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# The release of prostanoids during the acute pulmonary response to *E. coli* endotoxin in anaesthetized cats

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**1** The administration of *E. coli* endotoxin (2 mg/kg i.v.) to anaesthetized cats results in a characteristic acute pulmonary response. This consists of increases in pulmonary artery pressure and airways resistance and a reduction in lung compliance.

**2** Plasma concentrations of prostaglandin $E_2$ ($PGE_2$), $PGF_{2\alpha}$, thromboxane $B_2$ and 6-keto $PGF_{1\alpha}$ were measured by radioimmunoassay in aortic and pulmonary arterial blood samples before, during and after the acute pulmonary response to endotoxin.

**3** Endotoxin administration resulted in the rapid release of $PGF_{2\alpha}$ and thromboxane $B_2$ from the lungs. The time course of this release was parallel to that of the pulmonary hypertensive and airways responses to endotoxin. $PGE_2$ and 6-keto $PGF_{1\alpha}$ were released more gradually and with greater variations between individual animals.

**4** During the delayed shock phase (2 h after endotoxin) the concentrations of $PGE_2$, $PGF_{2\alpha}$ and 6-keto $PGF_{1\alpha}$ were once again elevated in both the aorta and pulmonary artery. Thromboxane $B_2$ concentrations were not increased at this time.

**5** These results suggest that $PGF_{2\alpha}$ and thromboxane $A_2$ may be mediators of the acute pulmonary responses to endotoxin.

## Introduction

The intravenous administration of *Escherichia coli* endotoxin to anaesthetized cats results in an almost immediate pulmonary arterial hypertension, an increase in airways (smooth muscle) resistance and a reduction in lung compliance (Parratt, 1973; Parratt, Coker, Hughes, Macdonald, Ledingham, Rodger & Zeitlin, 1982). There is good evidence that these effects result from the release of substances derived from arachidonic acid. Thus, these pulmonary responses are mimicked by the intravenous administration of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), there is a parallel variation in sensitivity of individual cats to endotoxin and to $PGF_{2\alpha}$ (Parratt *et al.*, 1982) and the endotoxin-induced responses are prevented by pretreatment with various cyclo-oxygenase inhibitors (Parratt & Sturgess, 1974; 1976; 1977) or with the prostaglandin antagonist, polyphloretin (Parratt & Sturgess, 1977). The purpose of the present experiments was to determine whether various active derivatives of arachidonic acid or their breakdown products ($PGF_{2\alpha}$, $PGE_2$, 6-keto $PGF_{1\alpha}$, thromboxane $B_2$ ($TxB_2$)) are released during the acute endotoxin response, particularly from the lungs. A preliminary account of this work was presented to the British Pharmacological Society (Coker, Hughes, Parratt, Rodger & Zeitlin, 1981).

## Methods

Cats of either sex were prepared for the measurement of haemodynamic (Parratt, 1973) and respiratory (Houston & Rodger, 1974) parameters. They were anaesthetized with sodium pentobarbitone (42 mg/kg i.p.) with additional doses (6 mg/kg) being administered intravenously when required. A catheter placed in the aortic arch via the left carotid artery was used for pressure measurement and blood sampling. Cannulation of a femoral vein allowed the administration of anaesthetic and endotoxin. The trachea was cannulated and, after performing a left thoracotomy, ventilation with room air was maintained using a Palmer positive pressure ventilation pump (rate 27 strokes/min; stroke volume about 20 ml/kg). An 18G needle-tipped catheter was inserted 'downstream' directly through the wall of the pulmonary artery and used for pressure measure-

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ment and blood sampling. Blood pressures were measured with Statham P23 1D resistance type transducers recorded on a Mingograf 82 ink-jet recorder (Siemens-Elema) along with a lead III electrocardiogram.

Transpulmonary pressure (Ptp) was measured with a Statham differential pressure transducer (model PM15); one inlet port was connected to a side arm of the tracheal cannula with the other inlet port left open to the atmosphere. Airflow ($\dot{V}$) was measured with a mesh screen pneumotachograph (Mercury Electronics, model F2–12 mm) connected to a second Statham differential transducer. Electrical integration of the resulting signal (using a Grass 7P10 integrator) gave a measure of tidal volume ($V_t$). All three parameters (Ptp, $\dot{V}$ and $V_t$) were recorded on a Grass 4 channel curvilinear polygraph (model 7). Airways resistance ($\Delta Ptp/\Delta \dot{V}$) was calculated from transpulmonary pressure and airflow records at isovolumic points on the tidal volume trace, as described by Amdur & Mead (1958). Lung compliance ($\Delta V_t/\Delta Ptp$) was calculated from the tidal volume and transpulmonary pressure records at points of zero airflow (i.e. at the beginning and end of inspiration).

Rectal temperature was monitored with a copper-constantan thermocouple (Ellab) and maintained at approximately 37 °C by means of a heated table. Arterial blood samples were taken at regular intervals and analysed for $O_2$ and $CO_2$ tensions ($PO_2$ and $PCO_2$) and pH using an IL 213 blood gas anlyser (Instrumentation Laboratories). Prior to administration of endotoxin the stroke volume of the respiration pump was adjusted to maintain arterial $PCO_2$ in the range 18 to 25 mmHg and $PO_2$ in the range 75 to 90 mmHg, with pH ranging from 7.46 to 7.52 units.

*Prostanoid measurement*

Blood samples were taken at various times from the aorta and pulmonary artery and analysed for $PGE_2$ and $PGF_{2\alpha}$, or for $TxB_2$ and 6-keto $PGF_{1\alpha}$ (the stable breakdown products of thromboxane $A_2$ and prostacyclin, respectively) using radioimmunoassay techniques (Coker, Clarke & Zeitlin, 1982). Each blood sample (2 ml) was withdrawn with a plastic syringe and transferred to a polypropylene centrifuge tube containing 20 µl indomethacin solution (1 mg/ml in ethanol) and 40 µl EDTA solution (70 mg/ml of $[CH_2.N(CH_2.COOH).CH_2.COONa]_2.2H_2O$ dissolved in 0.9% w/v NaCl). The samples were kept on ice until centrifugation, not more than 1 h later, at 2000 *g* for 10 min. The plasma was removed and stored at −20 °C until assay. Aliquots of plasma (250 µl) were acidified and the prostanoids extracted with ethyl acetate. These extracts were then evaporated to dryness under reduced pressure at 37 °C. The recovery of the prostanoid being measured was monitored in each sample using the appropriate tritiated internal standard. Sample extracts and standards were then redissolved in phosphate-buffered saline and tritiated $PGE_2$ or $PGF_{2\alpha}$ (Amersham), or $TxB_2$ or 6-keto $PGF_{1\alpha}$ (New England Nuclear) was added followed by the appropriate specific antibody (Institut Pasteur Production). After overnight incubation at 4 °C the antibody-bound and free prostanoids were separated by means of dextran-coated charcoal. An aliquot of the antibody-bound fraction was placed in Biofluor Scintillant and counted in a Packard Tri-Carb 460 liquid scintillation counter. With the above procedures the detection limits were 60 pg/ml for $PGE_2$, 40 pg/ml for $PGF_{2\alpha}$, 20 pg/ml for thromboxane $B_2$ and 100 pg/ml for 6-keto $PGF_{1\alpha}$.

*Experimental protocol*

After stable baseline values for haemodynamics and blood gases had been established blood samples were taken from the aorta and pulmonary artery for prostanoid analysis. Five minutes later *E. coli* endotoxin (Difco, lipopolysaccharide B 055:B5, 3923–25), 2 mg/kg suspended in 0.9% w/v NaCl solution, was injected intravenously over 30 s. Blood samples for prostanoid analysis were obtained 2, 7, 30 and 120 min after the administration of endotoxin. In order to limit the volume of blood removed from individual cats, two groups of animals were studied. In the first (Group A) samples were analysed for $PGE_2$ and $PGF_{2\alpha}$, and in the second (Group B) $TxB_2$ and 6-keto $PGF_{1\alpha}$ were measured.

## Results

The administration of *E. coli* endotoxin to anaesthetized cats results in a characteristic acute pulmonary and systemic response. This consists of a marked elevation of pulmonary artery pressure together with profound, although transient, reduction in systemic arterial pressure (Parratt, 1973). The peak response generally occurs 2 to 3 min after the injection of endotoxin (Figure 1). There are also concomitant changes in respiratory function. Transpulmonary pressure increases whereas airflow and tidal volume decrease (Figure 2). Thus there is a marked increase in airways resistance and reduction in lung compliance. In the present control (endotoxin alone) cats this amounted to about +200% and −50% respectively (Tables 1 and 2).

The effects of endotoxin on haemodynamics and the plasma concentrations of $PGE_2$ and $PGF_{2\alpha}$ in the cats in Group A are detailed in Table 1. In the control state, prior to endotoxin, the concentrations of $PGF_{2\alpha}$ in the pulmonary artery and the aorta were similar.

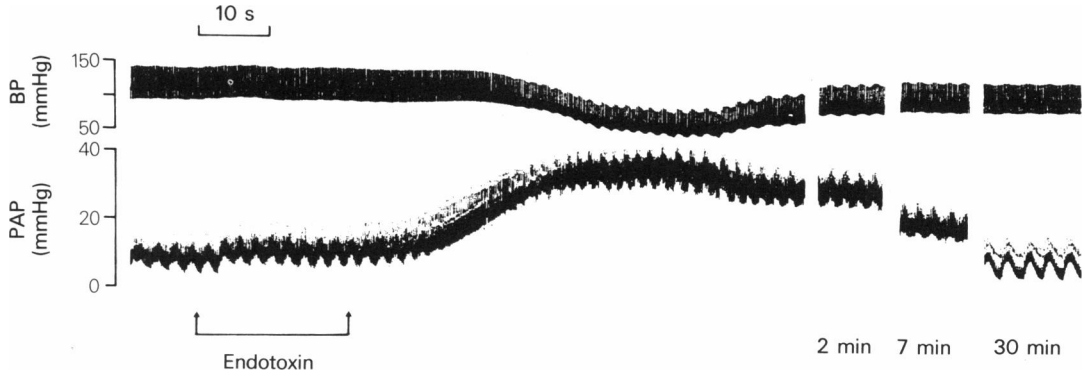


**Figure 1** The effect of the slow intravenous injection of *E coli* endotoxin (2 mg/kg) on systemic arterial blood pressure (BP) and pulmonary artery pressure (PAP).

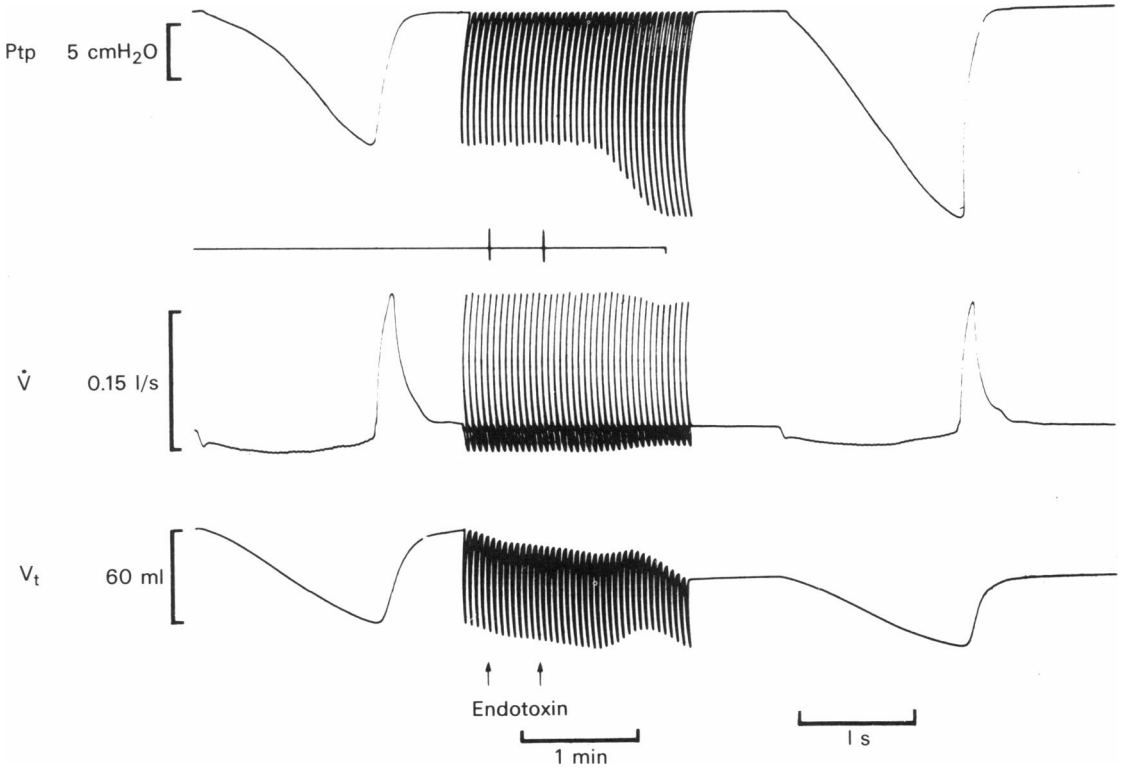


**Figure 2** Effects of endotoxin (2 mg/kg intravenously) on, from above, transpulmonary pressure (Ptp), airflow ($\dot{V}$) and tidal volume ($V_t$). The record shows (at two different speeds) that endotoxin administration results, within 30 s, in a marked increase in Ptp coupled with a reduction in expiratory airflow and tidal volume. There is thus a marked increase in airways resistance ($\Delta$ Ptp/$\Delta$ V) and a reduction in compliance ($\Delta$ Vt/$\Delta$ Ptp).

**Table 1** Effects of endotoxin (2 mg/kg i.v.) on haemodynamics and plasma concentrations of Prostaglandin $E_2$ ($PGE_2$) and $PGF_{2\alpha}$ in cats in group A

| | *Heart rate* (beats/min) | *Mean arterial pressure* (mmHg) | *Mean pulmonary artery pressure* (mmHg) | *$PGF_{2\alpha}$ (pg/ml)* Aorta | *$PGF_{2\alpha}$ (pg/ml)* Pulmonary artery | *$PGE_2$ (pg/ml)* Aorta | *$PGE_2$ (pg/ml)* Pulmonary artery |
|---|---|---|---|---|---|---|---|
| 5 min pre-endotoxin | 182 ± 15 | 96 ± 6 | 14 ± 1 | 135 ± 29 | 155 ± 29 | 490 ± 198 | 495 ± 126 |
| †2 min post-endotoxin | 130 ± 24* | 32 ± 5** | 42 ± 4** | 724 ± 97** | 487 ± 68* | 738 ± 244 | 578 ± 102 |
| 7 min post-endotoxin | 156 ± 21 | 65 ± 8 | 29 ± 7 | 296 ± 40* | 431 ± 61* | 823 ± 239 | 1039 ± 250 |
| 30 min post-endotoxin | 184 ± 24 | 72 ± 9 | 21 ± 3 | 176 ± 11 | 314 ± 77 | 715 ± 193 | 1158 ± 285 |
| 120 min post-endotoxin | 200 ± 28 | 78 ± 13 | 14 ± 2 | 516 ± 143 | 1094 ± 412 | 1209 ± 210** | 2186 ± 372* |

†Changes in pulmonary compliance and airways resistance at this time were −57 ± 6% and +251 ± 42% respectively
Each value is the mean ± s.e. mean, $n = 5$. *$P < 0.05$; **$P < 0.01$; paired t test compared with pre-endotoxin values.

Two minutes after endotoxin administration both aortic (Figure 3) and pulmonary arterial $PGF_{2\alpha}$ concentrations increased significantly but there was a greater increase in aortic blood than pulmonary arterial blood. This indicates that $PGF_{2\alpha}$ may be released from the lungs after endotoxin administration. By 7 min post-endotoxin, the $PGF_{2\alpha}$ concentrations were decreasing and aortic values (Figure 3) were lower than those in pulmonary arterial blood. At 30 min post-endotoxin both the aortic and pulmonary arterial $PGF_{2\alpha}$ plasma concentrations were not significantly different from control; haemodynamic and respiratory parameters had also returned to values not significantly different from control.

The plasma concentrations of $PGE_2$ in aortic and pulmonary arterial blood were also measured in this group of cats. During the first 30 min after endotoxin administration the $PGE_2$ concentrations tended to increase but the changes were much less uniform than those observed for $PGF_{2\alpha}$ and they were not statistically significant (Table 1). In Figure 3 the values of $PGE_2$ and $PGF_{2\alpha}$ in each individual cat have been plotted. This figure illustrates the marked, rapid increases in $PGF_{2\alpha}$ in the aorta and the similar, less marked changes in the pulmonary artery. It can also be seen that the changes in $PGE_2$ were less consistent, and that there was much greater variation in the plasma concentrations of $PGE_2$ between different

**Table 2** Effects of endotoxin (2 mg/kg i.v.) on haemodynamics and plasma concentrations of thromboxane $B_2$ and 6-keto $PGF_{1\alpha}$ in cats in group B

| *Time* | *Heart rate* (beats/min) | *Mean arterial pressure* (mmHg) | *Mean pulmonary artery pressure* (mmHg) | *Thromboxane $B_2$ (pg/ml)* Aorta | *Thromboxane $B_2$ (pg/ml)* Pulmonary artery | *6-keto $PGF_{1\alpha}$ (pg/ml)* Aorta | *6-keto $PGF_{1\alpha}$ (pg/ml)* Pulmonary artery |
|---|---|---|---|---|---|---|---|
| 5 min pre-endotoxin | 184 ± 8 | 100 ± 8 | 14 ± 1 | 160 ± 65 | 255 ± 45 | 1006 ± 190 | 1201 ± 163 |
| †2 min post-endotoxin | 151 ± 18* | 48 ± 11** | 39 ± 2** | 832 ± 115** | 585 ± 52* | 2323 ± 437* | 1505 ± 280 |
| 7 min post-endotoxin | 180 ± 12 | 100 ± 9 | 28 ± 2* | 488 ± 55** | 446 ± 38 | 2107 ± 377* | 1584 ± 295 |
| 30 min post-endotoxin | 194 ± 11 | 90 ± 11 | 12 ± 1 | 234 ± 32 | 329 ± 26 | 1796 ± 333** | 1737 ± 280 |
| 120 min post-endotoxin | 198 ± 7 | 90 ± 14 | 10 ± 2 | 153 ± 28 | 255 ± 57 | 2295 ± 598* | 2472 ± 557* |

†Changes in pulmonary compliance and airways resistance at this time were −43 ± 8% and +149 ± 54% respectively.
Each value is the mean ± s.e. mean, $n = 7$. *$P < 0.05$; **$P < 0.01$; paired t test compared with pre-endotoxin values.

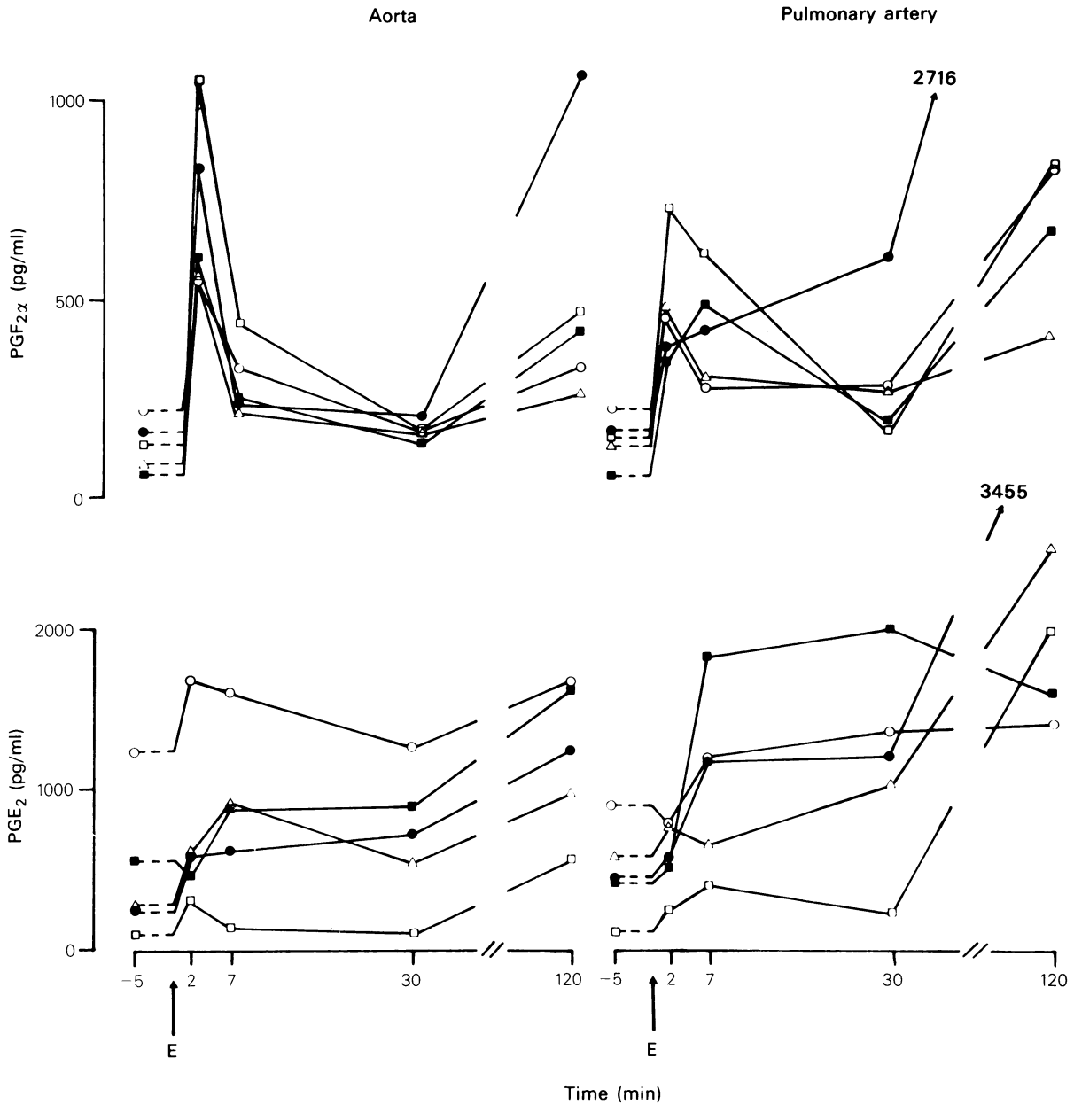


**Figure 3** Plasma concentrations of prostaglandin $E_2$ ($PGE_2$) and $PGF_{2\alpha}$ in cats in group A. Each symbol represents one individual cat.

animals. In most of the animals which exhibited increases in $PGE_2$ concentrations following endotoxin administration, these changes occured more slowly than the corresponding changes for $PGF_{2\alpha}$, i.e. reaching a peak at 7 min rather than 2 min post-endotoxin.

Saline was given to two animals instead of endotoxin and in these cats there were no increases in $PGE_2$ or $PGF_{2\alpha}$ throughout the course of the experiment. Similarly there were no major changes in arterial or pulmonary artery pressure (Figure 4), or air-

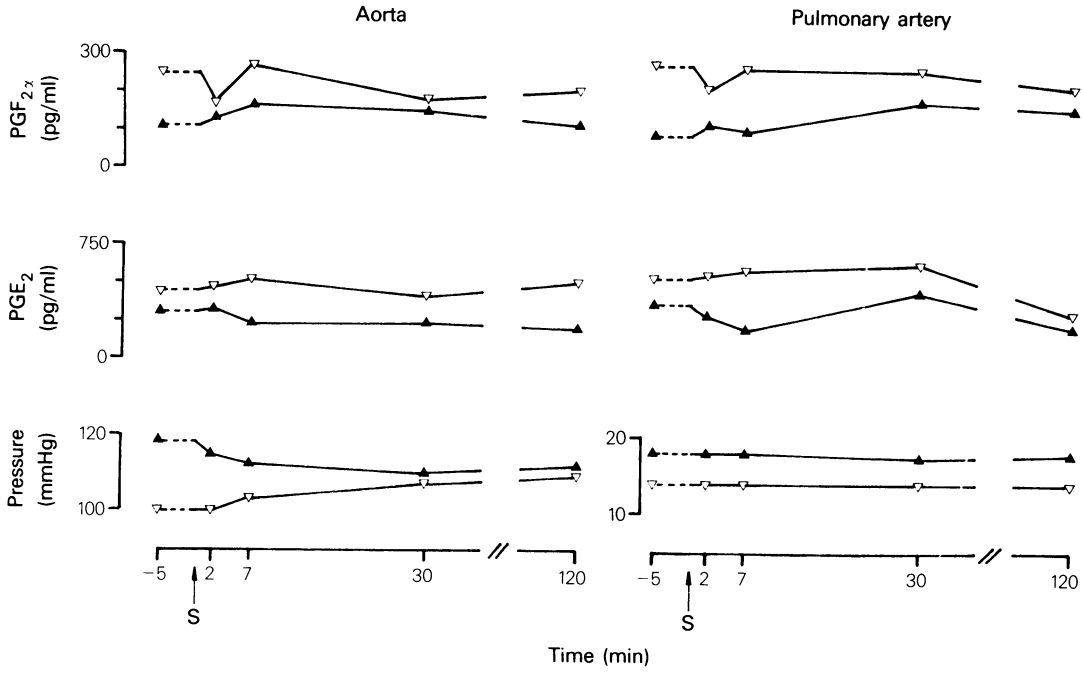


**Figure 4** Plasma concentrations of prostaglandin $E_2$ ($PGE_2$) and $PGF_{2\alpha}$, and blood pressures in the two cats which received saline (S) instead of endotoxin. Each symbol represents one individual cat.

ways resistance and lung compliance. This indicates that the increased prostanoid concentrations seen in Group A cats were caused by endotoxin administration and that the removal of ten 2 ml blood samples over the 2 h experimental period does not significantly alter circulating prostanoid concentrations. Similar experiments in our laboratory have shown that there were no increases in $TxB_2$ or 6-keto $PGF_{1\alpha}$ concentrations in pentobarbitone-anaesthetized cats over an eight hour period. For example, in 5 cats the control value for thromboxane $B_2$ in aortic blood was $220 \pm 125$ pg/ml and 1 and 3 h later the concentrations were $200 \pm 67$ and $110 \pm 31$ pg/ml respectively; the corresponding 6-keto $PGF_{1\alpha}$ concentrations were $1140 \pm 308$, $900 \pm 268$ and $710 \pm 98$ pg/ml (Sharma, 1981).

$PGE_2$ and $PGF_{2\alpha}$ concentrations were measured in two further cats, both of which died approximately 10 min after the injection of endotoxin. At 2 min post-endotoxin the systolic pulmonary arterial pressures in these cats were 58 and 60 mmHg respectively and the corresponding aortic $PGF_{2\alpha}$ concentrations were 4,620 and 4,430 pg/ml. These $PGF_{2\alpha}$ values are four times higher than the concentrations found in any of the surviving animals (see Figure 3). In most cats the systemic hypotension observed after endotoxin administration is transient, but neither of these cats recovered from the initial hypotension, mean arterial pressure being 11 and 23 mmHg respectively 7 min post-endotoxin. At this time the corresponding aortic $PGE_2$ concentrations were 11,120 and 8,020 pg/ml. Again these values are four to five times greater than the values measured in the animals which survived the acute response to endotoxin. These results suggest that the severity of the acute response to endotoxin may be related to the amount of prostanoids released from the lungs.

A second group of cats (Group B) was used to study the effects of endotoxin on the concentrations of $TxB_2$ and 6-keto $PGF_{2\alpha}$, the stable breakdown products of $TxA_2$ and prostacyclin respectively. These results are detailed in Table 2 along with the effects of endotoxin on the haemodynamic and respiratory parameters in this group of cats. The pattern of thromboxane release during the acute response to endotoxin was similar to that observed for $PGF_{2\alpha}$ in Group A (Figure 3). Thromboxane was released rapidly into aortic blood and there were also increased concentrations of thromboxane $B_2$ in the pulmonary artery, although these changes were less marked that those in the aorta (Figure 5). It can also be seen from Figure 5 that prior to endotoxin there appeared to be some uptake of $TxB_2$ by the lungs. During the acute response to endotoxin the lungs

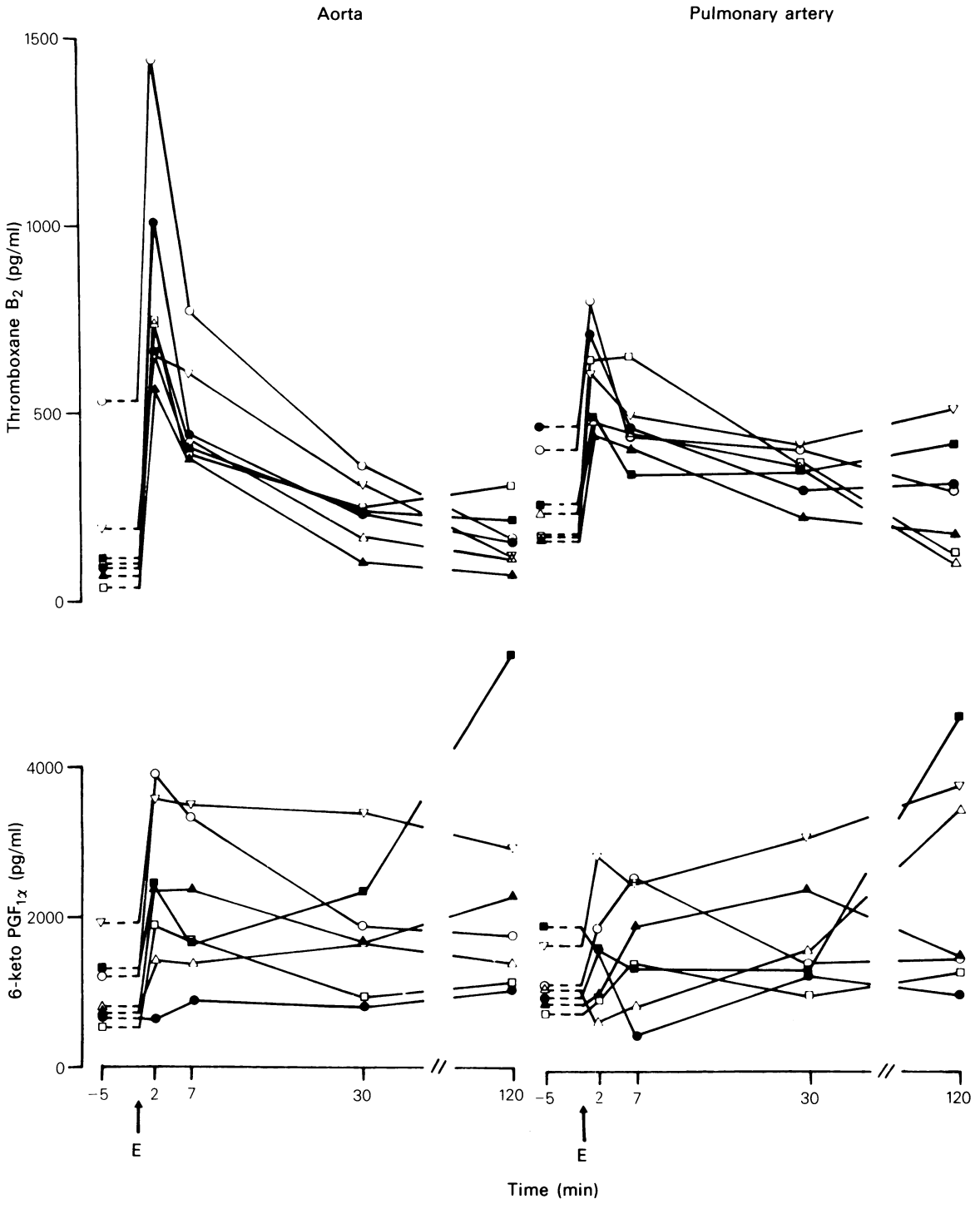


**Figure 5** Plasma concentrations of thromboxane $B_2$ and 6-keto $PGF_{1\alpha}$ in cats in Group B. Each symbol represents one individual cat.

produced thromboxane, but by 30 min post-endotoxin the situation had reverted to one of thromboxane uptake across the lungs. There was also some similarity between the pattern of release of 6-keto $PGF_{1\alpha}$ in Group B and that of $PGE_2$ in Group A cats (Figure 3). In most individual cats (see Figure 5) aortic and pulmonary arterial 6-keto $PGF_{1\alpha}$ concentrations increased after endotoxin administration although only the aortic changes were statistically significant (Table 2).

Thus the acute haemodynamic and respiratory responses to endotoxin in anaesthetized cats are accompanied by the rapid, marked release of the pulmonary vasoconstrictor prostanoids, $PGF_{2\alpha}$ and $TxB_2$ from the lungs whereas there are more generalised increases in the systemic vasodilator prostanoids $PGE_2$ and prostacyclin.

As well as the acute response to endotoxin in anaeshetized cats there is also a delayed shock phase commencing 1 to 1.5 h after administration (Parratt, 1973). During this phase, systemic arterial pressure and cardiac output decrease, which may lead to underperfusion of organs such as the liver and kidneys. Plasma prostanoid concentrations were measured 2 h after the injection of endotoxin at which time all the surviving cats were showing signs of the onset of the delayed shock phase. The concentrations of $PGE_2$ and $PGF_{2\alpha}$ are detailed in Table 1 and Figure 3 and those for thromboxane $B_2$ and 6-keto $PGF_{1\alpha}$ in Table 2 and Figure 5. At 2 h post-endotoxin $PGE_2$, $PGF_{2\alpha}$ and 6-keto $PGF_{1\alpha}$ concentrations were all increased compared with pre-endotoxin values, whereas $TxB_2$ levels were not elevated. The pulmonary arterial values of $PGE_2$, $PGF_{2\alpha}$ and 6-keto $PGF_{1\alpha}$ were higher than the aortic blood concentrations. This suggests that during the delayed shock phase, unlike the acute response to endotoxin, prostanoids are not released from the lungs but from other areas such as the gastrointestinal tract, liver and/or kidneys.

## Discussion

The evidence has been accumulating (see *Introduction*) that the pulmonary responses that occur following bacterial endotoxin administration, and perhaps also in clinical sepsis, are due to substances derived from arachidonic acid. The purpose of the present study was to obtain direct evidence for the pulmonary release of such derivatives by sampling blood entering and leaving the lungs of anaesthetized cats given *E. coli* endotoxin. We assume that no release or uptake of these substances takes place across the left heart and therefore that blood sampled from the ascending aorta close to the aortic valves is representative of pulmonary venous blood.

Since it is not possible to measure all four prostanoids in each cat (this would require the removal of excessive volumes of blood which may lead to haemorrhagic shock) we have assumed for the purposes of this discussion that $TxB_2$ concentrations would have been elevated in cats in Group A and similarly $PGF_{2\alpha}$ concentrations would have been increased in Group B cats. We have based this assumption on the fact that in patients with septic shock there is a significant correlation between $TxB_2$ and $PGF_{2\alpha}$ concentrations in arterial blood (Parratt *et al.*, 1982).

The results demonstrate that under control conditions, the levels of $PGE_2$, $PGF_{2\alpha}$, $TxB_2$ and 6-keto $PGF_{1\alpha}$ in aortic blood are similar to those found in pulmonary arterial blood. Under resting conditions there is no significant pulmonary release of these substances; but there was some evidence in individual cats (Figures 3 and 5) for an active pulmonary uptake from systemic venous blood. Very soon after endotoxin administration, however, there was a marked (three to fivefold) increase in the plasma concentrations of $PGF_{2\alpha}$ (Table 1) and $TxB_2$ (Table 2); this was more marked in aortic (? pulmonary venous) blood than in pulmonary arterial blood and may indicate the active release of these substances from the lungs, although the exact source (blood borne elements, vascular endothelium, lung parenchyma) is impossible to determine from this type of study. Similarly, it is not possible to calculate from these results the actual amount released. This would require an accurate measurement of blood flow both to and from the lungs; this is not easy during the marked circulatory changes (severe pulmonary hypertension, system arterial hypotension, reduced left ventricular filling, marked bradycardia; Parratt, 1973) that occur in the early stages of endotoxin shock.

The release of various prostanoids from the lungs following endotoxin administration has been reported in other species (Anderson, Tsagaris, Jubiz & Kuida, 1975; Frölich, Ogletree, Peskar & Brigham, 1980; Demling, Smith, Gunther, Flynn & Gee, 1981; Hüttemeier, Watkins, Peterson & Zapol, 1982). The work of Hüttermeier *et al.*, (1982) in leukopaenic sheep suggests that circulating leucocytes are part of the source of endotoxin-induced thromboxane release. The results of our present study confirm that prostanoids are also released from the lungs during the acute pulmonary response to endotoxin in the cat.

We were especially interested in considering the possibility that the release of arachidonic acid derivatives determines the severity of the initial pulmonary response to endotoxin administration. Certainly, plasma levels of $PGF_{2\alpha}$ and $TxB_2$ are highest, especially in aortic blood, at the peak of the pulmonary response, i.e. at 2 min post-endotoxin. As these plasma prostanoid concentrations decrease so do the

airways and pulmonary vascular responses and 30 min after endotoxin, pulmonary artery pressure, airways resistance and lung compliance are near normal, as are the plasma concentrations of both thromboxane and $PGF_{2\alpha}$ (Tables 1 and 2). Thus the time course of the pulmonary responses is parallel to that of the release of $PGF_{2\alpha}$ and $TxB_2$ from the lungs. Perhaps the best evidence for a relationship between the severity of the initial pulmonary response and the amount of prostanoids released, comes from the two animals which died during this acute shock phase. Both these cats had massive aortic concentrations of $PGF_{2\alpha}$ and $PGE_2$. These values were twenty to forty times normal and indeed four times higher than the maximum concentrations found in the survivors (Figure 3). It is not unreasonable to suggest that these animals died during the initial shock phase because of the greater release of arachidonic acid derivatives with marked brochoconstrictor and pulmonary vasoconstrictor, or systemic vasodilator effects. At present we do not know which prostanoid, if either, is responsible for lethality. The inability of these two cats to recover from the intial systemic hypotension may be a direct effect of the marked increase in $PGE_2$ or a secondary event resulting from acute left heart failure as a consequence of $PGF_{2\alpha}$-induced pulmonary vasoconstriction. Other workers have suggested that in sheep, the magnitude of the pulmonary hypertensive response to endotoxin is related to thromboxane synthesis (Frölich *et al.*, 1980) and Demling, Smith, Gunther, Flynn & Gee (1981) noted a temporal correlation between prostanoid production and changes in the pulmonary microcirculation.

One of the pieces of evidence implicating $PGF_{2\alpha}$ in the pulmonary responses to endotoxin was the close similarity between these responses and those to intravenously injected $PGF_{2\alpha}$ (Parratt *et al.*, 1982). The present study now provides evidence that this substance is indeed released during the early stages of endotoxin shock but does not prove beyond question that $PGF_{2\alpha}$ is the only, or even the main, mediator involved. For example, $TxA_2$ is also released in similar amounts and with a similar time course. Much less is known about the pulmonary effects of the highly unstable $TxA_2$ in this model, although unpublished studies in this laboratory with the thromboxane-like endoperoxide analogue, U-46619, demonstrate that this substance also mimics the acute pulmonary effects of endotoxin. In other models (isolated tracheal smooth muscle; airways insufflation pressure in guinea-pigs) there is evidence that $TxA_2$ (generated by incubation of arachidonic acid with human platelets) is a more potent airways constrictor than is $PGF_{2\alpha}$ (Svensson, Strandberg, Tuvens & Hamberg, 1977).

The question as to whether $PGF_{2\alpha}$ or $TxA_2$ is the more important mediator of the pulmonary responses of endotoxin could be studied by administering specific inhibitors of thromboxane synthetase. This should prevent the formation of $TxA_2$ but still allow generation of $PGF_{2\alpha}$, perhaps in increased amounts. Preliminary studies (Ball, Parratt & Zeitlin, 1982) indicate that thromboxane may well be the more important mediator of the pulmonary hypertensive effect of endotoxin. In the present study $TxA_2$ and $PGF_{2\alpha}$ were generated by endotoxin in almost equal amounts (Tables 1 and 2) with values around 800 pg/ml at 2 min and 300 to 500 pg/ml at 7 min, when there are still pronounced pulmonary effects. These latter values are of the same order as those observed in the plasma of patients with septic shock with evidence of pulmonary dysfunction (Parratt *et al.*, 1982). Taken together, these results support the suggestion that $TxA_2$ and $PGF_{2\alpha}$ are involved in clinical sepsis and may contribute to the pathophysiology of the shocked lung syndrome (Parratt *et al.*, 1982).

One further unanswered question concerns the role of vasodilator prostanoids in shock. Substantial amounts of prostacyclin and $PGE_2$ appear to be generated as a result of endotoxin administration (Tables 1 and 2) and these may counteract the effects of $TxA_2$ and $PGF_{2\alpha}$ on the lungs and circulation. The time course of prostacyclin and $PGE_2$ release differs from that of $TxA_2$ with elevated levels well into the delayed shock phase (2 h after endotoxin). Surprisingly, $TxB_2$ concentrations were not elevated at this time (Table 2). The release of prostacyclin by endotoxin in rabbits has been reported recently by Rampart, Bult & Herman (1982) who have provided evidence that this is dependent upon activation of complement. Exogenous prostacyclin has also been shown to reverse lethal endotoxaemia in dogs (Krausz, Utsunomiya, Feuerstein, Wolfe, Shepro & Hechtman, 1981) and to decrease endotoxin-induced lung injury in sheep (Demling, Smith, Gunther, Gee & Flynn, 1981).

This present study provides direct evidence that, in the anaesthetized cat, $PGF_{2\alpha}$ and $TxA_2$ are released from the lungs during the acute pulmonary response to endotoxin, and that $PGE_2$ and prostacyclin concentrations are also elevated. Further work is required to elucidate the possible roles of the various prostanoids in endotoxin shock.

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