline load experiment was carried out in eight patients with a forced expiratory volume in one second (FEV₁) of 0.79–2.00 l, Pao₂ of 7.2–11.0 kPa, and Paco₂ of 4.5–7.4 kPa. Clinical status, spirometric values, and arterial blood gas tensions were similar on these two occasions 1–3 months apart.

DATA ANALYSIS

Reproducibility was assessed by the correlation of repeatability.¹⁶ Groups of patients were compared by analysis of variance with Scheffes test. Multivariate correlation analysis of the parameters measured was performed. Stepwise multiple regression analysis was used to assess the importance of renal blood flow, glomerular filtration rate, aldosterone and vasopressin levels, and autonomic function on urinary volume and sodium excretion.

Results

With the exception of aldosterone levels at times 180 and 240 minutes, all results from the saline loading and DTPA renograms were repeatable with an acceptable coefficient of repeatability for sodium excretion, renal function, plasma electrolytes, and osmolality (results with editor).

The groups were similar for age and weight, although groups B and C were shorter. FEV₁, glomerular filtration rate and renal blood flow were corrected for this. Arterial oxygen tensions were significantly lower in the oedematous group (p<0.001) but, surprisingly, there was no difference in Paco₂ between the groups. Likewise, lung function (FEV₁ as % of predicted) was also lowest in the oedematous group C (p<0.05).

All patients in the oedematous group C had evidence of a subclinical autonomic neuropathy (p<0.001). Three patients in group B also had a definitely abnormal autonomic score. The heart rate response to standing (30:15 ratio) was the most individually discriminatory test, the results between the groups being significant (p<0.001). Both glomerular filtration rate and renal blood flow were significantly different (p<0.05) between the groups, being particularly low in group C (table 1).

During dynamic saline loading the urine volume excreted was significantly lower in group B and even worse in group C (p<0.01). The final urine sodium excretion, in absolute units and as a percentage of the saline load infused, was significantly different between the groups (p<0.001), the oedematous group C excreting half the load excreted by the control group A. A greater fraction of the filtered sodium was reabsorbed in the more oedematous groups (p<0.05). Free water reabsorption was significantly different (p<0.001) between all groups. The oedematous group C were least

able to excrete a concentrated urine. There was no difference between the groups in terms of serum sodium levels or osmolality (fig 1).

Plasma aldosterone levels were significantly raised at times -30 and 0 minutes before the infusion in group C, but the levels did suppress appropriately and, although the aldosterone levels in this group were higher than in the other two groups, the difference was not significant (fig 1).

Likewise, plasma vasopressin levels were insignificantly raised in group C. In all groups

the saline infusion-induced rise in osmolality caused an appropriate rise in vasopressin (fig 1) which was greatest in patients in group C in whom the level of vasopressin was inappropriately raised for the level of serum osmolality at 240 minutes (fig 5). During the dynamic oral water load the urine volume excreted was least in group C ($p<0.01$) (table 1). Serum osmolality responses were similar whilst aldosterone and vasopressin (fig 2) were insignificantly higher in patients in group C.

Eleven patients had evidence of a subclinical

Figure 1 Mean (SE) plasma levels of aldosterone and vasopressin and serum osmolality during saline loading in patients with COPD. □ = control group A, ■ = non-oedematous group B, ● = oedematous group C. * $p<0.05$.

Figure 2 Mean (SE) plasma levels of aldosterone and vasopressin and serum osmolality during oral water loading in patients with COPD. □ = control group A, ■ = non-oedematous group B, ● = oedematous group C.

Table 2 Comparison of mean (SD) values in patients with and without evidence of a subclinical autonomic neuropathy

Parameter	Normal autonomic function (n=13)	Subclinical autonomic neuropathy (n=11)
Age (years)	66 (6)	69 (5)
Height (cm)	168 (7)	155 (6)*
Weight (kg)	80 (9)	71 (15)
Oedema	None	8
FEV ₁ (% predicted)	40 (12)	30 (10)*
Pao ₂ (kPa)	8.9 (1.0)	6.9 (0.7)***
Paco ₂ (kPa)	5.8 (1.0)	6.1 (0.9)
Results during saline loading:		
Urine volume (ml)	353 (96)	240 (89)*
% sodium load excreted	32 (10)	19.5 (10)**
Free water clearance (ml/min)	-1.6 (0.5)	-0.9 (0.4)**
GFR (ml/min)	80 (14)	65 (14)*
RBF (% cardiac output)	17.5 (4.3)	12.6 (4.3)*
Results during oral 15 ml/kg water load:		
% water load excreted	76 (29)	56 (23)*
Free water clearance (ml/min)	0.5 (0.8)	-0.1 (0.4)*
Urine osmolality at end (mosmol)	240 (74)	324 (89)*

FEV₁ = forced expiratory volume in one second; Pao₂, Paco₂ = arterial oxygen and carbon dioxide tensions; GFR = glomerular filtration rate; RBF = renal blood flow.

*p<0.05, **p<0.01, ***p<0.001 comparing groups by the Mann-Whitney U test.

autonomic neuropathy (table 2). They were more likely to be oedematous (eight cases), had worse lung function (p<0.05), were more hypoxaemic (p<0.001) but not hypercapnic, excreted less of the sodium load (p<0.01) and water load (p<0.05), and their glomerular filtration rate and, particularly, their renal blood flow were lower. Aldosterone levels were raised at rest before the saline load but responded appropriately to the challenge and were insignificantly higher for the rest of the experiment (fig 3). Likewise, their vasopressin levels were higher, rose further as osmolality increased, and remained high at the end of the experiment despite a falling serum osmolality (figs 4 and 5). During water loading the vasopressin levels were higher in the patients with autonomic dysfunction group (fig 4). There was good correlation between autonomic dysfunction and sodium and urine excretion (table 3).

Stepwise multiple regression analysis of factors influencing sodium excretion during salt

Figure 3 Mean (SE) plasma levels of aldosterone and vasopressin during saline loading in patients with COPD. □ = patients with normal autonomic function (n=13), ◆ = patients with autonomic dysfunction (n=11). *p<0.05.

loading showed that the 30:15 ratio was the most significant (t=5.9, p<0.001) and only renal blood flow (t=2.5, p<0.05) was also significant. For urinary volume only the 30:15 ratio reached significance (t=4.2, p<0.001).

Table 3 Multivariate correlation analysis during saline and oral water loading (n=24)

Parameter 1	Parameter 2	r	p
Saline loading:			
Sodium excretion	v Arterial oxygen tension	0.71	<0.001
	v FEV ₁ (% predicted)	0.47	<0.05
	v Renal blood flow	0.50	<0.05
	v 30:15 heart rate ratio on standing	0.77	<0.001
	v Autonomic index	0.55	<0.01
	v Aldosterone (time 0)	-0.52	<0.01
Urine volume	v Arterial oxygen tension	0.55	<0.01
	v FEV ₁ (% predicted)	0.55	<0.01
	v Renal blood flow	0.42	<0.05
	v 30:15 heart rate ratio on standing	0.74	<0.001
	v Autonomic index score	-0.49	<0.01
	v Aldosterone (time 0)	-0.52	<0.05
30:15 ratio	v Fractional sodium reabsorption	-0.82	<0.05
	v Free water clearance	-0.63	<0.01
Oral water loading:			
% water load excreted	v Vasopressin (time 0, 60 min)	-0.43	<0.05
	v Vasopressin (time 120 min)	-0.51	<0.01
	v 30:15 heart rate ratio	0.41	<0.05
	v Arterial oxygen tension	0.58	<0.05
	v FEV ₁	0.43	<0.05
Autonomic index	v Urine volume	-0.42	<0.05
	v Vasopressin (time 60)	0.41	<0.05
	v Glomerular filtration rate	-0.47	<0.05
	v Free water clearance	-0.42	<0.05

Figure 4 Mean (SE) plasma levels of vasopressin during oral water loading in patients with COPD. □ = patients with normal autonomic function (n=13), ◆ = patients with autonomic dysfunction (n=11). *p<0.05.

Figure 5 Mean (SE) plasma levels of vasopressin plotted against serum osmolality during the osmolar changes produced by intravenous saline and oral water loading in patients with COPD. $\square$ = patients with normal autonomic function ($n=13$), $\blacklozenge$ = patients with autonomic dysfunction ($n=11$). Values between lines are normal.

During the water load only vasopressin levels at time 120 were significant ($t = -2.4$, $p < 0.05$), the 30:15 ratio being the second most important factor ($t = 2.0$, $p < 0.1$) associated with water excretion.

Discussion

The results of the saline load test performed in an outpatient setting were acceptably reproducible. Our results show that patients with hypoxaemic COPD have an impaired ability to excrete sodium and water loads. Unlike previous studies^{5,6,17} this impairment was related to the severity of hypoxaemia rather than the degree of hypercapnia. The use of P_{aO_2} to differentiate between groups might have biased this. However, the lack of association between sodium and water excretion and P_{aCO_2} raises questions as to whether some of the earlier reports were confounded by concomitant oxygen therapy which would have raised both P_{aO_2} and P_{aCO_2} . The reduction in sodium and water excretion is unlikely to be due to hypoxaemia alone as it is not seen in chronically hypoxic high altitude dwellers.¹⁸

The results in our control group were similar to those obtained in normal subjects¹⁹ and in those with mild COPD.⁵ Patients with COPD with more severe disease developed an impaired ability to excrete sodium and water with an increased fractional sodium reabsorption even before they developed oedema. They had apparently preserved renal and endocrine function but did show evidence of a developing subclinical autonomic neuropathy.

Oedematous patients had a significant inability to excrete sodium and water loads. There was a decline in renal blood flow and glomerular filtration rate, together with the development of a subclinical autonomic neuropathy and a small increase in plasma aldosterone and vasopressin levels. The results in the autonomic neuropathy group were similar to those seen in patients with oedema.

This is the first report of an association between the inability to excrete a sodium load and parasympathetic autonomic dysfunction in hypoxaemic COPD. However, a similar diminution in vagal parasympathetic function with preservation of sympathetic tone is reported in congestive cardiac failure²⁰ and in alcohol-induced cirrhotic ascites where there is a vagal neuropathy, hyponatraemia,¹⁰ and an excessive secretion of vasopressin.

Autonomic dysfunction could be important. In animal models cervical vagotomy abolishes diuresis²¹ and natriuresis.²² The increased tubular reabsorption of solute-free water produced by interruption of the parasympathetic afferent pathways is mediated by increased levels of vasopressin.²³

The autonomic function test that best associates with the impairment in sodium and water handling is the baroreceptor-mediated heart rate response to standing (30:15 ratio). This supports the observation that patients with hypoxaemic COPD have a reduced baroreceptor sensitivity.²⁴

The parasympathetic nervous system is not believed to have a direct effect on renal function. However, arterial baroreceptor function might regulate sympathetic tone. Interruption of the vagus in the neck of rabbits causes a significant increase in renal sympathetic nerve activity with abolition of the reflex fall in sympathetic tone associated with an increase in effective blood volume.²⁵ Our hypertonic saline load would be expected to increase the effective blood volume transiently. A failure to interpret this increase correctly could partly explain the impaired sodium excretion. More detailed study of autonomic and baroreceptor function is needed to determine its importance in the sodium and water retention seen in patients with COPD.

Although plasma aldosterone levels were higher in the oedematous patients before the experiments, most of the results were within the normal range and responded appropriately to saline and water challenges. Furthermore, angiotensin converting enzyme inhibition does not improve the chronic impairment in sodium excretion seen in patients with COPD.⁷ This suggests that stimulation of the renin aldosterone system is not the main cause of the failure to excrete sodium. The slightly raised aldosterone levels⁴⁵ might be a consequence of stress, increased sympathetic tone,⁸ reduction in renal perfusion, alteration in intrarenal haemodynamics, or diuretic therapy. The association of baseline plasma aldosterone levels with sodium excretion and fractional reabsorption might reflect increased renal sympathetic tone.⁸ Renal nerve activity may interact with the prevailing intrarenal pressure to modulate the release of renin.²⁶

Plasma vasopressin levels tended to be higher in the oedematous patients and were significantly higher in the group with autonomic dysfunction. Most measurements during the hypertonic saline load test were within the normal limits for serum osmolality, the exception being at 240 minutes in both the autonomic dysfunction and oedematous groups.

This accentuated prolonged rise in plasma vasopressin levels in response to the hypertonic saline load is similar to that seen in baroreceptor denervated animals.²⁷

During conditions of hypo-osmolality induced by the water loading, vasopressin levels were above the expected range in the more oedematous and autonomic dysfunctional patients. The fall in vasopressin levels on lowering serum osmolality suggests that, although its secretion is still under osmotic control, non-osmotic factors play an important part in maintaining raised levels in the more hypoxaemic oedematous patients. This resetting of the osmoreceptor threshold is also seen in congestive cardiac failure and cirrhosis. In patients with congestive cardiac failure it is believed that the reduction in cardiac output²⁸ is sensed by ventricular receptors (high pressure receptors in the carotid sinus and aortic arch) as a reduction in the apparent effective blood volume. The decreased afferent impulses to the hypothalamus via the mid brain increases vasopressin release. In patients with cor pulmonale cardiac output is normal.²³ However, the reduced neural traffic caused by a vagal and glossopharyngeal neuropathy could be interpreted centrally as a reduction in circulating effective blood volume. This would increase vasopressin release and stimulate sympathetic drive. Such a possible mechanism is suggested by the association between baroreceptor autonomic dysfunction (30:15 ratio) and the raised vasopressin levels seen in the more hypoxaemic patients.

The poor correlation between vasopressin levels and urine volume suggest that the raised levels of vasopressin are not the sole explanation for the observed impairment in water excretion. Likewise, the impaired excretion of water and sodium in patients with COPD is not due to a failure of secretion of atrial natriuretic peptide²⁹ or brain natriuretic peptide.³⁰

Renal blood flow was significantly reduced in the oedematous patients. The results in the control group and those without oedema were similar to the quoted normal range of 16.5–22.5% of cardiac output seen in healthy young adults.¹⁴ The decline in renal blood flow with severity of hypoxaemia, and its association with impairment of sodium and water load excretion,⁴ is in accordance with previous studies.^{31 32}

The reduction in the glomerular filtration rate in the oedematous group was less significant. Although most studies have failed to show a significant decline, the glomerular rate does tend to be lower in oedematous patients.^{18 31 32} Although this group was at the lower limit of normal (range 60–110 ml/min), only one patient had a glomerular filtration rate of less than 50 ml/min and no patient had a raised serum creatinine level. These values are unlikely to cause significant renal impairment or to account for the degree of salt and water retention. The greater reduction in renal blood flow than in glomerular filtration rate increases the filtration fraction, raises peritubular colloid oncotic pressure and, thus, might be one explanation for the observed increase in tubular sodium reabsorption.⁴

Our oedematous patients had the greatest fractional reabsorption of sodium and a less negative free water clearance. The increased sodium reabsorption at the proximal tubules limits the volume of urine and solute delivered to the more distal segments where free water is generated for excretion. A similar mechanism may account for the sodium and water retention seen in cirrhotic ascites³³ and congestive cardiac failure.³⁴ Although diuretic-induced sodium depletion reduces the excretion of a water load by the same mechanism,³³ this is unlikely to account for our results. No patients were hyponatraemic, diuretics were stopped for three days before the test, and the results in the five patients on diuretics were similar to their fellow group members (results not shown). Alternatively, the increased sympathetic nerve activity seen in patients with COPD³⁵ may directly increase fractional sodium reabsorption and sodium retention via a proximal tubular effect.^{36–38}

In conclusion, patients with severe COPD have an impaired ability to excrete sodium and water which, in this study, was associated with severity of hypoxaemia rather than degree of hypercapnia. The failure to excrete sodium and water may be multifactorial. Sodium and water homeostasis involves an interplay of hormonal, neural, and vascular mechanisms. The pathological process which occurs in severe COPD upsets this regulation and leads to a perturbation in the many factors involved. In an individual one or other of these factors may be the most important. A fall in renal blood flow and the development of a subclinical parasympathetic autonomic neuropathy, particularly that part involved with baroreceptor function, might be important. A reduction in glomerular filtration rate and small elevations of aldosterone and vasopressin levels might contribute, but their role as major causative factors is unclear. This is the first study to associate autonomic nerve dysfunction with impairment of sodium and water excretion in cor pulmonale. The importance of this homeostatic process warrants further investigation.

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