Biomarkers of Lung Injury in Cardiothoracic Surgery

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CHAPTER 7

Summary and conclusion

Methods for quantifying the degree of lung injury are mostly limited to measuring physiological changes (alveolar-arterial oxygen pressure difference, intrapulmonary shunt, degree of pulmonary edema, pulmonary compliance and pulmonary vascular resistance) or to measure generic biomarkers of inflammation. In this aspect, lung specific biomarkers are an appealing alternative for quantifying the degree of lung injury. We investigated if and which lung injury biomarkers were useful for identifying and quantifying post-operative lung injury in the setting of cardiothoracic surgery.

Though many biomarkers for lung injury are known, they are not often incorporated in clinical studies on new procedures or new medical equipment. Nevertheless, the potential clinical applications are significant for (currently available) lung injury biomarkers; they enable early detection of patients with subtle injury when these biomarkers are adequately sensitive and specific.

This leads to the the central question of this thesis, which was to investigate if and which lung injury biomarkers were useful for identifying and quantifying post-operative lung injury in the setting of cardiothoracic surgery. To answer this question, **Chapter 2** starts with an overview of literature, which showed that degranulation products of neutrophils are often used as a biomarker. The choice for their use follows also from the fact that the degranulation products have detrimental effects on the pulmonary tissue themselves. However, these substances are not lung specific. On the other hand, lung epithelium specific proteins, such as surfactant protein D (SP-D), Clara cell 16 kD (CC16) and soluble receptor for advanced glycation end products (sRAGE), offer more specificity and slowly find their way into more clinical studies.

In **Chapter 3** we explored the utility of several lung epithelium specific proteins as lung injury markers during coronary artery bypass surgery, and secondly, if the omission of cardiopulmonary bypass (off-pump) during surgery resulted in lower plasma concentrations of these lung epithelium specific proteins. We found that the lung epithelium specific proteins SP-D and CC16 were sensitive markers of lung injury and concluded that they can be useful in the setting of cardiothoracic surgery. Furthermore, we showed that after coronary artery bypass grafting, with or without the use of cardiopulmonary bypass, higher SP-D and CC16 plasma concentrations were associated with more lung injury as assessed by the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2 ratio) and the alveolar-arterial oxygen gradient ($Aa\text{-}O_2$ gradient) early on the intensive care unit.

There are several possible explanations for the increase of lung epithelium specific proteins. First, injury to the alveolar capillary membrane leads to increased permeability of the membrane. Second, there is increased production or secretion of lung epithelium specific proteins. And third, there may be a decrease in renal clearance leading to accumulation of these proteins in the circulation [8]. The increase in elastase plasma

concentration, and its association with a SP-D, supports the notion of increased permeability of the alveolar capillary membrane after cardiopulmonary bypass. This is thought to be the result of an inflammatory reaction induced by cardiopulmonary bypass, as described previously. This increase in permeability of the alveolar capillary membrane was found to be temporary, however, since plasma concentrations of lung epithelium specific proteins returned to baseline within one day.

Our second finding was that during and after coronary artery bypass grafting, the rise in lung epithelium specific proteins was less in the group without cardiopulmonary bypass as opposed to the group with cardiopulmonary bypass. It is known that omitting cardiopulmonary bypass during coronary artery bypass grafting can reduce the inflammatory reaction [9, 10]. Therefore, it may be expected that omitting cardiopulmonary bypass can also reduce the occurrence of diffuse tissue injury and thereby reduced leakage of lung epithelium specific proteins form the alveolar compartment to the bloodstream.

In **Chapter 4** we investigated the effect of cardiopulmonary bypass with pulsatile flow on lung function in elderly patients undergoing aortic valve replacement surgery. We found that there was no difference in the clinical outcome parameters. Only the pulmonary vascular resistance index showed a small beneficial effect when pulsatile flow was applied, i.e. in that it not exceeded baseline values whereas when continuous flow was used the pulmonary vascular resistance index increased by almost 50%.

The topic of pulsatile flow is one with much controversy. Pulsatile flow is thought to be beneficial in preventing lung injury by means of better perfusion of the bronchial artery. The advantages of bronchial artery perfusion have been demonstrated in a porcine model in which the bronchial artery was actively perfused by connecting it to the cardiopulmonary bypass circuit [11]. By active perfusion of the bronchial artery, detrimental metabolic and ultrastructural changes of lung tissue where significantly reduced. Furthermore, a reduction of inflammatory substances in bronchoalveolar lavage fluid was shown. In our study, the extra energy generated with pulsatile flow was also expected to result in better perfusion of the capillaries, supplying more oxygenated blood, antioxidants and/or nutrients to the ischemic lung. However, we found that pulsatile flow did not result in appreciable clinical benefits, except for lower pulmonary vascular resistance. Also at a subclinical level of lung injury, as assessed by lung injury biomarkers, we observed no difference between continuous or pulsatile perfusion.

In **Chapter 5** we investigated the effect of intraoperative cell salvage on lung injury after cardiac surgery. We found that intraoperative cell salvage decreased injury to the alveolar-capillary membrane as assessed by the lung injury markers CC16 and sRAGE and that it resulted in shorter postoperative mechanical ventilation times. We also found a reduction of systemic inflammatory mediators when a cell salvage device was used.

As a basic blood conservation strategy, cardiotomy suction blood was collected and

retransfused to the patient. This retransfused blood has been shown to be proinflammatory [12], detrimental to haemostasis [13] and can increase pulmonary vascular permeability. By applying mechanical cell salvage, the 'activated' plasma fraction of the shed blood is removed. This plasma fraction contains cytokines, leukocyte activation products, lipids and other pro-inflammatory mediators. We therefore used the cell salvage device to also process cardiotomy suction blood during cardiopulmonary bypass in order to minimize organ injury [14]. The benefits of this approach were apparent by the significant reduction in cytokines and systemic leukocyte degranulation enzymes. Furthermore, we found a reduction in pulmonary dysfunction as indicated by lower CC16 and sRAGE plasma concentrations and shorter mechanical ventilation times in the group where a cell salvage device was employed. The Aa-O_2 gradient, however, did not show any difference between groups. As the formation of atelectasis is also an important factor for increasing the Aa-O_2 gradient, it could be considered that this clinical marker is not always sensitive enough for assessing lung injury.

Not only cardiopulmonary bypass, but also genetic factors may contribute to pulmonary injury and lung failure after transplantation. **Chapter 6** was different from the other chapters, as it did not use the plasma concentration of a biomarker to identify and/or quantify pulmonary injury. Instead we investigated whether the presence of a certain genotype of three frequently occurring SP-D single nucleotide polymorphisms, which could possibly influence the innate immune defense system of an individual, related to primary graft dysfunction (PGD) and patient survival after lung transplantation. We found that one of the SP-D polymorphisms, the Ala/Ala genotype of the Ala160Thr polymorphism, was associated with primary graft dysfunction and survival: patients carrying this SP-D genotype were twice as likely to develop primary graft dysfunction after transplantation and had a 59% increased risk to die during follow-up as compared to the dominant Ala/Thr genotype.

An explanation for the effect of the Ala/Ala genotype of the Ala160Thr polymorphism in the recipient on PGD and mortality after lung transplantation is not immediately evident. We speculate that recipient SP-D, produced extrapulmonary, still exerts an important effect on innate immune defense after lung transplantation. If we search for a mechanism by which the Ala/Ala genotype exerts its influence, one could reason that the function of the protein is altered; hereby compromising the innate immune system of the recipient. The Ala160Thr polymorphism lies on the collagen like domain of SP-D and since the polymorphism is changing one of the amino acids in the protein, it is possible that this leads to altered plasma concentration, protein oligomerization or protein function. However, since we did not formally measure SP-D plasma concentrations or establish protein oligomerization, limited conclusions can be drawn on the mechanistic link between the Ala160Thr polymorphism, PGD and/or patient survival. This deserves

further research in a newly planned prospective study.

Conclusion

In this dissertation we explored the use of lung injury biomarkers for identifying and quantifying lung injury after cardiothoracic surgery. To answer this question we have used various cardiothoracic studies that applied different interventions. These interventions were expected to reduce the degree of lung injury (among other things), which in turn would be measurable by different plasma concentrations of lung injury biomarkers. We have shown that coronary artery bypass surgery without the use of cardiopulmonary bypass resulted in less lung injury and that this correlated with lower plasma concentrations of lung injury biomarkers. The same was true for a study where intraoperative cell salvage was the intervention during open heart surgery. The use of pulsatile flow did not result in a reduction of lung injury; likewise there was no difference in plasma concentrations of lung injury biomarkers.

To conclude, lung injury biomarkers can serve as a surrogate endpoint for evaluating new procedures and/or medical equipment in cardiothoracic surgery research. For this purpose a panel of biomarkers, in conjunction with physiological markers, is most informative, especially when biomarkers for alveolar type I and II cell injury are incorporated.

References

[1] Bots ML, Buddeke J, van Dis I, Vaartjes I, Vissseren FLJ. Hart- en vaatziekten in Nederland 2015. Den Haag: Nederlandse Hartstichting; 2015.

[2] Goldman S, Zadina K, Moritz T, Ovitt T, Sethi G, Copeland JG, et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. Journal of the American College of Cardiology. 2004;44(11):2149–56.

[3] Bots ML, van Dis I, Koopman C, Vaartjes I, Vissseren FLJ. Hart- en vaatziekten in Nederland 2013. Den Haag: Nederlandse Hartstichting; 2013.

[4] Ng CSH, Wan S, Yim APC, Arifi AA. Pulmonary Dysfunction After Cardiac Surgery. Chest. 2002;121(4):1269–1277.

[5] Edmunds LH. Inflammatory response to cardiopulmonary bypass. The Annals of Thoracic Surgery. 1998;66(5 Suppl):S12–6.

[6] Wan S, LeClerc JL, Vincent JL. Inflammatory Response to Cardiopulmonary Bypass: Mechanisms Involved and Possible Therapeutic Strategies. Chest. 1997;112(3):676–692.

[7] Miller BE, Levy JH. The inflammatory response to cardiopulmonary bypass. Journal of Cardiothoracic and Vascular Anesthesia. 1997;11(3):355–66.

[8] Lakind JS, Holgate ST, Ownby DR, Mansur AH, Helms PJ, Pyatt D, et al. A critical review of the use of Clara cell secretory protein (CC16) as a biomarker of acute or chronic pulmonary effects. Biomarkers. 2007;12(5):445–467.

[9] Nesher N, Frolkis I, Vardi M, Sheinberg N, Bakir I, Caselman F, et al. Higher Levels of Serum Cytokines and Myocardial Tissue Markers During On-Pump Versus Off-Pump Coronary Artery Bypass Surgery. Journal of Cardiac Surgery. 2006;21(4):395–402.

[10] Greilich PE, Brouse CF, Rinder HM, Jessen ME, Rinder CS, Eberhart RC, et al. Monocyte Activation in On-Pump Versus Off-Pump Coronary Artery Bypass Surgery. Journal of Cardiothoracic and Vascular Anesthesia. 2008;22(3):361–368.

[11] Schlensak C, Doenst T, Preußer S, Wunderlich M, Kleinschmidt M, Beyersdorf F. Cardiopulmonary bypass reduction of bronchial blood flow: A potential mechanism for lung injury in a neonatal pig model. The Journal of Thoracic and Cardiovascular Surgery. 2002;123(6):1199–1205.

[12] Westerberg M, Bengtsson A, Jeppsson A. Coronary surgery without cardiotomy suction and autotransfusion reduces the postoperative systemic inflammatory response. The Annals of Thoracic Surgery. 2004;78(1):54–9.

[13] de Haan J, Boonstra PW, Monnink SH, Ebels T, van Oeveren W. Retransfusion of suctioned blood during cardiopulmonary bypass impairs hemostasis. The Annals of Thoracic Surgery. 1995;59(4):901–7.

[14] Djaiani G, Fedorko L, Borger MA, Green R, Carroll J, Marcon M, et al. Continuous-flow cell saver reduces cognitive decline in elderly patients after coronary bypass surgery. Circulation. 2007;116(17):1888–95.