Effect of Sodium Balance on Arterial Blood Pressure and Renal Responses to Prostaglandin A, in Man

By Lawrence R. Krakoff, Daisy De Guia, Nicholas Vlachakis, Jennie Stricker, and Marvin Goldstein

ABSTRACT

The effect of sodium balance on systemic arterial blood pressure and the renal response to intravenous infusion of prostaglandin A₁ (PGA₁) was studied in hypertensive subjects. PGA₁ (0.4 μg/kg min⁻¹) was infused for 1 hour in ten hypertensive subjects who were receiving a constant diet containing 40 mEq of sodium and 80 mEq of potassium. During PGA₁ infusion a significant fall in both systolic and diastolic arterial blood pressure occurred. There was a significant rise in urine flow rate, renal plasma flow, and urine sodium excretion; plasma renin activity (PRA) rose slightly but not significantly. Eight of the ten subjects and one additional subject were then placed on furosemide (80 mg/day) for 1 week. In all subjects, a significant weight loss and a rise in midday PRA occurred with the administration of the diuretic. Systolic blood pressure fell, but diastolic pressure was unchanged. Following salt depletion with furosemide, PGA₁ infusion studies were repeated. PGA₁ then produced no significant change in systolic or diastolic blood pressure. Urine flow, renal plasma flow, and urine sodium excretion rose, but the degree of increase was markedly less than that observed prior to furosemide administration. In the salt-depleted subjects, a significant rise in PRA occurred during PGA₁ infusion. The results indicate that volume depletion diminishes the systemic and renal hemodynamic response to infused PGA₁ but enhances the PRA response. The increased PRA response during PGA₁ infusion observed in salt-depleted subjects might in part account for the blunted hemodynamic changes. Alternatively, recent evidence indicates that the enhanced production of endogenous vasodilating prostaglandins which occurs in the salt-depleted state might account for the diminished hemodynamic responses to exogenous PGA₁.

KEY WORDS plasma renin activity sodium excretion potassium excretion renal plasma flow vasodilator glomerular filtration rate furosemide

Several prostaglandins are potent vasoactive substances in man. The principal hemodynamic alterations that occur with the infusion of either prostaglandin E₁ (PGE₁) or prostaglandin A₁ (PGA₁) are (a) renal vasodilation resulting in increased renal blood flow without significant change in filtration rate, (b) reduction in systemic vascular resistance resulting in lowered arterial blood pressure, and (c) compensatory increase in cardiac rate and stroke volume leading to increased cardiac output (1–4). Increased renal blood flow alone occurs at low doses of the prostaglandins and is accompanied by diuresis and natriuresis (3–5). It has been suggested (6) that natriuresis caused by prostaglandins is due solely to their vascular action; thus, they act like other renal vasodilators.

The profound effects of the prostaglandins on sodium excretion and renal perfusion suggest a possible interaction with the renin-angiotensin system. However, prior studies of the effect of prostaglandins on renin secretion have not revealed a uniform pattern. Direct infusion of PGE₁ and PGE₂ into the canine renal artery in concentrations sufficient to cause natriuresis and increased renal plasma flow without a change in systemic arterial blood pressure do not significantly alter renin secretion (7). When much larger doses of PGE₁ are infused into the aorta above the kidneys in dogs, increased plasma renin activity accompanied...
by natriuresis and decreased arterial blood pressure without a significant alteration in renal plasma flow has been observed (8). PGA\textsubscript{i} infusion in either normal human subjects or subjects with high blood pressure has produced variable and inconsistent alterations in plasma renin activity as assessed by bioassay techniques (1, 3, 4).

Sodium and extracellular fluid volume metabolism are unquestionably important determinants of renal function and renin secretion by the kidney. The studies reported in this paper were designed, therefore, to assess the role of sodium balance in modifying the effect of PGA\textsubscript{i} on urine flow, sodium and potassium excretion, glomerular filtration rate, renal plasma flow, and renin secretion.

**Methods**

Eleven hypertensive patients were admitted to the Clinical Research Center, Mount Sinai Hospital, 2 weeks after all antihypertensive medication had been discontinued, and informed consent was obtained. On admission the patients were placed on constant diets containing 40 mEq of sodium and 80 mEq of potassium. Arterial blood pressure in the supine and standing position was recorded twice daily and body weight was recorded each morning. A 24-hour urine sample for analysis of sodium, potassium, and creatinine was collected daily. Appropriate diagnostic studies including serum electrolytes, rapid sequence intravenous pyelography, and urine catecholamine metabolite determinations revealed no evidence of secondary hypertension in any patient.

After 5 days on the constant diet, plasma renin activity (PRA) was determined with specimens obtained at midday after 3 hours of ambulation. The next day patients remained supine in bed after awakening, and breakfast was withheld. Renal clearance studies were then carried out in the hydrated state for determination of urine flow, glomerular filtration rate (measured by inulin clearance), renal plasma flow (measured by para-aminohippuric acid [PAH] clearance), sodium excretion, and potassium excretion. After two to three control periods, a control specimen for determination of PRA was obtained. Then PGA\textsubscript{i} (0.4 \( \mu \text{g/kg min}^{-1} \)) was infused intravenously with a constant-infusion peristaltic pump (Sigma motor) for 60 minutes. Seven additional PGA\textsubscript{i} infusion studies were carried out in hypertensive subjects who were receiving varying sodium intakes.

**Analytical Methods**

Sodium and potassium were determined by flame photometry (Instrumentation Labs). Inulin and PAH were measured colorimetrically, and clearances were calculated by standard methods (9). PRA was assessed by radioimmunoassay of angiotensin I generated during complete inhibition of plasma angiotensinase and converting enzyme (10).

**Results**

**Effect of PGA\textsubscript{i} Infusion on Arterial Blood Pressure and Renal Function in Subjects on Constant Diet.**—The effect of PGA\textsubscript{i} infusion on ten subjects studied on the constant diet is shown in Table 1. In eight of ten subjects, systolic arterial blood pressure fell more than 10 mm Hg and diastolic arterial blood pressure fell 5 mm Hg or more during PGA\textsubscript{i} infusion. Urine flow rose in all subjects. The glomerular filtration rate rose by 10 ml/min in six of ten subjects and fell in only one subject; in the other subjects, glomerular filtration rate was not significantly altered. Renal plasma flow rose in all but one subject. Although urine sodium excretion rose during PGA\textsubscript{i} infusion in all subjects, the degree of rise was quite variable as the increase in sodium excretion due to PGA\textsubscript{i} varied from 52 to 618 \( \mu \text{Eq/min} \). Urine potassium excretion rose during PGA\textsubscript{i} infusion in nine of ten subjects; however, the degree of increase in potassium excretion was also highly variable.

**Effect of Furosemide on Body Weight, Arterial Blood Pressure and Midday Plasma Renin Activity.**—Following the period of constant diet nine subjects were placed on furosemide (80 mg/day) for 6 days. Table 2 shows the body weight, the arterial blood pressure in the supine and standing positions, and the midday upright PRA values in subjects on the constant diet before and after 6 days of furosemide therapy. All subjects showed a weight loss varying from 0.7 to 2.5 kg. Arterial blood pressure fell more when the subjects were in the standing position than when they were in the supine position. PRA uniformly rose. Table 2 also shows the statistical comparisons for the changes in weight, arterial blood pressure, and PRA due to furosemide. There was a significant fall in weight and systolic blood pressure in both the supine and the standing position. Diastolic arterial blood

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1Kindly supplied by Dr. Natoo Patel of the Upjohn Company, Kalamazoo, Michigan.
TABLE 1

Effect of PGA Infusion in Subjects on Constant Diet

<table>
<thead>
<tr>
<th>Systemic arterial blood pressure (mm Hg)</th>
<th>Urine flow rate (ml/min)</th>
<th>Glomerular filtration rate (ml/min)</th>
<th>Renal plasma flow (ml/min)</th>
<th>Urine sodium excretion rate (mEq/min)</th>
<th>Urine potassium excretion rate (mEq/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>PGA1</td>
<td>Control</td>
<td>PGA1</td>
<td>Control</td>
<td>PGA1</td>
</tr>
<tr>
<td>1 186/110</td>
<td>137/94</td>
<td>8.2</td>
<td>14.4</td>
<td>75</td>
<td>95</td>
</tr>
<tr>
<td>2 160/100</td>
<td>153/90</td>
<td>3.3</td>
<td>9.3</td>
<td>85</td>
<td>102</td>
</tr>
<tr>
<td>3 132/90</td>
<td>124/81</td>
<td>1.5</td>
<td>3.3</td>
<td>97</td>
<td>146</td>
</tr>
<tr>
<td>4 168/108</td>
<td>145/95</td>
<td>8.0</td>
<td>15.0</td>
<td>96</td>
<td>98</td>
</tr>
<tr>
<td>5 182/110</td>
<td>180/108</td>
<td>12.0</td>
<td>20.0</td>
<td>83</td>
<td>88</td>
</tr>
<tr>
<td>6 140/100</td>
<td>130/95</td>
<td>8.6</td>
<td>11.4</td>
<td>148</td>
<td>118</td>
</tr>
<tr>
<td>7 210/140</td>
<td>197/135</td>
<td>14.0</td>
<td>18.6</td>
<td>112</td>
<td>136</td>
</tr>
<tr>
<td>8 215/126</td>
<td>200/130</td>
<td>9.0</td>
<td>20.5</td>
<td>85</td>
<td>91</td>
</tr>
<tr>
<td>9 205/133</td>
<td>180/114</td>
<td>8.1</td>
<td>16.6</td>
<td>86</td>
<td>111</td>
</tr>
<tr>
<td>10 180/108</td>
<td>162/100</td>
<td>6.2</td>
<td>16.7</td>
<td>103</td>
<td>160</td>
</tr>
</tbody>
</table>

Mean ± SE 175 ± 9/113 ± 5 161 ± 9/104 ± 6 8.6 ± 1.2 14.5 ± 1.7 97 ± 7 115 ± 8 360 ± 36 535 ± 62 142 ± 20 435 ± 76 68 ± 7 98 ± 9

PGA1 was infused at a rate of 0.4 µg/kg min⁻¹ for 60 minutes.

TABLE 2

Body Weight, Arterial Blood Pressure, and Plasma Renin Activity before and after Furosemide-Induced Salt Depletion

<table>
<thead>
<tr>
<th>Control diet</th>
<th>Furosemide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>Arterial blood pressure (mm Hg)</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Supine</td>
<td>Standing</td>
</tr>
<tr>
<td>2</td>
<td>81.6</td>
</tr>
<tr>
<td>3</td>
<td>68.1</td>
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<tr>
<td>4</td>
<td>54.6</td>
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<tr>
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<tr>
<td>9</td>
<td>99.4</td>
</tr>
<tr>
<td>10</td>
<td>106.0</td>
</tr>
</tbody>
</table>

Mean ± SE 78.1 ± 5.5 190 ± 9/109 ± 6 156 ± 9/104 ± 5 1.2 ± 0.4 76.3 ± 5.4 153 ± 8/101 ± 7 187 ± 11/84 ± 8 6.4 ± 1.4

Change from control -1.8 ± 0.3* -16 ± 5/7 = 4 19 ± 6/10 = 7 5.3 ± 1.2*

Samples for determination of PRA were drawn at midday after 3 hours of ambulation. The fall in blood pressure with furosemide was statistically significant only for the systolic pressure.

*P < 0.005.
†P < 0.05.
Effect of PGA\textsubscript{i} Infusion on Arterial Blood Pressure and Renal Function after the Administration of Furosemide.—The effect of PGA\textsubscript{i} infusion on subjects treated with furosemide is shown in Table 3. PGA\textsubscript{i} infusion reduced systolic arterial blood pressure more than 10 mm Hg in only two subjects. Similarly, only two of nine subjects had a fall in diastolic arterial blood pressure of 5 mm Hg or more during PGA\textsubscript{i} infusion. Urine flow rose in all subjects during PGA\textsubscript{i} infusion. However, glomerular filtration rate showed little change. PGA\textsubscript{i} infusion caused a rise in renal plasma flow in all subjects in which it was determined. Urine sodium excretion also rose during PGA\textsubscript{i} infusion in all subjects studied, but the degree of rise was again highly variable. Urine potassium excretion rose in five of nine subjects during PGA\textsubscript{i} infusion and fell in three subjects.

Effect of PGA\textsubscript{i} Infusion on Plasma Renin Activity.—The level of PRA before and after PGA\textsubscript{i} infusion in subjects on the constant diet and in subjects after salt depletion due to furosemide is shown in Figure 1. In subjects on the constant diet, PRA rose during PGA\textsubscript{i} infusion only when control PRA was greater than 0.5 ng/ml hour\textsuperscript{-1}. Following furosemide administration, all subjects showed a significant rise in PRA during PGA\textsubscript{i} infusion. The relationship between the increase in PRA due to PGA\textsubscript{i} and the control level of PRA is shown in Figure 2 which includes all 19 studies of subjects on the constant diet before and after furosemide treatment and 7 additional studies of subjects ingesting diets of varying sodium content. The regression equation and the statistical analysis indicate a highly significant direct correlation between the control PRA and the increase in PRA due to PGA\textsubscript{i} infusion.

Comparison of PGA\textsubscript{i} Infusion in Subjects before and after Salt Depletion with Furosemide.—The contrasting effects of PGA\textsubscript{i} infusion on arterial blood pressure, renal function, and PRA in subjects ingesting the constant diet and after furosemide-induced salt depletion are shown in Table 4. It is apparent that PGA\textsubscript{i} had a more profound hypotensive effect in subjects studied on the constant diet than it did in subjects studied after salt depletion. The increases in urine flow and renal plasma flow during PGA\textsubscript{i} infusion were significantly greater in subjects studied on the constant diet than it was in
subjects studied after furosemide administration. The mean increase in urine sodium excretion due to PGA was 53% higher in subjects studied on the constant diet than it was in subjects studied after furosemide administration. However, the difference between these increases in sodium excretion was not statistically significant. The change in potassium excretion due to PGA infusion did not appear substantially different in the two groups.

PGA infusion did not produce a significant mean change in PRA in the subjects studied on the constant diet alone. In contrast, furosemide-treated subjects demonstrated a uniform, significant increase in PRA during PGA infusion.

**Discussion**

In the present study the arterial blood pressure and the renal responses to PGA infusion at a relatively low dose (0.4 μg/kg min⁻¹) were evaluated in hypertensive subjects during two states of sodium balance. Initially, the effect of PGA was studied in subjects maintained on a constant diet of moderately low sodium intake (40 mEq/day). On this regimen PGA infusion caused a small but highly significant reduction in arterial blood pressure that agreed with the results of Lee et al. (11).
Urine flow, renal plasma flow, and sodium and potassium excretion were uniformly increased. PRA rose with PGA1 only in those subjects who tended to have higher control PRA levels. However, in those subjects with lower control PRA levels (<0.5 ng/ml hour⁻¹) PGA1 infusion had little effect on PRA.

Following sodium depletion with furosemide, PGA1 infusion had no significant effect on arterial blood pressure. Although urine flow, sodium excretion, and renal plasma flow rose with PGA1 infusion, the degree of increase in these measurements was less than that observed prior to furosemide administration. These data suggest that induced extracellular fluid volume depletion reduces the vasodilatory response to exogenously administered PGA1. The consistent rise in PRA observed in furosemide-treated subjects during PGA1 infusion may partly account for the preservation of arterial blood pressure and the smaller increase in renal plasma flow. This finding is in agreement with recent studies indicating the importance of the renin-angiotensin system in the maintenance of arterial blood pressure in sodium-depleted dogs (12).

The increase in PRA produced by PGA1 was approximately 110% above the control PRA as indicated by the slope of the regression line in Figure 2. This finding suggests that PGA1 caused an increase in renal renin secretion, since in similar subjects renal venous renin activity averaged only 30% above peripheral PRA levels (13).

Current theories on the control of renin release have emphasized either the macula densa of the distal renal tubule, a renal vascular receptor, or direct adrenergic mechanisms (14–17). In the present investigation PGA1 produced a significant increase in PRA in the salt-depleted subjects in association with a modest natriuresis and a rise in renal plasma flow but caused no change in arterial blood pressure. It seems unlikely that the increased urine sodium excretion rate could account for the rise in PRA, since the natriuresis of prostaglandins is best related to decreased proximal tubular reabsorption of salt and water resulting in enhancement of distal tubular, i.e., macula densa, sodium supply (6, 7, 18). This mechanism has been compared with saline infusion (6) which, like dietary salt loading, lowers PRA (19, 20).

The rise in PRA that was produced by PGA1 in the furosemide-treated subjects was accompanied by renal vasodilation and increased renal blood flow without a fall in perfusion pressure. Recent studies emphasize that the renal vascular receptor mechanism for control of renin release depends on a fall in renal perfusion pressure and is mediated by renal vasodilatation (21, 22).

It is possible that the rise in PRA observed during PGA1 infusion was mediated through a baroreceptor adrenergic mechanism independent of renal vasodilatation (16, 17, 22). If an adrenergic mechanism accounted for the increase in PRA accompanying PGA1 infusion in these studies, variable effects on PRA might be expected from higher doses of PGA1 which might inhibit release of the sympathetic neurotransmitter (23).

In one report it has been suggested that PGE1 might have a direct renin-releasing effect in dogs. However, large doses of the lipid were used in this study producing hypotension and tachycardia (8). Direct infusion of PGE1 or PGE2 in the canine renal artery in doses insufficient to cause systemic hemodynamic effects produced no effect on renin secretion (7). Other renal vasodilators, papaverine or acetylcholine, have no direct effect on renin secretion when they are infused into the renal artery (22, 24).

Prostaglandins PGA2, PGE2, and PGF2α have been identified in extracts of the renal medulla from several species (25, 26). A substance with PGE1-like activity has been detected in canine renal venous blood (27). The concentration of this substance in renal venous blood appears to increase after infusion of angiotensin II or norepinephrine into the renal artery (28). It has been observed in these experiments that the increase in PGE2 activity in renal venous blood is concurrent with the recovery of renal blood flow toward control levels despite continued infusion of vasoconstrictors. The participation of these prostaglandins in control of intrarenal circulation has been suggested. Recent studies indicate that prostaglandins of the A series are detectable in human plasma and may be increased in salt-depleted normal subjects (29). All of these observations indicate that in the salt-depleted state there might be increased production of the vasodilating prostaglandins mediated by enhanced action of the renin-angiotensin system. Elevated concentrations of endogenous prostaglandins of the E and A series might then blunt any further vasodilation by infused PGA1 on the basis of simple dose-response relationships. Although this mechanism might explain the diminished hemodynamic responses to PGA1 infusion observed in salt-depleted subjects, it does not account for the marked rise in PRA that occurred.
SODIUM BALANCE AND PROSTAGLANDIN A\(_1\)

Whether the vasoactive prostaglandins function as circulating hormones or only as local mediators remains unclear. The changes in the arterial blood pressure and renal response to PGA\(_1\) produced by diuretic-induced volume depletion which we have observed indicates that sodium and fluid balance may be important determinants of the cardiovascular action of these vasoactive lipids.

**Acknowledgment**

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**References**


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