CONTRIBUTION OF PROSTAGLANDINS TO THE RENAL CIRCULATION IN CONSCIOUS, ANESTHETIZED, AND LAPAROTOMIZED DOGS

Norberto A. Terragno, D. Alicia Terragno, and John C. McGiff

In 1973 Lonigro et al. reported that the rate of release of prostaglandin E₂ (PGE₂) within the kidney is a determinant of resting renal blood flow (RBF). However, their study was conducted in anesthetized dogs in which the renin-angiotensin system was greatly activated consequent to laparotomy. Increased generation of angiotensin, a potent stimulus to synthesis of prostaglandins (PGs), presumably elevated renal levels of PGE₂ and, thereby, created a PG-dependent component of RBF. This could be identified by the fall in RBF evoked by administration of inhibitors of PG synthesis. Thus, in the acutely stressed dog increased release of PGE₂ contributes to maintaining RBF, an effect which is uncovered by inhibition of PG synthesis. The latter results in a decline in RBF. In contrast, under more physiological conditions, when renal PG levels are presumed to be low, inhibition of PG synthesis should have little effect on the renal circulation. This interpretation is based primarily on the study of Lonigro et al. in acutely surgically stressed anesthetized dogs when viewed in the light of recent studies in unanesthetized dogs. In the latter studies, in contrast to that of Lonigro et al., RBF was usually unaffected by administration of aspirin-like drugs. This interpretation has also received support in a recent study in the anesthetized dog in which the effects of inhibitors of PG synthesis on the renal circulation were shown to be related to the degree of activation of the renin-angiotensin system.

In the present study we have varied experimental conditions while measuring changes in the activities of the renin-angiotensin system and renal PGs. We were particularly interested in: (1) the contribution of PGs to the renal circulation in the conscious dog at rest when compared to the anesthetized dog subjected to the stress of acute laparotomy; (2) the influence of experimental conditions on the release of renal PGs and the effects of inhibitors of PG synthesis on this release; and (3) the relationship between changes in the activity of the renin-angiotensin system and changes in the concentration of PGs in renal venous blood.

**Methods**

Five male mongrel dogs, weighing 25-30 kg, were anesthetized with sodium pentobarbital (30 mg/kg, iv) and maintained with 5 mg/kg, iv, as required. Under sterile conditions, the left kidney was exposed through a retroperitoneal incision and its artery and vein were dissected free from the surrounding tissues. A flow transducer with inside diameter of 3.5-4.5 mm was placed on the renal artery. The left renal vein was cannulated with polyethylene tubing (Clay-Adams, PE 160, outside diameter 1.6 mm) inserted through the corresponding spermatic vein to obtain blood samples. An indwelling polyethylene tube (Clay-Adams, PE 90, outside diameter 1.3 mm) was inserted into the lower aorta through a branch of the femoral artery to record mean aortic blood pressure (MABP). The intravascular catheters and the flow probe cables were brought through a subcutaneous tunnel to the back of the dog, exteriorized at the level of the 10th thoracic vertebra; the retroperitoneal incision was closed by planes. The catheters were filled with dilute heparinized saline and flushed daily; in addition, the venous catheter was rinsed after each blood collection. Penicillin (900,000 U) was given intramuscularly at the end of surgery and then daily.
for 4 days. RBF was measured with a gated square wave electromagnetic flow meter (Statham SP2202) and MABP with a Statham strain gauge manometer (P23Db); both were recorded on a multichannel direct-writing oscillograph (Hewlett-Packard 7720-9A). A period of at least 1 week, and usually 2 weeks, preceded the first experiment; intervals between experiments were no less than 4 days.

The dogs were considered to be in good health as evidenced by stability of body weight, absence of fever, normal eating habits, mood, activity, and the daily report of a veterinarian. After the last experiment the dogs were anesthetized, the abdominal cavity was opened, and the positions of the flow meter probe and cannulas were determined. The renal artery was found to be adherent to the flow transducer; this was due to the periarterial formation of fibrous tissue. At this time the electrical zero of the electromagnetic flow meter was verified by mechanical occlusion of the renal artery. Electrical and mechanical zeros showed good correspondence, not differing by more than 10 ml/min.

For comparison of the effects of inhibition of PG synthesis in the conscious dogs of Table 1 with the effects in anesthetized-laparotomized dogs, we used two earlier studies1,9 as a major source of data for the latter group (dogs 1-14 of Table 3). In addition, two of the conscious dogs (dogs 15 and 16 of Table 3) were subjected to the same experimental procedures as were used in the former studies;1,9 i.e., anesthetized with morphine sulfate (2 mg/kg, subcutaneously) and chloralose (100 mg/kg, iv) after which a laparotomy was performed.

PG assays were performed according to our previously described procedures.1,9 Briefly, 50 ml of renal venous blood was collected in ethanol. The mixture was filtered and evaporated and the acidic lipids were separated from the neutral lipids by extraction with ethyl acetate followed by extraction with potassium phosphate buffer and finally by chloroform. The acidic lipids so obtained were separated by thin-layer chromatography on 0.5-mm-thick silica gel plates with chloroform-methanol-acetic acid (18:2:1 by volume). Eluates from thin-layer chromatographic plates were reconstituted in 0.9% saline and bioassayed using the superfusion technique,10 which we adapted for PG bioassay in vitro.10 The sensitivity of the bioassay for PGs of the E series, when 50 ml of blood were used, varied between 0.004 and 0.002 ng/ml of blood, whereas for PGs of the F series the range of sensitivity was 0.01-0.05 ng/ml of blood, since in every instance we were able to detect quantities as little as 1 and 2.5 ng and frequently 0.2 and 1.0 ng of PGE2 and PGF2α, respectively, in the total sample which represented the purified extract of 50 ml of blood. A value of 0.01 ng/ml, which is below the upper limits of the usual threshold of sensitivity, was chosen when PGs could not be detected in the sample for the statistical analysis of the tables. The concentration of PGs was not corrected for losses of 60% which are constant and which result from the extraction and chromatographic purification of the blood samples. We have indicated the results of the assay in terms of nanograms per milliliter of "PGE" or "PGF" rather than the more cumbersome PGE-like or PGF-like substances.

Plasma renin activity was measured by the radioimmunoassay technique of Sealey and associates.12 Blood (5 ml) was obtained from the renal vein, collected in plastic tubes containing ethylenediaminetetraacetic acid (EDTA), centrifuged at 2,000 rpm at 4°C for 20 minutes, separated, and stored at -10°C until assayed. Plasma renin activity was measured by radioimmunoassay of angiotensin I generated during a 1-hour incubation with endogenous substrate. Angiotensin I antibody and labeled angiotensin I were obtained from Squibb.

Indomethacin was dissolved in 10 ml of absolute ethanol and diluted with Krebs' solution to give a final concentration of 1 mg/ml for intravenous injection. Control solutions containing identical concentrations of ethanol and Krebs' solution did not affect RBF when they were administered intravenously. Meclofenamate as the sodium salt was diluted in 0.9% saline and bioassayed using the superfusion technique,10 which we adapted for PG bioassay in vitro.10 The sensitivity of the bioassay for PGs of the E series, when 50 ml of blood were used, varied between 0.004 and 0.002 ng/ml of blood, whereas for PGs of the F series the range of sensitivity was 0.01-0.05 ng/ml of blood, since in every instance we were able to detect quantities as little as 1 and 2.5 ng and frequently 0.2 and 1.0 ng of PGE2 and PGF2α, respectively, in the total sample which represented the purified extract of 50 ml of blood. A value of 0.01 ng/ml, which is below the upper limits of the usual threshold of sensitivity, was chosen when PGs could not be detected in the sample for the statistical analysis of the tables. The concentration of PGs was not corrected for losses of 60% which are constant and which result from the extraction and chromatographic purification of the blood samples. We have indicated the results of the assay in terms of nanograms per milliliter of "PGE" or "PGF" rather than the more cumbersome PGE-like or PGF-like substances.

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![Graph](image-url)

**FIGURE 1** In a chronically instrumented, conscious dog, administration of indomethacin did not affect renal blood flow (RBF), mean aortic blood pressure (MABP), or the concentrations in renal venous blood of prostaglandin E-like ("PGE") and prostaglandin F-like ("PGF") substances, expressed in nanograms per milliliter of blood. Time scale: each section of trace equals 8 minutes.
Mean renal vascular resistance was calculated as the quotient of MABP and RBF and was expressed as mm Hg/ml per min. Significant differences between control and experimental periods for RBF, MABP, and PG concentration were determined by the Student's t-test based on paired and unpaired observations. The Wilcoxon rank sum test was used for analysis of nonparametric data. The significance of the relationship between concentrations of PGs and plasma renin activity in renal venous blood was determined by calculating correlation coefficients. P values of 0.05 or less were considered statistically significant.

**Results**

In conscious dogs, intravenous administration of indomethacin in doses of either 2, 5, or 10 mg/kg of body weight, did not affect RBF, MABP, renal vascular resistance, or PG concentrations in renal venous blood (Figs. 1 and 2, Table 1). When the largest dose, 10 mg/kg, was used (four of the 10 experiments of Table 1), bloody diarrhea occurred within 2-3 hours after its administration in each instance. In one experiment, meclofenamate, given in a dose reported to inhibit PG synthesis in acute experiments, affected neither RBF nor renal venous PG levels. The values for RBF and MABP accord with published values in unanesthetized dogs. The effects of anesthesia alone, either pentobarbital (30 mg/kg) or chloralose (100 mg/kg) given intravenously, were studied in three dogs and their response to indomethacin was determined (Table 2). These anesthetic agents by themselves did not affect either MABP, RBF, or the concentrations of PGs in renal venous blood. In the presence of anesthesia alone indomethacin (10 mg/kg) given intravenously did not greatly affect renal vascular resistance or PG levels in renal venous effluent. In the one experiment

**Table 1** Effect of Indomethacin* on Blood Pressure, Renal Blood Flow, and Renal Prostaglandin Levels in Conscious Dogs

<table>
<thead>
<tr>
<th>Drugs (mg/kg)</th>
<th>C, -20 min</th>
<th>E, 15 min</th>
<th>E, 25 min</th>
<th>C, - 20 min</th>
<th>E, 15 min</th>
<th>E, 25 min</th>
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<td>95</td>
<td>90</td>
<td>240</td>
<td>245</td>
<td>240</td>
<td>0.12</td>
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<tr>
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<td>110</td>
<td>110</td>
<td>250</td>
<td>220</td>
<td>220</td>
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<tr>
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<td>100</td>
<td>100</td>
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<td>300</td>
<td>300</td>
<td>0.03</td>
<td>0.03</td>
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<tr>
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<td>105</td>
<td>110</td>
<td>150</td>
<td>135</td>
<td>150</td>
<td>0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>I (5)</td>
<td>100</td>
<td>110</td>
<td>110</td>
<td>210</td>
<td>195</td>
<td>200</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>I (5)</td>
<td>100</td>
<td>95</td>
<td>100</td>
<td>135</td>
<td>126</td>
<td>126</td>
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<td>0.04</td>
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<tr>
<td>I (5)</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<td>193</td>
<td>207</td>
<td>0.02</td>
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<tr>
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<td>100</td>
<td>123</td>
<td>148</td>
<td>148</td>
<td>0.01†</td>
<td>0.01†</td>
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<tr>
<td>I (10)</td>
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<td>105</td>
<td>95</td>
<td>172</td>
<td>164</td>
<td>164</td>
<td>0.01†</td>
<td>0.01†</td>
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<tr>
<td>I (10)</td>
<td>110</td>
<td>90</td>
<td>85</td>
<td>105</td>
<td>100</td>
<td>120</td>
<td>0.05</td>
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</table>

Mean 101 101 99 189 183 188 0.05 0.05 0.07 0.11

± SE 2 2 3 20 19 18 0.01 0.01 0.02 0.03

P NS NS NS NS NS

*PGE" and "PGF" = prostaglandin E-like and F-like substances; C = control; E = experimental; M = meclofenamate; I = indomethacin; NS = not significant. Time indicates the moment when readings were made or blood samples drawn. 0 min corresponds to the time of administration of prostaglandin synthetase inhibitor. Differences between control and experimental periods were analyzed for significance.

* In one experiment, meclofenamate was used.

† These values signify that prostaglandins were not detected in the sample. As the assay permits detection of 0.02 ng/ml blood of prostaglandins, the value 0.01 ng/ml blood was arbitrarily assigned in these experiments.
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Table 2  Effect of Indomethacin on Blood Pressure, Renal Blood Flow, and Renal Prostaglandin Levels in Anesthetized Dogs

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<td>0.04</td>
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<tr>
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Indo = Indomethacin; ND = not detectable (i.e., <0.02 ng/ml blood); other abbreviations as in Table 1.

of Table 2 in which RBF decreased slightly after administration of indomethacin, a reduction of 16 ml/min occurring. PG levels in renal venous blood also declined slightly.

To reevaluate the previous findings in acutely surgically stressed dogs in which PG synthetase inhibitors decreased RBF and PG levels in renal venous blood, two additional experiments were conducted in anesthetized dogs after laparotomy, according to the methods described in our previous study. These dogs (dogs 15 and 16 of Table 3) had been studied while conscious several days previously and had failed to respond to indomethacin in doses which, in the presence of anesthesia and laparotomy, resulted as in those of the previous studies, in large increases in renal vascular resistance (Fig. 2). However, after anesthesia and laparotomy, administration of indomethacin increased MABP by 10–15 mm Hg and decreased RBF by 20–30% (Table 3).

In Figure 2, comparison of conscious dogs with anesthetized-laparotomized dogs revealed similar control renal vascular resistances for each group. However, PG levels varied greatly between the groups before giving indomethacin. Thus, "PGE" concentrations in renal venous blood in anesthetized-laparotomized dogs averaged 8-fold greater than those of conscious dogs; the corresponding "PGF" levels were about 2-fold greater. The importance of these levels of PGs for maintaining RBF in laparotomized dogs became evident after inhibition of PG synthesis.

Table 3  Effect of Indomethacin (I) on Blood Pressure, Renal Blood Flow and Renal Prostaglandin Levels in Anesthetized, Laparotomized Dogs

<table>
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<tr>
<th>Dog</th>
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<th>E, 15 min</th>
<th>E, 25 min</th>
<th>C, –20 min</th>
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</table>

Mean 110 128 131 194 122 108 0.39 0.04 0.16 0.12
±SE 6 5 5 15 13 16 0.09 0.02 0.04 0.11

P <0.001 <0.01 <0.001 <0.001 <0.005 NS

Abbreviations as in Table 1. Differences between control and experimental periods were analyzed for significance.

* These values signify that prostaglandins were not detected in the sample. As the assay permits detection of 0.02 ng/ml blood of prostaglandins, the value 0.01 ng/ml blood was arbitrarily assigned in these experiments.
Thus, indomethacin produced a rapid rise in renal vascular resistance which became greater than 2-fold that of control renal vascular resistance within 25 minutes. At 40 minutes (not shown in Fig. 2) renal vascular resistance was not significantly different from the value obtained at 25 minutes. Concomitantly, renal venous concentrations of PGs had declined to levels which by 25 minutes after giving indomethacin were similar to those observed in the conscious dog. In the conscious dog indomethacin affected neither renal vascular resistance nor the concentrations of PGs in renal venous blood which were, as noted, much lower than in the acutely surgically stressed dog. Further, the principal PG in renal venous blood was related to the experimental conditions. Thus, "PGE" levels were less than "PGF" levels in renal venous blood in the conscious dog and were not significantly changed by giving indomethacin, viz., ratios of PGE to PGF were 0.7:1.0 before and 0.5:1.0 after administration of indomethacin. However, in the anesthetized-laparotomized dog, the mean renal venous concentration of "PGE" was greater than 2-fold that of "PGF" (PGE:PGF, 2.4:1.0) before indomethacin. After indomethacin administration to the acutely surgically stressed dog, PG levels and the ratios of their concentrations in renal venous blood became similar to those of the conscious dog, viz., PGE:PGF was 0.3:1.0. In one experiment in a conscious dog PGs were not detected in arterial blood. As the arterial blood levels of PGs are small, usually less than 0.02 ng/ml, and as most of the PGs are removed from the arterial blood on passage across the kidney because of the high intrarenal activity of PG-catabolizing enzymes, the venous concentrations indicated above reflect primarily intrarenal levels of PGs.

Plasma renin activity and the concentration of "PGE" were determined simultaneously on samples of renal venous blood obtained from conscious dogs (three), before and after giving indomethacin, and in anesthetized dogs (six), four of which were laparotomized (Fig. 3a). The concentration of "PGF" was also determined on these samples in two of the conscious dogs and in five of the six anesthetized dogs (Fig. 3b). Plasma renin activity and "PGE" were closely correlated over a wide range of their concentrations in renal venous blood (r = 0.81; P < 0.001). In contrast, plasma renin activity and "PGF" concentration in renal venous blood were not correlated (r = 0.373; P > 0.05).

Discussion

In the present study the renal circulatory effects of inhibitors of PG synthetase varied with experimental conditions. Neither chloralose nor pentobarbital anesthesia affected basal renal venous PG levels, and indomethacin had little effect on RBF in the presence of either anesthetic agent alone. In the conscious dog, PG concentrations in renal venous blood were considerably less than those in the chloralose-anesthetized-laparotomized dog and indomethacin affected neither renal vascular resistance nor the levels of PGs, even in doses having major toxic effects. The failure of indomethacin to decrease RBF in the conscious dog confirms the studies of Zins and of Swain et al. Doses of indomethacin 1/3 those that were without effect in the conscious dog, when given to the anesthetized-laparotomized dog, induced large increases in renal vascular resistance. This was associated with reduction of renal venous PG concentrations to those levels observed in the conscious dog. Thus, there appears to be a component of renal PGs which resists even doses of indomethacin (10 mg/kg) that elicit bloody diarrhea. The significance of this component, although now undetermined, invites reconsideration of the possible contribution of PGs, particularly those of renal cortical origin, to resting RBF. Inasmuch as the inhibitory effect of aspirin-like drugs on PG synthesis varies with either experimental conditions or the hormonal background, the inability of indomethacin to decrease RBF in unanesthetized dogs may reflect the operation of one of these factors. Indeed, another aspirin-like compound, meclofenamic acid, reduced RBF in conscious dogs when indomethacin was without effect. Further, after acute blood loss aspirin has been reported to affect renal vascular resistance differently from indomethacin. These differences among the nonsteroidal anti-inflammatory compounds may signify important differential effects of these drugs on PG-metabolizing enzymes, including synthetase, which could contribute to their effects on RBF. Moreover, the possibility of species-dependent effects of indomethacin should be considered,

![Figure 3](http://circres.ahajournals.org/lookup/fig/3)

**Figure 3** The relationship between plasma renin activity (PRA) (ordinates) and the log of the concentration (abscissae) of prostaglandin E-like substances ("PGE") (panel a) and F-like substances ("PGF") (panel b) in renal venous blood of conscious, anesthetized, and surgically stressed dogs. PRA is expressed in nanograms of angiotensin I generated per milliliter of plasma after 1 hour of incubation. Concentrations of "PEG" and "PGF" are expressed in nanograms per milliliter of blood.
e.g., in the conscious rabbit indomethacin decreases RBF. 18

Although the significance of a possible PG-dependent component of RBF in the conscious dog remains to be resolved, it is clear that acute stress, such as hemorrhagic hypotension 19 or laparotomy, 1 evokes a several-fold increase in the production of renal PGs above "basal levels." Changes in synthesis of PGs by the kidney not only affect RBF but also its intrarenal distribution, particularly that fraction distributed to the inner cortex and medulla. The evidence for this was first obtained by Itskovitz et al. 20 in the isolated blood-perfused kidney of the dog and has since been demonstrated in a number of experimental preparations, 21-24 including the unanesthetized rabbit. 18 Thus, the renal circulatory effects of enhanced PG synthesis in the acutely stressed dog are readily revealed by administration of an aspirin-like compound that results in a large reduction of RBF, primarily that component to the inner cortex and medulla. 20, 21, 23 It should be recalled that the zonal distribution of PG synthesis within the kidney is opposite to that of renin, 20 the highest activity being noted in the papilla and inner medulla, the least in the renal cortex. This anatomical arrangement in large part determines the results of increased PG synthesis and its effects on the distribution of intrarenal blood flow.

Angiotensin II was the first vasoactive hormone demonstrated to release PGs from the kidney. 2 The present study suggests that increased release of renin and subsequent generation of angiotensin evoked by the acute experimental procedure increased renal PG levels. Thus, the level of activity of the renin-angiotensin system was highly correlated with renal PG levels as indicated by corresponding changes in the concentrations of plasma renin activity and "PGE" in renal venous blood. This correlation did not obtain for "PGF." PGs of the E series can be shown to oppose the renal effects of angiotensin, whereas those of the F series cannot. 26 We conclude that increased production of PGE 2 , a potent renal vasodilator, 26 helps restore RBF toward its resting level in the face of those stimuli that activate the renin-angiotensin system.

Under basal conditions, a major PG-dependent component of RBF cannot be detected in the dog by administration of inhibitors of PG synthesis. The significance of a basal release, albeit low, of PGs from the canine kidney remains to be determined, as it is unaffected by inhibitors of PG synthesis. Further, these basal levels, if they arise in the renal cortex, 14 may represent a much larger component most of which is destroyed locally. The heavy concentration of PG-catabolizing enzymes in the renal cortex 14 and their relative paucity in the renal medulla provide the biochemical grounds for this hypothesis. Testing this proposal requires simultaneous measurements under basal conditions of rates of PG synthesis and catabolism for the cortex and medulla, each considered separately. This awaits the development of methods, presently unavailable in vivo.

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