EFFECTS OF PROSTAGLANDIN A₂ AND E₂ ON RENAL FUNCTION
AND RENIN RELEASE

TOSHIHIRO MATSUMURA, TAKETOSHI KISHMOTO, TSUTOMU MAEDA,
MASANOBU MAEKAWA, YOUICHI ABE* AND KENJIRO YAMAMOTO*

Effects of prostaglandin A₂ (PGA₂) and E₂ (PGE₂) on renin release and
intrarenal blood flow distribution were studied in dogs anesthetised with
pentobarbital. Plasma renin activity (PRA) was measured by radioimmunoas-
say. Intrarenal distribution of blood flow was determined by means of a
radioactive microsphere method.

Intrarenal arterial administration (IRA) of PGA₂ at a rate of 0.1 µg/min
caused an increase in renal blood flow (RBF) and a slight increase in urine
flow (UF) without any change of renal arterial pressure (RAP). Renal venous
PRA was slightly but significantly increased following PGA₂ infusion into the
renal artery (0.1 µg/min).

Doses of PGA₂ (0.5 µg/min, IRA) and PGE₂ (0.1 µg/min, IRA) had maxi-
imum effect on RBF without changing RAP. Both PGA₂ (0.5 µg/min, IRA)
and PGE₂ (0.1 µg/min, IRA) increased RBF, UF and urinary sodium and
potassium excretion, but did not influence on Glomerular filtration rate
(GFR).

PGA₂ (0.5 µg/min, IRA) increased significantly arterial and renal venous
PRA while, PGE₂ (0.1 µg/min, IRA) had no effect on arterial or renal venous
PRA.

Concerning the intrarenal distribution of blood flow, both PGA₂ (0.5 µg/
min, IRA) and PGE₂ (0.1 µg/min, IRA) resulted in an increased flow rate in
each cortical zone, but the zonal response pattern was not uniform and was
characterized by a progressively proportional increase in flow from the
superficial to the deep cortex. Thus, the percentage distribution was signifi-
cantly changed, showing a redistribution of blood flow from the superficial
cortex to the deep cortex.

Intravenous administration (IV) of 0.5 µg/min PGA₂ reduced blood pres-
sure by 15–20 mmHg but did not change RBF. UF showed a slight decrease
following PGA₂ infusion intravenously (0.5 µg/min, IV) and increased signifi-
cantly arterial and renal venous PRA. PGE₂ (0.5 µg/min, IV) caused a reduc-
tion in RAP by 10–15 mmHg. RBF and UF showed a small increase follow-
ing PGE₂ infusion intravenously (0.5 µg/min). Both arterial and renal venous
PRA were increased by intravenous administration of 0.5 µg/min PGE₂, but

Key Words:
Prostaglandin A₂ and E₂
Renin
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Renal blood flow
Glomerular filtration rate
Urine flow

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Dept. of Urology, Osaka City University Medical School, Osaka, Japan
*Dept. of Pharmacology, Osaka City University Medical School, Osaka, Japan

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the difference was not significant. The data suggested that both PGA₂ and PGE₂ have similar effects on renal hemodynamics and urine formation. It is likely that PGA₂ stimulates renin release but PGE₂ does not.

The kidney in addition to urine production controls blood pressure through some humoral factors.

Numerous studies show that the renin-angiotensin system elevates blood pressure while the antihypertensive effect of the kidney has been the subject of much discussion for a long time. In 1965 Lee et al. presented evidence that prostaglandin E₂ (PGE₂), and medullin later renamed PGA₂ present in the renal medulla have vaso depressor properties. PGs have been isolated from the renal medulla by many investigators and a prostaglandin-dehydrogenase has been found in the renal cortex.

The hypotensive action of PGA₂ and PGE₂ seems to be due to their direct action on the peripheral vasculature. In the kidney, PGA and PGE increase renal blood flow and solute and water excretion.

In addition to the presence of PGs in the renal medulla, increased levels of prostaglandin-like substances have been found in renal venous blood in response to a number of physiological stimuli such as renal nerve stimulation and renal ischemia and also administration of noradrenaline and angiotensins II.

Physiologically, there may be some correlation between renin and PGs, however, at present the effect of PGs on renin release is not certain.

The purpose of this investigation was to examine the effects of PGA₂ and PGE₂ on renal function and renin secretion as well as the effect on intrarenal distribution of blood flow which may correlate with the renal function.

METHODS

Mongrel dogs weighing 13–18 kg were anesthetized with intravenous pentobarbital sodium at a dose of 30 mg/kg and maintained by the administration of 30–50 mg as needed. The kidney was denervated by division of all visible nerve fibers and sharp dissection of tissue connected to the renal hilum proximal to the renal artery.

Renal blood flow (RBF) was measured by an electromagnetic flowmeter (Nihon-Koden MF-25) and zero flow was established by renal artery occlusion in situ. Flow calibration proved to be linearly reproducible and base-line drift was negligible. Renal arterial pressure was considered equal to the aortic pressure measured at the level of the renal artery. Systemic arterial blood was collected from the right brachial artery, and renal venous blood was collected via a catheter in the renal vein through the left splanchnic or ovarian vein. A No. 23-gauge needle was introduced into the left renal artery proximal to the flow probe for intra-arterial administration of PG and intra-venous administration of PG was performed through the left brachial vein. After surgical preparation was completed, a loading dose of creatinine, 100 mg/kg was given intravenously, followed by a maintenance dose of 50 mg/kg per hour.

GFR was measured by creatinine clearance. Sodium and potassium were measured with a flame photometer. Osmolality was measured by freezing-point depression (Fiske osmometer).

PRA was determined by radioimmunoassay of angiotensin I according to the technique described by Stockigt. All blood samples (5 ml with 5 mg EDTA) were centrifuged for 10 min at 4°C to obtain plasma.

Dimericarol and 8-hydroxyquinoline sulphate were added to inhibit the converting enzyme and angiotensinase during the incubation period (3 hours) while angiotensin was formed at 37°C. An automatic γ-counter (Toshiba, PDI-111/112) was used to determine radioactivity.

The values are given in nanograms of angiotensin I produced per 1 ml plasma per 37°C 3 hr. incubation time and expressed as ng/ml.

Distribution of cortical blood flow was determined with radioactive microspheres (3M Company, St. Paul, Minn. U.S.A.) by the technique described in a previous paper. Briefly, a suspension of 15-μm diameter plastic microspheres was injected into the left ventricle through a catheter introduced via the left carotid artery. It contained a 0.5 mg bead mass representing approximately 220,000 microspheres.

Sequential injections were performed using microspheres labeled with different gamma emitters.

The cortical zones were numbered sequentially from capsule to medulla. Total RBF, measured by a flowmeter, was equated with cortical
TABLE I EFFECTS OF PGA₂ (0.1 µg/min IRA) ON RENAL ARTERIAL PRESSURE, RENAL BLOOD FLOW, URINE FLOW AND PLASMA RENIN ACTIVITY. a (n=5)

<table>
<thead>
<tr>
<th></th>
<th>Renal Arterial Pressure mmHg</th>
<th>Renal Blood Flow ml/min</th>
<th>Urine Flow ml/min</th>
<th>Arterial PRA equivalent to angiotensin I ng/ml</th>
<th>Renal Venous PRA equivalent to angiotensin I ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>125±7.5</td>
<td>213.1±31.1</td>
<td>0.7±0.1</td>
<td>13.1±5.4</td>
<td>16.9±8.1</td>
</tr>
<tr>
<td>Control 2</td>
<td>124±7.6</td>
<td>213.0±30.8</td>
<td>0.7±0.1</td>
<td>13.5±6.3</td>
<td>17.2±9.0</td>
</tr>
<tr>
<td>PGA₂ (0.1 µg/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>121.6±6.4</td>
<td>258.4±39.4</td>
<td>2.0±0.5</td>
<td>20.7±7.8</td>
<td>27.3±9.2</td>
</tr>
<tr>
<td>20 min</td>
<td>121.6±6.5</td>
<td>266.9±37.7</td>
<td>2.2±0.4</td>
<td>22.5±8.2</td>
<td>22.1±8.0</td>
</tr>
<tr>
<td>30 min</td>
<td>120.6±6.5</td>
<td>261.7±34.9</td>
<td>2.0±0.4</td>
<td>22.8±8.4</td>
<td>24.0±8.5</td>
</tr>
<tr>
<td>40 min</td>
<td>120.0±6.5</td>
<td>260.2±35.9</td>
<td>1.9±0.4</td>
<td>25.4±9.4</td>
<td>25.6±11.0</td>
</tr>
<tr>
<td>50 min</td>
<td>119.0±6.7</td>
<td>256.3±34.9</td>
<td>1.9±0.4</td>
<td>26.0±11.9</td>
<td>27.4±11.9</td>
</tr>
<tr>
<td>Recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>120.0±6.5</td>
<td>224.3±29.7</td>
<td>0.9±0.2</td>
<td>22.7±10.8</td>
<td>23.3±11.6</td>
</tr>
<tr>
<td>20 min</td>
<td>122.0±7.1</td>
<td>217.6±32.0</td>
<td>0.9±0.2</td>
<td>24.0±12.7</td>
<td>24.5±12.8</td>
</tr>
<tr>
<td>30 min</td>
<td>119.0±6.4</td>
<td>209.7±33.4</td>
<td>0.9±0.2</td>
<td>22.1±12.3</td>
<td>23.7±12.1</td>
</tr>
</tbody>
</table>

a: All values except PRA are standardized to 100g of the kidney. Values are expressed as mean±standard error of the mean.
b: Significance from control analyzed by paired t test: p < 0.05
Abbreviations used are: n, number of animals; PRA, plasma renin activity; IRA, intrarenal arterial administration.

blood flow, since the renal medulla contained less than 1.3% of total renal counts. The volume of each cortex zone was approximated by calculations based on the formula for an ellipsoid. The volume of the individual cortex zones, expressed as percentages of total renal volume, were: zone 1, 27.0; zone 2, 21.9; zone 3, 17.3; zone 4, 12.2. After completion of the surgical procedures, 60 min were allowed during which the animals were constant in blood pressure (BP), RBF and urine flow (UF). The clearance period was 10 min, with arterial and renal venous bloods taken in the midpoint of each period. Control clearance (2 clearance period) were then performed after which PGA₂ or PGE₂ was infused continuously into the renal artery or brachial vein in doses of 0.1–0.5 µg/min for 40–60 min. Recovery clearances were performed for 30 min. The mean and SEM were calculated for all indices and the significance determined by Student's and paired t-test as appropriate.

RESULT

I) Preliminary experiment
In the present examination, doses of PGA₂ and PGE₂ which seemed to be the maximum effective ones on renal hemodynamics without any change of renal arterial pressure (RAP) were administered into the renal artery, and these effects on renin release and intrarenal distribution of blood flow were investigated. For this purpose, we performed a preliminary investigation to determine the intrarenal doses of PGs causing a significant change in renal hemodynamics without systemic changes. PGE₂, 0.5 µg/min into renal artery, lowered RAP by about 20 mmHg although RBF markedly increased during PGE₂ infusion. Infusion of 0.3 µg/min PGE₂ still reduced RAP slightly, but increased RBF similarly to 0.5 µg/min PGE₂.

0.1 µg/min of PGE₂ showed an increase in RBF which was the same as that of 0.3 µg/min PGE₂, without any change in systemic blood pressure. The effects of PGA₂ (0.7–0.8 µg/min) on RAP and RBF were almost same as those of PGE₂ (0.3–0.5 µg/min). 0.5 µg/min of PGA₂ increased RBF but had no effect on systemic BP. Therefore, the maximum effect of PGA₂ on RBF without change in systemic BP occurred at an infusion rate of 0.5 µg/min and that of PGE₂ occurred at a rate of 0.1 µg/min.

RBF was not further increased but RAP decreased much more at doses greater than 0.5
TABLE IIa. EFFECTS OF PGA₂ (0.5 μg/min IRA) ON RENAL FUNCTION, a [n=5]

<table>
<thead>
<tr>
<th></th>
<th>Renal Arterial Pressure mmHg</th>
<th>Renal Blood Flow ml/min</th>
<th>Glomerular Filtration Rate ml/min</th>
<th>Urine Flow ml/min</th>
<th>Urinary Sodium Excretion μEq/min</th>
<th>Urinary Potassium Excretion μEq/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>120.0±7.0</td>
<td>431.4± 65.4</td>
<td>96.2± 9.1</td>
<td>1.12±0.3</td>
<td>201.3±34.1</td>
<td>50.1± 7.6</td>
</tr>
<tr>
<td>Control 2</td>
<td>120.6±6.9</td>
<td>435.1± 65.2</td>
<td>105.4±11.9</td>
<td>1.42±0.3</td>
<td>247.2±31.1</td>
<td>53.7± 9.1</td>
</tr>
<tr>
<td>PGA₂ (0.5 μg/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>117.2±6.6</td>
<td>574.2± 88.7</td>
<td>101.6±13.0</td>
<td>2.92±0.6b</td>
<td>500.2±95.9b</td>
<td>87.0±11.6b</td>
</tr>
<tr>
<td>20 min</td>
<td>118.4±6.6</td>
<td>566.1± 83.6</td>
<td>108.7±12.7</td>
<td>2.62±0.6b</td>
<td>519.3±74.9b</td>
<td>88.4± 9.2b</td>
</tr>
<tr>
<td>30 min</td>
<td>119.2±6.1</td>
<td>564.2± 86.6</td>
<td>108.8±16.8</td>
<td>2.52±0.9b</td>
<td>429.9±81.3b</td>
<td>72.4±10.6b</td>
</tr>
<tr>
<td>40 min</td>
<td>118.4±6.5</td>
<td>600.5± 78.1</td>
<td>87.9±12.4</td>
<td>2.42±0.6b</td>
<td>490.7±109.9b</td>
<td>75.9±19.3b</td>
</tr>
<tr>
<td>Recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>121.8±6.2</td>
<td>500.5± 80.2</td>
<td>78.2± 5.8</td>
<td>1.42±0.2</td>
<td>299.6±36.9</td>
<td>57.6± 8.6</td>
</tr>
<tr>
<td>20 min</td>
<td>123.0±7.6</td>
<td>481.5±102.6</td>
<td>105.9± 6.1</td>
<td>1.42±0.1</td>
<td>329.3±39.7</td>
<td>61.3± 9.1</td>
</tr>
<tr>
<td>30 min</td>
<td>121.8±6.4</td>
<td>469.7± 98.6</td>
<td>94.8± 8.7</td>
<td>1.42±0.2</td>
<td>346.5±46.6</td>
<td>64.5± 6.9</td>
</tr>
</tbody>
</table>

a: All values are standardized to 100g of the kidney. Values are expressed as mean±standard error of the mean.
b: Significance from control analyzed by paired t test: p < 0.05
Abbreviations used are: n, number of animals; IRA, intrarenal arterial administration.

TABLE IIb. EFFECTS OF PGA₂ (0.5 μg/min IRA) ON PLASMA RENIN ACTIVITY, a [n=5]

<table>
<thead>
<tr>
<th></th>
<th>Arterial PRA equivalent to angiotensin I ng/ml</th>
<th>Renal Venous PRA equivalent to angiotensin I ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>7.9± 3.6</td>
<td>10.5± 5.0</td>
</tr>
<tr>
<td>Control 2</td>
<td>6.9± 2.4</td>
<td>9.8± 3.8</td>
</tr>
<tr>
<td>PGA₂ (0.5 μg/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>14.2± 4.5b</td>
<td>21.0±10.2b</td>
</tr>
<tr>
<td>20 min</td>
<td>21.8±10.1b</td>
<td>27.4±14.4b</td>
</tr>
<tr>
<td>30 min</td>
<td>22.0± 9.5b</td>
<td>32.7±15.5b</td>
</tr>
<tr>
<td>40 min</td>
<td>24.7± 9.2b</td>
<td>26.3±10.7b</td>
</tr>
<tr>
<td>Recovery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>16.0± 9.1</td>
<td>16.9± 9.6</td>
</tr>
<tr>
<td>20 min</td>
<td>10.7± 6.8</td>
<td>13.3± 8.5</td>
</tr>
<tr>
<td>30 min</td>
<td>10.5± 6.1</td>
<td>13.9± 9.4</td>
</tr>
</tbody>
</table>

a: Values are expressed as mean±standard error of the mean.
b: Significance from control analyzed by paired t test: p < 0.01
Abbreviations used are: n, number of animals; IRA, intrarenal arterial administration; PRA, plasma renin activity.

μg/min PGA₂ and 0.1 μg/min PGE₂. Terragno et al.²¹ reported that PGE₂ has a fivefold larger renal vasodilator potency than PGA₂. Accordingly, we chose 0.5 μg/min of PGA₂ and 0.1 μg/min of PGE₂ as the maximum doses for local action on the kidney.

(II) Effects of intrarenal arterial administration of 0.1 μg/min PGA₂ on renal function and PRA.

The data are summarized in Table I. The n value refers to the number of dogs utilized for examination. PGA₂ caused an increase in RBF by about 20% (p < 0.05) without any change in RAP. UF showed a significant increase (p < 0.05) in the periods 20, 30 and 40 min after PGA₂ infusion.

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Renal venous PRA increased significantly (p < 0.05) at 20 and 30 min after infusion of PGA₂ from control. Arterial PRA also increased significantly at 20, 30 and 40 min after PGA₂ infusion.

Both renal venous and arterial PRA were still higher than controls 30 min after stopping the infusion, but the difference was not significant.

(III) Effects of intrarenal arterial administration of 0.5 µg/min PGA₂ and 0.1 µg/min PGE₂ on renal function and PRA.

The data are summarized in Table IIa, IIb, IIIa and IIIb.

RAP was slightly reduced by PGA₂, but recovered immediately after stopping the infusion. Infusion of PGE₂ had no effect on RAP. RBF was increased by about 30% by PGA₂ (p < 0.05) and 44% by PGE₂ (p < 0.01) during infusion but soon recovered, after case of infusion. In spite of increased RBF, both PGA₂ and PGE₂ had no influence on GFR. PGA₂ induced an average 2.5 fold increase in UF (p < 0.05), a 2 fold increase in sodium excretion (p < 0.05) and a 1.7 fold increase in potassium excretion (p < 0.05). PGE₂ had a similar effect i.e., a 3 fold increase in UF (p < 0.05), 5.5 fold increase in sodium excretion (p < 0.05) and a 1.9 fold increase in potassium excretion (p < 0.05).

Osmolar clearance (Cosm) also increased but there was no change in free water reabsorption (T¹H₂O). Within 30 min of stopping the influ-

(IV) Effects of intravenous administration of 0.5 µg/min PGA₂ and PGE₂ on RAP, RBF, UF and PRA.

The data are summarized in Table IV, V.

RAP decreased significantly (p < 0.05) by 15–20 mmHg during PGA₂ infusion but RBF showed no change. UF decreased slightly during PGA₂ infusion and this was statistically significant at 20 min after starting the infusion and returning to control levels within 30 min. Both arterial PRA and renal venous PRA increased significantly (p < 0.01) following PGA₂ infusion. Arterial PRA was still high (p < 0.01) at 10 and 20 min in the recovery period, and renal venous PRA also showed a high level at 10 min, returning to the control level within 30 min. PGE₂ infusion also decreased RAP significantly (p < 0.01) by 10–15 mmHg. Both RBF and UF showed a slight increase following PGE₂ infusion but this was not significant.

During PGE₂ infusion, arterial PRA increased but not significantly. Renal venous PRA also increased during PGE₂ infusion and showed (a statistically) significant increase (p < 0.05) at 10 min, returning to the control level within 30 min.

(V) Effects of intrarenal arterial administration of 0.5 µg/min PGA₂ and 0.1 µg/min PGE₂ on intrarenal distribution of blood flow.

Effects of PGA₂ and PGE₂ on the flow rates of each cortex zone are presented in Table VI and Fig. 1.

In control conditions, tissue flow rates varied depending on the characteristic pattern described in previous publications, i.e., the flow rate of zone 2 exceeds that of zone 1, and there was a progressive decrease in the perfusion rate from zone 2 to zone 4. Both PGA₂ (0.5 µg/min) and PGE₂ (0.1 µg/min) resulted in a significant increase in total RBF and flow rate in all zones without any change of RAP.

The zonal response pattern was not uniform, but was characterized by a progressively proportional increase in flow from the superficial to the deep cortex. Percent distribution of total RBF in each zone at control and PGA₂, PGE₂ in-

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Table:

<table>
<thead>
<tr>
<th>Osmolar Clearance</th>
<th>Free Water Reabsorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>ml/min</td>
<td>ml/min</td>
</tr>
<tr>
<td>2.9±0.15</td>
<td>1.6±0.41</td>
</tr>
<tr>
<td>3.2±0.31</td>
<td>1.8±0.38</td>
</tr>
<tr>
<td>5.35±0.92b</td>
<td>2.41±0.49</td>
</tr>
<tr>
<td>5.82±0.90b</td>
<td>2.81±0.72</td>
</tr>
<tr>
<td>4.6±0.71b</td>
<td>2.1±0.44</td>
</tr>
<tr>
<td>5.66±1.37b</td>
<td>3.2±0.76</td>
</tr>
<tr>
<td>3.39±0.41</td>
<td>2.0±0.34</td>
</tr>
<tr>
<td>3.82±0.37</td>
<td>2.43±0.27</td>
</tr>
<tr>
<td>3.85±0.48</td>
<td>2.4±0.30</td>
</tr>
</tbody>
</table>

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TABLE IIIa. EFFECTS OF PGE₂ (0.1 µg/min IRA) ON RENAL FUNCTION.ᵃ (n=5)

<table>
<thead>
<tr>
<th>Arterial</th>
<th>Renal</th>
<th>Glomerular</th>
<th>Urinary</th>
<th>Urinary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure</td>
<td>Blood</td>
<td>Filtration</td>
<td>Flow</td>
<td>Sodium</td>
</tr>
<tr>
<td>mmHg</td>
<td>Flow</td>
<td>Rate</td>
<td>ml/min</td>
<td>µEq/min</td>
</tr>
<tr>
<td></td>
<td>ml/min</td>
<td>ml/min</td>
<td>µEq/min</td>
<td>µEq/min</td>
</tr>
</tbody>
</table>

Control 1  
123.0±6.4  
258.3±61.0  
58.7±9.7  
0.9±0.2  
156.3±58.1  
27.1±4.4

Control 2  
122.7±6.2  
289.9±68.1  
62.2±12.9  
1.1±0.3  
179.8±73.1  
36.4±8.3

PGE₂ (0.1 µg/min)  
10 min  
120.7±5.6  
413.3±58.8  
50.9±19.8  
2.3±0.7ᵇ  
298.5±125.2ᵇ  
45.9±4.0ᵇ

20 min  
116.7±4.8  
401.5±61.5ᶜ  
56.2±12.2  
3.3±0.8ᵇ  
490.7±150.3ᶜ  
58.4±7.0ᶜ

30 min  
120.0±5.0  
388.8±58.3ᶜ  
57.1±13.2  
3.6±1.0ᵇ  
529.7±185.7ᵇ  
52.8±7.5ᵇ

40 min  
120.5±5.1  
378.1±62.1ᶜ  
48.2±10.1  
3.3±0.7ᵇ  
503.4±145.3ᵇ  
53.4±6.2ᶜ

50 min  
116.7±4.4  
364.7±68.2ᶜ  
54.5±10.2  
3.1±0.7ᵇ  
493.1±146.1ᵇ  
53.5±5.2ᶜ

Recovery  
10 min  
115.4±4.2  
268.0±55.0  
47.3±9.2  
1.7±0.3ᵇ  
283.9±77.9ᵇ  
40.5±4.2

20 min  
116.1±4.3  
257.5±54.1  
54.8±10.6  
1.3±0.2  
214.6±56.6  
37.6±4.6

30 min  
116.0±4.3  
260.2±53.9  
54.3±10.7  
1.2±0.2  
202.6±52.1  
40.6±5.5

ᵃ: All values are standardized to 100g of the kidney. Values are expressed as mean±standard error of the mean.
b: Significance from control analyzed by paired t test: p < 0.05
c: Significance from control analyzed by paired t test: p < 0.01
Abbreviations used are: n, number of animals; IRA, intrarenal arterial administration.

TABLE IIIb. EFFECTS OF PGE₂ (0.1 µg/min IRA) ON PLASMA RENIN ACTIVITY.ᵃ (n=5)

<table>
<thead>
<tr>
<th>Arterial PRA</th>
<th>Renal Venous PRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>equivalent to angiotensin I</td>
<td>equivalent to angiotensin I</td>
</tr>
<tr>
<td>ng/ml</td>
<td>ng/ml</td>
</tr>
</tbody>
</table>

Control 1  
26.3±8.8  
23.8±2.2

Control 2  
22.3±7.0  
27.9±5.5

PGE₂ (0.1 µg/min)  
10 min  
26.5±5.7  
29.0±3.8

20 min  
26.0±7.5  
29.5±3.8

30 min  
25.3±7.6  
30.1±6.9

40 min  
17.6±4.6  
22.9±5.2

50 min  
22.1±6.0  
29.8±9.5

Recovery  
10 min  
18.2±5.9  
21.2±7.2

20 min  
19.6±6.9  
26.4±8.6

30 min  
13.9±5.2  
18.7±7.0

ᵃ: All values are expressed as mean±standard error of the mean.
Abbreviations used are: n, number of animals; IRA, intrarenal arterial administration;
PRA, plasma renin activity.

sion is presented in Fig. 1. This mode of expression incorporates the volume of each zone and the tissue flow rate. Both PGA₂ and PGE₂ resulted in a redistribution of cortical flow; i.e., a significant decrease in the percent of total flow in zone 1 and a significant increase (in percent of total RBF) in zone 2, 3 and 4.

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(I) Effects on renal hemodynamics

Intrarenal arterial administration of 0.5 μg/min PGA₂ and 0.1 μg/min PGE₂ caused an increase in RBF without any change of blood pressure, and there was no qualitative difference between the effects of PGA₂ and PGE₂. The increase of RBF during infusion of 0.5 μg/min PGA₂ and 0.1 μg/min PGE₂ were similar, and this observation is in agreement with an earlier study by Terragno et al.21 in which PGE₂ had a fivefold increase in renal vasodilator potency over PGA₂. It has been shown that the vasodilator action of PGA and PGE was not blocked by autonomic blocking agents such as atropine, propranolol and methysergide, and also antihistamines. Therefore it has been suggested that they act directly on peripheral blood vessels.7,8

The maintenance of GFR despite the increase in RBF suggests that the renal vasodilator effect of PGA₂ and PGE₂ is on the efferent rather than the afferent artery, or possibly they lower postglomerular resistance. This action is qualitatively identical with that of other vasodilators, such as acetylcholine 24, 25 and dopamine 26.

In regard to the effects of PG₂ on intrarenal distribution of blood, Johnston et al.9 and Martinez-Maldonado et al.10 have reported

### TABLE IV EFFECTS OF PGA₂ (0.5 μg/min IV) ON RENAL ARTERIAL PRESSURE, RENAL BLOOD FLOW, URINE FLOW AND PLASMA RENIN ACTIVITY, (n=5)

<table>
<thead>
<tr>
<th></th>
<th>Renal Arterial Pressure mmHg</th>
<th>Renal Blood Flow ml/min</th>
<th>Urine Flow ml/min</th>
<th>Arterial PRA equivalent to angiotensin I ng/ml</th>
<th>Renal Venous PRA equivalent to angiotensin I ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>117.5±5.1</td>
<td>360.8±65.8</td>
<td>1.1±0.2</td>
<td>20.8±6.2</td>
<td>25.1±9.7</td>
</tr>
<tr>
<td>Control 2</td>
<td>116.6±5.4</td>
<td>371.3±70.2</td>
<td>1.3±0.3</td>
<td>21.1±7.3</td>
<td>24.5±7.1</td>
</tr>
<tr>
<td>PGA₂ (0.5 μg/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>100.2±8.0²</td>
<td>398.8±70.6</td>
<td>0.9±0.2</td>
<td>45.6±14.3</td>
<td>64.8±20.4</td>
</tr>
<tr>
<td>20 min</td>
<td>96.6±7.2²</td>
<td>393.3±72.2</td>
<td>0.7±0.2²</td>
<td>48.5±15.8</td>
<td>66.6±21.1</td>
</tr>
<tr>
<td>30 min</td>
<td>98.0±7.2²</td>
<td>387.8±74.5</td>
<td>0.9±0.2</td>
<td>44.2±11.2</td>
<td>64.3±23.0</td>
</tr>
<tr>
<td>40 min</td>
<td>98.2±6.8²</td>
<td>381.1±77.5</td>
<td>0.9±0.2</td>
<td>46.0±13.2</td>
<td>48.4±13.3</td>
</tr>
<tr>
<td>50 min</td>
<td>98.0±6.0²</td>
<td>373.7±78.5</td>
<td>0.9±0.2</td>
<td>48.0±15.1</td>
<td>48.8±11.5</td>
</tr>
<tr>
<td>Recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>106.6±6.0</td>
<td>340.4±80.3</td>
<td>0.8±0.2²</td>
<td>31.6±6.3</td>
<td>35.4±7.9²</td>
</tr>
<tr>
<td>20 min</td>
<td>111.2±5.6</td>
<td>335.8±72.9</td>
<td>0.9±0.2</td>
<td>27.0±6.9</td>
<td>29.2±6.9</td>
</tr>
<tr>
<td>30 min</td>
<td>112.0±5.4</td>
<td>320.5±62.1</td>
<td>0.9±0.2</td>
<td>21.6±5.6</td>
<td>27.9±7.0</td>
</tr>
</tbody>
</table>

a: All values except PRA are standardized to 100g of the kidney. Values are expressed as means ± standard error of the mean.
b: Significance from control analyzed by paired t test: p < 0.05
c: Significance from control analyzed by paired t test: p < 0.01

Abbreviations used: n, number of animals; IV, intravenous administration; PRA, plasma renin activity.

Japanese Circulation Journal Vol. 42, August 1978
that PGE₂ increased renal plasma flow and this was associated with a decreased extraction ratio of PAH, suggesting that noncortical blood flow was increased. Since this method is based upon the biological transportation of PAH in the renal tubules, there is some disagreement with mechanical phenomena such as the blood flow. Carriere et al. have reported that the increase of RBF, measured by means of an inert gas washout method, following PGE₁ infusion occurred uniformly in the renal cortex. However, the results must be to carefully considered, because the method is not morphologically proven.

In our investigation, intrarenal distribution of blood flow was determined by means of the radioactive microsphere method which provides the most direct information of the currently available techniques. Both intrarenal arterial administration of 0.5 μg/min PGA₂ and 0.1 μg/min PGE₂ resulted in a significant increase in total RBF and flow rate in all zones.

The zonal response pattern was not uniform, but was characterized by a progressively proportional increase in flow from the superficial to the deep cortex. This finding agrees with a study by Chang et al.²⁹.

*Japanese Circulation Journal Vol. 42, August 1978*
The precursor of PGE$_2$, arachidonic acid, also increased RBF especially in the region corresponding to the juxtamedullary cortex, and indomethacin, the inhibitor of PGs synthetase, decreased the ratio of juxtamedullary to superficial cortical blood flow.$^{30}$ Other investigators have pointed out that indomethacin or meclofenamate reduced RBF, especially the inner cortex, and abolished the efflux of PG like material in the renal vein.$^{31,32}$ These findings provide evidence for a role of endogenous PGs as intrarenal regulators of inner cortical and medullary blood flow. Accordingly, the exogenous PGs on the increase of RBF and on the renal circulation are consistent with the effects of endogenous PGs.

(II) Natriuretic effects

The results of the present study demonstrated the natriuretic effects of intrarenal arterial administration of PGA$_2$ and PGE$_2$, which were accompanied by an increase in RBF independent of changes in GFR. The increase sodium excretion, without a significant change in GFR or plasma sodium, must represent inhibition of tubular reabsorption. Johnston et al.$^{10}$ and Gross and Bartter$^{12}$ have reported that the effect of PGE$_1$ on natriuresis may be mediated either by a reduction in peritubular oncotic pressure or by an increase in hydrostatic pressure in the peritubular capillaries with an attendant increase of RBF. However, Martinez-Maldonado et al.$^9$ have suggested that in vivo PGE depressed collecting duct permeability to water. In vitro, it has been shown that PGE$_1$ blocks vasopressin-induced transport of water across the toad bladder and the isolated rabbit collecting tubule.$^{33,34}$ Therefore a direct tubular action of PG cannot be excluded.

In the present study, intrarenal arterial administration of PGA$_2$ and PGE$_2$ resulted in a progressive increase in flow from the superficial to the deep cortex. It is considered that this increase in juxtamedullary blood flow with an attendant increase in medullary blood flow increased medullary washout in the counter current exchange system. Consequently the osmotic gradient of tubular fluid in the medulla was lowered and the concentration of urine was reduced indicating the possibility of natriuresis. Martinez-Maldonado et al.$^9$ have observed that PGE$_1$ lowered papillary tissue nonurea solute concentration. In the present study, the decrease in urinary osmolality was noticed at the occurrence of natriuresis. Our findings suggest that the natriuretic effects of PGA$_2$ and PGE$_2$ are mainly due to a hydrodynamic effect follow-
ing increase in RBF and the increase of medullary wash out in the counter current exchange system following redistribution on RBF.

(III) Effects on renin release

The reports concerning the correlation between PGs and renin are few. In 1967 Vander\textsuperscript{13} reported that PGE produced no detectable effect on renin release in dogs. Werning et al\textsuperscript{35} have reported that higher doses of PGE\textsubscript{1} increased renin secretion and they thought that the elimination of sodium and water by natriuretic effects of PGE\textsubscript{1} caused an increase in renin secretion. In 1974 Larsson et al\textsuperscript{36} reported that arachidonic acid increased PRA, and that conversely inhibition of PG-biosynthesis with indomethacin led to a decrease in PRA. In recent studies in man, intravenous infusion of PGA\textsubscript{1}\textsuperscript{37,38} or PGE\textsubscript{1}\textsuperscript{39} was associated with reduction in blood pressure and diuresis, but concerning a change of PRA the results were not clear. In our study, the intrarenal arterial administration of PGA\textsubscript{2} and PGE\textsubscript{2} showed qualitatively the same effect on renal hemodynamics and urine formation, but there was different effect on renin release between PGA\textsubscript{2} and PGE\textsubscript{2}, i.e., PGA\textsubscript{2} increased both arterial and renal venous PRA but PGE\textsubscript{2} had no effect. Renin release from juxtaglomerular cell (JGC) is controlled by changes in renal circulation, plasma sodium balance and the load of sodium to the macula densa and sympathetic nervous system.

Our findings demonstrated that there was no qualitative difference on the renal circulation between intrarenal arterial administration of PGA\textsubscript{2} and PGE\textsubscript{2}. Further, since PGE\textsubscript{2} has a stronger vasodilator potency than PGA\textsubscript{2}, if renin was released by changes in the renal circulation, PGE\textsubscript{2} should increased renin release. Therefore the increase of PRA following PGA\textsubscript{2} infusion was not explained by changes in the renal circulation. However, intravenous administration of 0.5 μg/min PGA\textsubscript{2} increased both arterial and renal venous PRA significantly and was accompanied by a fall in renal arterial pressure of about 15–20 mmHg. Intravenous administration of 0.5 μg/min PGE\textsubscript{2} also reduced renal arterial pressure about 10–15 mmHg with an attendant increase in arterial and renal venous PRA, but this was not significant.

Recently Abe et al\textsuperscript{24} have reported that renin secretion increased following a small reduction in renal arterial pressure when the renal vasculature was dilated to the physiological maximum by acetylcholine.

In the investigation of Werning et al\textsuperscript{35} the increase in renin release was accompanied by a marked increase in RBF associated with a reduction in blood pressure of about 20 mmHg, so there is a possibility that renin release is due to a reduction in renal perfusion pressure accompanied by dilation of the renal vasculature. However, it was considered that renin was not released by a direct effect of PGE\textsubscript{1}.

Though it has been shown that the changes in plasma sodium concentration control renin release\textsuperscript{41} in the present study, PGA\textsubscript{2} and PGE\textsubscript{2} had no influence on plasma sodium and plasma potassium.

Vander and Carlson\textsuperscript{42} and Nash et al\textsuperscript{43} have proposed that renin release is controlled by the rate of sodium transport across the macula densa into the interstitium, the so-called macula densa theory.

Our results demonstrated that the effects of PGA\textsubscript{2} and PGE\textsubscript{2} infused into renal artery on the urine formation were qualitatively identical. Further, it has been shown that the diuretic effects of PGs are qualitatively same as the effect of acetylcholine.

The effects on renal circulation are similar and acetylcholine did not increase renin release\textsuperscript{24} Therefore, the stimulation of renin release with PGA\textsubscript{2} was not explained by merely the natriuretic and renal vasodilatative effects of PGA\textsubscript{2}.

The sympathetic nervous system\textsuperscript{44–47} particularly the β-adrenergic mechanism\textsuperscript{48–51} probably controls renin secretion. In the present study, since all kidneys were denervated and the intrarenal arterial administration of PGA\textsubscript{2} had no influence on the systemic circulation, it was not considered that the sympathetic nervous was stimulated following PGA\textsubscript{2} infusion and PG suppressed norepinephrine release\textsuperscript{52}

Therefore, sympathetic neural stimulation of renin release with PGA\textsubscript{2} is not likely.

Recently it has been shown that cyclic-AMP (C-AMP) stimulates renin release\textsuperscript{53–56} and PGs may increase or decrease the production of C-AMP in various tissues.

Fichman et al\textsuperscript{38} reported that PGA\textsubscript{1} increased the excretion of C-AMP in urine, which suggested that PGA\textsubscript{1} increased the production of C-AMP in the kidney. PGA\textsubscript{2} may increase C-AMP production in the renal cortex and stimulate renin release. PGE\textsubscript{2} may also increase C-AMP production in the renal cortex and therefore it is unknown whether PGA increases the production of C-AMP specifically compared with PGE. We
did not measure the urinary C-AMP concentration in this study, so the effect of PGA2 on the renin release mediated by C-AMP was not examined. Larsson et al.30,36 have reported that intrarenal arterial administration of arachidonic acid increased renal venous PRA associated with an increase in RBF. These effects were blocked by indomethacin which suggested that endogenous PG stimulated renin release.

However, an increase of PGA synthesis was not confirmed in our experiment. Our findings suggested that PGA2 caused an increase in renin release possibly through its direct action on the juxtaglomerular cell but PGE2 had no effect on renin release.

REFERENCES