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THE EFFECT OF INDOMETHACIN ON THE CARDIOVASCULAR AND METABOLIC RESPONSES TO *E. coli* ENDOTOXIN IN THE CAT

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1 The response of pentobarbitone-anaesthetized cats to the intravenous administration of *E. coli* endotoxin (2 mg/kg) consisted of acute pulmonary vasoconstriction (3-5 min after the injection) and a secondary shock phase characterized by delayed systemic hypotension, decreased central venous pressure and cardiac output, and metabolic acidosis with arterial lactate levels three to four times normal. Only one of 25 animals survived 6 hours.

2 Indomethacin (10 mg/kg), administered intravenously 30 min before the endotoxin, reduced both systemic arterial pressure and myocardial blood flow. It abolished the pulmonary vasoconstriction induced by endotoxin.

3 Indomethacin modified some of the characteristic features of the delayed, endotoxin shock phase. Systemic hypotension was not observed and the blood pressure in the indomethacin-treated cats 1, 2 and 4 h after endotoxin was 30 mmHg higher than in those cats administered endotoxin alone. The decrease in arterial pH was also significantly delayed. Six out of 15 animals survived 6 hours.

4 It is suggested that indomethacin may abolish the initial pulmonary hypertension and oedema by antagonizing the release, or vasoconstrictor effect, of histamine and that part of its action during the shock phase is due to inhibition of prostaglandin release.

Introduction

A number of investigators have confirmed the original observation of Northover & Subramanian (1962) that non-steriodal analgesic-antipyretic drugs antagonize the vasodepression elicited by endotoxin administration in the dog (Erdös, Hinshaw & Gill, 1967; Solomon & Hinshaw, 1968; Hall, Hodge, Irvine, Katic & Middleton, 1972). In the cat, the response to the administration of a lethal dose of *E. coli* endotoxin consists of an acute phase (manifested by a marked rise in pulmonary pressure and transient decrease in systemic arterial pressure and in myocardial contractility) and a delayed (shock) phase characterized by systemic hypotension, a reduced stroke volume and a severe metabolic acidosis (Parratt, 1973). The purpose of the present experiments was to determine the effect of indomethacin on these two quite distinct responses to endotoxin.

Methods

Forty cats of either sex were anaesthetized with sodium pentobarbitone (30 mg/kg, i.p.) and ventilated with room air using a Palmer positive-pressure pump (rate 20/min; stroke volume 40-60 ml). Rectal and mid-oesophageal temperatures were recorded with direct recording thermocouples (Ellab, Copenhagen). Systemic (carotid) arterial blood pressure and dP/dt, right atrial pressure, left ventricular pressure and dP/dt and pulmonary artery pressure were measured as recently described (Parratt, 1973) and recorded, together with the electrocardiogram, on an eight channel ink-jet writing recorder (Elema-Schönander Mingograph 81). Mean pressures, where appropriate, were obtained by electronic integration and systolic ejection time was measured (in ms) from the beginning of the upstroke of the central aortic pressure pulse to the trough of the incisural notch. Cardiac output was measured by thermodilution, myocardial blood flow by a heat clearance technique (Parratt, 1973) and the temperature curves recorded on two Kipp and Zonen BD5 recorders. External cardiac work, stroke volume, myocardial vascular resistance and peripheral vascular resistance were calculated as previously described (Parratt & Winslow, 1971).

Blood samples (1-2 ml) were taken anaerobically from a catheter in the carotid artery and

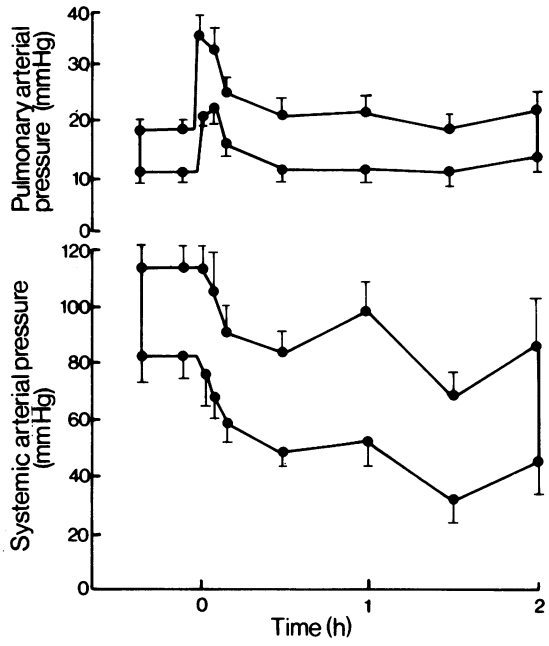

Fig. 1 The effect of the intravenous administration of *E. coli* endotoxin (2 mg/kg at time 0 h) on systolic and diastolic pulmonary arterial pressures (mmHg, above) and on systolic and diastolic systemic arterial pressures (mmHg, below). The values are mean ± s.e. mean.

analysed for oxygen and carbon dioxide tensions, and pH, with appropriately calibrated electrode systems (Radiometer, Copenhagen). The pH electrode was calibrated by means of standard buffers and the oxygen and carbon dioxide electrodes with gas mixtures, the oxygen and carbon dioxide concentrations of which had been measured with a modified Lloyd-Haldane apparatus. Oxygen and carbon dioxide tensions were corrected for any temperature difference between the electrode system (usually 37.3°C) and the animals' mid-oesophageal (or aortic) temperature by means of the blood-gas calculator described by Severinghaus (1966), which was also used to calculate arterial base excess. Arterial lactate was measured by the Hohorst enzymatic method with a Boehringer test combination for L-lactate and (by courtesy of Dr B.L. Furman) plasma glucose was measured with a Beckman analyser.

All the cats received *E. coli* endotoxin (Difco Laboratories, 055:B5) suspended in 0.9% w/v sodium chloride solution and administered slowly by intravenous injection in a dose of 2 mg/kg. Fifteen of the cats were given an intravenous injection of indomethacin (10 mg/kg, dissolved in a phosphate buffer pH 8) 30 min before the endotoxin.

Results

Responses to E. coli *endotoxin*

(a) Effects on the pulmonary circulation. As previously described (Parratt, 1973), the administration of *E. coli* endotoxin in the cat produced a marked elevation of pulmonary artery pressure, maximal 3-5 min after the end of the injection. In the present series, the pulmonary artery pressure immediately before endotoxin administration was 19 ± 1 mmHg (systolic); 10 ± 1 mmHg (diastolic) and 13 ± 1 mmHg (mean). Three minutes after endotoxin, the corresponding pressures were 35 ± 4, 21 ± 2 and 27 ± 4 mmHg; these were all significantly ($P < 0.001$) higher than the pre-endotoxin values. This elevated resistance to flow in the pulmonary vascular bed (calculated as an 8-12-fold increase by Parratt, 1973) resulted in pulmonary oedema, hyperpnoea and considerable difficulty in breathing. Seven cats died in this acute phase and the lungs were grossly oedematous and haemorrhagic at autopsy. In the survivors, pulmonary arterial pressure gradually returned towards pre-endotoxin levels over the next 20-30 min and remained within the normal range throughout the rest of the experiment (4 hours). These changes in pulmonary arterial pressure are illustrated in Figure 1.

(b) Effects on the systemic circulation. Beginning two to three beats after the commencement of the rise in pulmonary artery pressure, systemic arterial pressure fell, often to levels below 50 mmHg. There was recovery to slightly below control levels within 2-4 min and thereafter there was a gradual decrease in pressure (Fig. 1) such that most of the animals died within 2-3 hours. Six of the 25 animals (24%) survived 4 h with arterial pressures (124 ± 14 mmHg systolic and 98 ± 10 mmHg diastolic) rather higher than those before endotoxin. Only one cat (4%) survived beyond 6 hours.

Right atrial pressure was elevated in the acute (3-5 min) phase (from a mean of +0.9 ± 0.3 mmHg pre-endotoxin to +3.9 ± 1.3 mmHg after 3 min; $P < 0.001$). Thereafter, right atrial pressure fell markedly over the subsequent 3 h period (Table 1), presumably due to peripheral pooling of blood and decreased venous return.

(c) Effects on cardiac function. The acute cardiac response to endotoxin administration consisted of a marked reduction in dP/dt *max* and

occasional ventricular extrasystoles. There was substantial recovery between 3-4 min of the injection and thereafter dP/dt *max* was not significantly changed from the control (pre-endotoxin) value of 3704 ± 390 mmHg s^{-1}, being a mean of 3785 mmHg s^{-1} at 1 h and 4257 mmHg s^{-1} at 4 hours. Left ventricular end-diastolic pressure (LVEDP) tended to decrease after endotoxin, from +3.0 ± 1.1 mmHg (pre-endotoxin) to a mean of +1.3 mmHg, +1.9 mmHg and +2.2 mmHg after 1, 2 and 3 h, respectively. This reduced left ventricular filling pressure presumably also resulted from a decreased venous return (since right atrial pressure was also reduced during this period, Table 1), and was reflected in the gradual reduction in both stroke and minute volume (Table 1). The reduction in myocardial blood flow (Table 1) is almost certainly the result of the decreased systemic perfusion pressure; there were no significant changes in myocardial vascular resistance.

(d) Effects on arterial blood gases and base excess, pH, lactate and plasma glucose. The effects of thoracotomy and positive-pressure ventilation on arterial blood gases, pH, lactate and plasma glucose are shown in Table 2. A slight degree of hyperventilation (arterial P_{CO_2} 23 ± 2 mmHg) was required to obtain an adequate arterial blood

Table 1 Haemodynamic effects of *E. coli* endotoxin (2 mg/kg i.v.) in anaesthetized cats (mean ± s.e., 6-25 observations).

		Post-endotoxin			
	Control	*1 h*	*2 h*	*3 h*	*4 h*
Carotid artery pressure (mean; mmHg)	101 ± 6	72 ± 6*	75 ± 10***	79 ± 14	77 ± 20
Heart rate (beats/min)	205 ± 7	218 ± 7	212 ± 11	235 ± 11***	234 ± 18
Right atrial pressure (mean; mmHg)	+0.9 ± 0.3	−1.1 ± 0.5**	−0.8 ± 0.8***	−0.25 ± 0.63	–
Cardiac output (ml min^{-1} kg^{-1})	122 ± 9	114 ± 13	100 ± 13***	97 ± 3**	75 ± 2*
Systolic ejection time (ms)	123 ± 7	107 ± 5	98 ± 6*	90 ± 6**	97 ± 9*
Myocardial blood flow (as myocardial thermal conductivity increment, ΔK, c.g.s. units x 10^{-4})	2.3 ± 0.8	1.7 ± 0.4	1.4 ± 0.4	1.8 ± 0.3	–
Number of survivors	25	18	14	11	6†

* $P < 0.0005$; ** $P < 0.005$; *** $P < 0.025$.
† 1 animal survived 6 hours.

Table 2 Comparison of arterial blood gases, pH, lactate and plasma glucose in cats administered *E. coli* endotoxin (mean ± s.e., n = 6-18).

	Control		*Indomethacin treated*	
	Pre-endotoxin†	*2 h post-endotoxin*	*Pre-endotoxin*	*2 h post-endotoxin*
P_{O_2} (mmHg)	97 ± 4	92 ± 4	95 ± 6	94 ± 6
P_{Co_2} (mmHg)	23 ± 2	20 ± 2	–	–
pH (units)	7.470 ± 0.040	7.196 ± 0.038*	7.500 ± 0.080	7.380 ± 0.05
Lactate (mg/100 ml)	8.9 ± 1.6	27.7 ± 7.2***	15.7 ± 3.0	47.1 ± 9.8**
Glucose (mg/100 ml)	192 ± 47	120 ± 28	209 ± 36	168 ± 30

† The corresponding values for spontaneously breathing cats were: P_{O_2} 94 ± 3 mmHg, P_{CO_2} 27 ± 2 mmHg, pH 7.317 ± 0.011 units, lactate 6.7 ± 0.9 mg/100 ml and glucose 106 ± 6 mg/100 ml.
* $P < 0.0005$; ** $P < 0.005$; *** $P < 0.025$.

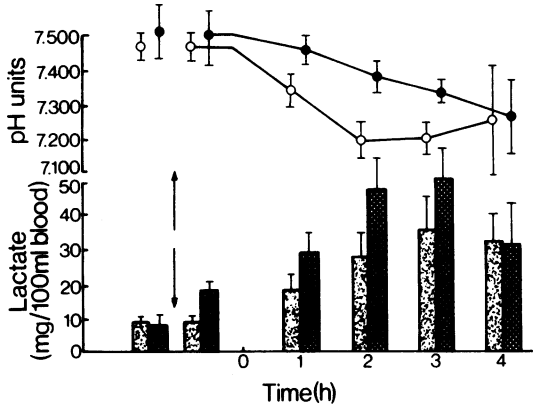

Fig. 2 The effect of endotoxin (2 mg/kg at time 0 h) on arterial pH and lactate levels in control cats and in cats pretreated with indomethacin (10 mg/kg, at the arrow). Values are means and s.e. mean. The pH difference between the two groups was significant ($P < 0.05$) at 1, 2 and 3 hours. Control (○) and stippled column; indomethacin (●) and cross-hatched columns.

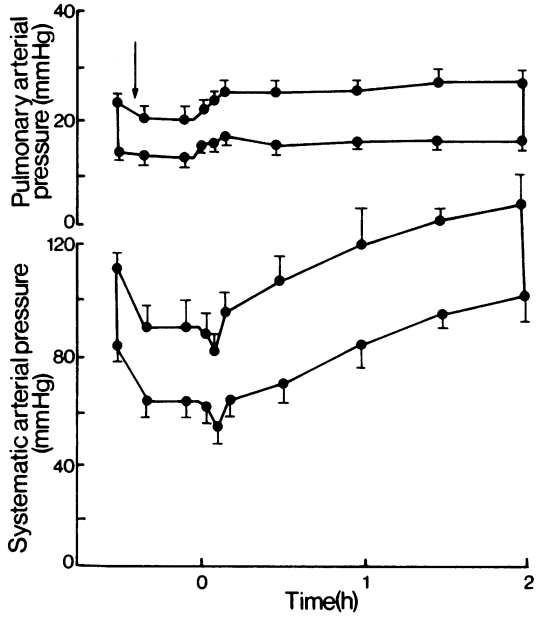

Fig. 3 The effect of endotoxin (2 mg/kg at time 0 h) on systolic and diastolic pulmonary arterial pressures (mmHg, above) and on systolic diastolic systemic arterial pressures (mmHg, below) in cats pretreated with indomethacin (10 mg/kg, at the arrow). The acute pulmonary vasoconstrictor response to endotoxin was abolished (compare Fig. 1) and there was no delayed fall in systemic arterial pressure. Values are means ± s.e. mean.

oxygen tension. An arterial P_{CO_2} of 27-33 mmHg is normal in anaesthetized, spontaneously breathing, cats (see Parratt, 1973; 1974).

Endotoxin administration resulted in a substantial metabolic acidosis (Table 2). The arterial base excess had fallen from -10.1 ± 1.6 mEq/l to -18.9 ± 2.1 mEq/l at 2 h and this was associated with a two- to eight-fold increase in blood lactate. The time course of these effects is illustrated in Figure 2. Plasma glucose, which was substantially elevated after thoracotomy, was decreased 2 h after endotoxin (Table 2).

The effect of indomethacin on the cardiovascular and metabolic responses to endotoxin

The intravenous administration of indomethacin resulted in substantial reductions in systemic and pulmonary blood pressures and in cardiac output and a slight reduction in left ventricular dP/dt *max* (from 3844 ± 421 to 3429 ± 473 mmHg s^{-1}). This occurred despite an elevation in LVEDP (from a mean of +2.0 to a mean of +2.3 mmHg). Some of these changes are outlined in Table 3. In two cats given indomethacin alone, there was little substantial recovery in systemic blood pressure over a 2 h experimental period.

After indomethacin, endotoxin failed to elevate pulmonary artery pressure significantly (Fig. 3) and the decrease in systemic pressure, which was a marked and characteristic feature of the acute phase in the control animals, was only slight. Thereafter, systemic arterial pressure tended to rise and, 1 h and 2 h after endotoxin, the mean value was significantly ($P < 0.005$) higher than in the cats given endotoxin alone (compare Figures 1 and 3). It is clear that indomethacin prevented the fall in pressure which follows the administration of endotoxin and delayed the reduction in cardiac output and in right atrial pressure (Tables 1 and 3). LVEDP (2.3 ± 0.4 mmHg after indomethacin) fell only slightly in response to endotoxin, being a mean of 1.6 ± 0.5 mmHg at both 1 h and 3 h periods. Of the 15 cats pre-treated with indomethacin, eight (53%) were alive 4 h and six (40%) 6 h after endotoxin. Table 3 makes it clear that almost all (13) of the indomethacin-treated cats survived longer than 3 h; those that died during the 3-4 h post endotoxin period usually did so following sudden, and unaccounted for, systemic hypotension. The delay in the onset of the shock phase in cats pre-treated with indomethacin was also clearly seen in the results obtained from arterial blood sampling. The arterial pH tended to

Table 3 Haemodynamic effects of *E. coli* endotoxin (2 mg/kg i.v.) when administered 30 min after indomethacin (10 mg/kg).

		30 min post indomethacin	Post-endotoxin			
	Control		1 h	2 h	3 h	4 h
Carotid artery pressure (mean; mmHg)	110 ± 5	78 ± 6	99 ± 6**	106 ± 6*	84 ± 11	103 ± 21
Heart rate (beats/min)	191 ± 9	180 ± 11	205 ± 10	210 ± 10	209 ± 8	213 ± 11***
Right atrial pressure (mean; mmHg)	+1.2 ± 0.4	+1.1 ± 0.4	+1.0 ± 0.4	+1.1 ± 0.3	+0.8 ± 0.3	+0.9 ± 0.4
Cardiac output (ml min^{-1} kg^{-1})	101 ± 11	81 ± 18	107 ± 2	99 ± 3	79 ± 2	54 ± 13**
Systolic ejection time (ms)	132 ± 5	140 ± 8	117 ± 6**	101 ± 5*	97 ± 4*	88 ± 8*
Myocardial blood flow (as myocardial thermal conductivity increment ΔK, c.g.s. units x 10^{-4})	2.8 ± 0.7	1.7 ± 0.6	2.3 ± 0.6	2.2 ± 1.1	1.3 ± 0.2	2.7 ± 1.6
Number of survivors	15	15	14	14	13	8†

*$P < 0.0005$; **$P < 0.005$; ***$P < 0.025$. Compared with corresponding values in Table 1.
† Six animals survived 6 hours.

fall more gradually (Fig. 2) despite the fact that substantial elevations in arterial lactate occurred.

Discussion

The results obtained from the present experiments show clearly that the administration of indomethacin abolishes the acute pulmonary vasoconstriction which follows the administration of *E. coli* endotoxin in the cat. This result is similar to that obtained with acetylsalicylic acid, which has been shown to prevent the acute increase in right atrial, or central venous, pressure in this species (Greenway & Murthy, 1971; Hall *et al.*, 1972). Like acetylsalicylic acid (Murthy & Greenway, 1972) indomethacin also prevented endotoxin-induced pulmonary oedema and haemorrhagic lesions. In the dog, the predominant acute effect of endotoxin consists of hepatic arterial and venous constriction, elevation of portal venous pressure and subsequent hepatic pooling. Since this effect is also prevented or reduced by aspirin (Solomon & Hinshaw, 1968) and by indomethacin (Erdös *et al.*, 1967; Culp, Erdös, Hinshaw & Holmes, 1971) this may point to a common mediator (or mediators) in both species. Of the possible candidates, histamine would seem the most likely. It is released as a result of a complex reaction involving endotoxin, platelets and a plasma factor (Vick, 1960). In the cat, released histamine causes pulmonary vasoconstriction (particularly on the venous side) and endotoxin-induced vasoconstriction is reduced by the prior administration of the histamine liberator compound 48/80 (Parratt, 1973). The fact that indomethacin also prevents endotoxin-induced pulmonary vasoconstriction suggests either that it interferes with the release of histamine by endotoxin or that it antagonizes its effects on the pulmonary vascular bed. There is evidence from an isolated vascular smooth muscle preparation (guinea-pig mesenteric vein) that indomethacin antagonizes histamine-induced vasoconstriction (Northover, 1967) in doses not so very different from those one might expect to find in the blood after the intravenous administration of 10 mg/kg.

Despite the fact that the acute pulmonary vasoconstriction was abolished by indomethacin, all the cats pre-treated with the drug showed some evidence of the secondary shock phase. This is characterized by a marked metabolic acidosis, elevation of arterial lactate (Lucas & Kitzmiller, 1972 and Table 2) and reductions in right atrial and systemic arterial pressures, cardiac output and systolic ejection volume and time (Parratt, 1973 and Table 1). These are all consistent with peripheral pooling of blood, a reduced tissue perfusion

pressure and cellular hypoxia. Indomethacin modified some, but not all, of these delayed effects of endotoxin. The most pronounced modification was the prevention of the delayed reduction in systemic arterial pressure. In fact, over the 4 h period, the blood pressure tended to rise in the indomethacin-treated animals and at 1 and 2 h the pressure in the indomethacin group was a mean of 30 mmHg higher than in the group given endotoxin alone. One explanation for this might be that indomethacin inhibited the release of prostaglandins, which have been demonstrated in the plasma of dogs after endotoxin administration (Collier, Herman & Vane, 1973; Kessler, Hughes, Bennett & Nadela, 1973). There is certainly evidence of inhibition by indomethacin of the release of prostaglandin which occurs during splenic nerve stimulation (Ferreira, Moncada & Vane, 1971) and recently Vane's group (Collier *et al.*, 1973) have shown that, in the dog, indomethacin abolished the output of prostaglandins which occurred during hypotension induced by haemorrhage or endotoxin. In the present study, the elevation in blood pressure that occurred after endotoxin in the indomethacin-treated cats could be explained on the basis of Hedqvist's hypothesis (for references, see Hedqvist, 1972) that prostaglandins of the E series are released on adrenergic nerve stimulation and that they exert a local inhibitory action on further neuronal noradrenaline release. This would also explain the marked elevation of circulating catecholamines which occur after endotoxin administration both in cats and dogs (Hall & Hodge, 1971) and the maintenance of indices of myocardial contractility such as left ventricular dP/dt (Parratt, 1973 and the present paper) until the terminal stages of shock.

Despite the maintenance of an adequate tissue perfusion pressure in cats pretreated with indomethacin, other characteristics of the delayed shock phase were still apparent. Cardiac output and systolic ejection time were still reduced and there was a substantial metabolic acidosis, with marked lactate production. It was of interest, however, that the decrease in arterial blood pH was significantly delayed in the indomethacin-treated cats; this was also observed by Erdös *et al.* (1967) and by Culp *et al.* (1971) in dogs. In our experiments there was no clear relationship between arterial pH and lactate levels following endotoxin and this is apparent from Figure 2. Although indomethacin delayed the decrease in arterial pH following endotoxin, lactate levels were, if anything, higher than in the cats administered endotoxin alone. This may suggest that other acid substances are released into the circulation during the shock phase.

It is difficult to draw any valid conclusions from the present experiments regarding the ultimate effect of indomethacin on survival in endotoxin shock. Although 40% of the animals given indomethacin survived 6 h (compared with only 4% in those given endotoxin alone) all of these cats had a substantial metabolic acidosis and a decreased cardiac output at 4 hours. At this time, the peripheral vascular resistance was about twice normal. The question as to whether indomethacin is affording protection against endotoxin shock by inhibiting prostaglandin synthesis, or whether it has a separate and more fundamental action, such as stabilization of lysosomal membranes, remains to be answered. It should be possible to provide some information on this point by using agents (a) which have a demonstrable stabilizing effect on lysosomal membranes (such as chloroquine) and (b) which have a distinct action in inhibiting prostaglandin release (such as synthetic analogues of prostaglandin precursors).

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