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# Early, Low-Dose Pulmonary Surfactant Administration in Infants with Post-Cardiotomy Acute Respiratory Distress Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial

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# Abstract

**Background:** Acute respiratory distress syndrome (ARDS) following cardiopulmonary bypass (CPB) in infants is associated with high morbidity and mortality, driven in part by surfactant dysfunction. While exogenous surfactant is a mainstay for neonatal respiratory distress syndrome, its efficacy in pediatric ARDS remains unproven. This study tested the hypothesis that early, low-dose surfactant therapy improves outcomes in infants with post-cardiotomy ARDS.

**Methods:** In this single-center, double-blind, randomized, placebo-controlled trial, we enrolled infants (≤3 months; weight ≤6 kg) who developed moderate-to-severe ARDS ($PaO_2/FiO_2$ ≤300 mmHg by PALICC-2 criteria) within 6 hours after CPB. Participants were randomly assigned (1:1) to receive a single endotracheal dose of surfactant (15 mg/kg) or an equivalent volume of saline placebo within 24 hours postoperatively. The primary outcome was the duration of invasive mechanical ventilation. Secondary outcomes included lengths of pediatric intensive care unit (PICU) and hospital stay, oxygenation indices, and safety.

**Results:** Between August 2023 and August 2025, 128 infants were included in the intention-to-treat analysis (65 surfactant, 63 placebo). Groups were well-balanced at baseline. Surfactant administration significantly reduced ventilator duration (69.0 ± 49.6 h vs. 106.2 ± 89.7 h; mean difference −37.1 h, 95% CI −61.2 to −13.0; $P < 0.01$) and shortened PICU stay (14.3 ± 7.8 d vs. 17.9 ± 8.2 d; $P < 0.05$) and hospital stay (22.0 ± 11.0 d vs. 26.0 ± 9.1 d; $P < 0.05$). The surfactant group demonstrated a 26.3% reduction in total hospitalization costs (160.45 ± 44.00 vs. 217.71 ± 155.56 ×10³ CNY; $P = 0.005$) and exhibited superior lactate clearance (1.19 ± 0.55 vs. 1.58 ± 1.01 mmol/L; $P < 0.01$) and $PaO_2/FiO_2$ ratios (292.0 ± 126.3 vs. 229.5 ± 85.6; $P < 0.01$) at 48 hours. No surfactant-related adverse events occurred. Subgroup analyses suggested enhanced benefit in neonates (≤28 d) and low-birth-weight infants (<3.3 kg).

**Conclusions:** Early, low-dose surfactant administered within 24 h after surgery is safe, cost-effective, and associated with improved gas exchange, reduced ventilator dependency, and shorter ICU and hospital stays in infants with post-cardiotomy ARDS. These findings support further evaluation in multicenter trials.


# Background

Acute respiratory distress syndrome (ARDS) is a leading cause of morbidity and mortality following corrective surgery for congenital heart disease (CHD) with cardiopulmonary bypass (CPB) in infants [1, 2]. The reported incidence of post-cardiotomy ARDS in this population approaches 22%, frequently resulting in prolonged mechanical ventilation, extended pediatric intensive care unit (PICU) stays, and substantial healthcare resource utilization [3, 4].

The pathophysiology of CPB-induced lung injury is multifactorial, involving a systemic inflammatory response triggered by contact activation, ischemia–reperfusion injury, and hemodilution [5, 6]. A central consequence is the disruption of pulmonary surfactant homeostasis, leading to both quantitative

deficiency and qualitative dysfunction [7, 8]. Surfactant, a lipoprotein complex essential for reducing alveolar surface tension and maintaining pulmonary compliance, is inactivated by inflammatory mediators and plasma proteins that extravasate into the alveoli, promoting atelectasis, ventilation–perfusion mismatch, and refractory hypoxemia [9].

While exogenous surfactant replacement therapy is life-saving in neonatal respiratory distress syndrome (NRDS) [10], its role in pediatric ARDS has yielded inconsistent results. Prior trials, such as the CALIPSO study, evaluated surfactant as a rescue therapy for established ARDS of varied etiologies with mixed outcomes [11, 12]. Post-cardiotomy ARDS in infants represents a unique clinical context where surfactant dysfunction is a primary, early event in the pathogenesis, suggesting a potential therapeutic window for early intervention [13, 14]. However, the optimal timing, dosing, patient selection criteria, and cost-effectiveness of such an approach remain poorly defined.

Given the high disease burden, strong pathophysiological rationale, and the critical need for economic evaluations in pediatric critical care, we conducted a randomized, placebo-controlled trial to test the hypothesis that early administration of a single, low dose of exogenous surfactant reduces the duration of invasive mechanical ventilation and is cost-effective in infants who develop moderate ARDS following CPB surgery for CHD.

## Methods

# Study design and oversight

This was a single-center, double-blind, randomized, placebo-controlled, parallel-group trial conducted in the PICU of Fuwai Hospital, Beijing, China. It was initiated in August 2023 and completed in August 2025 after receiving approval from the Ethics Committee of Fuwai Hospital, CAMS&PUMC (2023–2033). All parents or guardians provided written informed consent for their infant before joining the study, reflecting the commitment to ethical research practices. The trail was registered in the Chinese Clinical Trial Registry (ChiCTR2500104855 ||http://www.chictr.org.cn/), it was a retrospective registration and the registration date was 2025-06-24. An independent Data and Safety Monitoring Board (DSMB) provided oversight for patient safety and conducted a pre-specified interim analysis. The database from this study was approved to be shared by Fuwai Hospital.

## Participants

Eligible participants were infants aged ≤ 3 months, weighing ≤ 6 kg, scheduled for CHD surgery requiring CPB with an anticipated duration of ≥ 90 minutes, and classified as Risk Adjustment for Congenital Heart Surgery (RACHS-1) category 2–5. Enrollment required the development of moderate-to-severe ARDS within 6 hours postoperatively, as defined by the Pediatric Acute Lung Injury Consensus Conference-2 (PALICC-2) criteria: an oxygenation index (OI) ≥ 4 and a $PaO_2/FiO_2$ ratio ≤ 300 mmHg, accompanied by bilateral infiltrates on chest imaging not fully explained by cardiac failure or fluid overload [15].

Key exclusion criteria included: residual hemodynamically significant cardiac lesions, palliative surgery, and postoperative left ventricular ejection fraction ≤ 35%, intraoperative decision for extracorporeal membrane oxygenation (ECMO) support, known congenital airway malformations, or major congenital anomalies /significant extracardiac comorbidities.

## Randomization and blinding

Eligible infants were randomly assigned in a 1:1 ratio to receive either surfactant or placebo. A computer-generated randomization sequence with variable block sizes was prepared by an independent statistician. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes. An unblinded pharmacy team prepared identical syringes containing either surfactant or 0.9% saline placebo. All treating clinicians, nursing staff, outcome assessors, and data analysts remained blinded to group assignment throughout the study.

## Intervention

The intervention consisted of a single endotracheal instillation of 15 mg/kg of calf lung-derived pulmonary surfactant (Calsurf; Shuanghe Pharmaceutical, Beijing, China) or an equivalent volume of saline placebo, administered within 24 hours of PICU admission following ARDS confirmation. Installation was performed via a catheter inserted into the endotracheal tube, with the total dose divided into three aliquots. Following each aliquot, the infant was repositioned sequentially (left lateral decubitus, supine with head elevated 30°, right lateral decubitus). Manual bag ventilation with 100% $FiO_2$ was provided for 1 minute after each aliquot and for 5 minutes following the complete dose. Continuous sedation and neuromuscular blockade were maintained for at least 4 hours post-administration to minimize coughing and promote uniform pulmonary distribution.

## Standardized perioperative and postoperative care

All surgical procedures were performed by senior congenital cardiac surgeons using standardized techniques. Postoperative management in the PICU adhered to strict institutional protocols for lung-protective ventilation (tidal volume 6–8 mL/kg predicted body weight, with titrated positive end-expiratory pressure), hemodynamic support, sedation-analgesia, and infection prophylaxis, consistent with current international guidelines [16, 17]. The decision to extubate was made by the treating clinical team based on standardized weaning criteria, independent of the research team.

# Outcomes

The primary outcome was the total duration of invasive mechanical ventilation, defined as the time from postoperative PICU admission to successful extubation (without reintubation within 48 hours).

Secondary outcomes included:

1. Length of PICU stay.
2. Total postoperative hospital length of stay.
3. Oxygenation parameters ($PaO_2/FiO_2$ ratio, arterial lactate, oxygenation index) measured at 24, 48, and 72 hours post-intervention.
4. A composite safety endpoint comprising in-hospital mortality, need for cardiopulmonary resuscitation within 24 hours of intervention, requirement for ECMO or high-frequency oscillatory ventilation, and incidence of nosocomial infections.
5. Economic outcomes: Total direct medical costs from randomization to hospital discharge.

## Economic evaluation

A prospective cost-effectiveness analysis was performed from the healthcare system perspective. Direct medical costs included surfactant acquisition, mechanical ventilation (per day), PICU stay (per day), hospital ward stay (per day), medications (vasoactive drugs, sedatives, antibiotics), and costs associated with laboratory tests and imaging studies. Unit costs were obtained from the hospital finance department based on 2024 national reimbursement rates.

# Statistical analysis

Sample size calculation was based on historical institutional data (mean ± SD postoperative ventilator duration = 120 ± 24 hours). To detect a 10% reduction (12 hours) with 80% power and a two-sided α level of 0.05, 63 patients per group were required. Allowing for a 5% dropout rate, a total sample size of 132 infants was targeted.

Statistical analyses were performed using IBM SPSS Statistics (version 25.0) and R (version 4.2.2). Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range, IQR) based on normality assessment using the Shapiro-Wilk test. Between-group comparisons for continuous variables utilized Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. The primary analysis followed the intention-to-treat principle. Pre-specified subgroup analyses were conducted for neonates (≤ 28 days) and low-birth-weight infants (< 3.3 kg). Cost data were log-transformed for analysis due to right-skewness. Bootstrapping with 1000 replications was used to estimate 95% confidence intervals for cost differences and ICERs. A two-sided P-value < 0.05 was considered statistically significant.

## Results

### Study population

A total of 8167 children were screened for eligibility, of whom 132 were randomized. After exclusions, 128 infants were included in the intention-to-treat analysis (65 in the surfactant group, 63 in the placebo group; see Fig. 1 for the study flowchart). Baseline demographic and clinical characteristics, including age, weight, sex, RACHS-1 category, CPB and aortic cross-clamp times, and preoperative organ function, were well-balanced between the two groups (Table 1). Preoperative respiratory support requirements and baseline oxygenation indices were also comparable.

### Primary and secondary outcomes

Surfactant administration significantly reduced the duration of mechanical ventilation by approximately 37 hours compared to placebo (69.0 ± 49.6 hours vs. 106.2 ± 89.7 hours; mean difference −37.1 hours, 95% CI −61.2 to −13.0; $P < 0.01$). Consequently, the surfactant group had significantly shorter PICU stays (14.3 ± 7.8 days vs. 17.9 ± 8.2 days; $P < 0.05$) and hospital stays (22.0 ± 11.0 days vs. 26.0 ± 9.1 days; $P < 0.05$; Table 2). Kaplan-Meier analysis for time to successful extubation demonstrated significant separation between the groups, favoring the surfactant group (log-rank $P < 0.01$; Fig. 2).

### Physiological outcomes

Baseline arterial lactate levels and oxygenation parameters were similar between groups. Following the intervention, the surfactant group demonstrated significantly better lactate clearance at 24 hours ($P < 0.05$), with differences becoming more pronounced at 48 and 72 hours ($P < 0.01$). The $PaO_2/FiO_2$ ratio and oxygenation index also showed significant improvement in the surfactant group at 48 hours ($PaO_2/FiO_2$: 292.0 ± 126.3 vs. 229.5 ± 85.6, $P < 0.01$; OI: 5.43 ± 2.7 vs. 6.63 ± 2.26, $P < 0.01$), and these benefits were sustained at the 72-hour mark (Table 3).

### Cost-effectiveness analysis

The economic evaluation revealed that early, low-dose surfactant administration was not only clinically superior but also economically advantageous. The total hospitalization cost was significantly lower in the surfactant group compared to the control group (160.45 ± 44.00 vs. 217.71 ± 155.56 $\times 10^3$ CNY; mean difference -57.26 $\times 10^3$ CNY, 95% CI -96.12 to -18.40; $P = 0.0051$), representing a 26.3% reduction in total medical costs (Table 2). The intervention demonstrated a dominant cost-effectiveness profile. The significantly smaller standard deviation in the treatment group's costs (44.00 vs. 155.56 $\times 10^3$ CNY) indicates more predictable and stable resource utilization compared to conventional management.

### Safety

The intervention was well tolerated. No instances of acute hemodynamic compromise, significant hypoxemia, or airway obstruction attributable to surfactant administration occurred. All infants survived to hospital discharge. No patient in either group required ECMO or high-frequency oscillatory ventilation. The rates of nosocomial infections and other adverse events were similar between the groups. One patient in the control group required continuous renal replacement therapy, whereas no patient in the surfactant group did (Table 2).

### Subgroup analyses

Pre-specified subgroup analyses confirmed the reduction in ventilator days and shorter length of stay in neonates (≤28 days) receiving surfactant. In the low-birth-weight subgroup (<3.3 kg), surfactant administration was associated with higher $PaO_2/FiO_2$ ratios at 48 hours and shorter PICU and hospital stays compared to placebo (Tables 3, 4).

# Discussion

This randomized, double-blind, placebo-controlled trial provides robust evidence that early, low-dose exogenous surfactant therapy improves clinically meaningful outcomes and is cost-effective in infants with post-cardiotomy ARDS. The 35% reduction in the duration of mechanical ventilation is both statistically significant and clinically substantial, translating into shorter ICU and hospital stays, alongside significant cost savings, without an increase in adverse events.

Our findings advance the field by addressing critical limitations of prior studies. Unlike earlier trials that investigated surfactant as a rescue therapy in heterogeneous pediatric ARDS populations [11, 12], we focused on a homogeneous, high-risk cohort in which surfactant dysfunction is a primary pathophysiological event [8, 9, 18]. The early intervention window (within 24 hours postoperatively) strategically targets the incipient phase of lung injury, potentially mitigating the vicious cycle of ventilator-induced lung injury and progressive inflammation [13, 14, 19]. The low dose (15 mg/kg) was a pragmatic choice, aiming to supplement the endogenous pool rather than replace it entirely, which may minimize the risks of airway occlusion and reduce overall treatment cost [20].

# Economic implications and value-based care

The economic evaluation provides crucial evidence for healthcare decision-makers. The significant reduction in total hospital costs (approximately 26.3% per patient) establishes early surfactant therapy as a dominant strategy—improving outcomes while reducing expenditures. This finding challenges the perception that novel biologic therapies in critical care are invariably cost-increasing [21]. The cost savings were primarily driven by reduced ventilator and ICU days, which are major cost drivers in postoperative cardiac care. The more predictable and lower variance in costs within the treatment group further enhances its value proposition for healthcare systems, allowing for better budgeting and resource planning [22].

# Mechanistic insights and phenotypic response

The pronounced treatment effect observed in neonates (≤ 28 days) and low-birth-weight infants (< 3.3 kg) offers compelling mechanistic and clinical insights. The < 3.3 kg threshold is physiologically relevant, approximating the mean birth weight of term newborns in contemporary Chinese cohorts and identifying a subgroup with heightened biological vulnerability [23]. The enhanced benefit in these patients likely stems from convergent developmental and physiological factors. The lungs of neonates and low-birth-

weight infants are structurally and functionally immature, with a simpler alveolar architecture that may promote more homogeneous distribution of the instilled surfactant [24]. More critically, their endogenous surfactant system is both quantitatively limited and qualitatively immature, with a smaller, more labile pool that is exquisitely sensitive to CPB-induced inactivation by inflammatory mediators and plasma proteins [8, 18, 25]. Consequently, exogenous supplementation provides a proportionally greater rescue effect. Furthermore, these infants exhibit higher metabolic rates and body surface area-to-weight ratios, increasing oxygen consumption and the work of breathing. Surfactant dysfunction thus imposes a disproportionate cardiopulmonary strain, making the rapid restoration of alveolar stability and efficient gas exchange especially critical—an effect reflected in the marked improvements in $PaO_2/FiO_2$ and lactate clearance we observed. This finding underscores a precision medicine principle: the greatest absolute benefit from an intervention may be derived by targeting the most vulnerable, identifiable subgroups [26].

# Strengths and limitations

The key strengths of our study include its randomized, double-blind, placebo-controlled design, rigorous methodology, inclusion of a comprehensive economic evaluation, and focus on a well-defined, high-risk population. However, several limitations should be acknowledged. First, the single-center design may affect the generalizability of our findings, although the high patient volume and standardized protocols at our center strengthen internal validity. Second, while subgroup analyses were pre-specified, they should be considered exploratory and hypothesis-generating due to the sample size. Third, the cost analysis reflects the context of the Chinese healthcare system; applicability to other healthcare systems with different cost structures requires further validation. Finally, the optimal dosing strategy, including the potential need for re-dosing, and the precise mechanisms underlying the differential response based on age and weight warrant further investigation through pharmacokinetic studies and advanced imaging techniques.

# Conclusions

In infants who develop moderate-to-severe ARDS following CPB surgery for CHD, early administration of low-dose surfactant within 24 hours is safe, cost-effective, and associated with significantly improved oxygenation, reduced ventilator dependency, and shorter ICU and hospital stays. The benefits appear most pronounced in neonates and low-birth-weight infants (< 3.3 kg), suggesting these subgroups may derive the greatest clinical and economic advantage. These results provide a strong rationale for conducting a larger, multicenter randomized trial to confirm efficacy, refine patient selection criteria, and inform evidence-based clinical guidelines for managing post-cardiotomy respiratory failure in this vulnerable population.

# Declarations

### Acknowledgements

Not applicable

### Author contributions

Z-RY and WX drafted the article and made contributions to the acquisition of data. LX and L-ZY participated in the analysis and interpretation of data and made substantial contributions to the acquisition of data. Z-RY, WX and L-SJ participated in the design and refinement of the study protocol. L-SJ, Y-KM and Z-BQ performed all surgical procedures and participated in revising it critically for important intellectual content. All of the authors had given final approval for the version to be published. All authors read and approved the final manuscript.

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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

The Institutional Review Board of Fuwai Hospital, CAMS&PUMC approved the study and protocol (approval number: 2023-2033). The trial was conducted in accordance with the ethical principles of the “Declaration of Helsinki,” the International Conference on Harmonisation–Good Clinical Practice (ICH-GCP) guideline, the “Quality Management Standards for Drug Clinical Trials” of the Chinese Food and Drug Administration (CFDA), the “Medical Devices Clinical Trial Quality Management Standards” of the CFDA, the “Ethical Review Measures for Biomedical Research Involving Humans” of the National Health Commission of China, and other relevant national laws and regulations. Informed consent by the study participant or a legally authorized representative was given prior to inclusion in the study.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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## Tables

Tables 1 to 4 are available in the Supplementary Files section.

## Figures

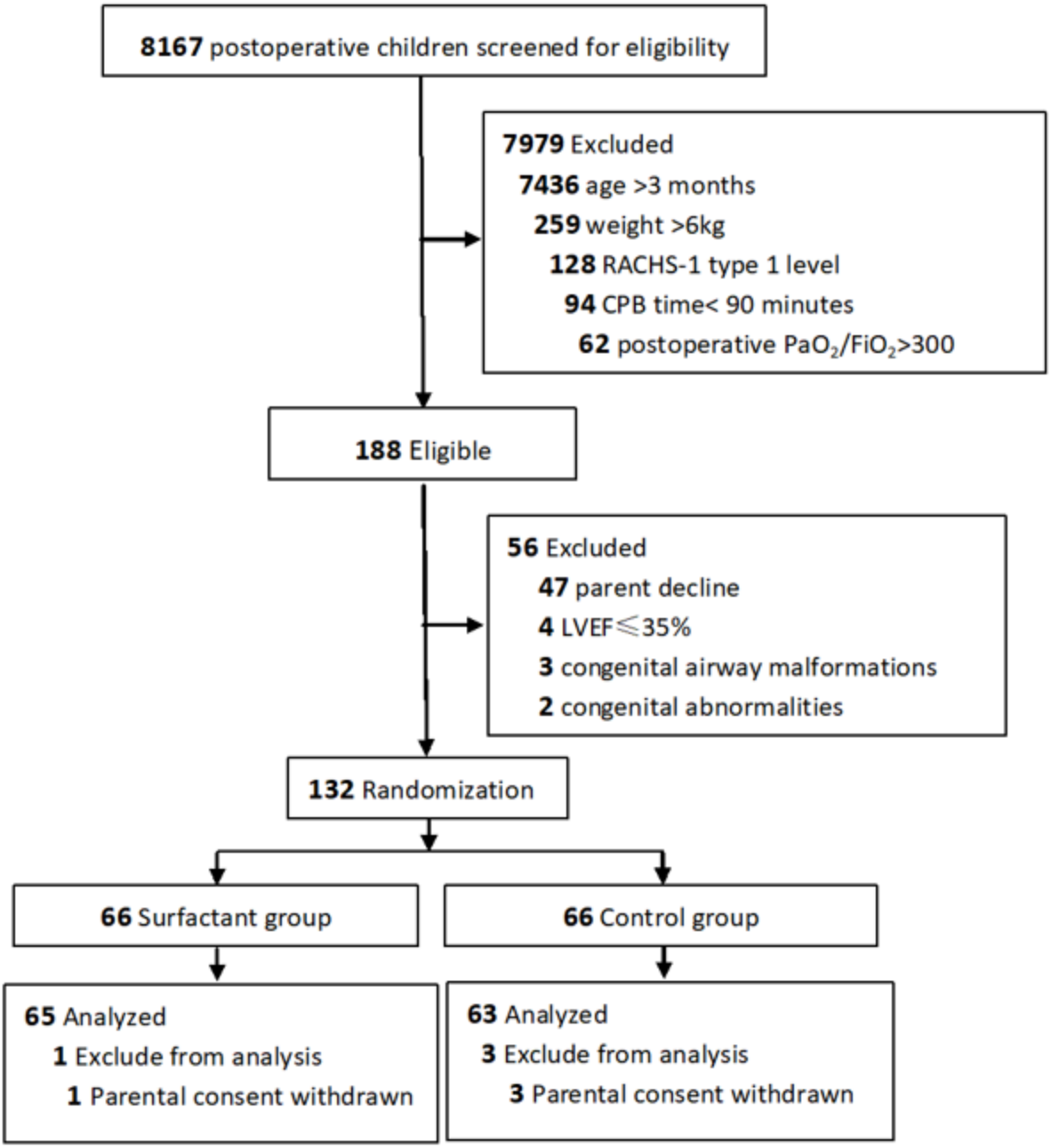



**Fig1.** Study flowchart. CPB: cardiopulmonary bypass.

**Figure 1**

See image above for figure legend

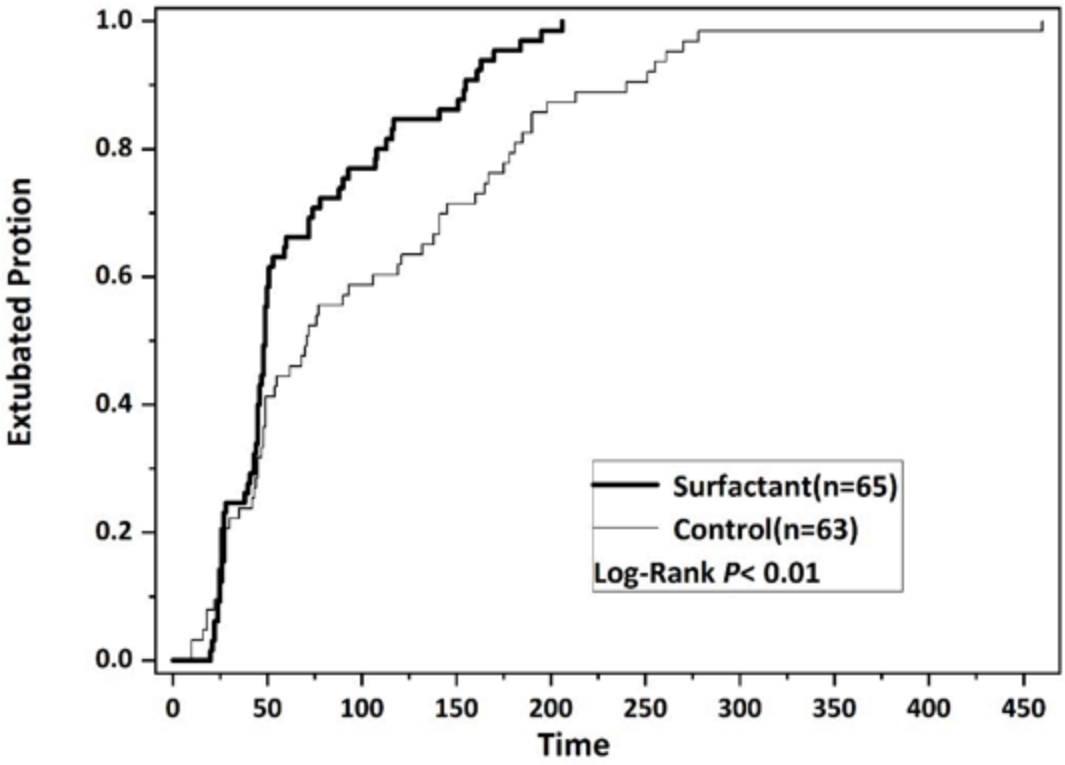



**Fig2. Extubated proportion of surfactant compared with control**

**Figure 2**

See image above for figure legend

# Supplementary Files

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