Laboratory Investigations

Haemodynamic, diuretic and hormonal responses to prostaglandin E_1 infusion in halothane anaesthetized dogs: comparison among epidural lidocaine, epidural fentanyl and epidural saline

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Deliberate hypotension decreases blood loss and transfusion but it may be accompanied by adverse effects due either to the hypotensive agents themselves or to haemodynamic alterations. Prostaglandin E_1 (PGE_1) has the advantage of a diuretic effect coupled with systemic hypotension. To elucidate the mechanisms by which PGE_1 induces diuresis we compared the haemodynamic, diuretic and hormonal responses to PGE_1 infusion simultaneously with epidural lidocaine (EP-L n = 7), epidural fentanyl (EP-F n = 8) or epidural saline (CONT n = 7) in halothane anaesthetized mongrel dogs. All groups developed a decrease in mean arterial pressure during PGE_1 infusion (from 105 ± 24 to 77 ± 18 mmHg in EP-L; 106 ± 19 to 79 ± 13 mmHg in the EP-F; and 129 ± 14 to 106 ± 18 mmHg in the CONT groups (mean ± SD)) ($P < 0.05$). In the EP-F and CONT groups urinary output increased during PGE_1 infusion (from 4.31 ± 1.89 to 6.15 ± 2.03 $ml \cdot min^{-1}$ and 2.71 ± 1.23 to 4.48 ± 1.66 $ml \cdot min^{-1}$ ($P < 0.05$), respectively) and was accompanied by increases in renal blood flow (from 87.0 ± 40.7 to 111.0 ± 42.8 $ml \cdot min^{-1}$ and from 121.6 ± 46.6 to 158.4 ± 64.9 $ml \cdot min^{-1}$ ($P < 0.05$), respectively) and in fractional excretion of sodium (FE_{Na}) (from 4.78 ± 3.88 to 7.63 ± 5.20% in CONT group). Plasma epinephrine concentration increased after laparotomy in the CONT group (from 0.09 ± 0.08 to 0.17 ± 0.14 $pg \cdot ml^{-1}$) ($P < 0.05$) and antidiuretic hormone (ADH) concentration increased after laparotomy (from 6.9 ± 5.2 to 21.0 ± 13.0 $pg \cdot ml^{-1}$ in EP-F and from 8.1 ± 6.2 to 45.8 ± 29.9 $pg \cdot ml^{-1}$ in CONT groups). Plasma renin activity increased after laparotomy in the EP-L group (from 2.00 ± 1.37 to 4.72 ± 2.73 $mg \cdot ml^{-1} \cdot hr^{-1}$) ($P < 0.05$). The results suggest that the mechansim of the PGE_1-induced diuretic effect includes increases in renal blood flow while

Key words

ANAESTHETIC TECHNIQUES: epidural fentanyl, epidural lidocaine, hypotension;

HORMONES: antidiuretic, catecholamines, plasma renin activity, prostaglandins;

KIDNEY: diuresis.

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renal sympathetic innervation is maintained and in FE_{Na} in the presence of elevated plasma ADH concentration.

L'hypotension contrôlée diminue les pertes sanguines et le nombre de transfusions mais peut aussi s'accompagner des effets indésirables des agents hypotenseurs ou de ceux des changements hémodynamiques. La prostaglandine E_1 (PGE_1) a l'avantage de provoquer la diurèse tout en exerçant son activité hypotensive. Pour élucider les mécanismes selon lesquel la PGE_1 induit la diurèse, nous avons comparé simultanément les réponses hémodynamiques, diurétiques et hormonales à la perfusion de PGE_1 pendant une épidurale à la lidocaïne (EP-L n = 7), au fentanyl (EP-F n = 8) ou au soluté physiologique (CONT n = 7) chez des chiens batards anesthésiés à l'halothane. Tous présentent une baisse de la pression artérielle moyenne pendant la perfusion de PGE_1 (de 105 ± 24 à 77 ± 18 mmHg pour le groupe EP-L, de 106 ± 19 à 79 ± 13 mmHg pour le groupe EP-F; de 129 ± 14 à 106 ± 18 pour le groupe contrôle: moyenne ±SD, $P < 0,05$). Dans les groupes EP-F et CONT le débit urinaire augmente pendant la perfusion de PGE_1 (de 4,31 ± 1,89 à 6,15 ± 2,03 $ml \cdot min^{-1}$ et de 2,71 ± 1,23 à 4,48 ± 1,66 $ml \cdot min^{-1}$ respectivement: $P < 0,05$) et s'accompagne d'une augmentation du débit sanguin rénal (de 87,0 ± 40,7 à 111,0 ± 42 $ml \cdot min^{-1}$ et de 121,6 ± 46,6 à 158,4 ± 64,9 $ml \cdot min^{-1}$ respectivement: $P < 0,05$); dans le groupe CONT, l'excrétion fractionnée de sodium (FE_{Na}) augmente (de 4,78 ± 3,88% à 7,63 ± 5,20%). La concentration d'épinéphrine plasmatique augmente après la laparotomie dans le groupe CONT (de 0,09 ± 0,08 à 0,17 ± 0,14 $pg \cdot ml^{-1}$: $P < 0,05$) et la concentration d'ADH augmente après la laparotomie (de 6,9 ± 5,2 à 21,0 ± 13,0 $pg \cdot ml^{-1}$ dans le groupe EP-F et 8,1 ± 6,2 à 45,8 ± 29,9 $pg \cdot ml^{-1}$ dans le groupe CONT). L'activité de la rénine plasmatique augmente après la laparotomie dans le groupe EP-L (de 2,00 ± 1,37 à 4,72 ± 2,73 $mg \cdot ml^{-1} \cdot h^{-1}$: $P < 0,05$). Ces résultats suggèrent que les mécansismes de l'induction de la diurèse par la PGE_1 comprennent des augmentations du débit sanguin rénal lorsque l'innervation sympathique est conservée et de la FE_{Na} en présence d'une élévation de la concentration plasmatique d'ADN.

Deliberate hypotension is commonly used, especially during neurosurgical and orthopaedic procedures, to reduce blood loss, thereby decreasing the need for blood transfusion, and keeping a dry operative field.[1] However, depending on the drugs used, it may have some disadvantages such as a transient decrease of renal function[2] and an increase in intracranial pressure.[3,4] Prostaglandin E_1 (PGE_1) is widely used to produce deliberate hypotension[1,5] whilst maintaining renal perfusion.[6]

The increase in urinary flow produced by PGE_1 is via two mechanisms; the release or dilatation of the renal arteries from the constriction induced by surgical stress, endogenous catecholamines and/or angiotensin,[7] and an increase in urinary sodium excretion[8,9] via the renal distal tubulus in the presence of increased plasma antidiuretic hormone (ADH) concentration.[10-13] In patients undergoing major surgery with general anaesthesia, an increase in urinary output by PGE_1 infusion can be expected in the presence of increased renal sympathetic activity and increased plasma catecholamines and ADH concentrations. However, in patients undergoing surgery with lumbar or thoracic epidural anaesthesia using local anaesthesia, plasma catecholamine and ADH concentrations are suppressed[14,15] and renal sympathetic outflow is blocked, and these may result in decreased systemic blood pressure and decreased renal perfusion.[16] Therefore, as our recent clinical data indicated,[17] PGE_1 may not increase urinary output in patients undergoing surgery with epidural anaesthesia using local anaesthesia. Epidural fentanyl anaesthesia is widely used during abdominal or lower extremity surgery, but is not accompanied by sympathetic block. However, it is not clear if epidural fentanyl anaesthesia blocks the stress-response to surgery and, hence, whether diuresis induced by PGE_1 infusion can be expected during epidural fentanyl anaesthesia.

In this study we evaluated the diuretic effect by four variables: urinary output, renal blood flow, creatinine clearance (Ccr), and fractional excretion of sodium excretion (FE_{Na}). The purpose of the study was to compare the haemodynamic, diuretic and hormonal responses to PGE_1 infusion simultaneously in halothane anaesthetized mongrel dogs among epidural lidocaine, epidural fentanyl and epidural saline groups, and to elucidate further the mechanism of PGE_1-induced diuretic effect with regard to renal sympathetic activity and interaction with hormonal alterations during laparotomy.

Methods

The study protocol was approved by the ethics committee, Animal Experiment Center, University of Tsukuba, Japan, and the local ethics committee, Department of Anesthesiology, Institute of Clinical Medicine, University of Tsukuba, Japan. Twenty-two mongrel dogs (8.6–15.5 kg) were randomly assigned into three groups; epidural lidocaine (EP-L) ($n = 7$) epidural fentanyl (EP-F) ($n = 8$), and epidural saline (CONT) ($n = 7$) groups.

Anaesthesia was induced with thiamylal, 10 $mg \cdot kg^{-1}$, *iv*, tracheal intubation was facilitated with succinylcholine, 1 $mg \cdot kg^{-1}$, *iv*. Anaesthesia was maintained with halothane 1.0 to 1.5% and oxygen, 1 $L \cdot min^{-1}$, in air under controlled ventilation. Pancuronium bromide, 0.1 $mg \cdot kg^{-1}$, *iv*, was given when necessary. The halothane concentration was adjusted according to mean blood pressure after laparotomy and before PGE_1 infusion to ±25% of baseline value or to >90 mmHg.

After induction of general anaesthesia, an epidural catheter was placed via the $L_{1/2}$ interspace using 18G Minikit™, Portex, U.S.A. Then, in the supine position, arterial, pulmonary and central venous lines were placed via the right femoral artery and vein using 1% lidocaine subcutaneous infiltration. Baseline haemodynamic and hormonal data were determined before laparotomy (Baseline). Epidural administration was as follows; the drugs were 2% lidocaine without epinephrine in the EP-L group, 0.001% fentanyl without epinephrine in the EP-F group, and physiological saline in the CONT group. A bolus of 6 ml was given as the initial dose and a continuous infusion, 4 $ml \cdot hr^{-1}$, was continued during the study period. Ten minutes after the initial epidural administration a midline laparotomy was performed from the xiphoid process to the pubic joint, and were placed an electromagnetic flow meter probe, 4 mm diameter, was attached to the left renal artery. The flow probe was calibrated primarily using automatic calibration from 0 to 200 $ml \cdot min^{-1}$ and then connected to the blood flow meter (Electric Blood Flowmeter, Nippon Kouden, Japan) and an appropriate recorder. Polyethylene tubes were placed in both ureters after their separation from the bladder. The abdominal wound was kept open by a wound retractor and covered with surgical drapes during the study.

Lactated Ringer's solution was infused during the study at 15 $ml \cdot kg^{-1}$ for the first hour followed by 10–15 $ml \cdot kg^{-1} \cdot hr^{-1}$ to maintain pulmonary capillary wedge pressure (PCWP) level as high as 4–10 mmHg. Lead II of the ECG was monitored continuously and arterial blood pressure (AP), heart rate (HR), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and central venous pressure (CVP) were recorded continuously via a transducer and an appropriate amplifier and the recorder (Monitoring Kit™, Baxter, U.S.A. and Polygraph™, NEC Sanei, Japan). Cardiac output was determined by thermodilution technique at baseline, and 15 and 30 min after the start of each urine collection. Arterial blood was withdrawn before laparotomy (baseline), and 15 min after the start of each urine collection for arterial blood gas analysis (pHa, PaO_2, $PaCO_2$ and base excess), and for serum creatinine, sodium, and potassium concentrations, serum osmolarity, and plasma hormonal concentration determinations. Blood samples for hormonal study were centrifuged and stored at −40°C until determination. In the EP-F group serum fentanyl concentration in the blood sample withdrawn during the first urine collection was determined using radioimmuno assay with a detection limit of 0.1 $\mu g \cdot ml^{-1}$.

After stable urinary output of > 1.0 $ml \cdot kg^{-1} \cdot hr^{-1}$ was obtained, an exact one-hour urine sample was collected. Next, dogs received PGE_1 infusion, 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, via the central venous line. After blood pressure and heart rate became stable, approximately 20 min after the start of infusion, a second precise one-hour urine sample was collected. Then the PGE_1 infusion was stopped. After blood pressure and heart rate became stable, approximately 30 min after the cessation of PGE_1 infusion, a third exact one-hour urine sample was collected. With each urine sample, volume, creatinine, and sodium concentrations were determined. After the study, dogs were autopsied to confirm proper epidural catheter placement, and the range of spread of solution in the epidural space was determined from the colour change produced by pioctanine dye, 6 ml, injected via the epidural catheter.

Plasma epinephrine and norepinephrine concentrations were determined using HPLC-electrochemical detection assay, ADH, cortisol and ACTH concentrations were determined using radioimmunoassay, and PRA was determined in terms of its enzymatic activity using radioimmunoassay. The limits of detection and the interassay coefficients of variation were 1 $pg \cdot ml^{-1}$ and 2.3% for epinephrine, 3 $pg \cdot ml^{-1}$ and 2.3% for norepinephrine, 0.2 $pg \cdot ml^{-1}$ and 8.0–8.3% for ADH, 0.1 $ng \cdot ml^{-1} \cdot hr^{-1}$. and 5.1–9.4% for PRA, 2 $pg \cdot ml^{-1}$ and 2.6–9.9% for ACTH, and 0.3 $\mu g \cdot dl^{-1}$ and 4.1–5.8% for cortisol, respectively. Creatinine and sodium concentrations were determined by an ACA SX discrete clinical analyzer, Dupont, U.S.A., and a NOVA6 Electrolyte analyzer, NOVA Biomedical, U.S.A., respectively. Arterial blood gas analysis was made using NT-450, Corning, U.S.A.

Minute urinary output, creatinine clearance (Ccr), and the fractional excretion of sodium (FE_{Na}) were calculated for each urine sample[18] using the following formula:

$$Ccr = \frac{\text{U-Cre} * \text{one-hour urine volume}}{\text{S-Cre} * 60} \ (ml \cdot min^{-1})$$

where
U-Cre: urinary creatinine concentration,
S-Cre: serum creatinine concentration.

$$FE_{Na} = \frac{\text{U-Na} * \text{S-Cre}}{\text{S-Na} * \text{U-Cre}} * 100 \ (\%)$$

where
S-Na: serum sodium concentration
U-Na: urinary sodium concentration.

Statistical analysis

Baseline haemodynamic and plasma hormonal concentration data, and RBF, minute urinary output, Ccr, and FE_{Na}, and before PGE_1 infusion were compared among the three groups using ANOVA. Bonferroni's correction

TABLE I Haemodynamic data (mean ± SD)

Items/Group	*Baseline*	*Pre-PG*	*During-PG*	*After-PG*
MAP (mmHg)				
EP-L	130 ± 31	105 ± 24*	77 ± 18*	99 ± 25*
EP-F	114 ± 22	106 ± 19*	79 ± 13*	102 ± 16*
CONT	122 ± 19	129 ± 14	106 ± 18*	133 ± 13
HR (bpm)				
EP-L	169 ± 22	106 ± 16*	109 ± 31*	106 ± 22*
EP-F	174 ± 19	130 ± 16*	148 ± 26*	118 ± 15*
CONT	167 ± 12	160 ± 14	168 ± 19	152 ± 19
CVP (mmHg)				
EP-L	6.2 ± 4.1	4.5 ± 3.2	4.6 ± 3.7	5.7 ± 3.7
EP-F	3.2 ± 2.2	2.8 ± 1.6	2.6 ± 2.0	2.7 ± 1.5
CONT	6.7 ± 3.0	6.7 ± 3.0	6.3 ± 3.0	6.7 ± 3.0
SVR (dyne · sec · cm^{-5})				
EP-L	2880 ± 1020	4010 ± 1120*	2720 ± 850†	3610 ± 940*
EP-F	2590 ± 910	3310 ± 1070*	2450 ± 700†	3640 ± 910*
CONT	2330 ± 360	3570 ± 1170*	2700 ± 920†	4110 ± 1200*
MPAP (mmHg)				
EP-L	24 ± 7	16 ± 5*	16 ± 5*	18 ± 3
EP-F	18 ± 6	17 ± 3	19 ± 3	16 ± 3
CONT	20 ± 2	19 ± 3	17 ± 3*	19 ± 3
PCWP (mmHg)				
EP-L	7.6 ± 2.9	6.6 ± 2.7	6.0 ± 2.0	8.0 ± 1.8
EP-F	5.1 ± 1.6	5.3 ± 2.2	4.8 ± 1.8	4.4 ± 1.8
CONT	5.7 ± 2.5	5.7 ± 2.4	5.9 ± 2.4	5.6 ± 2.4
PVR (dyne · sec · cm^{-5})				
EP-L	398 ± 126	425 ± 177*	436 ± 186	450 ± 165
EP-F	294 ± 105	371 ± 73*	431 ± 98*	435 ± 106
CONT	279 ± 66	370 ± 50*	305 ± 67	459 ± 108
CO (L · min^{-1})				
EP-L	3.6 ± 0.9	2.1 ± 0.5*	2.3 ± 0.8*	2.2 ± 0.8*
EP-F	3.6 ± 0.7	2.5 ± 0.4*	2.7 ± 0.8*	2.3 ± 0.4*
CONT	4.1 ± 0.4	3.2 ± 0.5*	3.4 ± 0.6*	2.8 ± 0.5*

MAP: mean arterial pressure; HR: heart rate; MPAP: mean pulmonary arterial pressure; CVP: central venous pressure; PCWP: pulmonary capillary wedge pressure; SVR: systemic vascular resistance; PVR: pulmonary vascular resistance; CO cardiac output.
Pre-PG: before PGE_1 infusion; During-PG: during PGE_1 infusion; After-PG: after stopping PGE_1 infusion.
*$P < 0.05$ vs Baseline. †$P < 0.05$ vs Pre-PG; no intergroup difference in changes after laparotomy and during PGE_1 infusion.

was applied as appropriate. Each haemodynamic variable and plasma hormonal concentration before, during and after PGE_1 infusion were compared with baseline values using ANOVA and paired t test. The RBF, Ccr and FE_{Na} values during and after PGE_1 infusion were compared with their values before PGE_1 using ANOVA and paired t test as above. A P value < 0.05 was considered to indicate statistical significance.

Results

There were no differences in the baseline values of haemodynamic, diuretic and arterial blood gas variables and the total infused volume of lactated Ringer's solution during the study among the three groups (Tables I and II, Figure). In all groups PGE_1 infusion elicited decreases in MAP (from 105 ± 24 to 77 ± 18 mmHg in EP-L, from 106 ± 19 to 79 ± 13 mmHg in EP-F, and from 129 ± 14 to 106 ± 18 mmHg in CONT groups) ($P < 0.05$), but no changes in HR, CO, MPAP, CVP, and PCWP (Table I). During PGE_1 infusion MAP was lower in the EP-L group than in the CONT group ($P < 0.05$) (Table I). Plasma fentanyl concentration in EP-F group was 0.3 ± 0.2 $\mu g \cdot ml^{-1}$, ranging from 0.1 to 0.5 $\mu g \cdot ml^{-1}$.

One-hour urinary output in the period before PGE_1 infusion was >2.3 $ml \cdot kg^{-1}$ in all three groups. In the

TABLE II Laboratory findings (mean ± SD)

Items/Group	*Baseline*	*Pre-PG*	*During-PG*	*After PG*
Arterial blood gas analysis				
PaO_2 (mmHg)				
EP-L	174 ± 66	149 ± 43	138 ± 59	141 ± 63
EP-F	255 ± 27	232 ± 60	218 ± 59	221 ± 65
CONT	188 ± 88	188 ± 77	185 ± 72	181 ± 74
$PaCO_2$ (mmHg)				
EP-L	31 ± 4	33 ± 6	36 ± 9	31 ± 7
EP-F	31 ± 4	37 ± 5	36 ± 5	35 ± 6
CONT	29 ± 7	32 ± 5	32 ± 4	31 ± 4
pH				
EP-L	7.37 ± 0.09	7.30 ± 0.09	7.30 ± 0.14	7.33 ± 0.09
EP-F	7.41 ± 0.04	7.35 ± 0.07	7.30 ± 0.05	7.34 ± 0.04
CONT	7.38 ± 0.12	7.40 ± 0.09	7.38 ± 0.08	7.41 ± 0.08
BE ($mEq \cdot L^{-1}$)				
EP-L	−7.0 ± 3.1	−8.0 ± 3.6	−8.6 ± 5.0	−8.9 ± 6.3
EP-F	−3.9 ± 3.1	−6.3 ± 1.8	−6.9 ± 1.6	−6.7 ± 1.8
CONT	−7.3 ± 3.7	−7.4 ± 3.5	−7.9 ± 2.9	−6.4 ± 3.5
K^+ ($mEq \cdot L^{-1}$)				
EP-L	3.2 ± 0.4	3.1 ± 0.4	3.1 ± 0.5	3.1 ± 0.2
EP-F	3.0 ± 0.4	3.2 ± 0.7	3.2 ± 0.2	3.4 ± 0.4
CONT	3.2 ± 0.5	3.0 ± 0.4	3.0 ± 0.4	3.1 ± 0.4
Haematocrit (%)				
EP-L	32 ± 6	31 ± 7	30 ± 8	29 ± 6*
EP-F	30 ± 6	29 ± 5	27 ± 6*	28 ± 4*
CONT	31 ± 4	28 ± 5*	27 ± 4*	26 ± 4*
Serum glucose ($mg \cdot dl^{-1}$)				
EP-L	99 ± 24	113 ± 47	125 ± 61	116 ± 41
EP-F	119 ± 27	120 ± 22	96 ± 19*	105 ± 40
CONT	125 ± 34	170 ± 75	159 ± 41	159 ± 46
Plasma osmolarity ($mOsm \cdot kg^{-1}$)				
EP-L	292 ± 10	292 ± 10	296 ± 7	302 ± 6
EP-F	291 ± 8	295 ± 11	294 ± 12	290 ± 17
CONT	295 ± 13	294 ± 10	300 ± 11	304 ± 9*

BE: Base excess.
Pre-PG: before PGE_1 infusion; During-PG: during PGE_1 infusion; After-PG: after stopping PGE_1 infusion.
*$P < 0.05$ vs Baseline; no intergroup difference in changes after laparotomy and during PGE_1 infusion.

EP-L group, PGE_1 infusion did not elicit changes in RBF, urinary output, and FE_{Na}, while in the EP-F and CONT groups, PGE_1 infusion increased RBF, urinary output, and FE_{Na} ($P < 0.05$) (Figure). Percent changes in RBF, urinary output and FE_{Na} in the EP-F and CONT groups were greater than those in the EP-L group ($P < 0.01$) (Figure (A)). In the EP-F group, RBF increased from 87 ± 41 to 111 ± 43 $ml \cdot min^{-1}$, urine output increased by from 4.31 ± 1.89 to 6.15 ± 2.03 $ml \cdot min^{-1}$ and FE_{Na} increased from 6.15 ± 2.01 to 8.26 ± 4.13%, and in CONT group, RBF increased from 122 ± 47 to 158 ± 65 $ml \cdot min^{-1}$, urinary output increased by from 2.71 ± 1.23 to 4.48 ± 1.66 $ml \cdot min^{-1}$ and FE_{Na} increased from 4.78 ± 3.88 to 7.63 ± 5.20% (Figure (A), (B), (D)). Creatinine clearance remained the same as baseline during PGE_1 infusion in the EP-F and CONT groups, but decreased in EP-L group (from 25.2 ± 16.5 to 20.3 ± 2.6 $ml \cdot min^{-1}$) $P < 0.05$ (Figure (C)).

Plasma epinephrine concentration increased after laparotomy (from 0.09 ± 0.08 to 0.17 ± 0.14 $pg \cdot ml^{-1}$) $P < 0.05$ and remained elevated during PGE_1 infusion in the CONT group (Table III). Plasma norepinephrine concentration did not change during the study in the EP-F or CONT groups, but decreased during and after PGE_1 infusion in the EP-L group. Plasma ADH concentration increased after laparotomy and during PGE_1 infusion from 6.9 ± 5.2 to 21.0 ± 13.0 $pg \cdot ml^{-1}$ in EP-F and from 8.1 ± 6.2 to 45.8 ± 29.9 $pg \cdot ml^{-1}$ in the

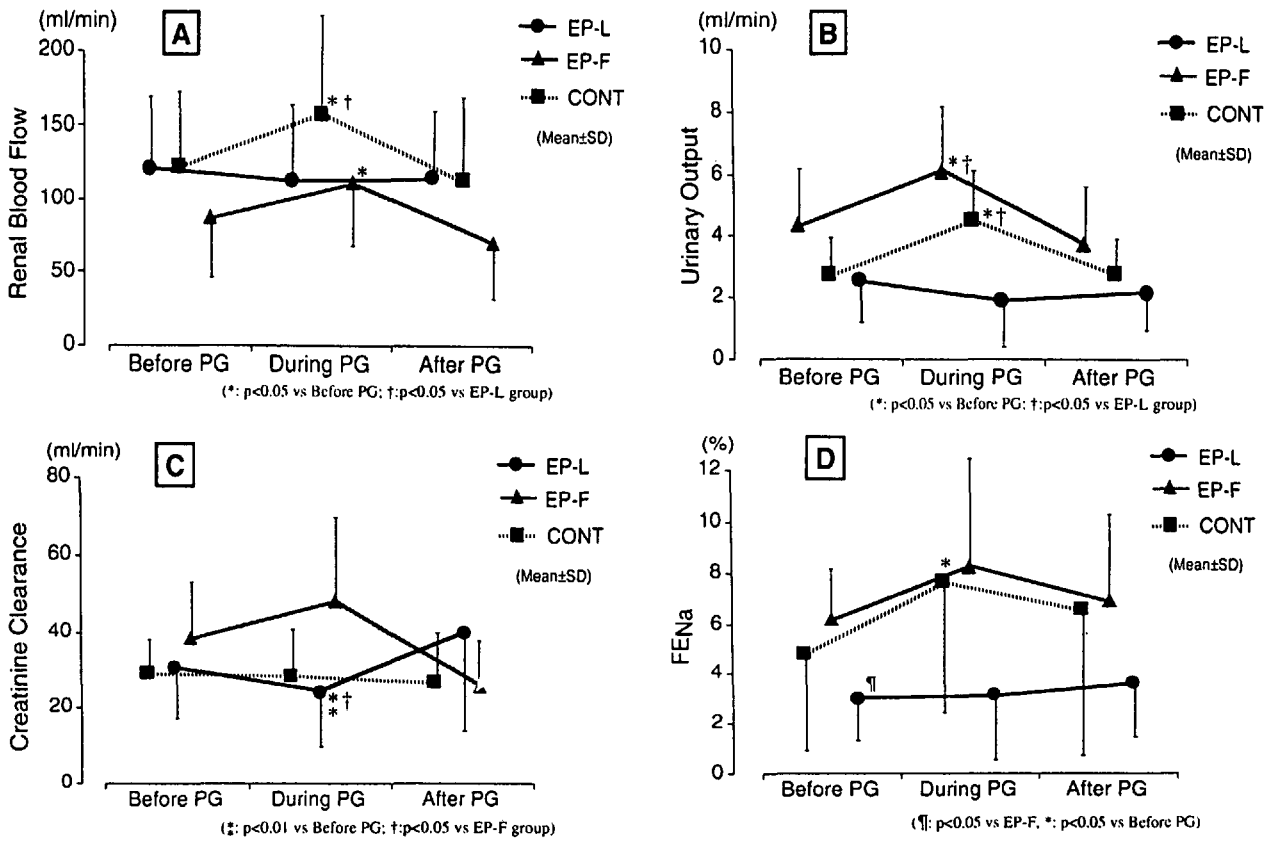

FIGURE The diuretic effect induced by PGE_1 infusion in the three groups, showing (A) renal blood flow (RBF), (B) urinary output, (C) creatinine clearance (Ccr) and (D) fractional excretion of sodium (FE_{Na}). In the EP-F group, RBF, urinary flow increased during PGE_1 infusion compared with Baseline and with those changes in EP-L group. In the CONT group, RBF, urinary flow, and FE_{Na} increased compared with Baseline and with those changes in EP-L group (except for FE_{Na}). In EP-L group, RBF, urinary flow and FE_{Na} did not change during PGE_1 infusion, and Ccr decreased during PGE_1 infusion compared with Baseline and with change in the EP-F group.

CONT groups, ($P < 0.05$) but not in the EP-L group. Plasma renin activity increased after laparotomy (from 2.00 ± 1.37 to 4.72 ± 2.73 mg · $ml^{-1} \cdot hr^{-1}$) and during PGE_1 infusion in EP-L group, but decreased during PGE_1 infusion from 2.28 ± 0.94 to 1.76 ± 0.48 mg · $ml^{-1} \cdot hr^{-1}$ in the CONT group ($P < 0.05$). Plasma ACTH concentration increased after laparotomy and remained elevated until the end of the study in all three groups. Plasma cortisol concentration showed small increases in the EP-L and CONT groups, and remained at similar levels in the three groups.

Discussion

The principal findings of the study are that first, in the EP-L group the increases in RBF, urinary output and FE_{Na} during PGE_1 infusion were prevented; PRA was increased but without increases in plasma epinephrine and ADH concentrations after laparotomy. This finding supports our clinical observations.[17] Secondly, in the EP-F group, during PGE_1 infusion there were increases in RBF and urinary output, and Ccr and FE_{Na} were maintained.

Haemodynamic changes in the EP-L group during PGE_1 infusion were comparable with those in the EP-F and CONT groups: PGE_1 was associated with decreased MAP and SVR but no change in HR, MPAP, CO and PCWP, which is different from our clinical observation.[17]

It is reported that PGE_1 dilates the renal artery in the presence of surgical stress and catecholamine- and/or angiotensin-induced renovascular constriction.[7] In animal studies,[8,19-21] PGE_1 increased renal blood flow but did not affect Ccr, which was considered to indicate that PGE_1 dilates not only afferent but also efferent arterioles in animals[8] so that the filtration ratio was not increased. In the present study, Ccr was not increased during PGE_1 infusion in the EP-F and CONT groups which suggests that PGE_1 had a vasodilating action on both renal afferent and efferent arterioles in dogs. On the other hand, Ccr decreased during PGE_1 infusion in the EP-L group,

TABLE III Plasma hormonal concentrations (mean ± SD)

Items/Group	*Baseline*	*Pre-PG*	*During-PG*	*After-PG*
Epinephrine ($pg \cdot ml^{-1}$)				
EP-L	0.10 ± 0.08	0.03 ± 0.02	0.02 ± 0.01	0.03 ± 0.02
EP-F	0.12 ± 0.21	0.15 ± 0.13	0.14 ± 0.13	0.15 ± 0.24
CONT	0.09 ± 0.08	0.17 ± 0.14	0.25 ± 0.44	0.23 ± 0.43
Norepinephrine ($pg \cdot ml^{-1}$)				
EP-L	0.08 ± 0.05	0.06 ± 0.04	0.02 ± 0.01*‖	0.03 ± 0.01*‖
EP-F	0.07 ± 0.02	0.07 ± 0.02	0.09 ± 0.03	0.09 ± 0.05
CONT	0.11 ± 0.07	0.11 ± 0.09	0.13 ± 0.10	0.10 ± 0.08
Antidiuretic hormone ($pg \cdot ml^{-1}$)				
EP-L	8.3 ± 3.2	9.9 ± 5.5	14.6 ± 6.7	7.5 ± 5.1
EP-F	6.9 ± 5.2	21.0 ± 13.0*	23.7 ± 19.8	19.5 ± 27.8
CONT	8.1 ± 6.2	45.8 ± 29.9*‡	45.5 ± 37.4 *‡	7.5 ± 3.1
Plasma renin activity ($ng \cdot ml^{-1} \cdot hr^{-1}$)				
EP-L	2.00 ± 1.37	4.72 ± 2.73*§	5.50 ± 4.16*§	4.90 ± 3.10*
EP-F	1.28 ± 0.44	1.36 ± 1.09	1.44 ± 0.70	1.32 ± 0.89
CONT	2.20 ± 0.54	2.28 ± 0.94	1.76 ± 0.48*	1.42 ± 0.70*
ACTH ($pg \cdot ml^{-1}$)				
EP-L	34.0 ± 12.8	61.4 ± 10.0†	66.4 ± 8.2†	64.3 ± 16.7†
EP-F	35.7 ± 12.2	62.5 ± 23.3*	60.3 ± 23.1*	47.7 ± 15.3
CONT	44.4 ± 14.1	65.0 ± 26.2*	69.4 ± 34.3*	56.8 ± 23.8
Cortisol ($\mu g \cdot dl^{-1}$)				
EP-L	6.23 ± 2.04	7.74 ± 1.82*	7.07 ± 1.65	7.80 ± 1.52*
EP-F	6.51 ± 1.66	5.99 ± 1.76	6.36 ± 1.94	6.57 ± 2.28
CONT	8.54 ± 1.28	10.01 ± 1.97*¶	9.16 ± 2.58	9.71 ± 3.03

Pre-PG: before PGE_1 infusion; During-PG: during PGE_1 infusion; After-PG: after stopping PGE_1 infusion. *$P < 0.05$ vs Baseline; †$P < 0.01$ vs Baseline; Intergroup differences in changes: ‡$P < 0.05$ vs EP-F and EP-L groups, ¶$P < 0.05$ vs EP-F group; §$P < 0.05$ vs EP-F and CONT groups; ‖$P < 0.05$ vs CONT group.

which suggests that renal sympathetic denervation coupled with PGE_1-induced hypotension prevented the diuretic effect.

Urinary sodium excretion is augmented by PGE_1 in the presence of increased plasma ADH concentration.[10-13] Bonnet *et al.*[14] and ourselves[17] have reported that ADH concentration during surgery under epidural anaesthesia using local anaesthetics was less than that during general anaesthesia, and this is similar to the present results. Intravascular volume distribution and a surgical procedure may affect the diuretic effect but in this study the fluid infused and the surgical procedures were similar in the three groups. Therefore, the difference in PGE_1-induced effects on FE_{Na} among the groups may be due to the difference of plasma ADH concentration.[23,24] In addition, it is possible that the decreased perfusion pressure in the EP-L and EP-F groups might have contributed to the absence of an increase in FE_{Na}.[25,26]

Renin is secreted in response to changes in perfusion pressure at the afferent arteriole and in solute delivery to the distal tubulus.[27] Also, renal sympathetic nerve stimulation or an infusion of catecholamine increases renin secretion.[27,28] In the EP-L group, the PRA level was elevated after laparotomy and during PGE_1 infusion in spite of renal sympathetic denervation,[28] which suggests possible renal hypoperfusion.[27,29] On the other hand, in the EP-F and CONT groups, the PRA level did not change after laparotomy and during PGE_1 infusion, which suggests that renal perfusion was maintained[27] during PGE_1 infusion. The PGE_1-induced diuretic effect was observed to be greatest in the CONT group, and secondly in the EP-F group, which suggests that the stress-response to lapartomy was less in the EP-F than in the CONT group and this may be related to the level of renal sympathetic activity. These observations support previous reports.[7,10-13] Plasma ACTH concentration increases soon after severe trauma, although the mechanism is not clear.[30].

In oliguric subjects or patients in whom residual urinary volume is small, Ccr may not be a reliable test of glomerular function.[31,32] In this study, one-hour urinary output was >1 $ml \cdot kg^{-1}$ and bilateral ureters were cannulated to the collector to reduce residual urine to zero.

In conclusion, epidural lidocaine prevented and epidural fentanyl preserved PGE_1-induced diuresis. The re-

sults of this study demonstrated that the mechanism of the PGE_1-induced diuretic effect in dogs includes an increase in RBF under preserved renal sympathetic activity and/or elevated plasma catecholamines concentrations, and an increase in FE_{Na} in the presence of elevated plasma ADH concentration.

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