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Surfactant and lung function following cardiac surgery

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Introduction

Cardio-pulmonary bypass (CPB) is associated with prolonged mechanical ventilation (PMV) in the intensive care unit (ICU),[1] and an increase in morbidity and mortality.[2] Surfactant dysfunction could result in atelectasis and contribute to PMV.[3] However, it is unclear whether cessation of mechanical ventilation, with resultant atelectasis, and the use of a foreign bypass circuit during CPB, would affect the concentration of surfactant constituents and whether this, in turn, is associated with PMV.

Pulmonary surfactant, which increases lung compliance and opposes atelectasis by reducing alveolar surface tension,[4] is produced in the lung by alveolar type II cells. It is comprised of 10% protein[4], predominantly the surfactant proteins A, B, C & D, and 90% phospholipid, which can be separated into large surfactant aggregates (LA) and small surfactant aggregates (SA).[5] LA, the metabolic precursors to SA, are the greatest contributors to reduction of surface tension.[5]

In models of acute lung injury, LA are disproportionately converted to SA, resulting in an increased SA:LA ratio.[6] This depletion of LA stores is associated with decreased lung compliance and function.[6] Normal surfactant functioning and production is an important contributor to decreasing atelectasis and the need for PMV.[7] Intra-operative atelectasis, accompanied by inflammation in the alveoli, has been associated with reduced intra-operative gas exchange, and the need for PMV.[8]

During CPB, ventilation is often ceased allowing the lungs to collapse to functional residual capacity (FRC) for prolonged periods. In addition, exposure of patient blood to the foreign bypass circuit may result in the systemic inflammatory response syndrome (SIRS), which is also a significant contributing factor to surfactant concentration and activity, and therefore atelectasis.[9]

The purposes of this study are to examine the effect of CPB during cardiac surgery on surfactant composition and whether changes are associated with decreased respiratory function and prolongation of mechanical ventilation in these patients. Specifically, we aimed to examine the effect of both cessation of mechanical ventilation and the effects of the bypass circuit (extracorporeal circulation) on the above factors. Respiratory function was assessed by using the post-operative ratio of the partial pressure of oxygen in arterial blood (PaO_2) to the fraction of inspired oxygen (FiO_2) and the length of mechanical ventilation. We hypothesized that CPB would be associated with an increase in SA concentration, and thereby an increase in the SA:LA ratio among cardiac surgery patients, compared to patients undergoing cardiac surgery without CPB, and that this change in surfactant composition would be associated with more prolonged mechanical ventilation in the CPB group.

Methods

Overview

This retrospective exploratory study extends our previous examination of lung surfactant in chronic heart failure (CHF) patients, compared to non-CHF patients, immediately prior to cardiac surgery at Flinders Medical Centre in South Australia.[10] This study is an analysis of the data collected from the previous study, with a specific focus on the use of CPB and the effects on lung functioning.

Twenty patients (10 with CHF and 10 with no CHF) were recruited in the previous study, and underwent pre-operative bronchoalveolar lavage (BAL). Patients in the previous study differed clinically only in parameters of CHF, and the aim was to determine whether surfactant composition (SA, LA and surfactant protein B) differed in patients with CHF and non-CHF after cardiac surgery.[10] It was found that there was no difference in surfactant composition between the two groups.[10] For the previous study, the inclusion and exclusion criteria, management of cardiac surgery patients, CPB and off-pump procedure, bronchoalveolar lavage sampling and surfactant analysis are

Abbreviations: CPB, cardio-pulmonary bypass; PMV, prolonged mechanical ventilation; ICU, intensive care unit; LA, large surfactant aggregates; SA, small surfactant aggregates; FRC, functional residual capacity; SIRS, systemic inflammatory response syndrome; PaO_2, partial pressure of oxygen in arterial blood; FiO_2, fraction of inspired oxygen; CHF, chronic heart failure; BAL, bronchoalveolar lavage; CABG, coronary artery bypass graft; IU, international unit; PEEP, positive end-expiratory pressure; NYHA, New York Heart Association; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; ELF, epithelial lining fluid; LVEDD, left ventricular end-diastolic diameter; E:A, mitral valve inflow E-wave velocity:mitral valve inflow A-wave velocity

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mentioned below since the current study is based on the previous study.

This study complies with the Declaration of Helsinki. The Southern Adelaide Clinical Human Research Ethics approved the protocol and all participants provided written informed consent.

Inclusion and exclusion criteria

Patients were assessed for suitability in the previous study. For the inclusion criteria in the previous study, patients needed to be ≥18 years of age and be admitted to undergo coronary artery bypass graft (CABG) and/or valvular surgery at Flinders Medical Centre, Adelaide, South Australia. Patients needed to be inactive smokers, defined as having quit smoking more than 6 months previous. In the previous study, patients with CHF needed to have a clinical diagnosis of ambulatory stable CHF of at least 6 months duration, however this was not an inclusion criteria in the current study since the primary analysis was not assessing CHF.

Exclusion criteria for the previous study included the presence of primary respiratory co-morbidities, end-stage renal failure, neuromuscular disease, active smoking (including having quit ≤6 months ago), or hospitalization with CHF or myocardial infarction within the previous 6 weeks.

Rationale for sample size

The rationale for the sample size is based on the previous study. Sample size for the previous study was based on surfactant content examined between the two groups (CHF and non-CHF) using Independent Samples t Test.[10] Based on an effect size (d) of 1.41[11] between the CHF and non-CHF groups, and an $\alpha = 0.05$ and $\beta = 0.80$, 9 subjects per group were required[10]. To allow for increased variance in clinical subjects the aim was to enroll 12 patients per group in the previous study, however given the strict inclusion and exclusion criteria, 20 patients were recruited altogether in the previous study.[10]

Data collected for these 20 patients were used in the current study. A further two patients were included in the current study, who did not meet the strict definition of CHF for the previous study but who met the other inclusion and exclusion criteria. These two patients were included in the current study since the primary analysis of this study was not assessing CHF.

Procedures

Management of cardiac surgery patients

Premedication with temazepam or lorazepam preceded induction of general anesthesia in both groups. Induction was with fentanyl, midazolam and pancuronium, supplemented with sevoflurane and/or propofol. CPB patients had a standard heparinization protocol, with 300 international units (IU) per kg heparin bolus prior to venous cannulation, 10,000 IU in CPB pump prime, with a target activated-clotting time of >400 seconds pre-CPB. Off-pump patients received a stat dose of 10,000 IU heparin prior to commencement of CABG, with a target activated-clotting time of >200 s.

CPB procedure

The patients in this study were assigned by the treating cardiac surgeon to undergo CPB or off-pump cardiac surgery based on best practice principles for each patient and not for the study purposes. Lungs were deflated during CPB. Left internal mammary artery conduit was harvested using a similar method in both CPB and off-pump CABG surgery.

CPB using a S5 arterial roller pump (LivaNova™PLC, UK), was instituted after positioning of an ascending aortic (arterial) and venous (single two-stage atrial or bicaval) cannulae. The circuit included a hard-shell membrane oxygenator (Capiox® RX25, Terumo Corporation), biopassive tubing (Phisio, LivaNova™ PLC, arterial circuit 3/8" venous 1/2"), a 40 μm arterial line filter (AL40, Pall Corporation, Port Washington, NY) and a 0.2 μm pre-CPB filter (Prebypass Plus®, Pall Corporation). The circuit was primed with 1 L Plasmalyte solution, 500 mL of Gelofusine (CABG) or 4% albumin (aortic valve replacement), 50 mL 8.4% sodium bicarbonate solution, 50 mL Hartmann's solution, and 10,000 IU Heparin.

Before initiation of CPB, retrograde autologous priming was performed with a target volume of 250 mL if the predicted CPB hemoglobin level was <11 g/dL. CPB management included arterial non-pulsatile target flow rate of 1.8–2.4 L/min/m^2, alpha-stat pH management with target PaO_2 100–250 mmHg, gravity venous drainage, and tepid systemic temperature management (nasopharyngeal temperature 34–35 °C) with no active cooling and mean arterial pressure target of 40–80 mmHg.

After placement of the aortic cross-clamp, cardioplegic arrest was induced with tepid (34 °C) hyperkelemic blood cardioplegia (30 mmol/L) at induction and maintained with intermittent doses (16 mmol/L) delivered either anterograde or retrograde as required. Target nasopharyngeal temperature for separation from bypass was >36 °C with rewarming rate <0.5 °C per 2 min and arterial outlet temperature <37 °C.

Transfusion of red blood cells during CPB was triggered when hemoglobin level was <7 g/dL. Restrictive IV fluid administration was used routinely intra-operatively. Routinely shed mediastinal blood was collected using cell salvage (Xtra, LivaNova™ PLC) in isolated CABG procedures, and cardiotomy suction and cell salvage in procedures other than isolated CABG. Salvaged blood was processed if sufficient volume was available for processing or when residual CPB circuit blood was processed (if last CPB hemoglobin was <9 g/dL), otherwise residual circuit blood was returned to the patient via IV infusion.

Off-pump procedure

Off-pump cardiac surgery was performed through a median sternotomy. Coronary targets and hemodynamics were assessed prior to conduit harvesting, and a restrictive fluid protocol maintained by anesthesia, acknowledging some fluid loading may be required to undertake off-pump CABG surgery. In all patients, stabilization was achieved with the Octopus stabilizing device (Medtronic, Minneapolis). Distal anastomoses were performed with the use of flow-through shunts, and were performed in a similar manner with 6-0 or 7-0 polypropylene sutures. Inferior wall targets were grafted first, followed by lateral, then anterior left-ventricular territories. Proximal anastomoses were performed with partial aortic clamping using a side biter clamp. Temperatures were maintained throughout the procedure by utilizing a combination of a Bair Hugger™ system (3M™, USA), warming blanket, hot line fluid warmer, and humidified ventilation circuit.

Patients treated off-pump received mechanical ventilation including positive end-expiratory pressure. Intermittent periods of reduced ventilation and apnea were required during surgery.

Variables and measures

Patient profile (age, gender, smoking status, co-morbidities and medications), and current diagnostic details including pre-operative echocardiographic parameters, New York Heart Association class, and the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) scores were recorded. The EuroSCORE II utilizes objective risk factors for early mortality in cardiac surgical patients, and is based on one of the largest and most accurate databases in European cardiac surgical history, with a high published validity.[12] Data for the EuroSCORE II came from medical records and patient history. All factors contributing to the EuroSCORE II were individually and independently collected and were recorded in a Cardiothoracic Unit database

at Flinders Medical Centre. This database is subject to regular audits and reviewed as part of quality and safety standard maintenance.

Post-operative clinical outcomes were recorded for patients, which included length of mechanical ventilation (both intra- and post-operative), PaO_2:FiO_2 ratio, ICU and hospital total length of stay. Post-operative chest X-ray scores were based on the Murray Score for Acute Lung Injury.[13] This independently validated score incorporates consolidation on the chest X-ray, the PaO_2:FiO_2 ratio, the level of PEEP used, and the lung compliance (mL/cmH_2O), to provide a measure of the severity of acute lung injury[14] and is routinely used in ICU settings to help select patients for extracorporeal membrane oxygenation. The score ranges from 0 to 4, with a higher score indicating increasing severity of lung injury.[14]

BAL was performed pre- and post-operatively. Whilst under anesthesia, 60 mL of sterile saline was instilled into the wedged subsegmental middle lobe or lingual bronchus and withdrawn. During BAL the patient was placed on a FiO_2 of 1.0 and the pulse oximeter oxygen saturation continuously monitored. A single pre-operative venous plasma sample was also obtained from all participants for quantification of urea (Quantichrom™ Urea Assay Kit, BioAssay Systems, CA).

Pre- and post-operative BAL samples were analysed for surfactant lipid and protein content (SA, LA, and total protein), as previously described.[10] Briefly, BAL was centrifuged at 150×*g* for 5 min at 4 °C to pellet cells. BAL supernatant was assayed for urea, and total soluble protein (Micro BCA™ Protein Assay Kit, Pierce Biotechnology, IL). The remaining BAL supernatant was centrifuged for 5 min at 40,000×*g* to separate LAs and SAs. Lipid was extracted and total phosphorous quantified, as previously described[15]. Limit of detection for this assay is 0.2 ug P and the coefficient of variation for intra-assay = 4.8%, and inter-assay = 9.8%. Epithelial lining fluid (ELF) content of the BAL was estimated using plasma and BAL urea concentration.[16]

Data collection

Pre-surgery BAL was collected after induction of anesthesia but before the start of cardiac surgery. Post-surgery BAL was collected when the patient was clinically stable within the first 2 h after the cardiac surgery, before they were extubated.

Surgical and anesthetic data were independently and prospectively collected during the cardiac surgery procedure, by two experienced research nurses, to account for inter-rater reliability. The remaining data (length of mechanical ventilation, ICU and hospital length of stay, PaO_2:FiO_2 ratio and EuroSCORE II) were obtained from databases established by the ICU and Cardiothoracic Unit at Flinders Medical Centre, South Australia. These data were independently collected by multiple trained data collectors for the purpose of audit and is unlikely to be subject to bias for the purpose of this study. These databases undergoes automated internal validation processes in addition to on-site audits by trained auditors from the Australian and New Zealand Intensive Care Society, which indicate that these data are generally of high completeness, reliability and consistency.

Chest X-rays and arterial blood gas samples were done as soon as the patient arrived at the ICU after the cardiac surgery. The Murray Score for Acute Lung Injury was individually calculated by the investigator for the purpose of this study.

Statistical methods

Data collected both pre- and post-procedure was retrospectively analysed, and statistical analyses performed to compare both groups. Statistical analyses were performed using PASW 23.0 software (SPSS Inc., Chicago, IL). Normalized data was detected using a Quantile-Quantile plot, skewed data was normalized using logarithmic transformations and outliers were detected using the Grubbs' test and subsequently removed.

Linear Mixed Models Analysis was used to assess whether the change in concentration of bronchoalveolar surfactant constituents in ELF from the pre- to post-operative period within the CPB and off-pump groups was statistically significant between the groups. The assumptions for the use of this analysis were assessed and the data log were transformed where necessary. The analysis involved the concentration of LAs and SAs and SA:LA ratio as the dependent variables, and the following were the independent variables: CBP vs off-pump surgery (group effect) and pre- and post- surgery (time effect). The 'fixed effects' for this analysis were group, time and group*time for the interaction model. The 'repeated effect' was time; compound symmetry was used for the 'repeated covariance type', and the 'covariance structure' was diagonal.

Relationships between continuous variables were examined by Spearman's Rank Correlation Coefficient. Mann–Whitney *U* test was applied for the pre- and post-operative analysis of variables between the two groups. Between groups comparisons of categorical variables were examined using Pearson's Chi-Square Test. A p-value ≤ 0.05 was used as the standard for statistical significance.

The use of inhaled anesthetic agents and CPB circuit primers were not used as covariates in this study, since we did not have access to this data (type and amount of anesthetic agents and CPB circuit primers). We did not include the severity of CHF, or the presence of other co-morbidities such as diabetes, the smoking status, or the use of certain medications as covariates in this study due to the small sample size.

Results

Of the total 22 patients included in this retrospective analysis, 15 patients received CPB and 7 received off-pump surgery (Table 1). The median EuroSCORE II and proportion of patients with NYHA III was not significantly different between groups (Table 1). Clinically diagnosed heart failure was identified at admission in nine patients in the CPB group (60%) and only two patients in the off-pump group (29%). This resulted in greater left atrial area, left ventricular end diastolic diameter and mitral valve inflow E-wave velocity: mitral valve inflow A-wave velocity in the CPB group (Table 1).

There was no difference in BAL small aggregate concentration between the two groups (Fig. 1A). A significant difference in BAL large aggregate concentration per mL ELF between the off-pump and CPB groups ($p = 0.003$, Fig. 1B) may have contributed to a trend toward an increase in the small to large aggregate ratio in the CPB group ($p = 0.051$; Fig. 1C).

The duration of CPB was 73.7 ± 20.53 min (mean ± SD). Intra-operative fluid balance was higher and length of mechanical ventilation longer in the CPB group (Table 2). However, this was not associated with an increase in ICU or hospital total length of stay. No other clinical parameters were significantly different between the groups, including duration of surgery (Table 1: median of 235 (192–285) min for the CPB group and 220 (210–315) min for the off-pump group; $p = 0.91$).

Discussion

In this retrospective exploratory study, we examined the effects of CPB (both cessation of mechanical ventilation and the effects of the bypass circuit) during cardiac surgery, on surfactant composition and whether changes were associated with a decrease in respiratory function (including PaO_2:FiO_2) and resultant prolongation of mechanical ventilation in these patients. The implementation of CPB during cardiac surgery was associated with changes in alveolar surfactant, which may contribute to the increase in time on mechanical

Table 1
Clinical and demographic characteristics of the sample.

	Off-pump	CPB	*P*
n	7	15	
Age (years)	76 (64–78)	73 (59–80)	0.80
Gender (male)	4 (57%)	13 (87%)	0.12
Ex-Smoker (quit for >5 years)	5 (71%)	6 (40%)	0.22
Co-Morbidities			
Hypertension	6 (71%)	7 (47%)	0.23
Diabetes	1 (14%)	5 (33%)	0.35
Atrial Fibrillation	Nil	2 (13%)	0.31
Medications			
ACE Inhibitors	4 (57%)	9 (60%)	0.90
ARB	3 (43%)	3 (20%)	0.26
β-Blocker	6 (86%)	9 (60%)	0.23
Spironolactone	Nil	4 (27%)	0.13
Loop Diuretic	2 (29%)	8 (53%)	0.23
Statins	5 (71%)	10 (67%)	0.82
Aspirin	6 (86%)	11 (73%)	0.52
Calcium antagonists	2 (29%)	2 (13%)	0.39
Digoxin	1 (14%)	Nil	0.13
Clopidogrel	1 (14%)	5 (33%)	0.35
Clinical parameters			
EuroSCORE II	2.1 (0.7–2.3)	1.6 (0.7–2.1)	0.94
NYHA III	1 (14%)	7 (47%)	0.14
CABG	7 (100%)	10 (67%)	**0.02**
Aortic valve replacement	Nil	5 (33%)	0.08
Mitral valve surgery	Nil	2 (13%)	0.31
Combined surgery	Nil	2 (13%)	0.31
Duration of surgery (minutes)	220 (210–315)	235 (192–285)	0.91
Echocardiographic parameters			
Ejection Fraction (%)	55 (40–66)	60 (45–69)	0.59
E:A	0.7 (0.6–0.8)	1.2 (0.9–1.9)	**0.00**
E:E'	14.0 (7.5–16.8)	16.0 (9.6–21.0)	0.31
LVEDD (cm)	4.6 (4.6–5.1)	5.0 (4.9–6.1)	**0.04**
Left atrium area (cm^2)	17 (17–23)	24 (20–27)	**0.01**
TR gradient (mmHg)	21.0 (19.5–42.5)	37.0 (29.5–43.8)	0.33

Total sample size: 22 patients. Data are presented as median (25th–75th percentiles) and analysed by Mann–Whitney *U* test and categorical variables as number (%) and analysed by Pearson's Chi-Square Test using PASW 22.0 software (SPSS Inc., Chicago, IL). $p \leq 0.05$ are highlighted in bold. ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; NYHA, New York Heart Association; CABG, coronary artery bypass graft; E:A, mitral valve inflow E wave velocity:mitral valve in flow A wave velocity; E:E', mitral valve in flow E wave velocity:mitral annular velocity; LVEDD, left ventricular end diastolic diameter; TR, tricuspid regurgitation.

ventilation in this group. Specifically, there was a decrease in the LA concentration in ELF from pre- to post-surgery with an increase in the BAL SA:LA ratio, which is a novel finding for the adult population undergoing CPB for cardiac surgery. Despite a greater percentage of CHF patients in the CPB group, the median EuroSCORE II and proportion of patients with NYHA III was not significantly different between groups, which allowed independent analysis of the effect of CPB on lung function.

The increase in the BAL SA:LA ratio post-operatively in patients receiving CPB is a pattern observed in an acute lung injury model as a reaction to lung inflammation.[7] This similar process may be occurring in patient lungs post-CPB, whereby LA are disproportionately converted to SA to aid in reduction of surface tension[6]. These findings are consistent with a study in the paediatric population where LA concentration in BAL decreased after CPB, resulting in an increase in BAL SA:LA ratio.[17]

Lung inflammation and injury induced by the cessation of mechanical ventilation and SIRS during CPB may result in dysfunction of alveolar type II cells, inactivation of LA by lung oedema and, or, leakage of LA across an inflamed alveolar capillary membrane,[18] increasing the lung SA:LA ratio in the CPB group, resulting in PMV. Patients treated off-pump received mechanical ventilation including PEEP, which potentially reduced the degree of atelectasis and maintained LA production due to the application of stretch to the alveoli,[19] and may have in a relatively lower SA:LA ratio compared to the CPB group. It is likely a combination of these parallel influences are involved, and should be addressed in further studies with a larger sample size.

While CPB may be expected to exacerbate lung injury due to atelectasis, re-perfusion injury and SIRS, studies also indicate that lung injury during cardiac surgery may be due to anesthetic and surgical techniques, independent of the use of CPB,[20–22] Factors hypothesized to be associated with lung injury included direct contact with the lungs during cardiac surgery, inflammation induced by surgical trauma, high oxygen concentrations with a fixed tidal volume, and the effects of anesthetic drugs on surfactant function.[20,22] Atelectasis may also occur in off-pump patients due these factors, as well as changes in chest wall and alveolar compliance during mechanical ventilation.[23] Furthermore, inhaled anesthetic agents are associated with a reduction in surface tension lowering capacity and exert damage on surfactant-producing alveolar epithelial cells.[24] These variations in the use of anesthetic and surgical techniques would be difficult to control for, but future studies designed to compare standardized surgical and anesthetic protocols are required in order to adequately elucidate the individual contributions of each of these factors.

The CPB group had a significantly greater intra-operative fluid balance which could be related to the hemodilution and systemic heparinisation used during CPB.[25] A more detailed analysis of the volume of fluids administered intra-operatively could not be undertaken given that we did not have access to types of fluids administered, volume of blood loss, as well as volume of heparin used in the CPB group. This would need to be further evaluated in future studies, since hemodilution is associated with an increase in interstitial edema in organs such as the lungs, possibly contributing to surfactant dysfunction, atelectasis and PMV in this cohort.[25] The finding for intra-operative fluid balance could have also been explained by a greater duration of surgery in the CPB group, which would result in a greater volume of fluids administered. However, the groups did not differ significantly in the duration of surgery (Table 1). It was expected that the CPB group would have a greater duration of surgery given the complexity of the CPB procedure.

Previous studies have demonstrated longer hospital and ICU stays[26] and decreased PaO_2:FiO_2 post-operatively[27] in patients receiving CPB compared to off-pump CPB. In our study, the CPB group did not have more severe lung injury, as indicated by the Murray Score for Acute Lung Injury and maximum/minimum PaO_2:FiO_2 in the first 24 h post-operatively, nor did they have longer ICU or hospital total length of stay. These results were unexpected, given the findings of the changes to LA concentration and longer length of mechanical ventilation in the CPB group. It is possible that this is due to the sample size being too small and group sizes being unbalanced, which would make it difficult to detect significant results for these factors.

Off-pump patients in our study receiving PEEP during the surgery had a shorter length of mechanical ventilation, suggesting a requirement for future studies examining the effect of PEEP (during or after CPB) on surfactant concentrations and length of mechanical ventilation in patients receiving CPB.

Overall, the difference in length of mechanical ventilation and LA surfactant concentrations between the CPB and the off-pump group may be related to three main factors found in this study. These are, lung deflation to FRC during cessation of mechanical ventilation during CPB, SIRS induced by CPB due to a foreign circuit and reperfusion injury, and, or, greater intra-operative fluid balance in the CPB group. These factors may be associated with surfactant dysfunction, atelectasis and PMV.

Limitations

The small sample size and unbalanced group sizes are the greatest limitations of this study, and could have limited the ability to find

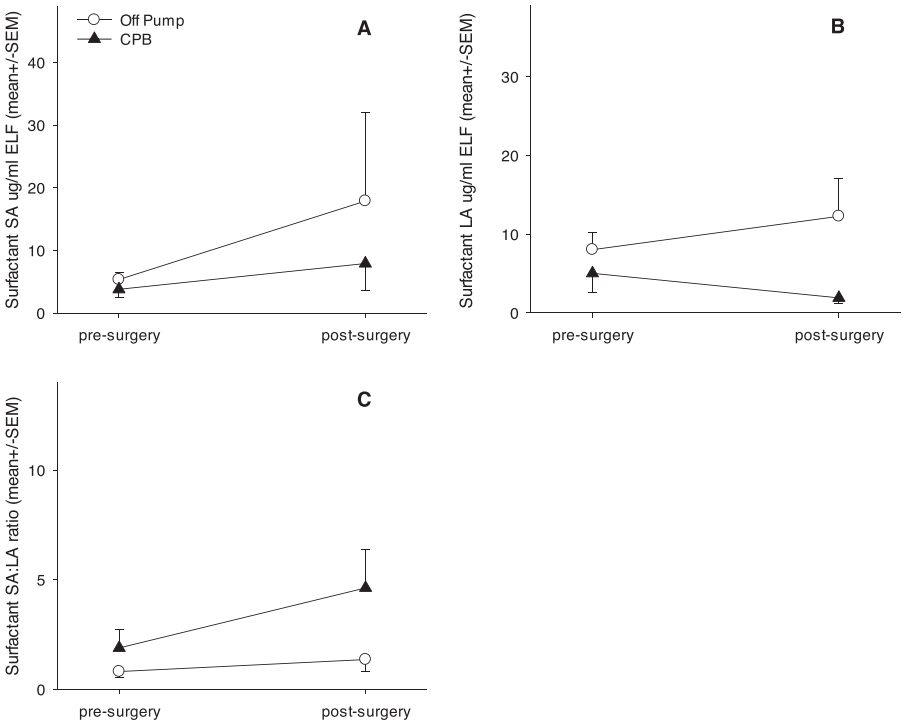

Fig. 1. Bronchoalveolar surfactant components in epithelial lining fluid (ELF) comparison between CPB and off-pump group pre- and post-surgery analysed using linear mixed models. Group = CPB vs off-pump; Time = pre-surgery vs post- surgery: (A) Small aggregates (SAs), *P* values – Group = 0.368, time = 0.199, group*time = 0.509, (B) large aggregates (LAs), *P* values – Group = 0.003, time = 0.483, group*time = 0.294, (C) small to large aggregate ratio (SA:LA), *P* values – Group = 0.051, time = 0.133, group*time = 0.308.

significant relationships in the data. Future studies would need to involve a larger sample size, more even patient numbers between groups and greater homogeneity of patient cohorts with stricter inclusion and exclusion criteria. The variations in anesthetic and surgical techniques were difficult to control for in this study, and thus further studies would need to involve a standardized anesthetic and surgical protocol. The limitation to a single post-operative sample of BAL decreases the ability to discern temporal changes associated with CPB on surfactant. However, repeated sedation and BAL sampling may not be feasible given the unstable state of many patients post-operatively.

Table 2
Intra- and post-operative clinical outcomes for the sample.

	Off-pump	CPB	p
n	7	15	
Intraoperative fluid balance (ml)	525.0 (200.0–1198.9)	1760.0 (1220.0–1965.0)	**0.01**
PaO_2:FiO_2 min first 24 h	122.8 (48.0–186.0)	52.5 (44.0–84.0)	0.16
PaO_2:FiO_2 max first 24 h	405.7 (278.6–464.0)	373.7 (263.8–407.1)	0.25
Plasma Creatinine max 24 h (μmol/L)	79 (74–98)	87 (79–125)	1.00
Plasma Bilirubin max 24 h (μmol/L)	14 (7.0–19)	16 (13–25)	0.15
Plasma CK max 24 h (IU/L)	323 (253–546)	379 (249–476)	0.29
MV length (intra- to post-operative) (h)	9.3 (7.9–20.7)	16.3 (11.5–94.4)	**0.02**
ICU LOS (h)	24.5 (21.1–121.3)	51.3 (24.0–163.0)	0.31
Hospital LOS (days)	6 (6–8)	7 (5–15)	0.59

Total sample size: 22 patients. Data are presented as median (25th–75th percentiles) and analysed by Mann–Whitney *U* test using PASW 22.0 software (SPSS Inc, Chicago, IL). $p \leq 0.05$ are highlighted in bold. Hb, hemoglobin; PaO_2:FiO_2, partial pressure of oxygen in arterial blood to fraction of inspired oxygen ratio; CK, creatine kinase; MV, mechanical ventilation; ICU, intensive care unit; LOS, length of stay.

It was difficult to exclude patients with heart failure given that the sample size was small. CHF is independently associated with PMV,[28] since there is associated interstitial edema and reduced alveolar-capillary gas diffusion in CHF patients.[29] Further studies would need to use the severity of heart failure as a covariate, as well as the presence of co-morbidities such as diabetes, smoking status, or the use of certain medications as covariates in this study.

The use of inhaled anesthetic agents, CPB circuit primers and types and quantities of fluids administered intra-operatively were not used as covariates in this study, as we did not have access to this data, which is a limitation in this study. The CPB group had a significantly greater intra-operative fluid balance, which could not be explained by the duration of surgery since this was not significantly different between groups (Table 1). The small sample size might have limited the ability for us to find a significant difference in duration of operation between groups. It is important that future studies assess the type and quantity of inhaled anesthetic agents, CPB circuit primers and intra-operative fluids.

Conclusion

In this retrospective exploratory study, there was a difference in pulmonary surfactant LA concentration following cardiac surgery in patients who underwent CPB compared to those treated without the use of CPB (off-pump). This is a novel finding in adult patients undergoing CPB. This difference in the more surface-active component of surfactant in the CPB group may be associated with the longer length of mechanical ventilation in the ICU in CPB patients found in this study. This observation warrants confirmation with larger cohorts. Future studies should include examining the effect of PEEP and lung recruitment versus lung deflation on surfactant concentrations for patients receiving CPB, and whether this reduces the length of mechanical ventilation.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.hrtlng.2018.08.004.

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