will be given to the incorporation of other nutrients into brain cholesterol and the schedule of drug administration.

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Alterations in the Hemodynamic Response to *E. coli* Endotoxin with Changes in the Acid-Base State.* (30004)

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Acid-base abnormalities in shock have aroused interest from both pathophysiologic and therapeutic standpoints(1-7). Alterations in vascular responsiveness related to blood pH and pCO_2 have been reported(8-13), as have been the relationships of blood pH to the release(14,15) and activity(16-19) of some of the vasoactive substances known to be involved in endotoxic shock.

Because of casual observations of unusual hemodynamic responses to endotoxin in deranged acid-base states, it was decided to undertake a systematic study of the vascular responses to endotoxin with varying pH and pCO_2. The early vascular reaction to endotoxin in the dog was found to be attenuated at low pCO_2 levels. There was, however, no loss of the usual response(20) to histamine under these conditions.

Methods. Twenty-nine adult mongrel dogs weighing 25 to 30 kg were used. Acid-base disturbances were produced in 23 dogs and 6 were used as controls. The animals were anesthetized with sodium pentobarbital (30 mg/kg) and a cuffed tracheal tube was inserted.

Metabolic acidosis was produced by slow infusion of 0.1 N hydrochloric acid *via* a femoral vein. Respiratory acidosis was attained by controlled respiration of a mixture of 90% oxygen and 10% carbon dioxide. Respiratory alkalosis was produced by overventilation with an intermittent positive pressure respirator using either 100% oxygen or compressed air. Metabolic alkalosis was brought about by infusion of 1.0 N sodium bicarbonate *via* the femoral vein. All animals, including the controls, received from 10-15 ml/kg of fluid. The control animals and those with respiratory acid-base abnormalities received normal saline. Those animals with metabolic derangements received enough normal saline to bring the total volume of fluid to 10-15 ml/kg. Only one kind of acid-base disturbance was produced in a single animal and the order of the experiments was random. Frequent anaerobic arterial blood samples were drawn from the femoral artery before and after the administration of endotoxin. The pH, pCO_2 and bicarbonate concentration of these samples were determined by the Astrup method(21).

Portal venous pressure (PVP) and femoral arterial pressure (FAP) were recorded continuously with Statham pressure transducers and an oscillograph *via* polyethylene catheters inserted into a splenic vein and a femoral artery. *E. coli* endotoxin (0111:B4-Difco) was given in a dose of 5 mg/kg. The same

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TABLE I. Hemodynamic Responses to Endotoxin with Varying pH and pCO_2.

	No. dogs	Avg pH	Avg pCO_2	Avg (HCO_3), mM/l	ΔPVP,* mmHg	ΔFAP,† mmHg
Control	6	7.38	39.0	22.4	19 ± .82	−72 ± 8.8
Respiratory alkalosis	6	7.60	11.4	10.8	7 ± .99	−14 ± 9.5
Respiratory acidosis	6	7.17	62.9	22.5	13 ± 2.38	−52 ± 19.2
Metabolic alkalosis	5	7.68	51.5	55.0	12 ± 1.90	−36 ± 15.6
Metabolic acidosis	6	7.23	24.9	10.8	4 ± 2.08	−10 ± 10.0

* Avg change in portal venous pressure ± S.E.
† Avg change in femoral arterial pressure ± S.E.

batch number was used for all experiments. The animal was then followed for 180 minutes or to death. In some experiments histamine was given in a dose of 20 μg of histamine per kg.

Results. The results are summarized in Table I. Three typical experiments in Fig. 1 contrast the effects of endotoxin at normal pH and pCO_2 with the response at low pCO_2. In Fig. 2 and 3 the average maximum changes in portal venous pressure and femoral arterial pressure during the initial endotoxin response are shown for varying pCO_2 values. Hemodynamic responses to endotoxin were least at low pCO_2 whether the pH was elevated or decreased. At high pCO_2 the initial responses were also depressed, but to a lesser

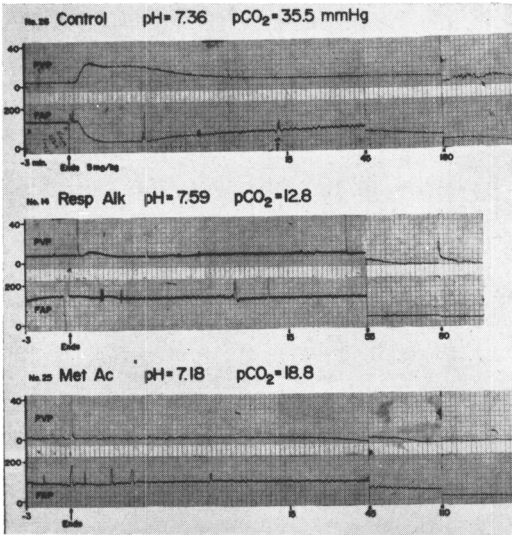
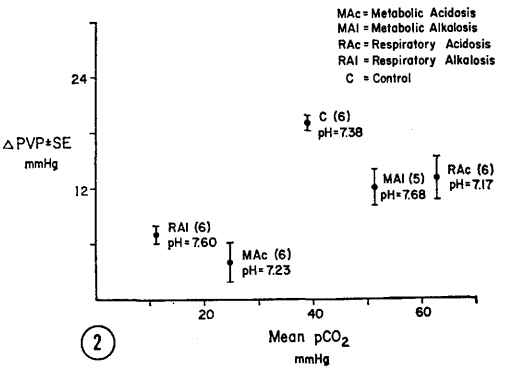


FIG. 1. Changes in portal venous pressure (PVP) and femoral artery pressure (FAP) after administration of endotoxin; top panel: control, middle panel: high pH and low pCO_2, bottom panel: low pH and low pCO_2. Note that under conditions of low pCO_2 there is little initial response to endotoxin.



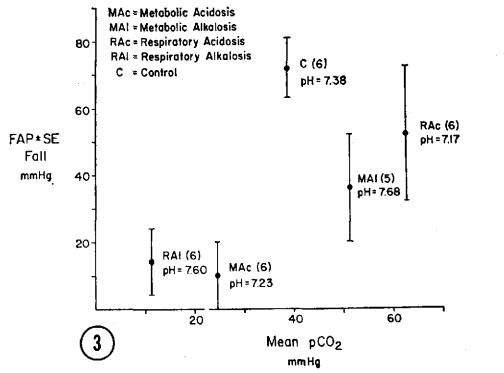


FIG. 2. Grouped average increase in portal venous pressure (± S.E.) shown as a function of the average blood pCO_2.

FIG. 3. Grouped average decrease in femoral arterial pressure (± S.E.) shown as a function of the average blood pCO_2.

degree and with more overlap of the control values. This suggests that pCO_2 is a more critical determinant than pH of the initial response to endotoxin. Fig. 4 shows representative tracings from histamine experiments. Although, as noted in the preceding experiments, there was essentially no initial hemodynamic response to endotoxin during severe respiratory alkalosis or metabolic aci-

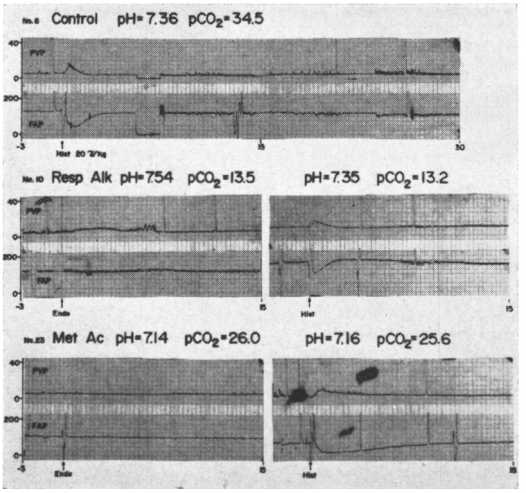


FIG. 4. Response to endotoxin and histamine at low pCO_2 levels; top panel: control response to histamine, middle and bottom panels: response to endotoxin and histamine under conditions of respiratory alkalosis and metabolic acidosis respectively. Note that in the same experimental preparations there was the usual response to histamine (20 μg of histamine base/kg).

dosis at low pCO_2, the usual vascular response to histamine was unchanged. Despite diminished initial responses at low blood pCO_2 the later progressive systemic hypotension and ultimate fatal outcome were not affected.

Discussion. These data suggest that the initial hemodynamic reaction to endotoxin is attenuated with a low blood pCO_2. It is not, however, increased at high pCO_2. The most brisk initial vascular responses to endotoxin under these experimental conditions occurred in the control animals. Other workers(11) have shown that high pCO_2 levels produce a decrease in vascular resistance by direct action on the blood vessels which is independent of histamine. It has been reported (16-19) that at high pCO_2 levels the vascular response to catecholamines is significantly decreased whereas the response is normal at low pCO_2 levels. Therefore, the diminished response to endotoxin and unchanged response to histamine observed in these experiments at a *low* pCO_2, suggest that either other mediator substances which lose vascular activity at low pCO_2 are involved, or that the rapid early release of mediator substances is inhibited by the low blood pCO_2.

Because of the above findings it is important that the acid-base state be defined in studies of the hemodynamic effects of endotoxin.

Summary. 1. An attenuated initial hemodynamic response to endotoxin was observed in adult mongrel dogs under conditions of low blood pCO_2 at both high and low pH. 2. No change in vascular responsiveness to histamine was found under these same conditions. 3. No change in the later phase of progressive systemic hypotension and death was observed.

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