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

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Summary, general discussion and future perspective

SUMMARY OF FINDINGS

This thesis addressed pulmonary complications, i.e. acute lung injury and ARDS, after cardiac surgery and aimed towards better understanding, prediction, and prevention. The thesis was subdivided in three parts and the findings are summarized part by part:

PART 1.

To increase the pathophysiological understanding of the development of acute lung injury after cardiac surgery we studied (a) the alveolar epithelial side of the alveolar-capillary junction and (b) the role of respiratory viruses.

By means of mini bronchoalveolar lavages, we determined inflammatory biomarkers (differential cell counts, IL8 and HNE) in the perioperative time period and we assessed mucociliary clearance by assaying the two major soluble mucins (MUC5AC and MUC5B). We showed a marked increase in the concentrations of MUC5AC and MUC5B in bronchoalveolar fluid of patients after heart surgery and a significant association between the increase of MUC5AC and the severity of lung injury and ICU length of stay. The increase of mucins may simply be one of many reflections of the activation of inflammation that takes place after cardiac surgery, but an etiologic role in the development of lung injury and ARDS after heart surgery cannot be ruled out, especially since the perioperative mucin increase was greater than that of other biomarkers.

To investigate the role of respiratory viruses in the development of lung injury after cardiac surgery we included two studies in this thesis:

- Firstly, we conducted a large cohort study, indirectly investigating the influence of viruses on cardiac surgery using the fact that a patient underwent cardiac surgery in the influenza season as a proxy for a higher frequency of respiratory virus infection. We found a higher frequency of ARDS (9 versus 5%) and a longer duration of mechanical ventilation after cardiac surgery in the influenza season.
- In the second study, we investigated the actual presence of respiratory viruses in miniBAL material of asymptomatic elective cardiac surgery patients. A variety of mostly low virulent respiratory virus RNA, all with high CT-values, was detected, regardless of the season in which patients were operated. A relationship with respiratory outcome could not be established.

PART 2.

To investigate whether biomarkers can predict acute lung injury after cardiac surgery, we studied (a) the inflammatory patterns generated at the endothelial side of the alveolar-capillary junction, and (b) the pre-to-postoperative change of proADM in plasma in relation to development of acute lung injury.

At first, the state of the vascular endothelium side, as part of the alveolar-capillary junction, was further investigated by applying direct flowcytometry to peripheral blood samples taken in the perioperative period from cardiac surgery patients. We demonstrated that, already preoperatively, there was an activated inflammatory system, i.e. higher platelet activatability by means of TRAP and a neutrophil activation pattern with higher expression of both CD11CD18 and CD62L, in the group of patients that developed an acute lung reaction after cardiac surgery. In the same group of patients, we also found a more pronounced inflammatory response in the postoperative time course with increased platelet activation and evident neutrophil activation, i.e. Increase in ligand CD11CD8 and decrease in L-selectin expression CD62. Whether the findings in peripheral blood reflect of cause the status of alveolar endothelium and lung injury remains an important question.

Furthermore, we focused on proADM in plasma, as a multi-potent and biologically active peptide affecting vasomotor status and an important marker of inflammation. To consider the effect of CPB and the surgery itself, a known important factor in the risk of acute lung injury and ARDS, we measured the change of ProADM from pre- to direct post-surgery. This proADM change was a good predictor of the risk of developing ARDS, prolonged duration of mechanical ventilation and increased length of ICU stay. Moreover, the use of this parameter improved the currently used risk model for cardiac surgery, i.e. the EuroSCORE (1).

PART 3.

To investigate whether prophylactic corticosteroids can prevent unfavorable (respiratory) outcomes in cardiac surgery and other ICU patients we conducted three different studies.

In the first retrospective methodological study, the difference in corticosteroid prescribing behavior between anesthesiologists (physicians' preference) was used as an instrument for an instrumental variable analysis (IVA) (2). These findings were compared with an almost simultaneously published RCT on steroid use in cardiac surgery (3). The use of physician's preference as an instrument of IVA was feasible. However, there was no beneficial effect of steroids on cardiac surgical patients in general, and this result was in line with the RCT findings.

Secondly, we conducted a meta-analysis on corticosteroid prophylaxis in cardiac surgery patients, showing similar results: no beneficial effect on mortality could be demonstrated. However, a beneficial effect of steroids was visible on a few important secondary outcome measures: fewer pulmonary complications (including pulmonary oedema, infection or prolonged postoperative ventilation for respiratory failure), less atrial fibrillation and fewer wound infections. The higher incidence of myocardial infarction could not be explained.

The third study comprised a meta-analysis on steroids in a different patient population with ARDS, namely CoVID-19 ICU patients. This study showed a beneficial effect of steroids on duration of ventilation duration, length of ICU stay and mortality. The trend that corticosteroids delay viral clearance and increase opportunistic infections however seems logical but needs further evaluation for their importance in future.

GENERAL DISCUSSION

In this thesis, we come to five main conclusions and additional important remarks:

PART 1. Pathophysiology

1. *Perioperative bronchoalveolar Muc5AC increase was associated with development of acute lung injury and prolonged ICU stay.*

Concentrations of mucins in airway lavage fluid are increased peri-operatively from induction of anesthesia until admission to the ICU, and the increase in MUC5AC is related to the severity of lung injury as measured by P/F ratio. Not only mucins, but in fact all measured biomarkers increased peri-operatively. Thus, the increase of mucins may simply be one of many reflections of the activation of inflammation that takes place after cardiac surgery. However, the magnitude of increase is five- to tenfold for MUC5B and MUC5AC and thereby much more pronounced than the increase of other biomarkers. Additionally, MUC5AC was the only biomarker that was significantly associated with relevant clinical endpoints, such as the severity of lung injury and the length of stay in the ICU. Thus, we cannot rule out that mucins have an etiologic role in the development of lung injury and ARDS after heart surgery.

These findings are in line with other studies. Children with respiratory complications after cardiac surgery showed significantly higher MUC5AC levels than did children without respiratory complications. And the increase of total mucin during cardiopulmonary bypass showed positive correlation with alveolo-arterial oxygen difference (4). Furthermore, in critically ill patients with acute lung injury (ALI), MUC5AC levels in

bronchoalveolar fluid were more than 58-fold increased (5). In normal airways, mucins cover the epithelial surface of the respiratory tract, and mucin production is maintained at a relatively low level to promote mucociliary clearance of inhaled and trapped substances. In pathologic conditions such as asthma, bronchitis, and acute respiratory distress syndrome, however, mucus production is excessive and instead limits mucociliary clearance, and in the small peripheral airways this may lead to mucus plugging and airway obstruction, with ultimately impaired gas exchange. However, the strong association between MUC5AC and lung injury does not necessarily imply that mucins play a direct etiologic role in acute lung injury. Indeed, increased mucin expression could also be just a reflection of the proinflammatory state without a specific causal role.

Our findings must again be put into the perspective of the intrinsic limitations of sampling in the alveolar lavage: (a) Introducing the miniBAL catheter without bronchoscopic guidance leads to an unknown sampling location (6), (b) varying and uncertain dilution factor (7), (c) sampling error: only a limited part of the alveolar space is sampled and it is not clear whether this is representative of the rest of the lung. (6) For these reasons – which as of yet cannot be corrected for - it is difficult to translate findings of sampling in alveolar lavage fluids to the real pulmonary condition.

Another limitation of this study is the fact that BAL is an invasive procedure, performed only while patients were on a mechanical ventilator. A few patients with a good postoperative performance state were already extubated at ICU arrival and were not part of this analysis, which introduces a bias towards the more severe patients. However, the correlation of IL8, HNE, neutrophils, MUC5B and MUC5AC, and the inversed proportional association of MUC5AC with P/F ratio suggest that further research into the inflammatory parameters in the alveolar space could certainly be useful. Finally, the bronchoalveolar lavage is primarily only a reflection of the end product of the mucociliary apparatus: mucus. It would certainly be interesting to also investigate the epithelium of the peripheral lung at the cellular level, to see how other interactants beside mucus i.e. the goblet cells, the club cells, and the pneumocytes, change as acute lung injury and ARDS develops or are changed before.

2. *A contributing role for respiratory viruses in the development of ARDS after cardiac surgery could not be established.*

In our studies, on the one hand, there was an increased development of ARDS and an increased duration of mechanical ventilation during the influenza season, which in fact is only circumstantial evidence that a viral trigger may have played a role in ARDS after cardiac surgery. On the other hand, when measuring the presence of viruses in elective cardiac surgery patients, a relationship with pulmonary complications could not be demonstrated.

The latter rather explorative study, however, showed that asymptomatic elective cardiac surgery patients do carry respiratory viruses both during and outside the influenza season. Almost all of these viruses, however, were low pathogenic and had a low load (high CT values) which might explain their yet non-significant role in development of ARDS (virus group 3/6 and non-virus group 16/43).

Although our studies were inconclusive about the role of respiratory viruses in development of ARDS after cardiac surgery, their role has not been definitively ruled out either. It would still be useful to know how many of the patients who develop ARDS after cardiac surgery actually carry a virus in their respiratory tract. In particular, it would be interesting to learn which specific viruses, and with what CT value, do significantly contribute to the development of ARDS.

PART 2. Prediction

3. *Preoperative increased platelet-activatability and neutrophil activation is related to lung injury. Cell activation patterns in cardiac surgery patients allow us to identify patients that develop lung injury early and may improve preoperative risk models.*

We demonstrated that prior to commencement of cardiac surgery an upregulated inflammatory state is present in patients who develop (acute) lung injury. The observed higher platelet-activatability and signs of a higher neutrophil turn over before surgery, and a typical neutrophil activation pattern later could well contribute to more severe acute lung injury in this respect.

Indeed, one has to be cautious to equate the results of assessments in the peripheral bloodstream with the processes that actually take place at the alveolar-capillary junction. When the vascular endothelium and neutrophils become activated, it initiates a process of tethering, rolling, adhesion, crawling and transmigration (8,9) of the neutrophils. Because of this process, these cells, however, cannot be longer measured in the peripheral blood. Much more invasive research, i.e. taking blood and alveolar samples simultaneously could prove if findings are relevantly associated. Maybe even taking lung biopsies, would be necessary to gain more insight into the local processes at the alveolar-capillary junction and if and how they can be studied by more accessible biomarkers .

Furthermore, the contribution of the CPB circuit cannot be assessed from our results. Platelets and neutrophils namely can also be activated when they come into contact with the synthetic tubing. It is plausible to assume that the process of neutrophil- and platelet activation will take place in the CPB (10), while some of the activated cells

might also be captured in the CPB circuit. Sequential sampling in the in- and outlet cannulas from the circuit would therefore give more insight in the inflammatory role of the CPB circuit.

Hence, whether the higher level of platelet activatability and neutrophil turn-over that we found in patients that developed lung injury, is due to a common (causal) factor or that patients who develop a lung reaction can actually be recognized by such parameters remains difficult to answer. On the other hand, activated inflammation before surgery in this regard likely contributes to the mechanisms we know to play a role in lung injury. Flow cytometry hence could be a valuable addition to current scoring systems and help to better recognize patients who are facing a complicated course.

4. *Development of ARDS post cardiac surgery could be predicted with the pre-to-post surgery increase of proADM. Adding proADM to existing scoring systems, such as the EuroSCORE, ameliorated the predictive capacity.*

By using this two-point biomarker as a predictor of ARDS, it was possible to consider the impact of the surgery itself in addition to the usual risk factors. After all, the duration of the CPB (11,12), and the operative injury itself (12) are both well-known risk factors for the development of ARDS and are reflected by the proADM increase. The use of this biomarker, would make it possible to quantify surgery related risk factors shortly after admittance at the ICU and identify patients with a higher risk for development of ARDS.

Then almost directly the question rises “What can we do with that information?” Unfortunately, except for supportive care, no disease modifying therapy is currently available (13). If causality – in other words if ADM would play a role in later lung injury – our knowledge about the ARDS risk should lead to faster and better deployment of the components of specific therapy influencing this pathway. Till then, supportive therapy, such as lung protective ventilation and stringent fluid policy (14), and probably administration of corticosteroids to prevent worse outcome remain. (this thesis, 15)
Most preferable is a biomarker that discriminates at a timepoint when choices can still be made: before the operation. With a large proADM increase, the damage has already been done and the highest achievable remains damage control in the form of rapid adjustment of good supportive care. Only when better treatment modalities for ARDS are available, this biomarker in sequential samples can play a role in the treatment of ARDS

PART 3. Prevention

5. *The use of corticosteroids does not prevent ARDS or other unfortunate outcomes in cardiac surgery in general, though they are very effective in other ARDS patient groups.*

Meta-analyses (16) and both the DECS and the SIRS trial (3,17) have been performed to study the effect of corticosteroids in cardiac surgery patients. Our studies show similar results: prophylactic steroids are not useful for cardiac surgical patients, in general. On the contrary, steroids are notorious for their side effects on the muscle and nervous system, glucose regulation, and immune system; all factors that one would want to keep optimal in the recovery phase after major surgery.

Even though we are all aware of their side effects, many experts in the field do provide these medicines to a select group of patients, i.e. expert-based personalized medicine. From a pathophysiological point of view, the administration of corticosteroids in a subgroup of patients can certainly be rationalized: there is a group of patients who are at high risk of development of SIRS or ARDS after surgery (i.e. complex surgery, duration of CPB, multiple transfusions, amongst others). In that group, regardless of all these RCTs and meta-analyses, clinicians feel lower thresholds for the use of corticosteroids. Since there was an actual effect on secondary pulmonary outcomes, it could be similar to the history of mechanical ventilation in prone position in ARDS (18-20): the clinician knows the effect from practice and continues to apply it, but the scientific basis lags behind expert observations.

It therefore seems likely that within the total group of cardiac surgical patients, a subgroup can be identified, in which the effect of corticosteroids is valuable. These patients are likely the ones prone for development of an inflammatory respons, i.e. patients undergoing complex interventions and procedures with expected long pump runs (re-operations, complex surgery). In addition, consideration should be given to include the preoperative inflammatory biomarker profile, which was shown (in this thesis) to identify patients prior to their surgery for their (pulmonary) complicated course.

FUTURE PERSPECTIVE

Because the general population is aging (21), health care is becoming more expensive, (22) and accessibility will become an increasing problem due to staff shortages in all branches of health care (23). Therefor, it is more and more important to take steps in the (near) future towards personalized pinpointed medicine. In this regard, with the

advancement of surgical and non-surgical techniques, it is increasingly possible to present patients with a choice of treatment. Examples of this are open heart surgery versus catheter techniques (24, 25), or limitation of interventions to strictly necessary or even refraining from the intervention due to too high risk.

To make these patient- and conditions-specific considerations, it is very important to make a thorough risk assessment before the procedure, so that a patient can be you can inform the individual patient better about his/ her specific risk profile associated with the operation and which alternatives, if any, are available. There are the well-known scoring systems for this risk assessment: EuroSCORE, frailty score, NYHA score, CCS, ASA score, but further optimization and personalization of these scoring systems certainly is desirable.

To make the transition to more personalized medicine, further research is necessary. The directions of research one might think about are:

1. To increase the knowledge of pathophysiology at the alveolar side of the alveolar-capillary junction in patients who develop acute lung injury and ARDS after cardiac surgery and find easily accessible and measurable biomarkers that reflect the junctional condition. Furthermore, gaining more insight at the local level clearly offers better possibilities for (drug) intervention strategies, which reduce postoperative morbidity and mortality and improve the postoperative quality of life.
2. To increase knowledge of pathophysiology at the vascular endothelium side of the alveolar capillary junction. Insight in increased activation and increased turn-over of cells involved in the inflammatory response both increases pathophysiological (etiological) insight as well as prognostic insight. And both can lead to tailored, more patient-centered therapy.
3. To Identify avoidable risk and, with this, enable also avoidance of risk. In relation to this thesis, this would be further exploration of the role of viruses in development of ARDS after cardiac surgery and developing smart vaccination or screening strategies.
4. To improve risk prediction scores with biomarkers, such as proADM. In this regard, it is important that the biomarker provides a good reproduction of the patient's current inflammatory state on top of current scoring systems, which reflect the patient's history and performance state.
5. To expand tailor-made advice and treatment. With the help of the above mentioned more pathophysiological based biomarkers this will become better achievable.
6. An important challenge is to find treatment modalities that limit or inhibit the systemic inflammatory response, the catalyst of ARDS in cardiac surgery patients. The current expert-based personalized medicine with regard to the administration of corticosteroids could be further explored in the high-risk population. In addition, other targeted anti-inflammatory interventions could be investigated in especially the high-risk population.
7. Furthermore, the rapidly emerging innovative technologies could play a role in, for example, the development of more hypo-inflammatory CPB circuits to at least minimize all contributing factors to the development of inflammation.

All the above-described items, and probably many others, can bring us closer towards better understanding, prediction, and prevention of ARDS after cardiac surgery and will contribute to developing the most optimal form of personalized care.

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