Role of Angiotensin II in Renal Prostaglandin E₂ Production After Furosemide Administration

AKIO FUJIMURA AND AKIO EBIHARA

SUMMARY The role of plasma angiotensin II (Ang II) in furosemide-stimulated renal prostaglandin E₂ (PGE₂) production was evaluated in eight healthy subjects. Urine was collected for 60 minutes after furosemide administration (20 mg i.v.) with or without captopril pretreatment, and urinary excretion of PGE₂, sodium, and furosemide was determined. Plasma renin activity (PRA) and Ang II were also measured before and 60 minutes after furosemide administration. Urinary PGE₂ excretion, PRA, and Ang II increased after furosemide administration without captopril pretreatment, and there was a significant correlation between the increment in Ang II and that in urinary PGE₂ excretion. Urinary PGE₂ excretion and Ang II did not increase after furosemide administration with captopril pretreatment. These results suggest that Ang II may play an important role in furosemide-stimulated PGE₂ production. (Hypertension 11: 491-494, 1988)

KEY WORDS • furosemide • prostaglandin E₂ • angiotensin II

Furosemide, a potent loop diuretic, is a widely used therapeutic agent for treatment of hypertension and congestive heart failure. Some effects of furosemide are reported to be partly dependent on renal prostaglandin E₂ (PGE₂) produced by furosemide administration.¹,² This elevation in renal PGE₂ production, as reflected by urinary PGE₂ excretion,³ following furosemide administration could be mediated directly by inhibition of renal 15-hydroxyprostaglandin dehydrogenase⁴ and 9-ketoreductase⁵ activities. Since furosemide activates the renin-angiotensin system, the elevated levels of angiotensin II (Ang II) may in turn stimulate synthesis of renal PGE₂.⁶

To determine whether the indirect action of Ang II plays an important role in furosemide-induced renal PGE₂ production, we investigated urinary PGE₂ excretion after furosemide administration with or without pretreatment with captopril, an oral converting enzyme inhibitor, in healthy subjects.

Subjects and Methods

Protocol

Eight healthy male subjects, 22 to 28 years old, gave informed consent to the protocol and were studied on three separate occasions. The subjects were requested to refrain from sexual activity and not to take nonsteroidal anti-inflammatory drugs for at least 48 hours before the study. Sodium intake was not restricted until the night before the study. Urine was collected for 24 hours on the day before each study. After fasting overnight, subjects were given 400 ml of water to drink at 0900, 1030, 1200, and 1300 and were asked to void at 1300. The subjects remained supine throughout the study except for 1 to 2 minutes of standing to pass urine. In the first study, urine was collected for 60 minutes after administration of vehicle (10 ml of saline) at 1300. In the second study, 10 ml of saline containing 20 mg of furosemide was injected intravenously after voiding urine at 1300. In the third study, the procedure of the second study was repeated but a blood sample was also obtained and 50 mg of captopril was given orally at 1200. These three studies were performed at 7-day intervals.

Analytical Procedures

Blood samples for measurement of plasma renin activity (PRA) and Ang II were collected into tubes containing EDTA and kept on ice. After centrifugation at 2000 g at 4°C for 20 minutes, the plasma was separated. Plasma and urine samples were immediately frozen and stored at −20°C in a freezer that had no cyclic system for defrosting and were analyzed within 2 weeks.
PRA\textsuperscript{7} and Ang II\textsuperscript{8} were measured by radioimmunoassay. Urinary sodium was determined by a flame photometer (Model 775-A, Hitachi, Tokyo, Japan). Urinary furosemide was measured using high performance liquid chromatography.\textsuperscript{9} Urinary PGE\textsubscript{2} was measured by radioimmunoassay after extraction according to the method of Jaffe et al.\textsuperscript{10} with a slight modification. In brief, after 0.2 N hydrochloric acid was added to 1 ml of urine to adjust to a pH of 3 to 5, the sample was defatted with 3 ml of n-hexane to which 3 ml of acetic acid and ethylisopropanol (1:1, vol/vol) mixture was added and mixed well, then the organic layer was separated with 5 ml of ethylacetate acid and water (2:3, vol/vol) mixture. The upper layer was evaporated, and the residue dissolved with a 1-ml mixture of benzene, ethyl acetate, and methanol (60:40:2, vol/vol). The extract was then applied onto the minicolumn (8 X 160 mm) packed with 1.5 g of silicic acid, and the fraction of PGE\textsubscript{2} was collected. The recovery rate of PGE\textsubscript{2} was 85.0 ± 5.0\% (n = 7). PGE\textsubscript{2} was not converted to prostaglandin A\textsubscript{2} in this extraction procedure. PGE\textsubscript{2} was measured by radioimmunoassay using a kit (Clinical Assays, Travenol, Deerfield, IL, USA) after conversion to prostaglandin B (PGB) by treating with 0.1 ml of 1 N sodium hydroxide and heating at 100°C for 5 minutes. Greater than 90\% of PGE\textsubscript{2} was converted in the alkalinizing process to PGB. The cross-reactivity of anti-PGB antibody was 100\% with PGB, 22.2\% with prostaglandin A\textsubscript{1}, less than 0.1\% with prostaglandin A\textsubscript{2}, 12.3\% with prostaglandin E\textsubscript{1}, less than 0.1\% with PGE\textsubscript{2}, less than 0.1\% prostaglandin F\textsubscript{1\alpha} (PGF\textsubscript{1\alpha}), and less than 0.1\% prostaglandin F\textsubscript{2\alpha}. Tritium-labeled PGE\textsubscript{2} (1000 cpm) was added to the urine for correction of the recovery rate. The sensitivity of this assay was 20 pg/ml of urine, and the intra-assay and interassay coefficients of variation were 10\% (\(x = 48\) pg/ml; n = 15) and 13\% (\(x = 48\) pg/ml; n = 15), respectively. Urinary captopril did not interfere with this assay.

### Table 1. Urine Volume and Urinary Excretion of PGE\textsubscript{2}, Sodium, and Furosemide

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study 1 (vehicle)</th>
<th>Study 2 (furosemide)</th>
<th>Study 3 (captopril + furosemide)</th>
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</thead>
<tbody>
<tr>
<td>Urine volume (ml/hr)</td>
<td>456 ± 36*</td>
<td>1210 ± 42</td>
<td>1049 ± 91</td>
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<tr>
<td>Urinary PGE\textsubscript{2} (ng/hr)</td>
<td>11.4 ± 3.9*</td>
<td>73.5 ± 7.8</td>
<td>10.5 ± 0.9*</td>
</tr>
<tr>
<td>Urinary sodium (mEq/hr)</td>
<td>18 ± 4*</td>
<td>104 ± 4</td>
<td>85 ± 9</td>
</tr>
<tr>
<td>Urinary furosemide (mg/hr)</td>
<td>—</td>
<td>10.65 ± 0.62</td>
<td>9.71 ± 0.51</td>
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</table>

Values are means ± SE of eight subjects.
*p < 0.01, compared with values for Study 2.

### Table 2. PRA and Plasma Ang II After Administration of Furosemide With or Without Captopril Pretreatment

<table>
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<th>Plasma variable</th>
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<tr>
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<td>0 min</td>
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<tr>
<td>Study 2 (furosemide)</td>
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<tr>
<td>PRA (ng Ang I/ml/hr)</td>
<td>1.7 ± 0.5</td>
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<tr>
<td>Ang II (pg/ml)</td>
<td>13.6 ± 1.8</td>
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<tr>
<td>Study 3 (captopril + furosemide)</td>
<td>7.1 ± 2.3</td>
</tr>
<tr>
<td>PRA (ng Ang I/ml/hr)</td>
<td>8.1 ± 1.1</td>
</tr>
<tr>
<td>Ang II (pg/ml)</td>
<td>8.1 ± 1.1</td>
</tr>
</tbody>
</table>

Values are means ± SE of eight subjects. ANG I = angiotensin I.
*p < 0.01, †p < 0.05, compared with values at 0 minutes.

There were significant correlations between the increment in Ang II and that of urinary PGE\textsubscript{2} after furosemide administration (Figure 1).

Urine volume and urinary excretion of sodium and furosemide after furosemide administration were not influenced by captopril pretreatment (see Table 1). There were significant correlations between urinary...
furosemide excretion and the increment in urine volume \((n = 16, r = 0.56, p < 0.05)\) and in urinary sodium excretion \((n = 16, r = 0.55, p < 0.05)\). However, there was no significant correlation between the increment in urinary \(\text{PGE}_2\) excretion and that in urine volume or urinary sodium excretion after furosemide administration without captopril pretreatment.

**Discussion**

The present study demonstrates that urinary \(\text{PGE}_2\) excretion increases significantly after furosemide administration and this increment is completely inhibited by captopril pretreatment. The present study also reveals a high degree of correlation between changes in plasma Ang II concentration and in urinary \(\text{PGE}_2\) excretion during the study without captopril pretreatment. These observations confirm and extend a previous report by Attallah et al., who suggested that the effect of furosemide on renal \(\text{PGE}_2\) production is mediated through the action of Ang II. Ang II is reported to stimulate \(\text{PGE}_2\) synthesis in the kidney, in cultures of renal medullary interstitial cells, and in isolated glomeruli. On the basis of these observations, the observed increment in furosemide-induced renal \(\text{PGE}_2\) production can be entirely accounted for by the concurrent increase in Ang II. The obliteration of this response by captopril pretreatment provides additional support for this thesis. For these reasons, the effect of furosemide on the prostaglandin degrading enzymes appears negligible.

Furosemide increases urinary excretion of several prostaglandins, including \(\text{PGE}_2\) and 6-keto-\(\text{PGF}_1 \alpha\) in humans. Ang II stimulates arachidonic acid release through Ang II-activated phospholipase \(A_2\), and subsequent prostaglandin biosynthesis. Ang II has been shown to stimulate \(\text{PGE}_2\) and 6-keto-\(\text{PGF}_1 \alpha\) production by isolated human glomeruli. Therefore, the increase in urinary 6-keto-\(\text{PGF}_1 \alpha\) after furosemide administration also might be decreased by captopril, although this was not examined in the present study.

As the urinary \(\text{PGE}_2\) excretion after captopril alone was not determined in the present study, a direct effect of the drug on urinary \(\text{PGE}_2\) excretion could not be evaluated. However, since captopril is reported to increase plasma levels of \(\text{PGE}_2\), it is not likely that captopril prevents the increment in urinary \(\text{PGE}_2\) excretion after furosemide administration by a mechanism other than inhibition of its furosemide-related effect.

The contribution of renal \(\text{PGE}_2\) to the mechanism of action of furosemide is still debated. After furosemide was administered intravenously, urinary \(\text{PGE}_2\) increased rapidly during the first 15 to 30 minutes and this increase was related to natriuresis in two studies, but not in a third. In the present study, the urine volume and urinary sodium excretion responses to furosemide administration were not influenced by captopril pretreatment, although urinary \(\text{PGE}_2\) excretion was remarkably reduced. Moreover, there were no significant correlations between the increment in urinary \(\text{PGE}_2\) and that in urine volume or urinary sodium excretion after furosemide administration without captopril pretreatment. Our results agree with the work of Nadler et al., which demonstrated that Ang II by itself stimulates \(\text{PGE}_2\) excretion without affecting urine volume and urinary sodium excretion. Therefore, it may be concluded from the present study that renal \(\text{PGE}_2\) does not play an important role in the diuretic and natriuretic effects of furosemide.

**Acknowledgments**

We thank Dr. David C. Kem of the University of Oklahoma for critically reading the manuscript and for his helpful comments. We also thank Hoechst Japan Ltd. (Tokyo, Japan) for measuring urinary concentrations of furosemide.

**References**

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Inhaled risk of renal function as a consequence of the renin-angiotensin system, changes in renal function may be anticipated in susceptible individuals. Patients in severe congestive heart failure whose renal function may depend on the balance between renin-angiotensin-system activity and treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy with ACE inhibitors. Some hypertensive patients with no apparent previous renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with propranolol or other medications that may block the enzyme renin.

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Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were diarrhea (3%), headache (2%), nausea (1%), and orthostatic effects (1%).

Clinical adverse experiences occurring more frequently than 1% but not at least twice daily dosage within the range of 10 to 40 mg/day in the hypertensive patients treated with VASOTEC were comparable to placebo.

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