Furosemide-Induced Natriuresis Is Augmented by Ultra-Low-Dose Captopril but Not by Standard Doses of Captopril in Chronic Heart Failure

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Background. Ten chronic heart failure patients were studied on three occasions in randomized double-blind fashion to compare the acute hemodynamic, neurohormonal, and renal sodium-handling responses to 1 mg captopril versus 25 mg captopril, both in the absence of loop diuretic therapy and during furosemide-stimulated natriuresis.

Methods and Results. Compared with placebo, 1 mg captopril caused nonsignificant decreases in mean arterial pressure and circulating angiotensin II level and had no effect on glomerular filtration rate as determined by $^{51}$Cr-EDTA elimination. Captopril (25 mg) produced marked suppression of serum angiotensin II with or without oral furosemide (both $p<0.002$), a marked decrease in mean arterial pressure ($p<0.0001$) that was accentuated by furosemide ($p<0.00001$), and a decrease in glomerular filtration rate ($p=0.0007$). No difference from placebo in renal sodium excretion was noted with either 1 mg or 25 mg captopril in the absence of furosemide. In contrast, while 25 mg captopril caused slight attenuation of the natriuretic response to furosemide, 1 mg captopril significantly enhanced furosemide-induced natriuresis ($p<0.05$). No correlation was found in our patients between the natriuretic effect of furosemide and either absolute mean arterial pressure or change in mean arterial pressure during the furosemide phase of each study session. This suggests that blood pressure is not the important factor mediating the divergent renal responses to furosemide of the two captopril dosage regimens.

Conclusions. We propose that in the face of furosemide-induced postglomerular vasodilatation in chronic heart failure, captopril at a starting dose of 1 mg (but not 25 mg) preserves enough circulating angiotensin II to maintain efferent arteriolar tone and thus glomerular filtration, while offsetting the anti-natriuretic renal tubular effects of angiotensin II. (Circulation 1992;86:439–445)

KEY WORDS • captopril • furosemide • natriuresis • chronic heart failure

Furosemide is used on a widespread basis in chronic heart failure (CHF) for its potent natriuretic actions. However, furosemide increases circulating levels of the already activated renin-angiotensin–aldosterone system (RAAS) via its direct renin-releasing action$^{1,2}$ and via its negative effects on extracellular fluid balance.$^{3}$ This RAAS activation may attenuate to some degree the efficacy of the loop diuretic in excreting salt and water.$^{4}$

Angiotensin converting enzyme (ACE) inhibitors have an established role in the treatment of CHF through multiple favorable effects on cardiac and systemic hemodynamics, on biochemical indices, and on neurohumoral systems.$^{4,5}$ In this latter context, the coprescription of an ACE inhibitor with furosemide in CHF should offset the RAAS activation produced by the loop diuretic, thus augmenting its diuretic and natriuretic effects.

In practice, several studies have demonstrated that on instituting ACE inhibitor therapy in CHF, the requirement for diuretics does not fall and, acutely at least, may even increase.$^{6-9}$ This potentially deleterious acute consequence of ACE inhibition may result from alterations in systemic blood pressure or neurohumoral activation or from changes in glomerular dynamics brought about by the ACE inhibitor–loop diuretic combination.

The aim of the present study was to determine whether a very low starting dose (1 mg) of the ACE inhibitor captopril might better preserve the natriuretic response to furosemide in CHF than the conventional higher dose of 25 mg. By contrasting the responses of several hemodynamic and neurohumoral parameters to the two captopril dosage regimens, we sought to identify the mechanisms for the initial attenuation of furosemide-induced natriuresis by standard doses of ACE inhibitors in CHF.

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J.G.M. was supported by a Cruden Medical Research Scholarship from the Scottish Hospital Endowments Research Trust. A.D.S. was supported by the Wellcome Trust.

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Received August 7, 1991; revision accepted May 4, 1992.
TABLE 1. Clinical Characteristics of Patients

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<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>NYHA grade</th>
<th>LVEF (%)</th>
<th>Furosemide dose (mg)</th>
<th>Other drugs</th>
<th>MAP baseline (25 mg CPT)</th>
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<td>1</td>
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<td>F</td>
<td>III</td>
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<td>114 (86)</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association functional grading; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure minus pretreatment baseline value; CPT, cumulative pressor test. *Patient in atrial fibrillation with controlled ventricular rate. Remaining patients in sinus rhythm.

Methods

Study Population

Clinical details of all patients studied are given in Table 1. Ten patients with CHF secondary to left ventricular dysfunction were studied. The etiology of the ventricular dysfunction was ischemic heart disease in all cases. Seven patients were male, and three were female. Patients were of the mean±SD age of 71±3 years. Seven patients were in New York Heart Association (NYHA) functional class III, and three patients were in class IIb. Left ventricular ejection fractions as determined by radionuclide ventriculography were in the range of 24% to 42%. All patients had been clinically stable on oral furosemide for at least 6 months before study. The median dose of furosemide was 80 mg/day (range, 40–200 mg/day). Three patients were also on 125 μg/day digoxin, but none were receiving vasodilators and none were on ACE inhibitors before study. Eight patients were in sinus rhythm, and two were in atrial fibrillation with controlled ventricular rate. All patients were in stable salt balance with 24-hour sodium excretion in the range of 100–150 mmol/24 hr as verified by 24-hour urine collections before each study period.

Study Design

Before inclusion, all patients gave written informed consent to a protocol approved by the Ethical Committee of Ninewells Hospital and Medical School, Dundee, where the study was performed. Patients were studied on three separate occasions between 9:00 AM and 5:00 PM at least 1 week apart (mean±SD, 7.8±0.3 days) in randomized, double-blind fashion. The randomization process resulted in a well-balanced outcome, as assessed by ANOVA, avoiding the possibility of a sequence effect. Patients attended the clinical laboratory at 8:30 AM on the study morning, having fasted from midnight the evening before study with particular avoidance of caffeine-containing beverages. Each patient’s usual dose of furosemide was halved on the day before study (or omitted if the dose was only 40 mg/day) and omitted on the study morning. On arrival, an 18-gauge intravenous cannula was inserted under local anesthetic into the left antecubital fossa. At 9:00 AM, subjects were asked to void to completion. Also at 9:00 AM, subjects were given a tablet of either placebo, 1 mg captopril, or 6.25 mg captopril (Bristol Myers Squibb, Hounslow, Middlesex, UK). Further doses of placebo, 1 mg captopril, or 25 mg captopril were given at 11:00 AM and 3:00 PM. With this latter dose, each patient’s usual daily oral dose of furosemide was coadministered. Patients remained nonambulant (either supine or sitting up in bed) during the 8-hour session apart from standing every 2 hours to empty their bladder. Female patients were supplied with a commode for this purpose. To ensure the voiding of a measurable volume of urine at each 2-hour interval, patients consumed 200 ml of water each hour from 9:00 AM until 4:00 PM inclusive. A light low-protein meal with no added salt was consumed at 1:00 PM on each study day.

Measurements

Supine blood pressure was measured in triplicate at baseline and then in duplicate every 15 minutes throughout the study using a semiautomatic sphygmomanometer (DINAMAP Vital Signs Monitor 1846, Critikon, Tampa, Fla.), with the cuff placed around the patient’s right upper arm. For the two patients in atrial fibrillation, additional manual blood pressure readings were made using a Hawksley random-zero sphygmomanometer to confirm the validity of DINAMAP readings. DINAMAP readings overestimated those obtained by the Hawksley by a mean±SD of 4±2 mm Hg. Hawksley readings were used in the analysis of blood pressure for those two patients. Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus one third of the pulse pressure. MAP for each 2-hour time interval was calculated as the mean value of all MAP readings during each individual 2-hour time period. Change in MAP (ΔMAP) was then calculated by subtracting the baseline (9:00 AM) MAP from the mean MAP for each 2-hour time interval. Baseline MAP was similar on all three study days. Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were estimated by established single-isotope injection techniques using I-125iothalamate and Scr-EDTA, respectively. Injections were given at 11:30 AM. ERPF was determined over the 44 minutes after injection, i.e., during the nondiuretic-treated phase of study, whereas GFR was determined over a 5½-hour period, incorporating the furosemide phase of study. Filtration fraction (FF) was...
calculated as GFR (ml/min)/ERPF (ml/min), and renal vascular resistance (RVR) was calculated as MAP (mm Hg)/[ERPF (1/min)×(1−hematocrit)].

Blood and Urine Sample Collection and Analysis

At 9:00 AM, after patients had lain supine for 30 minutes, baseline blood samples were drawn through the in-dwelling intravenous cannula for measurement of serum angiotensin II and plasma aldosterone. Further samples for the same measurements were drawn at 12:00 noon and 4:00 PM, coinciding with both the midpoint of urine collection periods and approximately with the peak ACE inhibitory activity of the appropriate oral doses of captopril, i.e., 1 hour after dose. Venous blood for plasma aldosterone was collected into chilled lithium heparin tubes, and samples for serum angiotensin II were collected into chilled plain glass tubes containing 0.5 ml of a solution comprising 0.05 M o-phenanthroline, 0.2 g/l neomycin, 0.125 M EDTA-dissodium salt, and 2% ethanol. Samples were centrifuged immediately at 3,000g for 15 minutes at 4°C and separated. Aldosterone samples were frozen at −20°C and angiotensin II samples at −70°C until analysis. Angiotensin II was measured by radioimmunoassay (RIA) after extraction from serum samples using the method of Morton and Webb. This method, using Sep-Pak C-18 cartridges (Waters Associates, Mass.), removes a higher proportion of residual nonspecific interference than other resins, including that caused by the high level of circulating angiotensin I occurring after ACE inhibition. Aldosterone was also measured by RIA using a commercially available kit (Serono Diagnostics Ltd., UK).

At the end of each 2-hour collection period, the volume of urine voided was recorded, and a 10-ml aliquot taken for determination of urinary sodium concentration. Urine aliquots were stored at −20°C until analysis. Urinary sodium concentration was measured by flame photometry (943 flame photometer, Instrumentation Laboratory, Ltd., UK). Sodium excretion rate (UNaV) over each 2-hour time interval was calculated in μmol/min as urine flow rate (ml/min) × urine sodium concentration (mmol/l).

Statistical Analysis

Differences between treatment schedules were tested for significance using ANOVA and paired t tests (Statgraphics software package). Results are expressed as mean values plus 95% confidence intervals unless otherwise stated.

Results

Serum Angiotensin II

Mean pretreatment circulating angiotensin II levels (pg/ml) were similar for placebo (38.2±4.6) and 1 mg captopril (39.6±3.9) study sessions while a significantly higher mean pretreatment level was noted for the 25 mg captopril session (48.2±4.4) (Figure 1). The reason for this discrepancy is not clear: it was not reflected in any difference in clinical status of the patients on the 25 mg captopril study day or in any significant difference in pretreatment readings for any of the other parameters studied. Captopril (1 mg) with or without furosemide caused only marginal reduction in circulating angiotensin II levels compared with placebo, and the changes were not statistically significant. In contrast, 25 mg captopril caused a marked, highly significant suppression of circulating angiotensin II either alone (p=0.0014 versus placebo) or in combination with furosemide (p=0.0016).

Plasma Aldosterone

There was a trend toward lowering of plasma aldosterone by 25 mg captopril with or without furosemide, but the change did not achieve statistical significance (Figure 2). Captopril (1 mg) alone or in combination with furosemide yielded plasma aldosterone levels almost identical to those recorded on placebo treatment.

Mean Arterial Pressure

Captopril (1 mg) caused an insignificant fall in MAP either alone or in the presence of furosemide (Figure 3 and Table 2). In contrast, a marked decrement in MAP was observed with 25 mg captopril alone (p<0.0001), an effect that was accentuated by 25 mg captopril in combination with oral furosemide (p<0.00001). The fall in MAP on 25 mg captopril was not predicted by either low pretreatment blood pressure (pretreatment MAP: MAP on 25 mg CPT, r=0.48, p=NS at 5% level) or high diuretic dose (Table 1). Furthermore, neither absolute MAP nor the change in this parameter was
significantly related to change in renal sodium excretion in response to captopril or furosemide (Table 2).

Renal Hemodynamic Indexes

The effect of different treatment regimens on ERPF, FF, and RVR is shown in Table 3. Compared with placebo, ERPF was not significantly altered by either 1 or 25 mg captopril. Neither FF nor RVR was significantly changed by 1 mg captopril compared with placebo, whereas both of these indexes showed a significant decrement in response to 25 mg captopril (both p<0.05 versus placebo).

GFR

GFR was not changed by 1 mg captopril, whereas 25 mg captopril caused a highly significant reduction in this parameter (p=0.0007) (Figure 4).

UNaV

Pretreatment UNaV was determined from a 24-hour urine specimen collected on the day before each study session. Compared with this baseline reading, sodium excretion was not changed acutely by placebo or by either dose of captopril in the absence of furosemide. The data shown in Figure 5 for captopril or placebo alone represent sodium excretion during the 11:00 AM−to−1:00 PM clearance interval.

Similar absolute values for the three treatments were recorded during the 9:00−11:00 AM and 1:00−3:00 PM clearance periods (data not shown). In contrast to the prefurosemide phase, 1 mg captopril significantly augmented the natriuretic response to furosemide (p<0.05). Although a trend toward attenuation of furosemide-induced natriuresis by 25 mg captopril was evident, this effect did not achieve statistical significance because of the wide confidence intervals.

Discussion

This study was performed to compare in a group of patients with moderately severe CHF the acute renal hemodynamic, neurohormonal, and natriuretic responses to a very low initiating dose (1 mg) of the ACE inhibitor captopril versus a standard dose of 25 mg. We were primarily interested in determining whether the low dose of captopril might better preserve the natriuretic response to the loop diuretic furosemide than 25 mg captopril, which attenuates this response acutely in CHF. However, we also examined the effects of the two captopril dosage regimens without the influence of the loop diuretic by asking patients to omit their oral furosemide initially on the study morning.

We observed no difference in UNaV between placebo treatment and 1 and 25 mg captopril in the absence of furosemide. Investigators have differed widely in their findings as to the acute effects of ACE inhibition on renal sodium handling in CHF. Studies have variably demonstrated an augmented response,13 an attenuated natriuresis,14−17 or no change.18,19 This is in contrast to the consistent finding of an enhancement of natriuresis by captopril in healthy human subjects.20,21 Such a dichotomy of response in the two groups only serves to emphasize the heterogeneity of CHF patients, in terms of both hemodynamic status and degree of neurohormonal activation. Added to this, the effects of ACE inhibition are multiple and diverse, some of which will favor and some of which will oppose natriuresis.5,17,22 In some instances, changes brought about by an ACE inhibitor in a single parameter may exert both natriuretic and antinatriuretic influences. Two such parameters examined in our study were the absolute level of circulating angiotensin II and the change in MAP yielded by different treatments. Thus, the suppression of circulating angiotensin II (and aldosterone) by 25 mg captopril will decrease RAAS-mediated tubular salt reabsorption, decrease afferent renal arteriolar constriction, and increase glomerular ultrafiltration coefficient, all acting to augment natriuresis.22,23 However, these effects may be offset by a fall in transcapillary hydrostatic pressure and glomerular filtration due to loss of angiotensin II−induced postglomerular vasoconstriction.22,23 Similarly, the marked fall in MAP resulting from systemic vasodilatation noted with high- but not low-dose captopril in our study will reduce renal perfusion pressure.20,22 However, this was compensated for by a fall in RVR, thus tending to restore renal perfusion and salt excretion.22 This cancelling out of

### Table 2. Lack of Relation Between Change in Urinary Sodium Excretion and Mean Arterial Pressure

<table>
<thead>
<tr>
<th></th>
<th>ΔUNaV: all Rx</th>
<th>MAP: (25 mg CPT)</th>
<th>ΔUNaV: all Rx</th>
<th>MAP: (25 mg CPT)</th>
<th>ΔUNaV: all Rx</th>
<th>MAP: (25 mg CPT)</th>
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<tr>
<td>Correlation coefficient (r)</td>
<td>0.145</td>
<td>0.489</td>
<td>0.225</td>
<td>0.105</td>
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<td>Significance level (p)</td>
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</table>

ΔUNaV, change in urinary sodium excretion in response to captopril (or placebo)/furosemide; MAP, absolute mean arterial pressure in response to captopril (or placebo)/furosemide; MAP<sub>1</sub>, mean arterial pressure on captopril (or placebo)/furosemide minus pretreatment baseline mean arterial pressure; MAP<sub>2</sub>, mean arterial pressure on captopril (or placebo)/furosemide minus mean arterial pressure on captopril (or placebo) alone; all Rx, all treatments data (placebo and 1 and 25 mg captopril); 25 mg CPT, data from 25 mg captopril treatment limb only; NS, not significant at 5% level.
positive and negative influences may account for the observed lack of difference in acute renal sodium handling responses to placebo, 1 mg captopril alone, or 25 mg captopril alone despite their contrasting effects on hemodynamic status and neurohumoral activation.

In contrast to the prefurosemide response, we observed markedly divergent effects of the three treatment regimens on furosemide-induced natriuresis. Compared with placebo, high-dose captopril caused slight attenuation of the natriuretic response to furosemide, in keeping with the findings of previous studies, whereas 1 mg captopril caused a striking enhancement of furosemide-induced natriuresis. It is unlikely that captopril at a dose of 1 mg would exert some additional positive effect not found with the higher dose, which would augment the natriuretic response to furosemide. Rather, it seems probable that captopril's pronatriuretic effects in antagonizing the renal tubular reabsorptive effects of angiotensin II are offset in the case of 25 mg captopril (but not 1 mg captopril) by a conflicting negative influence on the furosemide response. In this regard, there are a number of possible mechanisms to consider.

To begin with, captopril at a dose of 25 mg has been shown to reduce the renal tubular secretion of furosemide in normal humans. Because it is this renal tubular component that is pharmacologically active through reducing active chloride reabsorption in the loop of Henle, a reduction in tubular secretion by high-dose but not low-dose captopril could explain the divergence of response in our study. A major argument against this explanation is that the reduced tubular delivery of furosemide is a selective effect of captopril not observed with other ACE inhibitors such as enalapril, whereas inhibition of the furosemide natriuretic response has been demonstrated for enalapril as well as for captopril.

A second possible pharmacokinetic mechanism to consider is that high-dose but not low-dose captopril may interfere with the gastrointestinal absorption of furosemide. This was suggested in one animal study in salt-depleted rats by the observation that intravenous captopril caused less inhibition of furosemide-induced natriuresis than oral captopril. However, no similar study has been performed in humans, and this latter mechanism does not explain why, in the animal study, intravenous captopril should have had any effect at all on furosemide-induced natriuresis.

In addition to the circulating RAAS, there are several other neurohumoral systems, including prostaglandin and kinin systems and the recently recognized intrarenal tissue RAAS, that influence renal homeostasis and are affected by ACE inhibition. These systems are also influenced by the loop diuretic furosemide, at least in the case of prostaglandins and kinins. It is possible that high-dose captopril exerts an effect on one or more of these hormonal cascades that attenuates furosemide-induced natriuresis. Captopril (1 mg) may lack such an effect either because of lower dose per se or, in the case of an effect on the tissue RAAS, because of lack of intrarenal tissue penetration. In this context, both the intrarenal RAAS and the loop diuretic furosemide are thought to exert significant effects in redistributing intrarenal blood flow; in the case of furosemide, this effect may be integrally linked to its diuretic action. If this blood flow redistribution by furosemide were mediated by the intrarenal RAAS, one might anticipate interference with this effect and thus with natriuresis by high- but not low-dose captopril.

In our study, 1 mg captopril alone and in combination with oral furosemide caused a slight, insignificant fall in MAP compared with placebo. In contrast, 25 mg captopril and furosemide together caused a marked fall in MAP, an effect that was substantially greater than that produced by 25 mg captopril alone. Cleland et al have similarly demonstrated that the combination of an ACE inhibitor (enalapril) and oral furosemide accentuates the hypotensive response observed with the ACE inhibitor alone. It may be in our study that this enhanced
blood pressure drop with the high-dose captopril-furosemide combination allows MAP in some patients to fall below the renal autoregulatory threshold, causing an "autoregulatory break" in renal perfusion and resultant antinatriuresis. Accordingly, we carried out a detailed analysis of the relation between change in UNaV (ΔUNaV) over the 2 hours after furosemide administration and the absolute MAP during the same 2-hour period in response to 25 mg captopril and in response to all three treatments (Table 2). The data suggest that hypotension would not have explained the urinary sodium results. The strongest correlation of 0.489, obtained between UNaV and absolute MAP for the 25 mg captopril limb, was not significant at the 5% level. One could argue that if the number of subjects were increased to 20, this r value would be significant. However, against this we would make two points. First, that for a correlation coefficient of 0.489, r² is only 0.239; i.e., even were it significant, less than 25% of the variability in UNaV would be explained by its relation with MAP. Second, we have now carried out a larger study of 36 CHF patients (unpublished data) looking at the same relation of UNaV and absolute MAP, and instead of the relationship getting stronger it has become weaker and still not significant (r=0.15). The problems with this form of correlation analysis are, first, that it may not detect a threshold effect and, second, that the precise autoregulatory threshold for renal perfusion may vary considerably from patient to patient, in some cases being well below the threshold of 80 mm Hg found in normal humans. This problem can be partially but not totally overcome by relating change in sodium excretion to the change, i.e., fall, in MAP where, again, we found no significant relation (Table 2). This suggests but does not confirm that an effect on blood pressure is not the primary factor accounting for the difference in natriuretic response to furosemide observed with different doses of captopril.

Perhaps the most obvious yet most interesting explanation for this difference is that in CHF an elevated circulating level of angiotensin II may be required to facilitate the renal responses to furosemide. We propose the following mechanism. Intravenous furosemide has been shown to be a renal vasodilator in normal subjects and CHF patients. While the renovascular effects of oral furosemide have not been studied closely, the effects of oral and intravenous preparations on extrarenal vascular beds are similar, and there is indirect evidence that oral furosemide may also be a dilator of the glomerular efferent arteriole. The potent effect of angiotensin II in constricting this vessel may be a mechanism by which the peptide maintains glomerular hydrostatic pressure and, thus, GFR in the face of furosemide-induced postglomerular vasodilatation. The findings of our study support this as a likely mechanism. High-dose captopril caused a near-complete suppression of serum angiotensin II, a fall in FF and GFR, and an attenuation of furosemide-induced natriuresis. In contrast, 1 mg captopril caused only partial suppression of serum angiotensin II with preservation of furosemide. Thus, Cleland et al. noted in 12 CHF patients that while 10 mg enalapril alone caused no acute change in GFR, the combination of enalapril and furosemide caused a significant decline in this parameter and a reduction in salt and water excretion. Imbs et al. studied in anesthetized dogs the renal responses to the experimental loop diuretic ozolinone, which has two isomers. Both isomers are renal vasodilators, but only (−)-ozolinone has renin-releasing properties. An initial fall in GFR and FF because of postglomerular vasodilatation was observed with both (−) and (+) isomers, but recovery from this effect occurred only with (−)-ozolinone, simultaneous with its RAAS-activating action. This recovery in GFR and FF was inhibited by pretreatment with captopril. Packer et al. observed in a group of loop diuretic–treated CHF patients with low renal perfusion pressures and significant RAAS activation (as determined by plasma renin activity [PRA]) that creatinine clearance values, used as an index of glomerular filtration, fell after ACE inhibition. This effect did not occur in a second group of CHF patients with low perfusion pressures but low PRA, despite similar falls in MAP after ACE inhibition. This second group had lower starting values for creatinine clearance. Changes in creatinine clearance varied linearly and inversely with pretreatment values for PRA, and converting enzyme inhibition effectively abolished the pretreatment difference in renal function seen in high- and low-renin subgroups.

These findings collectively support our own observations by suggesting that the RAAS preserves GFR in diuretic-treated CHF patients by maintaining efferent arteriolar tone and independent of its effects in sustaining systemic arterial pressure. Interestingly, high-dose diuretic therapy has been identified as one of the few important factors likely to lead to functional renal insufficiency after acute ACE inhibition. This has been attributed to the marked hypotensive effects of initial ACE inhibition in the setting of diuretic-induced extracellular fluid volume contraction and RAAS activation. However, the findings of our own study would question this explanation, suggesting that it is the unopposed postglomerular vasodilator effect of high-dose diuretic therapy that accounts for the observed fall in creatinine clearance after ACE inhibition. By reducing diuretic dose before ACE inhibition, one certainly restores ECF volume and limits hypotension, but the crucial factor may be that one is also decreasing the vasodilator influence exerted on the efferent arteriole.

Several studies that have shown initial falls in furosemide-induced natriuresis and GFR after ACE inhibition have demonstrated recovery in these parameters after weeks or months. This phenomenon may relate to the findings of Mooser et al., who have demonstrated that, particularly with long-term administration, high-dose ACE inhibition may cause persistent suppression of ACE activity, whereas gradual recovery in circulating angiotensin II level occurs due to a compensatory rise in renin and angiotensin I, which are still partially converted to angiotensin II. Such repletion of circulating angiotensin II, by restoring efferent arteriolar tone, could account for the recovery in renal responses to furosemide during chronic ACE inhibition.

One potential criticism of our study is that the oral drugs administered were all given immediately before the clearance period under study. Furosemide and captopril are detectable in the blood of healthy volunteers at 10 and 15 minutes, respectively, after oral administration, with maximum plasma concentrations achieved after approximately 60 and 60–90 minutes,
respectively. Absorption and, thus, time to maximum concentration may be prolonged in CHF. Therefore, it is clear that for part of the 2-hour study interval, the parameters under evaluation will be uninfluenced by the treatments administered. However, this would act as a negative bias on our results, so that the actual differences in effects of different treatment regimens may be even more marked than these observed.

In summary, we have demonstrated in a group of patients with moderately severe CHF that 25 mg captopril produced substantial initial falls in MAP, circulating angiotensin II, and GFR, associated with a slight blunting of furosemide-induced natriuresis. In contrast, 1 mg captopril markedly augmented the natriuretic effect of furosemide in the same patients, possibly by preserving enough circulating angiotensin II to maintain efferent arteriolar tone and thus GFR, while partially offsetting the tubular and glomerular antinatriuretic effects of the RAAS.

Acknowledgments

The authors express their thanks to J. Orr for typing the manuscript and to J. Robson, L. McFarlane, W. Couttie, and G. Clark for technical assistance.

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doi: 10.1161/01.CIR.86.2.439

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/86/2/439

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