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

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PART TWO

Predicting lung injury after cardiac surgery

4

Leukocyte and platelet activation in cardiac surgery patients with and without lung injury: A prospective cohort study

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ABSTRACT

Objections: Development of acute lung injury after cardiac surgery is associated with an unfavorable outcome. Acute respiratory distress syndrome in general is, besides cytokine- and interleukin activation, associated with activation of platelets, monocytes and neutrophils. In relation to pulmonary outcome after cardiac surgery, leukocyte- and platelet-activation is described in animal studies, only. Therefore, we explored the peri-operative time course of platelet- and leukocyte- activation in cardiac surgery and related these findings to acute lung injury assessed via PaO2/FiO2 (P/F) ratio measurements.

Methods: a prospective cohort study was performed, including 80 cardiac surgery patients. At five timepoints, blood samples were directly assessed by flowcytometry. For time course analyses in low (<200) versus high (>/=200) P/F ratio groups repeated measurements techniques with linear mixed models were used.

Results: Already before the start of surgery platelet activatability (p =0.003 for Thrombin Receptor Activator Peptide and p=0.017 for Adenosine Di Phosphate) was higher, and expression of neutrophil activation markers was lower (CD18/CD11; p = 0.001, CD62L; p = 0.013) in the low P/F group. After correction for these baseline differences, the peri-and postoperative Thrombin Receptor Activator Peptide induced thrombocyte activatability was decreased in the low P/F ratio group (p 0.008), and a changed pattern of neutrophil activation markers was observed.

Conclusion: Prior to surgery, an upregulated inflammatory state with higher platelet-activatability, and indications for higher neutrophil turnover was demonstrated in cardiac surgery patients that developed lung injury. It is difficult to distinguish whether these factors are mediators, or also etiologically related to development of lung injury after cardiac surgery and further research is warranted.

INTRODUCTION

Cardiac surgery induces a systemic inflammatory response syndrome with an incidence of 42%, that can lead to concurrent single- or multiple organ dysfunction (1). Development of acute lung injury and even acute respiratory distress syndrome (ARDS) in this respect is reported in 0.5-20% of patients after cardiac surgery (1-3), and is associated with a complicated postoperative course (1, 3, 4), high mortality (50-90%) (2, 4-7), and significant long term physical and psychological sequelae (7).

The pathophysiology of postoperative acute lung injury is thought to lie in inflammation-induced disruption and increased permeability of the alveolar-capillary membrane, and development of pulmonary oedema (8). Furthermore, it is thought to be evoked by multiple successive factors, such as pre-existent impaired left ventricular function, use and duration of cardiopulmonary bypass (CPB), lung ischemia-reperfusion injury, transfusion of blood products, and complexity of surgery (2,5). Complement activation through both the classical and alternate pathways, and subsequently or concurrently released proinflammatory cytokines (TNF-α, IL-1, IL-2, IL-6, IL-8) and anti-inflammatory cytokines (IL-10, IL-1ra, TNFsr1 and 2, and transforming growth factor) influence the magnitude and severity of the inflammatory response after cardiac surgery and development of ARDS (5,9). A prominent role in the development of ARDS in general has been assigned to activated platelets, monocytes and neutrophils (10,11). Studies in cardiac surgery demonstrated that platelet- and leukocyte activation, and platelet-leukocyte aggregation was increased (8,12,13), and suggested endothelial adhesion and entrapment of platelets and polymorphonuclear neutrophils in the lungs (5,14). However, these studies have described flow cytometric patterns of platelets and leukocytes after cardiac surgery in general, but relating them to postoperative development of acute lung injury and ARDS has only been done to a limited extend in combination with other biomarkers (15), or in animal studies (14,16).

It was our hypothesis that increased platelet and leukocyte activation patterns, as can be measured by flow cytometry, would be present in cardiac surgery patients that developed acute lung injury as compared to cardiac surgery patients that did not develop acute lung injury. Therefore, in this study we aimed to further explore the intra- and postoperative time course of platelet activation and activatability, leukocyte activation and the platelet-leukocyte interactions in adult cardiac surgery patients and relate these findings to the occurrence of acute lung injury. Further insight into platelet- and leukocyte associated biomarkers related to acute lung injury after cardiac surgery is important for understanding the pathophysiology and to bring personalized preventive measures a step closer to clinical practice.

PATIENT POPULATION AND METHODS

Ethical statement

The study was approved by the Medical Ethical Committee (27-09-2011; protocol P11-117) of the Leiden University Medical Center and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (17). The trial was registered at the International Clinical Trials Registry Platform (NTR 5314, 26-05-2015) The Strobe statement checklist (18) is available in supplement Chapter 4.1. Written informed consent was obtained from all included patients on the day before surgery.

Study design and study population

A prospective cohort study was performed in of the ICU of a tertiary referral hospital, the Leiden University Medical Center in the Netherlands. Eligible patients were adults undergoing elective cardiac surgery. A dedicated researcher and laboratory technician were available to ensure immediate transportation of samples to the laboratory and direct analyses on a readily available flow cytometer in the laboratory on all consecutive study days. Therefore, patients could only be considered for inclusion, when surgery was planned early morning on a Monday or Tuesday. The maximal capacity was limited to one patient a week, and only when critical laboratory and research personnel were available. The selection of Monday or Tuesday did not introduce a bias of specific types of surgery as in our hospital all types of cardiac surgery are performed equally over weekdays. The exclusion criteria were inability to sign informed consent, being less than 18 years old, emergency operations, participation in another study, and pre-operative use of corticosteroids. The Follow up period was until discharge form the hospital.

Sample Size:
A formal sample size estimation was not possible because only a few earlier studies were available (12,19-23), and these studies were small (all less than 20 patients), research questions were various, and tests for platelet- or white blood cell activity were different from the methods we intended to use. Therefore, we applied a pragmatic approach to include as much patients as possible in the years that were assigned to conduct this study.

Perioperative care

All patients visited the pre-operative outpatient clinic for pre-operative screening. All patients were admitted one day before surgery. Perioperative care for cardiac surgery patients is standardized in the Leiden University Medical Center and follows a pre-established care path. All details regarding the peri-operative care are summarized in supplement Chapter 4.2.

Data collection

All pre-, intra- and postoperative data and clinical parameters were obtained from the electronic patient database (EPD) system of the hospital. This EPD is used preoperatively, in the operating room and in the ICU. In the ICU, continuous hemodynamic and ventilation monitoring is recorded. Four times per day an arterial blood gas analysis is done and more frequently on indication.

Sample collection

At five different time points blood samples were drawn (before the start of anesthesia/ surgery at the holding facility (T0), 1 hour after weaning of CPB (T1), T1+ 3 hours (T2), first postoperative day (T3), second postoperative day (T4). Samples were collected in lithium heparin vacuettes. Samples were transported to the laboratory and analyzed immediately after collection.

Flow cytometry analyses

The Beckman Coulter FC500MPL was used for flow cytometric analyses. A designated laboratory employee was available for our study. Before starting the actual measurements of our study samples, daily quality checks were performed to ensure the reliability and accuracy of the results. For platelet activation markers and leukocyte-platelet complexes, dilutions were created using 3% Bovine serum albumin (BSA)/ PBS).

Platelet activation: Fluorescein antibodies against CD61 (FITC) and CD62 (PE) were used as platelet activation markers. Adenosine diphosphate (ADP) and thrombin receptor activator for peptide (TRAP) were chosen as well-known examples respectively weak and strong platelet agonists, that in our hands showed good day to day reproducibility of agonist-concentration dependent aggregation responses. Analyses were done with eight increasing concentrations of the different agonists.

Leukocyte activation: White blood cells were adjusted to a maximum concentration of 20 x 106/ml in phosphate buffered saline (PBS), Fluorescein antibodies against Neutrophil CD66b (FITC) and activation markers CD11b/18 (PE), CD62L (PE) were used, Optilyse-C for lysis of the erythrocytes and Stem Count beads for calibration

Leukocyte-Platelet complex formation: White blood cells were adjusted to a maximum concentration of 20 x 106/ml in phosphate buffered saline (PBS). Fluorescein antibodies against monocyte CD14 (FITC), Neutrophil CD66b (FITC) and platelets CD42b(PE), for calibration beads Stem Count were used. Optilyse-C for lysis of the erythrocytes and Stem Count beads for calibration.

The above laboratory studies yielded dose response activation curves, from which the maximum, the minimum and the mean percentage, which is an equivalent of the area under the activation curve (24), of responsive cells can be derived. Since the mean percentage of responsiveness is an aggregate measure, reflecting both the maximum number of responsiveness and the minimum agonist concentration at which cells respond (24), it was decided to use the mean percentage. Results were expressed as mean percentage responsive cells in the dose-response activation curve.

Endpoints

The primary aims of this study were monitoring of the perioperative time course of leukocytes, platelets and their activation status and complex formation in adult cardiac surgery patients with and without acute lung injury. As a measure of lung injury, we used the PaO2/FiO2 ratio (P/F ratio). This is an objective tool to identify acute hypoxemic respiratory failure when supplemental oxygen and positive pressure ventilation is being administered, and, as such, a measure of acute lung injury and an important item in the definition of ARDS according to Berlin Criteria (25).

In thoracic surgery patients, a P/F ratio < 200 is associated with unfavorable outcome, and each increase in ARDS severity category, which is per definition only determined by a decline of the P/F ratio, is reported with a significant increase in morbidity and mortality (4). Hence, to distinguish mild from more severe and clinically more relevant lung injury patients, we dichotomized the P/F ratio in two subgroups of lung injury: moderate to severe impaired respiratory state (lowest postoperative P/F ratio < 200 mmHg) versus mildly impaired and normal respiratory state (lowest postoperative P/F ratio ≥ 200 mmHg).

To determine surgery-related lung injury, we used, analogous to these Berlin criteria, a maximum time period of 1 week after surgery. Although FiO_2 is notoriously unreliable once at low-flow oxygen supply (27,28), and PaO_2 is only measured on clinical indication at the general thoracic surgery ward and hence the P/F ratio was not available in extubated patients, it is unlikely that we missed patients who developed a low P/F ratio and lung injury on the ward, especially as all patients are transferred back to the ICU once (non-) invasive ventilation is mandatory.

Statistical analyses

in consultation with the Departments of Biomedical Data Sciences and Clinical Epidemiology of the Leiden University Medical Centre, a statistical analysis plan was defined in advance, before disclosure of the data. The statistical analysis was carried out according to plan.

Demographic and clinical characteristics are presented as mean (SD) or median (IQR) for continuous variables and as absolute values and percentages for categorical variables. For the normal/mildly impaired versus moderate/severe respiratory groups baseline characteristics were compared with a Fischer's exact test for categorical variables and Mann-Whitney U test for continuous variables.

Furthermore, the perioperative time course of white blood cells, platelets, platelet- and leukocyte activation, and platelet-leukocyte complex formation was tested for significance. Baseline differences in P/F ratio groups were tested with a T-test, and the further perioperative time course was tested with repeated measurements techniques, i.e. Linear Mixed Model. Of particular interest was the (a) effect of P/F ratio groups, i.e. high (>200) versus low (<200) P/F ratio and (b) effect of the time in the different P/F ratio groups. To distinguish baseline differences (i.e. at T0) from postoperative effects, the baseline value was compared in both P/F ratio groups, using T-test, and introduced as a variable in the repeated measurement analysis.

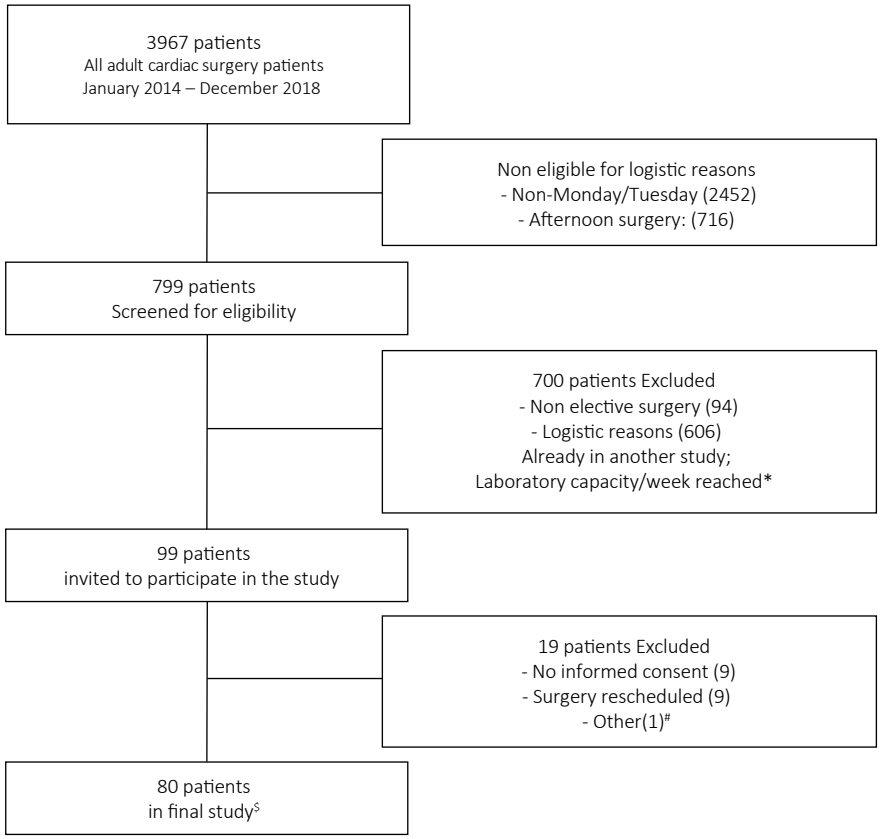
The statistical analyses were conducted using the SPSS (Statistical Package for the Social Sciences), release 25.0 (SPSS Inc., Chicago)

RESULTS

A total of 80 patients was included in this study from January 2014 to January 2018. In Figure 1 a flow chart of the inclusion process is shown. Four patients were excluded from the analyses, since they were already extubated when they arrived at the ICU, and no P/F ratios could be derived.

The patient characteristics are summarized in *Table 1*. Patients were predominantly middle-aged male, BMI was higher in the low versus high P/F ratio groups, left ventricular function was worse in the low compared to the high P/F ratio group, Euro-score was higher in the low P/F ratio group, and heart failure surgery was performed more frequently in the low P/F ratio group.

Figure 1. Flowchart inclusion



** A precise logistic network, consisting of a dedicated researcher and laboratory employee, was set up to ensure immediate transportation to the laboratory and direct analyses of blood samples on a readily available flow cytometer in the laboratory on all consecutive study days. Therefore, patients could only be considered for inclusion when surgery was planned early morning on a Monday or Tuesday. And maximal capacity was limited to one patient a week.*

 # IV access difficulties (history of chemotherapy) prohibited drawing blood form a peripheral vein. pre-operative blood sampling would mean additional invasiveness and was judged too burdensome for the patient.

$ 4 patients were excluded from analyses, since they were extubated at the operation room and no postoperative P/F ratio was available.

Table 1. Patient Characteristics

Characteristics		pF-ratio < 200 n = 23		pF-ratio ≥ 200 n = 53		p value*
Demographic parameters						
Age (yr) (mean, SEM)		66.6	2.1	65.0	1.2	0.583
Gender (male) (n, %)		12	55	26	49	0.147
BMI (kg/m^2) (mean, SEM)		25.8	1.9	21.7	0.7	0.217
Co-morbidity (n, %)						
Myocardial infarction in history		4	18	7	13	0.032
PCI in history		4	18	1	2	0.021
Thoracic surgery in history		0	0	2	4	0.491
Hypertension		9	41	14	26	0.147
Malignancy		0	0	1	2	0.707
Chronic kidney insufficiency		1	5	0	0	0.293
Chronic Liver disease		2	9	0	0	0.083
Diabetes		4	18	0	0	0.006
COPD		1	5	8	15	0.478
Smoking		12	55	21	40	0.205
Packyears (median, IQR)		12	50	20	25	0.493
Forced Vital Capacity (L) (median, IQR)		3.4	1.8	3.8	1.5	0.516
FEV1/VC (median, IQR)		69.5	8.6	74.4	9.6	0.328
Preoperative medication use (n, %)						
Diuretics		11	50	20	38	0,284
ACE blockers		13	56	25	47	0.195
Betablockers		15	65	29	55	0.276
Calcium antagonist		6	26	8	15	0.205
Statins		13	56	25	47	0.309
Thrombocyte aggretation blockers$		10	43	20	38	0.412
Ante-Surgery performance state (n, %)						
ASA	I	0	0	0	0	0.203
	II	4	18	5	9	
	III	16	73	41	77	
	IV	1	5	0	0	
LVEF	Good LVEF > 55%	9	41	23	43	0.048
	Reasonable LVEF 40-55 %	6	27	11	21	
	Moderate LVEF 25-40%	5	23	2	4	
	Poor LVEF < 25%	2	9	2	4	
	EuroSCORE 2 (logistic) (median, IQR)	3.0	7.7	2.2	2.3	0.014

Table 1. Continued

Characteristics	pF-ratio < 200 n = 23		pF-ratio ≥ 200 n = 53		p value*
Surgical parameters					
Surgical procedure (n, %)					
CABG	3	14	11	21	0.415
CABG + single valve	4	18	6	11	
CABG + multiple valve	1	5	1	2	
Single valve	5	23	13	25	
Multiple valve	1	5	6	11	
Thoracic Aorta surgery (±Valve/CABG)	4	18	13	25	
Heart failure surgery	3	14	4	8	
Other	2	9	4	8	
Surgical duration					
Surgery (min) (median, IQR)	360	126	345	90	0.361
Cardiopulmonary bypass (min) (median, IQR)	115	106	110	71	0.704
Corticosteroid therapy #					
Intraoperative use, overall (n,%)	8	36	11	21	0.450
Dexamethason 0,1-0,5 mg/kg	6	27	8	15	
Hydrocortison 100 mg	2	9	2	4	
Prednisolon 0,5 mg/kg	0	0	1	2	
ICU admittance risk Score					
APACHE IV (medIan, IQR)	58	17.7	44	19	0.012

** Chi square for categorial parameters. Means and T-test for normally distributed parameters. Median and Mann Withney for skewed distributed parameters.*

$ Antiplatelet therapy is discontinued 5-10 days before surgery, unless patients underwent recent coronary artery stenting or suffer from instable angina pectoris and had a semi-acute indication for surgery.

 # Patients that had an indication for corticosteroids pre-operatively were excluded from this study. Indications for intraoperative corticosteroid use are systemic inflammatory response with high vasopressor demand, allergic reaction and bronchospasm.

Abbreviations: APACHE Acute Physiology and Chronic Health Evaluation; ASA American Standards Association; BMI Body Mass Index; IQR Inter Quartile Range; FEV1 Forced Expiratory Volume in 1 second; LVEF Left Ventricular Ejection Fraction; PCI Percutaneous Coronary Intervention; SEM Standard Error of Means; VC Vital Capacity

Development of ARDS was more common in the low (P/F < 200) versus the high (P/F >/= 200) P/F ratio group (14/23 (64%) versus 9/53 (17%) (p<0.001). Furthermore, patients in the low P/F ratio group spent a longer time on the mechanical ventilator, had a longer ICU stay, and died more often *(Table 2)*.

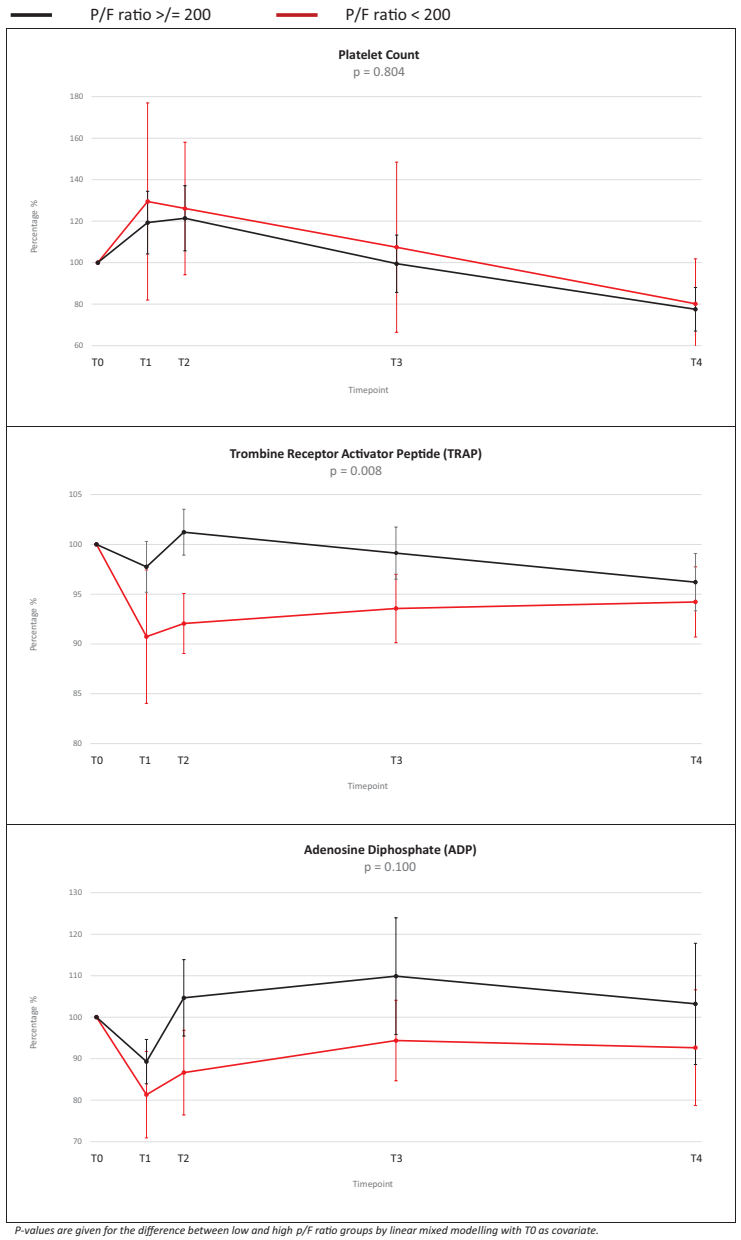
Table 2. Patient Outcome

Characteristics	pF-ratio < 200 n=23		pF-ratio ≥ 200 n=53		p value*
Outcome					
Ventilation time, minutes (median, IQR)	840.0	2704	675.0	405	0.005
Length of Stay ICU, hours (median, IQR)	43.5	161	22.5	3	0.047
Length of Stay hospital, days (median, IQR)	11.0	18	8.0	4	0.064
ARDS within 7 days after surgery (n, %)	14	64	9	17	< 0.001
Mortality (n, %)	2	9	0	0	0,088

**Chi square for categorial parameters. Means and T-test for normally distributed parameters. Median and Mann Withney for skewed distributed parameters. Abbreviations: ARDS Acute Respiratory Distress Syndrome; ICU Intensive Care Unit; IQR Inter Quartile Range*

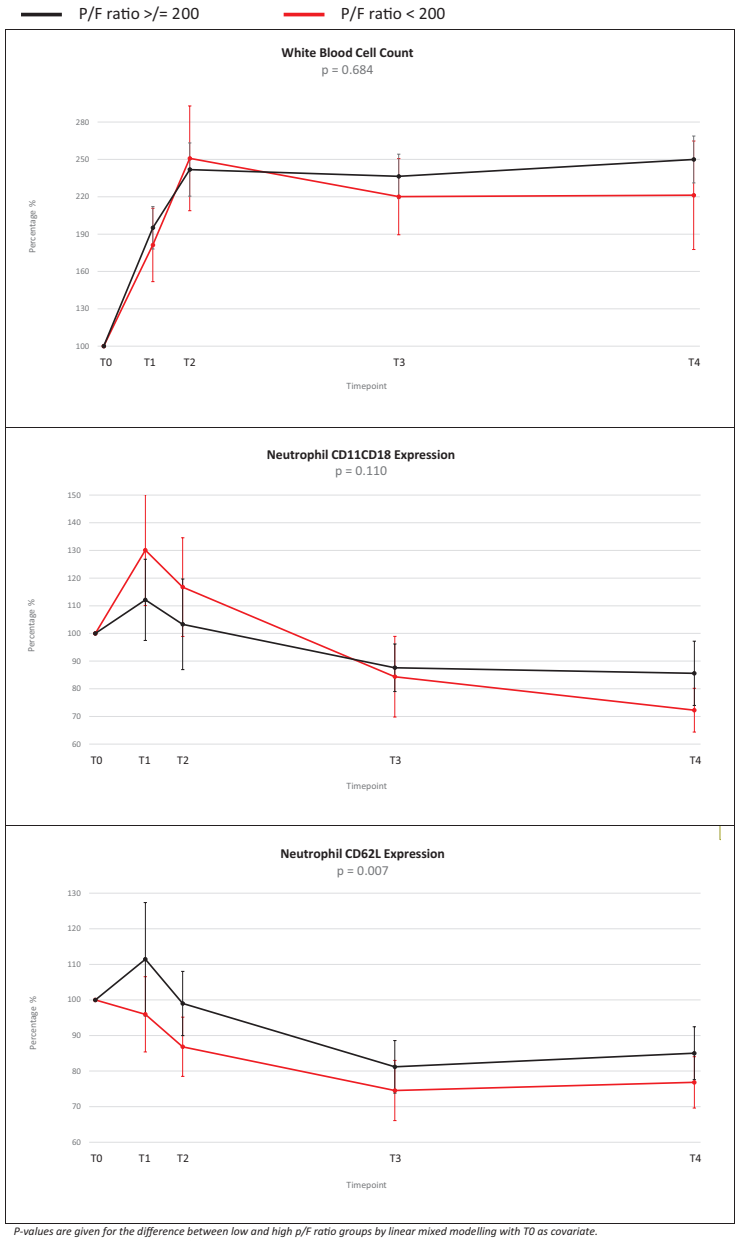
Already before the start of surgery (*Figure 2*), platelet activatability, as measured after adding ADP and TRAP, was higher in the low compared to the high P/F ratio group (p=0.003 for TRAP and p=0.017 for ADP). Expression of neutrophil activation markers was lower for both CD18/CD11 (p=0.001) and CD62L (p<0.013) in the low compared to the high P/F group. The perioperative time course of platelets, platelet activatability, WBC and neutrophil activation markers and leukocyte-platelet complex formation are shown in figures 2-4. To visually correct for the T0 differences, T0 is preset for both groups at 100% and the subsequent values are then shown in relation to this T0. In the time course analyses, only TRAP induced thrombocyte activatability decreased more in the low P/F ratio group (p=0.029). Additionally, a clear neutrophil activation pattern was observed in the latter group with increasing CD11CD18 and lowering of CD62L.

Figure 2. Platelets and platelet activatability in time for low (<200) and high (>/= 200) P/F ratio (adjusted for T0 difference)



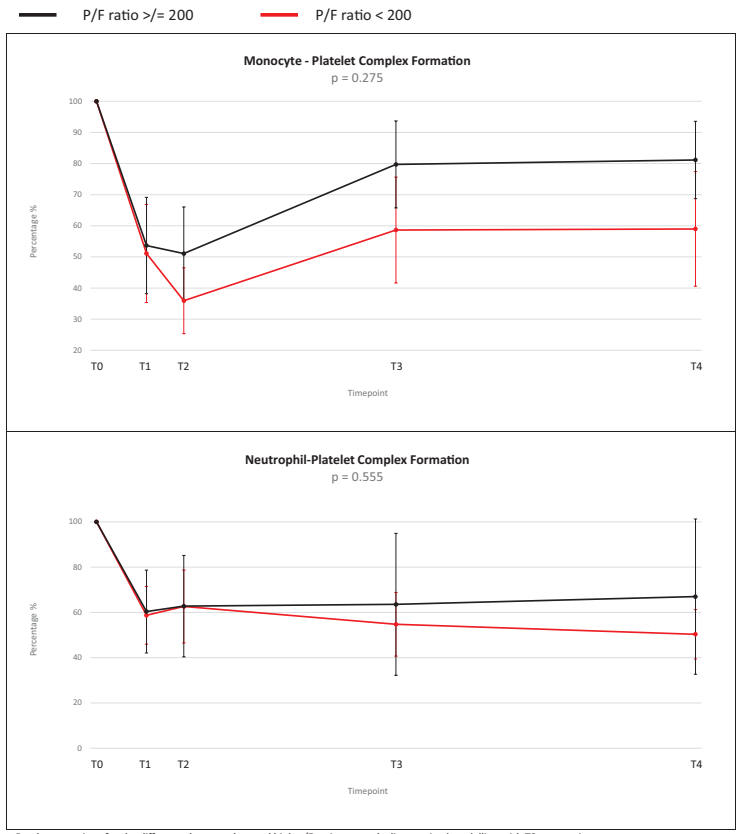
P-values are given for the difference between low and high p/F ratio groups by linear mixed modelling with T0 as covariate.
T0 = Pre-operative, T1 = End CPB + 1 hour, T2 = T1 + 3 hours, T3 = T1 + 18 hours, T4 = 2nd post operative day.

Figure 3. Leukocytes and Leukocyte activation in time for low (<200) and high P/F ratio (adjusted for T0 difference)



P-values are given for the difference between low and high p/F ratio groups by linear mixed modelling with T0 as covariate.
T0 = Pre-operative, T1 = End CPB + 1 hour, T2 = T1 + 3 hours, T3 = T1 + 18 hours, T4 = 2nd post operative day.

Figure 4. Complex formation in time for low (<200) versus high (>/= 200) P/F ratio (adjusted for T0 difference)



P-values are given for the difference between low and high p/F ratio groups by linear mixed modelling with T0 as covariate.
T0 = Pre-operative, T1 = End CPB + 1 hour, T2 = T1 + 3 hours, T3 = T1 + 18 hours, T4 = 2nd post operative day.

DISCUSSION

In this prospective cohort, we measured platelet and leukocyte associated biomarkers in the pre-, intra- and postoperative phase of 80 cardiac surgery patients and we related these biomarkers to the development of acute lung injury, defined by P/F ratio. We demonstrated that already before the start of surgery, a significantly higher capacity of platelets to be activated by ADP and TRAP was present in the patient group that developed acute lung injury as defined by P/F ratio < 200. Furthermore, lower expression of both CD11/CD18 and CD62L was present in the low P/F ratio group. After

correction of T0 differences, the post-operative course for the low P/F ratio group showed a significant decrease in the TRAP-induced platelet reactivity, and a typical pattern of the 2 neutrophil-activation markers: though not significantly different, neutrophil CD11/CD18 and CD62L expression showed an inversed change, i.e. increasing CD11/CD18 expression and decreasing CD62L expression, that could be interpreted as a higher turn-over of granulocytes in the lower P/F ratio group (29,30).
Some limitations of our study must be addressed, the most important of which is the sample size. Although, to our knowledge, this is the largest study of platelet and neutrophil activation in cardiac surgery patients and the first to relate this data to an acute lung reaction after cardiac surgery, still the sample size, based on pragmatic grounds, is not large enough to allow correction for- or in depth subgroup analyses of- the different types of surgery, steroid use, antiplatelet therapy, and other factors that might confound the outcomes in this study.

Secondly, the pre-operative flow cytometric differences in the two P/F ratio groups are not necessarily etiological factors in the development of pulmonary complications. They could also be mediators associated with other pre-operatively present co-morbidity, such as impaired left ventricular function, previous coronary artery disease, chronic heart failure, arteriosclerosis and atrial fibrillation; all well known risk factors itself for development of acute lung injury and unfavorable outcome after cardiac surgery (26), and all associated with increased inflammatory status, platelet activation, and endothelial driven hypercoagulability (27-30). In our study, these risk factors were more common in patients in the low P/F group and therefore, a (partly) non-causal or indirect relation of our biomarkers with this outcome cannot be excluded.

Furthermore, the local role of platelets and neutrophils (and their complexes) in the lung itself can not automatically be translated from measurements in circulating blood. In this respect it would have been interesting to study platelet and neutrophil activation status in blood and alveolar fluid concomitantly. Likewise, to clarify the role of the CPB, sequential sampling of blood in both inlet and outlet of CPB would have been informative.

Notwithstanding all the aforementioned limitations, clear differences in platelet activatability and neutrophil counts were demonstrated at baseline. Although, the low P/F group showed a more typical neutrophil activation pattern in the post-surgery time course with clear inverse reacting CD11CD18 (up) and CD62L (down), other parameters, when percentualized on baseline level, showed mostly not significant but discrete time courses after surgery in both outcome groups. From this it must be realized that differences in absolute values during the first postoperative days remain.

Although a non-etiological effect between flowcytometric results and outcome is uncertain and extrapolating whole blood results to pathophysiological processes in the lungs has important limitations, the results of our study cannot entirely be brushed off. Our findings suggest that preoperative presence of increased activatability of platelets, lower neutrophil activation marker expression (with possibly also a higher neutrophil turn-over) may have an etiologic role in the development of lung injury after heart surgery. The differences in biomarker baseline values between both study P/F ratio groups fit with the well-known pathophysiology of acute lung injury in other patients' groups. In previous studies in patients with ARDS, neutrophils indeed are shown to migrate to the inflamed tissue site, where a multistep of neutrophil-endothelial tethering, rolling, adhesion, crawling and transmigration takes place. Subsequently, neutrophil extracellular traps enable them to elicit their immunological action locally (4,31,32). In accordance, also earlier observational studies in cardiac surgery reported on activation of monocytes, neutrophils and platelets (12,13,16,20,33), endothelial transmigration and influx of these complexes in several organ systems as well (14,16,33). Such inflammatory processes could well be augmented if pre-surgery platelets and neutrophils are already activated as was the case in our low P/F group.

Despite the limitations of this study, especially the limited sample size, there are some important additional research questions that arise when considering the signals that emerged from this study. At first, it would be worthwhile to further explore thrombocyte and neutrophil activation patterns in predefined subgroups, such as the various subtypes of surgery, and in patients with and without antiplatelet therapy. Also, it would be interesting to further explore the activation patterns in patients that, according to prevailing practice, did receive postoperatively steroids versus those who did not. Furthermore, in this study, due to sample size, we were unable to do reliable prognostic studies and we refrained from making ROC curves and calculating sensitivity and specificity. However, in future studies, it would be valuable to explore prediction capacity of flow cytometric markers in addition to already known and applied prediction models. Finally, the peri-operative signals of thrombocyte and neutrophil activation in this specific study population of thoracic surgery patients and the association with pulmonary outcomes, might also be extended to other patient groups. It is well conceivable that similar processes play a role in other major surgery types, such as vascular/aortic surgery, large gastrointestinal surgery, and transplant surgery. Future studies are necessary to elucidate inflammatory responses and specifically the role of platelet and white cell activation after other types of major surgery.

CONCLUSION

We showed, 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. Further research, however, is needed and should at least involve (a) predefined subgroups (various surgery types, steroid use, antiplatelet therapy) (b) the role of the CPB circuit on platelets and neutrophils, (c) the influence of transfused blood products and (d) the neutrophil-platelet interactions at the alveolar-capillary lung level itself. If eventually, biomarkers on platelets and neutrophils, and lung vasculature interactions can be causally linked to acute lung injury, it would bring personalized medicine with patient-specific considerations with regard to interventions to be performed, expected outcomes, and specific preventive measures a step closer.

LIST OF ABBREVIATIONS

ADP:	Adenosine Di Phosphate
APACHE:	Acute Physiology and Chronic Health Evaluation
ARDS:	Acute Respiratory Distress Syndrome
ASA:	American Standards Association
BMI:	Body Mass Index
CABG:	Coronary Artery Bypass Grafting
CPB:	Cardio Pulmonary Bypass
EPD:	Electronic Patient Dossier
ICU:	Intensive Care Unit
IL:	Interleukin
IQR:	Inter Quartile Range
FEV1:	Forced Expiratory Volume as measured in 1 second
LVEF:	Left Ventricular Ejection Fraction
P/F ratio:	PaO2/FiO2 Ratio
PCI:	Percutaneous Coronary Intervention
SEM:	Standard Error of Means
TNF:	Tumor Necrosis Factor
TRAP:	Trombine Receptor Activator Peptide
VC:	Vital Capacity

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SUPPLEMETARY MATERIAL

Contains:

4.1 Strobe statement

4.2 Perioperative management in detail