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Activation of plasma protein systems and blood cells in neonatal respiratory distress syndrome

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Summary

Respiratory distress syndrome (RDS) or hyaline membrane disease (HMD), is the major cause of respiratory insufficiency among preterm newborn infants. Recently, Bambang Oetomo and Brouwers reported data from seven Dutch neonatal intensive care units (Bambang Oetomo and Brouwers, unpublished observation, 1990) that showed that 45 % of infants born below 33 weeks gestational age and 63% of those born below 30 weeks gestational age develop RDS. Prematurity reflected by surfactant deficiency and structural pulmonary immaturity is the main cause of neonatal RDS. Surfactant deficiency results in collapsed, liquid filled alveoli adjacent to aerated, dilated distal airways (respiratory and terminal bronchioli). Overdistension during each inspiration results in damage of the epithelial barrier of the distal airways. Within a few minutes of artificial ventilation or even spontaneous breathing disruption, necrosis and desquamation of the epithelial lining occurs. Disruption of the airway epithelium is accompanied with increased permeability of the alveolar-capillary membrane, which allows protein leakage predominantly into the lungs. Interstitial edema decreases lung compliance and impairs gas exchange. Intraalveolar edema contains plasma proteins, which contribute to formation of hyaline membranes and inactivate surfactant, which further impairs lung function. Furthermore, this process of early epithelial airway injury is accompanied with an exaggerated local inflammatory reaction, which is characterized by accumulation and activation of leukocytes and local release of inflammatory mediators. Both pulmonary edema formation and inflammation are considered to be important determinants of respiratory insufficiency in the acute phase of RDS and its late complication BPD. Several aspects of the neonatal RDS have been described in **Chapter 2** whereas pulmonary edema formation and inflammation have been discussed in detail in this chapter.

Aim of this thesis was to determine whether (1) simultaneous activation of plasma proteins and blood cells occurs in the early phase of neonatal RDS and (2) whether and by which mechanisms such systemic activation process could contribute to disease severity. Similarities between neonatal RDS and acute RDS (ARDS) regarding the development of proteinaceous edema and inflammation in the lungs underlied these questions. In ARDS it has been shown that simultaneous of clotting, fibrinolysis, kinin-kallikrein and complement is not a coincidental phenomenon but an important determinant of lung injury. Active compounds of these plasma protein systems are able to cause endothelial injury in the pulmonary vascular bed directly or indirectly by activation of circulating neutrophils and platelets. Previous to the studies presented in this thesis it was expected on the basis of several observations in preterm animals and infants that a systemic activation process as seen in ARDS plays a role in neonatal RDS. First, intravascular and intraalveolar fibrin depositions have been

observed in preterm infants with severe RDS indicating systemic clotting activation in these infants. Second, epithelial disruption has been demonstrated in ventilated surfactant-depleted lungs of PMN depleted adult rabbits, but additional damage and edema formation only occurred after reinfusion of activated PMN. Thus recruitment of circulating activated PMN in the lungs mediate further lung tissue injury. Third, it has been shown that increased permeability of the alveolar-capillary membrane in preterm lungs is primarily dependent on the degree of immaturity but will be aggravated by other factors. These are not only barotrauma or oxidative injury but might also be other factors such as systemic protein and cell activation since increased protein leak has been demonstrated in unventilated segments of preterm lamb lungs. Four, it has been suggested that several factors that predispose for RDS or complicate the course of RDS initiate or enhance the development of protein-rich edema and inflammation in the lungs by means of systemic protein and cell activation. Since activation of plasma proteins and cells were expected to be involved in the pathogenesis of RDS we have briefly reviewed composition and function of platelets and the clotting, fibrinolytic, kinin-kallikrein, and complement system in general in the first paragraph of **Chapter 3**. Furthermore, the role of monocytes/alveolar macrophages and polymorphonuclear leukocytes (PMN) in pulmonary host defense and injury were summarized in this paragraph. In the second paragraph of **Chapter 3**, we have described characteristics of clotting, fibrinolysis, kinin-kallikrein, leukocytes, and platelets in term and preterm newborn infants, whereas special attention have been paid to activation of these plasma proteins and cells in RDS.

The question whether simultaneous activation of plasma protein systems and blood cells occurs in the early phase of neonatal RDS has been addressed in **Chapter 4 and 5**. In a group of ten preterm infants requiring artificial ventilation from birth and with clinical and radiological signs of severe RDS, we found simultaneous activation of the clotting, fibrinolytic, and kinin-kallikrein system already within 12 to 24 hours of birth represented by increased T-AT III complex formation, increased t-PA plasma concentrations and increased plasma kallikrein activity respectively. Clotting activation was accompanied by a significant decrease of the platelet count. Clotting and fibrinolytic activity decreased in these infants within the first 2 to 3 days of life. F XIIa increased significantly in the IRDS infants from the third day of life. We observed kallikrein generation accompanied by decreased PKKI through-out the whole study period (**Chapter 4**). In a similar group of preterm infants, we observed a lower total leukocyte count, which was due to a lower PMN and monocyte count. In the IRDS infants the lower PMN count was accompanied by a lower plasma elastase- α_1 -PI concentration but a higher elastase- α_1 -PI/PMN ratio than in the reference infants. The latter suggests systemic activation of circulating PMN in the IRDS infants. Simultaneously, indications were obtained for systemic PAF release and

complement activation but not for systemic TNF- α release by circulating monocytes in these infants (**Chapter 5**).

In **Chapter 6, 7, 8 and 9**, we investigated the issue whether and by which mechanisms systemic activation of plasma protein systems and circulating blood cells could contribute to RDS severity. In **Chapter 6**, we studied the correlation between leakage of protein in lungs and activation of plasma proteins and blood cells in preterm ventilated rabbits of 28 and 29-d gestational age. We found signs of systemic activation of clotting, complement, and PMN in ventilated 28-d gestational age rabbits, as indicated, respectively, by increased plasma fibrin monomer concentrations, decreased plasma CH50 activity, and increased plasma beta-glucuronidase concentrations. We did not find signs of systemic activation in the ventilated 29-d gestational age group. Higher total protein concentrations in alveolar wash of the ventilated 28-d gestational age rabbits indicated protein leakage into the lungs and this protein leakage was more pronounced in the lungs of ventilated 28-d gestational age rabbits than in those of ventilated 29-d gestational age rabbits. We found that leakage of protein in lungs of preterm ventilated rabbits of 28-d gestational age is correlated with activation of clotting, complement and PMN in plasma. Therefore, we concluded that systemic activation of plasma proteins and blood cells likely contribute to lung injury by similar mechanisms as has been described in ARDS thus influencing RDS severity.

In **Chapter 7**, we have reported that activation of clotting, fibrinolysis, and kinin-kallikrein occurs in 17 preterm infants with severe RDS during the first 5 d of life, whereas such activation is almost absent in 16 preterm infants with mild/moderate RDS. In the severe RDS group, thrombin generation and t-PA release showed a slight but not significant decrease during the first 5 d of life. Kallikrein activity accompanied by decrease of PKKI was observed throughout the study period. Simultaneously, we observed a transient decrease of the neutrophil count and a steady decrease of the platelet count in the severe RDS group. In another study (**Chapter 8**) we observed a lower number of circulating total leukocytes, PMN, and platelets in a group of 18 preterm infants with severe RDS than in a similar group of 18 infants with mild/moderate RDS during the first 5 d of life. Simultaneously, circulating PMN of severe RDS infants released more elastase than those of mild/moderate RDS from d 2 to d 5. Circulating platelets of the severe RDS infants, especially those, who were not treated with indomethacin, released more TxB₂ than platelets of the mild/moderate infants from the third day of life.

In the studies presented in **Chapter 7 and 8**, we could not only demonstrate activation of plasma protein systems and blood cells in the severe RDS group but also a correlation between continuous measures of RDS severity (VEI, PaO₂/PAO₂ ratio) and plasma concentrations of products of these plasma protein systems. Thus activation of plasma protein systems and blood cells likely contribute to RDS severity according

to similar mechanisms as described in ARDS.

Despite increased release of t-PA indicating activation of fibrinolysis, fibrin depositions have been found in the pulmonary microcirculation and in the small airways of preterm infants with severe RDS. In **Chapter 9**, we have reported increased plasma concentrations of T-AT III complex and decreased platelet counts on the first and third day of life in 11 preterm infants with severe RDS indicating activation of clotting, which was almost absent in 15 preterm infants with mild/moderate RDS. Simultaneously, we have observed significantly higher t-PA plasma concentrations in the severe RDS group than in the mild/moderate RDS group, whereas plasma plasminogen and antiplasmin activity was similar in both groups. Therefore, adequate fibrinolytic activity seems to be questionable in these infants. Clotting activity in face of insufficient fibrinolysis may contribute to RDS severity by facilitating intravascular and intra-alveolar fibrin deposition, which has been described in preterm infants with severe RDS.

In all studies presented in this thesis, preterm infants with severe RDS showed low Apgar scores and low arterial umbilical PH values at birth indicating perinatal asphyxia. Hypoxemia, acidosis and tissue hypoperfusion due to perinatal asphyxia promote release of tissue factor, t-PA, activated complement components, bradykinin and PAF. In **Chapter 7 and 8** lower 5-minute Apgar scores and arterial umbilical PH values were positively correlated with more activation of clotting, fibrinolysis, kinin-kallikrein, PMN and platelets. We, therefore, suggested that perinatal asphyxia might initiate or contribute to systemic activation of plasma proteins and blood cells shortly after birth thus influencing RDS severity. Furthermore, the infants with severe RDS required higher oxygen concentrations in the inspired air and higher peak inspiratory pressures for adequate oxygenation and ventilation than the infants with mild/moderate RDS (**Chapter 7 and 8**). Higher FiO_2 and PIP values were correlated with more activation of clotting, fibrinolysis, kinin-kallikrein, PMN and platelets, and lower PMN and platelet counts throughout the study period. Both hyperoxia and positive pressure ventilation cause lung tissue destruction, which can be accompanied by factor XII and kallikrein activation. Factor XII activity contributes to clotting and fibrinolytic activity with subsequent PMN and platelet activation. High FiO_2 and PIP values may promote plasma protein and blood cell activation, but may, in turn, indicate increased ventilatory requirements representing increase RDS severity due to this activation process.

In this thesis, we have shown that simultaneous activation of plasma protein systems and blood cells occurs in preterm infants with RDS. We have demonstrated that systemic activation of plasma protein systems and blood cells is correlated with RDS severity. This activation process likely contribute to respiratory failure by increasing alveolar-capillary permeability and subsequent protein leakage into the

lungs. Intravascular and intra-alveolar fibrin formation, which is a characteristic feature in severe RDS that also contribute to respiratory insufficiency, might be promoted by insufficient fibrinolysis in face of unopposed clotting activation. Currently we do not know whether this process is associated with the inflammatory process in the lung. Time-dependent studies in preterm infants with RDS on the activation of plasma protein systems and blood cells and its relation to this local inflammatory process will further elucidate the role of this activation process in the pathogenesis of RDS. We suggest that factors such as perinatal asphyxia, barotrauma and hyperoxia promote edema formation and local inflammation in the lungs directly and indirectly by systemic activation of plasma proteins and cells. Since activation of plasma protein systems and blood cells likely contribute to respiratory failure in RDS these observations provide a biological rationale for exploring prophylactic and therapeutic modalities specifically focussed on this activation process (**Chapter 10**).