Role of Thromboxane A₂ in the Hypotensive Effect of Captopril in Essential Hypertension

KEI KUDO, KEISHI ABE, SATORU CHIBA, MAKITO SATO, MINORU YASUJIMA, MASAHIRO KOHZEKI, KEN OMATA, MASAYA TANNO, KAZUO TSUNODA, AND KAORU YOSHINAGA

SUMMARY We have previously reported that captopril stimulates thromboxane A₂ synthesis in patients with essential hypertension. In the present study, the hypotensive effects of captopril and OKY-046, a selective inhibitor of thromboxane A₂ synthetase, were studied in nine patients with essential hypertension to determine whether thromboxane A₂ is involved in the regulation of blood pressure. A single oral dose of OKY-046 (400 mg) decreased urinary thromboxane B₂ (a stable metabolite of thromboxane A₂) excretion significantly (from 113 ± 19.0 to 51.0 ± 6.1 pg/min; p<0.01) and increased urinary sodium excretion significantly (from 73.0 ± 15.3 to 113.0 ± 14.4 μEq/min; p<0.01), but no change was observed in mean arterial pressure. The administration of OKY-046 (600 mg/day) for 3 days induced a significant and sustained decrease in urinary thromboxane B₂ excretion, but it did not affect the mean arterial pressure. Although captopril (50 mg) alone induced a significant increase in urinary thromboxane B₂ excretion (from 91.4 ± 11.0 to 297.3 ± 30.8 pg/min; p<0.001) and a significant decrease in mean arterial pressure (from 97.0 ± 4.7 to 88.1 ± 5.1 mm Hg; p<0.01), captopril in combination with OKY-046 induced a decrease both in urinary thromboxane B₂ excretion (from 70.8 ± 12.3 to 54.2 ± 14.7 pg/min; p<0.01) and in mean arterial pressure (from 105.1 ± 3.8 to 84.2 ± 3.6 mm Hg; p<0.01). Thus, the hypotensive effect of captopril was potentiated by OKY-046. OKY-046 did not affect the changes in plasma renin activity and plasma aldosterone concentration and blunted urinary prostaglandin E₂ and 6-keto-prostaglandin F₁α excretion in response to captopril. These results indicate that thromboxane A₂ counteracts the hypotensive effect of captopril in patients with essential hypertension. (Hypertension 11: 147-152, 1988)

KEY WORDS • thromboxane A₂ • captopril • hypotensive mechanism • essential hypertension

THROMBOXANE A₂ (TXA₂) is a potent vasoconstrictor and platelet aggregating agent.¹² Some reports suggest that increased synthesis of TXA₂ is implicated in some pathological states such as angina pectoris³ and the development of atherosclerosis.⁴ A notable amount of TXA₂ synthetase activity has been demonstrated in the human kidney.⁵⁻⁷ Urinary thromboxane B₂ (TXB₂), a stable metabolite of TXA₂, is thought to reflect the renal synthesis of TXA₂. Recently, it has been reported that urinary excretion of TXB₂ was increased in patients with renal allograft rejection, systemic lupus erythematosus, or hepatorenal syndrome.⁶⁻¹⁰ As TXA₂ is a vasoconstrictor, TXA₂ is thought to be involved in the modulation of vascular tone.¹¹ However, the role of TXA₂ in the regulation of blood pressure and renal function has not been fully elucidated.

The renin-angiotensin and kallikrein-kinin systems are involved in the hypotensive mechanism of captopril.¹² Recently, interest has been also focused on prostanoiids. Captopril reportedly induces an increase in prostaglandin production in humans¹³,¹⁴ and experimental animals.¹⁵ Furthermore, indomethacin, an inhibitor of cyclooxygenase, has been shown to reduce the hypotensive effect of captopril in some patients with essential hypertension.¹⁶ A recent report from our laboratory showed that captopril, an inhibitor of angiotensin converting enzyme, induced a concomitant increase in urinary prostaglandin E (PGE) and TXB₂.
excretion in patients with essential hypertension.\textsuperscript{17} Thus, enhanced production of prostaglandins and 
TXA\textsubscript{2} may influence (i.e., either potentiate or blunt) 
the hypotensive effect of captopril.

In the present study, we investigated the effect of a 
selective inhibitor of TXA\textsubscript{2} synthetase, OKY-046, on 
blood pressure in patients with essential hypertension 
receiving captopril in an attempt to elucidate the role of 
TXA\textsubscript{2} in the hypotensive mechanism of captopril.

Patients and Methods

The present study was conducted in five male and 
and four female patients with essential hypertension ranging 
in age from 18 to 64 years old. They gave informed 
consent before the study. The diagnosis of essential 
hypertension was confirmed by history, physical and 
laboratory examinations, intravenous pyelography, 
determinations of plasma renin activity (PRA) and 
plasma aldosterone concentration (PAC), radioisotope 
renography and angiography. All patients had stopped 
taking antihypertensive medication at least 2 weeks 
before the study began and received a standard hospital 
diet throughout the study period.

Three different studies were performed.

Protocol 1: Effects of Short-term Administration of 
OKY-046

Eight patients with essential hypertension (4 men 
and 4 women; mean age, 40.0 ± 5.1 years) were exam-
ined to determine the short-term effects of OKY-
046, (E)-3-[4-(1-imidazolylmethyl)-phenyl]-2-tropen-
oic acid hydrochloride monohydrate (Ono Pharmaceutical, 
Osaka, Japan), on systemic blood pressure. 
Supine patients were studied after an overnight fast. Ex-
periments were performed between 0700 and 1300, 
during which time patients were not allowed to eat or 
drink. After baseline sampling of blood and urine for 
PRA, PAC, and urinary TXB\textsubscript{2}, a single oral dose of 
OKY-046 (400 mg) was administered at 0900. Blood 
samples were obtained 60 and 120 minutes after the 
administration of the drug. Blood pressure was moni-
tored at 10-minute intervals with an automatic blood 
pressure recorder (Model 203, Nihon Korin, Japan) for 
60 minutes in the control period and for the initial 2 
hours after OKY-046 treatment. Urine samples were 
collected every 2 hours: 0700 to 0900, the control or 
baseline period; 0900 to 1100, the first 2 hours after 
OKY-046 administration; and 1100 to 1300, the sec-
ond 2 hours after OKY-046 administration. Urine was 
collected and refrigerated at 4°C after each voiding, 
and aliquots of the urine samples were stored at 
−20°C until analysis.

Protocol 2: Effects of Subchronic Administration of 
OKY-046

Nine patients with essential hypertension (5 men 
and 4 women; mean age, 37.5 ± 5.1 years) were exam-
ined to determine the effect of OKY-046 on system-
ic blood pressure. The patients were given OKY-046, 
200 mg three times daily, for 3 days, and 24-hour urine 
samples were collected for sodium, potassium, and 
TXB\textsubscript{2} determinations. Systemic blood pressure was 
measured four times daily with the patients in the su-
pine position, and values were averaged for each day.

Protocol 3: Effects of Captopril in Combination with 
OKY-046

The effects of captopril were examined in nine pa-
tients with essential hypertension who had previously 
received either placebo or OKY-046 for 3 days as 
described in Protocol 2. After 3 days of either placebo 
or OKY-046, 200 mg three times daily, patients were 
studied supine after an overnight fast. Studies were 
performed between 0700 and 1300, during which time 
patients were not allowed to eat or drink. The last dose 
of placebo or OKY-046 (400 mg) was given at 0700, 
and a single oral dose of captopril (50 mg) was admin-
istered at 0900. Urine and blood samples were collect-
ed in the same way as described in Protocol 1. In this 
protocol, each patient was studied repeatedly while 
taking either placebo or OKY-046.

Laboratory Procedures

All blood samples were collected on ice and spun 
immmediately, and the plasma was separated and frozen 
until the time of assay. Urinary sodium and potassium 
were measured with a selective electrode of sodium 
and potassium, respectively (Technicon StatIon, Type 
II, Japan Technicon, Tokyo, Japan). PRA was deter-
mined by means of radioimmunoassay (RIA) of angio-
tensin I as described previously; PAC was also deter-
mined by RIA.\textsuperscript{18}

Urinary TXB\textsubscript{2}, extracted with chloroform and sepa-
rated by silicic acid column chromatography, was 
measured by RIA as described previously.\textsuperscript{19} The cross-
reactivity of anti-TXB\textsubscript{2} serum was 100% for TXB\textsubscript{2}, 
34% for 2,3-dinor TXB\textsubscript{2}, 0.36% for prostaglandin D\textsubscript{2}, 
0.03% for prostaglandin F\textsubscript{1α} (PGF\textsubscript{1α}), and less than 
0.01% for PGE\textsubscript{1α}, PGE\textsubscript{2}, prostaglandin A\textsubscript{1}, prostag-
landin B\textsubscript{2}, and 6-keto-PGF\textsubscript{1α}. Urinary PGE\textsubscript{2} was measured 
by the RIA as described previously.\textsuperscript{16, 20} The cross-
reactivity of anti-PGE\textsubscript{2} serum was 100% for PGE\textsubscript{2}, 
10.7% for PGE\textsubscript{1α}, 0.3% for prostaglandin A\textsubscript{1}, 0.04% 
for prostaglandin A\textsubscript{2}, and less than 0.01% for prostag-
landins B\textsubscript{1} and B\textsubscript{2}, TXB\textsubscript{2}, and 6-keto-PGF\textsubscript{1α}. In this study, 
the measurement of urinary PGE\textsubscript{2} was per-
formed only in female patients, as the concentration of 
PGE\textsubscript{2} in the urine of male subjects is affected by con-
tamination with seminal fluid.\textsuperscript{19, 21} The RIA of 6-keto-
PGF\textsubscript{1α} was performed on unextracted urine. The cross-
reactivity of anti-6-keto-PGF\textsubscript{1α} serum was 100% for 
6-keto-PGF\textsubscript{1α}, 14% for PGE\textsubscript{1α}, 2% for PGE\textsubscript{2} and 
PGF\textsubscript{1α}, and less than 1% for TXB\textsubscript{2} and PGE\textsubscript{2}.\textsuperscript{22} TXB\textsubscript{2} 
standard, anti-TXB\textsubscript{2} serum, and [\textsuperscript{3}H]TXB\textsubscript{2} were 
purchased in kit form (Model NEN-042) from New En-
land Nuclear, Boston, MA, USA. Anti-PGE\textsubscript{2} serum 
was purchased from Institute Pasteur, Paris, France. 
Standards of PGE\textsubscript{2} and 6-keto-PGF\textsubscript{1α} were 
purchased from Sigma Chemical (St. Louis, MO, USA). 
Anti-serum to 6-keto-PGF\textsubscript{1α} was a gift from Dr. Michael J. 
Dunn, Cleveland, OH, USA. \textsuperscript{[\textsuperscript{3}H]6-keto-PGF\textsubscript{1α} and 
[\textsuperscript{3}H]PGE\textsubscript{2} were purchased from New England Nuclear.
Statistics

The mean arterial pressure (MAP) was calculated from systolic and diastolic blood pressures in the conventional way. Group means are presented with the standard error of the mean as the index of dispersion. Statistical probability was evaluated using the paired \( t \) test.

Results

Short-term Effects of OKY-046 (Protocol 1)

The administration of OKY-046 induced a significant and sustained decrease in urinary TXB\(_2\) excretion when compared with the control value (Table 1). It also induced a significant increase in urine volume and urinary sodium or potassium excretion. However, MAP did not change significantly (106.7 ± 2.6 mm Hg at control, 103.1 ± 2.4 mm Hg at 60 minutes, and 102.1 ± 2.0 mm Hg at 120 minutes; Figure 1).

Subchronic Effects of OKY-046 (Protocol 2)

The administration of OKY-046 (600 mg/day) for 3 days induced a significant and sustained decrease in urinary TXB\(_2\) excretion when compared with the control value (Table 2). MAP, urinary potassium excretion, and urine volume did not change significantly, although a slight but insignificant increase was observed in urinary sodium excretion during the administration of OKY-046 on Day 1.

Effects of Captopril in Combination with OKY-046 (Protocol 3)

Captopril administration in combination with OKY-046 induced a significant decrease in MAP (from 105.1 ± 3.8 to 84.2 ± 3.6 mm Hg; control vs 60 minutes; \( p < 0.01 \)), as did administration of captopril with placebo (from 97.0 ± 4.7 to 88.1 ± 5.1 mm Hg; control vs 60 minutes; \( p < 0.01 \); see Figure 1). When measured as a change of MAP the administration of OKY-046 clearly potentiated the hypotensive effect of captopril (Figure 2).

As shown in Table 3, administration of captopril alone induced a significant increase in urinary TXB\(_2\) excretion (from 91.4 ± 11.0 to 297.3 ± 30.8 pg/min; control urine vs first posttreatment urine sample; \( p < 0.001 \)). It also induced increases in urine volume, urinary sodium, PGE\(_2\), and 6-keto-PGF\(_{1\alpha}\) excretion. On the other hand, treatment with OKY-046 completely inhibited the captopril-induced increase in urinary TXB\(_2\) excretion (see Table 3). The responses in PRA and PAC to captopril did not differ significantly between the patients given OKY-046 and those given placebo. Prior administration of OKY-046 did not change significantly the effect of captopril on PRA and PAC, whereas it blunted increases in urinary PGE\(_2\) and 6-keto-PGF\(_{1\alpha}\) excretion in these patients. To avoid the problem of contamination with seminal fluid in male subjects, urinary PGE\(_2\) excretion was measured only in 4 female subjects. Thus, potentiation of the hypotensive effect of captopril by OKY-046 was accompanied exclusively by the inhibition of captopril-induced TXA\(_2\) generation.

Discussion

In the present study in patients with essential hypertension, urinary excretion of TXB\(_2\) was significantly reduced by either short-term or subchronic administration of OKY-046. However, the MAP was not changed significantly in these experiments. Similar results have been reported using other selective inhibitors of TXA\(_2\) synthetase, such as dazoxiben or OKY-1581.\(^{23,24}\) It has been also reported that there was no consistent difference in the basal excretion of TXB\(_2\) between normal subjects and hypertensive patients.\(^{25}\) Thus, under basal conditions in which renal TXA\(_2\) synthesis is not increased, TXA\(_2\) may not play an important role in the regulation of blood pressure in patients with essential hypertension.

TXA\(_2\) and prostaglandin I\(_2\) (PGI\(_2\)) may exert opposite effects on platelet aggregation and vascular resistance. The balance between these two compounds has been suggested as one of the factors that determine platelet reactivity, endothelial thromboresistance, and vascular tone.\(^{26}\) Therefore, much attention has been focused on the TXA\(_2\)/PGI\(_2\) balance.\(^{27}\) An inhibitor of

<table>
<thead>
<tr>
<th>TABLE 1. Short-term Effects of OKY-046 Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine sample</strong></td>
</tr>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>0–2 hr posttreatment</td>
</tr>
<tr>
<td>2–4 hr posttreatment</td>
</tr>
<tr>
<td>( U_{\text{TXB}_2}V ) (pg/min)</td>
</tr>
<tr>
<td>113.0 ± 19.0</td>
</tr>
<tr>
<td>51.0 ± 6.1*</td>
</tr>
<tr>
<td>32.0 ± 5.9*</td>
</tr>
<tr>
<td>( U_{\text{Na}}V ) (µEq/min)</td>
</tr>
<tr>
<td>73.0 ± 15.3</td>
</tr>
<tr>
<td>113.0 ± 14.4*</td>
</tr>
<tr>
<td>79.0 ± 11.7*</td>
</tr>
<tr>
<td>( U_{\text{K}}V ) (µEq/min)</td>
</tr>
<tr>
<td>35.0 ± 6.9</td>
</tr>
<tr>
<td>49.0 ± 3.2*</td>
</tr>
<tr>
<td>34.0 ± 3.8*</td>
</tr>
<tr>
<td>UV (ml/min)</td>
</tr>
<tr>
<td>0.81 ± 0.20</td>
</tr>
<tr>
<td>1.49 ± 0.29*</td>
</tr>
<tr>
<td>0.47 ± 0.06*</td>
</tr>
</tbody>
</table>

*Results are means ± SEM of eight subjects. \( U_{\text{TXB}_2}V \) = urinary thromboxane \( \text{B}_2 \) excretion; \( U_{\text{Na}}V \) = urinary sodium excretion; \( U_{\text{K}}V \) = urinary potassium excretion; UV = urinary volume. \( *p < 0.01 \), compared with control urine value.
TABLE 2. Subchronic Effects of OKY-046

<table>
<thead>
<tr>
<th>Variable</th>
<th>MAP (mm Hg)</th>
<th>UTXB2 V (ng/day)</th>
<th>UNa V (mEq/day)</th>
<th>UKV (mEq/day)</th>
<th>UV (ml/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control day</td>
<td>112.0 ± 1.78</td>
<td>165.7 ± 17.8</td>
<td>217.0 ± 23.0</td>
<td>6.7 ± 4.7</td>
<td>1491.0 ± 132.0</td>
</tr>
<tr>
<td>Day 1</td>
<td>108.6 ± 2.06</td>
<td>52.8 ± 5.4*</td>
<td>235.0 ± 36.0</td>
<td>42.8 ± 4.4</td>
<td>108.6 ± 2.06</td>
</tr>
<tr>
<td>Day 2</td>
<td>108.2 ± 1.76</td>
<td>45.5 ± 7.6*</td>
<td>231.0 ± 24.0</td>
<td>31.2 ± 8.3</td>
<td>145.5 ± 7.6*</td>
</tr>
<tr>
<td>Day 3</td>
<td>107.8 ± 1.55</td>
<td>35.4 ± 5.0*</td>
<td>193.0 ± 20.0</td>
<td>34.4 ± 2.9</td>
<td>1520.0 ± 128.0</td>
</tr>
</tbody>
</table>

Results are means ± SEM of nine subjects. OKY-046 (600 mg) was administered on Days 1, 2, and 3. UTXB2 V = urinary TXB2 excretion; UNa V = urinary sodium excretion; UKV = urinary potassium excretion; UV = urinary volume. *p < 0.01, compared with control day value.

FIGURE 2. Changes in MAP after the administration of 50 mg of captopril alone (○) or 50 mg of captopril combined with a 4-day pre-treatment with OKY-046 (600 mg/day for 3 days and 400 mg/day for 1 day; ●). Results are means ± SEM. Single (p < 0.02) and double (p < 0.01) asterisks indicate significant difference compared with captopril treatment alone.

TXA2 synthetase may not only inhibit the production of TXA2 but also preserve or even enhance the production of PGI2. However, in the present study, OKY-046 did not increase urinary 6-keto-PGF1α or PGE2 excretion. In accord with our results, other inhibitors of TXA2 synthetase, such as OKY-1581 or dazoxiben, have been reported to decrease PGI2 production.28,29

In the present study, we confirmed our previous findings that the angiotensin converting enzyme inhibitor captopril increases urinary excretion of PGE2 and TXB2. OKY-046 blocked the captopril-induced augmentation in urinary TXB2 excretion. Furthermore, OKY-046 significantly potentiated the hypotensive effect of captopril in patients with essential hypertension. This potentiation of the hypotensive effect of captopril was accompanied by a reduction in urinary TXB2 excretion. Enhanced vasodilator prostaglandins, such as PGE2 and PGI2, are thought to play a role in the hypotensive effect of captopril.13,14,16 In the present study, however, pretreatment with OKY-046 blunted the captopril-induced PGE2 and 6-keto-PGF1α produc-

TABLE 3. Effect of Captopril in Essential Hypertensive Patients With or Without OKY-046 Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>0–2 hr posttreatment</th>
<th>2–4 hr posttreatment</th>
<th>Control</th>
<th>0–2 hr posttreatment</th>
<th>2–4 hr posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTXB2 V (pg/min)</td>
<td>91.4 ± 11.0</td>
<td>297.3 ± 30.8*</td>
<td>178.3 ± 31.9</td>
<td>70.8 ± 12.3</td>
<td>54.2 ± 14.7†</td>
<td>40.2 ± 6.7‡§</td>
</tr>
<tr>
<td>UPGE2 V (pg/min)</td>
<td>91.4 ± 16.9</td>
<td>198.8 ± 33.9</td>
<td>104.0 ± 10.2</td>
<td>94.4 ± 11.1</td>
<td>142.2 ± 33.4</td>
<td>92.0 ± 17.7</td>
</tr>
<tr>
<td>U6_keto_PGF1α V (pg/min)</td>
<td>182.5 ± 13.8</td>
<td>336.6 ± 64.7</td>
<td>273.8 ± 62.5</td>
<td>219.3 ± 28.6</td>
<td>210.5 ± 42.5</td>
<td>239.6 ± 53.3</td>
</tr>
<tr>
<td>UV (μl/min)</td>
<td>0.62 ± 0.07</td>
<td>1.94 ± 0.28*</td>
<td>0.70 ± 0.06</td>
<td>1.69 ± 0.34§</td>
<td>2.70 ± 0.37§</td>
<td>0.90 ± 0.14</td>
</tr>
<tr>
<td>UNa V (μEq/min)</td>
<td>98.2 ± 13.3</td>
<td>230.6 ± 22.6*</td>
<td>126.4 ± 13.7</td>
<td>172.8 ± 20.0</td>
<td>226.8 ± 29.6</td>
<td>142.1 ± 21.1</td>
</tr>
</tbody>
</table>

Results are means ± SEM of nine patients, except for U6_keto_PGF1α V, where results are means ± SEM of four female patients. UTXB2 V = urinary TXB2 excretion; UPGE2 V = urinary PGE2 excretion; U6_keto_PGF1α V = urinary 6-keto-PGF1α excretion; UV = urinary volume, UNa V = urinary sodium excretion; Ang I = angiotensin I; PAC = plasma aldosterone concentration.

*p < 0.001, †p < 0.02, ‖p < 0.05, compared with respective control values.
§p < 0.01, ‡p < 0.001, compared with respective captopril + placebo values.
tion but did not affect PRA and PAC. Thus, the OKY-
046-induced potentiation of the hypotensive effect of
captopril may be mediated by the inhibition of capto-
pril-induced TXA2 synthesis.

It is interesting that the TXA2 synthetase inhibitor exerted its effect on blood pressure not under basal conditions but when the renal TXA2 synthesis was increased by captopril treatment. It has been reported in experimental animals that TXA2 is not synthesized in the kidney under physiological conditions, but its synthesis is induced in certain pathological states of the kidney, such as hydronephrosis, renal vein constriction, or acute renal failure. These findings suggest that TXA2 may play a role in the regulation of blood pressure only under certain conditions in which TXA2 production is increased.

Recently, a thromboxane synthetase inhibitor, imi-
dazole, was reported to increase urinary sodium ex-
cretion in rats. In the present study, the short-term administration of OKY-046 induced a significant increase in urinary sodium excretion in patients with essential hypertension. The natriuresis was accompanied by the reduction of urinary TXB2 excretion. The subchronic administration of OKY-046 also induced a slight but insignificant increase in urinary sodium excretion and a weak diuresis. To clarify the mechanisms of the effects of TXA2 synthetase inhibitor on renal excretory function, further experiments are needed.

As discussed, the potentiation of the hypotensive effect of captopril with OKY-046 is supposedly due to the inhibition of TXA2 production in the kidney. However, we have not examined the effect of captopril on TXA2 synthesis in extrarenal tissues. Recently, it has been reported that TXA2 is also synthesized in human vascular wall. There is a possibility that captopril may also stimulate the production of TXA2 in vascular wall, which eventually reduces the hypotensive effect of the converting enzyme inhibitor. Thus, it may be more likely that the potentiation of the hypotensive effect of captopril with OKY-046 is mediated by the inhibition of TXA2 synthesis, not only in the kidney but also in the systemic vasculature.

In conclusion, our results suggest that TXA2 may be of negligible importance for the regulation of blood pressure under basal conditions. However, certain situations in which TXA2 production is increased by some disease or drugs such as converting enzyme inhibitors, TXA2 may play a role as a potent vasoconstrictor in the regulation of blood pressure in humans.

Acknowledgments

We are grateful to Dr. Michael J. Dunn of Case Western Reserve University (Cleveland, OH, USA) for the gift of anti-6-keto-PGF1α serum. We are also grateful for the excellent technical assistance of Kaori Matsuura, Keiko Shinashi, and Mayumi Nakayama and the secretarial assistance of Junko Okazaki.

References

3. Hirsh PD, Campbell WB, Willerson JT, Hilles LD. Prosta-
6. Morrison A, Thornton F, Blumberg A, Vaughan FD. Throm-
boxane A2 is the major arachidonic acid metabolite of human cortical hydronephrotic tissue. Prostaglandins 1981;21:471-481
7. Sner M, Ardaillou N, Sner JD, Ardaillou R. In vitro prosta-
glandin by human glomeruli and papillae. Prostaglandins 1982;23:855-864
10. Kronborg L, Radovan G, Zipser RD. Urinary excretion of prosta-
11. Svensson J, Fredholm BB. Vasoconstrictor effect of throm-
13. Mullane KM, Moncada S. Prostacyclin mediates the potentiat-
ed hypotensive effect of bradykinin following captopril treat-
15. Miyamoto M, Koike H, Ito K, Yamazaki M. Effects of capto-
16. Abe K, Ito T, Sato M, et al. Role of prostaglandin in the antihypertensive mechanism of captopril in low renin hyperten-
17. Kudo K, Abe K, Chiba S, et al. Urinary excretion of TXB2 af-
19. Chiba S, Abe K, Kudo K, et al. Sex- and age-related differ-
ces in the urinary excretion of TXB2 in normal human sub-
20. Yasujiuna M, Abe K, Kohzuki M, et al. Atrial natriuretic factor inhibits the hypertension induced by chronic infusion of nor-
21. Sato K, Abe K, Seino M, et al. Reduced urinary excretion of prosta-
glandin E in essential hypertension. Prostaglandins Leu-
kotrienes Med 1983;11:189-197
23. FitzGerald GA, Brash AR, Oates JA, Pedersen AK. Endog-
ous prostacyclin biosynthesis and platelet function during selec-
tion with a novel imidazole derivative, UK-38,485, on prosta-
25. Campbell WB, Holland OB, Adams BV, Gomez-Sanchez CE. Urinary excretion of prostaglandin \(E_2\), prostaglandin \(F_2\), and thromboxane \(B_2\) in normotensive and hypertensive subjects on varying sodium intake. Hypertension 1982;4:735–741


Role of thromboxane A2 in the hypotensive effect of captopril in essential hypertension.
K Kudo, K Abe, S Chiba, M Sato, M Yasujima, M Kohzuki, K Omata, M Tanno, K Tsunoda and K Yoshinaga

Hypertension. 1988;11:147-152
doi: 10.1161/01.HYP.11.2.147

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/11/2/147

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/