Title: EFFECTS OF ENDOTOXIN IN THE ISOLATED BLOOD PERFUSED PIG LUNG

Authors: S.D. Parker, M.D., A.T. Walman, M.D., R.J. Traystman, Ph.D. and G.H. Gurtner, M.D.

Affiliation: Department of Anesthesiology and Critical Care Medicine
The Johns Hopkins Medical Institutions, Baltimore, Maryland 21205

Introduction. Sepsis remains a common cause of adult respiratory distress syndrome (ARDS) in humans. Endotoxin has been used to produce a model of septic lung injury in the intact pig[1] and other animals. Increases in pulmonary vascular resistence (PVR) and extra vascular lung water (EVLW) have been shown.[2] In order to further delineate the components of the pulmonary response to endotoxin, we studied the effects of an endotoxin infusion in an isolated blood perfused pig lung. The use of this preparation has the advantage that important vascular determinants of edema formation such as pulmonary vascular pressures and flow can be precisely regulated, and the rate of edema formation can be directly measured.

Methods. Eight 20-25 kgm. pigs of both sexes were anesthetized with ketamine 8-10 mgm/kgm IM and 30 mgm/kgm sodium pentobarbital IV. Tracheastomies were performed and the animals were ventilated with room air at a tidal volume of 15 cc/kgm and a rate of 10/min. The chest was widely exposed and the heart and lungs left in situ. the animals were heparinized and exsanguinated via an aortic cannula over 7-10 minutes. Subsequently, the pulmonary artery and left atrial appendage were cannulated and perfusion established with autologous whole blood at flows of 20 cc/kgm/min with a Sarns blood pump. temperature of the perfusate was maintained at 38°C, 5% CO_2 was added to inspired air to maintain PCO_2 of the perfusate between 35-45 mm HG. $NaHCO_3$ was added as needed to maintain pH between 7.35-7.45. Hgb saturation remained $\geq$ 90%. Measured variables included pulmonary artery pressures (Ppa), airway pressures, left atrial pressures (Pla) , and lung weight change. The latter was recorded as the inverse of the weight of the perfusate reservoir and was recorded continuously. Ppa was allowed to stabalize before measurements of lung weight change were made. Pla was maintained negative by adjusting the height of the reservoir but was transiently raised to +5 mm Hg following measurement of lung weight change. Lung weight change was measured over 10 min and expressed in gms/minutes. E. coli endotoxin was given to 5 animals by continuous infusion into the pulmonary artery at 100 ugm/min and was discontinued when Ppa reached twice control levels. Ppa was then allowed to return to baseline and lung weight gain measured at negative and positive Ppa. Flow remained constant throughout. Group means were analyzed by the two sample T-test and were considered significant when P <.05.

Results. The stability of the preparation over variable time periods is demonstrated in Fig. #1 (control group), with Pla maintained zero or negative. Little progressive weight gain is noted with time. The endotoxin group, however, shows marked weight gain with Ppa following endotoxin, but also continues to show weight gain after Ppa has returned to near control levels (P < .05) (Fig. #1). Each line represents a single animal, with weight gain measured before and after endotoxin in this group. Furthermore, although some weight gain is seen in the control animals with positive left atrial pressures, a marked degree of weight gain is seen in amimals receiving endotoxin who then have left atrial pressures increased after return of Ppa to pre-endotoxin levels (P $\leq$.05) (Fig. #2).

Discussion. Marked pulmonary hypertension was seen following infusion of 600-1200 ugm. of endotoxin. Increased weight gain during this period probably reflects recruitment of pulmonary vasculature. Pulmonary artery pressures then tended to return to baseline over variable time periods but weight gain was substantially greater in the endotoxin group than in controls, reflecting edema formation. When the capillary bed was completely recruited by increasing Pla to positive levels, the rate of weight gain in the endotoxin group was dramatic, reflecting the marked propensity of the injured pulmonary vasculature to edema formation with the stress of increased left atrial pressures. This differs from previous models which investigated this effects by increasing perfusion to maintain constant Ppa.[3] Since flows remained constant in each animal throughout each experiment, this factor was eliminated as a variable influencing the amount of edema formation. We feel this model has promise in determining the factors responsible for edema formation in endotoxic lung injury. The characterization of pharmacologic interventions which inhibit the responses noted here warrants further investigation.

References.

1. Breslow M et al: Effects of catecholamines on organ blood flow during endotoxin shock in the pig. Fed. Proc. Abstr. 43:415, 1984
2. Borg T. et al: Endotoxin induced respiratory failure in a porcine model. Anest. V. 59, No. 3. A105, 1983
3. Mizus M et al: Pulmonary edema of acid lung injury is attenuated by agents that elevate cAmP. Circ. 68:III - 234, 1983