Role Of Endogenous Prostaglandins in Volume Expansion and During Furosemide Infusion in Conscious Dogs

VELLORE SREENIVASAN, M.D., BENJIMEN WALKER, PH.D., JOHN KRASNEY, PH.D., BASAB MOOKERJEE, M.D., AND ROCCO VENUTO, M.D.

SUMMARY The renal effects of two structurally dissimilar inhibitors of prostaglandin synthesis (Meclofenamate and RO-20-5720) were studied in conscious, chronically instrumented dogs during mild volume expansion and during a constant infusion of furosemide. When either inhibitor was administered following volume expansion, urinary excretion of PGEx and urine flow rate were reduced by more than 50%. In contrast, renal plasma flow fell by less than 10% while glomerular filtration rate, sodium excretion, and plasma renin activity (PRA) were unchanged. In separate studies, infusion of furosemide increased renal plasma flow, urine flow rate, sodium excretion, PRA, and urinary excretion of PGEx, while glomerular filtration rate fell below control level. Despite these hemodynamic alterations, the furosemide-induced diuresis and increase in PRA were only partly attenuated by prostaglandin inhibition. It is concluded that in conscious dogs, intrarenal prostaglandins modulate urine flow rate during mild volume expansion and play a major role in mediating the renal hemodynamic effects of furosemide. (Hypertension 3: 59-66, 1981)

KEY WORDS • renal prostaglandins • conscious animals • furosemide • renal hemodynamics • renin • inhibitors of prostaglandin synthesis

THE relative importance of intrarenal prostaglandins (PGs) in the regulation of renal function and renal hemodynamics requires clarification. A clear definition of the physiological role of renal PG synthesis is lacking, largely because the effect of the experimental conditions may vary the results. One such example is the marked alteration of renal PG release associated with anesthesia and surgical stress in the acute animal preparation.1 In addition, extracellular volume of the experimental animal can modify the influence of PG in the regulation of renal function.8

The objective of this investigation was to define under more physiological conditions the role intrarenal PG could have in mediating changes in renal blood flow (RBF) and renal excretory function induced by modest volume expansion or administration of furosemide. To circumvent the problems of anesthesia and surgery, the present study was performed utilizing awake, chronically instrumented dogs. The dogs were subjected to uniform volume expansion 1 hour before the experiments. The renal effects produced by administration of either of two structurally dissimilar inhibitors of PG synthesis (PI) were monitored, and urinary excretion of prostaglandin E2 was measured by radioimmunoassay as an indicator of renal PG synthesis.3

It has been reported that PI reduces the diuretic and renal hemodynamic effects of furosemide and additionally depresses the usual marked increase of plasma renin activity (PRA) that accompanies furosemide administration.4,5 However, these studies were performed in anesthetized animals,6,7 and the data were not correlated with renal PG release.4 Consequently, a second objective of this investigation was to analyze the role of renin PG in the diuretic and renal hemodynamic response to furosemide, and to further define the relationship between renal PG synthesis and both peripheral and renal vein renin activity (RVRA).
Six conditioned female mongrel dogs, selected for a docile temperament and weighing between 17 and 25 kg, were utilized in this study. After an initial 1 to 2 weeks of training to accustom them to the laboratory environment, the dogs were anesthetized with pentobarbital sodium and an abdominal laparotomy was performed under aseptic conditions. The left renal artery was dissected free, taking care not to damage the renal innervation; a previously calibrated electromagnetic blood flow transducer (Biotronex) was placed about the renal artery. A hydraulic occluder was positioned on the artery distal to the flow transducer to obtain mechanical blood flow zeros. The blood flow transducers were calibrated in an acute experiment to obtain mechanical blood flow zeros. The blood flow transducers were calibrated in an acute experiment.

A Silastic catheter was advanced up the left ovarian vein such that the catheter tip was placed in the left renal vein for sampling renal venous blood. Silastic catheters were also positioned in the inferior vena cava and the distal aorta via a femoral vein and artery respectively. The venous line was used for infusion of drugs and solutions, and the arterial allowed us to measure aortococci blood pressure and collect arterial blood samples. The flow probe lead and the catheters were routed subcutaneously to the lateral thoracic wall where they were exteriorized. The leads and catheters were protected by a custom-fitted nylon mesh jacket.

After a recovery period of several days, the dogs were reanesthetized with thiamylol sodium, and an episiotomy was performed under aseptic conditions to exteriorize the urethra.

The dogs were allowed to recover from the surgical procedures for at least 2 weeks prior to initiation of the experiments. During the recovery period the dogs were placed on ampicillin. At the time of the experiments the dogs were afebrile, had good appetites, and were able to exercise normally. The implanted catheters were kept filled with a mixture of heparin and chloramphenicol and were flushed periodically with heparin. The dogs were maintained on a standard laboratory diet (Wayne Dog Food) and given water ad libitum except during the experiments.

Experiments were performed in a sound-attenuated room with the room temperature maintained at 17°C to minimize panting. The dogs were partially supported by a modified Pavlov sling. Renal blood flow was obtained using a Biotronex BL-610 flow meter, and arterial blood pressure was monitored using a Statham P23AC pressure transducer. Recordings of phasic RBF and arterial pressure were obtained using a Grass 7D multichannel oscillograph. Zero RBF was established by periodic occlusion of the renal artery. Mean RBF and mean arterial pressure (MAP) were recorded periodically by electronic low-pass filtering. The average of three electronically meaned values was used as the reading for each experimental period. A Foley catheter was placed in the urinary bladder.

Methods

Experimental Protocols

Protocol 1

After the dog had become accustomed to the sling, peripheral arterial, renal venous, and peripheral venous blood samples were obtained for basal PRA, RVRA, sodium and potassium, osmolality, and hematocrit. Baseline urine samples were obtained for sodium, potassium, and osmolality. The animal was then volume-expanded by 2% of its body weight with 0.45 N saline over a period of 30 minutes via the venous catheter. A maintenance infusion of this solution equal to urine flow rate was continued for the duration of the study. Following volume expansion, a priming dose of 10% inulin solution (50 mg/kg) (Arnar Stone Laboratories) was administered intravenously as a bolus. This was followed by a maintenance infusion of inulin in 0.45 N saline at the rate of 0.96 mg/kg/min (0.5 ml inusate/min) with a Harvard pump. After 30 minutes of maintenance infusion, two successive 15-minute control clearance periods were timed. Following the control periods, either Meclofenamate (2mg/kg) or RO 20 5720 (1 mg/kg) was administered intravenously as a bolus dose. Two successive 15-minute clearance periods were timed, 30 minutes after the administration of either inhibitor.

Protocol 2

This protocol was identical to Protocol 1 in terms of the 2% body weight volume expansion and the control period. After the control period, a constant infusion of furosemide (Hoechst-Roussel) in 0.45 N saline was started at the rate of 0.016 mg/kg/min (0.5 ml infusion/min) with a Harvard pump and maintained throughout the rest of the experiment. (In separate studies, with an identical furosemide infusion, a steady diuresis was maintained for more than 3 hours in four studies in two different animals). The volume and sodium losses were replaced intravenously with 0.45 N saline on a continuous basis. Two successive 15-minute clearance periods were obtained during the furosemide diuresis beginning 30 minutes after initiation of the infusion. Either of the inhibitors was administered intravenously as a bolus, and two more successive 15-minute clearance periods were timed, 30 minutes after the inhibitor was administered.

In both protocols, midpoint peripheral arterial and renal venous blood samples were obtained during each clearance period for PRA, RVRA, inulin clearances, plasma sodium concentration, potassium concentration, osmolality, and hematocrit. Timed urine collections were also obtained for inulin clearance, sodium potassium, osmolality, and prostaglandin E2. The urine flow rate, RBF, and arterial blood pressure were continuously monitored throughout the experiment. Forty-eight hours were allowed to elapse before these animals were restudied.

Glomerular filtration rate (GFR) was estimated from the clearance of inulin. Plasma and urine inulin
concentrations were determined by direct resorcinol method without alkali treatment. Plasma and urinary sodium and potassium concentrations were determined by flame photometry (Model 143, Instrumentation Laboratory). Plasma and urine osmolality were measured by freezing point depression osmometer (Model 3L, Advanced Instruments). Peripheral and renal vein renin activity were determined utilizing a radioimmunoassay for angiotensin I. The assay employed a modification of the technique of Pickens et al.  

Urinary prostaglandin \( E_2 \) concentrations (\( uPGE_2 \)) were measured by radioimmunoassay using the method previously described by Walshe and Venuto. Urine specimens were kept frozen until the time of assay. Samples were chromatographed on silicic acid columns to separate the PGE fraction from other prostaglandins. The antiserum employed for the immunoassay was prepared against PGE\( _2 \) in rabbits by Drs. F. Dray and B. Charbonnel at the Institut Pasteur, Paris, France. This antibody has high affinity for PGE\( _2 \) and low affinity for other prostaglandins.

Results

Protocol 1

The effect of Meclofenamate (M) (2 mg/kg) or RO 20 5720 (1 mg/kg) on renal hemodynamics, urine flow rate (\( V \)), sodium excretion rate (\( uNa_v \)), and potassium excretion rate (\( uK_v \)) following mild volume expansion (VE) are presented in table 1. Twelve experiments were performed, six with each inhibitor. No change was noted in GFR, FF, MAP, \( uNa_v \), and \( uK_v \), but RPF fell by less than 10%. The urine flow rate fell in all experiments. Urinary concentration of Na and K and fractional excretion of these electrolytes were unaffected by inhibitor administration. The basal (prevolume expansion) \( uOsm \) not shown in table 1 was 1281 ± 130 mOsm/kg \( H_2O \), which fell

| Table 1. Effect of Prostaglandin Inhibition in Mildly Volume-Expanded Conscious Dogs |
|-------------------------------------|-------|-------|-------|-------|-------|-------|-------|
| Experiment | V (ml/min) | GFR (ml/min) | RPF (ml/min) | \( uNa_v \) (mEq/min) | \( uK_v \) (mEq/min) |
| no. type | C | PI | C | PI | C | PI | C | PI |
| 1 M | 4.1 | 2.5 | 99 | 99 | 373 | 387 | 0.07 | 0.10 | 0.05 | 0.02 |
| 2 M | 1.0 | 0.5 | 141 | 171 | 534 | 498 | 0.37 | 0.20 | 0.1 | 0.1 |
| 3 M | 0.4 | 0.3 | 101 | 83 | 360 | 306 | 0.05 | 0.01 | 0.06 | 0.04 |
| 4 M | 1.2 | 0.7 | 132 | 74 | 333 | 316 | 0.02 | 0.03 | 0.01 | 0.01 |
| 5 M | 3.3 | 2.6 | 122 | 115 | 290 | 337 | 0.18 | 0.39 | 0.10 | 0.06 |
| 6 M | 0.3 | 0.17 | 109 | 89 | 517 | 439 | 0.10 | 0.02 | 0.09 | 0.04 |
| 7 RO | 1.1 | 0.85 | 95 | 104 | 434 | 416 | 0.20 | 0.17 | 0.1 | 0.1 |
| 8 RO | 1.0 | 0.7 | 135 | 112 | 307 | 253 | 0.29 | 0.21 | 0.09 | 0.08 |
| 9 RO | 1.4 | 0.7 | 155 | 145 | 442 | 404 | 0.26 | 0.11 | 0.14 | 0.2 |
| 10 RO | 0.5 | 0.4 | 93 | 103 | 571 | 514 | 0.09 | 0.04 | 0.09 | 0.08 |
| 11 RO | 0.9 | 0.5 | 128 | 131 | 592 | 491 | 0.31 | 0.21 | 0.03 | 0.02 |
| 12 RO | 4.7 | 3.1 | 83 | 69 | 250 | 229 | 0.04 | 0.04 | 0.04 | 0.03 |
| Mean | 1.7 | 1.1 | 116 | 108 | 417 | 383 | 0.165 | 0.127 | 0.08 | 0.07 |
| SEM | 0.4 | 0.3 | 6 | 9 | 33 | 28 | 0.035 | 0.033 | 0.01 | 0.01 |

Abbreviations: C = control period; PI = prostaglandin inhibition period; M = Meclofenamate; RO = RO 20-5720; V = urine flow; \( uNa_v \) = urinary sodium excretion rate; \( uK_v \) = urinary potassium excretion rate. All values depicted represent the sum of both kidneys.
to 876 ± 199 mOsm/kg H$_2$O ($p < 0.005$) subsequent to volume expansion but returned to basal levels of 1278 ± 254 mOsm/kg H$_2$O ($p < 0.001$) during the prostaglandin inhibition period.

Renin data were available in only five or six experiments with Meclofenamate and four of six experiments with RO. Following expansion, the basal PRA and RVRA fell from 1.09 ± 17 and 1.25 ± 0.22 to 0.65 ± 0.8 and 0.73 ± 0.6 ng/ml/hr respectively ($p < 0.01$). No change was noted in PRA or RVRA, however, when either inhibitor was administered following volume expansion (fig. 1).

Figure 2 depicts the $^6$PGE$_{s}$ and $^6$PGE$_{v}$. Administration of either inhibitor after volume expansion caused a fall in both $^6$PGE$_{s}$ and $^6$PGE$_{v}$. The $^6$PGE$_{s}$ fell from 736 ± 152 to 316 ± 51 pg/ml ($p < 0.01$), and the $^6$PGE$_{v}$ fell from 855 ± 157 to 260 ± 48 pg/min ($p < 0.01$).

Protocol 2

The effects of a constant furosemide infusion (FI) following VE on renal hemodynamics $V$, $^uNa^v$, $^uK^v$, are presented in table 2. Also included are changes observed with these parameters when either of the inhibitors was administered during a constant furosemide diuresis. Six experiments were performed with M and five with RO. In these dogs with mild volume expansion, a constant FI decreased $^uNa$ from 222 ± 45 to 113 ± 3.0 mEq/liter ($p < 0.01$) and $^uK$ from 103 ± 20 to 32 ± 17 mEq/liter ($p < 0.01$). As expected, $V$, $^uNa^v$, and $^uK^v$ all increased. Fractional excretion of both Na and K increased from 0.93% ± 0.13% to 14.0% ± 0.7% and 15.2% ± 2.8% to 71% ± 6.0% respectively (both $p < 0.01$). Both GFR and FF fell; RPF increased in every experiment, however, and MAP remained constant at 99 ± 4 mm Hg.

Administration of M or RO during FI resulted in a fall in $V$, $^uNa^v$, and FeNa, which dropped from 14.0 ± 0.7 to 8.0 ± 0.6 ($p < 0.01$). The $^uNa$ fell from 113.3 ± 3.0 to 88.0 ± 4.0 mEq/liter and the $^uK$ from 32 ± 17 to 16 ± 3 mEq/liter, but these changes were not significant. The RPF and GFR both fell, while MAP continued to be unchanged.

The renin data from Protocol 2 are shown in Figure 3. These data were available in six experiments, three with each inhibitor. The FI increased the PRA and RVRA from the suppressed control levels. Administration of either inhibitor resulted in a decrease in PRA but not in RVRA. It is important to note that, following PI, PRA as well as RVRA remained above the pre-furosemide levels.

The urinary excretion of prostaglandin E$_{s}$ is depicted in figure 4. During FI, although the concentration of PGE fell from the control level, total excretion of PGE was increased more than twofold in the presence of the markedly raised $V$. Administration of either M or RO further reduced $^6$PGE$_{s}$, but this change was just below statistical significance. The $^6$PGE$_{v}$, however, fell to a level nearly identical to the control value (fig. 4) despite the continued increased $V$.
TABLE 2. Effect of Prostaglandin Inhibition During Constant Furosemide Infusion Following Mild Volume Expansion in Conscious Dogs

<table>
<thead>
<tr>
<th>Experiment</th>
<th>V (ml/min)</th>
<th>GFR (ml/min)</th>
<th>RPF (ml/min)</th>
<th>FF</th>
<th>$^{{\text{U} \text{Na}}}^{{\text{V}}}$ (mEq/min)</th>
<th>$^{{\text{U} \text{K}}}^{{\text{V}}}$ (mEq/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. type</td>
<td></td>
<td>C</td>
<td>F</td>
<td>PI</td>
<td>C</td>
<td>F</td>
</tr>
<tr>
<td>1 M</td>
<td>0.95</td>
<td>20.0</td>
<td>11.4</td>
<td>147</td>
<td>106</td>
<td>88</td>
</tr>
<tr>
<td>2 M</td>
<td>1.30</td>
<td>20.7</td>
<td>12.2</td>
<td>127</td>
<td>107</td>
<td>90</td>
</tr>
<tr>
<td>3 M</td>
<td>1.03</td>
<td>19.5</td>
<td>8.8</td>
<td>119</td>
<td>105</td>
<td>75</td>
</tr>
<tr>
<td>4 M</td>
<td>1.13</td>
<td>17.2</td>
<td>10.3</td>
<td>104</td>
<td>89</td>
<td>82</td>
</tr>
<tr>
<td>5 M</td>
<td>0.43</td>
<td>8.5</td>
<td>3.4</td>
<td>109</td>
<td>69</td>
<td>60</td>
</tr>
<tr>
<td>6 M</td>
<td>1.90</td>
<td>15.8</td>
<td>12.1</td>
<td>71</td>
<td>83</td>
<td>67</td>
</tr>
<tr>
<td>7 RO</td>
<td>0.93</td>
<td>19.5</td>
<td>13.8</td>
<td>162</td>
<td>115</td>
<td>87</td>
</tr>
<tr>
<td>8 RO</td>
<td>0.42</td>
<td>12.6</td>
<td>9.4</td>
<td>129</td>
<td>106</td>
<td>79</td>
</tr>
<tr>
<td>9 RO</td>
<td>0.48</td>
<td>17.4</td>
<td>13.3</td>
<td>120</td>
<td>98</td>
<td>94</td>
</tr>
<tr>
<td>10 RO</td>
<td>0.42</td>
<td>17.6</td>
<td>15.3</td>
<td>120</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>11 RO</td>
<td>1.02</td>
<td>12.4</td>
<td>10.3</td>
<td>77</td>
<td>77</td>
<td>68</td>
</tr>
<tr>
<td>Mean</td>
<td>0.91</td>
<td>16.5</td>
<td>10.9</td>
<td>117</td>
<td>96</td>
<td>81</td>
</tr>
<tr>
<td>SEM</td>
<td>0.14</td>
<td>1.2</td>
<td>0.95</td>
<td>9</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

**p** values based on comparisons of C to F and F to PI.

Abbreviations: C = control period; F = constant furosemide infusion period; PI = prostaglandin inhibition period. Other abbreviations are as noted in Table 1. All values depicted are for the sum of both kidneys.

---

**Figure 3.** Effect of inhibitors of prostaglandin synthesis on plasma renin activity and renal vein renin activity during a constant furosemide infusion, following mild volume expansion. Clear bars are for control periods (C), stippled bars are for furosemide infusion period (F), and solid bars are for prostaglandin inhibition period (PI). Values are means ± se. *p < 0.01, **p < 0.05, comparing control to furosemide and furosemide to prostaglandin inhibition periods.

**Figure 4.** Effect of inhibitors of prostaglandin synthesis on urinary concentration of prostaglandin $E_2$ ($^{{\text{U} \text{PGE}}}^E$) and urinary prostaglandin $E_2$ excretion rate ($^{{\text{U} \text{PGE}}}^E$) during a constant infusion of furosemide following mild volume expansion. Clear bars are for control periods (C), stippled bars are for prostaglandin inhibition period (PI). Values are means ± se. *p < 0.01, as compared to control to furosemide and furosemide to prostaglandin inhibition period.
Discussion

Compounds that inhibit cyclo-oxygenase-mediated conversion of arachidonic acid to prostaglandins appear to have effects on renal function that are greatly altered by the physiological setting in which the study occurs. Inhibitors of prostaglandin synthesis (PI) cause renal vasoconstriction and alter the intrarenal distribution following blood flow in experimental animals that are anesthetized. In contrast, Zins and subsequently other investigators have reported that there are only minimal renal hemodynamic alterations when PI are administered to conscious animals and man. These observations indicate that stress leads to an apparent dependence of renal vasomotor tone upon PG which cannot be demonstrated in conscious, resting animals.

In most of the previously cited studies in which the influence of PI was examined in both conscious and anesthetized animals, the level of PG synthesis has only been surmised. To correlate actual changes in renal PG synthesis and release with the observed renal functional changes induced by PI, we analyzed levels of urinary PGE\textsubscript{2} in the present study. Although several renal PGs are derived from arachidonic acid metabolism, PGE\textsubscript{2} is a major synthetic product and should reflect the formation of other metabolites of arachidonic acid, with the possible exception of PGI\textsubscript{1}.

The results from Protocol 1 confirm those reported by previous investigations using conscious animals. The administration of either Meclofenamate or RO 20 5720 led to a slight reduction in renal plasma flow, while the glomerular filtration rate was unchanged. These mild hemodynamic adjustments occurred in concert with a prominent reduction of urinary PGE\textsubscript{2}. The only other significant alteration was a reduction of urine flow rate (V). This depression of V may be a consequence of the antagonist interrelationship between endogenous antidiuretic hormone (ADH) and PG of the E series. While there was probably partial suppression of the levels of circulating ADH by our volume expansion, it is unlikely that complete inhibition of ADH release was achieved since the urine-to-plasma osmolality ratio was greater than unity. Hence, reduction of antagonist PG levels would be expected to potentiate the effects of available ADH and therefore reduce V. Changes in peritubular Starling forces and increased proximal tubular reabsorption could not be excluded as having contributed to the reduced V.

This observed reduction in V during PI is consistent with the observations reported by Altshehler et al. using conscious dogs and by Dusing et al. in conscious rats. The latter group also found a fall in V when PI was administered after sodium-loading in the rat. Sodium excretion of \(^{22}Na^+\) was unchanged during the antidiuresis in the present study, whereas Altshehler et al. and Dusing et al. reported a decline in \(^{22}Na^+\) after PI. This apparent discrepancy may be related to the different sodium loads presented to the animals in these various studies. The dogs in the present study received only 40 mEq of sodium during the volume expansion phase whereas the dogs studied by Altshehler et al. received 77 mEq and the rats studied by Dusing et al. received 50% more sodium than our dogs on a relative weight basis.

Differences in the mode of volume expansion and sodium load may partly account for the variant results reported by Kirschenbaum and Stein. These investigators studied conscious dogs undergoing water diuresis during an infusion of 5% dextrose and found that either Meclofenamate or RO 20 5720 caused an increase in \(^{22}Na^+\) while V was unchanged. In quantitative terms, this increase in \(^{22}Na^+\) was small since urine sodium levels prior to PI were low. During water diuresis, endogenous ADH should be near maximally suppressed; consequently, administration of PI would be expected to have little effect on V.

However, the increment of \(^{22}Na^+\) after PI reported by Kirschenbaum and Stein is difficult to reconcile with our observation that \(^{22}Na^+\) was unchanged during PG inhibition. Altshehler et al. reported that there was no change in \(^{22}Na^+\) during water diuresis after PI in conscious dogs. We performed four water diuresis experiments in two dogs and also observed no change in \(^{22}Na^+\) after PI. Moreover, in human subjects, oral indomethacin failed to change Na excretion in one study and only slightly reduced Na excretion in a second study when the subjects in both groups were ingesting approximately 150 mEq Na daily.

The aforementioned observations indicate that the effect of PI on \(^{22}Na^+\) in conscious man and animals is modest and that it is probably related to the renal sodium load. In support of this view, Tan et al. demonstrated in rats that increasing sodium intake is associated with increased urinary PGE\textsubscript{2} excretion. Thus, in stressful situations and during sodium-loading, renal hemodynamics and sodium excretion may be more dependent upon intrarenal PG activity, and hence the functional consequences of treatment with PI would be predictably more dramatic.

Prostaglandin E causes a natriuresis in animals when administered in large doses by either the intravenous or intraarterial route. The natriuretic action of PGE\textsubscript{2} appears to be partly related to renal vasodilation. In addition, studies on the isolated perfused tubules indicate that PGE\textsubscript{2} can cause direct tubular inhibition of sodium reabsorption. Thus, if PGE\textsubscript{2} exerts a natriuretic effect, PI would be expected to produce an antinatriuretic effect, particularly under conditions of sodium-loading.

Previous studies in both animals and man have demonstrated a reduction in PRA following administration of PI. In Protocol 1, administration of PI failed to influence PRA and RVRA. However, in this circumstance PRA and RVRA had been depressed from the control levels by volume expansion. It is possible that further suppression of renin activity was either nondetectable or that renin activity and prostaglandin synthesis become disassociated at low renin levels in conscious dogs.

In our second experimental protocol, we found that a constant intravenous infusion of furosemide caused...
a sustained diuresis, natriuresis, increased PRA, RVRA, and increased RPF, combined with decreases in GFR and renal vascular resistance. The PGE$_2$ excretion increased twofold. In contrast to Protocol 1, where PI failed to influence GFR and only slightly reduced RPF, administration of PI during the sustained infusion of furosemide caused a reduction of RPF to nearly 20% below the control pre-furosemide levels, and there was further depression of GFR.

The mechanism responsible for the observed decline of GFR with sustained furosemide infusion alone is not readily apparent.$^{26}$ The renal hemodynamic consequences of furosemide could result from an interaction between the observed increases in both renal activity and PG synthesis (as reflected by urinary PGE$_2$). The PGE$_2$ and perhaps other PG antagonize the action of angiotensin on the renal vasculature and may further stimulate renin release.$^{19, 21, 26}$ In this setting PI caused a profound concomitant decline of RPF and GFR, while PRA and RVRA remained elevated. Perhaps the decline of intrarenal PG synthesis as reflected by urinary PGE$_2$, in association with a persistence of the elevated renin levels, could account for the reduction of both RPF and GFR when PI is given during furosemide diuresis.

Additional mechanisms, however, could be evoked to explain the depression of GFR when PI is given with furosemide. While we found that PI alone does not alter GFR, as in Protocol 1, it is conceivable that furosemide could act upon other enzymes and a pharmacokinetic interaction could occur independent of any renin-prostaglandin interaction. It is known, for example, that PI can interfere with a number of enzymes in addition to PG synthetase$^{20}$ and these agents also increase the half-life of furosemide.$^{20}$

The finding of the blunting influence of PI on both the renal hemodynamic adjustments and the diuresis produced by furosemide is supported by data from other investigators using different preparations and species.$^{2, 7-9}$ Although Bailie et al.$^{26}$ found that PI had no influence on the furosemide diuresis in dogs, their animals were studied under anesthesia and the diuresis was produced by large bolus doses of furosemide. Our study is the first to describe the influence of PI on renal function in conscious dogs during continuous furosemide diuresis, and to correlate these renal changes with urinary excretion of PGE$_2$.

In summary, these data demonstrate the only modest effect of PI on renal function in mildly volume-expanded, resting conscious dogs, in the presence of markedly reduced renal PGE$_2$ release. Furthermore, these studies suggest that the diuretic action of furosemide involves two mechanisms. One mechanism is related to altered renal hemodynamics and increased PG release; the second appears to be independent of both renal PG synthesis and renal hemodynamics.

**Acknowledgments**

The authors acknowledge the expert technical assistance of Pat Hysert, Cathy Hubbard, Peter Barone, Joseph Balweirczak, and Jeffrey Exeter, and the secretarial assistance of Sandra Anzalone.

---

**References**

26. Johnstone H, Herzog J, Luuler D: Effect of prostaglandin E$_2$ on...
Role of endogenous prostaglandins in volume expansion and during furosemide infusion in conscious dogs.

V Sreenivasan, B Walker, J Krasney, B Mookerjee and R Venuto

_Hypertension_. 1981;3:59-66
doi: 10.1161/01.HYP.3.1.59

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 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/3/1/59

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/