Interaction of Angiotensin Converting Enzyme Inhibition and Atrial Natriuretic Factor

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The interaction of angiotensin converting enzyme (ACE) inhibition and atrial natriuretic factor (ANF) was investigated in six supine, sodium-replete, normal volunteers who received captopril (10 mg i.v. bolus followed by 10 mg/hr constant infusion) or vehicle superimposed on background 3-hour, constant, low-dose (1.5 pmol/kg/min) infusions of human ANF (99-126). Plasma converting enzyme activity was significantly inhibited but this had no effect on endogenous plasma ANF concentrations. ANF infusions, with or without captopril, caused similar increases in plasma ANF concentrations, and calculated metabolic clearance rates for ANF were unchanged. Similarly, blood pressure, heart rate, renal blood flow, glomerular filtration rate, and renal electrolyte excretion, including ANF-induced natriuresis, were unaffected by captopril. The combination of ANF plus captopril produced a significant increase in plasma aldosterone (79±8 vs. 60±6 pmol/l, p<0.05), cortisol (406±52 vs. 265±29 nmol/l, p<0.05), adrenaline (119±21 vs. 76±10 pg/ml, p<0.05), and noradrenaline (319±49 vs. 215±38 pg/ml, p<0.05) compared with time-matched placebo data. Converting enzyme inhibition, in the absence of major changes in blood pressure or renal blood flow, has little effect on ANF metabolism or renal bioactivity. However, ACE inhibition and ANF combined may interact to increase activity of the hypothalamo-pituitary-adrenal axis and sympathetic nervous system by unknown mechanisms. (Hypertension 1989; 13:193-199)

Atrial natriuretic factor (ANF) with its diverse actions on renal and hemodynamic function and vasoactive hormone activity continues to attract attention as a potentially major regulator of body fluid volume and arterial pressure. In many tissues ANF and the renin-angiotensin system appear to be counterbalanced. Angiotensin converting enzyme (ACE) inhibitors are now employed with increasing frequency in the treatment of both hypertension and heart failure. Recent trials demonstrate that ACE inhibitors improve survival in heart failure and preserve renal function in diabetic patients. Further major expansion in the use of these agents is likely. For these reasons, study of any possible interaction between ANF and ACE activity is relevant to the physiology of sodium balance and may have important clinical consequences.

Already there is a body of circumstantial evidence pointing to an interaction between ACE inhibition and ANF. Initial in vitro studies suggested that converting enzyme inhibitors slowed the metabolism of ANF. In vivo animal experiments have shown either enhancement or no change in ANF-induced natriuresis after ACE inhibition. Studies in humans are divided as to whether ACE inhibition raises or lowers endogenous plasma ANF levels, but a fall in ANF-induced natriuresis during ACE inhibition has been a consistent finding. However, none of these studies used a sustained low-dose or "physiological" level of ANF infusion, nor has the effect of ACE inhibition on the metabolic clearance rate of ANF been assessed formally. The fact that ACE inhibitors alone may affect systemic arterial pressure and renal blood flow, both of which influence the renal response to ANF, further increases the difficulty in interpreting changes in ANF bioactivity during ACE inhibition.

We examined the hypothesis that, at physiological dose levels of ANF, standard doses of converting enzyme inhibitor alter the metabolic clearance of, and biological actions of, ANF. We further wished to establish whether such an interaction, if present, was independent of changes in systemic and renal hemodynamics or sodium status. We studied the interaction of ANF with ACE inhibition in a group of normal subjects under strictly standardized conditions of high sodium diet and semi-
Subjects and Methods
Six normal male volunteers (29–54 years; 62–82 kg, mean 71 kg) gave informed consent before participating in the study. The experimental protocol was accepted by the Hospital Ethical Committee. Each subject was studied on two separate occasions, 1–4 weeks apart, on the fourth day of identical, constant sodium (300 mmol/day) and potassium (80 mmol/day) diets. On one study day, subjects received infusions of human atrial natriuretic factor-(99–126) [ANF-(99–126)] and vehicle; on the other study day, they received ANF and a converting enzyme inhibitor (captopril). Infusions were administered single-blind and in balanced, random order.

To confirm sodium balance and dietary compliance, 24-hour urine samples were collected on the second and third days of each diet period to measure sodium, potassium, and creatinine.

On the fourth day of each diet period, subjects came to the study room having fasted from 9 PM the previous evening. Immediately after completing the day 3 24-hour urine collection at 7 AM, the volunteers assumed the semirecumbent position for the remainder of the infusion period. Separate intravenous cannulae were placed in superficial veins of both right and left forearms for infusion and blood sampling purposes. Control blood samples were obtained before a bolus injection of para-aminohippuran (PAH) (0.015 ml/kg body wt of 20% wt/vol solution). Constant rate infusions of PAH (2.5 ml 20% solution/hr) diluted in 5% dextrose and given in a total volume of 15 ml/hr, were maintained for the remainder of the infusion period. Between 7:30 and 8:00 AM, regular measurements of blood pressure and heart rate (every 15 minutes, with an automated Rose Box, Electronic Research and Development, Dunedin, New Zealand) were commenced and preinfusion blood samples were obtained for baseline plasma hormone levels, routine plasma biochemistry and a full blood count. At 8:00 AM, constant rate infusions of human ANF-(99–126) (1.5 pmol/kg/min administered in Haemaccel in a total volume of 15 ml/hour) were commenced and continued for 3 hours. At 9:30 AM (halfway through the 3-hour ANF infusion period), additional infusions of either captopril (10 mg bolus followed by 10 mg/hr in 15 ml Haemaccel) or vehicle in identical volumes were administered for the remaining 1.5 hours until completion of the ANF infusion. At 11:00 AM, infusions of both ANF and either captopril or vehicle were stopped. The subjects remained supine until follow-up observations were completed at 11:30 AM. Blood samples were obtained for ANF and plasma renin activity (PRA) assays at 30-minute intervals from 7:30 to 11:30 AM inclusive. Samples for aldosterone, cortisol (enzyme-linked radiosorbent assay), catecholamines, and automated multianalyzer plasma biochemistry profiles were drawn at the expected overall effect of treatment) and to the 5-hour urine collection indexes.

Results
Studies were completed without incident and data collection was complete. Twenty-four-hour urinary sodium excretion on the third day of the diets was 267±12 mmol (mean±SEM) and 274±13 mmol before captopril and vehicle study days, respectively (NS).

Plasma concentrations of ANF, converting enzyme activity, and serial blood pressure and heart rate data are shown in Figure 1. The expected highly significant fall in plasma converting enzyme activity with captopril to 23% of time-matched
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FIGURE 1. Plasma angiotensin converting enzyme (ACE) activity, plasma atrial natriuretic factor (ANF) concentrations, heart rate, and arterial pressure in six normal volunteers receiving infusions of ANF (1.5 pmol/kg/min) with (•) and without (○) concomitant infusion of captopril (10 mg i.v. bolus followed by 10 mg/hr). Captopril significantly suppressed ACE activity (p<0.001) but plasma ANF, heart rate, and blood pressure (systolic and diastolic) did not change significantly with ACE inhibition.

placebo values (p<0.001) was not associated with any significant change in plasma ANF, blood pressure, or heart rate. In both captopril and vehicle study phases, ANF infusions significantly increased plasma ANF (p<0.001) to plateau concentrations approximately 20 pmol/l above similar preinfusion and postinfusion levels (Figure 1). Calculated metabolic clearance rates (for 9:30–11:00 AM, the captopril or vehicle infusion period) were similar for both phases (4.31±0.76 and 4.72±0.84 l/min, respectively, NS). At 11:30 AM, when exogenous ANF had been cleared but converting enzyme inhibition persisted, endogenous plasma ANF values with and without captopril did not differ (11.8±1.4 and 11.7±1.4 pmol/l, respectively, NS, Figure 1).

Urine volume and excretion of electrolytes and creatinine for both 5-hour urine collection periods, with and without captopril, are illustrated in Figure 2.

No variable was significantly altered by captopril and, in particular, there was no attenuation of natriuresis (mean of 370 and 323 μmol/min for captopril and vehicle from 7:00 AM–12:00 noon, respectively, NS). During the 12:00 noon–5:00 PM period, urine indexes were not significantly affected by captopril, although sodium excretion for this period was actually greater after captopril than after vehicle in five cases (NS, Figure 2).

Creatinine clearance, an indicator of glomerular filtration rate, and PAH clearance, an indicator of effective renal plasma flow, were unchanged by captopril (Table 1).

Plasma renin activity (PRA) and concentrations of aldosterone and cortisol are shown in Figure 3. PRA was, as expected, markedly suppressed by the combined effects of high salt diet, recumbent position, and ANF infusion. Although values rose slightly in two cases, there was no significant overall change in PRA after captopril was given. Unexpectedly, we observed an interruption in the downward trend in plasma concentrations of both aldosterone (p<0.05) and, more obviously, cortisol (p<0.01) during captopril. At 11:00 AM, immediately before cessation of infusions, captopril phase values for both hormones were significantly greater than time-matched vehicle phase levels (Figure 3). In the case of cortisol this effect persisted at 30 minutes postinfusion (Figure 3).

A similarly timed significant enhancement in plasma concentrations of noradrenaline (p<0.05) and, more clearly, adrenaline (p<0.05) was also associated with administration of captopril (Figure 4).

Discussion

The current study documents the effects of acute inhibition of plasma converting enzyme activity in the course of low-dose infusions of ANF. Endogenous plasma ANF concentrations, metabolic clearance of ANF, renal blood flow, glomerular filtration rate, and renal electrolyte excretion were not affected by the addition of captopril to background infusions of ANF. Unexpectedly, the combination of ANF plus captopril caused a significant increase in plasma values of aldosterone, cortisol, and catecholamines.

The absence of change in endogenous plasma ANF levels (Figure 1, 11:30 AM) with acute ACE inhibition stands in contrast to reports by Wilkins et al12 and Mann et al.13 However, in both these studies an ACE inhibitor, either captopril12 or enalapril,13 was given for 48 hours12 or 4 days13 before remeasurement of plasma ANF. Thus, duration of dosing may alter effects on plasma ANF. However, although Wilkins and his colleagues12 observed a dose-related rise in plasma ANF in sodium-replete men taking captopril, Mann et al13 reported a clear fall in sodium-depleted subjects given enalapril. These contradictory results, and the absence of an acute effect in the current study, suggest that the observed changes in plasma ANF
are not specific to ACE inhibition and may reflect changes in hemodynamic and sodium status during acute or chronic ACE inhibitor therapy. In particular, ACE inhibition in sodium-depleted subjects will lower systemic arterial and central (atrial) pressures, which will curtail secretion of ANF. In the current study, a deliberate effort was made (by means of high sodium intake, recumbent posture, and the short-term study design) to dissociate inhibition of ACE from any major change in arterial pressure or sodium balance. In these circumstances ACE inhibition does not affect plasma ANF concentrations.

The effect of ACE inhibition on steady-state concentrations of ANF in humans in the course of ANF infusions has not been previously documented. Wilkins et al employed short-term (15 minutes), high-dose infusions of ANF and reported a nonsignificant trend toward higher intrainfusion plasma ANF values. Gaillard et al gave bolus injections of ANF (100 μg) and reported a similar, slight, and statistically insignificant trend toward higher peak ANF values after enalapril. We chose a dose (1.5 pmol/kg/min) and duration (3 hours) of ANF that induced plasma ANF concentrations within the lower part of the clinical pathophysiological range, which allowed steady-state values of plasma ANF to be established, and which is known to exert biological effects, including natriuresis. The dose of captopril used (total 25 mg) is standard. Hence, levels of both plasma ANF and ACE inhibition were likely to reflect physiological or clinical circumstances. The metabolic clearance rate of ANF was not significantly changed. This suggests carboxypeptidase activity is not of major importance in ANF metabolism. However, an indirect effect may occur if blood pressure or blood flow, or both, to ANF clearance sites are lowered significantly by ACE inhibition. Certainly, changes in posture alter ANF clearance, presumably by such mechanisms. Comparisons of ANF clearance during ACE inhibition, with and without hypotension,

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**TABLE 1.** Creatinine and para-Aminohippuran Clearance

<table>
<thead>
<tr>
<th>Time</th>
<th>Captopril</th>
<th>Placebo</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ml/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7:00 AM-12:00 noon</td>
<td>130±15</td>
<td>134±23</td>
<td>NS</td>
</tr>
<tr>
<td>12:00 noon-5:00 PM</td>
<td>113±16</td>
<td>122±16</td>
<td>NS</td>
</tr>
<tr>
<td>7:00 AM-5:00 PM</td>
<td>122±15</td>
<td>128±19</td>
<td>NS</td>
</tr>
<tr>
<td>PAH clearance (ml/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-captopril or placebo (9:30 AM)</td>
<td>501±64</td>
<td>515±76</td>
<td>NS</td>
</tr>
<tr>
<td>Post-captopril or placebo (11:00 AM)</td>
<td>472±56</td>
<td>508±77</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Creatinine clearances were calculated using 5-hour urine creatinine excretions from separate (7:00 AM-12:00 noon, 12:00 noon-5:00 PM) and combined (7:00 AM-5:00 PM) serial 5-hour collections together with the mean of five serial plasma creatinine measurements (UVIP), para-Aminohippuran (PAH) clearances calculated from plasma samples taken in duplicate (10 minutes apart) within the 20-minute periods before 9:30 and 11:00 AM using the equation: clearance = infusion rate/steady state plasma concentration - plasma value before PAH administration.
and studies incorporating other classes of hypotensive agents together with measurements of regional blood flow are required to clarify this point.

Several groups have demonstrated attenuation of ANF-induced natriuresis by ACE inhibition. However, in these studies, it is likely that important hemodynamic variables were altered by ACE inhibition. Mean arterial pressure values were appreciably and significantly lowered by chronic ACE inhibition in the studies reported by Wilkins et al and Gaillard and colleagues. The report by Brown provides no information concerning the effects of ACE inhibition on blood pressure. Since subjects were seated in this study with consequent renin–angiotensin–aldosterone system (RAAS) activation, some fall in pressure with captopril would be expected. The critical role of renal perfusion pressure in dictating the natriuretic response to ANF has been well established by observations in humans and experimental animals. While the exact relation between changes in arterial pressure and ANF-induced natriuresis remains to be fully documented, it seems likely that the reduced natriuresis reported by others is due to the hypotensive effects of ACE inhibition. Studies incorporating hypotensive agents other than ACE inhibitors should help clarify this issue. In the present study, changes in blood pressure with captopril were trivial, renal hemodynamics (glomerular filtration rate and renal plasma flow) were similar, and natriuresis was unchanged.

Baseline sodium status also markedly modifies the natriuretic response to ANF. The subjects studied by Wilkins et al had notably (though not of statistical significance) lower pre-ANF sodium excretion rates after captopril treatment, and it is possible that this reflected relative sodium depletion leading to an attenuated natriuretic response to ANF. We circumvented this potential source of confusion by placing subjects on a constant sodium
intake diet that was sufficiently high to ensure sodium repletion or relative sodium loading despite any intercurrent influences that might have led to minor gains or losses in body sodium between study days.

The conditions of our study also precluded any major background changes in renal blood flow or glomerular filtration rate, and these variables were also unchanged by captopril (Table 1). Gaillard et al documented a shift in baseline PAH clearance between study days, further adding to difficulty in interpretation of data from that study.

Combined captopril and ANF infusions modestly but significantly enhanced plasma concentrations of aldosterone, cortisol, and catecholamines (Figures 3 and 4). To our knowledge, this unexpected and intriguing constellation of effects from combining these agents has not been previously reported. The simultaneous increase in both aldosterone and cortisol strongly suggests an adrenocorticotrophic hormone (ACTH) effect. The less pronounced response of aldosterone is consistent with this suggestion as sodium loading would be expected to reduce the mineralocorticoid but not glucocorticoid responses to ACTH. The simultaneous rise in plasma adrenaline indicates enhanced secretion from the adrenal medulla and the associated increase in noradrenaline values suggest this may reflect an overall increase in sympahtetic nervous system activity. The overall hormonal profile is suggestive of a mild stress or "fight or flight" response to challenge with both agents in combination.

However, the effect mediating such a response is difficult to discern. No subjects were aware of whether captopril or vehicle was being given, and no symptoms of any sort were either spontaneously reported or elicited on direct questioning during either study phase. A significant depressor effect of combined therapy might well elicit such a response, but changes in both blood pressure and heart rate were negligible (Figure 1). It is conceivable that subjects maintained arterial pressure unchanged by virtue of exact compensation for the blood pressure-lowering influence of the combined infusions through activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis. However, such perfect pressure homeostasis seems unlikely. Studies incorporating continuous recording of intraarterial pressure that would enable detection of any early and rapidly compensated transient falls in blood pressure, may clarify this point.

The stimulus to aldosterone is the more remarkable in view of the expected suppressant effect of either ANF or ACE inhibition alone. Furthermore, either agent alone in the present conditions would be expected, if anything, to diminish rather than enhance sympathetic activity.

The evidence concerning the relation between angiotensin II (Ang II) and plasma ACTH in humans is controversial. Whereas some authors have shown inhibition of plasma ACTH with infusion of Ang II, the opposite effect has also been reported. In any case, baseline RAAS activity was demonstrably suppressed in the current study, which mitigates against a major anti-Ang II effect mediating the observed hormone response. Hence, the mechanisms underlying the current observations remain obscure but, in view of the future therapeutic potential of combined ANF-enhancing and ACE-inhibiting treatment in such conditions as hypertension and heart failure, this interaction clearly warrants further study.

In conclusion, our data suggest that converting enzyme inhibition per se, in the absence of background RAAS activation (and consequently without major effects on blood pressure or renal blood flow) exerts little effect on either the metabolic clearance of ANF or its renal bioactivity. The addition of captopril superimposed on a background low-dose infusion of ANF causes modest enhancement of plasma aldosterone, cortisol, and catecholamine concentrations. The mechanisms underlying this interaction are uncertain, but this phenomenon may be of clinical significance in future cardiovascular therapeutic practice and warrants further investigation.

Acknowledgments

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