Title: ACUTE PULMONARY DYSFUNCTION INDUCED BY COMPLEMENT ACTIVATION

Authors: T. Borg, M.D., B. Gerdin, M.D., R. Hällgren, M.D., O. Warolin, B.Sc., and J. Modig, M.D.

Affiliation: Departments of Anesthesiology, Surgery and Internal Medicine, University Hospital, S-750 14 Uppsala, Sweden

Introduction. Adult respiratory distress syndrome (ARDS) frequently occurs after septic and traumatic shock. This syndrome is characterized by an increase in capillary permeability with interstitial and alveolar edema. Sepsis and trauma can activate the complement system. Activated complement components induce aggregation of polymorphonuclear cells and entrapping of such cell aggregates in the lung. This sequence of events has been considered an important pathogenic factor in ARDS. We have therefore infused pigs with complement-activated plasma and studied the effects on pulmonary function.

Material and methods. Pigs weighing 23-35 kg were anesthetized with ketamine hydrochloride i.v. A tracheostomy was performed. Via the neck vessels catheters were inserted into the superior caval vein and aortic arch. A Swan Ganz catheter was introduced into a branch of the pulmonary artery. A left atrial catheter was inserted through a small left-sided thoracotomy. The animals breathed air spontaneously and received glucose 2.5% in saline i.v. Cardiac output ($\dot{Q}_t$) was measured by thermodilution technique. Right atrial (MRAP), pulmonary arterial (MPAP), pulmonary capillary wedge (MPCW) and left atrial (MLAP) blood pressures were determined by pressure transducers. Arterial and mixed venous blood were analysed using a Radiometer automatic blood gas analyzer. Hemoglobin, white cells and platelet counts were determined using a coulter counter. Differential counts were made on air-dried coverslip smears. Clotable plasma fibrinogen was determined spectrophotometrically. Lung biopsies were taken during the first minutes of i.v. infusion of complement-activated plasma (CAP) for microscopic examination. At sacrifice, the lungs were excised, carefully drained of blood, weighed, dried in air at 100°C for 3 days, and re-weighed. The calculated wet/dry lung weight ratio was used as an indicator of pulmonary edema.

Procedures. Blood, 7 ml/kg b.w., was drawn into heparinized syringes. After centrifugation the red cell mass was reinfused and the plasma was incubated with zymosan at 37°C for 15 min. The zymosan was removed by centrifugation and CAP was infused into the superior caval vein over approximately 10 min. The cycle was repeated four times with an interval of 1 h. Group 1 (control animals; n=8) received non-activated plasma at a rate of 7 ml/min. Group 2 (n=9) received CAP at the same infusion rate. Group 3 (n=9) received CAP at two infusion rates, 7 ml/min during the first two infusions and 14 ml/min during the last two infusions. In an additional four pigs isolated granulocytes were incubated in vitro with insoluble IgG aggregates (agg IgG) to induce a release of the cellular humoral content. After centrifugation the cell and agg IgG free supernatant was infused into the superior caval vein. Granulocytes were also aggregated in vitro using CAP and after washing infused into the superior caval vein. Three other pigs were pretreated with i.v. indomethacin (10 mg/kg b.w.), whereafter CAP was infused.

Results. Infusion of CAP caused an immediate but transient decrease in circulating polymorphonuclears (PMNs). Simultaneous measurement of PMNs in the superior caval vein and aorta showed a significantly greater reduction on the arterial side compared with the venous side indicating transient trapping of PMNs in the lungs. Microscopic examination of lung biopsies taken during CAP infusion showed an abundance of PMN aggregates in the microcirculation. Control animals did not show any infusion related changes in circulating PMNs, nor were any PMN aggregates found in the lungs. Platelet counts and fibrinogen did not show any infusion related changes either in control animals or in animals given CAP. During the first minute of CAP infusion, MPAP increased more than twofold concomitant with a triplicate increase in MRAP. MPCWP increased, on an average, 75%, and MLAP, after a transient increase, was unchanged. $\dot{Q}_t$ was not significantly changed. Total pulmonary vascular resistance increased more than twofold, due to an increase in resistance of both the arterial and the venous sides. The more rapid infusion of CAP (group 3) caused a more profound pulmonary vascular response. The control animals (group 1) did not show any infusion related vascular changes. In groups 1 and 2 venous admixture ($\dot{Q}_s/\dot{Q}_t$) did not change either during infusion or at the end of the observation period, approximately 5 h after start of the first infusion. In group 3 however, 6 of 9 animals showed an infusion related significant increase in $\dot{Q}_s/\dot{Q}_t$. In these 6 animals $\dot{Q}_s/\dot{Q}_t$ increased significantly, on an average, 40% at the end of the observation period. Although $\dot{Q}_s/\dot{Q}_t$ increased significantly in these 6 animals, the wet/dry lung weight ratio was not significantly increased, compared with group 1. Infusion of the supernatant from agg IgG activated granulocytes caused a similar pulmonary vascular response as infusion of CAP, while infusion of in vitro aggregated granulocytes did not cause any vascular reaction. Pretreatment with indomethacin inhibited the pulmonary vascular response but did not prevent the PMN aggregation.

Conclusions. CAP mediates a transient trapping of PMNs in the pulmonary microcirculation and a dose-dependent transient pulmonary arterial and venous constriction. The vascular response is not due to PMN aggregates as such, but is mediated by substances released from activated PMNs. The vascular reaction but not the PMN aggregation is prevented by indomethacin, suggesting that prostaglandin synthesis is involved in the pulmonary vascular response. Prostaglandins may be released either directly from activated granulocytes or from the lung tissue itself in response to activated granulocyte products. A more rapid infusion can increase $\dot{Q}_s/\dot{Q}_t$, which in essence is a "dry" vaso- and bronchioli constrictive reaction and not caused by edema. Using the present experimental model we were unable to provoke ARDS, characterized by a permeability increase and edema, suggesting that other factors besides complement-mediated PMN aggregation are needed for this syndrome.

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