Primary complications after cardiac surgery: towards better understanding, prediction, and prevention

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General introduction
and outline of the thesis

PREFACE

Cardiac surgery and Inflammation

A frequent complication of cardiac surgery is the development of a systemic inflammatory response syndrome (SIRS). Several reports describe an incidence between 5 and 50% (1-3). Although the exact pathophysiology is not yet unraveled, important steps have been made that have deepened the knowledge and understanding of SIRS after cardiac surgery. Multiple factors lead to activation of the inflammatory response, of which the most important are the surgical trauma itself (4), direct contact of blood with the synthetic surfaces of the cardio-pulmonary bypass (CPB), ischemia-reperfusion injury, and blood transfusion (5). Surgical injury induced release of mitochondrial damage-associated molecular patterns (DAMPs) (6-8), complement activation through classical-, lectin- (9), and alternative pathways (7, 10-12), the subsequent or concurrent release of proinflammatory cytokines (Tumor Necrosis Factor(TNF)-α, Interleukin (IL)-1beta, IL-2, IL-6, IL-8) (7, 12), and anti-inflammatory cytokines (IL-10, IL-1RA, TNFsr1 and 2, and Transforming Growth Factor (TGF)-beta) (7), and the activation of platelets and neutrophils (resulting in rolling, tethering, endothelial -induced adhesion and -transmigration) (7, 13), result in endothelial injury. As a consequence of this inflammatory response, patients can develop multiple organ dysfunction with a complicated postoperative course and an unfavorable overall outcome (1-3).

ARDS

One of the most sensitive organs to the effects of SIRS are the lungs. As a result of the dysregulated systemic inflammation, a local inflammatory response in the lung itself starts and leads to development of acute lung injury and even of an adult respiratory distress syndrome (ARDS) (14). ARDS was first described in 1967 by Asbaugh et al. (15).

In order to overcome issues regarding the reliability and validity of the AECC ARDS definition (16), the Berlin ARDS definition task force came to a new definition of ARDS in 2012 (17), that is currently still in use and summarized in table 1. For the studies, i.e. the study populations, described in this thesis , the 2024 adjustments of the ARDS definition, pertaining to non-intubated patients and resource-limited countries, are of limited relevance (18).

There are over sixty defined causes of ARDS, but in all of them systemic inflammation plays a causal role in the development of local alveolar injury, typical for ARDS. DAMPs and neutrophils are attributed a key role in this process (19). DAMPs are recognized by Pattern Recognition Receptors (PRR), such as Toll like receptors (TLR), C-type Lectine receptors (CLR), RIG-1-like receptors (RLR) and NOD like receptors (NLR) These PRRs induce activation of a cascade of pro-inflammatory cytokines such as tumor necrosis

Table 1. Berlin ARDS definition

1.	Onset within 7 days after a known clinical insult or new or worsening respiratory symptoms		
2.	Bilateral opacities "that are consistent with pulmonary edema" on Chest X-ray or CT-scan, that are - not fully explained by effusion, atelectasis or masses - not exclusively due to a cardiac cause or fluid overload		
3.	Presence of an Identified risk factor for ARDS *If absent, an objective assessment (e.g. echocardiography) is necessary to exclude hydrostatic edema*		
4	Categorization of ARDS severity	MILD	PaO_2/FiO_2 = 201-300
		MODERATE	PaO_2/FiO_2 = 101-200
		SEVERE	$PaO_2/FiO_2 \leq 100$
5.	Minimum PEEP setting or CPAP: 5 cm H2O *PaO2/FiO2 setting assessed on mechanical ventilation; CPAP criterion used for the diagnosis of mild ARDS*		

CPAP continuous positive airway pressure; PEEP positive end expiratory pressure; $Pa0_2/FiO_2$: ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen

factor, and interleukins (IL) IL-1beta, IL-6, and IL-8 (20-23). Both locally activated and from out of the blood marginalized neutrophils (24) produce toxic substances through degranulation of proteases (19), and form neutrophil extracellular traps (NETs)(19). One of the four serine proteases present in neutrophil granules is Human Neutrophil Elastase (HNE) (25). HNE plays a pivotal role in microbial clearance. When extracellular HNE release is dysregulated, It can remodel the airways and lung parenchyma by (A) goblet cell metaplasia and increased mucine (Muc) production (MUC5AC, MUC4 and MUC1), and (B) promoting a sustained inflammatory response through TLRs and progressive damage of the alveolar-capillary membrane (20-23), leading to further capillary leakage and oncotic driven accumulation of protein-rich exudate in the alveoli (20, 26-28). Increase in interstitial fluid, combined with damage to the alveolar epithelium, eventually causes the air spaces to fill with proteinaceous edema and even bloody fluid and debris from degenerating cells. Loss of ability to upregulate alveolar fluid clearance and loss of functional surfactant (20, 29) further deteriorate pulmonary function and lead to impaired gas-exchange, decrease of compliance and pulmonary hypertension.

Although in one of the latest systematic reviews of randomized trials on this subject steroids seems to provide an effective approach to reduce the risk of death in ARDS patients (30), other pharmaceutical interventions for adults with ARDS have not been proven useful up to now, (31) and treatment of ARDS mostly comes down to supportive

care (32). Over the years the options for supportive care have been expanded with much more sophisticated mechanical ventilation strategies (32-35), neuromuscular blockade, (36) prone-positioning, (37) and the use of veno-venous Extra Corporeal Membrane Oxygenator (ECMO) in adult intensive care setting (38), and this has improved the outcome of ARDS patients (32).

ARDS and cardiac surgery

Cardiac surgery with the use of CPB is one of the well-known causes of development of acute lung injury and even of ARDS. The reported incidence varies from 1 to 8% (27, 39-41). The diagnosis ARDS in these patients is particularly difficult, since a certain extent of heart failure and hence cardiogenic pulmonary edema might also play a role in the clinical and radiologic picture (27). The cause of ARDS after cardiac surgery lies in the many successive and necessary actions and events, associated with open heart surgery, such as CPB, transfusion of blood products, ischemia reperfusion injury, mechanical ventilation, large volume shifts, and the direct surgical insult (27, 42).

In addition to these inevitable surgery related factors, concurrent presence of respiratory viruses, such as influenza, SARS-CoV-2, cytomegalovirus (CMV), herpes simplex virus (HSV), and respiratory syncytial virus (RSV) might also contribute to ARDS, since they are well known for their ability to cause disruption of the alveolar architecture by causing excessive inflammation (43). Indeed, development of COVID-19 in the postoperative phase of cardiac surgery patients is associated with adverse outcomes (44-46), and cardiac surgery in the influenza season is followed by an increased risk of developing ARDS, and prolonged dependency of mechanical ventilation, ICU- and hospital stay (47, 48).

Development of ARDS after cardiac surgery is associated with high mortality (15-80 %) (40, 42), and significant long term physical and psychological sequelae (42, 49). Considering the fact that worldwide >800,000 patients per year undergo coronary artery bypass grafting (CABG) surgery and approximately 150,000 patients undergo valve surgery (50, 51), ARDS undoubtedly represents a significant unmet medical need with profound economic implications (42).

RATIONALE OF THIS THESIS

To improve the outcome of the many cardiac surgery patients that trust their lives in the hands of cardiothoracic surgeons, anesthesiologists and intensivists, it is important to better understand, better predict, and, if possible, better prevent and treat the most severe pulmonary sequelae of cardiac surgery.

Increasing pathophysiological understanding might in multiple ways lead to improvement of pre- and peri-operative care by:

- Strengthening of current prediction models (EuroSCORE) (52): Expanding current risk models with inflammation markers that are more representative for the actual pulmonary state (53), will lead to better recognition of patients at risk for an unfavorable outcome.
- Guiding pre-operative therapeutic considerations: Recognition of patients at risk can guide therapeutic choices: one could reduce the complexity of the operation by limiting interventions, choosing a different type of valve, or even opting for a catheter-mediated procedure.
- Avoidance of preventable contributing factors: If viruses would appear to play a role in development of ARDS, preoperative screening or even vaccination could be a rational intervention.
- Adjusting perioperative management: Early identification of developing ARDS, could drive specific therapeutic decisions before, during and after surgery (e.g. Hb trigger and transfusion of blood products).

Understanding the risks for and the mechanisms leading to ARDS after cardiac surgery is therefore very important, and could be a first step towards personalized medicine (54), with interventions that offer best results for the specific patient.

THE OUTLINE OF THE THESIS

The aims of this thesis can be summarized in 3 sub-themes:

1. To increase the pathophysiological understanding of the development of lung injury, i.e. ARDS, after cardiac surgery.
2. To investigate whether biomarkers can predict lung injury after cardiac surgery.
3. To investigate whether prophylactic corticosteroids can improve (respiratory) outcomes in cardiac surgery and other ICU patients.

This thesis consists of 3 different parts, each part containing studies related to the different objectives, as formulated above.

Part one – Pathophysiology

With the studies in this part we aimed to gather insight in the pathophysiology of acute lung reaction after cardiac surgery. Perioperative alveolar inflammatory markers were assessed in relation to P/F ratio, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, and a measure of lung injury. Furthermore, the role of an (asymptomatic) viral infection in relation to development of unfavorable outcome in cardiac surgery patients was investigated.

Broncho-alveolar biomarker profile

In the first study perioperative miniBAL samples were assessed for multiple markers of inflammation at the broncho-alveolar epithelium. In this way, the perioperative change of the pulmonary inflammatory cascade, as implicated in ARDS in general, was studied. The different types of white blood cells, IL-8, neutrophil degranulation protease Human Neutrophil Elastase (HNE), and their effect on MUC5AC and MUC5B, as representatives of the mucocilliary clearance (MCC) apparatus, were investigated with linear regression (ANOVA). Both their relation to P/F ratio and their commutual correlations were analyzed.

Asymptomatic viral infections

In the second and third study the role of respiratory viruses in the development of ARDS after cardiac surgery was investigated.

The second study was a retrospective cohort study of 2013 patients. We compared, duration of mechanical ventilation, the incidence of ARDS, length of ICU stay, and mortality in patients that underwent cardiac surgery in the Influenza season with patients that underwent cardiac surgery in the low/no influenza season, using multi variable analyses. In this study, we took the influenza season as a surrogate for respiratory virus infection, assuming that during the season there are more patients who subclinically had or during admission acquired respiratory viruses.

The third study, an observational prospective cohort study, explored the actual presence of respiratory viruses in cardiac surgery patients. All patients were free of symptoms, as pre-operatively screening was carried out by an anesthesiologist and a thoracic surgeon, and surgery would have been postponed when a respiratory tract infection was suspected. Viral load and the types of viruses present in the patients were recorded. Furthermore, presence of respiratory viruses was related to seasonality and clinical outcome parameters, such as P/F ratio, ventilation time and ICU stay.

Part two – Prediction

The next study, on an eighty-patient prospective cohort of cardiac surgery patients, describes the predictive pre-operative value of platelet and leukocyte activation, and their complex formation in the peripheral blood, as a possible expression of processes on the vascular endothelium side of the alveolar capillary junction. Activation patterns were compared between patients with a less favorable pulmonary outcome (i.e. a low <200 $Pa0_2/FiO_2$ (P/F) ratio) versus those with a better outcome (high > 200 P/F ratio).

In cardiac surgery prediction models are used to estimate patients' risk for adverse outcomes after cardiac surgery. The EuroSCORE is a frequently used model (52) and in recent studies on this subject it was suggested that incorporation of biomarkers in risk models is feasible and useful (54). Most risk scores, however, only weigh the pre-operative risk, but do not take into account the impact of surgery itself.

The fifth study, a prospective cohort study, focused on peri-operative pro-adreno-medullin (ProADM) increase to predict outcome. In particular, the additional value of pre-to-postoperative proADM-change to the EuroSCORE by multivariable logistic regression was assessed for prediction of ARDS and other clinical outcomes after cardiac surgery. Adding a "change over time during surgery"- marker to regular prediction scores, allows early identification of patients at risk for developing an ARDS or a protracted clinical course and enables targeted preventative interventions.

Part three – Prevention

To reduce SIRS after cardiac surgery, corticosteroid prophylaxis has been used for decades. A Cochrane meta-analysis (55), however, did not show a beneficial effect, nor did a large randomized DECS-trial on this subject (56, 57).

The first study in this part is a prospective cohort study, applying the instrumental variable analysis (IVA) by using the physician's preference as a pseudo-randomization instrument, to assess the effect of perioperative corticosteroid use on adverse outcomes in cardiac surgery patients. In this study the outcomes after the IVA were also compared to the outcomes in the DECS trial, that was published at the same time.

The second study is an update of our earlier systematic meta-analysis (55), and includes all RCTs published until March 2019. The primary aim of this review was to determine the effect of prophylactic corticosteroids on mortality in adult cardiac surgery with CPB. Secondary aims were to examine the effect of corticosteroids on complications of adult cardiac surgery, such as myocardial adverse events (including fatal and non-fatal myocardial infarction), pulmonary adverse events (including pulmonary oedema, infection, or prolonged postoperative ventilation for respiratory failure), atrial fibrillation, surgical site infection, gastrointestinal bleeding and duration of stay in the intensive care unit (ICU) and hospital.

The third and final study in this part was prompted by the special circumstance of the recent COVID-19 pandemic occupying ICUs with COVID patients. In that time, not much cardiac surgery was performed, and other important study questions were to be answered. Therefore, we conducted another meta-analysis on steroids in ARDS, but now, understandably, in a different study population. When this study was performed medical science was swamped by a tsunami of literature, often of varying quality and not seldomly retracted from even leading journals. During the initial waves of the COVID-19 pandemic different therapeutic interventions for COVID-19 patients followed each other in rapid succession, along with the evidence for these interventions. In the second wave, when the first promising results of the Recovery trial (58) began to circulate across the many (social) media channels, we conducted this meta-analysis to what is now de corner stone of COVID treatment at the ICU. Besides the the clinical effect of corticosteroids in COVID-19 patients on mortality, and need for mechanical ventilation, we also studied viral clearance, opportunistic infections, and antibiotic use.

CONCLUSIONS AND REFLECTION

After the three main parts the results of this thesis are summarized, followed by a discussion, general conclusions and future perspectives. Finally, the thesis is concluded with a Dutch summary, curriculum vitae, reference list and acknowledgments.

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