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Prostaglandins and thromboxane in the delayed phase of shock induced by *Serratia marcescens* endotoxin

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1 The cardiovascular and metabolic effects of an endotoxin derived from *Serratia marcescens* were examined in anaesthetized, spontaneously-breathing cats. There was a marked initial elevation of right atrial pressure (the result of pulmonary vasoconstriction) and decreases in systemic arterial pressure and in arterial P_{O_2}.

2 The 'delayed' effects of endotoxin shock in this species (1–8 h) consisted of a reduced cardiac output and decreased urinary excretion. Blood pressure and myocardial contractility (assessed from measurement of left ventricular (LV) *dP/dt* and LV end-diastolic pressure) were maintained throughout this phase. There was evidence of a metabolic (lactic) acidosis largely compensated by hyperventilation.

3 Plasma levels (both arterial and mixed venous blood samples) of prostaglandin (PG)E_2, $PGF_{2\alpha}$, 6-keto $PGF_{1\alpha}$ and thromboxane (TX)B_2 were measured by radioimmunoassay techniques. Endotoxin administration caused substantial increases in the plasma levels of all four derivatives of arachidonic acid, especially between 1 and 6 h.

4 Separation of the endotoxin-treated cats into survivors and non-survivors showed that the non-survivors had significantly higher circulating levels of PGE_2, TXB_2 and $PGF_{2\alpha}$. It is suggested that TXB_2 and $PGF_{2\alpha}$ might contribute to some of the detrimental effects of endotoxin (e.g. pulmonary, mesenteric, renal vasoconstriction; platelet aggregation with resulting organ failure) and that prostacyclin may be beneficial in endotoxin shock in this species.

Introduction

There is considerable evidence that certain metabolites of arachidonic acid participate in the pathophysiology of endotoxin shock. For example, in cats, aspirin pretreatment abolished the early effects of *Escherichia coli* endotoxin (pulmonary hypertension and oedema; systemic hypotension) although not the later mesenteric ischaemia and systemic hypotension (Greenway & Murthy, 1971). Pretreatment with indomethacin, flurbiprofen or meclofenamate similarly modifies the acute pulmonary effects of endotoxin in this species (Parratt & Sturgess, 1974; 1976; Parratt *et al.*, 1982). However, although indomethacin administration after the onset of shock fails to modify survival significantly (Parratt & Sturgess, 1975a) the repeated administration of sodium meclofenamate prevents systemic hypotension during the later stages of endotoxin shock, delays both the fall in cardiac output and the metabolic acidosis, and increases survival (Parratt & Sturgess, 1975b). These non-steroidal anti-inflammatory agents have in common the property of inhibiting cyclooxygenase (Flower, 1974).

The ability of several such drugs to modify at least some of the effects of endotoxin suggests that arachidonic acid derivatives are involved. Indeed, increased concentrations of prostaglandin (PG)$F_{2\alpha}$ and thromboxane (TX)B_2 have been observed following endotoxin administration in this species and have been associated with the early and acute pulmonary effects of endotoxin (pulmonary hypertension, increased airways resistance, reduced lung compliance; Coker *et al.*, 1982; 1983). However, most of the available evidence suggests that anti-inflammatory drugs are less effective in preventing the delayed effects of endotoxin administration.

In the present study, the haemodynamic and metabolic effects of *Serratia marcescens* endotoxin have been examined in anaesthetized cats, since there are clinical reports of an increasing incidence of

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Serratia marcescens infections being sometimes associated with shock (Crowder *et al.*, 1971; Yu, 1979). The concentrations of PGE_2, $PGF_{2\alpha}$ and 6-keto $PGF_{1\alpha}$ and TXB_2 (the major degradation products of prostacyclin and TXA_2, respectively) in the arterial and venous systemic circulations were determined, in order to assess their roles in the effects of endotoxin, particularly during the delayed phase of shock.

Methods

Fifteen cats of either sex, weighing 2–4 kg, were deprived of food overnight. Sodium pentobarbitone, 42 mg kg^{-1} body weight was given intraperitoneally, and further doses of 6 mg kg^{-1} were given intravenously as required. Body temperature was maintained at 37 ± 1°C. The trachea was cannulated and the animals breathed spontaneously; occasionally positive pressure ventilation was necessary, using room air at a rate of 20 strokes min^{-1} and a stroke volume of 25 ml kg^{-1}.

Catheters containing heparinised (30 i.u.ml^{-1}) sodium chloride solution (154 mmol l^{-1}) were placed in the femoral vein for endotoxin administration and, via the right external jugular vein, into the right atrium to record right atrial pressure. The left femoral artery was cannulated to record arterial pressure. A stiff catheter was placed in the left carotid artery and manoeuvred into the left ventricle to record left ventricular pressure. Standard limb leads, attached to intradermal needles, were used to record the electrocardiogram. Cardiac output was determined by the thermodilution method using room temperature 0.9%w/v NaCl solution (saline); for this a thermocouple was inserted via a femoral artery to lie in the descending aorta, and a reference thermocouple, together with a direct recording thermocouple was placed in the rectum (Parratt, 1974). Animals received 100 i.u. heparin kg^{-1} on completion of surgery.

Intravascular pressures (arterial, right atrial and left ventricular) were recorded with Statham P23 1D transducers and an eight channel ink-jet recorder (Siemens Elema mingograph 82). Certain parameters were simultaneously displayed on an oscilloscope (Racal Instruments). Left ventricular end-diastolic pressure (LVEDP) was measured from left ventricular pressure tracings recorded at high gain. The rate of change of left ventricular pressure (LV *dP/dt*) was monitored with a differentiating circuit and mean (arterial and right atrial) pressures were obtained by electronic integration.

Blood pH and gases were determined, from anaerobic (0.5 ml) samples taken from the femoral artery, with a calibrated blood gas analyser (Instrumentation Laboratories). Plasma concentrations of PGE_2, $PGF_{2\alpha}$ 6-keto $PGF_{1\alpha}$ and TXB_2 were determined by radioimmunoassay, from blood samples (3 ml) taken from the right atrium and left ventricle (see below).

The effects of *Serratia marcescens* endotoxin (lipopolysaccharide B, Difco Laboratories) were examined in a group of 10 cats, whilst a group of 5 cats served as controls. One h after the completion of surgical procedures, baseline measurements were made of blood pH and gases, and haemodynamic parameters. A dose of 2 mg kg^{-1} endotoxin, dissolved in 2 ml saline, was administered via a femoral vein, with the control cats receiving saline alone. Blood pH and gases and cardiac output were measured at hourly intervals, whilst intravascular pressures were assessed at 2, 5, 15 and 30 min post-endotoxin and then at hourly intervals. For the determination of plasma PGE_2, $PGF_{2\alpha}$ 6-keto $PGF_{1\alpha}$ and TXB_2 concentrations, blood was taken from the right atrium at 0 h (before baseline measurements) and at 1, 3, 6 and 8 h after endotoxin; blood was also taken in some cats from the left ventricle at 0 h and at 1, 3, and 8 h after endotoxin for comparative measurements. The animals were studied for a period of up to 8 h.

Radioimmunoassay of arachidonic acid derivatives

Plasma concentrations, in both arterial and venous blood, of PGE_2, $PGF_{2\alpha}$, 6-keto $PGF_{1\alpha}$ (the main metabolite in this species of prostacyclin) and TXB_2 (the main, inactive, metabolite of TXA_2) were determined by radioimmunoassay techniques developed within the department and described in full by Coker *et al.* (1982). Each blood sample was collected in a plastic syringe, placed immediately in a plastic tube at 4°C containing indomethacin (30 μg in ethanol) and sodium edetate (EDTA) (4.2 mg in saline) and centrifuged within 40 min (at 4°C and at 2,000 *g* for 10 min). Plasma samples were stored at −20°C until assayed.

The detection limits, determined from the assay of standard amounts of these compounds, were 10 pg for PGE_2 and TXB_2 and 25 pg for $PGF_{2\alpha}$ and 6-keto $PGF_{1\alpha}$. Although recoveries of labelled prostanoids from plasma were determined for each individual sample, for the purposes of assessing the technique the mean recoveries were also determined for each of three assays (when *n* was at least 40 samples) carried out at different times during the experimental period. The range of these recoveries ranged from 86.9 to 95.6% for PGE_2, from 84.0 to 93.6% for $PGF_{2\alpha}$, from 70.6 to 97.1% for 6-keto $PGF_{1\alpha}$ and from 79.3 to 95.2 for TXB_2 The coefficient of variation never exceeded 11%.

In the text more attention is paid to changes in the levels of these substances in plasma during shock

than to absolute values. A similar approach has been recommended by Granstrom & Kindahl (1978).

Statistical analysis

Results are quoted as the mean ± one standard deviation (s.d.) unless otherwise stated. In cases where the data were sequential the response was expressed in terms of the area under the time curve. Since the data were not always normally distributed, statistical analysis for significant differences between groups were performed using the Mann-Whitney U test which is not distribution-dependent. The survival of animals beyond certain periods of time was analysed, for significant differences between groups, by the Fisher exact probability test. The behaviour of individual animals within a group time was analysed using a two-way analysis of variance by ranks. Details of these tests can be found in Siegel (1956). Unless otherwise stated, significance levels are given at 5%.

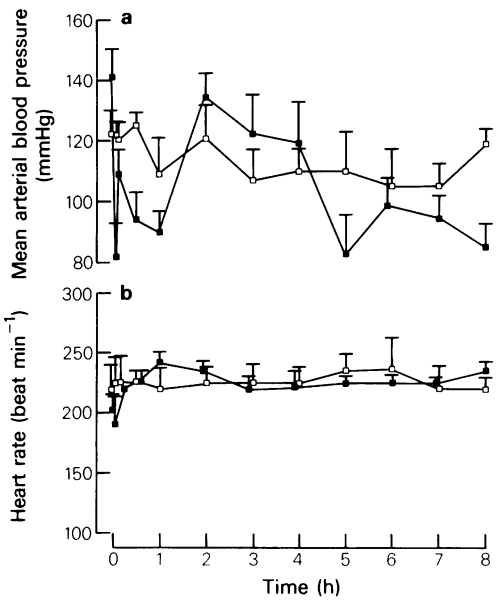

Figure 1 (a) Arterial blood pressure (mean, mmHg) and (b) heart rate (beats min^{-1}) in cats administered either *S. marcescens* endotoxin (2 mg kg^{-1}; closed symbols) or saline (open symbols) over the eight hour experimental period. Values are means ± s.e.mean where $n = 5$ (saline group) or from 5–10 (endotoxin group). The values at time zero are those immediately before the endotoxin (or saline) injection.

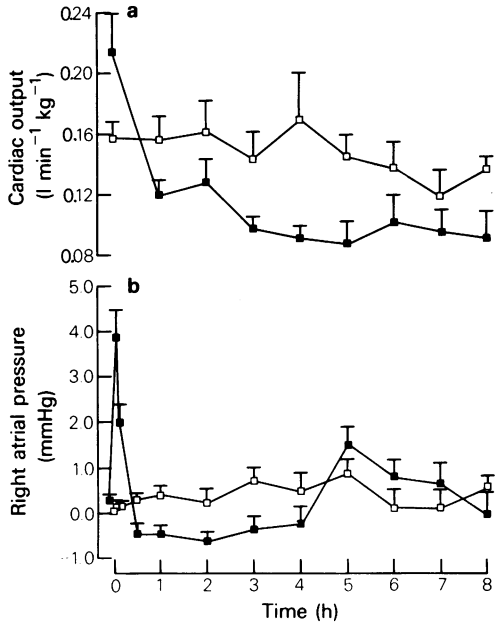

Figure 2 (a) Cardiac output (1 $min^{-1}kg^{-1}$) and (b) right atrial pressure (mmHg) in cats administered either *S. marcescens* endotoxin (2 mg kg^{-1}; closed symbols) or saline (open symbols) over the eight hour experimental period. Values are means ± s.e.mean where $n = 5$ (saline group) or from 5–10 (endotoxin group). The values at time zero are those immediately before the endotoxin (or saline) administration.

Results

Haemodynamic effects of S. marcescens *endotoxin*

These are illustrated in Figures 1 and 2. At 2 min post-endotoxin the arterial blood pressure and cardiac output were significantly reduced and the right atrial pressure significantly increased (to 3.9 ± 0.4 mmHg; $P < 0.025$). Left ventricular (LV) pressure and LV dP/dt max. (119 ± 18 mm Hg and 3700 ± 950 mm Hg s^{-1}, respectively) were also significantly reduced ($P < 0.02$) at this time; LV end-diastolic pressure (EDP) was unchanged. During the 5–10 min period, arterial blood pressure, right atrial pressure and LV*dP/dt max* recovered to values not significantly different to those in the control group and remained thus up to 7 h post-endotoxin, except for a significant ($P < 0.05$), but temporary, decline in arterial blood pressure at 5 h. In contrast, cardiac output remained significantly depressed ($P < 0.025$) throughout the entire 8 h experimental period (Figure 2).

During the 1–4 h post-endotoxin period, right atrial pressure was reduced significantly (Figure 2) but thereafter was not significantly different to that of the control group. Left ventricular pressure and *dP/dt max* were unchanged relative to control in the 1–4 h period following endotoxin administration whilst arterial blood pressure, heart rate and LVEDP in the endotoxin-treated animals were not significantly different from the control group throughout the entire 8 h experimental period.

In three additional cats, urine excretion was measured following cannulation of both ureters after a mid-line abdominal incision. These cats were continuously infused with 6 ml $kg^{-1} h^{-1}$ of saline intravenously. Endotoxin markedly reduced urinary excretion (4.9 ± 2.4 $\mu l\ min^{-1} g^{-1}$ kidney before endotoxin to $2.27 \pm 2.94 \pm \mu l\ min^{-1} g^{-1}$ between 0 and 0.5 h and to 0.12 ± 0.14 $\mu l\ min^{-1} g^{-1}$ at 0.5–2 h.

In the control, saline-treated, group the various haemodynamic parameters did not change significantly during the entire 8 h experimental period. The initial values were: arterial blood pressure 122 ± 9 mmHg; heart rate 220 ± 17 beats min^{-1}; right atrial pressure 0.3 ± 0.1 mmHg; cardiac output 0.15 ± 0.01 l $min^{-1} kg^{-1}$; *LV dP/dt max* 5500 ± 1675 mm Hg s^{-1} and LVEDP 0 mm Hg (Figures 1 and 2).

Effects of S. marcescens *on blood gases and pH*

Arterial blood pH and P_{O_2} of cats administered endotoxin were significantly lower at 1 h than those in the baseline period ($P < 0.05$ and $P < 0.025$, respectively). These subsequently recovered to values not significantly different from those in the control group (Table 1) although calculations of base-excess at 2 and 3 h indicated a significant metabolic acidosis. This was confirmed in a separate small series of cats administered *S. marcescens* endotoxin; this increased plasma lactate from 0.16 ± 0.24 mmol l^{-1} in the control period to 2.44 ± 2.23 mmol l^{-1} at 1 h and 4.19 ± 3.69 mmol l^{-1} at 2 h post-endotoxin. There was a tendency for hyperventilation to occur with time in both endotoxin and control cats (Table 1).

Effect of S. marcescens *on plasma prostanoid and thromboxane concentrations*

The plasma concentrations of PGE_2, $PGF_{2\alpha}$, 6-keto $PGF_{1\alpha}$ and TXB_2 in both the control and endotoxin groups are shown in Table 2. At 1 h post-endotoxin, there were significant increases in both arterial and venous concentrations of $PGF_{2\alpha}$ ($P < 0.01$ and $P < 0.001$, respectively), 6-keto $PGF_{1\alpha}$ ($P < 0.01$)and TXB_2 ($P < 0.01$), and in the venous concentration of $PGF_{2\alpha}$ ($P < 0.01$) At 3, 6 and 8 h post-endotoxin, the arterial and venous concentrations of $PGF_{2\alpha}$ and TXB_2 were not significantly different from those of the control group but both arterial and venous concentrations of PGE_2 and 6-keto $PGF_{1\alpha}$ were significantly elevated at 3, 6 and 8 h (Table 2). Five of the ten cats administered endotoxin had died by 8 h, 3 during the 1–1.5 h period and 2 between 4–6 h. The cats that died in shock were compared to those that survived shock with regard to possible differences in either haemodynamic or metabolic responses. There were no significant differences in any of the haemodynamic parameters between survivors and non-survivors, except for a significantly higher right atrial pressure at 2 min post-endotoxin in the survivors (suggesting a more pronounced initial pulmonary response). There were also no significant differences in blood pH, P_{O_2} and P_{CO_2} between the two groups. The PGE_2, $PGF_{2\alpha}$, 6-keto $PGF_{1\alpha}$ and TXB_2 concentrations in the surviving and non-surviving cats were also not significantly different at 1 h. Subsequently, the 6-keto $PGF_{1\alpha}$ concentrations were not

Table 1 Arterial blood pH, P_{O_2} and P_{CO_2} in spontaneously breathing cats administered saline (controls) or *S. marcescens* endotoxin (2 mg kg^{-1})

Time	*Saline treated cats*			*Endotoxin treated cats*		
(h)	*pH* (units)	P_{O_2} (mm Hg)	P_{CO_2} (mm Hg)	*pH* (units)	P_{O_2} (mm Hg)	P_{CO_2} (mm Hg)
0	7.435 ± 0.055(5)	99.5 ± 11.0(5)	30.5 ± 14.5(5)	7.370 ± 0.040(8)	93.5 ± 8.5(8)	29.0 ± 7.5(5)
1	7.455 ± 0.055(5)	98.0 ± 15.5(5)	23.0 ± 11.0(5)	7.328 ± 0.055(8)*	76.5 ± 18.5(8)*	20.5 ± 3.5(5)
2	7.450 ± 0.045(5)	96.0 ± 9.0(5)	22.0 ± 5.5(5)	7.325 ± 0.040(7)	84.5 ± 9.5(7)	20.5 ± 5.5(5)
3	7.450 ± 0.065(5)	94.0 ± 9.0(5)	21.4 ± 8.9(5)	7.315 ± 0.065(7)	88.0 ± 8.0(7)	24.0 ± 5.5(5)
4	7.415 ± 0.075(5)	98.5 ± 18.0(5)	22.0 ± 11.0(5)	7.340 ± 0.075(6)	87.5 ± 8.0(5)	26.0 ± 6.5(5)
5	7.470 ± 0.055(5)	100.5 ± 9.0(5)	18.0 ± 6.5(5)	7.350 ± 0.100(5)	85.0 ± 7.8(5)	23.5 ± 9.0(5)
6	7.450 ± 0.040(4)	101.0 ± 10.0(4)	17.5 ± 6.5(4)	7.410 ± 0.050(5)	95.5 ± 14.5(5)	21.5 ± 4.5(4)
7	7.410 ± 0.070(4)	100.5 ± 4.0(4)	18.3 ± 7.5(4)	7.375 ± 0.035(5)	100.0 ± 9.0(5)	20.0 ± 5.5(5)
8	7.450 ± 0.070(4)	99.5 ± 15.0(4)	19.5 ± 7.5(4)	7.385 ± 0.050(5)	95.5 ± 5.5(5)	21.5 ± 3.5(5)

The results are expressed as mean ± s.d., number of observations in parentheses.
*Significantly different from control, $P < 0.05$.

Table 2 Plasma concentrations of prostaglandin (PG)E_2, $PGF_{2\alpha}$, 6-keto $PGF_{1\alpha}$ and thromboxane (TX)B_2 in cats administered saline (controls) or *S. marcescens* endotoxin (2 mg kg^{-1})

Time (h)	Compound	*Saline treated cats* Venous concentration ($ng\,ml^{-1}$)	*Saline treated cats* Arterial concentration ($ng\,ml^{-1}$)	*Endotoxin treated cats* Venous concentration ($ng\,ml^{-1}$)	*Endotoxin treated cats* Arterial concentration ($ng\,ml^{-1}$)
0	PGE_2	0.10 ± 0.07(5)	0.04 ± 0.02(5)	0.12 ± 0.11(10)	0.05 ± 0.03(9)
	$PGF_{2\alpha}$	0.62 ± 0.42(5)	0.45 ± 0.31(5)	0.27 ± 0.38(10)	0.19 ± 0.15(9)
	6-keto $PGF_{1\alpha}$	1.51 ± 0.45(5)	1.14 ± 0.69(5)	1.33 ± 0.70(10)	1.19 ± 0.42(9)
	TXB_2	0.17 ± 0.09(5)	0.22 ± 0.28(4)	0.16 ± 0.06(10)	0.19 ± 0.12(9)
1	PGE_2	0.08 ± 0.05(5)	0.05 ± 0.02(5)	1.11 ± 0.98(10)*	0.37 ± 0.22(4)*
	$PGF_{2\alpha}$	0.82 ± 0.74(5)	0.50 ± 0.26(5)	1.40 ± 0.76(10)*	0.33 ± 0.12(4)
	6-keto $PGF_{1\alpha}$	1.09 ± 0.36(5)	0.90 ± 0.60(5)	12.25 ± 10.44(10)*	17.11 ± 3.22(4)*
	TXB_2	0.22 ± 0.11(5)	0.20 ± 0.15(5)	0.52 ± 0.25(10)*	0.56 ± 0.38(4)*
3	PGE_2	0.05 ± 0.02(5)	0.03 ± 0.02(5)	0.77 ± 1.54(7)*	0.11 ± 0.17(3)*
	$PGF_{2\alpha}$	0.59 ± 0.45(5)	0.39 ± 0.16(5)	0.59 ± 0.58(7)	0.15 ± 0.10(3)
	6-keto $PGF_{1\alpha}$	0.83 ± 0.20(5)	0.71 ± 0.22(5)	4.33 ± 3.15(7)*	1.51 ± 0.74(3)*
	TXB_2	0.23 ± 0.13(5)	0.11 ± 0.07(5)	0.20 ± 0.08(7)	0.15 ± 0.14(3)
6	PGE_2	0.04 ± 0.02(4)		1.18 ± 2.10(5)*	
	$PGF_{2\alpha}$	0.42 ± 0.14(4)		0.38 ± 0.49(6)*	
	6-keto $PGF_{1\alpha}$	0.72 ± 0.28(4)		6.16 ± 6.15(5)*	
	TXB_2	0.14 ± 0.12(3)		0.15 ± 0.17(6)	
8	PGE_2	0.07 ± 0.04(4)	0.02 ± 0.01(3)	0.16 ± 0.11(5)*	0.10 ± 0.03(3)*
	$PGF_{2\alpha}$	0.41 ± 0.26(3)	0.30 ± 0.01(3)	0.23 ± 0.14(4)	0.10 ± 0.08(4)
	6-keto $PGF_{1\alpha}$	0.78 ± 0.34(3)	0.66 ± 0.05(3)	2.94 ± 2.51(3)	2.14 ± 1.48(4)*
	TXB_2	0.19 ± 0.21(3)	0.29 ± 0.33(3)	0.42 ± 0.64(4)	0.14 ± 0.09(5)

The results are expressed as mean ± s.d., number of observations in parentheses.
*Significantly different from control, $P < 0.05$.

significantly different in the two groups, but the PGE_2, $PGF_{2\alpha}$ and TXB_2 concentrations during the 3–6 h period in the non-survivors were significantly higher ($P < 0.01$) than those in the survivors (PGE_2: survivors 0.21 ± 0.11 $ng\,ml^{-1}$, non-survivors 3.06 ± 1.30 $ng\,ml^{-1}$; $PGF_{2\alpha}$: survivors 0.23 ± 0.4 $ng\,ml^{-1}$, non-survivors 1.25 ± 0.34 $ng\,ml^{-1}$; 6-keto PGF_{1x}: survivors 4.13 ± 4.77 $ng\,ml^{-1}$, non-survivors 6.11 ± 4.04 $ng\,ml^{-1}$; TXB_2: survivors 0.14 ± 0.07 $ng\,ml^{-1}$, non-survivors 0.31 ± 0.10 ng ml^{-1}.

In the control group of cats plasma PGE_2, $PGF_{2\alpha}$ and TXB_2 concentrations did not change significantly over the 8 h period but the 6-keto $PGF_{1\alpha}$ concentrations tended to decrease with time (Table 2). At the commencement of the study the concentration of PGE_2 in venous plasma was significantly higher than that in arterial plasma ($P < 0.025$); there was no significant difference, at any time, between the arterial and venous concentrations of $PGF_{2\alpha}$, 6-keto $PGF_{1\alpha}$ and TXB_2. Four of the five cats survived the 8 h experimental period.

Discussion

As far as we have been able to ascertain, this is the first investigation in the cat of the actions of *S. marcescens* endotoxin. As with *E. coli* endotoxin (Parratt, 1973) there were two distinct phases in the response. The early phase (within 5–10 min of endotoxin administration) was characterized by an increased right atrial pressure, indicating pulmonary hypertension; systemic arterial pressure, left ventricular pressure and LV *dP/dt max* were reduced at this time. During the later, delayed, shock phase (1–8 h), the cardiac output was reduced and was associated with a reduced right atrial pressure (between 1–4 h) and left ventricular systolic pressure (between 4–8 h). Except for an early decrease in blood pH and P_{O_2} (at 1 h), pH was maintained at near-normal levels by increasing the degree of hyperventilation; lactic acidaemia was present indicating a substantial, but compensated metabolic acidosis. These effects are very similar to those described in this species following the administration of endotoxin derived from *E. coli* (Parratt, 1973).

Marked increases in the circulating concentrations of PGE_2, $PGF_{2\alpha}$, 6-keto $PGF_{1\alpha}$ and TXB_2 occurred at 1 h after giving endotoxin. The concentrations of PGE_2 and 6-keto $PGF_{1\alpha}$ remained elevated in the endotoxin-treated animals throughout the study. However, the non-survivors had higher PGE_2, $PGF_{2\alpha}$ and TXB_2 concentrations up to the time of death compared to the survivors. On the basis of their known circulatory and platelet effects we would sug-

gest that $PGF_{2\alpha}$ and TXB_2 may be associated with those actions of endotoxin detrimental to survival.

Elevated PGE_2 and $PGF_{2\alpha}$ concentrations have been observed in the pulmonary, portal and renal circulations of several species after endotoxin administration (Anderson *et al.*, 1975; Herman & Vane, 1976; Fletcher *et al.*, 1976). Increased concentrations of TXB_2 have been observed in the rat after *Salmonella enteritidis* endotoxin (Cook *et al.*, 1980) and in the cat during the early phase of *E. coli* endotoxaemia (Parratt *et al.*, 1982; Coker *et al.*, 1983).

There is no evidence that activation of prostaglandin synthetase contributes to the increased circulating concentrations of prostaglandins in endotoxaemia (Blackwell *et al.*, 1976); indeed, depressed prostaglandin synthetase activity has been observed in the renal medulla of endotoxin-treated rabbits (Bhattacharjee & Phylactos, 1978). Further, the conversion of radiolabelled arachidonic acid to PGE_2 and 6-keto $PGF_{1\alpha}$ was diminished by endotoxin in the isolated rabbit peritoneum (Bult *et al.*, 1979), possibly by inhibition of prostaglandin synthetase and/or an increased release of endogenous arachidonic acid. In the liver of endotoxin-treated rats there is evidence for an increased release of arachidonic acid (Conde *et al.*, 1980). In addition, several organs isolated from rats and rabbits following endotoxin treatment have a depressed metabolism of PGE_2 and $PGF_{2\alpha}$ (Nakano & Prancan, 1973; Blackwell *et al.*, 1976; Harper *et al.*, 1980).

A consideration of the cardiovascular and platelet actions of arachidonic acid metabolites may assist in understanding their possible role in the pathophysiology of feline endotoxin shock. Prostacyclin dilates the feline pulmonary vascular bed (Hyman & Kadowitz, 1979) and may act to limit the pulmonary vasoconstriction present in the early stage of endotoxaemia. $PGF_{2\alpha}$ constricts the feline pulmonary vasculature (Parratt & Sturgess, 1977) and TXA_2 is a constrictor agent in all vascular beds studied (Moncada & Vane, 1979). The mesenteric ischaemia present in the later stage of endotoxaemia may contribute to the lethal effects of endotoxin at this stage (Greenway & Murthy, 1971). In the feline mesenteric circulation, both $PGF_{2\alpha}$ and TXA_2 are vasoconstrictor agents (Dusting *et al.*, 1979) whereas prostacyclin inhibits the vasoconstrictor responses to nerve stimulation, noradrenaline and angiotensin.

Endotoxin administration also results in platelet aggregation (Horowitz *et al.*, 1962), fibrin deposition and disseminated intravascular coagulation (Schoendorf *et al.*, 1971), which contribute to multiple organ failure (Baue, 1975). Derivatives of arachidonic acid, especially prostacyclin and thromboxane, are involved in haemostasis by their actions on platelet aggregation; TXA_2 is a potent inducer and prostacyclin a potent inhibitor, of platelet aggregation (Moncada & Vane, 1979). Prostacyclin disaggregates platelets in the circulation and inhibits thrombus formation (Higgs *et al.*, 1977). Endotoxin-induced platelet aggregation, fibrin deposition and disseminated intramuscular coagulation might therefore be mediated, in part, by activation of thromboxane and this would contribute to multiple organ failure. One important consequence of this would be renal failure (Wardle, 1975). This might well occur early in shock, as suggested by our preliminary data on urine excretion.

From a consideration of the actions of derivatives of arachidonic acid, it appears that $PGF_{2\alpha}$ and TXA_2 may contribute to the adverse pulmonary and mesenteric ischaemia in feline endotoxin shock; in addition, TXA_2 may induce platelet aggregation. Prostacyclin, on the other hand, might be beneficial in endotoxin shock because of its dilator actions on these regional vascular beds, and its inhibition of platelet aggregation. Several studies in the rat have indicated the deleterious effects of TXA_2 in endotoxin shock (Cook *et al.*, 1980; Wise *et al.*, 1980) whereas prostacyclin infusion increased survival in a canine model of endotoxin shock (Fletcher & Ramwell, 1980). In the present investigation, there were increased circulating concentrations of prostacyclin throughout the delayed phase of endotoxin shock. The non-survivors had marked increases in the circulating concentrations of $PGF_{2\alpha}$ and TXB_2 compared to the survivors. The lack of any marked beneficial effect of several non-steroidal anti-inflammatory agents during the delayed phase of feline endotoxin shock may be due to their inhibition of the synthesis of all the metabolites of arachidonic acid; the use of specific antagonists and synthesis inhibitors may further clarify the role of arachidonic acid metabolites in the delayed phase of feline endotoxin shock.

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