

## 10. Summary

### 10.1. Background

#### Activation of Matrix Metalloproteinases in Acute Lung Injury after Cardiopulmonary Bypass in pigs

Surgery involving the use of cardiopulmonary bypass (CPB) can be associated with several serious postoperative complications, including pulmonary dysfunction, which may result in a postperfusion syndrome.

Matrix metalloproteases (MMPs) seem to be essential component in the development of this lung injury. They belong to the family of proteolytic enzymes and they are able to degrade specific protein components of extracellular matrix. Other members of this family of enzymes include collagenases, stromelylinases and gelatinases. They are produced and excreted by a variety of different cells. Polymorph neutrophils (PMN) produce MMP-9 and MMP-8, which are stored in their intracytoplasmic granula. During inflammatory reactions, which may be induced by a variety of different mediators, PMN degranulation occurs, releasing the stored MMPs. MMP-2 is produced mainly by fibroblasts. MMPs are set free as zymogens and are activated by different mediators.

This study was designed to investigate the expression of MMP-2 and MMP-9 in the bronchoalveolar lavage fluid (BALF) and to compare it with a number of other variables used to characterise the inflammatory cascade and pulmonary function, and which are known to change as a result of the pulmonary dysfunction associated with CPB.

### 10.2. Method

The appropriate governmental authority approved the experimental protocols used in the present study. Eighteen intubated minipigs were subjected to a cardiopulmonary bypass for 60 minutes. Bronchoalveolar fluid (BALF) samples were collected before CPB, 5 and 180 minutes post CPB. Subsequently, the concentration of MMP-2, MMP-9, interleukin activity (IL-1 $\beta$ , IL-8, TNF- $\alpha$ ), PNM and proteins were measured

in the BALF samples. Furthermore the lung compliance,  $AaDO_2$ , and  $Q_s/Q_T$  were calculated as variables indicative of the efficiency of pulmonary gas exchange. Finally, biopsies of the lung were obtained and the water content of these tissue sample was estimated. MMP-2 and MMP-9 activities in each sample were determined by zymographic analysis and evaluated by computer. The data were evaluated using a computer statistical analysis program SPSS Version 8, Chicago Illinois, USA.

### 10.3. Results

The MMP-activity of MMP-2 and MMP-9 increased significantly 5 and 180 minutes post CPB compared to the baseline values obtained prior to instigation of CPB. Similar changes developed with the interleukines, the proteins in the BALF,  $AaDO_2$ , lung  $Q_s/Q_T$ , compliance, the water in the lung tissue and the PMN. However the changes in BALF metalloproteinase enzyme concentrations failed to show a correlation with any of the other variables measured. All the remaining values were evaluated for correlation with the parameters of gas exchange  $AaDO_2$  and  $Q_s/Q_T$  180 minutes post CPB.

### 10.4. Conclusion

MMP-2 and MMP-9 release occurs as part of the inflammatory reaction induced by CPB, as does the migration of PMNs in the lung and the release of interleukins. We investigated the supposition that the release of metalloproteinase enzymes induces an increase in permeability of the pulmonary capillaries which is responsible for the pulmonary dysfunction associated with CPB. However, we failed to find a correlation with changes in the concentration of other recognised mediators of inflammation or variables used to characterise pulmonary gas exchange. There may have been an influence from Tissue inhibitors of matrix metalloproteases, which cannot be confirmed in this study, nevertheless it would be a possible explanation for the absence of correlation between the metalloproteinase enzyme concentrations and the other variables measured. More knowledge about the assignment and activation of MMPs at the time of acute lung injury is needed. It will be of considerable clinical impor-

tance to identify the exact function of these enzymes with special regard to both their mechanism of action and their roll in tissue injury in the lung as a result of CPB.