Haemodynamic and hormone responses to acute and chronic frusemide therapy in congestive heart failure

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Summary

1. Since important interrelationships between haemodynamic and hormone indices are possible in cardiac failure, measurements of cardiac output, mean pulmonary artery pressure, plasma renin activity, angiotensin II and aldosterone were carried out before and during acute and chronic frusemide therapy in patients with oedematous heart failure who had been given digoxin.

2. Cardiac output fell significantly 90 min after acute frusemide injection, then returned to baseline. Mean pulmonary artery pressure declined steadily throughout the 4 h of observation.

3. These haemodynamic changes occurred in the absence of major hormonal fluctuations and related presumably to direct vascular and diuretic actions of frusemide.

4. With more chronic (8-10 days) oral frusemide therapy, reciprocal changes between haemodynamic and hormone indices were observed. As the diuretic response to frusemide diminished, cardiac output and pulmonary artery pressure declined whereas the renin–angiotensin system was activated. Statistically significant inverse correlations were observed between these haemodynamic and hormone indices.

5. In both acute and chronic phases of the study, fluctuations in aldosterone levels were regulated by the renin–angiotensin system whereas ACTH, plasma potassium and plasma sodium played, at best, supportive roles.

Key words: aldosterone, diuretic, haemodynamics, heart failure, renin–angiotensin.

Introduction

Diuretic therapy is of proven efficacy in both acute and chronic cardiac failure. Whereas haemodynamic and to a lesser extent hormonal responses to diuretic therapy in cardiac failure have been reported, their interrelationships in this clinical setting have been largely ignored. This is surprising, since considerable evidence exists to suggest that the renin–angiotensin system and cardiac performance may be intimately linked in patients with cardiac failure.

The present study was designed to clarify haemodynamic, hormone and electrolyte relationships in patients with chronic heart failure before and during diuretic therapy. With the advent of agents which block the production or action of angiotensin II (ANG II) we thought it particularly important to document the activity of the renin–angiotensin–aldosterone system along with haemodynamic indices.

Methods

The study protocol was approved by the Ethical Committee of the North Canterbury Hospital Board, and informed consent was obtained from each patient. Eleven patients (nine males and two females, ages 37–68 years) were studied. All subjects were, on admission to hospital, in congestive cardiac failure with a raised jugular venous pressure, cardiomegaly, a third heart sound and peripheral pitting oedema. The patients were placed on a constant dietary intake of sodium (40 mmol/day) and potassium (100 mmol/day) and fluid intake was fixed at 2 litres daily. Each subject was nursed in a bed in a sitting-up position. All medications were stopped and digoxin therapy (0.25–0.5 mg daily) was initiated.

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Acute frusemide study

After a run-in period of 2 or 3 days on the controlled diet, digoxin and bed rest, 10 patients received an intravenous bolus of frusemide (1 mg/kg body wt.) at 09.00 hours. Before frusemide and thereafter at 15-60 min intervals for 4 h, venous samples were drawn for hormone and electrolyte measurements and haemodynamic indices were recorded. Urine was collected at 30-60 min intervals after frusemide injection for volume and electrolyte determination.

Chronic frusemide study

In three of 10 patients who underwent the acute frusemide study and in one additional subject, haemodynamic and hormone measurements were carried out twice daily for 8–10 days. During this time, dietary sodium and potassium, fluid intake, body posture and digoxin therapy were held constant as described above. After a 2 or 3 day run-in period, oral frusemide therapy 80–240 mg daily was given. In three of the four patients, the first day of diuretic therapy was as described above, with frusemide (1 mg/kg) being injected intravenously. All urine was collected for measurement of creatinine (to assess completeness of daily collections), sodium and aldosterone excretion. Venous samples were drawn at 10.00 and 16.00 hours for hormone and electrolyte measurements and cardiac output and pulmonary artery pressures were determined daily (10.30 hours) in most cases.

Well-established assay techniques were used for the measurement of plasma renin activity (Dunn & Espiner, 1976), ANG II (Nicholls & Espiner, 1976), plasma aldosterone (Ito, Woo, Haning & Horton, 1972), urine aldosterone (Nicholls, Espiner, Donald & Hughes, 1974) and plasma cortisol (Murphy, 1967). Sodium and potassium in plasma and urine were measured by flame photometry. A Swan–Ganz catheter was placed into the pulmonary artery under sterile conditions for measurement of pulmonary artery pressures and cardiac output (thermal dilution or direct Fick method). Cardiac output was the mean of three recordings on each occasion.

Statistical analyses were carried out by using Student's t-test for paired data and the product moment correlation coefficient.

Results

The aetiology of cardiac failure is shown in Table 1. A diagnosis of beriberi in three patients was confirmed by endomyocardial biopsy. All patients completed the study without complication. Symptomatic improvement was the rule although this was not quantified objectively. In six patients, spontaneous diuresis (24 h urine volume greater than the 2 litres fluid intake) was initiated by bed rest, before frusemide was injected.

Acute frusemide study

Urine was collected in nine of the 10 patients after intravenous frusemide. The mean 4 h volume was 1726.6 ml (range 1096–3080 ml), mean urine sodium was 190.4 mmol (range 89–281 mmol) and the mean potassium ex-

<table>
<thead>
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<th>Patient no.</th>
<th>Aetiology of heart failure</th>
<th>Cardiac output (l/min)</th>
<th>Mean pulmonary artery pressure (x 11 mmHg)</th>
<th>Plasma renin activity (0.15–1.5 nmol h⁻¹ l⁻¹)</th>
<th>Plasma ANG II (10–40 pmol/l)</th>
<th>Plasma aldosterone (155–550 pmol/l)</th>
<th>Plasma sodium (135–145 mmol/l)</th>
<th>Plasma potassium (2.5–5 mmol/l)</th>
<th>Plasma cortisol (110–970 nmol/l)</th>
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cretion over 4 h was 33.8 mmol (range 13–95.5 mmol). Baseline haemodynamic, hormone and electrolyte indices are shown in Table 1. Cardiac output was clearly elevated in two patients with beriberi (Table 1). Mean pulmonary artery pressure was elevated (greater than 11 mmHg) in all but two patients (Table 1). Initial values of plasma renin activity, ANG II, and plasma aldosterone were within normal limits in most subjects, although there was a considerable range for each of these indices (Table 1). Plasma sodium was reduced in some and a negative correlation was noted between baseline plasma sodium concentration and cardiac output \( r = -0.6869, P < 0.05 \). A negative relationship was also seen between baseline plasma sodium and plasma activity \( r = -0.4350 \) but did not reach levels of statistical significance. There were no significant correlations between baseline levels of plasma renin activity or ANG II with either cardiac output \( r = -0.1647 \) and \( -0.4248 \) respectively) or mean pulmonary artery pressure \( r = -0.3609 \) and 0.1466 respectively).

Cardiac output decreased slightly after frusemide injection, reached a nadir at 90 min, then returned to baseline (Fig. 1). Mean pulmonary artery pressure declined rapidly in response to frusemide and continued to fall throughout the 4 h observation period (Fig. 1). Plasma levels of renin, ANG II and aldosterone showed an overall rise within 30 min of frusemide injection but only the increment in ANG II was statistically significant (Fig. 1). Three patients, in fact, showed either no change or a fall in plasma renin activity. For all results \( n = 80 \), correlations between concurrent levels of plasma renin activity and aldosterone \( r = 0.8869 \), ANG II and aldosterone \( r = 0.4369 \) and plasma renin activity and ANG II \( 2r = 0.5311 \) were significant \( P < 0.001 \).

Whereas plasma sodium levels did not change overall during the 4 h study, plasma potassium had fallen significantly by 15 min and reached a nadir \( 0.49 \) mmol/l below baseline) at 180 min (Fig. 1). This fall in plasma potassium was highly significant \( P < 0.001 \) 30 min after frusemide injection by which time urine potassium excretion was minimal (mean 11.3, range 2–40 mmol).

The pattern of haemodynamic, hormone and electrolyte responses to frusemide injection was similar in those with high output cardiac failure to patients with low output failure.

**Chronic frusemide study**

The haemodynamic and hormone responses to oral frusemide therapy were similar in the four patients studied. Detailed results from one patient are shown in Fig. 2. Initially, oral frusemide (80–240 mg daily) induced a vigorous diuresis and natriuresis, but the urinary response diminished with continued therapy (Fig. 2). Cardiac output and mean pulmonary artery pressure remained steady or increased at the time of peak natriuresis, but fell to below baseline values in the later study days (Fig. 3). These two indices ran a parallel course in each patient although in only two were the relationships statistically significant \( P < 0.05 \).

The pattern of plasma renin activity, ANG II and plasma aldosterone responses was the reciprocal of that for cardiac output and mean pulmonary artery pressure. From baseline values which varied between moderate elevation to below the normal range for control subjects, these three indices either fell or remained low until the phase of diminishing natriuretic response to
Fig. 2. Haemodynamic, hormone and electrolyte measurements in a patient with chronic congestive heart failure before and during 8 days of oral frusemide therapy. The discontinuous line in the urine sodium sector indicates daily dietary sodium intake.

frusemide, when parallel increments to high levels were observed (Figs. 2, 3). In each patient there were statistically significant correlations between concurrent plasma renin activity and ANG II \((r = 0.5183 \text{ to } 0.9856, P < 0.05 \text{ to } < 0.001)\), plasma renin activity and plasma aldosterone \((r = 0.7449 \text{ to } 0.9567, P < 0.001)\), and between ANG II and plasma aldosterone \((r = 0.5646 \text{ to } 0.9445, P < 0.05 \text{ to } < 0.001)\). As noted above this pattern of hormonal change was the opposite of that for cardiac output and mean pulmonary artery pressure. Overall, there was an inverse correlation between plasma renin activity and cardiac output \((r = -0.4319, P < 0.05, n = 31)\), and between ANG II and cardiac output \((r = -0.4185, P < 0.05, n = 31)\). In individual patients these indices were inversely related \((r = -0.3967 \text{ to } -0.8591)\) but statistical significance was achieved in only three instances since the number of readings was not great \((n = 5-10)\). Mean
pulmonary artery pressure related inversely to plasma renin activity \( (r = -0.4235 \text{ to } -0.7743) \) and ANG II \( (r = -0.3767 \text{ to } -0.8591) \) in every patient, although statistical significance \( (P < 0.05) \) was achieved in only three subjects. Urine aldosterone excretion, an integrated index of 24 h aldosterone secretion, followed closely the pattern of plasma aldosterone fluctuations (Fig. 2).

Baseline and subsequent levels of plasma cortisol, and plasma sodium and potassium varied independently of plasma aldosterone except in one patient in whom an inverse relation between plasma sodium and plasma aldosterone \( (r = -0.8260, P < 0.05) \) was found. In this patient, but not in the other three, plasma sodium correlated inversely and significantly \( (P < 0.01 \text{ and } P < 0.05) \) with concurrent plasma renin activity \( (r = -0.8475) \) and ANG II levels \( (r = -0.8272) \).

Discussion

Whereas there have been separate studies of the haemodynamic and the hormonal responses to diuretic therapy in congestive heart failure, few reports have documented both responses in the same patient. In experimental cardiac failure maintenance of arterial pressure is dependent upon the renin–angiotensin system (Watkins, Burton, Haber, Cant, Smith & Barger, 1976; Williams, Davis, Freeman, DeForrest, Seymour & Rowe, 1979), and angiotensin-controlled aldosterone production contributes to the volume overload (Watkins et al., 1976; Morris, Davis, Zatzman & Williams, 1977; Freeman, Davis, Williams, DeForrest, Seymour & Rowe 1979; Williams et al., 1979). Of clinical relevance are reports that blockade of the renin–angiotensin system may improve cardiac function in some patients with congestive heart failure (Curtiss, Cohn, Vrobel & Franciosa, 1978; Gavras, Faxon, Berkoben, Brunner & Ryan, 1978; Davis, Ribner, Keung, Sonnenblick & LeJemtel, 1979).

In the current study of acute frusemide injection no significant correlation between plasma renin activity or ANG II with either cardiac output or mean pulmonary artery pressure was noted. After intravenous frusemide a small and temporary fall in cardiac output occurred and a steady decline in mean pulmonary artery pressure was observed over a 4 h period. This fall in pulmonary artery pressure preceded the natriuresis, which suggests that an effect on vascular smooth muscle, particularly venous capacitance vessels, was responsible for much of the early response (Dikshit, Vyden, Forrester, Chatterjee, Prakash & Swan, 1973). Despite the fall in pulmonary artery pressure and the later diuretic response the increments in renin, ANG II and aldosterone were small in most patients. These observations contrast with those in subjects with normal cardiac function, in whom frusemide injection elicits clearcut increases in plasma renin activity (Rosenthal, Boucher, Nowaczynski & Genest, 1968; Hesse, Nielsen & Lund-Jacobsen, 1975).

The reason for the lack of responsiveness of the renin–angiotensin system to acute frusemide injection in chronic congestive heart failure is not clarified by our study, but may relate to increased renal afferent arteriolar blood flow and augmented delivery of sodium and chloride to the macula densa (both tending to inhibit renin release) without significant stimulation of volume receptors. It is interesting to note that reduced or delayed activation of renin secretion was observed during sodium-depleting manoeuvres by Judson & Helmer (1971) in patients with markedly reduced cardiac output. Distension of pulmonary and atrial segments in dogs has been shown to reduce renin secretion (Zehr, Hasbargen & Kurz, 1976) and it is possible that decrements in right atrial pressure, which normally increase plasma renin activity (Kiwoski & Julius, 1978), fail to do so in patients with grossly abnormal baseline pressures in the right atrium and pulmonary artery. A further possibility is that digoxin therapy might have impaired renin release, since ouabain has been reported to diminish the renin response to frusemide in dogs (Blaine & Zimmerman, 1978) and digoxin may lower renin levels in man (Antonello, Cargnielli, Ferrari, Melacini & Montanaro, 1976). The steady, systematic decline in plasma potassium levels after acute frusemide injection was unexpected. Care was taken in blood sampling, centrifugation, storage and electrolyte analysis, thus a technical error seems unlikely. Since a highly significant fall in plasma potassium occurred when urinary excretion of the ion was minimal, the most likely explanation is a temporary shift in distribution of potassium from extra- to intra-cellular compartments. Certainly, loop diuretics may act on extrarenal tissues (MacKenzie, Cochran & Russell, 1975; Brazy & Gunn, 1976), and it is conceivable that stimulation of catecholamines by diuretic administration (Muentes, Alicandri, Agabiti Rosei, Motolese & Valori, 1975) may have contributed to shifts of potassium from extra- to intra-cellular sites (Lockwood & Lum, 1974).

In contrast to acute therapy, oral frusemide given for 8–10 days was associated with marked changes in both hormonal and haemodynamic
indices. Cardiac output and mean pulmonary artery pressure remained relatively unchanged early in the natriuretic phase and later fell when the natriuretic response to frusemide was diminishing. In all four patients mean pulmonary pressure had returned to the normal range at the study’s completion. Changes in plasma renin activity. ANG II, as well as aldosterone were reciprocally related to the changes noted in haemodynamic measurements. On the days of peak natriuresis, plasma renin activity and ANG II remained low or fell below baseline values, and later increased to very high values coincident with the decline in mean pulmonary artery pressure and cardiac output. The initial fall in renin and ANG II levels coincided with maximum natriuresis, and was presumably dictated by a combination of increased delivery of sodium and chloride to the macula densa, and improved renal perfusion which would diminish renal arteriolar baroreceptor input to renin release. As previously suggested (Espiner, Jagger, Tucci & Laufer. 1969; Nicholls et al., 1974), it seems likely that activation of the renin–angiotensin–aldosterone system occurs with continued diuretic therapy once oedema fluid has been absorbed and excreted. Part of this activation may follow from decreased delivery of sodium or chloride to the macula densa as well as from stimulation of renal afferent arterioles. A further factor stimulating renin release may be a fall in cardiopulmonary blood volume (Kiowski & Julius. 1978: Thames, 1978). Consistent with this possibility is our finding of inverse relationships between mean pulmonary artery pressure and both plasma renin activity and ANG II levels in each of the four patients studied.

Although there were insufficient haemodynamic measurements to determine causal relationships it is possible that the fall in cardiac output observed in the final days of oral frusemide injection was a consequence of a rise in peripheral resistance induced by increasing levels of ANG II (Curtiss et al., 1978). Further work is needed to determine the possible benefits (Davis et al., 1979) or disadvantages of angiotensin blockade in these patients.

The present study further confirms the importance of the renin–angiotensin system in the regulation of aldosterone production during diuretic therapy in patients with congestive heart failure. The pattern of hormone secretion during chronic diuretic therapy as previously described (Nicholls et al., 1974) was again evident and was further supported by the finding of a similar pattern in plasma ANG II. That these hormonal variations relate to changes in circulatory dynamics as shown in this study has important implications for the pathophysiology and treatment of congestive heart failure.

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References


Frusemide in heart failure


