TITLE: CARDIOPULMONARY INJURY PRODUCED BY LEUKOTRIENE D_4 IN ANESTHETIZED DOGS

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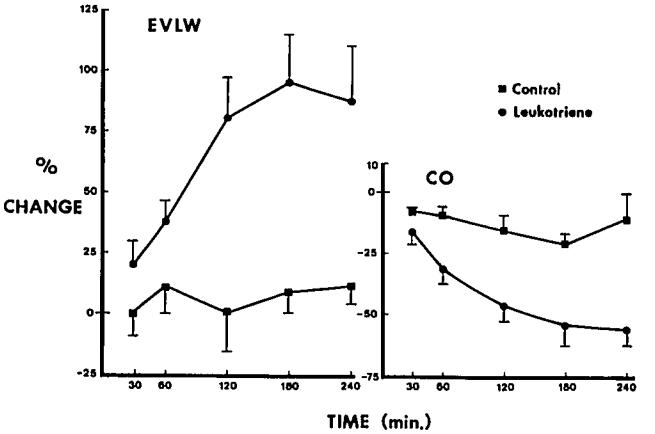
INTRODUCTION: Leukotrienes (LT) (previously slow-reacting substance) have recently been isolated and proven to be potent mediators of allergic and inflammatory processes. Among other effects, LT cause bronchoconstriction (human, dog), myocardial depression (human, sheep) and increased capillary permeability (human skin, hamster cheek pouch, in vitro rabbit lung model). LT may be important mediators of pulmonary capillary permeability changes in disease states such as ARDS. The present study determined pulmonary and hemodynamic changes produced by intravenously administered LTD_4 in the intact anesthetized dog.

METHODS: Ten mongrel dogs (17-22 kg) were anesthetized with thiamylal (20 mg/kg IV, then 5 mg/kg/hr) with pancuronium (1 mg/hr) added later for muscle relaxation. Mechanical ventilation was established with a tidal volume of 15 ml/kg, an FiO_2 of 1.0 and a ventilatory rate adjusted to keep the end-tidal CO_2 34-38 torr. A 5F thermistor-tipped arterial lung water catheter and a 7F thermodilution pulmonary artery (PA) catheter were positioned via femoral cutdown in the femoral and pulmonary arteries respectively. Normal saline was administered prior to baseline measurements to achieve a pulmonary artery wedge pressure (PAWP) of 3-5 mmHg. A 10 cm esophageal balloon was positioned during spontaneous respiration approximately 5 cm above the diaphram using an inspiratory occlusion test[1] with the esophageal pressure (Pes) to tracheal pressure (Pt) ratio greater than 0.96. Inspiratory flow rate (IFR), measured with a pneumotachograph, was adjusted to 40 liters/min and Pes and Pt were measured with a differential pressure transducer to obtain transpulmonary pressure (TPP). Recordings were made of baseline measurements which included heart rate (HR), mean arterial pressure (MAP), pulmonary artery pressure (PAP), PAWP, central venous pressure, airflow and TPP. Plateau TPP was obtained using a 1.5 second inspiratory hold. Cardiac output (CO) was determined by thermodilution and extravascular lung water (EVLW) by the thermal-dye double indicator dilution technique.[2] CO, EVLW, peak TPP and plateau TPP were expressed as a mean of three determinations. Four animals served as controls, while 6 dogs received LTD_4 (.25 µg/kg) via the proximal port of the PA catheter. Baseline measurements were repeated 30 minutes post injection and then every hour for four hours. The dogs received no intravenous fluids after LT administration except that necessary for anesthetic administration and EVLW determinations. Statistical analysis utilized two-way repeated measures analysis of variance and t-test with level of significance at $P<.05$.

RESULTS: The control group demonstrated no difference from the LT group in baseline EVLW, CO, PAWP, or the total volume of crystalloid administered. The response to LT was variable, identifying a responder group (4 dogs) and a nonresponder group (2 dogs), the latter showing < 7% increase in EVLW, < 8% decrease in CO and no increase in inspiratory airway resistance (Raw). The responder group demonstrated a significant increase in EVLW (5.5 ± .7 to 10.3 ± .6 ml/kg, mean ± SE), and decrease in CO (227 ± 21.4 to 95.3 ± 5.8 ml/kg/min) with concommitant increases in pulmonary and systemic vascular resistances, however Raw did not increase. At 180 and 240 min, the PAWP in the responder group increased over controls (8 ± 2 vs. 3 ± 1, mmHg), however lung injury was evident at 60 min (figure) and no animal developed a PAWP > 12. MAP, PAP, arterial oxygenation and Qs/Qt did not change significantly in either control or LT groups.

DISCUSSION: Intravenous LTD_4 caused a significant cardiopulmonary injury without evidence of bronchoconstriction. These changes occurred using smaller dosages of LT (.25 ug/kg) than other studies reporting airway constrictor effects (asthmatic dogs given aerosolized LT 1 ug/kg)[3] and hemodynamic changes (rats given 4 ug/kg).[4] Since late and only modest increases in hydrostatic pressure occurred, the contribution of the myocardial depression to the pulmonary injury is felt to be minor. The variability in response, which has been observed by others in studies of LT, may offer insights to the unpredictable nature of ARDS in humans. Possible mechanisms for the variability observed in this study include compensatory increases in pulmonary lymphatic flow preventing accumulation of EVLW, variability in serum ionized calcium concentrations, or variable interactions with other mediators.



EVLW and CO in the LT responder group (n=4) were significantly different than the control group (n=4) at 60, 120, 180 and 240 min ($P<.05$). Values are percent change from baseline, mean ± SE.

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