Title: N-ACETYLCYSTEINE IN THE PREVENTION OF THE ADULT RESPIRATORY DISTRESS SYNDROME
An experimental study in pigs

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Introduction. ARDS is an acute pulmonary disorder characterized by the accumulation of granulocytes within the lower respiratory tract. The activated granulocyte is most likely important in the pathogenesis of lung injury by virtue of its broad armamentarium of granular enzymes, toxic oxygen radicals and arachidonic acid metabolites. The concept that granulocytes may induce pulmonary and cardiovascular failure characteristic of ARDS suggests that potential beneficial therapeutic strategies may be designed to suppress granulocyte recruitment to the lung, to modulate granulocyte activation or to depress the oxidative damage by use of toxic oxygen radical scavengers. Treatment with a drug which might interfere with granulocytes and their release of various substances should be of interest. Such a drug is N-acetylcysteine (NAC). The present study focused on the effects of NAC in a porcine endotoxin model similar to the human ARDS syndrome.

Material and methods. Sixteen pigs of the Swedish native breed, of both sexes, weighing 20-30 kg, were used. Only healthy pigs with a baseline PaO_2 > 10 kPa and a mean pulmonary arterial pressure (MPAP) < 2.7 kPa during spontaneous air-breathing after a 1.5 h equilibration period were included. Anesthesia was induced with ketamine hydrochloride 500 mg i.v. + 0.5 mg atropine i.v. and was maintained with a continuous i.v. infusion of ketamine at a dose of 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$. Tracheostomy was performed. During catheterization and thoracotomy the animals were mechanically ventilated with 70% N_2O in O_2. After completion of the preparation and throughout the equilibration and observation periods, the animals breathed air spontaneously. To counteract atelectases caused by the anesthesia and the supine position, the lungs were hyperinflated every h using a PEEP of 8 cm H_2O. One arterial and 4 central venous catheters were inserted via the right common carotid artery and the right external jugular vein. A 7F Swan Ganz catheter equipped with a thermistor was introduced via the left external jugular vein into a main branch of the pulmonary artery. A 5F catheter supplied with a thermistor near its tip was inserted through the right femoral artery into the abdominal aorta. Through a small thoracotomy, a catheter was introduced into the left atrium. A chest drainage tube was placed in the left pleural space and connected to a suction bottle with a water seal. The urinary bladder was cannulated through a small suprapubic incision. All animals received 4 $ml \cdot kg^{-1} \cdot h^{-1}$ of 2.5% balanced saline glucose solution, to which ketamine had been added, via a superior caval vein. Standard physiologic methods were used. Extravascular lung water (EVLW) was determined by the thermal-dye double-indicator dilution technique (9310 lung water computer; Edwards Labs, Santa Ana, CA).

Experimental protocol and results. After catheterization, an equilibration period of 1.5 h was allowed before baseline measurements. Three pigs, serving as controls, received NAC (see below) without endotoxin (E) for 6 h, and no notable physiological changes were found. Leukocyte count, however, increased significantly by 15%. Five pigs received a continuous infusion of E (O111:B4, Difco Labs, Detroit, MI) alone for 6 h and displayed a 90% decrease in leukocyte count and a 66% decrease in platelet count. A 4-fold increase in venous admixture (Qva/Qt), a nearly 2-3-fold increase in MPAP and a progressive decline in cardiac output (Qt) of 60% were documented. EVLW increased 66%, mean arterial pressure (MAP) decreased 46% and oxygen delivery decreased 52%, leading to metabolic acidosis. Three animals died during the observation period between 4 and 6 h after start of E. At this time point they had the highest MPAP, lowest Qt, highest pulmonary vascular resistance, lowest oxygen delivery and lowest pH noted in this study. The 8 pigs, pretreated with NAC 150 $mg \cdot kg^{-1}$ which was continued at 20 $mg \cdot kg^{-1} \cdot h^{-1}$, showed a significantly attenuated response to E. Thus, leukocyte and platelet counts decreased 70% and 48%, respectively. Physiologically Qva/Qt increased 2.5-3-fold, MPAP increased 1.3-2-fold and Qt decreased 32%. EVLW increased 27%, MAP decreased 27% and oxygen delivery decreased only 33%, which kept the pH in the normal range. All these animals survived the observation period of 6 h, a significant difference from the E alone group.

Discussion. We showed that NAC significantly attenuated all monitored hematologic and pathophysiologic changes in this endotoxin model of ARDS in pigs. We further demonstrated that the survival rate was significantly higher in NAC treated animals. This is consequent to a better maintained cardiac output and thereby better preservation of tissue perfusion and oxygenation. In addition to a reported free radical scavenger effect of NAC, our results support the assumption that NAC may counteract leukocyte and platelet aggregation in the lung and thereby contributing to the beneficial outcome. The fact that NAC does not completely abolish all pathophysiologic responses to endotoxemia could be due to dosage or distribution factors as well as to the complexity of the endotoxin response, which may involve additional multiple pathologic pathways. Encouraged by these positive results and by the safety of i.v. NAC, we are currently using NAC in a similar dosage regimen in a randomized double-blind clinical study.

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