Role of the Renin-Angiotensin System in Prostaglandin E₂-Induced Hypertension

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SUMMARY The effects of chronic (8 days) intrarenal prostaglandin E₂ (PGE₂) infusion on arterial pressure and renal function were assessed using unilaterally nephrectomized dogs maintained on a fixed sodium intake of 55 mEq/day. During 5 days of continuous intrarenal PGE₂ infusion (2 μg/min) alone, both urine output and water intake increased markedly, and urine osmolality fell. Despite nearly a 9-fold increase in both plasma aldosterone concentration and plasma renin activity, daily sodium excretion exceeded intake values an average of 10–15 mEq/day, and plasma sodium concentration tended to fall. Concomitantly, arterial pressure increased from 104 ± 3 to 113 ± 2 mm Hg (p < 0.05) on Day 5. Infusion of saralasin (40 min) transiently lowered pressure from 112 ± 6 to 91 ± 7 mm Hg. PGE₂ was infused in combination with SQ 14,225 for 3 additional days, resulting in a fall in arterial pressure to a steady-state value of 82 ± 1 mm Hg. Concomitant with the fall in pressure, water and electrolyte excretion decreased during SQ 14,225 + PGE₂ infusion but, nonetheless, remained above control levels. In another group of dogs, continuous (6 days) intravenous infusion of prostaglandin F₂α, at 25 μg/min, had relatively moderate effects on water and electrolyte excretion and did not alter arterial pressure. Thus, it is unlikely that intrarenal conversion of PGE₂ to PGF₂α, with subsequent release into the systemic circulation, contributed to the PGE₂-induced pressure rise. We conclude that chronic intrarenal PGE₂ infusion results in mild hypertension, which is dependent upon the renin-angiotensin system, and is associated with polyuria, polydipsia, and moderate natriuresis. (Hypertension 2: 529–537, 1980)

KEY WORDS • prostaglandin E₂ • sodium and water balance • plasma renin activity • arterial pressure • angiotensin blockade • prostaglandin F₂α

We HAVE recently demonstrated that chronic (8 days) intrarenal prostaglandin E₂ (PGE₂) infusion resulted in a 3-fold increase in urine output and moderate sodium loss. Despite a sustained diuresis and natriuresis, mean arterial pressure (MAP) increased 10–15 mm Hg, which was associated with a concomitant, 10-fold rise in plasma renin activity (PRA). The high degree of correlation (r = 0.96; p < 0.001) between the rise in PRA and MAP suggested that the mild hypertension observed during intrarenal PGE₂ infusion was causally related to the concurrent increase in PRA.

Another mechanism, however, independent of the renin-angiotensin system, may have been operative during intrarenal PGE₂ infusion and have contributed to the observed increase in MAP. The enzyme PGE₂-9-ketoreductase has been isolated from renal tissue of most species studied and catalyzes the conversion of PGE₂ to prostaglandin F₂α. In contrast to PGE₂-induced vasodilation, PGF₂α has been shown to be vasoressor when administered intravenously in both conscious and anesthetized dogs. Although the specific mechanism involved in the pressor activity of PGF₂α remains unclear, it is possible that intrarenal conversion of PGE₂ to PGF₂α, with subsequent release into the systemic circulation, may account for the hypertensive response to intrarenal PGE₂ infusion.

Our present study was therefore designed to examine the role of the renin-angiotensin system and the possible contribution of PGF₂α in the arterial pressure response to chronic intrarenal PGE₂ infusion. Two groups of unilaterally nephrectomized dogs were used in this study. In the first group, involvement of the renin-angiotensin system to the pressure rise observed with PGE₂ infusion was assessed by either inhibiting the formation of angiotensin II (AII) with SQ 14,225 or by blocking the effects of AII with saralasin. After the arterial pressure response to intrarenal PGE₂ infusion had reached a plateau, the AII competitive antagonist, saralasin, was infused acutely. In addition, the effects of continuous intravenous infusion of the angiotensin I converting enzyme inhibitor, SQ 14,225, on renal function, PRA, and MAP were examined during the last 3 days of an 8-day intrarenal PGE₂ in-
fusion period. In a second group of dogs, the hypotension that intrarenal conversion of PGE₂ to PGF₂α may have contributed to the pressure rise observed during PGE₂ infusion was examined. In this group, the effects of chronic (6 days) intravenous PGF₂α infusion on renal function, PRA, and MAP were assessed.

Methods
Experiments were performed on 12 mongrel dogs (20.0 ± 0.9 kg), which were equally divided into two groups.

Group 1
Two weeks prior to experimental procedures, chronic indwelling catheters were implanted into the aorta and vena cava via the right femoral artery and vein and tunneled subcutaneously to the nape of the neck. A chronic indwelling silastic catheter was implanted into the urinary bladder and exteriorized through the abdominal wall. The left kidney was exposed using a retroperitoneal flank approach, and a polyvinyl catheter was inserted into the left renal artery and exteriorized at the neck. To eliminate any compensatory interactions by the contralateral kidney, the right kidney was removed. Prior to continuous intrarenal infusion, the renal artery catheter was maintained patent by flushing daily with isotonic saline and filling the catheter with heparin (1,000 U/ml). The femoral catheters were similarly flushed twice weekly.

During the 2-week convalescent period, the animals were housed in metabolic cages and conditioned to daily handling. The dogs were then fitted with a backpack, which housed a Statham pressure transducer, positioned at heart level, as previously described. During this time and subsequent experimental periods, the daily diet consisted of two 15-oz cans of dog food which provided < 5 mEq sodium and 40-50 mEq potassium (h/d Prescription Diet, Riviana Foods, Inc.) Water was provided ad libitum.

Daily sodium intake was fixed at approximately 55 mEq/day by the continuous intrarenal and intravenous infusion of sterile isotonic saline. The intravenous infusion of 310 ml saline/day (48 mEq sodium) was accomplished using a continuous Sage roller pump (Model 375A). An additional 48 ml saline/day (7 mEq sodium) were infused directly into the renal artery using a Harvard (Model 935) infusion pump. A disposable Cathivex Millipore filter was connected in series with the renal infusion line to minimize passage of bacteria and contaminants. Sodium and water balance was monitored daily. Throughout the entire experiment, MAP was recorded continuously 24 hours/day from the femoral artery catheter with a Grass polygraph (Model 7D) and a Statham pressure transducer. Body temperature was measured periodically, and ampicillin was given (250 mg/orally, twice daily) to minimize infection.

Group 2
This group of animals, which were to receive an intravenous infusion of PGF₂α, was handled in an identical fashion as the dogs in Group 1 with the following exceptions. Following a right-sided nephrectomy, a sham exposure of the left kidney was performed. In addition, daily sodium intake was fixed at 55 mEq/day by the continuous intravenous infusion of isotonic saline using both the Harvard and Sage infusion pumps.

In all experiments, both PGE₂ and PGF₂α were dissolved in 95% ethanol and stored at 4°C. This served as a stock solution from which an aliquot was then diluted with normal saline and added to the infusion syringe twice daily.

Experimental Protocol
Group 1
Following the establishment of electrolyte and water balance, a 3-day control period was observed. Intrarenal PGE₂ infusion was then begun at a rate of 2 μg/min and continued for 8 days. During the last 3 days of intrarenal infusion, a continuous intravenous infusion of SO 14,225 (an angiotensin I converting enzyme inhibitor) was administered at 14 μg/kg/min. Infusions of PGE₂ and SQ 14,225 were then terminated, and the dogs were observed for 4-5 days. In addition, after the arterial pressure response to intrarenal PGE₂ infusion had reached a plateau, we assessed the effect on arterial pressure of an acute (40 min) infusion of the angiotensin II competitive antagonist, saralasin, at 6 μg/kg/min.

Group 2
After sodium balance had been achieved, a 3-day control period was observed. Intravenous PGF₂α infusion was then begun at 25 μg/min and continued for 6 days. The infusion was then terminated, and a 4-day recovery period followed. Glomerular filtration rate (GFR) was determined on 2 days of the control period, Days 2 and 4 of the intravenous PGF₂α infusion period, and on at least 2 days during recovery.

In both groups of animals, blood samples were drawn between 8:00 and 10:00 a.m. during the control, experimental, and recovery periods for the measurement of PRA, plasma aldosterone concentration (PAC), plasma sodium concentration, and hematocrit. Water intake, independent of infused volumes, was measured daily. In addition, the acute changes in the urine flow, sodium excretion, and MAP were examined for 4 hours following both the initiation and termination of both PGE₂ and PGF₂α infusions.

Analytical Methods
Arterial blood was collected in iced sodium-EDTA vacutainer tubes for PRA determination using a radioimmunoassay procedure for angiotensin I (New England Nuclear). Samples were similarly collected in
lithium-heparin vacutainer tubes for PAC determination using a radioimmunoassay procedure (Diagnostic Products 125I aldosterone kit). Plasma and urinary electrolyte concentrations were determined by flame photometry (Instrumentation Laboratory, Inc., IL 343), and total urinary and plasma osmolality was measured by freezing-point depression using an Advanced Instruments osmometer (Model 3R).

The GFR was estimated by the clearance of sodium [125I] iothalamate (Glofil 125, Abbott Laboratories). Plasma and urinary concentrations of iothalamate were determined by gamma emission in Searle (Series 1185) counter. Each daily value recorded for GFR represents the average of three consecutive 20-minute clearance periods. Hematocrit was measured by the micromethod. The daily 24-hour pressure record was analyzed by averaging steady-state MAP values at the end of each hour over the entire 24-hour recording period.

All values presented represent the mean ± the standard error of the mean (SEM). Statistical analyses included Student's t test for paired and unpaired observations, which were applied to determine the significance (p < 0.05) of changes from control values during the experimental periods.

Results

Effect of PGE2 and SQ 14,225 Infusion on Urine Volume and Water Intake

The sequential changes in urine output, water intake, and urine osmolality during intrarenal PGE2 infusion are depicted in figure 1. Both urine output and water intake increased markedly, nearly 4- and 7-fold, respectively, in association with a 70% reduction in urine osmolality.

Infusion of SQ 14,225 reversed this trend, although urine output and water intake remained significantly greater than initial control values. Urine osmolality was unaltered during SQ 14,225 infusion.

Upon termination of PGE2 and SQ 14,225 infusions, complete normalization did not occur since water intake and urine output remained greater than initial control values and urine osmolality was depressed.

Effect of PGE2 and SQ 14,225 Infusion on Sodium Balance and PAC

As evident in figure 2, daily sodium excretion was increased from 56.3 ± 2.0 mEq/day to an average 71.7 ± 3.8 mEq/day during intrarenal PGE2 infusion. Thus, sodium excretion exceeded daily intake by approximately 15 mEq/day, resulting in negative sodium balance. Concomitantly, plasma sodium concentration tended to fall. Intrarenal PGE2 infusion also resulted in a significant rise in PAC. From a control average of 7.5 ± 1.8 ng/dl, PAC increased to a plateau of 55.5 ± 7.8 ng/dl.

Although plasma sodium concentration was unchanged during SQ 14,225 infusion, sodium excretion returned to control values during the first 2 days of converting enzyme inhibition. Sodium excretion then increased to 89.6 ± 5.5 mEq/day, a value that exceeded sodium excretion rates observed during intrarenal PGE2 infusion alone. PAC returned to control values during SQ 14,225 infusion.

Following the termination of PGE2 and SQ 14,225 infusion, plasma sodium and aldosterone concentrations, as well as daily sodium excretion, were no different than control values.
Effect of PGE₂ and SQ 14,225 Infusion on MAP and PRA

As illustrated in figure 3, MAP increased gradually during intrarenal PGE₂ infusion. From an average control value of 104 ± 3 mm Hg, MAP increased to 108 ± 5 mm Hg during the first 24 hours and continued to increase, reaching a maximum of 113 ± 2 mm Hg on Day 5. Concurrently, PRA increased from 0.5 ± 0.1 ngAI/ml/hr during control to 4.4 ± 1.4 ngAI/ml/hr on Day 4, nearly a 9-fold increase.

Continuous SQ 14,225 administration was characterized by a precipitous fall in MAP to a steady value of 82 ± 1 mm Hg, while PRA continued to increase. Upon termination of PGE₂ and SQ 14,225 infusion, both MAP and PRA approached initial control values, although the latter remained significantly elevated above pre-infusion values, averaging 0.9 ± 0.1 ngAI/ml/hr on Day 12.

Figure 4 summarizes the results of an acute 40-minute infusion of saralasin in five of the dogs described above. After the arterial pressure response to intrarenal PGE₂ infusion had reached a plateau (Days 3-5) and MAP had increased from 103 ± 4 to 112 ± 6 mm Hg, the analog inhibitor of AII decreased MAP significantly to 91 ± 7 mm Hg.

Transient Effects of PGE₂ Infusion

The immediate effects observed during the first 4 hours of both the onset and termination of intrarenal PGE₂ (and SQ 14,225) infusion are summarized in table 1. Urine flow increased from 0.33 ± 0.04 ml/min to 1.34 ± 0.16 ml/min during the first hour and continued to increase reaching a maximum of 1.89 ± 0.35 ml/min during the fourth hour. Sodium excretion showed a similar trend increasing from 42.5 ± 5.5 to 176.7 ± 18.5 µEq/min during the first 60 minutes and continued to increase, reaching 203.4 ± 20.7 µEq/min during the fourth hour. The MAP was unchanged during this time.

Upon cessation of intrarenal PGE₂ and intravenous SQ 14,225 infusion, minute urine flow fell initially but then increased from 0.99 ± 0.20 ml/min during control to a maximum of 1.28 ± 0.25 ml/min during the

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Control†</th>
<th>60 min</th>
<th>120 min</th>
<th>180 min</th>
<th>240 min</th>
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<tbody>
<tr>
<td>( \dot{V}_u )</td>
<td>0.33 ± 0.04</td>
<td>1.34 ± 0.16§</td>
<td>1.27 ± 0.22§</td>
<td>1.56 ± 0.30§</td>
<td>1.89 ± 0.35§</td>
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<td>( E_{Na} )</td>
<td>42.5 ± 5.5</td>
<td>176.7 ± 18.5§</td>
<td>147.5 ± 16.9§</td>
<td>175.0 ± 25.5§</td>
<td>203.4 ± 20.7§</td>
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<tr>
<td>MAP</td>
<td>105 ± 3</td>
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<td>105 ± 4</td>
<td>104 ± 4</td>
<td>108 ± 5</td>
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Terminate PGE₂ and SQ 14,225 infusion

<table>
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<th>Variable*</th>
<th>Control†</th>
<th>60 min</th>
<th>120 min</th>
<th>180 min</th>
<th>240 min</th>
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<tr>
<td>( \dot{V}_u )</td>
<td>0.99 ± 0.2</td>
<td>0.88 ± 0.36</td>
<td>1.06 ± 0.28</td>
<td>1.24 ± 0.27</td>
<td>1.28 ± 0.25§</td>
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<tr>
<td>( E_{Na} )</td>
<td>67.5 ± 9.9</td>
<td>53.7 ± 26.3</td>
<td>67.2 ± 22.2</td>
<td>83.0 ± 16.8</td>
<td>81.5 ± 14.8</td>
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<tr>
<td>MAP</td>
<td>83 ± 3</td>
<td>83 ± 2</td>
<td>83 ± 2</td>
<td>82 ± 2</td>
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</tr>
</tbody>
</table>

*Abbreviations are as follows: \( \dot{V}_u \) = minute urine flow (ml/min); \( E_{Na} \) = sodium excretion (µEq/min). MAP = mean arterial pressure (mm Hg).

†\( n = 4 \).

‡Control values for \( \dot{V}_u \) and \( E_{Na} \) represent the average of two consecutive 20-minute clearance periods.

§p < 0.05.
fourth hour. A similar trend in sodium excretion was observed. That is, sodium excretion decreased initially and then increased from 67.5 ± 9.9 μEq/min during control to 81.5 ± 14.8 μEq/min during the fourth hour. The MAP was unchanged upon cessation of PGE and SQ 14,225 infusion.

Effect of PGF on Urine Output and Water Intake

Effects of chronic intravenous PGF infusion on urine volume, water intake, GFR, and urine osmolality are summarized in figure 5. Both urine output and water intake tended to increase, but not significantly, during the first 2-3 days of PGF infusion and then declined toward initial control values. The GFR and urine osmolality were unaltered during PGF administration.

When the infusion was terminated on Day 6, there was a significant reduction in urine output to 272 ± 56 ml/day when compared to the initial control average of 719 ± 184 ml/day. Urine output then increased and was no different than control for the remainder of the recovery period. Water intake, GFR, and total urine osmolality were unchanged upon termination of PGF infusion.

Effect of PGF on Sodium Balance

As depicted in figure 6, plasma sodium concentration was unaltered during PGF infusion. However, a biphasic response in daily sodium excretion was noted. From a control average of 54.8 ± 4.9 mEq/day, sodium excretion increased to 83.8 ± 8.0 mEq/day on Day one. Sodium excretion then decreased and was equal to or below daily intake during the last 4 days of the infusion period. Thus, following an initial sodium loss, the animals tended to retain sodium.

Following cessation of PGF infusion, sodium excretion fell markedly to 13.4 ± 1.8 mEq/day, after which restitution of sodium balance was achieved. Plasma sodium concentration was unaltered during the recovery period.

Effect of PGF on MAP, PAC, and PRA

The effects of intravenous PGF infusion on MAP, PAC, and PRA are summarized in figure 7. As illustrated, MAP was unaltered during PGF infusion, averaging 109 ± 4 mm Hg during control and 111 ± 2 mm Hg throughout the 6-day infusion period. However, PAC increased significantly from a control value of 5.2 ± 0.6 to 15.3 ± 4.2 ng/dl on Day two. Concurrently, PRA increased, but not significantly, from 0.6 ± 0.1 to 1.2 ± 0.3 ngAl/ml/hr. The PAC and PRA then declined to initial control values for the remainder of the infusion period and subsequent recovery period.

Transient Effects of PGF Administration

The acute effects of both the onset and cessation of intravenous PGF infusion on urine flow, sodium excretion, and MAP are summarized in table 2. As indicated, urine flow increased immediately from a control average of 0.52 ± 0.20 ml/min to a maximum of 1.47 ± 0.38 ml/min during the second hour. Concurrently, sodium excretion increased significantly from 49.8 ± 8.0 to 143.1 ± 10.5 μEq/min during the third hour. The MAP was unaltered during the first 4 hours of PGF infusion.

Upon termination of PGF infusion, urine flow decreased abruptly from 0.58 ± 0.11 to 0.29 ± 0.06 ml/min for the first 4 hours after infusion. Similarly, sodium excretion fell from 59.4 ± 8.0 to 25.4 ± 7.2 μEq/min during the first hour and continued to

Figure 5. Effects of continuous PGF infusion on urine output, water intake, glomerular filtration rate, and urine osmolality.

Figure 6. Effects of chronic PGF infusion on plasma sodium concentration and daily sodium excretion.
TABLE 2. Transient Effects of Both the Onset and Termination of Intravenous PGFαα Infusion at 25 μg/min in Six Dogs

<table>
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<tr>
<th>Variable*</th>
<th>Begin PGFαα infusion †</th>
<th>Control†</th>
<th>60 min</th>
<th>120 min</th>
<th>180 min</th>
<th>240 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vu</td>
<td>0.52 ± 0.20</td>
<td>1.39 ± 0.30†</td>
<td>1.47 ± 0.28†</td>
<td>1.42 ± 0.28†</td>
<td>1.18 ± 0.16†</td>
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<tr>
<td>ENa</td>
<td>49.8 ± 8.0</td>
<td>136.0 ± 16.8†</td>
<td>109.2 ± 21.8†</td>
<td>143.1 ± 10.5†</td>
<td>128.8 ± 13.3†</td>
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</tr>
<tr>
<td>MAP</td>
<td>109 ± 5</td>
<td>110 ± 6</td>
<td>112 ± 6</td>
<td>115 ± 6</td>
<td>116 ± 6</td>
<td></td>
</tr>
<tr>
<td>Terminate PGFαα infusion ‡</td>
<td>0.58 ± 0.11</td>
<td>0.29 ± 0.06</td>
<td>0.29 ± 0.02†</td>
<td>0.31 ± 0.07</td>
<td>0.29 ± 0.06†</td>
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</tr>
<tr>
<td>ENa</td>
<td>59.4 ± 8.0</td>
<td>25.4 ± 7.2†</td>
<td>18.6 ± 6.7†</td>
<td>14.0 ± 4.8†</td>
<td>13.5 ± 6.1†</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>109 ± 4</td>
<td>108 ± 5</td>
<td>105 ± 7</td>
<td>106 ± 8</td>
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</table>

*For abbreviations, see table 1.
†Control values for Vu and ENa represent the averages of 2 consecutive twenty-minute clearance periods.
‡p < 0.05.

decline, averaging 13.5 ± 6.1 μEq/min during the fourth hour. The MAP was unchanged by the cessation of PGFαα infusion.

In both groups of animals plasma osmolality, body weight, and hematocrit remained relatively unchanged throughout the experimental period.

Discussion

We have previously demonstrated that, contrary to an anticipated BP-lowering effect, chronic intrarenal PGE2 infusion results in mild hypertension.1 Although the concomitant increase in PRA suggested that the rise in MAP was causally related to the augmentation in PRA, the role of the renin-angiotensin system in the arterial pressure response to intrarenal PGE2 administration has not been previously examined.

Effect of PGE2 and SQ 14,225 on MAP and PRA

Although MAP remained unaltered during the first 4 hours of intrarenal PGE2 infusion, as observed in many short-term studies, it gradually rose, and by the fourth day of infusion MAP was elevated nearly 10 mm Hg. Our present study strongly indicates that the rise in arterial pressure was indeed a consequence of enhanced renin secretion. In support of this conclusion, PRA was increased nearly 9-fold, and the acute administration of saralasin, a competitive antagonist of AI, resulted in an abrupt fall in MAP of 21 mm Hg. Additionally, during continuous SQ 14,225 infusion, MAP fell from 113 ± 2 mm Hg to a steady-state level of 82 ± 1 mm Hg. Thus, administration of two dissimilar blockers of the renin-angiotensin system produced a significant fall in arterial pressure during intrarenal PGE2 infusion. The mechanism by which PGE2 enhances renin secretion is unclear. Previous studies suggest that the renin response is not entirely a result of sodium loss and contraction of the extracellular fluid volume, since intrarenal PGE2 infusion results in an immediate increase in PRA.

The marked fall in arterial pressure observed during SQ 14,225 infusion suggests that blockade of the renin-angiotensin system may have unmasked the BP-lowering potential of PGE2. However, it is uncertain that PGE2 can independently lower arterial pressure since the fall in arterial pressure during SQ 14,225 infusion was no different than that observed by others during converting enzyme inhibition alone. Harris et al.10 have recently demonstrated that oral administration of SQ 14,225 reduced arterial pressure 20% from a control value of 107 ± 2 mm Hg using conscious dogs with similar resting PRA values. Additionally, the data of Hall et al.11 would predict an arterial pressure reduction to approximately 80 mm Hg during chronic SQ 14,225 infusion using intact conscious dogs on a sodium intake of 50 mEq/day. Therefore, it is likely that the fall in arterial pressure can be explained by angiotensin blockade per se without the additional need of postulating an antihypertensive role for PGE2.

In 1966 Erdos and Yang12 demonstrated that the angiotensin I converting enzyme (kininase II) is also...
involved in the enzymatic degradation of two potent vasodepressor peptides, bradykinin and kallidin. Thus, it is possible that the hypotensive action of SQ 14,225 results not from decreased All levels but rather increased levels of circulating kinins. However, Vinci and associates have recently reported that plasma bradykinin levels were not altered during converting enzyme inhibition in both sodium replete and deplete human subjects, which is in agreement with previously published reports in man and conscious dogs. Also, Sen et al. have recently reported normalization of arterial pressure during converting enzyme inhibition in two-kidney Goldblatt hypertensive rats that had been pretreated with Trasylol, a kallikrein inactivator.

Nevertheless, conflicting reports have appeared. Williams and Hollenberg reported an increase in plasma bradykinin levels following converting enzyme inhibition. In addition, Swartz et al. have suggested that the hypotensive action of converting enzyme inhibition involves more than blockade of All formation. Clearly, additional studies are needed before the role of bradykinin in the BP-lowering response to converting enzyme inhibition is fully elucidated.

The greater fall in MAP during SQ 14,225 infusion as compared to short-term saralasin administration (31 vs 21 mm Hg respectively) was most likely a result of baroreceptor activation. The acute fall in pressure observed with saralasin would be expected to illicit a baroreceptor reflex response which, in turn, would obviate the BP-lowering effect of saralasin. During chronic administration of SQ 14,225, however, the arterial baroreceptors would be expected to adapt to lower pressures as arterial pressure gradually fell, allowing MAP to fall to a new level independent of the renin-angiotensin system.

Effect of PGF and SQ 14,225 on Water Balance

Intrarenal PGF infusion resulted in an immediate diuresis (table 1) in which water excretion was elevated proportionately greater than electrolyte excretion, since urine osmolality fell markedly (fig. 1). The observed diuresis was sustained throughout the PGF infusion period and was associated with an increase in plasma aldosterone and All levels and the degree of sodium loss. The return of PAC to control levels after cessation of PGF infusion continued. Nevertheless, daily sodium excretion continued to increase accompanied by a significant and sustained increase in All levels and aldosterone, both of which have sodium-retaining effects. This suggests that PGF was buffering the sodium-retaining hypertensive effects of All. Converting enzyme inhibition resulted in a reduction in sodium excretion to control levels, which was likely related to the fall in arterial pressure. However, sodium excretion increased on the third day of SQ 14,225 infusion to a level that exceeded that of intrarenal PGF infusion alone. Reasons for the changes in sodium excretion during this time appear to be the result of complex interactions occurring simultaneously, such as dramatic fall in renal perfusion pressure, decreased plasma levels of All and aldosterone, unmasking of the effects of PGF and/or its metabolites, and the possible nonspecific intrarenal effects of SQ 14,225 itself.

The marked increase in PAC during intrarenal PGF infusion was not unexpected in light of the observed increases in plasma All levels and the degree of sodium loss. The return of PAC to control levels during converting enzyme inhibition indicates a primary role for the renin-angiotensin system in sustaining elevated levels of plasma aldosterone during PGF infusion.

Effect of Intravenous PGF, Infusion

Dunn et al. have recently reported secretory rates for PGF, (PGF and PGF) using a variety of stimuli in the dog. The most potent stimulus for PGF synthesis was intrarenal bradykinin infusion, which resulted in an excretion rate of 505 pg PGF/g kidney/min. Based on an average kidney weight of 50g, this represents a secretion rate of 25 ng PGF/g/min. Thus, the intravenous infusion of 25 pg PGF/min in our present study greatly exceeded the renal secretory potential for PGF and should only exaggerate the effect of endogenous renal release of PGF on arterial pressure.

It is unlikely that intrarenal conversion of PGF to PGF, with subsequent release into the general circulation, contributed to the pressor response observed during chronic intrarenal PGF infusion, since intravenous PGF infusion did not alter arterial pressure either transiently (table 2) or chronically.
In contrast, Nakano and Cole reported a vasopressor response to an intravenous bolus injection of 8-10 µg PGF$_{2a}$/kg using anesthetized dogs. Anesthesia alone cannot account for the differences between the present and previous studies, however, since DuCharme et al. reported a pressor response to a similar intravenous bolus injection of PGF$_{2a}$ in conscious dogs. Alternatively, differences in doses and means of administration (bolus versus continuous infusion) of PGF$_{2a}$ may account for the observed discrepancies between the present and previous reports.

Intravenous PGF$_{2a}$ infusion resulted in an immediate diuresis and natriuresis (table 2). Although these responses were not sustained throughout the infusion period, urine output, water intake, and sodium excretion were elevated during Days 1-3 before returning to pre-infusion values. Daily sodium excretion actually fell below the daily intake level, which may have been associated with the concomitant rise in PRA and PAC. Upon cessation of PGF$_{2a}$ infusion, there was an immediate decrease in urine flow and sodium excretion, which was sustained during the first 24 hours of the recovery period. These changes may have resulted from the direct or indirect effects of PGF$_{2a}$ on renal function. Although PGF$_{2a}$ has been reported to be effectively cleared from the circulation during a single passage of the pulmonary circulation, it may be argued that, if pulmonary extraction is less than 100% or the degradative capacity of the lung was curtailed during continued infusion, an increase in arterial PGF$_{2a}$ concentration may have resulted, leading to a direct intrarenal response. Alternatively, the intrarenal conversion of PGF$_{2a}$ to PGE$_{2}$ may account for the PGE$_{2}$-like response to intravenous PGF$_{2a}$ infusion on the renal excretion of water and electrolytes. Indirect renal effects of PGF$_{2a}$ could have also resulted from changes in venomotor tone and alterations in cardiac output, changes in the activity of the central nervous system, or alterations in reflex activity arising from cardiopulmonary afferents.

The observed natriuresis and diuresis associated with intravenous PGF$_{2a}$ infusion in our present study differs from early reports in which intrarenal PGF$_{2a}$ infusion had no effect on the renal excretion of water and electrolytes. A wide range of doses were administered to anesthetized dogs in these studies, which may account for the conflicting results of the present study. Indeed, additional studies are necessary, especially using conscious dogs, before the effects of PGF$_{2a}$ on renal function, and possible mechanisms for such effects, can be defined.

In summary, our present study indicates that the hypertensive response to chronic intrarenal PGE$_{2}$ infusion in conscious dogs results from a sustained increase in renin secretion. In support, a 9-fold change in PRA was observed concomitantly with the change in MAP. Furthermore, blockers of the renin-angiotensin system resulted in a significant fall in arterial pressure. Although intrarenal PGE$_{2}$ infusion resulted in moderate sodium loss, despite high circulating levels of AII and aldosterone, it is unlikely that PGE$_{2}$ independently lowered arterial pressure. That is, the fall in MAP during PGE$_{2}$ and SQ 14,225 infusion was no different than that observed by others during SQ 14,225 administration alone. Also, the present study demonstrates that intrarenal conversion of PGE$_{2}$ to PGF$_{2a}$, with subsequent release into the general circulation, does not appear to contribute to PGE$_{2}$-induced hypertension, since continuous intravenous infusion of PGF$_{2a}$ did not alter MAP. However, PGF$_{2a}$ infusion did result in an immediate natriuresis and diuresis, suggesting a possible direct transient effect on the renal tubules, but such a conclusion awaits further clarification.

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