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Biomarkers of Lung Injury in Cardiothoracic Surgery

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Engels, G. (2017). *Biomarkers of Lung Injury in Cardiothoracic Surgery*. [Thesis fully internal (DIV), University of Groningen]. Rijksuniversiteit Groningen.

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CHAPTER 5

Intraoperative cell salvage during cardiac surgery is associated with reduced post-operative lung injury

Gerwin Engels, Jan van Klarenbosch, YJ Gu, Willem van Oeveren and Adrianus de Vries

Interactive CardioVascular and Thoracic Surgery. 2016;22(3):298-304.

Abstract

Objectives: In addition to its blood-sparing effects, intraoperative cell salvage may reduce lung injury following cardiac surgery by removing cytokines, neutrophilic proteases and lipids that are present in cardiotomy suction blood. To test this hypothesis, we performed serial measurements of biomarkers of the integrity of the alveolar-capillary membrane, leucocyte activation and general inflammation. We assessed lung injury clinically by the duration of postoperative mechanical ventilation and the alveolar arterial oxygen gradient.

Methods: Serial measurements of systemic plasma concentrations of interleukin-6 (IL-6), Myeloperoxidase, Elastase, Surfactant protein D (SP-D), Clara cell 16 kDa protein (CC16) and soluble receptor for advanced glycation endproducts (sRAGEs) were performed on blood samples from 195 patients who underwent cardiac surgery with the use of a cell salvage device (CS, n=99) or without (CONTROL, n=96).

Results: Postoperative mechanical ventilation time was shorter in the CS group than in the CONTROL group [10 (8-15) vs. 12 (9-18) h, respectively, $p = 0.047$]. The post-operative alveolar arterial oxygen gradient, however, was not different between groups. After surgery, the lung injury biomarkers CC16 and sRAGEs were lower in the CS group than in the CONTROL group. Biomarkers of systemic inflammation (IL-6, Myeloperoxidase and Elastase) were also lower in the CS group. Finally, mechanical ventilation time correlated with CC16 plasma concentrations.

Conclusion: The intraoperative use of a cell salvage device resulted in less lung injury in patients after cardiac surgery as assessed by lower concentrations of lung injury markers and shorter mechanical ventilation times.

Introduction

Concerns about adverse effects and the costs of allogeneic blood transfusions have promoted the use of cell salvage devices during cardiac surgery [1, 2]. Besides a reduction in allogeneic blood exposure, the use of cell salvage devices could have additional benefits, such as a decrease in lung injury.

Lung dysfunction is common after cardiac surgery [3]. Ischaemia during cardiopulmonary bypass (CPB) results in endothelial activation upon reperfusion [4], which promotes the adherence of phagocytes through expression of specific surface adhesion molecules [5]. This results in the release of neutrophilic proteases and other inflammatory mediators that cause injury to the alveolar-capillary membrane. As a consequence, physiological changes result in an impaired lung function.

The use of cell salvage devices is known to reduce circulating inflammatory mediators, such as cytokines [6, 7] and neutrophilic proteases [7, 8]. Due to a reduction of these inflammatory mediators, we hypothesized that injury to the alveolar-capillary membrane would be reduced as well, resulting in less leakage of pulmonary (epithelial)-specific proteins and less impairment of lung function.

To test this hypothesis, we performed serial measurements of biomarkers of the integrity of the alveolar-capillary membrane, leucocyte activation and general inflammation on patients undergoing cardiac surgery with or without the use of a cell salvage device. We assessed lung injury clinically by the duration of postoperative mechanical ventilation and the alveolar arterial oxygen gradient.

Materials and Methods

Study design

This study included 195 patients undergoing cardiac surgery in the University Medical Center Groningen. These patients consisted of all patients from two study arms (with and without cell salvage) in our hospital, and belonged to a larger randomized prospective multi-centre clinical trial, investigating the effect of cell salvage and/or leucocyte depletion on allogeneic blood exposure (ISRCTN 58333401). The main results have been published elsewhere [9].

A computer-generated randomization table was made with four groups, of which two groups (cell salvage and control group) were used for this study. Allocation was done with sealed, sequentially numbered envelopes. The study was not blinded for the intraoperative part, because the cell salvage device could not be concealed by its

size, noise and special suction tube. However, all other caregivers were blinded to the intervention.

Patients presenting for emergency operations, scheduled for off-pump coronary artery bypass grafting or aortic surgery and patients with known coagulation disorders except after the use of aspirin, clopidogrel or low-molecular-weight heparin were excluded. The local institutional review board approved the study protocol, and all patients gave their written informed consent.

In the cell salvage group (CS, n=99), all blood collected from skin incision until closure of the sternum including cardiotomy suction blood and residual heart-lung machine blood was processed with a cell salvage device (CATS, Fresenius AG, Bad Homburg, Germany). In the control group (CONTROL, n=96), a cell salvage device was not used. Thus, conventional cardiotomy suction was used and the residual blood from the heart-lung machine was retransfused to the patient through a standard blood transfusion set. In both groups, no leucocyte depletion filter was used.

Anaesthesia and surgery

Anaesthesia was induced and maintained by intravenous infusion of propofol and supplemented with sufentanil. Ventilatory management was aimed at normocapnia throughout the operation and in the intensive care unit (ICU), with an inspiratory oxygen fraction of 0.4, a positive end-expiratory pressure of 6 cmH_2O and a tidal volume of 6-8 ml/kg. Patients were extubated when they met standard criteria (awake and haemodynamically stable with an arterial partial oxygen pressure greater than 9 kPa on minimal ventilatory support). Pulmonary function was measured by the duration of postoperative ventilatory support and the alveolar-arterial oxygen gradient ($Aa\text{-}O_2$ gradient).

Surgery and CPB were according to established routine procedures. The extracorporeal circuit consisted of roller pumps (Stöckert Instrumente GmbH, München, Germany), a hollow fibre oxygenator (Dideco, Mirandola, Italy) and a standard 40 μm arterial line filter (Medtronic, Inc., Minneapolis, MN, USA), and was primed with 1000 ml Lactated Ringer's solution and 500 ml hydroxyethylstarch 10% (Fresenius AG, Bad Homburg, Germany). Unfractionated heparin was used to obtain an activated clotting time of greater than 400 seconds. Temperature was allowed to drift to 34°C.

Biochemical measurements

Blood samples were taken after induction of anaesthesia (Pre-op), at sternal wound closure (Post-op), 1 h after arrival at the ICU (1h ICU), 3 h after arrival in the ICU (3h ICU), the morning of the first postoperative day (Day 1) and the morning of the second postoperative day (Day 2). Plasma was obtained by centrifugation of whole

blood at 1100×g for 10 min. Hereafter, plasma was aliquoted and stored at −80°C for later analysis.

Plasma concentrations of interleukin-6 (IL-6), Surfactant protein D (SP-D) and soluble receptor for advanced glycation endproducts (sRAGEs) were determined by sandwich ELISA according to manufacturer's specification (R&D Systems, Minneapolis, MN, USA). Elastase plasma concentration was determined by means of sandwich ELISA (Affinity Biologicals, Inc., Ancaster, ON, Canada). Elastase isolated from human donor leucocytes (Merck KGaA, Darmstadt, Germany) served as a standard. Myeloperoxidase (MPO) plasma concentration was also determined by means of sandwich ELISA (HyTest LTD, Turku, Finland). MPO isolated from human donor leucocytes (HyTest LTD, Turku, Finland) served as a standard. Clara cell 16 kDa protein (CC16) was measured in plasma by means of an in-house developed sandwich ELISA. Recombinant human CC16 (R&D Systems) served as a standard. A monoclonal rat antibody to human CC16 (R&D Systems) was used as a capture antibody and a monoclonal mouse antibody to human CC16 (Hycult, Uden, Netherlands) was used as a detection antibody. All measurements were normalized to correct for haemodilution.

Data and data analysis

All values are summarized as mean and standard deviation, or median and interquartile range in case of a non-normal distribution. Student's t-test was used to compare means of continuous variables, and when variables were non-normally distributed, the Mann-Whitney U-test was used. Contingency tables and χ^2-tests were used for categorical variables. Correlations were assessed with the Spearman rank correlation tests. A two-way mixed ANOVA was used to compare serial data between groups, timepoints or their interaction. Violations of sphericity were Greenhouse-Geisser corrected. All tests performed in order to test the (null-) hypothesis of no difference were two-sided. A probability value less than 0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

Demographics and surgical characteristics

There were no differences with respect to the baseline demographic data, preoperative variables and surgical characteristics between the groups (Table 5.1).

Table 5.1: *Demographic data*

Variable	CS (n = 99)	CONTROL (n = 96)	p value[a]
Age [years]	66 (10)	68 (9)	0.211
Height [cm]	174 (9)	171 (10)	0.066
Weight [kg]	82 (14)	79 (13)	0.190
Male [no.]	69 (69%)	62 (65%)	0.546
EuroSCORE	4.9 (3.2)	5.9 (3.6)	0.060
Procedure [no.]			0.127
Valve	26	15	
CABG	66	68	
Valve + CABG	7	13	
Coexisting illness [no.]			
COPD	15	12	0.612
Hypertension	45	43	0.971
Diabetes	30	18	0.096
Previous CVA	3	7	0.205
Previous MI	21	22	0.959
Preoperative medication [no.]			
β-Blockers	73	71	0.871
ACE inhibitors	54	38	0.062
Calcium-channel blockers	25	25	0.871
Aspirin	49	55	0.251
Statins	65	60	0.881

Data are presented as mean (standard deviation) unless stated otherwise. CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; MI: myocardial infarct; ACE: angiotensin-converting enzyme. [a] Student's t-test or Pearson's χ^2-test used as appropriate.

Clinical outcome

The use of a cell salvage device resulted in significantly shorter ventilation times than when no cell salvage device was used [10 (8-15) vs 12 (9-18) h, $p = 0.047$, Table 5.2]. The Aa-O_2 gradient increased after surgery and returned to baseline on Day 1 and showed no difference between the groups (Table 5.3, $p = 0.343$). Similarly, the PaO_2/FiO_2 ratio showed an opposite trend, decreasing after surgery and returning to baseline on Day 1. Furthermore, the use of a cell salvage device resulted in less patients being exposed to allogeneic blood ($p = 0.001$, Table 5.2). There were no significant differences between the groups concerning postoperative morbidity, ICU stay or hospital stay (Table 5.2), although the median hospital stay was 1 day shorter in the CS group.

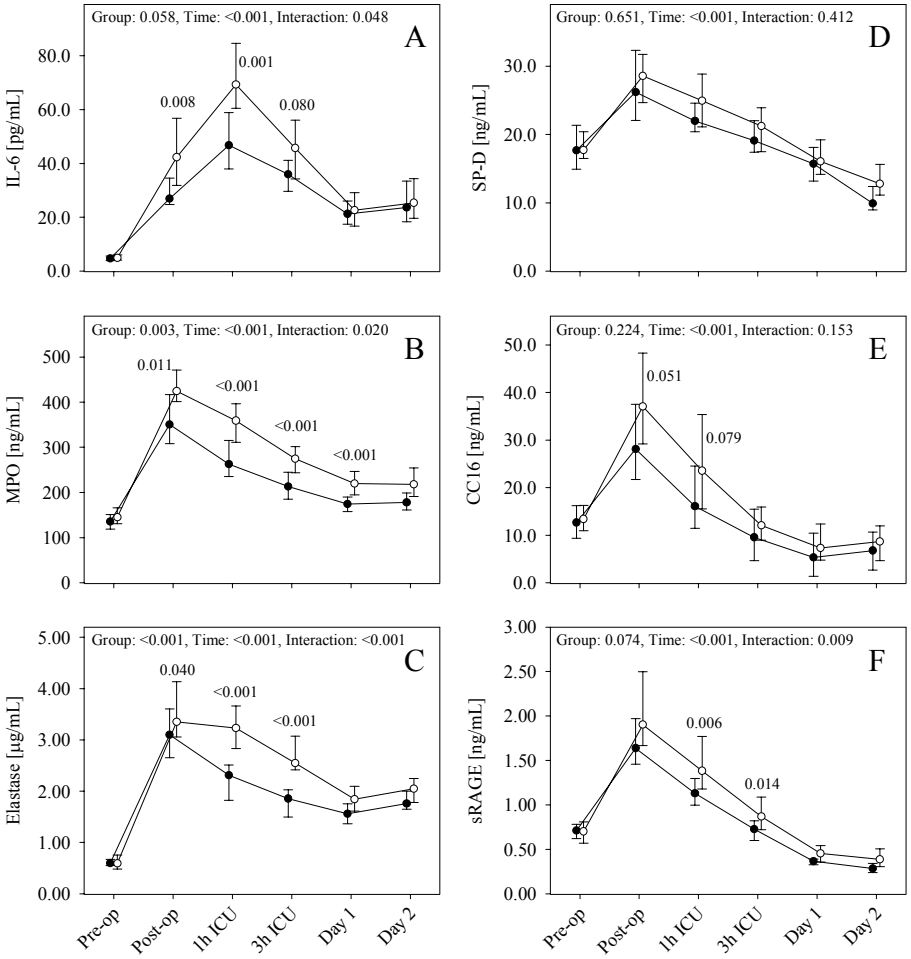

Figure 5.1: *The effect of cell salvage on serial measurements of plasma concentrations of biomarkers (median ± 95% CI) during cardiac surgery of (**A**) IL-6, (**B**) MPO, (**C**) elastase, (**D**) SP-D, (**E**) CC16 and (**F**) sRAGEs. Closed and open circles represent CS and CONTROL, respectively. Probability values depicted are from Mann–Whitney U-tests, testing for differences between groups at each individual time point. Additionally, probability values from two-way mixed ANOVA are depicted in the top of each subfigure. IL-6: interleukin-6; MPO: myeloperoxidase; SP-D: surfactant protein D; CC16: Clara cell 16 kDa protein; sRAGEs: soluble receptor for advanced glycation endproducts.*

Table 5.2: *Intra- and postoperative data*

Variable	CS (n = 99)	CONTROL (n = 96)	*p* value[a]
Intraoperative variables			
Cross-clamp time [min]	66 (29)	71 (31)	0.327
CPB time [min]	112 (45)	114 (50)	0.758
Allogenic blood exposure [no.]			0.001
None	57	31	
One or two units	23	31	
More than two units	19	34	
Residual volume HLM [ml]	972 (380)	1112 (474)	0.025
Fluid balance first 24 h [ml]	4031 (1925)	3962 (1647)	0.790
Postoperative morbidity [no.]			
Atrial fibrillation	36	35	0.498
Myocardial infarction	2	2	0.959
Cardiac dysrhythmia	6	9	0.363
Infections	10	12	0.844
Death	0	3	0.075
Ventilation time [h]	10 (8-15)	12 (9-18)	0.047
ICU stay [days]	1 (1-1)	1 (1-1)	0.425
Hospital stay [days]	8 (7-11)	9 (7-14)	0.107

Data are presented as mean (standard deviation) unless stated otherwise. ICU: intensive care unit; CPB: cardiopulmonary bypass. [a] Student's t-test, Mann–Whitney *U*-test or Pearson's χ^2-test used as appropriate.

Lung injury markers

Plasma concentrations of SP-D, CC16 and sRAGEs increased two- to three-fold by the end of operation (Figure 5.1D-F), after which concentrations returned to baseline and ended even lower than baseline concentrations on the first and/or second postoperative day.

Plasma concentrations of SP-D were not significantly different between groups during the study period. Postoperatively, CC16 plasma concentrations were higher in the CONTROL group than in the CS group [37.1 (18.0-65.5) vs 28.1 (7.3-53.2) ng/ml, respectively, $p = 0.051$, Figure 5.1E].

Plasma concentrations of sRAGEs were higher in the CONTROL group than in the CS group at 1 h in the ICU [1.13 (0.81-1.72) vs 1.38 (0.93-2.17) ng/ml, respectively, $p = 0.006$] as well as 3 h in the ICU [0.87 (0.56-1.32) vs 0.73 (0.48-1.02), respectively, $p = 0.014$, Figure 5.1F].

Plasma concentrations of CC16 showed an interesting association with ventilation

time (Table 5.4). The association got stronger with each successive time point.

Systemic inflammation markers

The plasma concentration of IL-6 increased three- to four-fold during operation (Figure 5.1A). Postoperatively, IL-6 concentrations were higher in the CONTROL group than in the CS group [42.3 (17.6-84.1) vs 27.0 (19.0-46.6) pg/ml, respectively, $p = 0.008$]. Plasma concentrations of Elastase increased almost six times during operation (Figure 5.1B). One hour in the ICU, the difference between the CONTROL group and the CS group was the largest [3.23 (2.41-4.44) vs 2.29 (1.39-2.85) μg/ml, respectively, $p < 0.001$]. Plasma concentrations of MPO exhibited a similar profile as that of Elastase (Figure 5.1C). Again, at 1 h in the ICU, the difference between the CONTROL group and the CS group was the largest [359 (256-426) vs 262 (210-372) ng/ml, respectively, $p < 0.001$]. During the study period, overall plasma concentrations of IL-6, Elastase and MPO were lower in the CS group than in the CONTROL group (Figure 5.1, $p = 0.048$, $p < 0.001$ and $p = 0.020$, respectively).

Haematological parameters and blood lipids

Leucocyte counts increased during and after surgery and overall counts were higher in the CS group than in the CONTROL group ($p = 0.022$, Table 5.3). Overall haemoglobin concentrations were also higher in the CS group ($p < 0.001$). Platelet counts were reduced in both groups at the end of operation and subsequently recovered; there were no differences between groups.

Subanalysis on chronic obstructive pulmonary disease status

Twenty-seven patients were documented for having chronic obstructive pulmonary disease (COPD), which comprised 14% of the study population. COPD was documented by prior physician's diagnosis, typical history, medication and occasionally additional spirometry before surgery. There was no difference in ventilation time between COPD patients and non-COPD patients [11 (8-16) vs 12 (8-16) h, respectively, $p = 0.677$]. Furthermore, COPD patients had similar ICU stay [1 (1-1) days] and hospital stay [9 (7-19) days].

The COPD patients also showed a similar profile in plasma concentrations of IL-6 (data not shown), but showed higher concentrations of MPO and Elastase throughout the whole study period, including the preoperative time point (Figure 5.2A and B). Interestingly, the lung injury biomarkers CC16 and sRAGEs showed lower postoperative

Table 5.3: *Blood cell counts, PaO_2/FiO_2 ratio and Aa-O_2 gradient*

Variable	Preop	Postop	1 h ICU	3 h ICU	Day 1	Day 2	p values[a] Groups	Time points	Interaction
Leucocytes (10^9/l)							0.538	<0.001	0.022
CS	5.6 (4.4-6.6)	10.0 (7.7-12.8)	12.4 (9.9-14.8)	13.6 (10.5-16.2)	14.7 (11.4-18.9)	15.5 (13.3-18.5)			
CONTROL	5.3 (4.2-6.6)	10.7 (7.8-13.2)	11.8 (9.1-15.5)	12.3 (9.9-15.1)	13.4 (11.1-16.7)	15.8 (13.7-19.5)			
Haemoglobin (mmol/l)							0.001	<0.001	<0.001
CS	7.46 (0.98)	5.02 (0.63)	6.05 (0.80)	6.37 (1.01)	6.55 (0.91)	6.48 (0.85)			
CONTROL	7.38 (0.98)	4.95 (0.60)	5.67 (0.70)	5.84 (0.80)	6.01 (0.74)	6.15 (0.76)			
Thrombocytes (10^9/l)							0.849	<0.001	0.113
CS	222 (176-249)	128 (101-157)	138 (114-176)	145 (113-184)	164 (118-200)	168 (126-194)			
CONTROL	198 (167-236)	124 (98-149)	141 (116-180)	151 (121-180)	158 (120-185)	153 (124-196)			
PaO_2/FiO_2 (mmHg)							0.549	<0.001	0.575
CS	289 (218-455)	231 (176-334)	239 (201-317)	279 (227-338)	234 (182-300)	NA			
CONTROL	328 (234-478)	247 (188-349)	255 (203-315)	271 (216-330)	272 (223-324)	NA			
Aa-O_2 gradient (mmHg)							0.343	<0.001	0.290
CS	116 (50-146)	151 (106-197)	136 (109-161)	126 (98-146)	131 (83-170)	NA			
CONTROL	102 (52-140)	141 (103-184)	139 (116-156)	129 (107-149)	114 (81-152)	NA			

Data are presented as mean (standard deviation) or median (interquartile range). NA: not available. [a] Two-way mixed ANOVA.

plasma concentrations in COPD patients than in non-COPD patients (Figure 5.2C and D).

Discussion

In this study, 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 sRAGEs and that it resulted in shorter postoperative mechanical ventilation times. We also found a reduction of systemic inflammatory mediators in the cell salvage group.

It is well known that CPB is responsible for an inflammatory reaction that leads to diffuse tissue injury and increased (pulmonary) vascular permeability [5]. In part this is caused by retransfusion of unwashed cardiotomy suction blood which is used as a basic blood conservation strategy. This retransfused blood has been shown to be pro-inflammatory [10] and detrimental to haemostasis [11]. When using mechanical cell salvage, the 'activated' plasma fraction of the shed blood is removed. This plasma fraction contains cytokines, leucocyte activation products, lipids and other pro-inflammatory mediators. We therefore used the cell salvage device to also process cardiotomy suction blood during CPB. This is different from most studies on intraoperative cell salvage; it has, however, been done before in order to minimize organ injury [12]. The benefits of this approach can be seen in the significant reduction in cytokines and systemic leucocyte degranulation enzymes in the CS group. The removal of cytokines and leucocyte degranulation enzymes in our study was in agreement with the results of others [6, 13].

One of the leucocyte degranulation enzymes, Elastase, has multiple effects on the respiratory epithelium; one of them is the reduction in integrity of the epithelium by cleaving E-cadherin [14]. At the end of the operation, this enzyme was higher in the control group than in the cell salvage group. Moreover, activated leucocytes generate and release reactive oxygen species [15], which also decrease the function of the endothelial barrier in the lung by disrupting intercellular tight junctions and redistribution of focal adhesions [16].

Another detrimental factor influencing lung function is reinfusion of lipid particles from the wound area into the circulation, which was possible in our CONTROL group. This could increase pulmonary dysfunction [17] and postoperative cognitive decline [12]. Although we did not formally measure unsaturated fatty acids, it is known that the cell salvage device used in this study (CATS) completely removes fat particles [18].

Indeed, we found a reduction in pulmonary dysfunction as indicated by lower CC16 and sRAGEs plasma concentrations and shorter mechanical ventilation in the CS group. The Aa-O_2 gradient, however, did not show any differences between groups. This could

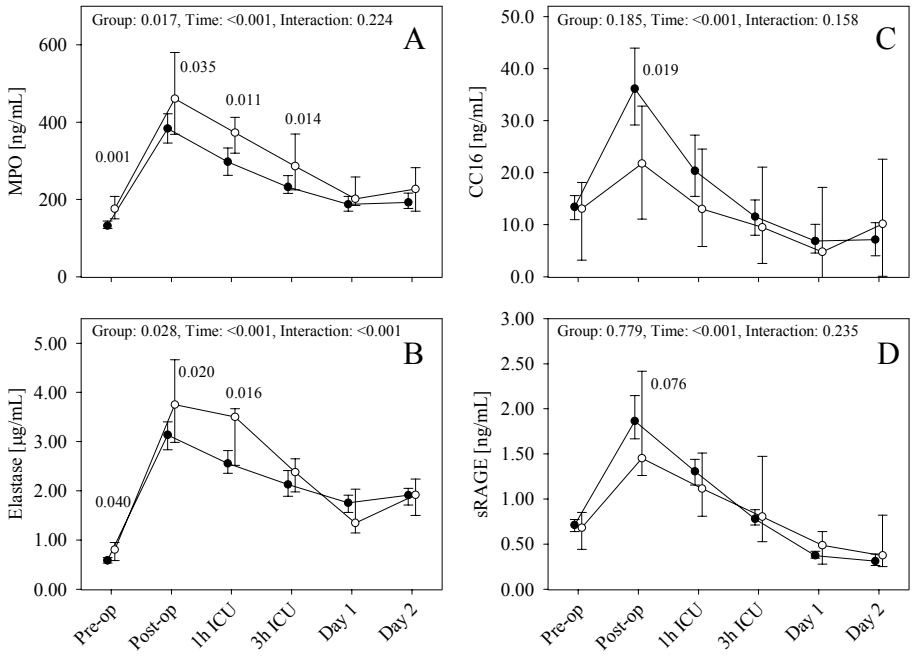

Figure 5.2: *The effect of COPD on serial measurements of plasma concentrations of biomarkers (median ± 95% CI) during cardiac surgery of (**A**) MPO, (**B**) Elastase, (**C**) CC16 and (**D**) sRAGEs. Closed and open circles represent non-COPD and COPD patients, respectively. Probability values depicted are from Mann–Whitney U-tests, testing for differences between groups at each individual time point. Additionally, probability values from two-way mixed ANOVA are depicted at the top of each subfigure. CI: confidence interval; MPO: myeloperoxidase; CC16: Clara cell 16 kDa protein; sRAGEs: soluble receptor for advanced glycation endproducts.*

indicate that this clinical marker is not always sensitive enough for assessing lung injury, as the formation of atelectasis is also an important factor for increasing the Aa-O_2 gradient.

The use of lung epithelium-specific protein concentrations as a measure for the permeability of the alveolar-capillary membrane has been shown in a rat model where acute lung injury was induced by infusion of lipopolysaccharides [19]. This resulted in increased plasma and decreased bronchoalveolar lavage fluid concentrations of CC16 and correlated with an increase of albumin in the bronchoalveolar lavage fluid. In healthy human subjects, plasma concentrations of CC16 also increased after inhalation of lipopolysaccharides, which was attributed to an increased permeability of the alveolar-

Table 5.4: *Association between CC16 plasma concentration [ng/ml] and ventilation time [h]*

Time point	All patients (n = 195)		Non-COPD (n = 168)		COPD (n = 27)	
	Spearman's ρ	p value	Spearman's ρ	p value	Spearman's ρ	p value
Preop	0.091	0.216	0.078	0.327	0.174	0.404
Postop	0.142	0.054	0.145	0.068	0.202	0.332
1 h ICU	0.159	0.030	0.135	0.088	0.303	0.132
3 h ICU	0.239	0.001	0.203	0.010	0.474	0.014

COPD: chronic obstructive pulmonary disease; CC16: Clara cell 16 kDa protein; ICU: intensive care unit.

capillary membrane [20].

Alveolar type I cells are the predominant source for sRAGEs and the protein is thought to aid in the removal and/or detoxification of proinflammatory products [21]. By binding these proinflammatory ligands, activation of cell surface-bound RAGEs is prevented. As a lung injury marker, increased plasma concentrations of sRAGEs are associated with a higher pulmonary leak index, indicating increased permeability of the alveolar-capillary membrane [22]. Our results also suggest that injury to the respiratory epithelium and subsequent disruption of the alveolar-capillary membrane increases its permeability, resulting in leakage of lung epithelium-specific proteins into the circulation. However, in the absence of concurrent measurements in bronchoalveolar lavage fluid, the conclusions that can be drawn from these data are limited.

On the other hand, one could argue that the concentration differences were not the result of injury to the alveolar-capillary membrane due to the reinfusion of unwashed blood, but simply due to the washing of the blood (removing lung epithelium-specific proteins) in the CS group. However, we showed that plasma concentrations of CC16 early on the ICU were associated with the postoperative ventilation time of patients. This would indicate that CC16 is indeed a marker of lung injury and that concentration differences between groups are not just the result of simply washing the blood but are more likely due to a difference in injury to the alveolar-capillary membrane.

Acute environmental exposure to noxious particles or gases (e.g. cigarette smoke) can cause short-term increases of CC16 and sRAGE plasma concentrations. Repeated exposures, however, can result in chronically decreased CC16 [23, 24] and sRAGEs plasma concentrations [25]. Furthermore, these clinical studies showed that CC16 and sRAGEs concentrations were associated with COPD prevalence and severity. Although baseline concentrations were not different, we noticed a diminished increase in CC16 and sRAGEs in reaction to cardiac surgery and anaesthesia in the COPD patients as opposed

to the non-COPD patients. Together with a higher inflammatory load of MPO and elastase, this could indicate a compromised protection of the respiratory system. Reduced lung injury markers along with higher inflammation markers makes the interpretation of lung injury markers more difficult in this subgroup. Furthermore, the absolute CC16 concentrations were lower in the COPD group than in the non-COPD group, whereas the association between CC16 concentration and ventilation time was stronger in the COPD group, adding to the difficulty of interpreting this biomarker. Despite the fact that our study was not designed nor sufficiently powered to evaluate the influence of COPD, these findings do warrant further investigation.

In summary, the intraoperative use of a cell salvage device, including salvage of cardiotomy suction blood, is associated with less lung injury in patients after cardiac surgery. The device washed out inflammatory mediators and lipids from shed blood. This in turn reduced injury to the alveolar-capillary membrane as shown by lower concentrations of lung epithelium-specific proteins. Moreover, this clinical study showed that the use of a cell salvage device shortened mechanical ventilation.

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