Captopril augments both basal and frusemide-induced natriuresis in normal man by suppression of circulating angiotensin II

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1. We studied the renal effects of reinfusing low dose angiotensin II (1 ng kg\(^{-1}\) min\(^{-1}\)) into seven salt-replete healthy volunteers after pretreatment with the angiotensin converting enzyme (ACE) inhibitor captopril (25 mg) to establish whether the natriuretic and renal haemodynamic responses to ACE inhibition in normal man result from suppression of circulating angiotensin II. In the same subjects we also studied the effect of captopril (25 mg) with and without exogenous angiotensin II (1 ng kg\(^{-1}\) min\(^{-1}\)) on the natriuretic response to intravenous frusemide (20 mg).

2. In the pre-frusemide study captopril increased absolute and fractional excretion of sodium and paraaminohippurate clearance but had no effect on inulin clearance.

3. Reinfusion of angiotensin II after captopril pretreatment completely suppressed the renal effects of ACE inhibition, yielding renal vasoconstrictor and antinatriuretic effects equivalent to those produced by infused angiotensin II in the absence of captopril.

4. Frusemide increased renal sodium excretion without affecting paraaminohippurate or inulin clearance. Captopril augmented frusemide-induced natriuresis and again this effect was reversed by angiotensin II reinfusion.

5. We conclude that captopril augments both basal and frusemide-induced renal sodium excretion in normal man. Our findings suggest that these renal responses to ACE inhibition may be mediated by inhibition of circulating angiotensin II, specifically its renal tubular salt-retaining actions, rather than via effects on other neurohumoral systems.

Keywords captopril angiotensin II frusemide natriuresis

Introduction

Controversy exists as to whether the natriuretic response to angiotensin converting enzyme (ACE) inhibitors in normal man (MacGregor et al., 1980) is mediated via antagonism of the circulating renin-angiotensin-aldosterone system (RAAS) or whether it results from kinin-mediated (Clappison et al., 1981) or prostaglandin-mediated (Usberti et al., 1986) effects or via effects on the recently recognised intrarenal tissue RAAS (MacFadyen et al., 1991).

In the present study we investigated in a group of healthy subjects pretreated with the ACE inhibitor captopril whether reinfusing exogenous angiotensin II (AII), which replaces circulating but not intrarenal AII (Reams et al., 1990), would reverse the renal natriuretic and haemodynamic responses to the ACE inhibitor. By this means we aimed to clarify the role of circulating AII, as opposed to tissue-derived AII or other neurohormonal systems, in the renal effects of ACE inhibition in normal man.

A second aim of our study was to examine the role of circulatory AII in the natriuretic response to the loop diuretic frusemide. Frusemide is known to activate the RAAS (Mackay et al., 1984) but it is unclear whether the resulting elevated AII level assists or opposes the effect of the drug: studies have variably demonstrated that AII inhibition augments (MacDonald et al., 1989), blunts (Chiu et al., 1984; Di Nicolantonio et al., 1987; Toussaint et al., 1989) or has no effect (Fujimura &
Ebihara, 1988; Kelly et al., 1983) on frusemide-induced natriuresis. In the present study, by investigating the effect of ACE inhibition on frusemide-induced natriuresis with and without reinfusion of exogenous AII, we aimed to determine whether the circulating RAAS facilitates or attenuates the natriuretic response to frusemide.

Methods

Seven normotensive healthy young male volunteers (aged 20–25 years) were studied after giving written informed consent to a protocol approved by the Ethics Committee of Ninewells Hospital and Medical School, Dundee, where the study was performed. For the 72 h preceding each visit subjects adhered to a similar meal plan. Before each study day volunteers submitted a 24 h urine sample to verify stable urinary sodium excretion in the range 140–180 mmol 24 h⁻¹.

Protocol

Volunteers were studied in the fasted state on four separate occasions at least a week apart in randomised single-blind fashion. Subjects attended the clinical laboratory at 08.30 h on the study morning when they were asked to void to completion and were then given a tablet of either placebo or 25 mg of the ACE inhibitor captopril (Bristol Myers Squibb Hounslow, Middlesex, UK). Subjects remained seated upright in bed for the next 4 h apart from standing at 20 min intervals to pass urine. Employing a standard overhydration protocol, subjects were asked to drink 20 ml kg⁻¹ water at 08.35 and 08.55 h. Thereafter, from 09.00 h onwards subjects emptied their bladder every 20 min and consumed the same volume of water as the voided urine plus 1 ml min⁻¹ for insensible losses. At 09.00 h bolus injections of 10 mg kg⁻¹ PAH (aminophippurate sodium, MSD, USA) and 50 mg kg⁻¹ inulin (Inutest, Laevosan-Gesellschaft, Germany) were followed by 15 mg min⁻¹ PAH and 25 mg min⁻¹ inulin (in 0.9% saline) infusions for the next 4 h. By 09.40 h subjects entered a state of stable fluid balance so that by 10.20 h a constant urine volume had been passed for two collection periods. At 10.20 h an infusion of angiotensin II (Hypertensin, Ciba Geigy, Switzerland) 1 ng kg⁻¹ min⁻¹ or placebo (dextrose 5%) was commenced and continued for 120 min. One hour into the latter infusion a single bolus injection of 20 mg frusemide (Antigen Ltd, Roscrea, Ireland) was administered intravenously. Blood pressure and heart rate were recorded every 10 min throughout the study using a semi-automatic sphygmomanometer (Dinamap Vital Signs Monitor 1846, Critikon, Tampa, Florida, USA) the cuff being placed around the subject’s left upper arm. Supine blood samples for measurements of circulating atrial natriuretic factor (ANF), aldosterone and catecholamines were drawn through a cannula in the left (non-infusion) forearm at 09.50 h (baseline sample), 10.50 and 11.50 h. In addition blood was sampled for plasma PAH and inulin and for haematocrit at the midpoint of each urine collection period. The four study sessions employed in randomised single-blind fashion the following treatment permutations:

placebo tablet + placebo infusion + i.v. frusemide 20 mg
captopril 25 mg + placebo infusion + i.v. frusemide 20 mg
placebo tablet + AII infusion + i.v. frusemide 20 mg
captopril 25 mg + AII infusion + i.v. frusemide 20 mg

Sample collection

Venous blood samples for catecholamines, aldosterone, PAH and inulin were collected into chilled lithium heparin tubes, samples for ANF into chilled potassium EDTA tubes each containing 200 µl (4000 kallikrein inhibitory units) aprotinin (Trasylol, Bayer, Germany) and those for sodium and osmolality into chilled plain glass tubes. Venous samples for AII were aliquoted into chilled plain glass tubes containing 0.5 ml of a solution comprising 0.05 m o-phenanthroline, 0.2 g l⁻¹ neomycin, 0.125 EDTA disodium salt and 2% ethanol. Samples were centrifuged immediately at 2000 g for 15 min at 4° C and separated. Serum AII and plasma catecholamine samples were stored at −70° C, the remaining serum and plasma samples being stored at −20° C. Urine aliquots (10 ml) were taken from each 20 min urine collection and stored at −20° C for later measurement of urine PAH/inulin, sodium and osmolality.

Sample analysis

Serum and urinary sodium were measured using an Instrumentation Laboratory 943 flame photometer, plasma and urinary PAH using a centrifugal analyser (Cobas Bio Hoffman La Roche, Basel, Switzerland) with p-dimethylaminobenzaldehyde (Sigma Chemical Co. Poole, Dorset, UK) as the colour reagent, and plasma and urinary inulin using a Pye Unicam SP6-500 u.v. spectrophotometer with resorcinol (Sigma Chemical Co.) as the colour reagent. Serum and urinary osmolality were determined by the freezing point depression method (Advanced Osmometer, Camlab, Gonotec, Germany). AII was measured after plasma extraction by Amprep C8 column (Amersham International plc, UK) using a commercially available radioimmunoassay kit (Immuno-diagnostics Ltd, UK). ANF samples were extracted through Am prep C8 column (Amersham International plc, UK) and analysed by radioimmunoassay kit (Amersham International plc, UK). Aldosterone was also measured by r.i.a. using a commercially available kit (Diagnostic Products Ltd, UK). Plasma catecholamines were assayed by the double-isotope radioenzymatic method of Brown & Jenner (1981). All samples for chemical and neurohumoral estimations were measured as single batches. The intra assay coefficients of variation were as follows: urinary PAH 1.7%, plasma PAH 2.1%, urinary inulin 1.2%, plasma inulin 2.1%, ANF 7.8%, aldosterone 6.6%, catecholamines 8.0%, AII 1.58%.

Analysis of results

Mean arterial pressure (MAP) was calculated for each 20 min interval from the average of three serial readings as diastolic BP + (systolic BP – diastolic BP)/3. Clearance (C) was calculated for different substances as UV/P
where \( U = \) urinary concentration, \( V = \) urine flow rate and \( P = \) plasma concentration. Inulin clearance (CINU) was used as a measure of glomerular filtration rate and PAH clearance (CPAH) as a measure of effective renal plasma flow (ERPF). Osmolar clearance (Cosm) and clearance of sodium (CNa) were also determined as UV/P and free water clearance (CH₂O) as V-Cosm. Using these indices the following parameters (expressed as percentages) were then calculated using established formulae:

- Fractional excretion of sodium (FENa)
  \[ \text{FENa} = \frac{CNa}{\text{CINU}} \]
- Fractional distal delivery of sodium (FDDNa)
  \[ \text{FDDNa} = \frac{(CNa + CH₂O)}{\text{CINU}} \]
- Fractional distal reabsorption of sodium (FDRNa)
  \[ \text{FDRNa} = \frac{CH₂O}{(CNa + CH₂O)} \]
- Filtration fraction (FF) = CINU/CPAH
- Also renal vascular resistance (RVR)
  \[ \text{MAP} = \frac{\text{ERPF}(\text{L min}^{-1})}{(1 - \text{Hct})} \]

**Statistical analysis**

Statistical comparisons between results obtained by the four treatment schedules were made using repeated measures analysis of variance (MANOVA, Statgraphics Software Package, USA).

**Results**

Results for the three separate 20 min urine collection periods after commencement of the AII or placebo infusion and prior to frusemide administration have been expressed as individual means (+95% confidence intervals) for the graphical data but have been expressed as a single mean (+95% confidence interval) over 60 min for the tabular data. A similar format of data expression has been followed for the three 20 min periods post-frusemide.

**Pre-frusemide response to captopril/AII (Figure 1, Table 1)**

a. Placebo tablet/AII infusion. As compared with the placebo/placebo limb, placebo/AII caused significant reductions in absolute rate of sodium excretion (UNaV) \((P < 0.001)\), fractional sodium excretion (FENa) \((P < 0.05)\) and ERPF \((P < 0.0001)\) but had no effect on GFR. A rise in renal vascular resistance (RVR) \((P < 0.0001)\) occurred and was associated with a small but significant rise in mean systemic arterial pressure (MAP) \((P < 0.0001)\). A significant reduction in urine flow rate (UV) \((P < 0.0001)\) and an increase in filtration fraction (FF) \((P < 0.0001)\) were observed. Significant reductions in FDDNa, reflecting increased reabsorption of sodium in the proximal nephron \((P < 0.0001)\) and increased FDRNa, indicating elevated distal nephron sodium

![Figure 1](image-url)
neither GFR as compared of each because the AII different from significantly 

Table 1 Urine flow rate (UV), renal vascular resistance (RVR), filtration fraction (FF), fractional distal delivery of sodium (FDDNa), fractional distal reabsorption of sodium (FDRNa), mean arterial pressure (MAP) and neurohormones: pre-frusemide response of seven subjects to placebo tablet/placebo infusion (PLAC), placebo tablet/AII infusion (AII), captopril tablet/placebo infusion (CPT) and captopril tablet/AII infusion (CPT/ AII). Results are mean (95% confidence interval)

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Treatment</th>
<th>CPT</th>
<th>CPT/AII</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV (ml min⁻¹)</td>
<td>17.9(1.2)</td>
<td>13.9(1.2)*</td>
<td>20.3(1.2)*</td>
<td>15.8(1.3)</td>
</tr>
<tr>
<td>RVR (mm Hg l⁻¹ min⁻¹)</td>
<td>79(2)</td>
<td>96(2)**</td>
<td>71(2)*</td>
<td>88(3)*</td>
</tr>
<tr>
<td>FF(%)</td>
<td>19.9(0.5)</td>
<td>22.3(0.5)*</td>
<td>18.9(0.5)*</td>
<td>22.3(0.5)*</td>
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<td>FDDNa(%)</td>
<td>11.3(0.8)</td>
<td>8.6(0.8)*</td>
<td>12.8(0.8)*</td>
<td>9.4(0.9)**</td>
</tr>
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<td>FDRNa(%)</td>
<td>92.8(0.9)</td>
<td>95.3(0.9)**</td>
<td>89.6(0.9)*</td>
<td>94.8(0.9)**</td>
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<td>MAP (mm Hg)</td>
<td>93(2)</td>
<td>99(2)*</td>
<td>90(2)</td>
<td>94(2)</td>
</tr>
<tr>
<td>Aldosterone (pg ml⁻¹)</td>
<td>110(44)</td>
<td>196(44)</td>
<td>101(44)</td>
<td>178(47)</td>
</tr>
<tr>
<td>ANF (pmol l⁻¹)</td>
<td>9.0(2.2)</td>
<td>7.3(2.2)</td>
<td>8.9(2.2)</td>
<td>8(2.3)</td>
</tr>
<tr>
<td>Noradrenaline (pg ml⁻¹)</td>
<td>0.56(0.08)</td>
<td>0.68(0.08)</td>
<td>0.50(0.09)</td>
<td>0.47(0.09)</td>
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<tr>
<td>Adrenaline (pg ml⁻¹)</td>
<td>0.038(0.006)</td>
<td>0.029(0.006)</td>
<td>0.019(0.007)</td>
<td>0.018(0.007)</td>
</tr>
<tr>
<td>Angiotensin II (pg ml⁻¹)</td>
<td>9.9(3.5)</td>
<td>19.4(3.5)**</td>
<td>—</td>
<td>22.9(3.8)***</td>
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</table>

*P < 0.05, **P < 0.01, ***P < 0.001, *P < 0.0001, **P < 0.00001 vs placebo.

reabsorption (P < 0.001) occurred. These changes occurred in association with a significant rise in serum AII (P < 0.001) and a rise in plasma aldosterone which did not achieve statistical significance. Plasma ANF, noradrenaline and adrenaline were unaffected by AII infusion.

b. Captopril tablet/placebo infusion This limb of study resulted in virtually opposite effects to those observed in (a). Increments in UNaV (P < 0.0001), ERPF (P < 0.01), FENa (P < 0.0001), UV (P < 0.05) and FDDNa (P < 0.05) were associated with reductions in RVR (P < 0.0001), FF (P < 0.05) and FDRNa (P < 0.05). Neither GFR nor MAP were affected by captopril/ placebo. Similarly, neurohormone levels were not significantly different from those observed with placebo/ placebo. All levels were not measured in this limb because the assay employed did not allow specific detection of the very low levels of AII attained following ACE inhibition without non-specific interference from angiotensin I.

c. Captopril tablet/AII infusion This limb resulted in very similar effects to those observed in (a). Decreases in UNaV (P < 0.001), ERPF (P < 0.001), FENa (P < 0.05) and FDDNa (P < 0.01) were associated with increases in RVR (P < 0.0001), FF (P < 0.0001) and FDRNa (P < 0.001). A similar serum serum level of AII was attained as in (a), and as in that limb, ANF and catecholamines were unaffected.

Frusemide response to captopril/AII (Figure 2, Table 2)

As compared with the pre-frusemide phase, administration of 20 mg frusemide intravenously at the midpoint of each limb of study resulted in a prompt 15–20 fold increase in UNaV and FENa during the first 20 min urine collection period post-injection without any significant effect on either ERPF or GFR. Over the subsequent two collection periods, a gradual decline was observed in the stimulatory effect of frusemide on natriuresis with again no significant change in ERPF or GFR.

d. Placebo tablet/AII infusion/frusemide injection As compared with the placebo tablet/placebo infusion/ frusemide injection limb, a reduction in ERPF (P < 0.0001) was observed without any effect on GFR. Rises in MAP (P < 0.0001), RVR (P < 0.001) and FF (P < 0.0001) occurred. The marginal reductions in UNaV and FENa were not statistically significant. Serum AII levels were increased (P < 0.05) while other neurohormones were unaffected.

e. Captopril tablet/placebo infusion/frusemide injection This limb resulted in an augmented natriuretic effect of frusemide during the first 20 min urine collection period after injection of the loop diuretic, with increases in UNaV (P < 0.05) and FENa (P < 0.05). ERPF showed a slight non-significant increment whilst GFR showed no significant change. Falls in RVR (P < 0.001) and FF(P < 0.001) occurred. None of the other parameters studied was significantly changed as compared with the placebo tablet/placebo infusion/frusemide injection limb.

f. Captopril tablet/AII infusion/frusemide injection Values for parameters of renal sodium excretion (UNaV, FENa, FDRNa, FDDNa) were very similar to those observed in (d). As in (d), a reduction in ERPF (P < 0.0001) and increase in FF (P < 0.001) maintained from the prefrusemide phase, were observed. AII levels showed a similar increment to that observed in (d) (P < 0.05) whilst other neurohormones remained unchanged.
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Figure 2 Absolute sodium excretion rate (UNaV), effective renal plasma flow (ERPF), glomerular filtration rate (GFR) and fractional excretion of sodium (FENa): response to placebo tablet/placebo infusion/frusemide (PLAC), placebo tablet/AII infusion/frusemide (AII), captopril tablet/placebo infusion/frusemide (CPT) and captopril tablet/AII infusion/frusemide (CPT/AII). Each point is mean of seven subjects +95% confidence interval. ○ pre-frusemide, * frusemide response. *P < 0.05, *P < 0.001, ++P < 0.0001.

Table 2 Urine flow rate (UV), renal vascular resistance (RVR), filtration fraction (FF), fractional distal delivery of sodium (FDDNa), fractional distal reabsorption (FDRNa), mean arterial pressure (MAP) and neurohormones: response to placebo tablet/placebo infusion/frusemide (PLAC), placebo tablet/AII infusion/frusemide (AII), captopril tablet/placebo infusion/frusemide (CPT) and captopril tablet/AII infusion/frusemide (CPT/AII)

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Treatment</th>
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<tr>
<td></td>
<td>31.7(1.9)</td>
<td>30.5(1.9)</td>
<td>32.3(1.9)</td>
<td>28.6(2)</td>
<td></td>
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<tr>
<td>UV (ml min⁻¹)</td>
<td></td>
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<td></td>
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<tr>
<td>RVR (mm Hg l⁻¹ min⁻¹)</td>
<td>82(3)</td>
<td>96(3)***</td>
<td>74(3)***</td>
<td>86(3)</td>
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<tr>
<td>FF(%)</td>
<td>20.2(0.6)</td>
<td>22.6(0.6)***</td>
<td>18.6(0.6)***</td>
<td>21.6(0.7)*</td>
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<tr>
<td>FDDNa(%)</td>
<td>54.7(5)</td>
<td>59.5(5)</td>
<td>46.3(5)</td>
<td>49.8(5.5)</td>
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<tr>
<td>FDRNa(%)</td>
<td>54.7(5)</td>
<td>59.5(5)</td>
<td>46.3(5)</td>
<td>49.8(5.5)</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>98(2)</td>
<td>105(2)**</td>
<td>97(2)</td>
<td>97(3)</td>
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<tr>
<td>Aldosterone (pg ml⁻¹)</td>
<td>166(57)</td>
<td>219(57)</td>
<td>146(57)</td>
<td>221(62)</td>
<td></td>
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<tr>
<td>ANF (pmol l⁻¹)</td>
<td>8.3(1.9)</td>
<td>7.6(1.9)</td>
<td>8.2(1.9)</td>
<td>7.5(2.1)</td>
<td></td>
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<tr>
<td>Noradrenaline (pg ml⁻¹)</td>
<td>0.68(0.08)</td>
<td>0.67(0.08)</td>
<td>0.53(0.08)</td>
<td>0.60(0.09)</td>
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<tr>
<td>Adrenaline (pg ml⁻¹)</td>
<td>0.033(0.01)</td>
<td>0.03(0.01)</td>
<td>0.015(0.01)</td>
<td>0.012(0.011)</td>
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<tr>
<td>Angiotensin II (pg ml⁻¹)</td>
<td>15.5(3.6)</td>
<td>22(3.1)*</td>
<td>—</td>
<td>25.6(4.3)*</td>
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*P < 0.001, **P < 0.0001, +P < 0.05.

Discussion
In this study we have demonstrated that the enhancement of natriuresis by captopril in healthy salt-replete subjects can be reversed completely by reinfusing low-dose AII, yielding an absolute sodium excretion rate equivalent to that produced by the same dose of AII in the absence of captopril. This suggests that captopril’s pronatriuretic effect in salt-replete individuals is mediated by inhibition of AII formation rather than via effects on
kinins (Clappison et al. 1981) or prostaglandins (Usberti et al., 1986).

Oral ACE inhibition is known to block both circulating and intrarenal tissue AII (MacFadyen et al., 1991). We assumed that exogenously infused AII after ACE inhibition would replace only circulating AII and not tissue AII. This assumption is strongly supported by the recent work of Reams et al. (1990) who demonstrated in dogs that while high concentrations of AII were measurable in all areas of the renal parenchyma, systemically infused radiolabelled AII was not detectable in any renal tissue. Since infused AII, which replaces only endogenous circulating AII and not tissue AII, reverses the natriuretic and renal haemodynamic effects of captopril, we suggest that the acute effects of captopril in augmenting natriuresis and renal perfusion are mediated primarily by inhibition of circulating rather than tissue derived AII. This suggestion is consistent with the work of de Leeuw et al. (1985) who observed that intrarenal infusion of an ACE inhibitor resulted in an increase in renal blood flow only when systemic ACE was involved and not when intrarenal ACE alone was inhibited.

The lack of any demonstrable change in inulin clearance in response to captopril in our study strongly suggests that captopril's pronatriuretic effect is not mediated via an increase in GFR. Furthermore, the impressive enhancement of fractional sodium excretion by captopril indicates a tubular natriuretic mechanism. The increase in fractional distal delivery and fall in fractional distal reabsorption of sodium in response to captopril support both proximal and distal tubular sites of action respectively.

In our study captopril enhanced by 30% the natriuretic response to intravenous frusemide during the first 20 min clearance period after loop diuretic administration. This effect is proportionately lower than the 60% enhancement of natriuresis by captopril in the pre-diuretic phase, but in absolute terms the effect in the frusemide phase is much greater (700 μmol min⁻¹ increment, vs 90 μmol min⁻¹ increment in pre-diuretic phase). The different baseline levels of natriuresis prior to frusemide administration (Figure 2) do not limit interpretation of results in the frusemide phase since the different ‘basal’ levels were produced not by poor experimental control but by the very influence under study, namely ACE inhibitor treatment. Such an effect will be present in any situation, including that encountered in clinical practice, where an ACE inhibitor is given along with a diuretic. Indeed, one could argue that captopril's pronatriuretic effect in the pre-diuretic phase may have resulted in a state of relative sodium depletion, thus leading to an attenuation and underestimation of its enhancing effects on frusemide-induced natriuresis.

This facilitatory effect of captopril on frusemide-induced natriuresis, as in the pre-diuretic phase, was associated with a marked increment in fractional sodium excretion which was completely suppressed by reinfusing AII, suggesting that captopril is again acting by antagonism of the tubular effects of the circulating RAAS. It is most unlikely that captopril's augmentation of frusemide-induced natriuresis is effected simply by increased renal delivery of frusemide secondary to increased renal blood flow: captopril has been shown to decrease by 50% the renal clearance of frusemide in normal man (Toussaint et al., 1989).

One other group have previously demonstrated that administration of an ACE inhibitor (ramipril) to normal man augments the natriuretic response to frusemide (MacDonald et al., 1989) but they did not study the role of the circulating RAAS in mediating this effect by reinfusing AII. Instead that group speculated on the importance of renal dopamine in the response, finding that ramipril enhanced the frusemide-induced increase in urinary free dopamine. It is conceivable that both AII and dopamine are important, the ACE inhibitor possibly acting by withdrawal of an inhibitory influence of AII on renal dopamine production.

Interestingly, we observed no increase in either PAH or inulin clearance in response to frusemide and an additional marginal increment in PAH but not inulin clearance following ACE inhibition. MacDonald et al. (1989) found virtually opposite effects, namely increases in PAH and inulin clearances following frusemide administration and a further increment in inulin but not PAH clearance in response to ACE inhibition. We cannot account for this disparity, although the observed haemodynamic effects of frusemide as reported in the literature do vary widely. Furthermore, MacDonald et al. (1989) used 30 mg rather than 20 mg frusemide and Brater (1979) has emphasised the difference in renal effects which can be observed with variation in dose of frusemide.

In summary, we have confirmed that the ACE inhibitor captopril augments renal sodium excretion in normal human subjects both in the non-diuretic treated and loop diuretic treated states. Our results suggest that in mediating these effects captopril acts mainly by inhibition of circulating AII formation rather than via its effects on other neurohumoral systems.

We acknowledge our thanks to Miss F. Zaccarini for typing the manuscript and to Sister J. Robson, Mrs L. MacFarlane, Mrs W. Couttie and Mr G. Clark for technical assistance.

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(Received 29 July 1991, accepted 11 February 1992)