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Furosemide Induced Release of Prostaglandin E to Increase Renal Blood Flow[1] (38982)

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We have shown previously that the increase in renal blood flow (RBF) induced by the potent natriuretic–diuretic agent, furosemide, can be blocked by indomethacin (1), an inhibitor of prostaglandin synthesis (2). In contrast to this blockade, the natriuretic action of furosemide was not markedly affected. Thus, while the increase in RBF induced by furosemide would appear to be mediated by release of prostaglandins, the natriuretic diuretic action of this agent would not appear to be mediated by a mechanism involving prostaglandins. In this report, further support for stimulation of release of prostaglandins is presented. Arterial and renal venous blood samples obtained before and after administration of furosemide were analyzed for prostaglandins as were samples obtained after indomethacin and again after a second administration of furosemide.

Methods. Four male mongrel dogs, weighing between 13 and 24 kg, were anesthetized with pentobarbital sodium (30 mg/kg iv) and the trachea was intubated. Mean arterial blood pressure (MAP) was monitored with a pressure transducer (Statham P23AA) via a carotid artery catheter. A jugular vein was catheterized for administration of solution and an infusion of 0.9% NaCl was administered at a rate of 4 ml/min. The left kidney was exposed via a retroperitoneal flank incision. A flow probe was placed around the renal artery and connected to a square wave electromagnetic flow meter (Carolina Medical Electronics) in order to measure total renal blood flow (RBF). If more than one renal artery was encountered, the experiment was not continued. MAP and RBF were recorded continuously on a Beckman Type R Dynograph. The ipsilateral ureter was cannulated in order to collect urine samples. A catheter was passed into the left renal vein via the left testicular vein so that renal venous blood samples could be collected. Arterial blood samples were obtained from a femoral artery or a carotid artery.

The protocol used was as follows. After surgery and stabilization of the preparation, arterial and renal venous samples of blood were obtained. Furosemide, 2 mg/kg, was administered via the jugular infusion and blood samples were taken at the time RBF was increased maximally. After the response to furosemide neared control levels, indomethacin, 5 mg/kg, was given via the jugular infusion. Blood samples were obtained 30 min later and then a second dose of furosemide was administered. At a time equivalent to when RBF was increased maximally after the first dose of furosemide, blood samples were again obtained (see Fig. 1).

Bloods were analyzed for prostaglandins E, F, and A using the method of Van Orden and Farley (3). Data were analyzed by Students' *t* test (paired comparisons) (4). A *P* value of less than .05 was used as the criterion of significance.

Results and Discussion. Figure 1 shows the effect of furosemide on renal blood flow and indicates the times when blood samples were withdrawn. The results of the analyses for prostaglandins E (PGE) are given in Table I. Prior to administration of furosemide, the arterial level of PGE was 213 pg/ml while the renal venous level was 264 pg/ml. Following administration of furosemide, RBF was increased significantly by 54 ± 4 ml/min from a pretreatment level of 196 ml/min. At the time of the maximal increase in flow, renal venous levels of PGE were increased signifi-

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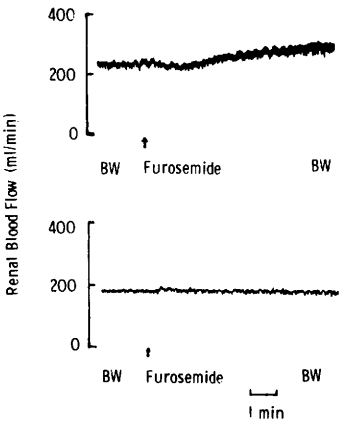

FIG. 1. Effect of furosemide on renal blood flow before (upper tracing) and after indomethacin (lower tracing). BW represents times at which arterial and renal venous blood samples were withdrawn.

cantly by 248 ± 68 pg/ml. No significant change occurred in arterial levels. Prior to a second administration of furosemide and 30 min after the administration of indomethacin, renal venous levels had fallen to 219 pg/ml. Following the second administration of furosemide RBF increased only 6 ± 4 ml/min. Samples of blood taken at the same interval that RBF was increased maximally after the first administration (Fig. 1) showed renal venous levels of PGE of 167 pg/ml. This level was less than the preadministration level and also 345 ± 59 pg/ml less than the seen after the first administration of furosemide.

In Table II, values for PGF are given. Furosemide did not significantly alter renal venous levels of PGF. Thus suppression of release of a constrictor prostaglandin does not appear to be involved in producing an increase in RBF.

In Table II, values for PGA are given. Furosemide did not significantly alter renal venous levels of PGA. Thus the release of this prostaglandin does not appear to be involved in the increase in RBF produced by furosemide.

The lack of effect of furosemide on renal venous levels of PGF and PGA indicates that furosemide does not stimulate synthesis and release of all prostaglandins. Only changes in renal venous levels of PGE were found. Thus, furosemide appears to cause a selective increase in the synthesis and release of renal PGE. Since PGE is known to dilate renal vasculature (5, 6) the stimulation of the synthesis and release of this substance in the kidneys by furosemide could be the mechanism by which furosemide causes an increase in RBF. This mechanism implies that PGE would act intrarenally to increase flow. Either secretion into the arterial vasculature or entrance by diffusion from venous segments would result in an intrarenal action. The high lipid solubility of the prostaglandins

TABLE I. EFFECT OF FUROSEMIDE ON ARTERIAL AND RENAL VENOUS LEVELS OF PROSTAGLANDIN E (pg/ml) BEFORE AND AFTER INDOMETHACIN (N = 4).

Treatments	Arterial	Renal vein	Diff ± SE
None	213±34	264±9	
Furosemide (first dose)	279±45	512±72	+248±68[ab]
Indomethacin	242±44	219±21	−293±73[ac]
Furosemide (second dose)	183±27	167±19	−345±59[ac]

[a] Significant difference.
[b] Compared to control level in renal vein.
[c] Compared to level in renal vein after first dose of furosemide.

TABLE II. EFFECT OF FUROSEMIDE ON ARTERIAL AND RENAL VENOUS LEVELS OF PROSTAGLANDIN F (pg/ml) BEFORE AND AFTER INDOMETHACIN (N = 4).

Treatments	Arterial	Renal Vein
None	104±22	110±20
Furosemide (first dose)	121±16	126±13
Indomethacin	127±38	107±12
Furosemide (second dose)	96±13	102±11

TABLE III. EFFECT OF FUROSEMIDE ON ARTERIAL AND RENAL VENOUS LEVELS OF PROSTAGLANDIN A (pg/ml) BEFORE AND AFTER INDOMETHACIN (N = 3).

Treatments	Arterial	Renal Vein
None	799±81	887±78
Furosemide (first dose)	847±171	789±142
Indomethacin	760±74	787±139
Furosemide (second dose)	904±96	1034±218

is compatible with diffusion into arterial segments.

Summary. Levels of PGE in renal venous blood were found to be significantly elevated at the time RBF was increased by furosemide. Following indomethacin, a second dose of furosemide failed to increase RBF and levels of PGE in renal venous blood were not elevated. Levels of PGF and PGA were not affected by furosemide. The increase of PGE in renal venous blood at the time of renal dilation supports the hypothesis that furosemide increases RBF by releasing PGE. An intrarenal action of the released PGE is implied by this mechanism.

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