The renin angiotensin aldosterone system and frusemide response in congestive heart failure

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- 1 To test the hypothesis that basal renin angiotensin aldosterone system (RAAS) activity impairs the acute natriuretic response to frusemide in patients with mild or moderate congestive heart failure (CHF), we studied eight adult volunteers with preserved renal function, stable New York Heart Association Class II or III CHF, and echocardiographic evidence of left ventricular dysfunction due to myocardial infarction, hypertension, or both causes.
- 2 All patients received three dosing regimens administered in random order: (a) intravenous frusemide: 40 mg bolus then 40 mg h⁻¹ for 3 h, (b) captopril: two 12.5 mg oral doses separated by 2 h, (c) combined dosing: the first captopril dose preceded the frusemide bolus by 30 min. Sodium balance on an 80 mmol day⁻¹ sodium diet was documented prior to each dosing regimen. Sodium excretion was quantitated in urine collected at intervals until 3.5 h after initiating drug administration. During this time, urine output was replaced intravenously with an equivalent volume of 0.45% saline.
- 3 Captopril significantly lowered plasma angiotensin converting enzyme (ACE) activity and plasma aldosterone concentration, and raised inulin clearance. The drug had essentially no effect on the time course or magnitude of frusemide's natriuretic effect. Maximal fractional sodium excretion during frusemide infused by itself and in combination with captopril was $24.7 \pm 1.9\%$ vs $28.2 \pm 3.8\%$, respectively (difference 3.5%; 95% CI, -4.0 to 11.0%; $P > 0.05$). Cumulative sodium excretion ending at 3.5 h was 429 ± 53 mmol when frusemide was given alone and 455 ± 69 mmol when captopril was added (difference, 26 mmol; CI, -121 to 174 mmol; $P > 0.05$). Captopril alone produced minimal changes in sodium excretion. The ACE inhibitor did not significantly alter urinary frusemide excretion, *p*-aminohippurate clearance, blood pressure or cardiac output.
- 4 In patients with compensated mild or moderate CHF, captopril does not acutely affect the delivery of frusemide to its active site or the ensuing natriuresis. Thus, it does not appear that basal RAAS activity significantly modulates acute diuretic response in this subset of CHF patients.

Keywords diuretic resistance angiotensin heart failure sodium frusemide captopril

Introduction

As part of the compensatory, homeostatic adjustments that accompany the failing left ventricle, retention of salt and water by the kidney substantially contributes to the pathophysiology of congestive heart failure (CHF). While increases in plasma volume can im-

prove cardiac performance via the Frank Starling mechanism, intravascular volume expansion can also lead to incapacitating pulmonary congestion and peripheral oedema. Consequently, maintenance of optimal plasma volume is an essential therapeutic

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goal in the treatment of CHF. Although angiotensin converting enzyme (ACE) inhibitors are useful in the treatment of heart failure because they can improve functional capacity and decrease the mortality rate [1–3], prior studies have shown that they alone are insufficient to manage the excess total body volume overload that often accompanies the failing heart [4, 5]. Thus, loop diuretics, the most efficacious class of natriuretic drugs, remain essential agents in the management of this condition.

Despite the proven efficacy of loop diuretics in patients with CHF, supranormal doses are typically required in order to achieve a natriuretic response [6–9]. The cause for resistance to these drugs is unknown. Prior studies have essentially excluded a pharmacokinetic cause [6–9]. Thus, some undefined pharmacodynamic abnormality is presumed culpable. It is possible that the same systems evoked by cardiac dysfunction that lead to renal sodium retention also counteract the natriuretic effect of loop diuretics. Among the neurohumoral systems modulating renal sodium excretion, the renin angiotensin aldosterone system (RAAS) is a potential contributor to diuretic resistance in CHF. The RAAS produces renal sodium retention via several mechanisms [10–12] and increased circulating levels of various components comprising this system have been noted in decompensated CHF [13, 14]. In severe CHF characterized by hyponatraemia, Dzau & Hollenberg showed that interruption of the RAAS axis for several days with captopril increased frusemide-induced natriuresis [15]. The mechanism for this effect has not been elucidated. Furthermore, it is not known if a similar beneficial action occurs in less severe forms of CHF. The purpose of this study was to determine if activation of the RAAS impairs acute diuretic response to frusemide in compensated forms of mild or moderate CHF. A second objective was to elucidate the mechanism by which ACE inhibition facilitates frusemide response in CHF.

Methods

Study population

We studied five male and three female patients (mean age 63 years, range 47 to 73 years) with symptomatic CHF and evidence of left ventricular dysfunction by echocardiography. Three of the subjects demonstrated New York Heart Association Functional Classification II and the remainder class III symptoms. The aetiologies of CHF were coronary artery disease in five patients and hypertension in an equal number (two subjects had evidence of both causes). Volunteers had experienced stable CHF symptoms for at least 1 month prior to study. Candidates with class IV symptoms, atrial fibrillation, angina pectoris, or significant renal insufficiency as defined by a creatinine clearance less than 40 ml min^{-1} were excluded from investigation. All patients signed informed consent documents approved by the Indiana University Medical Center Institutional Review

Board after explanation of the procedures to be performed.

Experimental protocol

The study was conducted in the General Clinical Research Center at Indiana University Hospital. All subjects had been receiving an ACE inhibitor and diuretic drug as part of their outpatient therapy for CHF. These agents were discontinued a minimum of 21 days and 5 days, respectively before the initial administration of a study drug. The study entailed three separate drug regimens. Patients were equilibrated for a minimum of 3 days before each study on a metabolic diet containing 80 mmol sodium, 80 mmol potassium, and 3 l of distilled water per day. Following sodium balance, documented prior to each study by daily weight and by 24 h urine sodium excretion, the patient was restricted from oral intake beginning at midnight in anticipation of study the next morning. An unblinded, randomized, three-way crossover design was utilized to compare the acute natriuretic response with frusemide and captopril administered alone and in combination.

The three dosing regimens consisted of:

- 1) Captopril – two 12.5 mg oral doses separated by 2 h.
- 2) Frusemide – a 40 mg intravenous bolus dose followed by a continuous 40 mg h^{-1} infusion for 3 h.
- 3) Captopril and frusemide – a combination of the two regimens with the first captopril dose preceding the initiation of frusemide by 30 min.

We chose this experimental paradigm in order to minimize captopril-induced changes in blood pressure while producing ACE inhibition. Continuous infusion of frusemide during the acute study ensured a natriuretic response during the time of greatest interruption of the RAAS by captopril. In the event that captopril caused increased sodium delivery to the thick ascending limb (TAL), residual transport capacity by this segment could blunt the natriuretic response. Therefore, we administered a large diuretic dose to inhibit completely TAL solute reabsorption [16].

All three dosing regimens were administered after an overnight fast. At approximately 07.00 h on each morning of drug study the patient voided and, except for bedside commode privileges, remained supine in bed until completion of the day's experiment. Inulin and *p*-aminohippurate (PAH) were administered via an intravenous catheter in one forearm to provide an estimate of glomerular filtration rate (GFR) and effective renal plasma flow, respectively. Bolus doses of inulin and PAH (loading doses were based on body weight) were followed by maintenance infusions (dosing rates based on estimated creatinine clearance) of the compounds to maintain steady-state target plasma concentrations of approximately 10 mg dl^{-1} and 1.5 mg dl^{-1} , respectively. A second intravenous catheter was placed in the contralateral arm for serial blood sampling.

Figure 1 depicts a schematic of the study paradigm. A 45 min equilibration period followed the bolus inulin and PAH doses. During this time, subjects ingested 20 ml kg⁻¹ distilled water. For each study, the volume of urine from a collection interval was replaced intravenously during the next interval with 0.45% saline. Two 30 min control urine collections and corresponding midpoint blood samples were obtained. This sampling corresponds to U₁, U₂, B₁, B₂ of Figure 1 for the 2 days that captopril was administered, and U₂, U₃, B₂, B₃ for the day that only frusemide was infused. Baseline inulin and PAH clearances and fractional sodium excretion (FENa) were quantitated by averaging the respective results from the two control periods. During the second control period, blood was also obtained for measurement of baseline plasma renin activity (PRA), plasma ACE activity and plasma aldosterone concentration (PAC). In the second control period, a 2-D echocardiogram with Doppler was performed for non-invasive determination of baseline cardiac output.

Upon completion of the second control period, the subject underwent one of the three experimental dosing regimens. On the 2 days that captopril was given, respective blood and urine samples corresponding to B₄ through B₈ and U₃ through U₇ of Figure 1 were obtained during the experimental period. Urine samples U₃ and U₄ were collected as a single, 1 h specimen. On the frusemide only day, blood samples B₆ through B₈ and urine samples U₄ through U₇ were obtained for measurement of inulin, PAH, and sodium concentrations. Frusemide concentration was also measured in all urine samples and ACE activity, PRA and PAC were determined in the above plasma samples. During captopril dosing, supine cuff blood pressure was obtained at baseline and every 15 min until 3 h, and at 3.5 h. Doppler echocardiography was repeated for cardiac output determination at 2 h on all study days.

Analytical methods

Urine and serum sodium were measured by flame photometry (Model 943; Instrumentation Laboratory, Lexington, MA). Inulin and PAH concentrations in serum and urine were quantitated by a colorimetric assay (Technicon[®] Autoanalyzer[®] II Single-Channel

Colorimeter, Technicon Instruments Corporation, Tarrytown, NY). We employed assays previously described by our laboratories to measure frusemide in urine by h.p.l.c. [17] and PRA, plasma ACE activity and PAC by radioimmunoassay [18, 19].

Statistical analysis

Cardiovascular and renal parameters Results are expressed as mean values $\pm$ s.e. mean. Urine and serum data were used to determine FENa and clearance of inulin and PAH, computing the values of these parameters according to standard methods [20]. For clearance estimates, the equation UV/P was employed where U and P represent marker concentration in urine and plasma, respectively and V represents urine flow rate. All subjects had baseline renal and cardiac functions assessed to verify intra-subject homogeneity before each of the three drug regimens. Baseline cardiovascular measures, and changes from baseline within a study day expressed as absolute and percentage differences, were compared between dosing days. Statistical tests of dosing days at each measurement time were conducted through repeated-measures analysis of variance that accounted for patients and treatments as sources of variability. The GFR vs time profiles were characterized in each patient and for each treatment by means of their linear trend. These trends, estimated via linear regression, were compared between treatments through the repeated-measures methodology. In the case of urine frusemide excretion, a paired *t*-test was applied to compare the combined regimen with frusemide alone. A *P* value of < 0.05 was considered statistically significant.

Biochemical parameters The variables ACE activity, PAC and PRA were converted for each subject to a ratio relative to pre-dose values and expressed as a percentage. The repeated measures over time were reduced to various summary response measures, such as the average value and the extreme value (either highest or lowest) from baseline (100%), and linear slope. These summary measures were compared between treatments by repeated measure analysis of variance with subjects and treatments as factors. Subsequent to an overall significance test pairwise *t*-test comparisons based on the overall error estimate were conducted to identify specific differences.

Results

There were no significant differences (*P* > 0.05) between study days in patients' pre-dose weight and renal sodium excretion. The mean weight and 24 h urine sodium excretion (and ranges) were 84.5 kg (74.8 to 92.9 kg), 84.5 kg (75.7 to 92.7 kg), and 84.6 kg (76.0 to 91.7 kg); and 40 mmol (10 to 117 mmol), 56 mmol (20 to 78 mmol), and 55 mmol (25 to 127 mmol) for the captopril, frusemide and combined dosing regimens, respectively. Thus, the group was

Figure 1 Schematic of the study paradigm for dosing with frusemide, captopril and the two drugs combined. Captopril, when administered, was ingested at times -30 and 90 min. Frusemide, when administered, was infused from 0 to 180 min. Intravenous inulin and PAH infusions were begun 45 min prior to initiating control urine collections. Consecutive urine and blood collections are displayed as U_N and B_N, respectively where N stands for the sample number (See Methods for details).

considered to be in comparable states of sodium balance on the morning of each dosing day.

Figure 2 depicts the urine sodium excretion rate for 60 min sampling periods during the administration of frusemide, captopril and both drugs. As expected, parenteral frusemide administration significantly increased sodium excretion rate for the 3.5 h study period. The diuretic bolus with continuous infusion produced a sustained response that was essentially constant over time. The co-administration of captopril did not significantly alter either the time course of sodium excretion or the total amount excreted. Cumulative sodium excretion ending at 3.5 h was 429 ± 53 mmol when frusemide was given alone and 455 ± 69 mmol when captopril was added (difference, 26 mmol; 95% CI, -121 to 174 mmol; $P > 0.05$). Furthermore, there was no difference in the maximal FENa between these two regimens. Maximal FENa during frusemide infused by itself and in combination with captopril was $24.7 \pm 1.9\%$ vs $28.2 \pm 3.8\%$, respectively (difference, 3.5%; CI, -4.0 to 11.0%; $P > 0.05$). The ingestion of captopril alone produced no change in the sodium excretion rate from baseline (Figure 2). Maximal FENa during this treatment was $1.0 \pm 0.3\%$ (difference from combination therapy, 27.2%; CI, 19.0 to 35.4%; $P < 0.05$). Captopril did not change the time course of urine frusemide excretion or the cumulative amount of diuretic drug excreted over the 3.5 h collection period. For the latter parameter there were 81 ± 8 mg vs 84 ± 11 mg of frusemide excreted in the presence and absence of captopril, respectively (difference, 3 mg; CI, -26 to 33 mg; $P > 0.05$).

Figure 2 Mean and s.e. mean urine sodium excretion rate results from eight CHF patients. Pre-dose control (C) and experimental data are shown for the dosing of captopril (▲), frusemide (■), and the two drugs combined (●). Captopril, when administered, was ingested at times -30 and 90 min. Frusemide, when administered, was infused from 0 to 180 min. Symbols for the experimental periods are placed at the times corresponding to the midpoint of the 60 min urine collection intervals.

Captopril had no effect on systemic blood pressure or cardiac output when given by itself or concurrently with frusemide (data not shown). The effect of the study drugs on renal function was also evaluated. As shown in Figure 3, renal PAH clearance did not change significantly for any of the three dosing regimens. Thus, no significant effect on effective renal plasma flow was seen between regimens or within a particular dosing day. When GFR data were analyzed by trend analysis, the changes over the observation period after captopril treatment were significantly different ($P < 0.05$) from the other two treatments. Frusemide with and without captopril did not significantly alter GFR.

The time courses of PRA, PAC and plasma ACE activity during the different dosing regimens are depicted in Figure 4. Captopril administration alone and in combination with frusemide significantly ($P < 0.05$) decreased ACE activity and PAC from control values. Frusemide alone had no significant effect on these parameters. Plasma renin activity significantly ($P < 0.05$) increased during the frusemide + captopril regimen to a mean of three times the baseline value.

Figure 3 Mean and s.e. mean inulin (panel a) and PAH (panel b) clearance results from eight CHF patients. Pre-dose control (C) and experimental data are shown for the dosing of captopril (▲), frusemide (■), and the two drugs combined (●). Captopril, when administered, was ingested at times -30 and 90 min. Frusemide, when administered, was infused from 0 to 180 min. Symbols for the experimental periods are placed at the times corresponding to the midpoint of the 60 min urine collection intervals.

Figure 4 Mean and s.e. mean plasma renin activity (PRA; panel a), plasma aldosterone concentration (PAC, panel b), and plasma angiotensin converting enzyme (ACE) activity (panel c) results from eight CHF patients. Pre-dose control (C) and experimental data are shown for the dosing of captopril (▲), frusemide (■), and the two drugs combined (●). Experimental period data are expressed as a percentage of the pre-dose control value. Captopril, when administered, was ingested at times -30 and 90 min. Frusemide, when administered, was infused from time 0 to 180 min.

During the frusemide treatment day, PRA doubled by the end of the 3 h observation period ($P < 0.05$ vs control value). Despite evidence for significant ACE inhibition by captopril, PRA was not significantly increased on the day that drug was given by itself. This finding suggests that the short loop feedback of angiotensin II on renin release is not the same in CHF as in normal individuals [21].

Discussion

This study evaluated the hypothesis that the RAAS impairs acute natriuretic response in patients with mild or moderate CHF. In these haemodynamically compensated patients with echocardiographic evidence of left ventricular dysfunction, we found that the acute administration of captopril did not enhance the natriuretic efficacy of frusemide. Because our dosing regimen produced significant ACE inhibition, yet had no influence on blood pressure or frusemide's time course of action, maximal effect, or cumulative response, our findings indicate that inhibition of basal RAAS activity in the absence of a depressor effect does not significantly alter acute natriuretic response in this subset of CHF patients.

While our results failed to demonstrate a role for the RAAS in modulating diuretic induced natriuresis, these findings should not be extrapolated to all cases of CHF. The degree of RAAS activation is in part dependent upon the severity of left ventricular dysfunction, severe decompensated CHF being associated with the highest circulating hormone levels [13, 14]. In a study evaluating the subacute effects of frusemide and captopril on renal function and hyponatraemia in patients with severe CHF characterized by hyponatraemia, Dzau & Hollenberg found evidence for a synergistic natriuretic effect for these drugs [15]. Captopril, titrated to a dose causing a 10 mm Hg decrease in systolic blood pressure, and frusemide were given individually and then together for several days. Based on mean daily 24 h urine

excretion data reported for each therapy, only combined treatment produced a diuretic effect and a negative sodium balance. These results suggest that in this stage of severe CHF, characterized by marked activation of PRA and PAC [13, 14], the RAAS plays a modulating role in the natriuretic response when ACE inhibition produces a significant fall in blood pressure.

Although captopril was shown to enhance frusemide response in patients with severe CHF, the mechanism for the synergistic natriuretic response is unknown. A number of captopril-related effects may be involved. Interruption of the RAAS by inhibiting ACE can reduce afterload and improve ventricular function [1]. This effect, along with a reduction in renal vascular resistance, would increase GFR and renal plasma flow [12]. The latter parameter is an important factor that helps determine the quantity of frusemide delivered into the urine and thus presented to the drug's active site in the TAL [22, 23]. In addition to these haemodynamic effects the RAAS facilitates renal tubule sodium uptake. Angiotensin II stimulates aldosterone release, which in turn enhances sodium reabsorption in the collecting duct [24, 25]. The peptide also acts directly on proximal tubule epithelial cells to increase sodium transport [10, 11]. In the absence of systemic RAAS activation, enhanced activity of the putative intrarenal RAS could still impair sodium excretion [27, 28]. Consequently, depending on which of these two systems is stimulated in CHF, ACE inhibition could facilitate frusemide response by increasing the amount of filtered sodium, by delivering greater amounts of frusemide to the TAL, or by impairing sodium reabsorption in non-TAL tubule segments.

Notwithstanding the findings by Dzau & Hollenberg as well as the theoretical reasons why ACE inhibitors facilitate the response to frusemide in CHF, there are other data indicating that these drugs can cause sodium retention and impair the renal response to diuretic agents [5, 6, 28–30]. In studies where blood pressure data were reported, these findings always occurred in association with a de-

pressor effect [28–30]. For example, Cleland *et al.* reported that oral frusemide given to patients with class III or IV CHF caused less renal salt and water excretion when administered after several days of enalapril dosing [28]. Struthers and colleagues found a qualitatively similar impairment in frusemide response with captopril [29, 30]. In those studies the response to oral frusemide was always evaluated after several doses of the ACE inhibitor had been given. Without avoiding significant decreases in blood pressure induced by the ACE inhibitor, other systems stimulating sodium retention would presumably be activated and could offset any natriuretic effect from RAAS inhibition [31].

In contrast to the above findings, another investigation reported that a total of 3 mg captopril given orally in three divided doses over 6 h (i.e. 1 mg per dose) produced no change in blood pressure and an enhancement in the frusemide-induced sodium excretion rate averaged over a 2 h collection period [29]. This captopril regimen caused no other significant changes in systemic or renal haemodynamic indices, or circulating angiotensin II and aldosterone concentrations. Thus, the investigators provided no evidence of inhibition of circulating ACE activity. It should be noted that while the authors showed a doubling in the sodium excretion rate with combined therapy, in fact the increase extrapolates to a rise from approximately 15 mmol to 30 mmol in the 2 h period following frusemide administration given in the absence and presence of captopril, respectively. In consideration of the intra-subject variability in oral frusemide's pharmacokinetic and pharmacodynamic properties, and the modest differences between sodium excretion seen in the study, it is possible that factors other than the low dose of captopril used were responsible for this response. Furthermore, given the heterogenous nature of CHF and the varied experimental designs among the cited investigations, it is not surprising that uniform results have not been found among all studies examining the combined effects of loop diuretics and ACE inhibitors.

In order to evaluate the importance of the RAAS in modulating diuretic response and to examine the potential mechanisms for a synergistic effect between captopril and frusemide, we employed an experimental design that attempted to avoid several of the confounding factors that might impair diuretic response. Because our goal was to assess the impact of basal RAAS activity on the diuretic response to frusemide, our study design differed from the

methods used by other investigators in several respects. These differences likely account for the disparate findings between our results and the other studies. In contrast to evaluating average response during several days of drug dosing, we focused on the acute effects. This approach permitted the impact of basal RAAS activity on frusemide response to be assessed. Patients with mild or moderate CHF were selected so that outpatient ACE inhibitor and diuretic therapies could be safely withdrawn while each volunteer maintained a stable intravascular volume state and RAAS activity between the three studies. These types of patients were also haemodynamically stable and volume replete, therefore, captopril could be dosed without causing a significant decrease in blood pressure. A reduced blood pressure could lead to anti-natriuresis [31] and thereby blunt the acute response to frusemide. Thus, we wanted to maximize the frusemide response while at the same time avoid a depressor effect. Administering 25 mg captopril in divided doses caused a rapid and sustained decrease in plasma ACE activity, yet did not lower blood pressure. While larger doses would have inhibited ACE more completely, a significant reduction in PAC associated with the dose employed indicates that this degree of ACE inhibition produced a physiological effect. Inasmuch as the investigation was performed under controlled conditions where blood pressure, volume status, and the RAAS remained stable during the course of the study, we feel that the results exclude a modulating influence by the RAAS on the natriuretic response in patients with compensated mild or moderate CHF. These findings, however, may not be applicable in situations where the drugs are chronically dosed or when patients with severe CHF are studied.

In summary, the co-administration of captopril with frusemide in patients with stable Class II or III CHF does not increase the acute natriuretic efficacy of the diuretic. It does not appear that basal RAAS activity impairs natriuretic response under these conditions. Further studies will be required to elucidate the mechanism for diuretic synergy in severe and decompensated CHF.

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