

Impairment in Preextubation Alveolar Gas Exchange Is Associated With Postextubation Respiratory Support Needs in Infants After Cardiac Surgery

OBJECTIVES: To determine if indices of alveolar gas exchange preextubation predict postextubation respiratory support needs as well as the need for escalation of therapies following infant cardiac surgery.

DESIGN: Retrospective chart review.

SETTING: Pediatric cardiac ICU in a quaternary-care teaching hospital.

PATIENTS: Infants less than 1 year old who underwent biventricular repair from January 2015 to December 2017.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Preextubation alveolar-arterial gradient, oxygenation index, oxygen saturation index, P_{aO_2}/F_{iO_2} ratio, and dead space ventilation (analyzed with both end-tidal carbon dioxide gradient and dead space fraction) were evaluated for each patient. All but dead space ventilation were associated with a higher level of noninvasive respiratory support immediately postextubation. Furthermore, impaired preextubation gas exchange was independently associated with escalation of respiratory support within the first 48-hour postextubation.

CONCLUSIONS: Validated measures of alveolar gas exchange can be used as a tool to assess postextubation respiratory support needs including the risk of escalation of respiratory support in the first 48-hour postextubation. Prospective study with implementation of extubation guidelines, both for readiness and determination of early postextubation support, is needed to validate these findings.

KEY WORDS: congenital heart surgery; extubation readiness; gas exchange; P_{aO_2}/F_{iO_2} ratio; postoperative care; pulmonary function

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Predicting extubation success in critically ill patients is an ongoing challenge for the intensivist (1–10). In PICUs, the frequency of extubation failure requiring reintubation ranges between 5% and 22% (11–13) and has been shown to be associated with greater morbidity and mortality (10, 12, 14). Data specific to cardiac critical care is limited, though the Pediatric Cardiac Critical Care Consortium (PC [4]) has reported that extubation failure requiring reintubation within 48 hours occurs in 5.4% of extubations within cardiac ICUs, with the only independent risk factor being prolonged duration of mechanical ventilation (15). There is a paucity of studies investigating the relationship between objective, validated measures of alveolar gas exchange preextubation and postextubation respiratory support needs in pediatric critical care, and no studies specific to infants following cardiac surgery (2, 7). Thus, we sought to investigate the association between preextubation alveolar

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gas exchange and postextubation respiratory support needs in infants after cardiac surgery.

METHODS AND MATERIALS

Study Design and Patients

This is a retrospective cohort study of patients less than 1 year old who underwent biventricular repair between January 2015 and December 2017. Only patients extubated between postoperative days 1 and 4 were included for the study. Patients extubated in the operating room or on postoperative day 0 were excluded as arterial blood gas data were inconsistently available, and this population was not the focus of our study. Patients extubated after postoperative day 4 were excluded since previous work by PC (4) has already shown prolonged duration of mechanical ventilation to be independently associated with extubation failure. Patients were also excluded if they had preoperative airway or lung abnormalities including patients with a tracheostomy, were mechanically ventilated prior to surgery, or had any history of extracorporeal membrane oxygenation or cardiopulmonary resuscitation. This study was approved by the Institutional Review Board at Texas Children's Hospital/Baylor College of Medicine (protocol number H-43199, approved August 17, 2018).

Data Collection

Demographic, diagnostic, and perioperative data were obtained from the electronic health record, our local PC (4) dataset, and an administrative query. The perioperative data fell into four distinct periods: preoperative, intraoperative, postoperative preextubation, and postextubation. Preoperative clinical data included age and anthropometrics at surgery, the presence of genetic syndromes or extracardiac anomalies, and preoperative respiratory support. Intraoperative data included The Society of Thoracic Surgery-European Association of Cardio-thoracic Surgery (STAT) mortality risk score, total anesthesia time, cardiopulmonary bypass time, and aortic cross-clamp time. Postoperative respiratory support and arterial blood gas data were reviewed at predetermined time intervals: 2 hours following arrival to the cardiac ICU, each morning until day of extubation, and prior to extubation. From these data points, several measures of hypoxemia and dead-space ventilation were calculated (**Supplemental Table 1**, <http://links.lww.com/CCX/A973>). Additional data collected

included the vasoactive inotrope score (VIS) calculated at the same time intervals as respiratory support, and cumulative opiate and benzodiazepine doses either the 24 hours preceding extubation or from postoperative ICU admission to extubation if the patient was intubated less than 24 hours. Postextubation respiratory support was collected immediately following extubation, at 24-hour postextubation, and at 48-hour postextubation.

Statistical Analysis

Analyses were performed with Stata (Software Version 15.1, Statacorp, College Station, TX). Patient characteristics and outcomes were summarized using mean with SD for normally distributed data, median with 25th and 75th percentiles for skewed data, and frequency with percentage. Gas exchange variables are compared by respiratory support and escalation using analysis of variance, quantile regression, chi-square test, and Fisher exact test. Unadjusted and multivariable logistic regressions assessed the association between characteristics and gas exchange labs with the odds of escalation of respiratory support within 48 hours. Receiver operator characteristic (ROC) curves assessed the predictive ability of gas exchange values for escalation of respiratory support within 48 hours. A *p* value of less than 0.05 was considered significant.

RESULTS

Over the 3-year study period, 303 infants underwent biventricular repair. After applying our exclusion criteria, 205 patients were analyzed for the study (**Fig. 1**). The median age at surgery was 102 days (interquartile range [IQR], 43–180 d) with a mean weight of 5.0 ± 1.6 kg. Concomitant extracardiac anomalies were uncommon though nearly a third of patients had Trisomy 21. The majority of surgeries (92%) fell into STAT 1-3 categories. Twenty percent of patients received preoperative respiratory support ranging from simple nasal cannula to noninvasive continuous positive airway pressure (CPAP) (**Table 1**).

The median duration to initial extubation for the cohort was 22 hours (IQR, 16–45 hr). At the time of extubation, median VIS for the cohort was 2.5 (IQR, 0.0–4.8). The median cumulative fentanyl dose was 11.8 $\mu\text{g}/\text{kg}$ (IQR, 0.0–32 $\mu\text{g}/\text{kg}$), and median cumulative midazolam dose was 0.1 mg/kg (IQR, 0.0–0.4 mg/

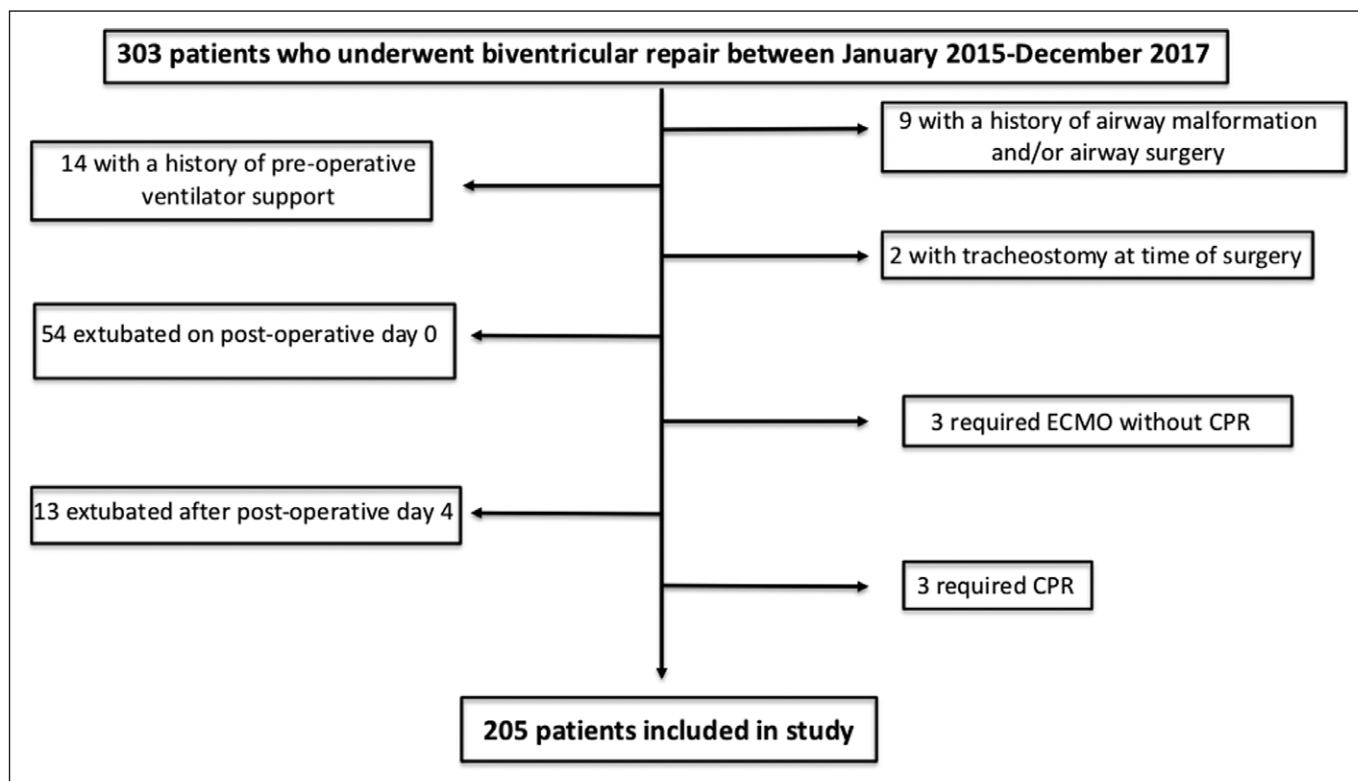


Figure 1. Over the 3-yr study period, 303 infants underwent biventricular repair. After applying our exclusion criteria, 205 patients were analyzed for the study. CPR = cardiopulmonary resuscitation.

kg) in the 24 hours preceding extubation or from post-operative ICU admission to extubation if intubated less than 24 hours.

The vast majority (90%) of patients were extubated to either simple nasal cannula or high-flow nasal cannula. Overall, worse preextubation gas exchange was associated with a higher level of respiratory support immediately postextubation for all indices of gas exchange except for arterial end-tidal carbon dioxide gradient and dead space fraction (Table 2).

Thirty patients (15%) had escalation of respiratory support during the 48-hour postextubation: five were reintubated, 15 had escalation to CPAP, nine escalated to high-flow nasal cannula, and one escalated from room air to simple nasal cannula. Oxygenation index (OI) and P_{aO_2}/F_{iO_2} (P/F) ratio were significantly worse in the cohort who had escalation of respiratory support compared with those who did not (Table 3).

Independent logistic regression identified preextubation alveolar-arterial (A-a) gradient, OI, and P/F ratio to each be independently associated with escalation of respiratory support within the first 48-hour postextubation (Table 4). No patient or operative characteristic was associated with escalation of respiratory support within the first 48-hour postextubation

(Table 5). In the ROC analysis, OI and P/F ratio had the highest association with escalation of respiratory support within the first 48-hour postextubation, with areas under the curve of 0.69 (95% CI, 0.58–0.79) and 0.68 (95% CI, 0.57–0.79), respectively. Furthermore, an OI greater than or equal to 2.5 (sensitivity of 63% and specificity of 62%) and a P/F ratio less than or equal to 316 (sensitivity of 67% and specificity of 64%) were the two cutoff points that showed the highest combination of sensitivity and specificity for predicting escalation of respiratory support within the first 48-hour postextubation (Supplemental Fig. 1, <http://links.lww.com/CCX/A974>).

DISCUSSION

This investigation represents the first report that identifies the association between preextubation alveolar gas exchange and postextubation respiratory support needs in infants after cardiac surgery. Our first observation was that patients with worse preextubation gas exchange were extubated to higher levels of respiratory support. It is difficult to ascertain, in the absence of standardized extubation practices at our institution, how physicians determined the level of

TABLE 1.
Patient and Perioperative Characteristics

Variables	All Subjects (n = 205)
Gender	
Female	87 (42.4)
Male	118 (57.6)
Race	
Caucasian	73 (35.6)
African American	23 (11.2)
Hispanic	86 (42.0)
Asian	17 (8.3)
Other	6 (2.9)
Gestational age	
Full term	155 (75.6)
Preterm	50 (24.4)
Age at surgery (d)	102 (43.0–180.0)
Weight at surgery (kg)	5 (1.6)
Weight:age z score at surgery	−1.8 (1.5)
Weight:height z score at surgery	−0.8 (1.6)
Height at surgery	57.8 (7.0)
Genetic syndromes	
None	127 (62.0)
Trisomy 21	21 62 (30.2)
Trisomy 18	18 1 (0.5)
Turner syndrome	2 (1.0)
DiGeorge syndrome	2 (1.0)
Other	11 (5.4)
Extracardiac anomalies	
None	183 (89.3)
Airway/respiratory	2 (1.0)
Gastrointestinal	8 (3.9)
Skeletal	5 (2.4)
Other	7 (3.4)
Preoperative respiratory requirements	
None	161 (78.5)
Simple nasal cannula/facemask	18 (8.8)
High-flow nasal cannula	16 (7.8)
Continuous positive airway pressure	10 (4.9)
Society of Thoracic Surgery-European Association of Cardio-thoracic Surgery categories	
1	80 (39.0)
2	51 (24.9)
3	57 (27.8)
4	17 (8.3)

(Continued)

TABLE 1. (Continued).
Patient and Perioperative Characteristics

Variables	All Subjects (n = 205)
Total anesthesia time (min)	480.5 (119.8)
Cardiopulmonary bypass time (min)	183 (122.0–232.0)
Aortic cross-clamp time (min)	127 (87.0–166.0)
Preextubation vasoactive inotrope score	2.5 (0.0–4.8)
Sedative medications received 24 hr prior to extubation odds ratio ICU admission to extubation (if intubated < 24 hr)	
Fentanyl (µg/kg)	11.8 (0.0–32.0)
Versed (mg/kg)	0.1 (0.0–4.0)

Data are presented as absolute number with percentages, mean with sd, or median with interquartile ranges.

respiratory support immediately following extubation. Specifically, we cannot ascertain whether postextubation support was ordered based on preextubation gas exchange derangements, work of breathing just prior to or during extubation, cardiovascular status, radiographic findings, provider preference, or a combination of these factors. Future work is needed to explore the association between preextubation gas exchange and appropriate utilization of immediate postextubation respiratory support in this cohort, specifically looking at the two most common used modalities: high-flow nasal cannula and simple nasal cannula. Adult literature suggests that high-flow nasal cannula may provide a physiologic benefit postextubation, as a recent meta-analysis showed that high-flow nasal cannula was associated with improved oxygenation, lower respiratory rate, and decreased

rate of extubation failure after planned extubations when compared with conventional oxygen therapies (16). Furthermore, two recent studies by Shioji et al (17, 18) examined that the use of high-flow nasal cannula for postextubation respiratory failure after cardiac surgery in children showed the application of high-flow nasal cannula, after the development of respiratory failure, and significantly lowered respiratory rates and rates of reintubation. However, none of these studies have correlated preextubation gas exchange with this potential postextubation therapeutic benefit. Thus, further work is needed to correlate these potential postextubation physiologic benefits of high-flow nasal cannula with indices of preextubation alveolar gas exchange to identify a cohort of patients who may benefit from high-flow nasal cannula prior to the development of postextubation respiratory failure as

TABLE 2.
Differences in Preextubation Gas Exchange Across Levels of Postextubation Respiratory Support Immediately Following Extubation

Gas Exchange Index	Room Air (n = 3)	Simple Nasal Cannula (n = 97)	High-Flow Nasal Cannula (n = 87)	Continuous Positive Airway Pressure (n = 18)	p
Oxygenation index	1.9 (1.8–1.9)	2 (1.7–2.7)	2.5 (2.0–3.4)	3.9 (2.3–4.9)	< 0.001
Alveolar-arterial gradient	72 (17–75)	64 (38–96)	85 (56–136)	123 (41–157)	0.011
Oxygen saturation index	3 (2.7–3.0)	2.8 (2.5–3.3)	3.2 (2.8–3.4)	3.4 (2.8–3.6)	< 0.001
Pao ₂ /Fio ₂ ratio	403 (398–513)	392 (270–467)	323 (248–400)	221 (178–388)	< 0.001
Arterial end-tidal CO ₂ gradient	2 (0–3)	3 (0–6)	4 (0–7)	5 (2–7)	0.338
Dead space fraction	0.1 (0.0–0.1)	0.1 (0.0–0.1)	0.1 (0.0–0.2)	0.1 (0.0–0.2)	0.485

Data are presented as medians with interquartile ranges. *p* values for medians generated using quantile regression with *p* < 0.05 are considered significant.

TABLE 3.**Comparison of Preextubation Gas Exchange in Patients With and Without Escalation of Respiratory Support Within 48-hr Postextubation**

Gas Exchange Index	No Escalation (n = 175)	Escalation (n = 30)	p
Oxygenation index	2.2 (1.8,3.0)	3.3 (2.2–4.2)	0.001
Alveolar-arterial gradient	76 (44–120)	107 (52–160)	0.052
Oxygen saturation index	3.0 (2.6–3.4)	3.1 (2.3–3.6)	0.660
PaO ₂ /Fio ₂ ratio	365 (260–437)	265 (192–370)	0.001
Arterial end-tidal CO ₂ gradient	3 (0–6)	5 (2–9)	0.104
Dead space fraction	0.1 (0.0–0.1)	0.1 (0.1–0.2)	0.109

Data are presented as medians with interquartile ranges. *p* values for medians generated using quantile regression with *p* < 0.05 are considered significant.

well as ensure appropriate and cost-effective use of high-flow nasal cannula.

Our analysis specifically identified three indices of gas exchange to be associated with escalation of respiratory support within the first 48-hour postextubation: A-a gradient, OI, and P/F ratio. This association, to the best of our knowledge, has not been reported on in the pediatric cardiac literature, and globally, there is a paucity of studies examining this association between preextubation gas exchange and escalation of respiratory support postextubation. Most of the data on this subject comes from adult literature, and the data are conflicting, with studies showing both an association between impairments in preextubation gas exchange and reintubation (19–21), as well as no significance on the need for reintubation (22, 23). Furthermore, limited work in the noncardiac PICU showed a correlation between preextubation P/F ratio and OI with extubation failure defined as needing reintubation, but

no data with regard to escalation of respiratory support independent of reintubation (2, 5, 24). Thus, our study identifies potential utilization of these objective lung function metrics prior to extubation in order to better match respiratory support following extubation. This will require follow-up studies in order to better illustrate and potentially validate the importance of gas exchange indices on extubation success.

In contrast to other reports, we did not observe an association between dead space ventilation and need for postextubation escalation of support. Devor et al (25) found that dead space fraction in biventricular cardiac patients to be independently associated with extubation failure in a small cohort of pediatric cardiac patients with a reportedly longer duration of mechanical ventilation compared with our cohort (51 vs 22 hr). Hubble et al (26) found that in an older cohort of general PICU patients, a greater dead space fraction was associated with extubation failure

TABLE 4.**Independent Logistic Regression Assessing Preextubation Gas Exchange and Need for Escalation of Respiratory Support Within the First 48-Hour Postextubation**

Gas Exchange Index	OR (95% CI)	p
Alveolar-arterial gradient (10 unit increase)	1.07 (1.00–1.15)	0.036
Oxygenation index	1.45 (1.05–2.01)	0.024
Oxygen saturation index	1.08 (0.53–2.18)	0.84
PaO ₂ /Fio ₂ ratio (10 unit increase)	0.94 (0.91–0.98)	0.002
Arterial end-tidal CO ₂ gradient	1.05 (0.98–1.13)	0.152
Dead space fraction (0.1 unit increase)	1.26 (0.91–1.76)	0.164

OR = odds ratio.

p values for medians generated using quantile regression with *p* < 0.05 are considered significant.

TABLE 5.

Independent Logistic Regression Assessing Patient Demographic, Preoperative, Intraoperative, and Postoperative Variables and Their Association With Escalation of Respiratory Support Within 48-hr Postextubation

Variable	OR (95% CI)	<i>p</i>	<i>n</i>
Weight	0.81 (0.63–1.04)	0.097	205
Weight:height z score	0.98 (0.78–1.24)	0.880	205
Weight for age z score	0.91 (0.72–1.14)	0.397	205
Height	0.95 (0.90–1.01)	0.081	205
Age at surgery	1.00 (0.99–1.00)	0.126	205
Gestational age	1.05 (0.90–1.24)	0.515	205
Preterm	0.93 (0.37–2.33)	0.884	205
Anesthesia time	1.01 (0.98–1.05)	0.544	205
Cardiopulmonary bypass time	1.01 (0.96–1.05)	0.736	205
Aorta cross-clamp time	1.00 (0.94–1.07)	0.945	205
Male	2.26 (0.95–5.37)	0.064	205
Cumulative fentanyl dose 24 hr preceding extubation	1.00 (0.99–1.01)	0.976	205
Cumulative versed dose 24 hr preceding extubation	1.06 (0.68–1.67)	0.791	205
Race			
Caucasian	Reference	0.417	205
African American	0.76 (0.20–2.99)	0.697	
Hispanic	0.59 (0.23–1.50)	0.272	
Asian	1.56 (0.43–5.64)	0.495	
Other	2.54 (0.41–15.55)	0.313	
Society of Thoracic Surgery-European Association of Cardio-thoracic Surgery category			
1	Reference	0.915	205
2	1.30 (0.48–3.56)	0.607	
3	1.31 (0.49–3.48)	0.585	
4	1.50 (0.36–6.18)	0.575	
Genetic syndrome	1.29 (0.59–2.84)	0.521	205
Extracardiac anomaly	0.91 (0.25–3.31)	0.889	205
Preoperative oxygen requirement			
No	Reference	0.445	205
Simple nasal cannula/facemask	2.43 (0.79–7.51)	0.123	
High-flow nasal cannula	0.90 (0.19–4.26)	0.897	
Continuous positive airway pressure	0.70 (0.08–5.85)	0.744	
Preextubation vasoactive inotrope score	0.98 (0.82–1.18)	0.866	205
Preextubation alveolar-arterial gradient (10 unit increase)	1.07 (1.00–1.15)	0.036	205
Preextubation oxygenation index	1.45 (1.05–2.01)	0.024	205
Preextubation oxygen saturation index	1.08 (0.53–2.18)	0.840	205
Preextubation PaO ₂ /FiO ₂ ratio(10 unit increase)	0.94 (0.91–0.98)	0.002	205
Preextubation arterial end-tidal CO ₂ gradient	1.05 (0.98–1.13)	0.152	205
Preextubation dead space fraction (0.1 unit increase)	1.26 (0.91–1.76)	0.164	205

OR = odds ratio.

defined as the need for reintubation as well as any need for non-invasive positive pressure ventilation. These findings were not replicated in our study and will need further exploration in our population.

Overall, the percentage of patients in our cohort who required reintubation within 48 hours of extubation was 2.4% (5/205), lower than the reported 5.4% in two recent large analyses from the PC (4) database (15, 27). Our observed lower rate of reintubation is multifactorial. Unlike registry reports, we had access to granular patient data, which allowed us to a priori exclude infants with airway or respiratory disease that may have placed the infant at higher risk for extubation failure and excluded them from this analysis. In addition, the PC (4) report included a more heterogeneous population of patients including those undergoing single-ventricle palliation, as well as patients with a higher percentage of STAT 4/5 diagnoses, and nonsurgical admissions (15, 27).

Given the retrospective nature of the study, there are several inherent limitations to the investigation. Though these data represent the experience at a single institution, there is practice variability among cardiac intensivists and lack of specific extubation protocols. Because we preselected the patient population to be studied, these findings are not generalizable across all pediatric cardiac surgery patients particularly those of greater surgical and medical complexity.

CONCLUSIONS

Commonly employed indices of gas exchange for assessment of lung function may be a useful tool to assess preextubation readiness and determine postextubation respiratory support modalities following infant cardiac surgery. Prospective study with implementation of extubation guidelines, both for readiness and determination of early postextubation support, is needed to validate these findings.

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This work was performed and data were collected at Texas Children's Hospital, Baylor College of Medicine, Houston, TX.

The authors have disclosed that they do not have any potential conflicts of interest.

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