

LIVER, BILIARY, AND PANCREAS

Human atrial natriuretic factor and renin-aldosterone in paracetamol induced fulminant hepatic failure

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Abstract

It has been postulated that deficiency of a putative natriuretic factor, or resistance to such a factor, may contribute to sodium retention in fulminant hepatic failure. Levels of plasma human atrial natriuretic factor (h-ANF), plasma renin activity, and aldosterone concentration were measured in 33 patients with fulminant hepatic failure due to paracetamol overdose, and 12 healthy control subjects. Levels of h-ANF were raised only in patients with evidence of severe renal impairment (serum creatinine $>300 \mu\text{mol/l}$ and urine output $<100 \text{ ml/24 hours}$). h-ANF values were median 4.15, range 2-9 pmol/l and 10.1, 1-25 pmol/l for the control and severe renal impairment groups respectively ($p<0.001$). In the latter plasma renin activity was raised compared to that in control subjects (median 19.8, range 1.04-41.7 and 2.86, 1.87-5.9 pmol/h respectively, $p<0.02$). Plasma aldosterone concentration was also raised in patients (2176, 199-6894 pmol/l compared to 368, 133-578 pmol/l in control subjects, $p<0.01$). Haemodialysis induced changes in circulating h-ANF which correlated with volume and right atrial pressure changes ($p<0.001$ and $p<0.05$ respectively). In six patients with no or mild renal failure infusion of 900 ml 5% human albumin solution caused a significant increase in plasma h-ANF ($p<0.05$) without natriuresis or diuresis, a finding compatible with the hypothesis that there may be resistance to h-ANF in this group. The present findings indicate that there is no deficiency of h-ANF in fulminant hepatic failure and that known mechanisms of h-ANF release are not impaired.

atrial natriuretic factor (h-ANF) has been identified as a natriuretic and diuretic substance which suppresses the activity of the renin-aldosterone system.⁵ It is secreted by the cardiac atria in response to rises in atrial pressure, through atrial wall stretch, and thus seems to have a role in blood volume regulation.⁶⁻¹¹ Changes of plasma h-ANF concentration within the physiological range are now known to produce characteristic renal and humoral effects of this substance in humans.¹²

The aim of the present study was to measure concentrations of h-ANF in fulminant hepatic failure and to examine its possible relation to the renin-aldosterone system. This relation was further examined by investigating the response of the above factors to fluid volume and right atrial pressure changes, induced by haemodialysis and by the infusion of 5% human albumin solution.

Patients and methods

Thirty eight patients, 18 men and 20 women (age range 17-66 years) with fulminant hepatic failure (development of encephalopathy within eight weeks of the onset of hepatic symptoms, in the absence of underlying liver disease) from paracetamol overdose were studied. Patients were excluded if (a) there was a past history of heart disease or arrhythmias; (b) they were receiving inotropic support; (c) the mean arterial pressure was less than 60 mmHg; (d) there was a greater than 15% change in pulse rate, mean arterial pressure, or right atrial pressure on three occasions one hour apart in the three hours before study; (e) there was rapidly changing coma grade¹³ in the three hours before study or there were any clinical signs of cerebral oedema during the preceding 24 hours; (f) there was evidence of haemorrhage.

The patients were allocated to one of the following three groups; group 1 (12 patients) comprised patients with no or only mild renal impairment, defined as plasma creatinine $<300 \mu\text{mol/l}$ and urine output $>600 \text{ ml/24 hours}$ or 300 ml/12 h . Group 2 consisted of 21 patients with severe renal failure, defined as plasma creatinine $>300 \mu\text{mol/l}$ and urine output $<100 \text{ ml/day}$. Group 3 comprised five patients who were recovering from fulminant hepatic failure after a paracetamol overdose, with per-

Volume homeostasis is frequently impaired in patients with fulminant hepatic failure, with sodium retention and an altered haemodynamic state of high cardiac output and a low systemic vascular resistance.^{1,2} Bernadi *et al* reported high plasma renin and aldosterone concentrations in fulminant hepatic failure and no correlation between plasma aldosterone concentration and renal sodium excretion.³ It has been postulated that a deficiency of a putative circulating natriuretic factor, or resistance to such a factor, may contribute to the sodium retention.⁴ Human

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TABLE I Serum biochemical measurements and prothrombin time (seconds prolonged) at entry into the study for normal control subjects and three groups of patients with fulminant hepatic failure. Group 1: no or mild renal failure; group 2: severe renal failure; group 3: recovering fulminant hepatic failure with persisting severe renal failure. Values expressed as median (range)

	Group 1 (n=12)	Group 2 (n=21)	Group 3 (n=5)	Control subjects (n=12)
Creatinine ($\mu\text{mol/l}$)	104 (53–259)	566 (337–1091)	719 (607–1100)	93 (57–103)
Sodium (mmol/l)	132 (129–137)	130 (129–133)	127 (112–133)	140 (138–143)
Bilirubin ($\mu\text{mol/l}$)	93 (51–138)	149* (80–265)	58 (37–162)	8 (3–15)
Albumin (g/l)	35 (32–41)	36 (31–40)	36 (31–41)	43 (39–46)
Prothrombin time (seconds prolonged)	42 (25–92)	96* (29–186)	33 (1–48)	–
Encephalopathy (No of patients):				
Grade I–II	6	6	0	0
Grade III–IV	6	15	0	0

Note: Group 2 values compared to group 3: * $p < 0.05$.

sisting severe renal failure requiring dialysis (predialysis plasma creatinine $> 500 \mu\text{mol/l}$ and urine volume $< 100 \text{ ml/24 hours}$), and no evidence of encephalopathy. From the last group blood samples were taken at least 18 hours after any previous dialysis. Group 3 was included as a 'renal failure' control group. As control subjects a group of 12 normal volunteers (age range 33–62 years) on a 22 mmol sodium daily restricted diet for five days before entry had venous blood samples taken without stasis, for h-ANF at 0900 hours while semirecumbent (trunk 45° to the horizontal) for 30 minutes, after an overnight fast. Their arterial blood pressure was measured by a mercury column sphygmomanometer.

To allow for stabilisation, patients were studied not less than 12 hours after admission. All patients were studied in the semirecumbent position. The level of the right atrium was taken as corresponding to the surface marking of the fifth intercostal space in the mid-axillary line. All patients were receiving 5% dextrose intravenously (1.5–2.0 l daily) and saline infusion was not administered for at least 24 hours preceding the study. Potassium supplements were given intravenously to maintain plasma concentrations of 4.0–5.0 mmol/l. None of the patients had received mannitol in the 24 hours before entry. Arterial pressure and right atrial pressure were measured via an indwelling intra-arterial cannula and a central venous line respectively (Simonsen and Weel Ltd, series 9000; Ames transducer AE 840). Mean arterial blood pressure and right atrial pressure was derived electronically.

Baseline biochemistry, prothrombin time, and grade of encephalopathy at the time of entry are given in Table I.

BASAL ASSESSMENT OF h-ANF AND HORMONAL STATE

At 0900 hours measurements of pulse rate, arterial blood pressure, and right atrial pressure were taken. Peripheral venous blood was taken without stasis for estimation of h-ANF, renin, aldosterone, creatinine, sodium, potassium, bilirubin, and prothrombin time. Samples for h-ANF and renin-aldosterone were taken into chilled tubes containing ethylenediamine tetra-

acetate (EDTA) and were centrifuged at 4°C for 10 minutes within 10 minutes of collection. Plasma was separated and stored at -70°C until assayed.

In cases where urine could be obtained, a timed collection was taken between 0800 and 0900 hours via an indwelling urinary catheter for urine sodium estimation. In the case of six anuric patients in group 2 urine was collected when available, over 2–24 hours.

EFFECT OF FLUID VOLUME CHANGES

The effect of haemodialysis was studied in 14 patients from group 2. After one hour of baseline observation measurements and peripheral venous blood samples were taken just before and 90 minutes after completion of haemodialysis. Dialysis was carried out using a Biospal 2400S cartridge in a Monitral 5 dialysis unit. Patients developing hypotension during haemodialysis (systolic blood pressure $< 90 \text{ mmHg}$) received measured volumes of 5% human albumin solution. For all patients 150 ml 0.9% sodium chloride solution containing heparin, was used to 'prime' the extracorporeal dialysis circuit and was accounted for in the final fluid balance estimation. Two patients developed cerebral oedema during dialysis, which was abandoned, and their data were excluded from the final analysis.

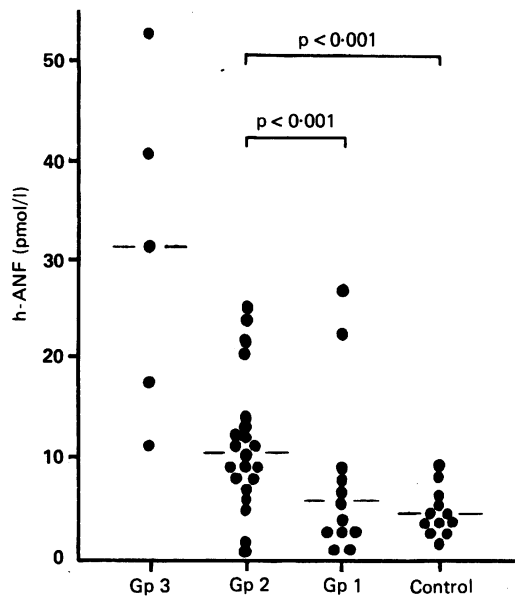
The effect of plasma volume expansion was studied in six patients from group 1 who were being monitored by a pulmonary artery flotation catheter. Patients with a low right atrial pressure ($\leq 2 \text{ mmHg}$) and pulmonary capillary wedge pressure ($\leq 5 \text{ mmHg}$) for more than 30 minutes received an infusion of 900 ml of human albumin solution over a period of 40 minutes, to a maximum right atrial pressure of 5–6 mmHg or pulmonary capillary wedge pressure of 10–12 mmHg. Venous blood samples were taken just before and 40 minutes after the end of the infusion. Urine was collected for the hour preceding the infusion and for an hour after the albumin infusion was completed for measurement of urine volume and sodium concentration.

ASSAYS

All samples for h-ANF were assayed in a single assay run by a sensitive radioimmunoassay after plasma extraction, as previously described.^{12,14} Assay sensitivity was 1 pmol/l and intra-assay variation 8%. Plasma renin activity was measured by the generation of angiotensin I, by a modification of the method of Menard and Catt,¹⁵ and aldosterone concentration with a Sorin radioimmunoassay kit (CIS, High Wycombe, Bucks) after solvent extraction of plasma.¹⁶ Serum creatinine was estimated by autoanalyser and plasma and urine sodium by flame photometry.

Results are expressed as median and range. Statistical analysis was carried out by the Wilcoxon two sample rank sum test and the Wilcoxon signed rank test for paired values, as appropriate. Tests of correlation were by the Spearman rank test. Level of significance was taken as $p < 0.05$.

Figure 1: Basal plasma concentrations of human atrial natriuretic factor (h-ANF) in patients with fulminant hepatic failure with no or mild renal failure (group 1) and with severe renal failure (group 2), in patients recovering from fulminant hepatic failure with persisting severe renal failure (group 3), and in control subjects (control).



Results

There was no difference between h-ANF concentration in control subjects and patients with no or mild renal failure (group 1) (2.0–9.0, median 4.15 and 1–28.6, median 6.1 pmol/l respectively). Concentrations were higher in patients with severe renal failure (group 2) when compared to control subjects or patients with no or mild renal failure (median 10.1, 1–25 pmol/l, $p < 0.001$, Fig 1). Values for right atrial pressure were similar in groups 1 and 2 (Table II). In group 3, predialysis h-ANF levels were even higher (11–53.2, median 31.5 pmol/l) when compared to those in control subjects ($p < 0.003$).

There was a positive correlation between h-ANF and right atrial pressure levels ($R = 0.67$, $p < 0.02$) within group 1, but not within group 2 predialysis. In group 1, h-ANF levels correlated weakly with plasma creatinine ($R = 0.6$, $p < 0.05$). There was a positive correlation for pooled values of plasma h-ANF and creatinine for groups 1, 2, and 3 ($R = 0.50$, $p < 0.002$). There was no correlation between h-ANF and mean arterial pressure in any group.

Plasma renin activity tended to be higher in all patient groups compared to controls, although statistical significance was not reached for group 1 ($0.05 < p < 0.1$) (Table II). There was an inverse correlation between plasma renin activity and mean arterial pressure in patients in group 1 ($R = -0.78$, $p < 0.01$, Fig 2), but not in group 2.

Aldosterone concentrations were raised in all patient groups compared to controls (Table II).

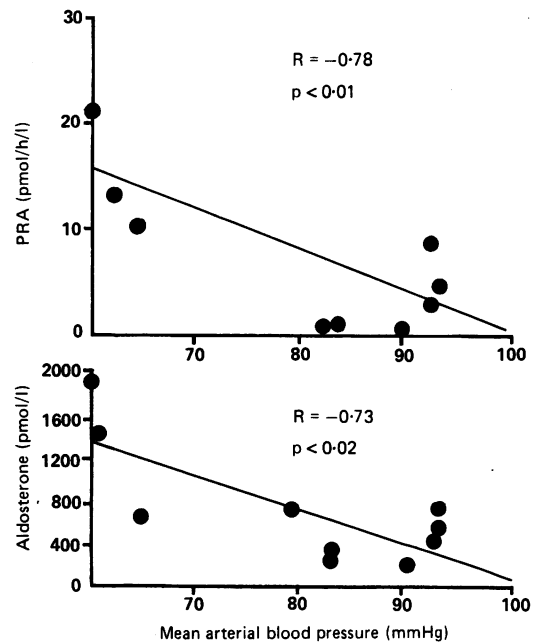


Figure 2: Plasma renin activity (PRA), aldosterone concentration, and mean arterial blood pressure in patients with fulminant hepatic failure with no or mild renal failure (group 1).

There was an inverse correlation between aldosterone and mean arterial pressure levels in group 1 ($R = -0.73$, $p < 0.02$, Fig 2), but not in group 2. There was a strong correlation between plasma renin activity and aldosterone concentration for combined values from all patient groups ($R = 0.978$, $p < 0.0001$).

Serum sodium was lower in all three groups of patients compared to control subjects (Table I).

Urine samples were available from only six patients in group 2 at 0900 hours, collected over periods ranging from 2–24 hours (total urine volume 5–80 ml). Median urine sodium excretion in these was 0.17 mmol/h (range 0.06–0.90 mmol/h). Urine was available from all 12 patients in group 1. Baseline urine sodium excretion was median 0.22 mmol/h (range 0.06–6.46 mmol/h). The distribution was skewed: in 10 of the 12 patients urine sodium was less than 0.4 mmol/h, in one 0.9 mmol/h, and in the remaining patient 6.46 mmol/h. There was no correlation between urine sodium excretion and h-ANF, plasma renin activity, or aldosterone.

RESPONSE TO VOLUME CHANGES

Effect of haemodialysis. Duration of haemodialysis was between 3.5 and 4.25 hours. Fluid

TABLE II Basal levels of right atrial pressure, mean arterial pressure, plasma renin activity, and concentrations of plasma atrial natriuretic factor aldosterone, and plasma creatinine. Values expressed as median (range) and are compared to normal control subjects

	Right atrial pressure (mmHg)	Mean arterial pressure (mmHg)	Plasma atrial natriuretic factor (pmol/l)	Plasma renin activity (pmol/ml/h)	Aldosterone (pmol/l)	Creatinine (μ mol/l)
Group 1 (n=12)	5.25 (-0.5–16)	83 (60–93)	6.1 (1–28.6)	6.8 (1.39–22.4)	637* (202–1917)	104 (53–259)
Group 2 (n=21)	6.12 (2–18)	90 (61–112.5)	10.1 (1–25)	19.8* (1.04–41.7)	2176** (199–6894)	566 (337–1091)
Group 3 (n=5)	–	86.5 (80–93.5)	31 (11.2–53.2)	6.94* (1.12–14.7)	580* (196–1680)	719 (607–1100)
Control subjects (n=12)	–	77.8 (70–105)	4.15 (2–9)	2.86 (1.87–5.9)	368 (133–578)	93 (57–103)

* $p < 0.02$; ** $p < 0.01$.

TABLE III Patients with no or mild renal failure before and after volume expansion with 900 ml of 5% human albumin solution (n=6). Hourly urinary volume and sodium excretion: Uvol and UNa respectively. Values expressed as median (range)

	Right atrial pressure (mmHg)	Mean arterial pressure (mmHg)	Plasma atrial natriuretic factor (pmol/l)	Plasma renin activity (pmol/ml/h)	Aldosterone (pmol/l)	UNa (mmol/h)	Uvol (ml/h)
Before	2 (-0.5-3)	62.5 (57-93.3)	3.75 (1.9-4)	13.45 (4.16-19.8)	693 (143-1830)	0.175 (0.06-6.46)	58 (30-102)
After	5.25* (3-7)	69.75 (58.5-93.3)	10.1* (6.2-23.3)	8.85* (1.39-17.7)	668 (202-1760)	0.42 (0.16-5.52)	80 (35-80)

*p<0.05.

volume changes at completion ranged from -1.35 to +1.0 litres, and change in right atrial pressure was -9.5 to +6.0 mmHg. Median plasma h-ANF levels before and after dialysis were 9.67 pmol/l (range 1-28.6) and 11.75 pmol/l (range 1-28.4) respectively. There was a positive correlation between change in right atrial pressure with change in h-ANF (Fig 3A) and between volume change and change in h-ANF (Fig 3B). Although plasma renin activity and aldosterone concentrations were decreased after dialysis (median 23.8 to 18.3 pmol/ml/h and 3621 to 2295 pmol/l respectively, p<0.03), these changes did not correlate with fluid volume or change in right atrial pressure.

Response to albumin infusion. Preinfusion plasma renin activity and aldosterone concentration were appreciably above the normal range (Tables II and III). Packed cell volume dropped significantly after albumin infusion (median 40%, range 28-44%, to 37%, range 27-40%, p<0.05). There was a significant rise in right atrial pressure (p<0.05) and plasma h-ANF concentration (p<0.05), with a corresponding decrease in plasma renin activity (p<0.05, Table III). Aldosterone concentration dropped in five patients and rose in one (not significant) and there was no change in urine volume or sodium excretion (Table III). Urine microscopy of preinfusion samples showed no casts in any of the six samples. Urine/plasma osmolality ratio was less than 1.09 in two cases and greater than 1.1 in four.

Discussion

Studies of the renin-aldosterone system and of

electrolyte and water balance are usually carried out after several days on a controlled sodium and potassium intake. Because of the rapid changes in the clinical condition of patients with fulminant hepatic failure it is not possible to do this. Saline infusion is avoided in these patients because of their tendency to retain sodium. For this reason patients are compared to healthy control subjects on severe sodium restriction. Although the criteria for inclusion were such that only relatively stable patients were entered, these limitations must be considered when interpreting the present results. Since patients did not receive saline for 24 hours before the study, it would be difficult to identify those with inappropriate sodium retention on the basis of urine sodium excretion alone. Therefore the 'dynamic' test of volume expansion was used in six patients who were not oliguric (group 1). Although specific tests to assess renal tubular function (urine acidification and excretion of amino acids and tubular proteins) were not performed in these six cases, the absence of casts in the urine suggests that acute tubular necrosis was not present at the time of study. The separation of patients into those with no mild renal failure and severe renal failure according to plasma creatinine and urine volume was empirical and was based on findings from a previous study by Wilkinson *et al*¹ in order to study patients at two ends of a continuous spectrum of renal impairment. In another study of paracetamol induced fulminant hepatic failure with renal failure Wilkinson *et al*¹⁷ reported that functional renal failure was present in about a third of cases, prerenal uraemia in 10-15%, and direct renal toxicity due to paracetamol causing acute tubular

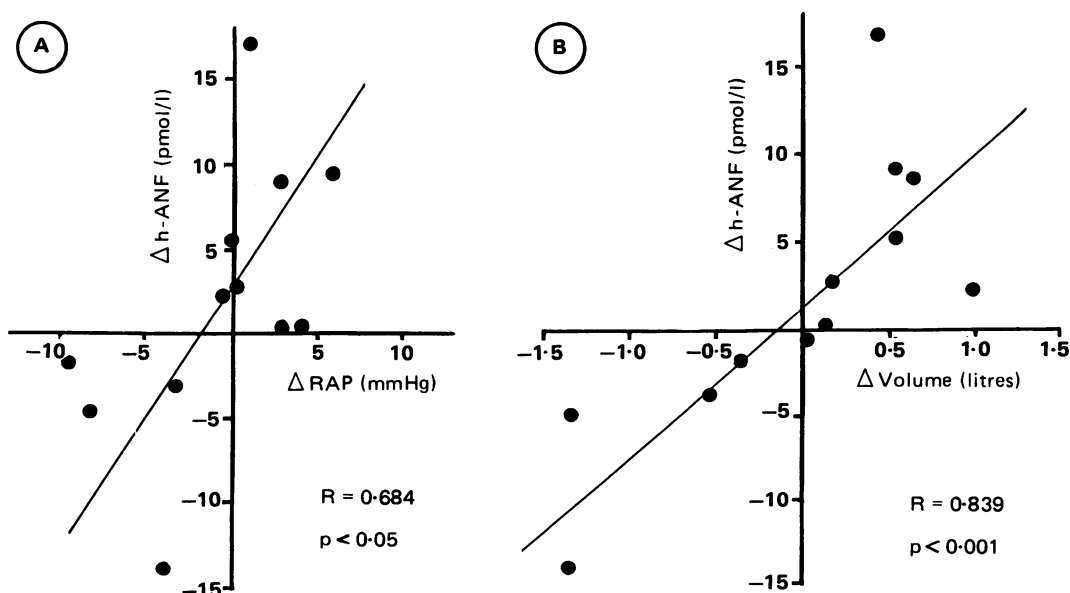


Figure 3: Haemodialysis induced net fluid volume balance (Δ Volume) and change in human atrial natriuretic factor concentration (Δ h-ANF) and changes in right atrial pressure (Δ RAP).

necrosis in more than 50% of cases. It is likely that most patients in group 2 belonged to the last category. Estimates of 24 hour urine sodium excretion from our data in group 2 may be unreliable, since collections were available from only six of 21 patients and were collected over different lengths of time. In addition, in this group of patients, during a 24 hour period of observation, urine is often passed intermittently and urine volume may vary unpredictably from zero to a few ml per hour. However, it seems likely that anuric patients in group 2 would be retaining sodium.

As saline was not administered for 24 hours before study, it is possible that the observed hyponatraemia in patients might be due to failure to generate free water, either due to inappropriately high levels of antidiuretic hormone or pronounced proximal reabsorption of sodium.

The results show that there is no deficiency of h-ANF in fulminant hepatic failure. In the presence of no or mild renal failure, basal h-ANF levels were similar to those in control subjects, but in patients who had developed severe renal failure they were raised. In patients recovering from fulminant hepatic failure with persisting severe renal failure h-ANF levels were even higher. These findings, along with the correlation of h-ANF to plasma creatinine concentration, suggest that the raised levels of h-ANF in fulminant hepatic failure are related to the presence of renal failure. The finding of similar right atrial pressure values in groups 1 and 2 would be compatible with the hypothesis that in the presence of renal failure factors other than increased atrial distension may be contributing to the raised levels of h-ANF, although it is possible that atrial volume may increase without a rise in atrial pressure. The importance of the kidney in the clearance of circulating h-ANF has been shown in previous studies of adults undergoing cardiac catheterisation, where there was significant extraction of circulating h-ANF by this organ,¹⁸ and by receptor-distribution¹⁹ and h-ANF clearance¹⁹⁻²¹ studies in animals. In the canine model, extraction of ANF by the kidney has been shown to be largely dependent on glomerular filtration rate.²⁰ Pronounced renal vasoconstriction with reduced glomerular filtration rate is common in fulminant hepatic failure,²¹ and thus may contribute to reduced extraction of h-ANF.

Basal aldosterone concentrations and plasma renin activity was raised in all patient groups,^{22, 23} although statistical significance was not reached in the case of those with mild renal impairment. In all groups aldosterone concentrations correlated well with plasma renin activity, suggesting that renin remains the major determinant of aldosterone concentrations in fulminant hepatic failure.²⁴ In the absence of severe renal failure, plasma renin activity and aldosterone concentrations were inversely proportional to mean arterial pressure, supporting previous observations which suggested that stimulation of the renin-aldosterone system may be a homeostatic response to hypotension.³

The correlation of changes in h-ANF with

volume and right atrial pressure changes induced by haemodialysis, for positive and negative net fluid balance, indicates that the known mechanisms involved in the plasma release of h-ANF are not impaired in fulminant hepatic failure. This was confirmed by the rise in circulating levels of h-ANF in response to albumin infusion in six patients with no or mild renal failure. The absence of natriuresis or diuresis in the latter is compatible with the hypothesis that resistance to h-ANF may contribute to sodium retention. It is possible that overactivity of renin-aldosterone, which did not drop to normal after volume expansion, may antagonise the action of h-ANF.

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