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Original Article

Perioperative Factors and Radiographic Severity Scores for Predicting the Duration of Mechanical Ventilation After Arterial Switch Surgery

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Objectives: Cardiac surgery on cardiopulmonary bypass (CPB) during the neonatal period can cause perioperative organ injuries. The primary aim of this study was to determine the incidence and risk factors associated with postoperative mechanical ventilation duration and acute lung injury after the arterial switch operation (ASO). The secondary aim was to examine the utility of the Brixia score for characterizing postoperative acute lung injury (ALI).
Design: A retrospective study.
Setting: A single-center university hospital.
Participants: A total of 93 neonates with transposition of great arteries with intact ventricular septum (dTGA IVS) underwent ASO.
Interventions: None.
Measurements and Main Results: From January 2015 to December 2022, 93 neonates with dTGA IVS were included in the study. The cohort had a median age of 4.0 (3.0-5.0) days and a mean weight of 3.3 ± 0.5 kg. About 63% of patients had ≥48 hours of postoperative mechanical ventilation after ASO. Risk factors included prematurity, post-CPB transfusion of salvaged red cells, platelets and cryoprecipitate, and postoperative fluid balance by univariate analysis. The larger transfused platelet volume was associated with the risk of ALI by multivariate analysis. The median baseline Brixia scores were 11.0 (9.0-12.0) and increased significantly in the postoperative day 1 in patients who developed moderate ALI 24 hours after admission to the intensive care unit (15.0 [13.0-16.0] *v* 12.0 [10.0-14.0], p = 0.046).
Conclusions: Arterial switch operation results in a high incidence of ≥48-hour postoperative mechanical ventilation. Blood component transfusion is a potentially modifiable risk factor. The Brixia scores also may be used to characterize postoperative acute lung injury.

Key Words: arterial switch operation; transposition of the great arteries; postoperative lung injury; mechanical ventilation; Brixia score

DESPITE SIGNIFICANT advancements in extracorporeal circulation and perioperative care, cardiac surgeries in neonates are associated with high morbidity and mortality.[1] Lung injury is one of the major organ injuries that frequently occur after cardiac surgery.[2] Transposition of the great arteries (TGA) is the second most common cyanotic congenital cardiac lesion. One subtype, dextroposition TGA with intact ventricular septum (dTGA IVS), requires definitive surgical correction (arterial switch operation [ASO]) during the first days of life to ensure optimal outcomes.[3,4] During the neonatal period, the lungs can be greatly compromised with significant pulmonary overcirculation. Mechanical ventilation, cardiopulmonary bypass (CPB), and blood transfusion further contribute to pulmonary insult, leading to delayed recovery.[5,6] In recent years, enhanced recovery and early extubation have become

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increasingly common in pediatric cardiac surgery.[7] Despite this, few studies address the perioperative factors that potentially could shorten postoperative mechanical ventilation and reduce lung injury in this patient population.

This study aimed to investigate the incidence and potential predictors of prolonged mechanical ventilation and lung injury after ASO. Furthermore, the conventional diagnostic tool for lung injury, such as the PaO_2/fraction of inspired oxygen (F_IO_2) (P/F) ratio, may be of limited utility in some congenital heart diseases due to their intracardiac shunts, including parallel circulation found in dTGA IVS preoperatively.[4] Thus, the secondary aim of this study was to assess the utility of the Brixia score[8,9] as a novel tool in characterizing lung injury in neonatal cardiac surgery.

Methods

Study Cohort

The Institutional Review Board at Boston Children's Hospital approved this retrospective cohort study. Neonates who underwent ASO from January 2015 to December 2022 were identified. Only neonates diagnosed with dTGA IVS were included in the study. Patient demographics, preoperative characteristics, operative variables, and postoperative outcomes were collected from the hospital's electronic medical records. Arterial blood gas data from the intraoperative baseline, post-CPB, postoperatively at intensive care unit (ICU) admission, and 6, 12, 24, and 48 hours after ICU admission were identified and used in statistical analysis. Patients diagnosed with tracheal, tracheobronchial, and laryngeal abnormalities and those with missing pertinent data (mechanical ventilation, CPB duration) were excluded.

In this study cohort, pressure-controlled ventilation was the primary mode of intraoperative mechanical ventilation. All patients received general anesthesia with a combination of volatile and intravenous anesthetics. Cuffed endotracheal tubes were used routinely. CPB circuit was primed with reconstituted whole blood to maintain hematocrit ≥30%. Additional blood product transfusion and coagulation management were based on thromboelastogram data and the discretion of the anesthesiologists. Salvaged blood and packed red cells were transfused when indicated to maintain hematocrit ≥30%. Methylprednisolone, 30 mg/kg, was administered during CPB in all patients. Postoperative and extubation management was under the discretion of cardiac intensivists and followed institutional protocols.

The duration of mechanical ventilation was determined as the interval from the end of operating room time (room-out time) and extubation time at the ICU. This did not include the duration of noninvasive bilevel and/or continuous positive ventilation if required after extubation. Perioperative and outcome data were compared between patients who were extubated within 48 hours and those extubated after 48 hours. The P/F ratio was calculated as PaO_2 divided by F_IO_2 at the corresponding time, oxygenation index (OI) as (F_IO_2 × mean airway pressure × 100) / PaO_2, and oxygen saturation index (OSI) as (F_IO_2 × mean airway pressure × 100) / SpO_2. Acute postoperative lung injury (ALI) was defined as a P/F ratio <300 at the 24-hour time point after postoperative ICU admission. Postoperative fluid balance was calculated as total fluid output − total fluid input from the corresponding postoperative day.

Brixia Scores

The authors adopted the Brixia score,[8] initially developed for grading severe acute respiratory syndrome coronavirus 2 pneumonia severity, to quantify lung abnormalities on perioperative chest radiographs. In this scoring system, the lungs were divided into 6 anatomic zones (upper, mid, and lower sections of the right and left lungs). The score in each lung zone was assigned based on the perceived radiographic abnormalities present in that zone: 0, no abnormality; 1, interstitial infiltrates; 2, interstitial predominance with alveolar infiltrates; and 3, alveolar dominance with interstitial infiltrates (Fig 1). The sum of the scores from these 6

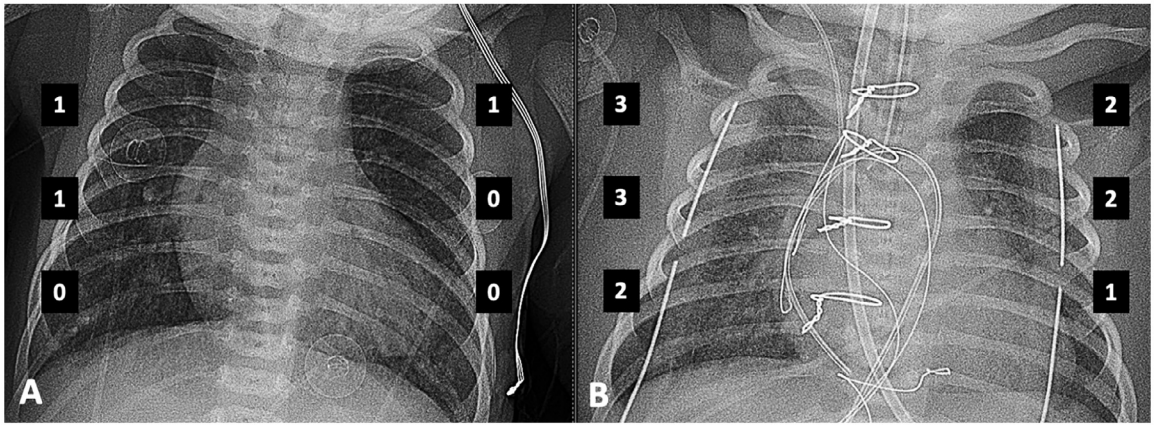

Figure 1. Chest radiographs of a dTGA/IVS patient demonstrate the assigned score of each lung zone. **(A)** Preoperative Brixia score (1+1+0+1+0+0) = 3. **(B)** Postoperative Brixia score (3+3+2+2+2+1) = 13.

lung zones was assigned as each radiograph's Brixia score (minimum 0, maximum 18).

Patients' Brixia scores were evaluated by 3 assessors (P.L., K.Y., and W.M.), who were all blinded to patients' perioperative and outcomes data during the scoring process. An experienced radiologist (A.T.) trained these 3 reading physicians to standardize the interpretation of the chest radiographs. As part of the training process and to further maximize reader agreement, the intraclass correlation coefficient (ICC) was calculated in 2 separate practice sessions before evaluating the patients' radiographs. For each patient, the authors identified 3 chest radiographs from the medical record, each corresponding to one of the following 3 time periods: preoperative, postoperative (at ICU admission), and postoperative (postoperative day 1 [POD1]). In cases in which multiple chest radiographs existed during the specified time period, the most recent preoperative image, the first image after ICU admission, and the first image on POD1 were selected for analysis. Chest radiographs were viewed using the hospital picture archiving and communication system (Synapse, Fujifilm Medical System). Standard image displays using preset window settings for optimal assessment of lung parenchyma were used during the scoring process. Each assessor independently scored all images in 4 separate sessions. The scores from each lung zone by each assessor were compared and discussed to determine the consensus Brixia scores for all the chest radiographs. All assessors agreed to the final Brixia scores.

Statistical Analysis

The authors used means and SD as summary statistics for continuous variables with a normal distribution and medians and IQRs for variables with nonnormal distributions. They used Student's *t* test or Mann–Whitney *U* test to compare continuous variables, depending on the normality of the distribution. Categorical variables were presented as frequencies and percentages, and the χ^2 test or Fisher exact test was used as appropriate. The authors conducted a logistic regression analysis to determine the association between the duration of mechanical ventilation and patient factors. Multivariate analysis was performed to determine the adjusted odds ratios with 95% CIs. The authors used Youden J-index to determine the variable cutoff points. The correlations between variables were provided by Pearson's correlation coefficient. They calculated ICC (2-way random-effects model) to determine the assessors' agreement with the Brixia scores. A p value of < 0.05 was considered to be statistically significant. These statistical analyses were performed using software STATA 17 (StataCorp, LLC, College Station, TX) and Prism 10 (GraphPad Prism version 10.0.0, GraphPad Software, La Jolla, CA).

Results

Characteristics of the Study Cohort

From January 2015 to December 2022, 2,911 cardiac surgeries with CPB were performed in neonates and infants younger 1 year of age. Among them, 93 neonates with dTGA IVS who underwent ASO were included in the study cohort. The perioperative data are shown in Table 1. Most were male sex (68%) with a median age of 4.0 (3.0-5.0) days and a mean weight of 3.3 ± 0.5 kg. About 45% underwent urgent balloon atrial septostomy (BAS) before arriving for definitive surgery, and most (76%) of the cohort received preoperative mechanical ventilation support at least briefly. Intraoperative baseline P/F ratios were 55.9 (49.1-65.9), which improved after ASO.

The median duration of postoperative mechanical ventilation for the entire cohort was 66.8 (41.7-94.5) hours. About 63% of patients required postoperative mechanical ventilation for 48 hours or more, with a median duration of 90.3 (68.6-124.8) hours. Postoperative infections and respiratory complications did not differ between the 2 groups (ie, those with and without ≥48 hours of mechanical ventilation), and there was no in-hospital mortality in the authors' study cohort.

Factors Associated With the Duration of Mechanical Ventilation

Patients with ≥48-hour mechanical ventilation had a higher incidence of prematurity, although the weight and age at surgery, preoperative mechanical ventilation, BAS, preoperative hemoglobin, and serum lactate were comparable with those without. Intraoperatively, these patients received a larger volume of salvaged red blood cells, cryoprecipitate, and platelet transfusions after CPB (Fig 2), and had a higher rate of delayed sternal closure. The transfusion volume of salvaged red blood cells was positively correlated with the volume of transfused platelets and cryoprecipitate (Pearson's $r = 0.60$, $p < 0.001$, $r = 0.45$, $p < 0.001$, respectively).

At ICU admission, although most patients (63%) developed low P/F ratios (<300), the ≥48-hour ventilation group had significantly higher P/F ratios (271.5 [191.0-380.0] *v* 197.0 [164.0-302.0], $p = 0.029$; Fig 3, A). However, at the postoperative 24-hour time, they later demonstrated significantly lower P/F ratios with a higher incidence of ALI (42.9 *v* 10.5%, $p = 0.012$). During ICU admission, they also had lower hemoglobin levels, received more packed red cell transfusions, and had more positive fluid balance. The fluid balance on POD1 was more positive in patients with ≥48 hours of mechanical ventilation (5.6 [−32.8 to 42.7] *v* −30.5 [−50.3 to 12.0]; $p = 0.024$), and was also a risk factor for prolonged mechanical ventilation (crude odds ratio [OR] 1.04 [1.01-1.08] $p = 0.03$). About 17% of patients received dexmedetomidine as part of ICU sedation. In those requiring ≥48-hour of ventilation, 13% were given dexmedetomidine, compared to 23% in those requiring <48 hours ($p = 0.26$).

The univariate and multivariate analyses are shown in Table 2. In the multivariate analysis, the authors did not find a significant association between the volume of salvaged red blood cells, platelets, or cryoprecipitate and prolonged mechanical ventilation. However, only the volume of platelet transfusion, not salvaged red blood cells or cryoprecipitate, was associated with ALI (adjusted OR 1.04 [1.00-1.08];

Table 1
Demographic and Perioperative Data

Demographic Data	Total (n = 93)	Ventilation <48 h (n = 34)	Ventilation ≥48 h (n = 59)	p Value	OR	95% CI	p Value
Age, median (IQR), d	4.0 (3.0-5.0)	3.5 (3.0-5.0)	4.0 (3.0-5.0)	0.160			
Gestational age, mean ± SD, wk	38.5 ± 1.7	39.0 ± 0.7	38.2 ± 0.2	0.016	1.26	0.98-1.62	0.07
Gestational age <37 wk, n (%)	10 (11.1)	0 (0.0)	10 (17.5)	0.011	n/a		
Male sex, n (%)	64 (68.8)	23 (67.6)	41 (69.5)	0.85			
Weight, mean ± SD, kg	3.3 ± 0.5	3.4 ± 0.4	3.2 ± 0.6	0.150			
Chromosome abnormality, n (%)	11 (11.8)	3 (8.8)	8 (13.6)	0.740			
Preoperative mechanical ventilation, n (%)	71 (76.3)	28 (82.4)	43 (72.9)	0.450			
Balloon atrial septostomy, n (%)	42 (45.2)	17 (50.0)	25 (42.4)	0.520			
Preoperative Hb, mean ± SD, g/dL	14.1 ± 1.9	14.3 ± 1.6	13.9 ± 2.0	0.350			
Preoperative platelet, mean ± SD, per uL	239.7 ± 66.4	245.4 (69.6)	236.4 ± 64.9	0.530			
Preoperative lactate, mean ± SD, mmol/L	2.1 ± 0.7	2.1 ± 0.6	2.2 ± 0.8	0.510			
Intraoperative and CPB data							
CPB time, mean ± SD, min	180.9 ± 39.0	183.5 ± 40.9	179.4 ± 38.1	0.630			
Cross-clamp time, mean ± SD, min	122.9 ± 23.8	130.5 ± 27.9	118.5 ± 20.1	0.018	0.98	0.96-1.00	0.02
Circulatory arrest, n (%)	19 (20.4)	5 (14.7)	14 (23.7)	0.420			
Modified ultrafiltration, n (%)	73 (78.5)	30 (88.2)	43 (72.9)	0.120			
CPB crystalloid, median (IQR), mL	370.0 (250.0-520.0)	362.5 (292.5-520.0)	370.0 (245.0-540.0)	0.960			
Surgical duration, mean ± SD, h	5.8 ± 1.0	5.7 ± 0.9	5.8 ± 1.0	0.430			
Delayed sternal closure, n (%)	14 (15.1)	0 (0.0)	14 (23.7)	0.002	n/a		
Intraoperative lactate, mean ± SD	1.7 ± 0.7	1.6 ± 0.7	1.8 ± 0.7	0.280			
Post-CPB lactate, mean ± SD	3.2 ± 0.6	3.1 ± 0.6	3.2 ± 0.6	0.550			
Tranexamic acid, mean ± SD, mg/kg	233.0 ± 40.8	234.4 ± 58.6	232.1 ± 26.0	0.790			
Post-CPB PRC, median (IQR), mL	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.290			
Post-CPB salvaged blood, median (IQR), mL/kg	22.8 (14.5-35.7)	17.1 (14.3-27.4)	29.6 (15.5-41.9)	0.007	1.04	1.01-1.08	0.01
Post-CPB FFP, median (IQR), mL/kg	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.450			
Post-CPB cryoprecipitate, median (IQR), mL/kg	7.8 (0.0-13.6)	5.2 (0.0-8.6)	8.3 (0.0-17.8)	0.014	1.09	1.02-1.16	0.01
Post-CPB platelet, median (IQR), mL/kg	19.8 (14.3-30.3)	18.5 (13.9-22.2)	22.5 (14.3-33.3)	0.043	1.04	1.01-1.08	0.03
Post-CPB transfused volume, median (IQR), mL/kg	54.0 (36.2-74.2)	41.2 (34.4-55.0)	58.5 (42.3-86.2)	0.002	1.03	1.01 1.05	0.009
Post-CPB epinephrine use, n (%)	58 (62.4)	20 (58.8)	38 (64.4)	0.660			
Postoperative data, outcomes							
Mechanical ventilation, median (IQR), h	66.8 (41.7-94.5)	33.5 (24.8-42.9)	90.3 (68.6-124.8)	< 0.001			
ICU length of stay, median (IQR), h	190.3 (141.6-249.8)	149.4 (118.2-183.6)	225.9 (174.7-323.7)	< 0.001			
Respiratory complications, n (%)	10 (11.5)	4 (13.3)	6 (10.5)	0.730			
Postoperative infection (any), n (%)	7 (7.5)	3 (8.8)	4 (6.8)	0.700			
Pacemaker insertion, n (%)	29 (31.2)	10 (29.4)	19 (32.2)	0.820			
Fluid balance POD0, median (IQR), mL/kg	3.2 (−9.7 to 18.4)	4.6 (−2.2 to 14.3)	2.6 (−12.7 to 20.3)	0.600			
Fluid balance POD1, median (IQR), mL/kg	−5.2 (−44.8 to 30.6)	−30.5 (−50.3 to 12.0)	5.6 (−32.8 to 42.7)	0.024	1.00	1.00-1.01	0.03
Fluid balance POD2, median (IQR), mL/kg	−50.9 (−80.6 to −28.2)	−44.2 (−75.3 to −27.4)	−53.4 (−103.9 to −31.9)	0.290			
PRC transfusion on POD0, n (%)	16 (17.2)	5 (14.7)	11 (18.6)	0.780			
PRC transfusion on POD1, n (%)	15 (16.1)	2 (5.9)	13 (22.0)	0.046	4.52	0.95-21.42	0.06
Postoperative to 24-h minimum Hb, median (IQR), g/dL	13.4 (12.5-14.4)	14.0 (13.3-14.6)	13.0 (12.2-14.0)	0.004	0.67	0.49-0.92	0.01
24 to 48 h minimum, median (IQR), g/dL	13.5 (11.7-14.7)	13.4 (11.7-14.4)	13.7 (11.6-14.9)	0.670			
Thromboelastogram data							
Angle, median (IQR)							
Rewarm	55.1 (50.1-62.2)	54.0 (49.8-63.3)	55.4 (50.4-61.6)	0.980			
ICU admission	64.0 (49.9-71.1)	58.1 (49.5-70.5)	64.8 (53.2-71.4)	0.370			
POD1	70.5 (66.7-74.2)	70.4 (62.7-72.6)	70.9 (66.9-75.1)	0.190			
Reaction (R), median (IQR)							
Rewarm	3.5 (2.8-5.1)	3.8 (2.8-5.1)	3.3 (2.8-5.0)	0.470			

(*continued*)

Table 1 (*continued*)

Demographic Data	Total (n = 93)	Ventilation <48 h (n = 34)	Ventilation ≥48 h (n = 59)	p Value	OR	95% CI	p Value
ICU admission	2.0 (1.3-4.6)	2.1 (1.3-6.7)	1.9 (1.2-4.5)	0.650			
POD1	1.3 (1.1-1.8)	1.5 (1.2-5.2)	1.3 (1.0-1.7)	0.051			
Maximum amplitude (MA)	45.7 (40.1-53.3)	47.0 (40.2-56.4)	45.4 (40.1-51.0)	0.300			
Rewarm, median (IQR)							
ICU admission	52.2 (40.0-63.4)	45.1 (40.0-61.9)	54.8 (40.0-64.7)	0.250			
POD1	66.5 (60.9-73.3)	62.6 (58.5-69.0)	67.6 (61.6-73.6)	0.060			
Clotting (K), median (IQR)							
Rewarm	6.9 (5.8-8.8)	6.6 (5.7-8.3)	7.2 (5.9-9.3)	0.360			
ICU admission	6.3 (5.3-7.5)	5.9 (4.5-7.5)	6.7 (5.6-7.9)	0.200			
POD1	6.5 (5.5-7.2)	5.9 (2.1-7.0)	6.7 (5.6-7.4)	0.097			
Respiratory variables							
P/F ratios, median (IQR)							
Intraoperative	55.9 (49.1-65.9)	53.8 (48.6-61.2)	57.7 (49.7-68.3)	0.087			
Post-CPB	198.0 (113.0-313.0)	188.0 (111.0-306.0)	216.0 (113.0-344.0)	0.630			
ICU admission	255.0 (167.5-348.0)	197.0 (164.0-302.0)	271.5 (191.0-380.0)	0.029	1.00	1.00-1.01	0.03
6-h	303.0 (251.0-368.5)	285.5 (252.0-380.0)	313.0 (245.0-360.0)	0.650			
12-h	335.0 (253.0-413.0)	341.5 (272.5-424.5)	303.0 (246.0-413.0)	0.410			
24-h	350.0 (271.0-410.0)	395.0 (310.0-420.0)	329.0 (255.5-386.5)	0.021	0.99	0.98-1.00	0.02
48-h	347.5 (273.0-404.0)		347.5 (273.0-404.0)				
P/F ratio <300, n (%)							
ICU admission	58 (63.0)	25 (73.5)	33 (56.9)	0.120			
6-h	42 (47.7)	19 (55.9)	23 (42.6)	0.280			
12-h	37 (43.5)	11 (34.4)	26 (49.1)	0.260			
24-h	26 (34.7)	2 (10.5)	24 (42.9)	0.012	6.38	1.34-30.27	0.02
48-h	16 (33.3)		16 (33.3)				
P/F ratio <200, n (%)							
ICU admission	33 (35.9)	18 (52.9)	15 (25.9)	0.013	0.31	0.13-0.76	0.01
6-h	10 (11.4)	4 (11.8)	6 (11.1)	1.000			
12-h	9 (10.6)	3 (9.4)	6 (11.3)	1.000			
24-h	6 (8.0)	0 (0.0)	6 (10.7)	0.330			
48-h	2 (4.2)		2 (4.2)				
Oxygenation index, median (IQR)							
ICU admission	3.6 (2.5-5.5)	4.1 (3.1-5.9)	3.3 (2.3-4.7)	0.067			
6-h	3.0 (2.2-3.7)	3.1 (2.1-3.5)	2.9 (2.3-3.7)	0.860			
12-h	2.3 (1.8-3.4)	2.1 (1.8-3.0)	2.6 (1.9-3.7)	0.200			
24-h	2.3 (2.0-3.2)	2.2 (1.9-2.5)	2.5 (2.0-3.4)	0.073			
48-h	2.6 (2.0-3.1)		2.6 (2.0-3.1)				
Oxygen saturation index, median (IQR)							
ICU admission	5.0 (4.0-6.9)	4.7 (3.6-5.6)	5.1 (4.2-8.0)	0.088			
6-h	3.6 (3.2-4.4)	3.6 (3.2-4.1)	3.7 (3.2-4.4)	0.380			
12-h	3.2 (2.8-3.7)	3.2 (2.8-3.6)	3.2 (2.8-4.0)	0.160			
24-h	3.2 (2.8-3.6)	3.2 (2.5-3.6)	3.2 (2.8-3.6)	0.740			
48-h	3.2 (2.7-3.6)		3.2 (2.7-3.6)				

NOTE. Data are presented as n (%), mean ± SD, or median (IQR).
Abbreviations: CPB, cardiopulmonary bypass; OR, crude odds ratio; PRC, packed red cells; FFP, fresh frozen plasma; POD, postoperative day; Hb, hemoglobin; P/F ratio, PaO_2/fraction of inspired oxygen ratio.

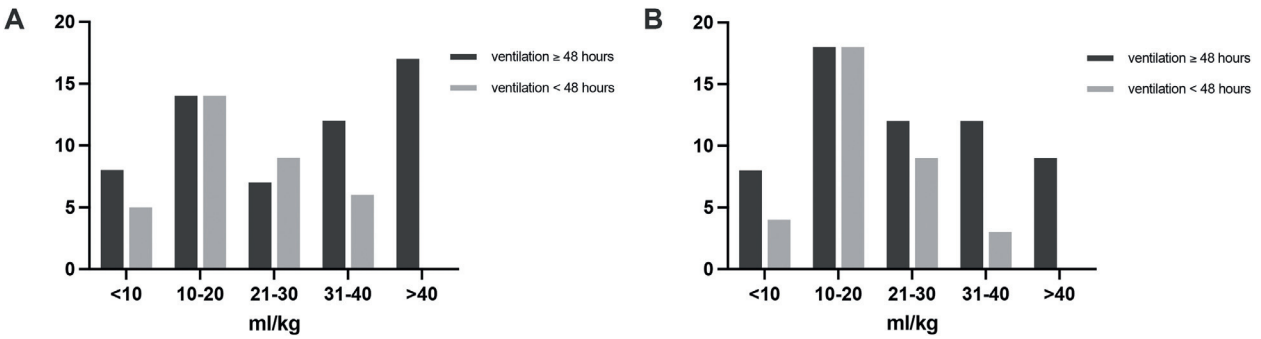

Figure 2. (A) Distribution of salvaged red blood cell transfusion volume. (B) Distribution of platelet transfusion volume.
Note: Y-axis, number of patients; X-axis, volume transfused (ml/kg).

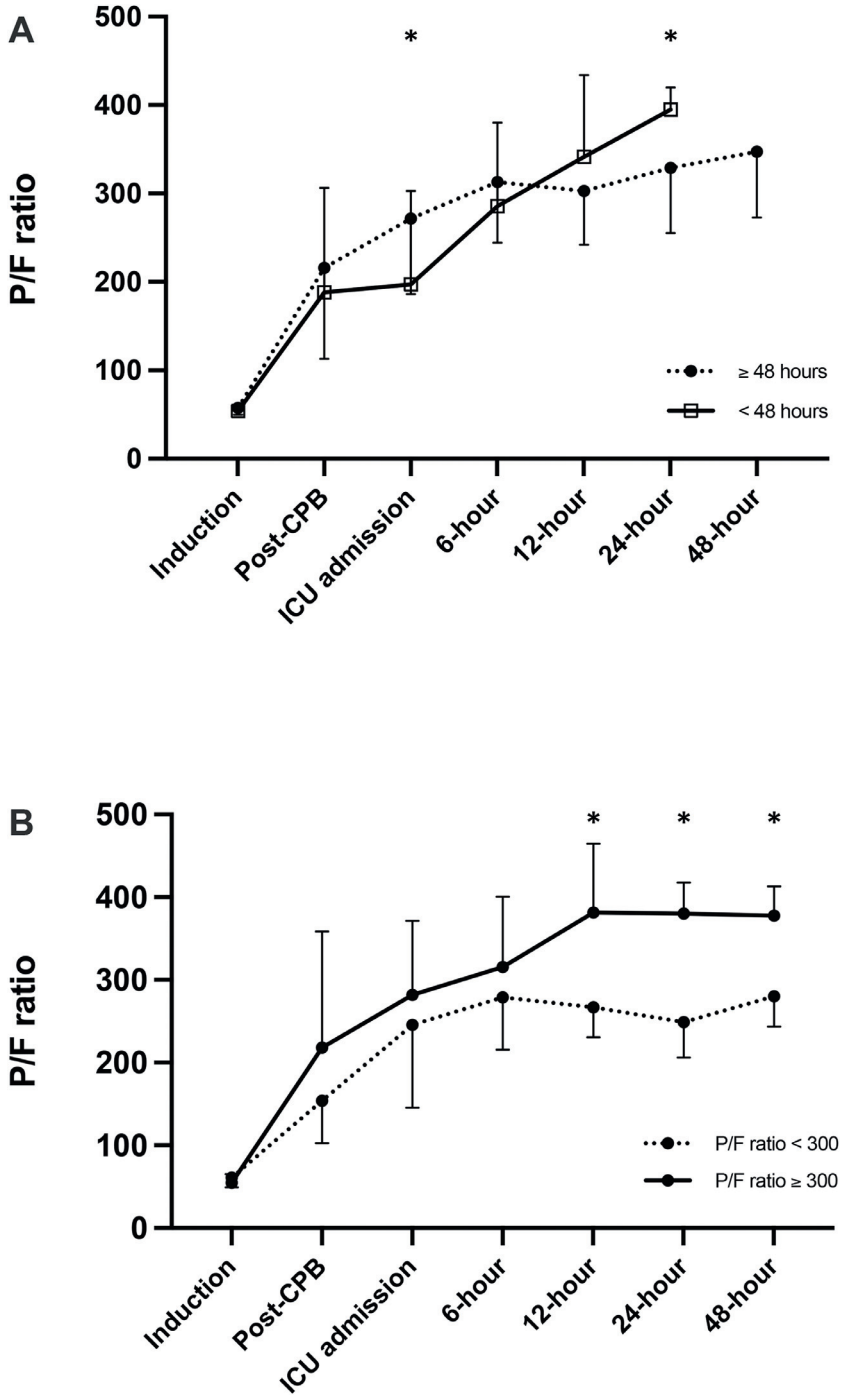

Figure 3. **(A)** Comparisons of P/F ratios from ICU admission to 48 hours between patients with ≥ 48 hours and < 48 hours of mechanical ventilation. **(B)** P/F ratios from ICU admission to 48 hours between patients who developed acute lung injury (24-hour P/F ratio < 300) compared with those who did not.

Note: Data are presented as median, IQR; * represents a statistically significant interval difference (p-value < 0.05) between groups.

Abbreviation: P/F ratio, PaO_2/FiO_2 ratio, POD, postoperative day.

p = 0.042). To further predict the probability of ≥48-hour ventilation duration in patients with dTGA IVS, the authors developed a logistic regression model from relevant factors, demonstrating the relationship between the salvaged red blood cell volume, the 24-hour P/F ratio, and the duration of ventilation. This regression model had an acceptable area under the receiver operating characteristic curve of 0.80 and had the Hosmer-Lemeshow probability of 0.52. From the model, it was demonstrated that for an equal volume of salvaged red blood cells received, patients with a 24-hour P/F ratio <300 had a higher predicted probability of prolonged mechanical ventilation (Fig 4).

The cutoff value of salvaged red blood cell volume at the maximum Youden J-index was 32.5 mL/kg, (crude OR of 6.11 [1.90-19.60]; p = 0.002), and platelets at 23.5 mL/kg, (crude OR 4.51 [1.63-12.50]; p = 0.004). Patients who received

Table 2
Univariate and Multivariate Analysis

Univariate Analysis	Crude OR	(95% CI)	p Value
Gestational age, wk	1.26	(0.98-1.62)	0.07
Cross-clamp time, min	0.98	(0.96-1.00)	0.02*
Post-CPB salvaged blood, mL/kg	1.04	(1.01-1.08)	0.01*
Post-CPB cryoprecipitate, mL/kg	1.09	(1.02-1.16)	0.01*
Post-CPB platelet, mL/kg	1.04	(1.01-1.08)	0.03*
Post-CPB transfused volume, mL/kg	1.03	(1.01-1.05)	0.009*
Fluid balance POD1, mL/kg	1.00	(1.00-1.01)	0.03*
RBC transfusion POD1	4.52	(0.95-21.42)	0.06
Postoperative to 24-h minimum Hb	0.67	(0.49-0.92)	0.01*
P/F ratio ICU admission	1.00	(1.00-1.01)	0.03*
24-h P/F ratio	0.99	(0.98-1.00)	0.02*
24-h P/F ratio <300	6.38	(1.34-30.27)	0.02*
P/F ratio <200 at ICU admission	0.31	(0.13-0.76)	0.01*
Multivariate analysis	adjusted OR	95% CI	p value
Ventilation ≥48 h†			
24-h P/F ratio <300	3.49	0.81-19.73	0.157
Post-CPB salvaged blood, mL/kg	1.04	0.98-1.10	0.148
Post-CPB platelet, mL/kg	1.00	0.94-1.08	0.805
Post-CPB cryoprecipitate, mL/kg	1.06	0.96-1.17	0.256
POD1 fluid balance	1.01	0.99-1.02	0.069
Gestational age, wk	0.55	0.62-0.99	0.05
Acute lung injury†			
Post-CPB salvaged blood, mL/kg	1.04	0.97-1.03	0.971
Post-CPB platelet, mL/kg	1.04	1.00-1.08	0.042*
Post-CPB cryoprecipitate, mL/kg	0.96	0.91-1.01	0.150
Logistic regression model for ventilation ≥48 h			
24-h P/F ratio <300	6.33	1.26-32.62	0.025*
Post-CPB salvaged blood, mL/kg	1.04	1.00-1.09	0.033*
POD1 fluid balance	1.01	0.99-1.01	0.152
Area under ROC curve = 0.795			

Abbreviations: CPB, cardiopulmonary bypass; Hb, hemoglobin; ICU, intensive care unit; OR, odds ratio; P/F ratio, PaO_2/F_IO_2 ratio; POD, postoperative day; PRC, packed red cells; ROC, receiver operating characteristic.

* Represents statistical significance.

† Post-CPB transfused volume was omitted because of collinearity.

>32.5 mL/kg salvaged red blood cells had significantly longer mechanical ventilation duration (92.9 [68.56-125.8] *v* 48.1 [35.33-73.58] hours; p < 0.001). Similarly, patients who received >23.5 mL/kg platelets had 81.9 (52.9-117.8) hours of mechanical ventilation compared to 49.0 (30.5-90.3) hours (p = 0.004).

Correlation Between OI and OSI

OI and OSI were moderately correlated at every observed interval in this patient cohort. Additionally, P/F ratios derived from the arterial PaO_2 were inversely correlated with OSI derived from peripheral SpO_2 readings; however, only weak correlations were observed.

Overall, the OI and OSI values were highest at ICU admission and decreased over time in the postoperative period. Unlike the P/F ratios, OI and OSI did not differ statistically between patients with and without ≥48 hours of mechanical ventilation, as shown in Table 3. However, patients who developed ALI had significantly higher OSI values observed at ICU admission and 12 hours postoperatively.

Brixia Scores, Mechanical Ventilation Duration, and Acute Lung Injury

Among the 75 patients for whom the 24-hour P/F ratio data were available, 26 patients (34.7%) developed ALI. Figure 3, B compares the P/F ratios between patients who developed ALI and those who did not. The P/F ratios were comparable at the time of ICU admission but were significantly lower at the 12-, 24-, and 48-hour time points in patients with ALI. Furthermore, an increase in the 12-hour PF ratio was associated with a reduced probability of ALI after adjusting for other factors (adjusted OR 0.99 [0.98-0.99]; p = 0.002).

Of the 281 radiographs assessed for Brixia scores, the ICC showed a satisfactory agreement among assessors (ICC = 0.85 [95% CI 0.81-0.88]; p ≤ 0.001). Overall, patients had a considerably high median baseline score (11.0 [9.0-12.0]), and both upper lung zones had higher scores than the rest of the lungs (Fig 5, A). The median postoperative Brixia scores increased slightly from the preoperative baseline but did not differ between those with and without ≥48 hours of postoperative ventilation (Table 3; Fig 5, B) Increased POD1 scores were associated with an increased risk of ALI (crude OR 1.22 [1.02-1.50]; p = 0.026); Fig 5, C; Table 4). Both postoperative ICU and POD1 scores also increased significantly in patients who had 24-hour P/F ratios <200 (Fig 5, D; Table 4). Lastly, an inverse correlation existed between the 24-hour P/F ratios and the POD1 Brixia scores (Pearson's r = −0.33, p = 0.004) (Table 5).The authors further categorized patients into 3 groups based on their Brixia scores (0-6, 7-12, and 13-18) (Fig 6) and found that patients with POD1 scores of 13 to 18 had significantly longer ICU length of stay compared to scores of 7 to 12. Additionally, post-CPB transfused volume (platelet, cryoprecipitate, and salvaged red cells) differed among the 3 groups, with patient scores of 13 to 18 receiving the largest transfusion volume (Fig 7).

Discussion

In this retrospective single-center study involving neonates diagnosed with dTGA IVS who underwent ASO, the authors found the following: (1) high incidence of acute lung injury and ≥48-hour mechanical ventilation, (2) perioperative factors that are associated with mechanical ventilation duration and acute lung injury, and (3) utility of Brixia scores as a predictor of acute lung injury in neonatal cardiac surgeries.

In recent years, the duration of mechanical ventilation and the use of enhanced recovery/fast-track protocols have emerged as important factors in improving outcomes and reducing healthcare costs.[7,10,11] With that notion, the authors' study evaluated the incidence and risk factors associated with postoperative ventilation in neonates undergoing ASO, considered as a moderate- to high-risk cardiac surgery.[12] They reported that approximately 60% of patients in their cohort required more than 48 hours of postoperative mechanical ventilation. This specific threshold was selected based on the characteristics of the authors' patient group, institutional practice, and previous studies of similar surgical procedures. Previous

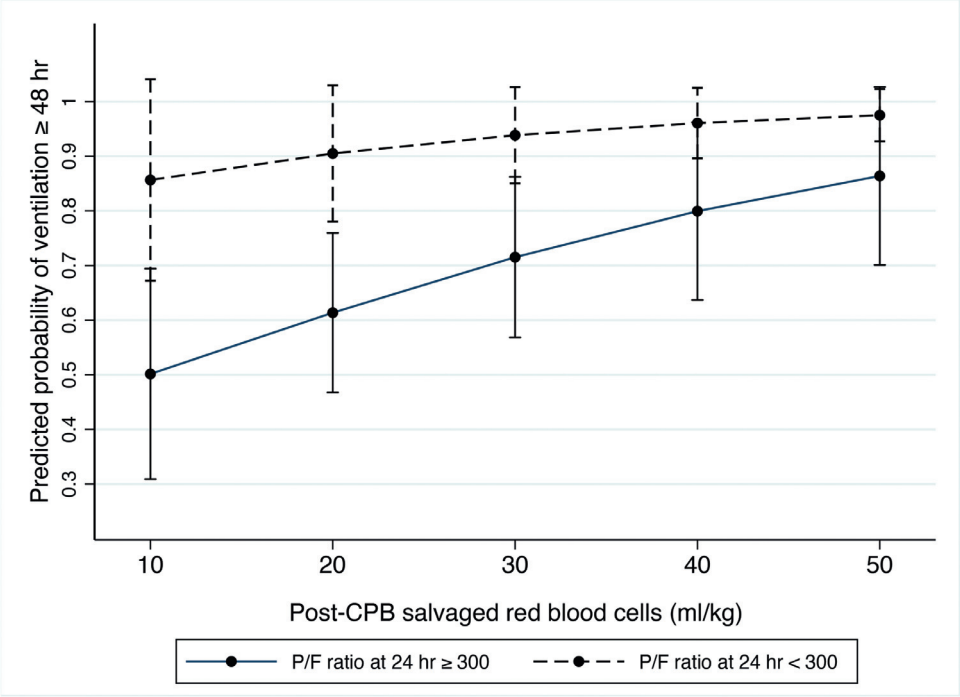

Figure 4. Predicted probability of prolonged mechanical ventilation based on the interaction between the volume of salvaged red blood cells received and 24-hour P/F ratios.

Note: date presented as predicted probability and 95% confidence interval.

Abbreviation: P/F ratio, PaO_2/F_IO_2 ratio.

studies reported varying durations of mechanical ventilation after ASO; interestingly, they ranged from on-the-table/early extubation to several days.[13-19] Although immediate/early extubation has been successful after ASO in previous reports, the authors' institution has not used such practice. Out of 93, only 8 patients in their cohort were extubated in fewer than 24 hours (median 23.0 [21.8-23.7]). It is challenging to compare one specific outcome (eg, duration of ventilation) among institutions as there are various contributing patient and perioperative factors. Early extubation is encouraged according to the European Association for Cardio-Thoracic Surgery dTGA IVS guideline.[20] However, high-quality studies, although limited to feasibility due to the nature of the cases, are needed to determine the benefits, risks, and optimal practice strategies to achieve the recommended target. Nonetheless, based on the authors' institution's data and by recognizing the need to enhance outcomes and align with current and future practice trends in the field, they determined the 48-hour threshold as the reasonable outcome in this study.

Predictors of mechanical ventilation duration after neonatal cardiac surgeries have been previously reported in cohorts comprising a wide range of congenital heart diseases[6,17,21-24]; these include prematurity, longer CPB time, surgical complexity, amount of transfused blood products, acute kidney injury, and inotropes use. Prematurity was reported as a preoperative risk factor for delayed extubation after ASO[24]; the authors found that none of the patients with <48 hours of ventilation was premature compared to 17% of their counterparts. The contribution of the immature lungs and increased pulmonary blood flow from intracardiac and extracardiac shunts in TGA

Table 3
Brixia Scores and Ventilation Duration

Brixia Scores	Total (n = 93)	Ventilation <48 h (N = 34)	Ventilation ≥48 h (N = 59)	p Value
Preoperative	11.0 (9.0-12.0)	10.0 (9.0-12.0)	11.0 (9.0-13.0)	0.350
Postoperative	12.0 (10.0-13.0)	11.0 (10.0-13.0)	12.0 (9.0-13.0)	0.970
POD1	12.0 (10.0-14.0)	12.0 (9.0-13.0)	12.0 (10.0-14.0)	0.180
Post − preoperative difference	1.0 (−2.0 to 3.0)	1.0 (−1.0 to 3.0)	0.0 (−2.0 to 3.0)	0.320
POD1 − preoperative difference	0.0 (−1.0 to 3.0)	0.0 (−2.0 to 2.0)	1.0 (0.0-3.0)	0.089
POD1 − preoperative difference	1.0 (−2.0 to 4.0)	1.0 (−2.0 to 4.0)	1.0 (−2.0 to 4.0)	0.740

Data are presented as median (IQR).
Abbreviation: POD, postoperative day.

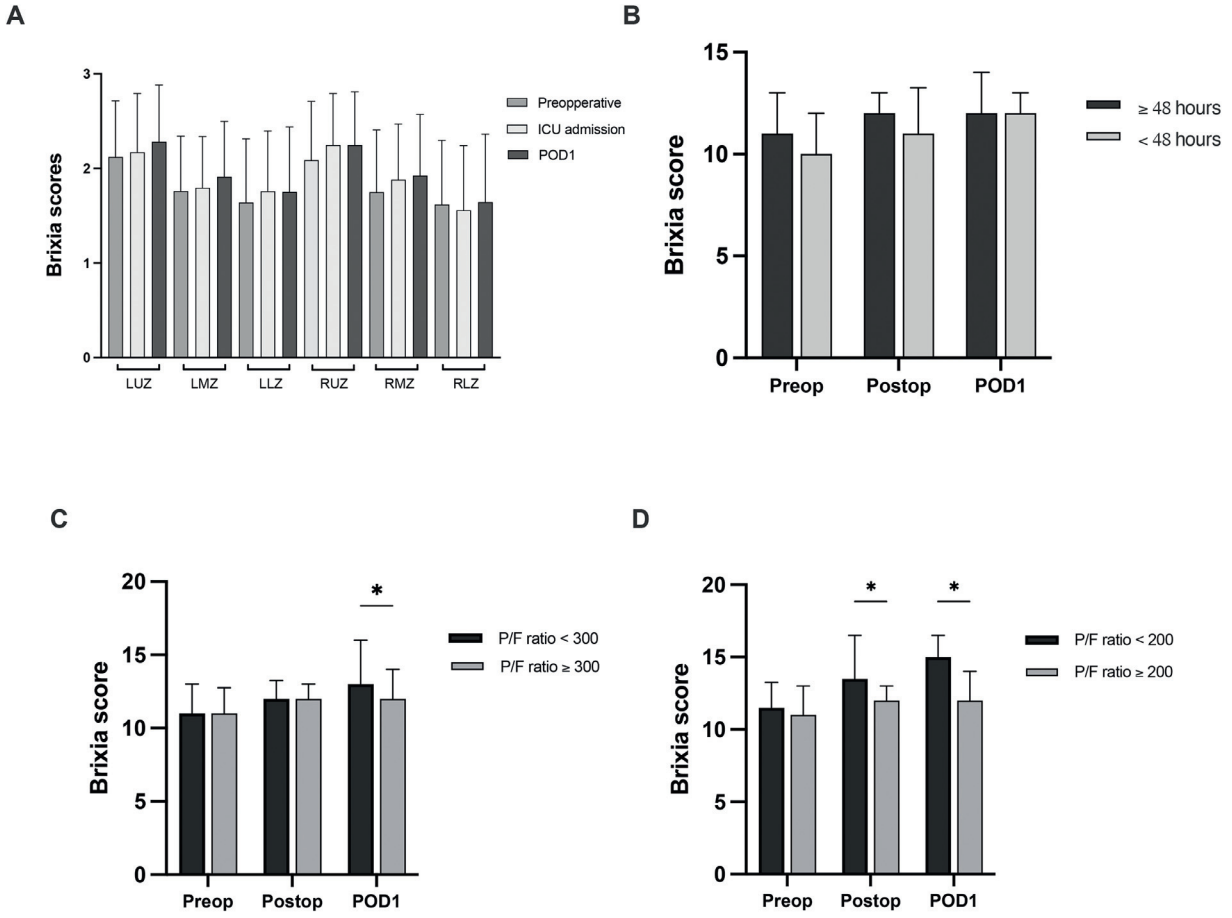

Figure 5. **(A)** Comparisons of Brixia scores from each lung zone at preoperative baseline, postoperative ICU admission, and POD1, **(B)** Comparisons of Brixia scores between patients with ≥ 48 and < 48 hours ventilation, **(C)** Comparison of Brixia scores between patients with and without ALI, **(D)** Comparison of Brixia scores between patients with and without 24-hour P/F ratio < 200.

Note: (A) Data are presented as mean, SD; (B) − (D) Data are presented as median, IQR;

* represents a statistically significant interval difference (p-value < 0.05) between groups.

Abbreviation: P/F ratio, PaO_2/FiO_2 ratio, POD, postoperative day; LUZ, left upper lung zone; LMZ, left middle lung zone; LLZ, left lower lung zone; RUZ, right upper lung zone; RMZ, right middle lung zone; RLZ, right lower lung zone.

might explain the findings. The authors also found that most patients had a brief period of mechanical ventilation preoperatively due to either needing cardiorespiratory support during BAS or apnea due to prostaglandin use. Patients were often extubated before surgery. Mechanical ventilation, although for a brief period, potentially could result in lung injury before surgery and lead to delayed lung function recovery.[5,25]

It should be noted that even though the ≥48 hours ventilation group had significantly higher P/F ratios in the early postoperative period, they later became lower than the <48 hours group. This is likely explained by the higher incidence of delayed sternal closure in this group (23.7% *v* 0%). Patients with delayed sternal closure had higher P/F ratios at ICU admission and at 6 hours (339.0 [275.0-414.0] *v* 239.5 [164.0-

Table 4
Brixia Score and Severities of Acute Lung Injury at Preoperative Baseline, Postoperative at ICU Admission, and POD1

Brixia Scores, median (IQR)	P/F Ratio ≥300 (n = 49)	P/F Ratio <300 (n = 26)	p Value	P/F Ratio ≥200 (n = 69)	P/F Ratio <200 (n = 6)	p Value
Preoperative	11.0 (8.5-12.5)	11.0 (9.0-13.0)	0.94	11.0 (9.0-13.0)	11.5 (11.0-12.0)	0.71
Postoperative	12.0 (10.0-13.0)	12.0 (10.0-13.0)	0.50	12.0 (10.0-13.0)	13.5 (12.0-16.0)	0.018*
POD 1	12 (9.0-14.0)	13.0 (12.6-16.0)	0.027*	12.0 (10.0-14.0)	15.0 (13.0-16.0)	0.046*

Abbreviations: ICU, intensive care unit; POD, postoperative day.

* Represents statistical significance.

Table 5
Correlation Analysis

Correlation Analysis	Pearson's Coefficient	p Value
OI and OSI (ICU admission)	0.42	< 0.001*
OI and OSI (6-h)	0.65	< 0.001*
OI and OSI (12-h)	0.65	< 0.001*
OI and OSI (24-h)	0.67	< 0.001*
OSI ICU and P/F ratio_ICU	−0.30	0.01*
OSI 6 h and P/F ratio 6 h	−0.45	< 0.001*
OSI 12 h and P/F ratio 12 h	−0.30	0.008*
OSI 24 h and P/F ratio 24 h	−0.33	0.01*
Preoperative Brixia		
P/F ratio intraoperative	0.14	0.204
P/F ratio post-CPB	0.02	0.876
ICU admission Brixia		
P/F ratio post-CPB	−0.03	0.779
P/F ratio ICU admission	0.15	0.159
P/F ratio 6 h	−0.10	0.366
P/F ratio 12 h	−0.14	0.202
P/F ratio 24 h	−0.16	0.164
POD 1 Brixia		
P/F ratio first ICU	0.06	0.564
P/F ratio 6 h	0.02	0.855
P/F ratio 12 h	−0.15	0.161
P/F ratio 24 h	−0.33	0.004*
P/F ratio 48 h	−0.09	0.560

Abbreviations: CPB, cardiopulmonary bypass; ICU, intensive care unit; OI, oxygenation index; OSI, oxygenation saturation index; P/F ratio, PaO_2/F_IO_2 ratio; POD, postoperative day.

* Represents statistical significance.

330.0], p = 0.002, 381.5 [285.0-513.0] *v* 293.5 [250.0-350.0], p = 0.031, respectively). They also exhibited longer mechanical ventilation duration (131.4 [99.1-187.7] *v* 49.3 [37.1-90.2], p < 0.001) with the median duration from ICU admission to chest closure procedure of 64.7 (minimum 18.85, maximum 108.18) hours.

It is not uncommon to replace coagulation factors and platelets during the post-CPB period in neonatal cardiac surgery. In the authors' cohort, similar to a recent study,[26] post-CPB platelet and cryoprecipitate transfusions were associated with prolonged mechanical ventilation. Furthermore, although salvaged blood is considered safe in pediatric cardiac surgeries[27-29] and routinely transfused at the authors' institution, they found that a larger transfused volume was associated with a longer ventilation duration. However, after adjusting for other variables, the salvaged blood or blood component volume was not associated with prolonged mechanical ventilation. Only platelet volume was associated with ALI, which was supported by a previous study in a pediatric cardiac surgery cohort.[21] It is also worth mentioning that only a few studies reported associations between transfused salvaged red blood cell volume and clinical outcomes in pediatric cardiac surgeries. The authors' median transfused volume was 22 (14.5-35.7) mL/kg for the entire cohort and 29 (15.5-41.9) mL/kg in the ≥48-hour ventilation group. In contrast, previous randomized trials involved pediatric cardiac patients who received an average volume of salvaged red blood cells up to 38 mL/kg.[27,29] In these trials, there was no association with prolonged ventilation. However, these studies included various patient diagnoses and ages, with limited emphasis on neonates. Further studies to determine the effects of salvaged blood and postoperative adverse outcomes in neonates are still needed. Although platelet transfusions are common in neonatal cardiac surgery, similar to the volume of salvaged red cells, the associations between platelet volume and clinical outcomes are not commonly reported. This warrants further studies to investigate whether the adverse outcomes resulted from the inflammatory response after transfusions or simply due to the excess alveolar and/or interstitial fluid. Some notable concerns for salvaged blood are the quality of the washed red blood cells and the increase in free hemoglobin due to hemolysis. Intraoperative blood processing increases red blood cell concentration and removes inflammatory mediators, but adversely increases red blood cell fragility with a higher tendency to hemolyze compared to nonwashed red blood cells.[30,31] Elevated free hemoglobin concentrations after pediatric cardiac surgery result in adverse outcomes, including infection, thrombosis, and death.[32] Furthermore, transfusing adult platelets to the very different physiologic environment of neonates may cause a developmental mismatch, leading to adverse events.[33] Platelets interact with various immune cells. Adult platelets, but not neonatal platelets, promote inflammatory responses through monocyte migration and neutrophil extracellular trap formation. These responses are hypothesized to contribute to transfusion-related organ injury in neonates receiving adult platelets, with the lungs being one of the affected organs.[33,34]

The authors also found that the ≥48-hour ventilation group had lower hemoglobin levels, higher positive fluid balance, and a higher incidence of blood transfusions after surgery. This may indirectly indicate that these patients experienced more blood loss, which resulted in more transfusions and worsened outcomes. The authors' findings were consistent with a large neonatal cardiac surgery cohort,[35] which found that patients with >10% weight-based fluid balance on POD2 had significantly longer postoperative ventilatory support and major postoperative complications. Another recent study on 643 pediatric cardiac surgery patients found that post-CPB red blood cells, cryoprecipitate, and platelet transfusions were associated with increased duration of mechanical ventilation, renal impairment, and mortality.[27] Thus, further emphasis should be placed on reducing transfusions through meticulous surgical hemostasis, CPB management, and optimal goal-directed transfusions. Interestingly, a recent study reported a transfusion-free rate of 52% for ASO in 100 consecutive neonates with dTGA. The combination of thromboelastometry and protocol-driven perioperative practice was employed successfully, which resulted in a low transfusion rate while maintaining optimal patient outcomes in this study. However, mechanical ventilation duration and other early postoperative outcomes were not reported.[36]

Dexmedetomidine, with known antiinflammatory and organ-protective effects,[37] is used commonly in cardiac anesthesia and postoperative sedation. It has been shown to shorten ventilation duration after pediatric cardiac surgery in clinical

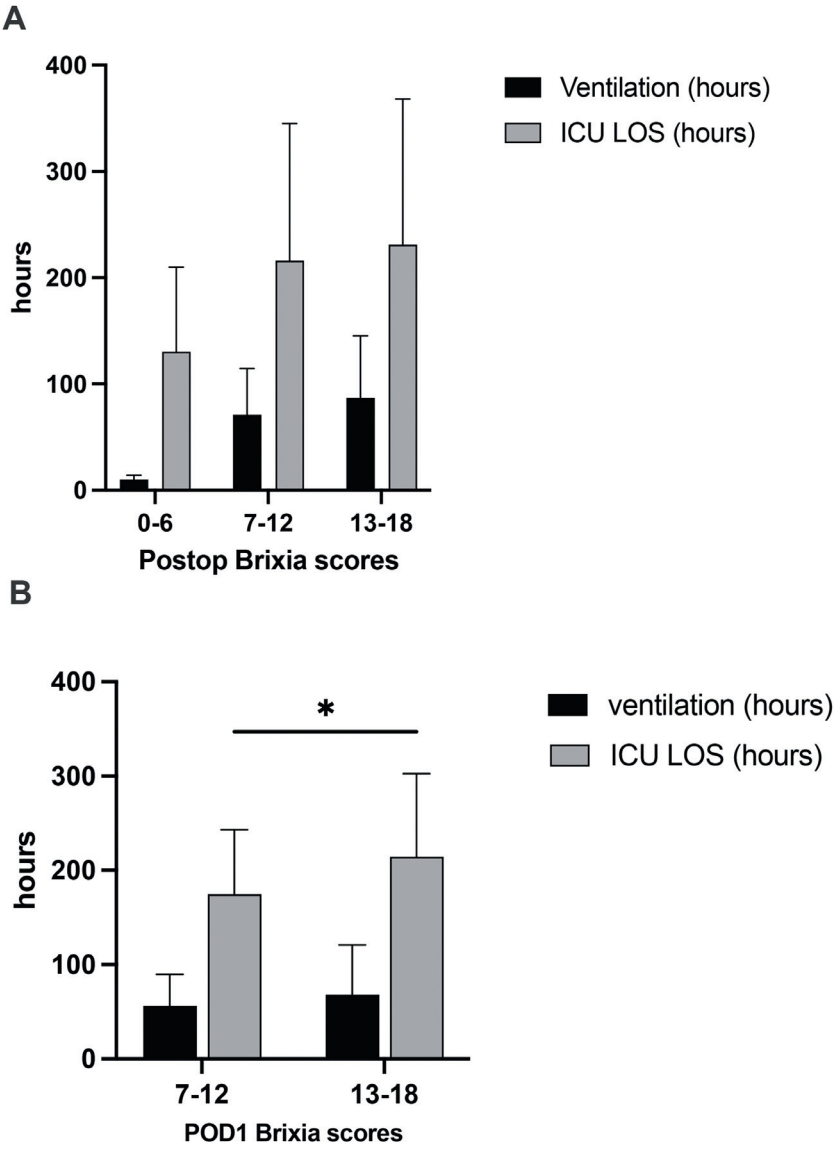

Figure 6. **(A)** Postoperative Brixia scores, mechanical ventilation duration, and ICU length-of-stay, **(B)** POD1 Brixia scores, mechanical ventilation duration, and ICU length-of-stay (LOS). Note: Data are presented as median, IQR; * represents p-value = 0.002 (two-way ANOVA).

trials, and is considered a part of early extubation protocols.[38,39] The authors found that the proportion of patients who received dexmedetomidine sedation was lower in the prolonged ventilation group, but the difference did not reach statistical significance.

Intracardiac mixing in congenital heart disease can make the diagnosis of lung injury with P/F ratio challenging. To better characterize postoperative lung injury and mechanical ventilation duration, the authors evaluated a novel chest radiographic scoring system, specifically the Brixia score.[8,9] During the COVID-19 pandemic, the Brixia score was developed for risk stratification of patients with COVID-19, and has later been adopted in various settings.[40] These scores have been shown to correlate well with patient outcomes and are practical in routine patient care.[40-42] The authors demonstrated that non-radiologists could report the scores with an acceptable interobserver agreement after training by a radiologist. They found that patients who later developed ALI had increased Brixia scores on the postoperative ICU admission and the first postoperative day. After ASO, it is likely that normal circulation has returned, and intracardiac mixing is negligible. Thus, the authors' findings suggested correlations between the Brixia score and alveolar gas exchange (POD1 Brixia and 24-hour P/F ratio had Pearson's $r = -0.3268$, $p = 0.004$). However, given the exploratory nature of their data, further studies are needed to evaluate its usefulness in characterizing respiratory outcomes, especially in those left with mixing of oxygenated and nonoxygenated blood after surgery. In the meantime, the authors' observations suggested that increased Brixia scores in the early postoperative period can be used to inform providers of the increased likelihood of adverse outcomes after ASO (ALI and increased ICU length of stay) and warrant proactive

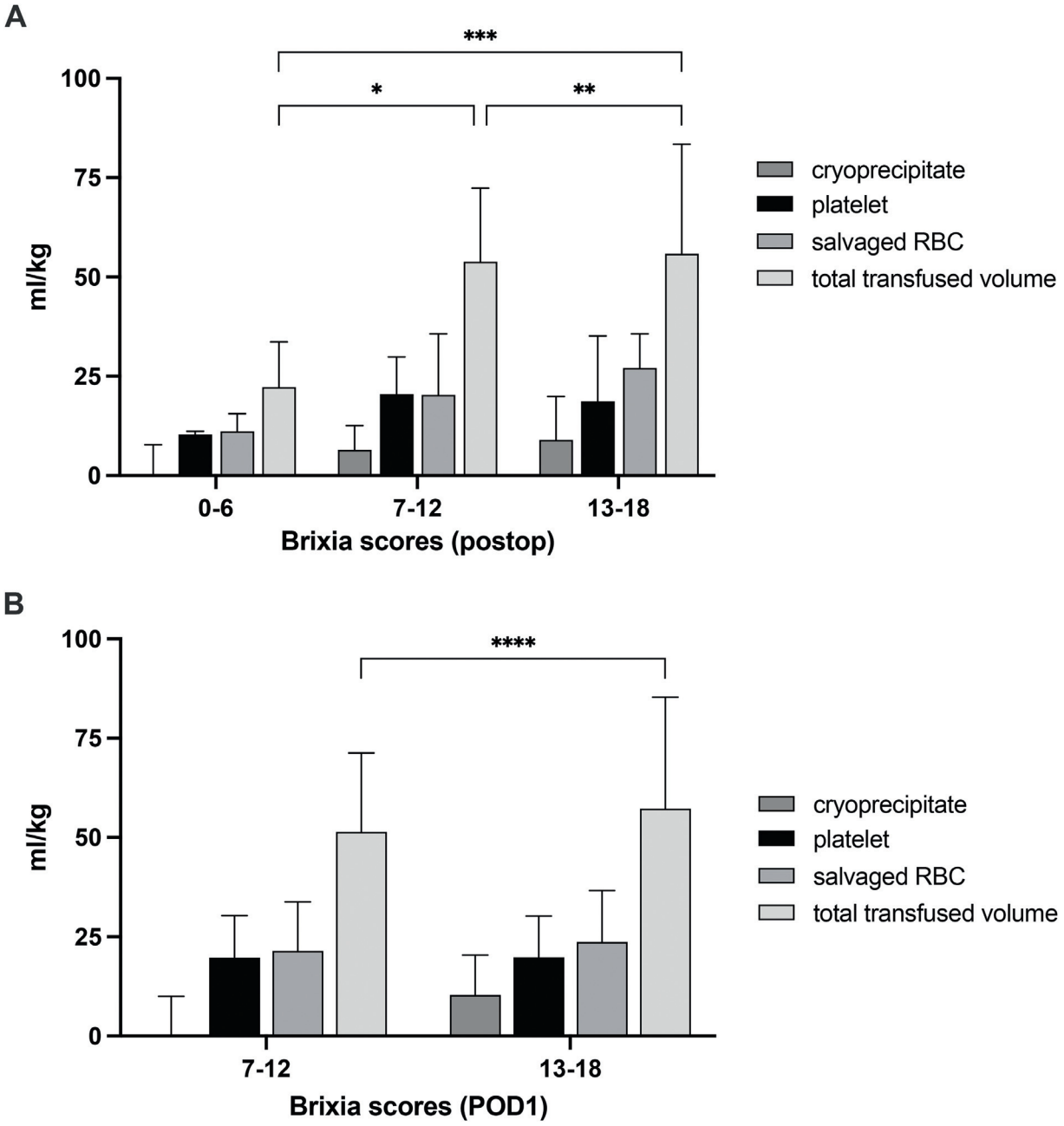

Figure 7. **(A)** Postoperative Brixia scores and volume of post-CPB transfusions. Note: Data are presented as median, IQR; * represents p-value = 0.047; ** p-value = 0.002; *** p-value = 0.001 (two-way ANOVA with Tukey's multiple comparisons). **(B)** POD1 Brixia scores and post-CPB transfusions. Note: Data are presented as median, IQR; * represents p-value < 0.001 (two-way ANOVA with Bonferroni's correction).

measures to facilitate early recovery. It also will be interesting to compare the radiographic findings from other institutions where immediate/early extubation is practiced commonly. The authors should emphasize that although the scoring method is straightforward, a brief training period is useful to ensure standardized readings.

Study Limitations

This study had the following limitations. Firstly, the authors' data were from a single institution with a relatively small sample size. Practice variations and potential improvements in patient care over the 8-year study period also should be considered. Secondly, their analysis did not include coronary anatomy and other surgical factors. Although this was a homogeneous dTGA IVS study group, these factors may contribute to postoperative outcomes. Thirdly, the authors did not analyze ICU sedation management and other provider-related factors that influenced the decision to extubate the patients. Finally, the presence of chest tubes and other devices may limit interpretations of the Brixia scores after cardiac surgeries.

Conclusions

This study concluded that most patients had ≥48-hour mechanical ventilation after ASO. The etiologies of postoperative lung injury and delayed recovery are likely multifactorial, with platelet transfusion being a potential modifiable risk factor. Thus, perioperative transfusion should be tailored to achieve satisfactory coagulation while maintaining optimal fluid balance. Further, the authors showed that the Brixia score, a straightforward chest radiograph scoring system, can be effective in quantifying postoperative lung injury after neonatal cardiac surgery, although additional study is needed to determine its diagnostic clinical utility.

Declaration of competing interest

None.

CRediT authorship contribution statement

Panop Limratana: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **Wiriya Maisat:** Investigation, Writing – review & editing. **Andy Tsai:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Koichi Yuki:** Conceptualization, Funding acquisition, Investigation, Project administration, Writing – review & editing, Methodology.

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