Title: METHYLPREDNISOLONE IN THE PREVENTION AND TREATMENT OF LUNG INSUFFICIENCY IN A PORCINE MODEL OF EARLY ARDS

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Introduction. Lung insufficiency (adult respiratory distress syndrome; ARDS) is often the major feature of multiple organ failure induced by sepsis. Corticosteroids have been used in the treatment of ARDS induced by sepsis, but a consensus regarding the effects of steroids has not emerged from available experimental and clinical data. We have developed an experimental model of early ARDS in pigs using a continuous intravenous infusion of endotoxin. To elucidate the role of corticosteroids in the prevention and in the therapy of ARDS, the animals were either pretreated with steroids or given steroids after initiation of lung insufficiency by endotoxin.

Methods. Pigs under ketamine anesthesia were tracheotomized. Catheters were placed in the superior vena cava, right atrium, pulmonary artery, left atrium, carotid artery and aorta for cardiovascular measurements. After instrumentation the animals were allowed a stabilization period of 1 h before baseline measurements. Cardiac output ($\dot{Q}_t$) was measured by thermodilution. Extravascular lung water (EVLW) was determined by thermo-dye technique. Blood gases were analysed in arterial and mixed venous blood. Hemoglobin, hematocrit and leukocyte count were determined using a coulter counter. After baseline measurements E.coli endotoxin (E) (0111:B4, Difco; 10 μg/kg/h) was continuously infused intravenously (i.v.) over 6 h and measurements were performed hourly. The animals breathed air spontaneously during the observation period. Ten pigs served as controls (I). Twenty pigs were given E without further treatment (II). Eight pigs were treated with methylprednisolone (MP; 60 mg/kg i.v.) before starting E, followed by a continuous i.v. infusion of MP (10 mg/kg/h) (III). Eight pigs were treated with MP (60 mg/kg + 10 mg/kg/h) beginning 2 h after starting E (IV). Following the 6 h observation period the animals were sacrificed with KCl and lung biopsies were taken.

Results. Group II had a 2-3fold increase in mean pulmonary artery pressure (MPAP), while $\dot{Q}_t$ decreased 30-40%, resulting in a 3-4fold increase in pulmonary vascular resistance (PVR). EVLW increased 50%. Venous admixture ($\dot{Q}_{va}/\dot{Q}_t$) increased 4-5fold with a peak level 4 h after the start of E. Oxygen uptake ($\dot{V}O_2$) increased 30%, while oxygen (O_2)-delivery decreased 40-50%, resulting in a more than 2fold increase in oxygen utilization coefficient (O_2-Uc). Leukocyte count rapidly decreased by 80%. Eleven animals died of respiratory and circulatory failure during the observation period. Microscopy showed pulmonary microvascular stasis, accumulation of polymorphonuclear cells, microatelectases and edema. Pretreatment with MP counteracted the rise in MPAP, improved $\dot{Q}_t$ and maintained it at a more stable level during E-infusion, thus largely abolishing the rise in PVR. EVLW and $\dot{Q}_{va}/\dot{Q}_t$ remained at baseline levels. $\dot{V}O_2$ was unchanged and O_2-delivery was better maintained resulting in only a small increase in O_2-Uc. The drop in leukocyte count was counteracted. All animals survived. Lung biopsies showed a fairly normal picture.

Starting MP 2 h after E resulted in a rapid fall in the elevated MPAP. The drop in $\dot{Q}_t$ was prevented and the rise in PVR was abolished. A further increase in EVLW was prevented and EVLW returned toward baseline level. MP also abolished a further rise in $\dot{Q}_{va}/\dot{Q}_t$. $\dot{V}O_2$ returned to baseline level after MP and a progressive decrease in O_2-delivery was counteracted, resulting in the prevention of a further increase in O_2-Uc. MP did not restore leukocyte count to baseline. All animals except one survived the observation period. Microscopy showed similar pulmonary changes as in group II although to a very attenuated degree.

Discussion. A reproducable porcine model of early ARDS and cardiovascular insufficiency resulting in slightly more than 50% mortality has been developed using the strain and the dosage regimen of E.coli endotoxin described by us. This model is analogous to the sequence of events following sepsis in man and provides an opportunity to investigate various treatments. High doses of methylprednisolone given before endotoxin largely prevent the pulmonary and cardiovascular response. High doses of methylprednisolone begun 2 h after endotoxin abolish further derangements in lung and cardiovascular functions and tend to restore them to normal. The clinical implications are that, given early in the course of sepsis in man, high doses of methylprednisolone may help to prevent the devastating respiratory and circulatory complications of this disease.