Hyponatraemia as a marker for high renin heart failure

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SUMMARY The factors that might activate the renin-angiotensin system in treated heart failure were explored. Serum Na^+ correlated inversely with plasma renin activity. The degree of congestive heart failure measured by right atrial pressure, pulmonary capillary wedge pressure, cardiac index, and systemic vascular resistance did not correlate with plasma renin activity. Similarly, renal function as measured by blood urea nitrogen, creatinine, and urinary Na^+ excretion did not correlate with plasma renin activity. In a prospectively screened group, seven patients with congestive heart failure who were found to be hyponatraemic had plasma renin activities greater than 15 ng/ml per h. Serial determinations in one patient showed plasma renin activity to vary inversely with the serum Na^+ . It is concluded that serum sodium can be used to identify those patients with congestive heart failure who have a high plasma renin activity. The value of identifying these high renin heart failure patients was seen in their response in four cases to specific therapy with a converting enzyme inhibitor.

The renin-angiotensin system may play an important homeostatic role in both experimental and clinical congestive heart failure.¹⁻⁴ Increased circulating angiotensin II could contribute to systemic vasoconstriction which supports blood pressure^{5,6} but also might adversely affect left ventricular performance.⁷ Plasma renin activity has been reported to vary widely in patients with heart failure^{2,8,9} but the mechanism of its stimulation and the reason it is raised in some patients but not in others is not understood.

Haemodynamics, renal function, or volume factors all might be expected to be capable of stimulating the renin-angiotensin system.^{8,10-14} Since recent reports have shown a beneficial haemodynamic response in patients with heart failure to agents that block the activity of the renin angiotensin system,^{2,15,16} an understanding of the factors that stimulate it in heart failure and the recognition of clinical correlates of high plasma renin activity might have important therapeutic implications.

In the present study we have explored the possible influence of haemodynamic and renal functional factors on plasma renin activity in a group of patients with moderate to severe heart failure, in hospital and carefully stabilised. The data confirm earlier work⁸ that there is a strong negative correlation of plasma renin activity with serum sodium and indicate that the former does not correlate with other measured variables. Furthermore, a low serum sodium appears to be a fairly reliable guide to high plasma renin activity in heart failure.

Subjects and methods

Forty-two patients underwent an extensive haemodynamic and renal evaluation. The patients were studied in a stable state after being in hospital for three to five days on a 43 or 86 mmol sodium and 100 mmol potassium diet. Thirty-eight of the patients were taking digoxin and all were taking diuretics (37 patients frusemide alone, and five patients frusemide and spironolactone). All cardiac drugs except antiarrhythmic agents were withheld on the day of the study. Informed consent was obtained from each patient for the study procedure which had been approved by the University Committee on the Use of Human Subjects in Research.

On the morning of the study the patients fasted. In 36 patients a thermodilution Swan-Ganz flow-directed balloon tipped catheter was inserted percutaneously from a vein in the antecubital fossa and advanced to a position in the pulmonary artery where inflating the balloon occluded a pulmonary artery branch. The brachial artery was percutaneously cannulated with an Amplatz 0.038 arterial catheter. Pressures were monitored with Bell and Howell 4-3271 transducers. Electrocardiographic monitoring was continuous throughout the study. Pressure and electrocardiogram were recorded on a Hewlett Packard multichannel direct writing recorder. Mean pressures were electronically integrated. Right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and brachial artery pressure in mmHg, and thermodilution cardiac outputs in l/min were

obtained. In the other six patients a venous line was passed from a vein in the antecubital fossa to obtain central venous pressure. Brachial artery pressure was measured by cuff sphygmomanometry and cardiac outputs were determined by the CO₂ rebreathing method using a Beckman LB2 gas analyser.¹⁷

After all catheters were positioned the subjects were allowed to rest for one hour. Haemodynamic measurements were then made and blood samples drawn for serum electrolytes, serum creatinine, and plasma renin activity by radioimmunoassay using a Renak assay (Roche) as described by Sealey *et al.*¹⁸ The day before the study a 24-hour urine sample was collected for determination of sodium and creatinine excretion.

Systemic vascular resistance was calculated using the formula:

$$\text{SVR (dyne s cm}^{-5}\text{)} = \frac{\text{AP} - \text{RA}}{\text{CO}} \times 80,$$

where SVR is systemic vascular resistance, AP is brachial artery pressure, RA is right atrial pressure, and CO is cardiac output. Pulmonary vascular resistance was calculated using the formula:

$$\text{PVR (dyne s cm}^{-5}\text{)} = \frac{\text{PA}}{\text{CO}} \times 80,$$

where PVR is pulmonary vascular resistance, and PA is pulmonary artery pressure.

These data were analysed using variable linear regression and Student's *t* test.

Results

Resting haemodynamic, renal functional, and electrolyte data for the 42 patients studied are presented in Table 1. The low cardiac index and high right atrial and pulmonary capillary wedge pressures reflect the severity of the heart failure. Renal function was modestly diminished as evidenced by the slightly increased blood urea nitrogen and creatinine.

The plasma renin activity ranged from 0.3 ng/ml

per h to 85.2 ng/ml per h (Fig. 1). The normal plasma renin activity in our laboratory ranges from 0 to 8.0 ng/ml per h. When the level of plasma renin activity was compared with the various aspects of haemodynamics, renal function, or electrolyte status, a strong ($p < 0.001$) inverse correlation ($r = -0.65$) between plasma renin activity and serum Na⁺ was found. No significant correlation was found between plasma renin activity and cardiac index, mean arterial pressure, pulmonary capillary wedge pressure, systemic vascular resistance, pulmonary vascular resistance, serum K⁺, serum creatinine, or blood urea nitrogen (Table 1).

The patients were divided arbitrarily into a low renin group (0 to 16 ng/ml per h) and a high renin group (> 16 ng/ml per h). There were 31 patients in the low renin group and 11 in the high renin group (Table 2). Serum Na⁺ for the low renin group

Fig. 1 Correlation between plasma renin activity (PRA) and serum Na⁺ in patients with congestive heart failure. The closed dots represent the 42 patients studied. The open squares represent the seven patients prospectively marked as having high plasma renin activity because they were at the time hyponatraemic.

Table 1 Haemodynamic and renal function in patients with heart failure and their correlation to plasma renin activity

	No.	Mean	Correlation (r)	p for correlation
CI (l/min per m ²)	42	2.1 ± 0.1	0.15	NS
MAP (mmHg)	42	86.0 ± 2.0	-0.15	NS
PCW (mmHg)	35	24.4 ± 1.2	0.13	NS
RA (mmHg)	42	8.2 ± 0.9	-0.03	NS
SVR (dyne s cm ⁻⁵)	41	1821 ± 108	-0.07	NS
PVR (dyne s cm ⁻⁵)	35	766 ± 58	0.12	NS
Urine Na ⁺ (mmol/24 h)	27	51.1 ± 7.4	-0.05	NS
Serum creatinine (mmol/l)	41	114.9 ± 8.8	-0.06	NS
BUN (mmol/l)	40	9.99 ± 1.07	0.08	NS
Serum K ⁺ (mmol/l)	41	4.1 ± 0.1	0.23	NS
Serum Na ⁺ (mmol/l)	49	137 ± 1	-0.65	0.001

CI, cardiac index; MAP, mean arterial pressure; PCW, pulmonary capillary wedge pressure; RA, right atrial pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; BUN, blood urea nitrogen.

Table 2 Haemodynamics and renal function in high renin heart failure vs low renin heart failure

	Low renin (31) (0.16 ng/ml per h)	High renin (11) (>16 ng/ml per h)	Probability (low vs high)
CI (l/min per m ²)	2.1 ± 0.1	2.2 ± 0.2	NS
MAP (mmHg)	87.1 ± 2.1	83.0 ± 2.9	NS
PCW (mmHg)	24.4 ± 1.2	25.0 ± 1.3	NS
RA (mmHg)	7.9 ± 1.1	9.0 ± 2.1	NS
SVR (dyne s cm ⁻⁵)	1876 ± 122	1675 ± 233	NS
PVR (dyne s cm ⁻⁵)	747 ± 73	815 ± 99	NS
Urine Na ⁺ (mmol/24 h)	49.5 ± 6.5	57.8 ± 30.1	NS
Serum creatinine (mmol/l)	114.9 ± 8.8	1.3 ± 0.1	NS
BUN (mmol/l)	9.28 ± 1.07	33 ± 4	NS
Serum K ⁺ (mmol/l)	4.1 ± 0.1	4.5 ± 0.1	0.05
Serum Na ⁺ (mmol/l)	139 ± 1	131 ± 2	0.001

averaged 139 ± 1 mmol/l vs 131 ± 2 mmol/l for the high renin group. This difference was highly significant ($p < 0.001$). Serum K⁺ was also found to be significantly different ($p < 0.05$) when the low renin group ($K = 4.1 \pm 0.1$ mmol/l) was compared with the high renin group ($K = 4.5 \pm 0.1$ mmol/l). In all other respects the groups were comparable. The degree of heart failure as measured by cardiac index, right atrial pressure, pulmonary capillary wedge pressure, systemic vascular resistance, or pulmonary vascular resistance was the same for both the high renin and low renin groups. Renal function as assessed by serum creatinine, blood urea nitrogen, and urinary Na⁺ excretion was also similar for both groups.

Since analysis of these data suggested that hyponatraemia might identify high renin patients, a prospective analysis was undertaken by screening all patients admitted to hospital at the University of Minnesota Hospital during a two-month period because of congestive heart failure. Seven of these screened patients were found to be hyponatraemic (serum Na⁺ 123–132 mmol/l). These patients were prospectively identified as having high renin heart failure. Subsequent plasma renin activity confirmed this in each patient: plasma renin activity ranged from 15.0 to 96.0 ng/ml per h (Fig. 1).

The dynamic relation between plasma renin activity and serum Na⁺ was shown in one patient whose clinical course is shown in Fig. 2. This patient with severe congestive heart failure was admitted to hospital for a viral pneumonia. Before being admitted his serum Na⁺ was normal and his plasma renin activity was low (3.2 ng/ml per h). During the acute illness he was found to be hyponatraemic. Plasma renin activity during that period was 71.2 ng/ml per h. With recovery, serum Na⁺ levels returned to normal and plasma renin activity fell to (14.8 ng/ml per h). Mean arterial pressure was unchanged during this period despite activation of the renin angiotensin system. The rise in plasma renin activity could not be accounted for on the basis of decreased renal function, since the blood urea nitrogen tended to fall during the high renin period.

Fig. 2 Changes in plasma renin activity (PRA), serum Na, blood urea nitrogen (BUN), and mean arterial pressure (MAP) with time in a patient with congestive heart failure. Plasma renin activity rose conspicuously at a time when the patient was hyponatraemic. Renal function did not deteriorate during this period as the blood urea nitrogen tended to fall. The high renin state was not accompanied by a rise in arterial pressure. To convert BUN figures to SI units, 1 mg/dl $\approx$ 0.357 mmol/l.

Discussion

The inverse correlation between plasma renin activity and serum Na⁺ noted in this series of patients with congestive heart failure proved diagnostically useful. As shown in Fig. 3, hyponatraemia appears to be a marker for high renin heart failure, since plasma renin activity in the hyponatraemic group (mean 38.5 ± 6.6 ng/ml per h) was significantly higher ($p < 0.001$) than plasma renin activity in those with normal serum sodium (mean 5.1 ± 0.8 ng/ml per h). Furthermore, in our prospective analysis all seven patients identified

Fig. 3 Plasma renin activity (PRA) in patients with normal serum sodium (Na) and in hyponatraemic patients. Plasma renin activity was significantly higher in the hyponatraemic group.

with hyponatraemia had plasma renin activities greater than 15 ng/ml per h.

An inverse correlation between plasma renin activity and serum Na^+ in heart failure has been known for some time. Brown and associates⁸ showed a very close inverse correlation in 17 untreated patients with heart failure. This strong inverse correlation was still present when 119 patients treated with diuretics and digitalis were analysed with the untreated patients. Hesse and co-workers¹⁹ showed a significant rise in plasma renin activity as serum sodium fell in 12 patients with heart failure. The present study confirms these observations. Furthermore, in these treated patients with moderate to severe congestive heart failure, neither severity of heart failure as measured by cardiac index, pulmonary capillary wedge pressure, or right atrial pressure nor degree of renal impairment as measured by blood urea nitrogen or creatinine played an important role in determining plasma renin activity.

A number of pathophysiological mechanisms could be responsible for this inverse correlation between plasma renin activity and serum Na^+ . Activation of the renin-angiotensin system results in increased levels of angiotensin II. The role of angiotensin II on renal absorption of Na^+ and water has been studied

by a number of investigators,^{8, 20, 21} who have suggested an angiotensin-mediated reduction in renal medullary blood flow. The resultant increase in medullary osmolarity could result in excessive water reabsorption. Angiotensin II by stimulating arginine vasopressin production could also contribute to increased water reabsorption^{22, 23} and hyponatraemia. We have recently shown raised arginine vasopressin levels in heart failure.²⁴ Finally, angiotensin II has been shown experimentally to stimulate the thirst centre and result in polydipsia.^{25, 26} The resultant hyponatraemia from any one or all of the above mechanisms could then directly stimulate renin secretion by a mechanism that is not entirely clear.^{27, 28} It is of interest that an inverse correlation between plasma renin and plasma sodium has been reported in hypertension.²⁹ Low serum sodium also is seen in the hyponatraemic hypertensive syndrome.³⁰ It is reasonable to assume that the same physiological mechanisms may be acting in the pathogenesis of hyponatraemia-hyper-reninaemia in all these situations.

Although plasma volume was not measured in these patients, the similar increases in right atrial pressure in the high and low renin groups and similar values for arterial pressure and cardiac output make it unlikely that differential stimulation of an intravascular volume receptor accounts for the high renin subgroup.

Although no correlation between plasma renin activity and serum K^+ was found, the potassium was significantly higher in the high renin than in the low renin group (Table 2). This trend is surprising, since high renin might be expected to induce secondary hyperaldosteronism³¹ and potassium infusion decreases renal renin secretion.^{32, 33} Furthermore, this difference in serum K^+ could not be accounted for by differing diuretic regimens. The values for serum K^+ for both groups, however, were well within normal limits and the serum K^+ therefore was not useful in predicting the plasma renin activity.

The emergence of drugs that interfere with the renin-angiotensin system has made identifying those patients with high renin states potentially of clinical importance. Congestive heart failure has been treated with saralasin, a drug that competitively inhibits angiotensin II⁹ and with converting enzyme inhibitors that block the formation of angiotensin II.^{2, 15, 16, 34, 35} The acute response to these drugs appears to be closely correlated with the baseline plasma renin activity.^{2, 35, 36} Table 3 shows the effectiveness of acute converting enzyme inhibition in four selected hyponatraemic patients with high renin heart failure. Mean arterial pressure and pulmonary capillary wedge pressure were significantly lowered and cardiac index significantly increased. Though preliminary

Table 3 Response of patients with high renin heart failure to one dose of captopril, an angiotensin converting enzyme inhibitor

Case No.	Na ⁺ (mmol/l)	PRA (ng/ml per h)	MAP (mmHg)	PCW (mmHg)	CI (l/min per m ²)	SVR (dyne s cm ⁻⁵)
1 B	132	70.0	75	26	2.2	1455
C			50	8	2.6	836
2 B	131	63.8	100	38	1.6	3409
C			45	9	2.4	1166
3 B	132	22.8	92	22	1.2	3163
C			60	9	1.6	1640
4 B	134	85.2	78	25	3.2	888
C			56	8	3.5	556
Mean±SD B			86±5	27.8±3.2	2.1±0.4	2229±557
C			53±3*	8.5±0.31*	2.5±0.3*	1050±208

B, baseline; C, after captopril.

*p<0.05.

reports suggest that converting enzyme inhibitors may have beneficial long-term effects even in low renin heart failure,³⁶ their mechanism of action in this setting is not entirely understood. Identification of high renin heart failure might be useful in selecting appropriate acute therapy. The present data suggest that a low serum sodium is a simple indicator of such cases and might identify patients who will acutely benefit most from therapy to inhibit the renin-angiotensin system.

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