TITLE: MECHANISMS OF ENDOTOXIN INDUCED PULMONARY EDEMA IN THE DOG

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Several studies of altered alveolar capillary permeability in sheep following live bacteria or E-Coli endotoxin have identified a biphasic pattern of response involving stereotyped changes in pulmonary vasomotor tone, lung lymph flow, and transpulmonary gradients of several prostanoids. We attempted to extend these observations to the dog by assessing the accumulation of extravascular lung water (EVLW) following shock doses (1.5 mg/kg I.V.) of endotoxin using a recently described technique of thermal green-dye double indicator dilution.

Methods: Eight mongrel dogs weighing between 22 and 33 kg were anesthetized with sodium pentobarbital, 20 mg/kg initially and then 2 mg/kg/hr by constant infusion. The dogs were intubated and ventilated with tidal volumes of 12 ml/kg at rates of 14-16/min with FiO_2 of 0.4. Catheters were placed in each femoral artery for measurement of mean arterial blood pressure (MAP), temperature, and green dye concentration. A pulmonary artery catheter was placed for determination of pulmonary artery (PAP) and pulmonary capillary wedge pressures (PCW). Baseline measurements of hemodynamic variables, blood gases, and lung water were obtained for each animal. Extravascular lung water measurements were made for control periods as well as for each time interval following endotoxin administration. After control determinations had been made, Escherichia coli endotoxin (Lot 026 B6: Control #702649; Difco Laboratories, Detroit, MI) in saline was infused over two minutes, to a final dose of 1.5 mg/kg. All hemodynamic and lung water measurments were then repeated at intervals of 15 min, 30 min, and then hourly for 6 hours following endotoxin. The results for the lung water determinations at each specific time after endotoxin were analyzed as the mean percentage change from control values for each animal and compared to the hemodynamic changes recorded at the same interval. Following the 6 hr period of measurement, all animals were sacrificed with sodium pentobarbital (80 mg/kg). All values, where appropriate, were examined by the t-test for unpaired values.

Results: All 8 animals survived the 6 hr period of observation without resusitative efforts of any kind. All animals sustained profound reductions in mean arterial, pulmonary capillary wedge pressure, and cardiac output within three min of endotoxin (*p <0.01 from control values). In marked distinction to the prior observations of mean PAP in the sheep however, 6 out of 8 dogs in our series displayed a consistent triphasic response of the pulmonary vasculature in which the mean PAP markedly decreased in parallel with the MAP followed in 2 min by an evanescent rise in pressure back towards baseline which stopped within 1 min and was followed by the third phase, that of a second, sustained fall in mean PAP. MAP, PAP, H.R., and C.O. remained depressed below baseline levels in 6 out of 8 dogs throughout the period of observation, but recovered to within 60-80% of control values by the end of the experiment. In 2 animals, the second phase of the mean PAP response, that of a brief rise in pressure was not seen and these animals mean PAP showed a consistent decline reaching a nadir within 5 min after the endotoxin bolus. In another 2 animals mean PAP showed a slow but continued rise over the 6 hrs attaining values 20-30% higher at termination than were observed during the control period. Endotoxin produced a consistent early increase in extravascular lung water as measured by double indicator dilution technique with a 28% mean increase over control values attained within 15 min after endotoxin (*p <0.05 from control values). Lung water increased in all animals despite mean reductions in PAP of 35% during the same time interval. Lung water continued to accummulate slowly over the ensuing period of observation reaching a maximum of 57% increase at 6 hrs. The rate of accummulation was greatest during the first 30 min after endotoxin (32% above control) and was seen to plateau at 4 hr into the study (55% above control).

Discussion: Recent reports of lung injury following endotoxin in sheep suggest a two phase process in which pulmonary vasomotor changes and permeability alterations operate to produce characteristic increases in lung lymph flow and lymph protein content. In the sheep, early and severe increases in pulmonary artery pressure are thought to trigger increases in lymph flow which are largely due to hydrostatic influences on fluid flux. A delayed second phase characterized by minimal elevations of mean PAP and marked increase in protein content of lymph is thought to represent the increased permeability phase. Our data in the dog however, points to consistent increases in extravascular lung water which occur and are associated with significant reductions in mean PAP and thus are not dependent on large increases in intravascular hydrostatic pressure. Endotoxin appears to produce early permeability changes in the dog not apparent in sheep. The demonstration that intrapulmonary synthesis of prostanoids may mediate some of the vasomotor and permeability changes seen following endotoxin in sheep should be addressed in other species since our data suggest significant differences in response profiles between the dog and the sheep.

Physiologic Responses Following Endotoxin in Dogs

Time	0"	15"	30"	1'	2'	3'	4'	5'	6'
HR (bpm)	150	110	118	136	130	132	122	128	117
MAP (mmHg)	123	58	60	68	77	78	88	83	106
CO (l/min)	3.7	1.1	1.6	2.1	2.8	2.7	3.0	3.1	3.3
PAP (mmHg)	13.0	7.6	8.2	9.8	11	10.6	11	11.2	11.3
PCW (mmHg)	4.0	0	0	1	1	1	1	1	1
EVLW (% control)	---	+28	+32	+33	+36	+48	+55	+55	+57

(Values are means for 8 animals)