Biomarkers of Lung Injury in Cardiothoracic Surgery

Engels, Gerwin

CHAPTER 1

Introduction & rationale

In the Netherlands, as in most developed countries, cardiovascular diseases are one of the main causes for high morbidity and mortality [1]. Certain cardiovascular diseases can result in the formation of atherosclerotic obstructions, which can reduce or completely inhibit blood flow to the heart. Fortunately, blood flow can be effectively restored by means of angioplasty or by bypassing the obstructed artery during open heart surgery. Annually, an estimated 800,000 bypass operations are performed worldwide [2]. And for the Netherlands, the number of bypass operations is about 11,000 a year [3].

These open heart surgeries, with or without the use of cardiopulmonary bypass, are still associated with some degree of pulmonary injury [4], which is attributed to the unique features of cardiothoracic surgery, in particular the use of cardiopulmonary bypass. The cardiopulmonary bypass, or heart–lung machine, is a device that takes over the function of the heart and lungs by oxygenating blood and pumping it through the body, maintaining circulation until the heart and lungs are able to return to normal functioning. The heart–lung machine allows cardiothoracic surgery to be performed on an arrested heart without the patient suffering from hypoxia.

Cardiopulmonary bypass with its characteristic properties, such as operative trauma, blood contact with artificial surfaces, low perfusion pressures with a non-pulsatile flow, haemodilution and allogeneic blood transfusion results in a systemic inflammatory response [5]. This inflammatory response together with the microemboli (lipoprotein, particulate or gaseous) generated during cardiopulmonary bypass can result in organ injury affecting the heart, brain, kidneys, intestine and lungs. The inflammatory reaction includes activation of the coagulation, kallikrein and fibrinolytic cascades, the complement system and release of cytokines and adhesion receptors. Subsequently, neutrophil-endothelial cell interactions liberate macrophage proteases and neutrophilic enzymes and increase vascular permeability and produce diffuse tissue injury [6, 7]. When lung injury is considered, the methods for quantifying the degree of 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 generic biomarkers of inflammation. In this aspect, lung specific biomarkers are an appealing alternative to quantify the degree of lung injury.

Another field in cardiothoracic surgery where lung injury is prominent is lung transplantation. A lot of research is performed, with help of biomarkers, to unravel the damaging cascades in ischemia-reperfusion injury. This form of injury is complemented with the obligatory immunological response associated with transplantation. Genetic factors, from the donor as well as the recipient, may play a role in the severity of lung injury and lung failure after transplantation. With this in mind, genetic research on biomarkers involved in the recipients innate immune defense system, might give insight

into how donor lungs function and survive after transplantation.

Ideally, biomarker research leads to a specific marker that reflects a disease of an organ or injury to an organ perfectly; additionally, any response to a therapeutic intervention should also be reflected by the biomarker in question. Although a lot of challenges have to be overcome to identify such a biomarker, their use is of increasing importance to medical research and clinical practice. The popularity of biomarker research becomes evident when the search phrase 'biomarker' is evaluated in PubMed, as more than 55,000 new academic publications were indexed in 2015 alone. However, their use in cardiothoracic surgery for identifying and quantifying post-operative lung injury has found limited use. This leads to the **rationale** 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.

In **Chapter 2**, the currently available lung injury biomarkers are introduced and the requirements that a biomarker ideally should meet are described. The proteins that have served as a lung injury biomarker thus far are discussed based on their origin and functionality, furthermore their associations with other lung diseases is discussed. Finally, the use of lung epithelium specific proteins as biomarkers is emphasized.

In **Chapter 3**, a clinical study is presented that evaluated the use of lung epithelium specific proteins for identifying and quantifying postoperative lung injury. The intervention of the study was elective coronary bypass surgery with or without the use of cardiopulmonary bypass, and it was expected that the use of cardiopulmonary bypass during surgery would result in more lung injury or lung dysfunction [8], and consequently higher plasma concentrations of lung epithelium specific proteins. Having identified the utility of lung epithelium specific proteins as biomarkers, **Chapter 4** continues with the model of coronary artery bypass surgery, only this time the intervention was the use of pulsatile flow during cardiopulmonary bypass, instead of continuous flow. The hypothesis was that pulsatile flow should yield better perfusion of the (peripheral) capillaries and the bronchial arteries by means of enhanced microvascular flow, and that this, in turn, should reduce any postoperative pulmonary injury. Here, the in chapter 3 identified lung biomarkers, along with clinical indicators, were used to identify and quantify pulmonary injury.

To continue the application of lung injury biomarkers, **Chapter 5** presents a clinical study were the effect of cell salvage during open heart surgery on postoperative lung injury was investigated. Blood transfusion is still common in patients undergoing open heart surgery, and is well known to increase morbidity and mortality [9]. Furthermore, blood transfusion may also cause lung injury and/or prolong mechanical ventilation and thus the length of stay on the intensive care unit [10]. To reduce the need for allogeneic blood transfusion, cardiotomy suction blood, collected from surgical field

and the pericardial cavity, together with the remaining volume of the heart-lung machine can be retransfused to the patient. However, before doing so, the collected blood is passed through a cell salvage device. In this device the collected blood is washed with a solution and thereafter centrifuged to obtain a red blood cell concentrate ready for retransfusion. In this process, plasma, platelets, leukocytes, free haemoglobin, and inflammatory substances such as cytokines and neutrophilic proteases are removed [11]. Besides reducing the exposure to allogeneic blood, the use of cell salvage devices was expected to have additional benefits, such as a decrease in postoperative lung injury.

Chapter 6 stands out from the other chapters as it does not use the plasma concentration of a biomarker to identify and/or quantify pulmonary injury. Instead, the genetic coding of surfactant protein D (biomarker), known to be important in the innate immune defense system, and its association with primary graft dysfunction and mortality following lung transplantation was investigated. There are three frequently occurring single nucleotide polymorphisms within the surfactant protein D gene that can result in an alteration of the amino acid sequence of the protein, and these polymorphisms are able to influence structure, function or plasma concentration of the protein [12, 13, 14]. Given the role of surfactant protein D in the innate immune system we hypothesized that the various genotypes, associated with their unique structure, function or plasma concentration of surfactant protein D, could result in a different outcome after lung transplantation.

Finally, **Chapter 7** provides a summary and discussion.

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):1269–77.

[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] e Silva AMRP, Saad R, Stirbulov R, Rivetti LA. Off-pump versus on-pump coronary artery revascularization: effects on pulmonary function. Interactive CardioVascular and Thoracic Surgery. 2010;11(1):42–5.

[9] Murphy GJ, Reeves BC, Rogers CA, Rizvi SIA, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation. 2007;116(22):2544–52.

[10] Koch C, Li L, Figueroa P, Mihaljevic T, Svensson L, Blackstone EH. Transfusion and Pulmonary Morbidity After Cardiac Surgery. The Annals of Thoracic Surgery. 2009;88(5):1410–1418.

[11] Damgaard S, Nielsen CH, Andersen LW, Bendtzen K, Tvede M, Steinbrüchel DA. Cell saver for on-pump coronary operations reduces systemic inflammatory markers: a randomized trial. The Annals of Thoracic Surgery. 2010;89(5):1511–7.

[12] DiAngelo S, Lin Z, Wang G, Phillips S, Ramet M, Luo J, et al. Novel, non-radioactive, simple and multiplex PCR-cRFLP methods for genotyping human SP-A and SP-D marker alleles. Disease Markers. 1999;15(4):269–81.

[13] Lahti M, Löfgren J, Marttila R, Renko M, Klaavuniemi T, Haataja R, et al. Surfactant Protein D Gene Polymorphism Associated with Severe Respiratory Syncytial Virus Infection. Pediatric Research. 2002;51(6):696–699.

[14] Crouch E, Rust K, Veile R, Donis-Keller H, Grosso L. Genomic organization of human surfactant protein D (SP-D). SP-D is encoded on chromosome 10q22.2-23.1. Journal of Biological Chemistry. 1993;268(4):2976–83.