Title: LONGITUDINAL DISTRIBUTION OF PULMONARY VASCULAR RESISTANCE DURING ENDOTOXIN-INDUCED PULMONARY HYPERTENSION IN SHEEP

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Introduction. Endotoxin administration produces pulmonary hypertension (PHTN) and pulmonary edema. Pulmonary edema following endotoxin administration may be due to increased capillary hydrostatic pressure and/or increased capillary permeability.[1] PHTN may be due to increased pulmonary arterial ($R_a$) and/or venous ($R_v$) resistance. If cardiac output is stable, increased $R_v$ will increase pulmonary capillary pressure (PCP), thereby exacerbating pulmonary edema. In order to clarify the role of increased PCP in endotoxin-induced pulmonary edema, we studied the longitudinal distribution of pulmonary vascular resistance (PVR) following endotoxin administration.

Methods. Eight male sheep were anesthetized with thiopental (20 mg/kg iv followed by an infusion of 5-20 mg/kg/hr), intubated, and ventilated with oxygen to maintain arterial $PCO_2$ between 35 and 45 mmHg. Systemic and pulmonary arterial catheters were inserted. Hemodynamic measurements included systemic arterial pressure, mean pulmonary arterial pressure (PAP), pulmonary arterial occlusion pressure (PAOP), central venous pressure, and heart rate. Cardiac output (CO) was measured in triplicate by thermodilution. Following baseline measurements, E. coli endotoxin (Sigma 055:B5) was infused over one hour at a dose of 2.5 ug/kg (n=4) or 5.0 ug/kg (n=4) and measurements were repeated every 30 minutes for four subsequent hours. Saline was infused to maintain PAOP at baseline values. With each set of measurements, three PAOP profiles were acquired at 200 Hz with an A/D converter. For each profile, a least squares fit to a biexponential decay was obtained and used to calculate PCP.[2] $R_a$ was calculated as (PAP - PCP)/CO and $R_v$ as (PCP-PAOP)/CO. Statistical analyses used repeated measures analysis of variance followed by the Newman-Keul's test with $P < 0.05$ considered significant.

Results. Both doses of endotoxin rapidly produced PHTN which then remained stable for the duration of the experiment (Table). There were no significant differences in any hemodynamic variable between the two doses of endotoxin. PCP rose in both groups and reached a maximum 30-60 minutes after the start of the endotoxin infusion. PCP then decreased in both groups and was not significantly different from baseline 30 min after completion of endotoxin administration. $R_a$ and $R_v$ both increased after endotoxin. $R_a$ remained elevated throughout the duration of the experiment but $R_v$ fell after the end of the endotoxin infusion and was not significantly different from baseline 30 min later.

Table: Pulmonary hemodynamics following endotoxin administration (2.5 ug/kg over 1 h)

| Time (from start of endotoxin) | PAP mmHg | PCP mmHg | PAOP mmHg | $R_a$ mmHg/l/min | $R_v$ mmHg/l/min |
|---|---|---|---|---|---|
| Baseline 0 h | 8.2 ± 2.4 | 4.65 ± 1.96 | 1.29 ± 0.28 | 1.42 ± 0.84 | 1.34 ± 0.83 |
| Endotoxin 0.5 h | 21.2 ± 2.2* | 10.4 ± 2.44* | 2.00 ± 1.86 | 4.31 ± 0.86* | 3.37 ± 0.60* |
| Endotoxin 1.0 h | 19.2 ± 3.0* | 8.52 ± 1.56* | 1.48 ± 0.32 | 3.70 ± 0.11* | 2.85 ± 0.54* |
| 1.5 h | 16.3 ± 1.9* | 6.14 ± 3.24 | 1.62 ± 2.10 | 4.07 ± 1.76* | 1.81 ± 1.05 |
| 2.0 h | 18.4 ± 1.0* | 6.66 ± 2.50 | 2.24 ± 2.04 | 4.07 ± 1.19* | 1.76 ± 0.48 |
| 3.0 h | 19.7 ± 2.9* | 5.47 ± 3.04 | 2.15 ± 1.15 | 4.96 ± 1.68* | 1.33 ± 1.15 |
| 4.0 h | 19.2 ± 2.2* | 4.48 ± 2.90 | 2.25 ± 0.66 | 5.88 ± 1.51* | 1.20 ± 0.93 |
| 5.0 h | 18.9 ± 1.8* | 5.55 ± 2.66 | 2.57 ± 0.81 | 5.34 ± 1.25* | 1.47 ± 1.14 |

Values are means ± standard deviation

*P < 0.05 compared to baseline

Discussion. Several authors have described a biphasic pulmonary response to endotoxin.[1,3] During the first phase, increased pulmonary lymph flow is associated with PHTN and normal capillary permeability; previous studies have therefore concluded that PCP is increased during this time. During the second phase, increased lymph flow is associated with increased capillary permeability. The first phase, which lasts 0.5-2 h, may be mediated by thromboxane while the second phase may be mediated by leukotrienes. In the present study, the longitudinal distribution of pulmonary vascular resistance following endotoxin administration also demonstrated two discrete phases. Initially, PHTN was due to increased $R_a$ and $R_v$ and PCP was elevated. One hour later $R_v$ and PCP decreased toward baseline, but PHTN persisted due to increased $R_a$. Additional studies are required to determine the longitudinal distribution of PVR in other models of acute respiratory failure and to identify the mediators of such changes.

References:

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