Br. J. Pharmac. (1984), **83**, 433–442

A new canine model of endotoxin shock

S.F. Evans[1], C.J. Hinds & J.G. Varley

Research Laboratory, Department of Anaesthesia and Intensive Care, St Bartholomew's Hospital, London EC1A 7BE

1 A new canine model of endotoxin shock has been developed in which spontaneous recovery of cardiovascular function is largely prevented, the haemodynamic effects of anaesthesia are minimized and intravascular volume replacement is given.

2 This model has been evaluated using two groups of five adult mongrel dogs anaesthetized with α-chloralose and breathing spontaneously. Animals in one group were anaesthetized, instrumented and given *Escherichia coli* (*E. coli*) endotoxin intravenously, whilst those in the control group were subjected only to anaesthesia and instrumentation.

3 *E. coli* endotoxin was given to dogs in the shock group as a bolus dose of 5 mg kg^{-1} followed by a continuous infusion at 2 mg $kg^{-1} h^{-1}$. This produced immediate, severe, cardiovascular depression, with precipitous falls in mean arterial pressure (MAP), cardiac index (CI), stroke index (SI) and left ventricular (LV) *dp/dt max*. There were associated increases in systemic and pulmonary vascular resistances. Arterio–venous oxygen content difference ($C(a-v)O_2$) increased after induction of shock, and animals developed a progressive metabolic acidosis. Increasing haemoconcentration occurred, as evidenced by a rising haematocrit (PCV). Hypovolaemia was reflected by a concurrent fall in pulmonary capillary wedge pressure (PCWP).

4 One hour after induction of shock, intravascular volume replacement was given in the form of a colloidal gelatin solution, as a bolus dose of 10 ml kg^{-1}, followed by a continuous infusion at 10 ml $kg^{-1} h^{-1}$. Volume replacement reversed haemoconcentration, restored PCWP and produced some haemodynamic improvement, although in general, severe cardiovascular depression persisted throughout a three hour observation period.

5 This severe endotoxin shock model has proved to be stable, reproducible and economical. It provides a useful preliminary test for new methods of treatment in hypodynamic endotoxin shock, as well as allowing investigation of acute metabolic and physiological changes.

Introduction

Animal models have been widely used for the investigation of septic shock, a condition which in man still carries a mortality of up to 50% (Schumer, 1979). Many workers have performed endotoxin-based experiments, and there is a wealth of literature describing the effects of endotoxin in different species of experimental animals (Halmagyi *et al.*, 1963; Brockman *et al.*, 1967; Kuida *et al.*, 1971; Balis *et al.*, 1978; Morris *et al.*, 1979). This subject has been comprehensively reviewed by Gilbert (1960).

However, concern has recently been expressed with regard to the clinical relevance of endotoxin models (Wichterman *et al.*, 1980) and alternatives which attempt to represent more exactly the clinical situation have been suggested. These have included the intravenous infusion of live bacteria into mongrel dogs, sheep, pigs and rhesus monkeys (Pool *et al.*, 1977; Hinshaw *et al.*, 1979; Fairman & Glauser, 1980; Gahos *et al.*, 1982). Other models have involved the induction of peritonitis, for example, by implantation of a septic sponge or by production of an infected, ischaemic gall bladder (Perbellini *et al.*, 1978; Raymond *et al.*, 1983). In practice, such preparations suffer from several disadvantages and endotoxin-based models may still be preferred for the initial evaluation of new methods of treatment and for the investigation of acute metabolic or physiological changes. Nevertheless, previously described canine models of endotoxin shock also have a number of limitations.

Although the reaction of the dog to the intravenous injection of endotoxin is well-documented and

[1] Correspondence.

reproducible (Lillehei & Maclean, 1959; Gilbert, 1960; Lillehei *et al.*, 1965; Morris *et al.*, 1979), most published data concern the circulatory effects of a single bolus dose. The relevance of such models to the clinical situation is limited since, in patients with endotoxaemia, there is probably a continuous slow leakage of endotoxin into the circulation from a nidus of sepsis. Furthermore, spontaneous recovery after a single bolus of endotoxin complicates the interpretation of subsequent haemodynamic events.

Acute canine models require the use of general anaesthesia, and it is important that a technique is chosen which minimizes haemodynamic disturbance. The majority of previous workers have used pentobarbitone as the principal anaesthetic agent. This may cause considerable cardiovascular depression, and in some animals can produce effects which mimic those of experimental shock (Lumb, 1963).

Finally, although hypovolaemia is an almost universal feature of septic shock (Cavanagh *et al.*, 1970), and early expansion of intravascular volume is a fundamental part of clinical management, previously-described canine endotoxin shock models have not included intravascular volume replacement.

We have, therefore, developed a new canine model which attempts to overcome these problems.

Methods

Healthy adult mongrel dogs of either sex, weighing 21.2 ± 0.98 kg (mean ± s.e.mean) were chosen. Animals were fasted overnight and no premedication was given. Anaesthesia was initially induced by injection of a 1% solution of methohexitone, 6–8 mg kg^{-1}, into a forelimb vein through an indwelling needle. Lignocaine hydrochloride 10% (1 ml) was added to the solution before injection in order to reduce local discomfort. Immediately following induction, a 1% solution of α-chloralose (Merck) was given at a dose of 40 mg kg^{-1}. This solution was freshly prepared in 0.9% w/v NaCl solution at 80°C and kept at 38°C in a water bath before being administered. The dogs were then left undisturbed in a quiet area for 30 min and supplemental oxygen was given via a nasal catheter at a rate of 3 l min^{-1}. This period allowed time for a satisfactory level of anaesthesia to be established (i.e. lack of response to stimulation, downward deviation of the eyes), and largely prevented sudden cardiovascular changes when the dogs were disturbed.

After this time, the animals were placed on an operating table, and a supplementary dose of α-chloralose, 20 mg kg^{-1}, was given if the level of anaesthesia was judged insufficient (*vide supra*). Animals were then instrumented acutely: electrocardiograph needle electrodes were applied and Portex 4FG or 5FG intravascular cannulae were inserted into both fore and hind limb vessels under direct vision. Another cannula was passed in the external jugular vein. A flow-directed thermodilution pulmonary artery catheter (Edwards Laboratories 93A-301-7F) was also introduced via the external jugular vein. A 110 cm 7F pigtail catheter was advanced into the left ventricle via the brachial artery. The central venous, pulmonary arterial, left ventricular and femoral arterial catheters were each connected to a Hewlett-Packard 1280 transducer and the output signals were monitored and recorded using a Hewlett-Packard 7786A monitor and 7700 paper recorder.

Maximal rate of rise of left ventricular pressure (LV *dp/dt max*) was continuously evaluated by means of a derivative computer. Cardiac output was measured intermittently using the thermodilution technique (Levett & Repogle, 1979), with an IL 701 cardiac output computer and IL 702 paper recorder (Instrumentation Laboratories, Lexington, Mass, USA). Measurements were made in triplicate at each measurement interval, using 5 ml boluses of 5% dextrose solution at 0°C.

All dogs were intubated with a 9.0 mm cuffed plastic endotracheal tube (Portex) after spraying the vocal cords and upper trachea with a 10% solution of lignocaine hydrochloride (3 mg kg^{-1}). The animals were then allowed to breathe a mixture of 30% oxygen in air via a Bain anaesthetic circuit. Fresh gas flow was adjusted to exceed three times the baseline minute ventilation in order to prevent significant rebreathing. Halothane at a concentration of 0.25% was added to the gas mixture from a Drager 'Vapor' vaporiser. Anaesthesia was maintained by injection of supplementary bolus doses of α-chloralose, one quarter of the induction dose, at two hourly intervals.

Central temperature was monitored in all animals using the thermistor at the distal end of the pulmonary artery catheter. Overhead radiant lights were used to maintain normal body temperatures throughout the experimental period in control animals, and during the baseline period in animals subsequently given endotoxin. In the latter group no attempt was made to influence body temperature changes after endotoxin was given, but ambient temperature was kept constant.

Cardiorespiratory measurements were made 15 min and immediately before induction of shock, and at 5, 30, 45, 60, 75, 80, 105, 135, 165 and 195 min thereafter. Derived physiological variables were calculated from the recorded measurements using standard formulae (see Appendix). Blood was also taken at these time intervals for arterial and mixed venous blood gas analysis and for estimation of packed cell volume. Blood gas analysis was performed using an IL 413 analyser (Instrumentation Laboratories, Lexington, Mass., USA), and oxygen contents were determined with a Lex 02 CON-TL

Table 1 Baseline values for cardiovascular function in anaesthetized animals

	Shock group		*Control group*	
	t = −15	*t* = 0	*t* = −15	*t* = 0
MAP (mmHg)	127 ± 5.8	135 ± 5.2	137 ± 4.7	135 ± 5.0
CI (ml min^{-1} kg^{-1})	200 ± 21	180 ± 24	170 ± 19	160 ± 17
SI (ml kg^{-1})	1.6 ± 0.1	1.4 ± 0.2	1.4 ± 0.2	1.2 ± 0.2
LV *dp/dt max* (mmHg s^{-1} × 10^3)	4.3 ± 0.5	4.3 ± 0.5	3.8 ± 0.5	3.8 ± 0.4
PCWP (mmHg)	5.4 ± 1.9	4.6 ± 1.6	6.2 ± 0.9	5.0 ± 0.7
TPRI (mmHgl^{-1} min kg^{-1})	678 ± 83	769 ± 90	880 ± 168	934 ± 185
PVRI (mmHgl^{-1} min kg^{-1})	47.0 ± 4.7	62.9 ± 10.5	45.1 ± 8.6	48.2 ± 15.0
C(a−v)O_2 (ml dl^{-1})	2.8 ± 0.6	2.8 ± 0.7	3.2 ± 0.3	4.0 ± 0.4
$\dot{V}O_2$ (ml min^{-1})	125.2 ± 29.1	108.2 ± 29.8	98.2 ± 8.8	118.1 ± 17.6
Temp (°C)	37.3 ± 0.9	37.3 ± 0.9	36.5 ± 0.2	36.6 ± 0.2
[H^+] (nM)	45.4 ± 1.8	43.6 ± 1.9	45.4 ± 1.5	44.8 ± 2.3
$Paco_2$ (kPa)	5.16 ± 0.40	5.08 ± 0.44	5.68 ± 0.23	5.48 ± 0.37
PCV (%)	45.6 ± 0.4	45.6 ± 0.8	41.6 ± 1.7	41.6 ± 1.7

t = time in minutes in relation to intravenous administration of endotoxin or vehicle. Results show mean values ± s.e.mean for five animals in each group. Key to symbols used: MAP = mean arterial pressure; CI = cardiac index; SI = stroke index; LV *dp/dt max* = maximal rate of rise of left ventricular pressure; PCWP = pulmonary capillary wedge pressure; TPRI = total peripheral resistance index; PVRI = pulmonary vascular resistance index; C(a−v)O_2 = arterio-venous oxygen content difference; $\dot{V}O_2$ = oxygen consumption; [H^+] = arterial hydrogen ion concentration; $Paco_2$ = arterial partial pressure of carbon dioxide; PCV = packed cell volume. Formulae used for calculation of CI, SI, TPRI and PVRI are given in the Appendix.

fuel cell analyser (Lexington Instruments, Waltham, Mass., USA). Packed cell volume (PCV) was measured on capillary tube samples spun in a microhaematocrit centrifuge.

Endotoxin shock was induced by intravenous administration of a bolus dose of Difco *E. coli* endotoxin 5 mg kg^{-1} (Difco Laboratories, West Moseley). Endotoxin was freshly prepared for each experiment as a 1% solution of lyophilysed solid in sterile water for bolus injection, and as a 0.5% solution for infusion. Batch no. 055.B5 was used for all experiments. The shock state was then maintained by immediately commencing an intravenous infusion of endotoxin at 2 mg kg^{-1} h^{-1}. One hour after induction of shock, the circulating volume was restored with a colloidal gelatin solution (Haemaccel, Hoechst), 10 ml kg^{-1} as a bolus dose followed by a continuous infusion at 10 ml kg^{-1} h^{-1}. Five animals (three male) received endotoxin, whilst a control group of five animals (four male) were subjected only to anaesthesia and instrumentation.

Numerical data are presented in the form of mean values ± s.e.mean. Statistical analysis of the differences between shock and control groups was performed using the two sample Student's *t* test. For within-group comparisons the paired *t* test was employed.

Results

There were no statistically significant differences between the two groups during the baseline pre-infusion period (Table 1). Both groups of dogs remained normocapnic after induction of anaesthesia, and there were no significant differences in $Paco_2$ values between shock and control animals (Figure 1). In both groups of animals, central temperature was maintained so that in the baseline period this was 36.6 ± 0.2°C in the control group and 37.3 ± 0.9°C in the group given endotoxin. Subsequently, analysis of variance confirmed that there were no significant changes in body temperature in either group. In the control dogs, mean arterial pressure (MAP) remained unchanged, although as the duration of

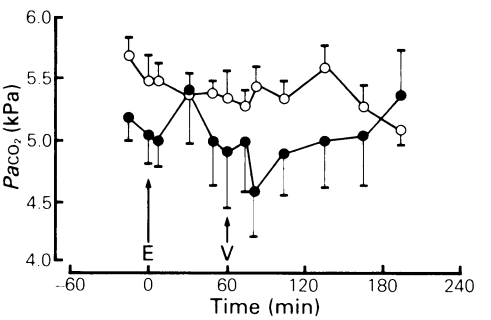

Figure 1 Blood $Paco_2$ values in control and endotoxin-shocked anaesthetized dogs. Results show mean values, with vertical lines representing s.e.mean for 5 dogs in each group; (●) endotoxin shock group; (○) anaesthetic only group. The arrows represent endotoxin administration (E) and volume replacement (V).

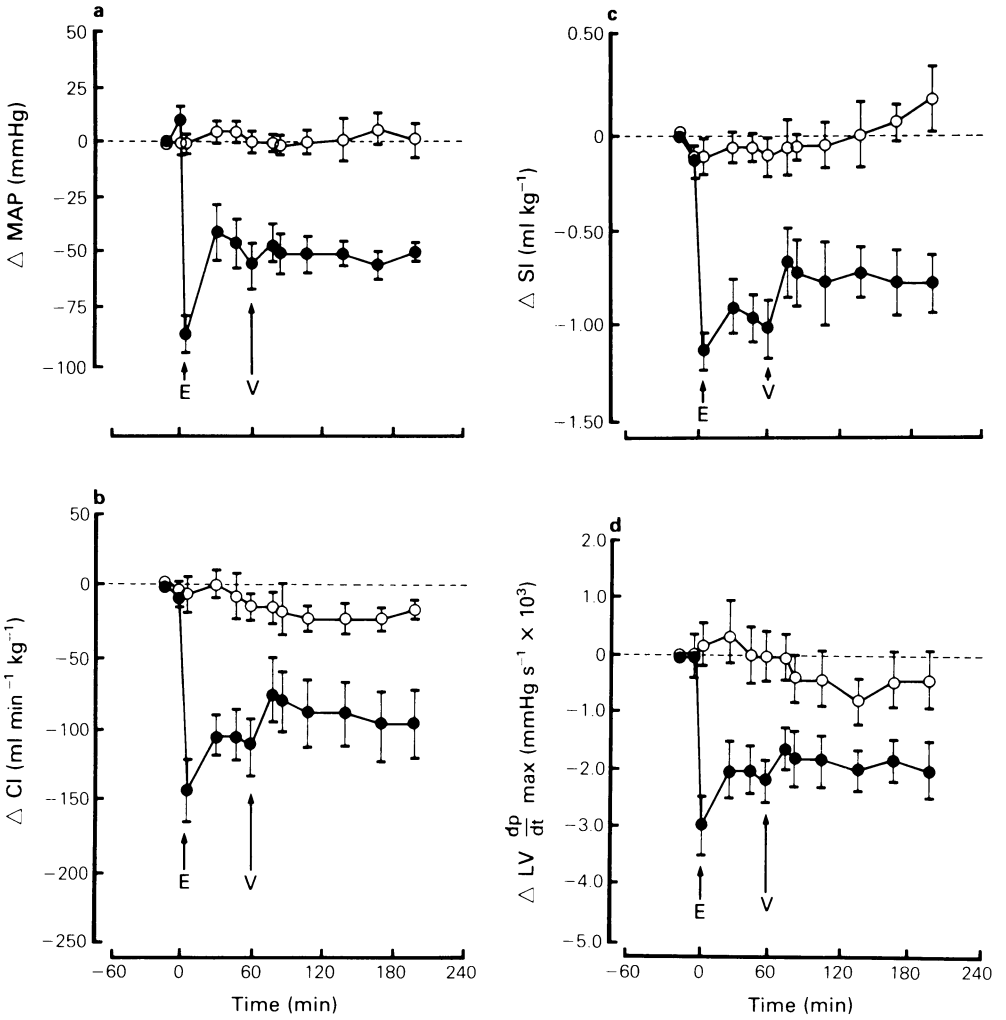

Figure 2 Changes in (a) mean arterial pressure (MAP), (b) cardiac index (CI), (c) stroke index (SI) and (d) left ventricular (LV) *dp/dt max* in control and endotoxin-shocked anaesthetized dogs. Results are calculated as mean changes from the t = − 15 values, with vertical lines showing s.e.mean, for 5 dogs in each group; (●) endotoxin shock group; (○) anaesthetic only group. The arrows represent endotoxin administration (E) and volume replacement (V).

anaesthesia increased, the cardiac index (CI) fell and total peripheral resistance index (TPRI) rose, both these changes becoming significantly different from baseline values at 165 and 195 min ($P<0.01$ and $P<0.05$ respectively; Figures 2 and 3). LV *dp/dt max* tended to fall concurrently although this change did not reach statistical significance. The stroke index (SI; Figure 2) and pulmonary capillary wedge pressure (PCWP; Figure 4) remained unchanged throughout. Oxygen consumption ($\dot{V}O_2$) tended to increase with time, and was significantly higher than the initial values ($P<0.05$) at 165 and 195 min. This was reflected in an increase in arterio–venous oxygen content difference ($C(a-v)O_2$) which became significant ($P<0.05$ or $P<0.01$) from 95 min onwards (Figure 5).

Administration of the endotoxin bolus resulted in immediate, severe cardiovascular depression with precipitous falls in MAP, CI, SI and LV *dp/dt max* (Figure 2), associated with increases in the TPRI and pulmonary vascular resistance index (PVRI; Figure 3). Five minutes after giving endotoxin, MAP had fallen by 84.6 ± 6 mmHg, CI by 150 ± 20 ml min^{-1} kg^{-1}, SI by 1.2 ± 0.1 ml kg^{-1} and LV *dp/dt max* by

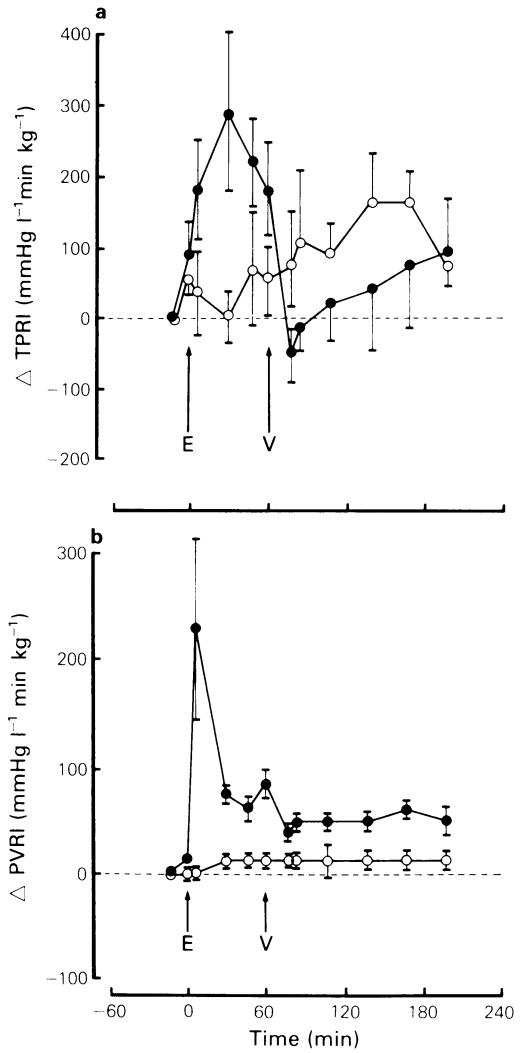

Figure 3 Changes in (a) total peripheral resistance index (TPRI) and (b) pulmonary vascular resistance index (PVRI) in control and endotoxin-shocked anaesthetized dogs. Results are calculated as mean changes from the t = − 15 values, with vertical lines showing s.e.mean, for 5 dogs in each group; (●) endotoxin shock group; (○) anaesthetic only group. The arrows represent endotoxin administration (E) and volume replacement (V).

$3.1 \pm 0.5\ \text{mmHg s}^{-1} \times 10^3$. TPRI had risen by $179 \pm 72\ \text{mmHg l}^{-1}\text{min kg}^{-1}$, and PVRI by $231 \pm 84\ \text{mmHg l}^{-1}\text{min kg}^{-1}$. All of these changes were statistically significant ($P < 0.05$).

Cardiovascular depression was maintained after introduction of the continuous infusion of endotoxin, and little spontaneous recovery occurred. MAP, SI, CI and LV *dp/dt max* remained significantly depressed ($P < 0.05$) when compared with control animals throughout the experimental period, although these differences just failed to reach statistical significance 75 and 105 min after endotoxin in the case of CI, and 105, 135 and 165 min after endotoxin in the case of LV dp/dt max (Figure 2). Mean TPRI reached a maximum 30 min after endotoxin administration, and then returned to baseline values after volume replacement with colloidal gelatin was given. Thereafter, TPRI tended to rise again, despite continuing

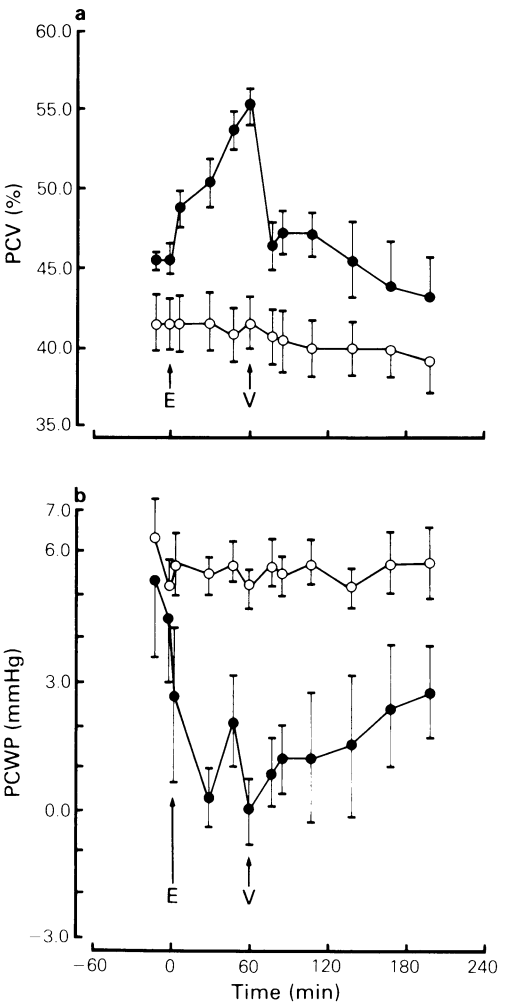

Figure 4 Values for (a) packed cell volume (PCV) and (b) pulmonary capillary wedge pressure (PCWP) as a function of time in control and endotoxin-shocked dogs. Results show mean values, with vertical lines representing s.e.mean, for 5 dogs in each group; (●) endotoxin shock group; (○) anaesthetic only group. The arrows E and V represent endotoxin administration and volume replacement, respectively.

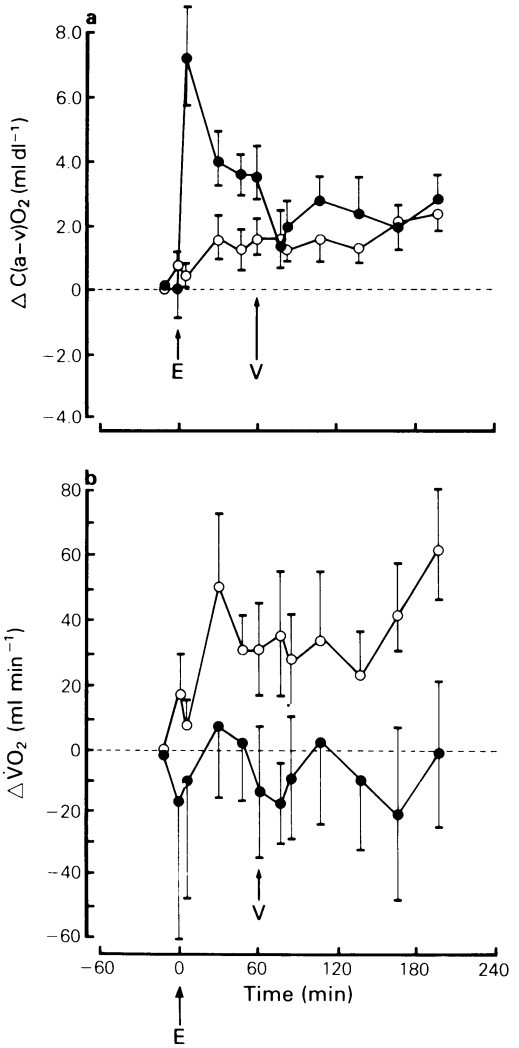

Figure 5 Changes in (a) arterio-venous oxygen content difference ($C(a-v)O_2$) and (b) oxygen consumption ($\dot{V}O_2$) in control and endotoxin-shocked anaesthetized dogs. Results are calculated as mean changes from the t = − 15 values, and vertical lines show s.e.mean, for 5 dogs in each group; (●) endotoxin shock group; (○) anaesthetic only group. E and V represent endotoxin administration and volume replacement, respectively.

volume infusion. There was considerable variability in the calculated values for TPRI and, as a result, differences between shock and control groups were not statistically significant. PVRI also rose immediately following endotoxin, and although there was a subsequent fall, it remained significantly higher in the shock group throughout the experimental period (Figure 3).

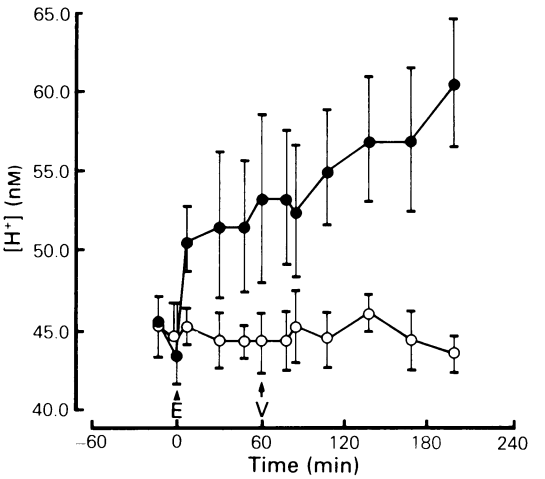

Figure 6 Arterial hydrogen ion concentration ($[H^+]$) values in control and endotoxin-shocked anaesthetized dogs. Results show mean values, and vertical lines represent s.e.mean, for 5 dogs in each group; (●) endotoxin shock group; (○) anaesthetic only group. E and V represent endotoxin administration and volume replacement, respectively.

$C(a-v)O_2$ rose steeply immediately after induction of shock, from a basal level in the anaesthetized animals of 2.8 ± 0.6 ml dl^{-1} to 9.9 ± 0.9 ml dl^{-1} 5 min after giving endotoxin. Thereafter $C(a-v)O_2$ fell to 6.3 ± 1.0 ml dl^{-1} at 45 min, remaining elevated above control values until volume replacement was given. The increase in $C(a-v)O_2$ reflected a fall in oxygen delivery, since $\dot{V}O_2$ remained essentially unchanged throughout the course of the experiment (Figure 5) (cf. values in the control animals).

Endotoxin shock produced marked haemoconcentration, resulting in an increase in PCV from $45.6 \pm 0.4\%$ to a maximum of $55.0 \pm 1.0\%$ 60 min after giving endotoxin. PCWP fell concurrently (Figure 4).

Shocked animals also developed a progressive metabolic acidosis, with arterial hydrogen ion concentration ($[H^+]$) rising from 45.4 ± 1.8 nM to 60.4 ± 4.1 nM by 195 min ($P < 0.05$ for comparison between shock and control groups: Figure 6).

Volume replacement with colloidal gelatin solution reversed haemoconcentration, returning PCV to $43.2 \pm 2.7\%$ by the end of the experimental period and reversing the trend of falling PCWP so that PCWP values 135 and 165 min after endotoxin were not significantly different from baseline (Figure 4). Volume replacement produced some improvement in measured and derived haemodynamic variables, returning TPRI (Figure 3) and $C(a-v)O_2$ (Figure 5) approximately to their baseline levels. CI and LV *dp/dt max* (Figure 2) also improved and were not

significantly different from control values ($P > 0.05$) at two and three measurement intervals respectively.

MAP and SI remained severely depressed, however, and generally cardiovascular depression persisted for the duration of the experiment. Fluid volume infused to shocked animals was found to exceed blood sampling volumes by 1153 ± 81 ml (50 ± 2 ml kg^{-1}).

Discussion

We have described a canine model of endotoxin shock which is reproducible and exhibits profound cardiovascular depression with only minimal recovery, despite volume replacement. Subsequent use of the model in our laboratory has confirmed these findings.

Mongrel dogs were chosen because of their characteristic and reproducible response to endotoxin administration (Lillehei & Maclean, 1959; Gilbert, 1960; Lillehei *et al.*, 1965). Nevertheless, as always, care must be exercised in extrapolating results of canine experiments to primates or man. For example, Brobmann *et al.* (1970) demonstrated marked differences in the effects of endotoxin on the mesenteric vasculature of dogs and rhesus monkeys.

The majority of published data obtained from canine models has concerned the circulatory effects of a single bolus of endotoxin. Widely different bolus doses (usually of *E. coli* endotoxin) have been used, ranging from as little as 0.1 mg kg^{-1} (Reynolds *et al.*, 1980) to 5 mg kg^{-1} (Alican *et al.*, 1962). The bolus dose of endotoxin used in this model (5 mg kg^{-1}) exceeds LD_{100} values quoted by previous authors (Brobmann *et al.*, 1970; White *et al.*, 1978) and was chosen in order to ensure induction of a profound shock state.

In general, a bolus of endotoxin produces an immediate, dramatic fall in blood pressure with almost complete recovery within about 30 min, after which slow and insidious cardiovascular depression supervenes until the death of the animal. Although the rapid onset of shock following a bolus injection of endotoxin is advantageous in minimizing delay, spontaneous recovery complicates the interpretation of subsequent haemodynamic events. Furthermore, a single bolus of endotoxin is probably less representative of the patient with endotoxaemia than is a continuous infusion. However, there is relatively little information available describing the effects of a continuous endotoxin infusion in animals. Aasen & Sangstad (1979) infused 2 mg kg^{-1} of *E. coli* endotoxin into dogs over a 3 h period, but this technique suffered the disadvantage of inducing a delayed and much slower fall in blood pressure than is generally seen after bolus administration.

There are also practical disadvantages inherent in those animal models of septic shock which are not based on endotoxin administration. In particular, the induction of shock is slow; the effects of an infusion of live bacteria as described by Hinshaw *et al.* (1979) develop only after about two hours, whilst in peritonitis-based models, animals may need to be studied over a period of several days (Perbellini *et al.*, 1978; Raymond *et al.*, 1983). In addition, chronic peritonitis is unpredictable and may induce either hyperdynamic or hypodynamic shock (Raymond *et al.*, 1983).

In our model the predictability and rapid onset of shock following bolus administration of endotoxin is combined with the sustained effects of a continuous infusion. The latter prevents spontaneous recovery and simulates the clinical situation in which endotoxin apparently 'leaks' into the circulation from a nidus of sepsis.

The haemodynamic effects of endotoxin in this model include a marked fall in CI, SI and LV *dp/dt max*, associated with increases in systemic and pulmonary vascular resistances. It is therefore representative of 'hypodynamic shock' in the human patient, which is often a late manifestation of sepsis and is associated with a high mortality and resistance to conventional methods of treatment. It should be noted that although LV *dp/dt max* was used in our study as an index of myocardial contractility, this measurement is influenced by other factors, including pulse rate, preload and afterload. The assessment of cardiac mechanical performance in shock has been critically reviewed by Goldfarb (1982). The significance of myocardial depression in septic shock remains controversial – early in the pathophysiological course of events, particularly when intravascular volume replacement is adequate, cardiac index may be supranormal and total peripheral resistance low. Later, as 'hypodynamic shock' develops, cardiac index falls. Although relative hypovolaemia may be important at this stage, other factors may be responsible for the reduction in cardiac output.

Several groups of workers, including Alican *et al.* (1962), Hinshaw *et al.* (1966), Cavanagh *et al.* (1970) and Hinshaw (1974) have suggested that myocardial depression in septic shock is a secondary phenomenon, manifested relatively late in the shock state, which occurs as a result of diminished venous return or coronary hypoperfusion. Conversely, Lefer & Martin (1970) and Lovett *et al.* (1971) have invoked primary myocardial failure due to release of a peptide which impairs cardiac function (myocardial depressant factor). Guntheroth *et al.* (1982) have recently produced good evidence for primary myocardial depression in a canine model, using several different parameters to measure contractility. In addition, there is evidence that the myocardium may

exhibit reduced sensitivity to catecholamines after administration of endotoxin (Geocaris *et al.*, 1973; Parratt, 1973).

The haemodynamic changes in our model are associated with an increased $C(a-v)O_2$ and a progressive metabolic acidosis. Since $\dot{V}O_2$ remains unchanged, this reflects a marked reduction in oxygen delivery as is seen in the hypodynamic phase of human septic shock.

Hypovolaemia is an almost universal accompaniment of septic shock, and a reduction in plasma volume is known to occur in primates given endotoxin (Cavanagh *et al.*, 1970). Our animals received volume replacement in an attempt to simulate the clinical situation in which intravascular volume replenishment is a fundamental part of the management of septic shock. Expansion of the circulating volume resulted in some cardiovascular improvement, and the changes in TPRI and $C(a-v)O_2$ induced by endotoxin were reversed. Nevertheless, in general, MAP, SI, CI and LV *dp/dt max* all remained severely depressed throughout. Assessment of the adequacy of volume replacement is complicated by fluid shifts and the influence of splenic contraction, as well as alterations in venous capacitance and ventricular compliance. However, as noted in the Results, our animals had received an excess of 50 ± 2 ml kg^{-1} of fluid over sampling volumes by the end of the experimental period. Furthermore, haemoconcentration was reversed and PCWP values were returned to levels indistinguishable from baseline.

The use of general anaesthesia in our model simplifies instrumentation and stabilization of the animals in the baseline period. An acute anaesthetized preparation also ensures that suffering of the animals is minimized. By including a control group of animals subjected to instrumentation and anaesthesia only, we have been able to demonstrate the minimal cardiovascular effects of our anaesthetic technique. Other workers (Brockman *et al.*, 1967; Adams *et al.*, 1979) have used different techniques of anaesthesia, but have not described a control group. The use of α-chloralose in our model avoids the cardiovascular depression associated with the use of barbiturate anaesthesia, which may actually mimic the effects of experimental shock (Lumb, 1963). This is likely to be exacerbated by the use of intermittent positive pressure ventilation. Cox (1972) has demonstrated that α-chloralose produces only transient cardiovascular depression and Arfors *et al.* (1971) showed little change in cardiovascular or respiratory function in dogs during six hours of α-chloralose anaesthesia. Although there is conflicting evidence as to its effects upon autonomic reflexes (Armstrong *et al.*, 1961; Cox, 1972; Cox & Bagshaw, 1979; Zimpfer *et al.*, 1981), in general, reflex activity is affected less by α-chloralose than by barbiturates. By using low doses of α-chloralose, artificial ventilation, with its attendant haemodynamic effects, was not required and the animals remained normocapnic throughout. However, it should be noted that respiratory depression may occur after α-chloralose if doses exceeding those described here are used. Halothane, 0.25%, was given as an adjunct to α-chloralose. The work of Bagshaw & Cox (1977) suggests that, at this concentration, its cardiovascular effects are minimal and halothane largely prevents the unwanted movements which have been described under chloralose anaesthesia (Balis & Monroe, 1964).

In conclusion, allowing for the limitations of acute canine endotoxin models, this model is reproducible, stable, economical and clinically relevant. It will allow investigation of acute physiological and metabolic changes in hypodynamic endotoxin shock and may provide a useful predictive test for new methods of treatment.

Appendix

$$\text{Cardiac index} = \frac{\text{cardiac output}}{\text{body weight}}$$

$$\text{Stroke index} = \frac{\text{cardiac index}}{\text{heart rate}}$$

$$\text{Total peripheral resistance index} = \frac{(\text{mean arterial pressure} - \text{central venous pressure})}{\text{cardiac index}}$$

$$\text{Pulmonary vascular resistance index} = \frac{(\text{mean pulmonary arterial pressure} - \text{pulmonary capillary wedge pressure})}{\text{cardiac index}}$$

This project was funded by the Joint Research Board at St Bartholomew's Hospital, London. The authors wish to thank Professor M. de Burgh Daly for his valuable advice during development of the model.

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(Received February 17, 1984.
Revised May 14, 1984.)