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Title: Prospective Multicenter Analysis of Extubation Failure after Neonatal Cardiac Surgery

Short Title: Extubation Failure after Neonatal Cardiac Surgery

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Abstract

Objectives: To describe the epidemiology of extubation failure and identify risk factors for its occurrence in a multicenter population of neonates undergoing surgery for congenital heart disease.

Study Design: We conducted a prospective observational study of neonates ≤ 30 days of age who underwent cardiac surgery at seven centers within the United States in 2015. Extubation failure was defined as reintubation within 72 hours of the first planned extubation. Risk factors were identified using multivariable logistic regression analysis and reported as odds ratios (OR) with 95% confidence intervals (CI). Multivariable logistic regression analysis was also conducted to examine the relationship between extubation failure and worse clinical outcome, defined as hospital length-of-stay in the upper 25% or operative mortality.

Results: We enrolled 283 neonates, of which 35 (12%) failed their first extubation at a median time of 7.5 hours (range: 1-70 hours). In a multivariable model, use of uncuffed endotracheal tubes (OR: 4.6; 95% CI: 1.8-11.6) and open sternotomy of 4 days or more (OR: 4.8; 95% CI: 1.3-17.1) were independently associated with extubation failure. Accordingly, extubation failure was determined to be an independent risk factor for worse clinical outcome (OR: 5.1; 95% CI: 2-13).

Conclusions: In this multicenter cohort of neonates who underwent surgery for congenital heart disease, extubation failure occurred in 12% of cases and was independently associated with worse clinical outcome. Use of uncuffed endotracheal tubes and prolonged open sternotomy were identified as independent and potentially modifiable risk factors for the occurrence of this precarious complication.

Abbreviations :

CI : confidence intervals

ECMO : extracorporeal membrane oxygenation

ICU : intensive care unit

LOS : length of stay

OR : odds ratio

PC4 : Pediatric Cardiac Critical Care Consortium

STAT mortality category : Society of Thoracic Surgeons-European Association for Cardio-thoracic Surgery Society Congenital Heart Surgery Mortality Category

VIS: vasoactive inotrope score

VI: ventilation index

Introduction

As surgical techniques and perioperative management of neonates undergoing surgery for congenital heart disease continue to evolve, mechanical ventilation continues to be a necessary and important component of postoperative management [1,2]. In a small but substantial number of neonates, initial attempts at extubation and liberation from mechanical ventilation fail and reintubation is required. Reintubation of these fragile patients is a high-risk procedure with potential for life-threatening consequences such as profound hypoxemia, cardiovascular instability, and cardiopulmonary arrest. Following reintubation, these neonates are then committed to another course of mechanical ventilation, with its inherent risks and exposures such as ventilator-associated infections, airway trauma, and the need for sedative infusions. In neonates and children undergoing cardiac surgery, extubation failure has been consistently associated with increased postoperative morbidity and mortality [3-7]. Prevention of this important complication is therefore an essential part of optimizing clinical outcomes in this patient population.

Unfortunately, assessment of extubation readiness in critically-ill neonates can be challenging [8]. In many cases, despite reassuring respiratory and hemodynamic indices, extubation failure still occurs. Initial studies focused on extubation failure after surgery for congenital heart disease in neonates, while providing some valuable insight, have been restricted to small single center cohorts and thus have had limited generalizability [6,7,9]. In a recent review of data from the Pediatric Cardiac Critical Care Consortium (PC4), only the presence of an underlying anatomic airway anomaly could be identified as an independent risk factor for extubation failure after neonatal cardiac surgery, but the analysis in this study was limited to the variables available within the registry [10]. We aimed to describe the epidemiology of extubation failure in a large multicenter population of neonates undergoing surgery for congenital heart disease. From these data, we aimed to identify risk factors for extubation failure and determine its impact on clinical outcome.

Materials & Methods

Study Population

All neonates who underwent surgery for congenital heart disease at seven tertiary care pediatric referral centers between January 1 and December 31, 2015 were considered for inclusion in the study. Patients were prospectively enrolled from the following institutions:

- Riley Hospital for Children, Indianapolis, IN – Coordinating center
- Children's Hospital of Michigan, Detroit, MI
- Cleveland Clinic, Cleveland, OH
- Arnold Palmer Hospital for Children, Orlando, FL
- Phoenix Children's Hospital, Phoenix, AZ
- Ann & Robert H. Lurie Children's Hospital of Chicago, IL
- American Family Children's Hospital, Madison, WI

The study was approved by the institutional review boards at all participating centers and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Due to the observational nature of the data collected, the need for informed consent was waived. Neonates less than 2.5 kg who underwent isolated ligation of patent ductus arteriosus, neonates with tracheostomy tubes in place at the time of cardiovascular surgery, and neonates who died or underwent tracheostomy without undergoing any planned extubation attempts were excluded from the analysis.

Operative Protocol and Postoperative Management

Postoperative management and the decision to extubate from mechanical ventilation was left to the discretion of the primary intensive care unit (ICU) teams at each institution. Postoperative management, assessment of extubation readiness, and assessment of endotracheal tube leak were determined by the standard practices of individual study centers and the clinical judgement of individual clinicians working in those centers.

Definitions

Extubation failure was defined as the need for reintubation within 72 hours of first attempted extubation from mechanical ventilation.[7] Patients who underwent endotracheal intubation and another period of mechanical ventilation that was initiated after 72 hours from the first extubation attempt were considered successful initial extubations. A comprehensive list of variables collected and additional definitions are included in Table 1 (online).

Statistical Analysis

Data are represented using descriptive statistics as follows: means with standard deviations for continuous normally distributed variables, medians with 25th percentiles and 75th percentiles for continuous skewed variables, and absolute counts with percentages for categorical variables. To determine the risk factors associated with extubation failure, we performed a bivariate analysis by comparing variables in neonates who required reintubation within 72 hours to those who extubated successfully on their first attempt using t-tests, Mann Whitney U tests, χ -square tests and Fisher's exact test as appropriate for individual variables. All variables with *P*-values < 0.2 on bivariate analysis were considered for inclusion in our multivariate logistic regression model. The multivariable model was also analyzed as a mixed model with a random effect for center. Linearity in the logit was examined for continuous variables prior to model-building; those with evidence of non-linearity were converted to categorical variables. Variables with *P*-values < 0.05 after multivariable analysis were then identified as independent risk factors for extubation failure after neonatal cardiac surgery.

To determine if extubation failure had an independent effect on clinical outcome, we dichotomized hospital LOS as upper 25% and lower 75%, and then defined prolonged LOS as patients in the upper (worst) 25%. Patients with prolonged LOS and patients who died prior to the cut-off value were categorized as having worse clinical outcomes as compared to the rest of

the cohort. Stepwise multivariable regression modeling was then performed to determine if extubation failure was independently associated with worse clinical outcomes. All statistical analyses were performed using STATA version 14 and SAS version 9.4.

Results

We prospectively enrolled 293 neonates underwent surgery for congenital or acquired heart disease in 2015. Ten patients died prior to any extubation attempts and were therefore not included in the analysis. Data were collected for the remaining 283 neonates, who were endotracheally intubated, received mechanical ventilation during their surgical repair or palliation, and had at least one extubation attempt. Median number of subjects enrolled at each institution was 30 (range: 17 - 71). Four institutions were categorized as small-to-moderate volume centers (range: 17 - 30 neonates) and three institutions were categorized as large volume (range: 55 - 71 neonates). Primary surgical procedures are provided in Table 2 (online), organized by STAT mortality category. [11,12] The most common operations performed were the arterial switch procedure (n=60) and the Norwood procedure (n=47).

Thirty-five patients (12%) failed their first extubation attempt at a median time of 7.5 hours after the attempt (range: 1-70 hours). The timing of extubation failure is summarized in Figure 1. The extubation failure rate ranged from 8% - 23% across the participating centers. Extubation failures were broadly distributed across STAT mortality categories and surgical procedures.(Table 2; online) The most common diagnosis implicated as the major contributor to extubation failure was cardiogenic shock (n=11, 31%). Other clinical findings implicated as important contributors to the extubation failures were pulmonary edema (n=7), apnea/hypopnea (n=5), atelectasis (n=3), chylous effusion (n=3), diaphragm paresis (n=3), and stridor (n=2), and hypercarbia (n=1). Vocal cord paresis did not contribute to any of the extubation failures in this cohort. Eight patients (23%) had residual cardiac lesions that were deemed to have possibly contributed to their extubation failures: 3 patients with two ventricle physiology had residual

aortic coarctations, 2 patients had moderate-to-large ventricular septal defects, 1 patient had moderate mitral regurgitation, 1 patient with hypoplastic left heart syndrome had moderate tricuspid regurgitation, and 1 patient had a small non-apex forming left ventricle.

Two patients suffered cardiac arrests at the time of reintubation. One of these patients was a male neonate born with hypoplastic left heart syndrome who underwent the Norwood procedure with Sano modification at 11 days of age and was extubated on postoperative day 12. He developed progressively worsening cardiac failure and cardiogenic shock, and upon reintubation at 59 hours post-extubation, he experienced cardiac arrest, prolonged cardiopulmonary resuscitation, and emergent cannulation for extracorporeal membrane oxygenation. Despite these efforts, the child ultimately died. The second patient was a male neonate with Williams Syndrome born with valvar and supravalvar aortic stenosis and coarctation of the aorta who underwent coarctectomy via end-to-end anastomosis at 3 days of age. He was extubated on postoperative day 2 then acutely deteriorated at 26 hours post-extubation resulting in cardiac arrest. He was immediately reintubated, but resuscitation efforts were unsuccessful and the patient did not survive.

Preoperative, perioperative, and postoperative characteristics of patients who failed their first extubation attempt are compared to patients who were successfully extubated in Tables 3 - 5 (online). Preoperatively, patients who failed extubation were more likely to have hypoplastic left heart syndrome or an underlying airway anomaly, or to require endotracheal intubation and remain on mechanical ventilation until surgery. Center volume or the presence of a dedicated cardiac ICU did not appear to influence the likelihood of extubation failure. Perioperatively, mean endotracheal tube inner diameter size (indexed to body surface area) was greater in patients who failed extubation. In addition, neonates who failed extubation were more likely to have been intubated with uncuffed endotracheal tubes and, as illustrated in Figure 2, this increased prevalence of uncuffed endotracheal tubes was largely responsible for the observed difference in endotracheal tube size. Postoperatively, patients who failed extubation were more

likely to have tachyarrhythmias and had longer durations of mechanical ventilation prior to their first extubation attempts. There was also a notable increase in the likelihood of extubation failure in patients who had an open sternotomy for 4 days or more. No patient in the study developed mediastinitis, and sternal wound infections were only observed in five patients, only one of which had an open sternotomy for 4 or more days. Patients who required open sternotomy for more than 4 days were, however, more likely to receive neuromuscular blockade (87%) as compared to the rest of the cohort (38%, $P<0.001$). At the time of extubation, PEEP tended to be greater than 5 cmH₂O more frequently in patients who failed extubation. The use of prophylactic peri-extubation dexamethasone was not statistically different between groups.

Two patients were extubated in the operating room immediately after surgery and the other 281 patients were extubated postoperatively in the ICU. Respiratory support provided upon extubation is compared in Table 5 (online), and the proportion of patients who required escalation of support are graphically described in Figure 3. Most neonates (n=155, 55%) were extubated to high-flow nasal cannula. The remaining neonates were extubated to room air or oxygen via nasal cannula (n=87, 31%) and non-invasive positive pressure ventilation (n=41, 14%). High-flow cannula was the preferred approach, but no significant advantage was observed with this modality or non-invasive positive pressure in regards to extubation failure.

The results of our multivariable logistic regression analysis are provided in Table 6. Use of an uncuffed endotracheal tube and duration of open sternotomy of 4 days or more were independently associated with extubation failure, in a model that also included hypoplastic left heart syndrome, underlying anatomy airway or respiratory anomaly, PEEP greater than 5 at the time of extubation, and duration of mechanical ventilation. Additional variables that were significant on bivariate analysis such as the presence of underlying genetic anomalies, ECMO, postoperative tachyarrhythmias, and serum lactate were not significant on multivariable analysis and had little effect on the multivariable model. Moreover, the effect of use of uncuffed endotracheal tubes and open sternotomy for 4 or more days remained significant when other

markers of disease complexity and severity such as STAT mortality category, duration of cardiopulmonary bypass, use of inhaled nitric oxide, VIS at 48 hours, or presence of a clinical significant residual lesion were added to the model. In the multivariable mixed model, the random effect of center was estimated to be zero.

Clinical outcomes were significantly worse in patients who failed extubation (Table 7; online). Neonates who failed their first extubation had significantly longer ICU and hospital stays as compared to patients who were successfully extubated, and mortality was significantly higher in neonates who failed their first extubation, 23% as compared to 0.4%. Neonates with lengths of hospital stay in the upper 25% (> 36 days) and neonates who died were categorized as having worse clinical outcomes. After stepwise multivariable regression analysis, extubation failure was an independent predictor of worse outcome after neonatal cardiovascular surgery. Other independent predictors of worse clinical outcome included single ventricle anatomy, genetic or chromosomal abnormality, presence of any non-cardiac anatomic abnormality, occurrence of infection or necrotizing enterocolitis during hospitalization (i.e., pre- or postoperatively), presence of a clinically-significant residual lesion, and duration of mechanical ventilation prior to the first extubation attempt. The results of this multivariable logistic model are provided in Table 8 (online).

Discussion

Extubation failure occurred in 12% of the patients in our heterogeneous population of neonates who underwent surgery for congenital heart disease. Our study is consistent with the recent review of the PC4 registry, which reported an extubation failure rate of 11% in 899 neonates who underwent cardiac surgery [10]. Not surprisingly, the risk of extubation failure in neonates recovering from cardiac surgery appears to be greater than the general population of children receiving mechanical ventilation in cardiac intensive care units, which was recently been reported to be 6% in a multicenter cohort [5]. We observed a range of extubation failure

rates across the seven participating centers in our study, from 8% - 23%, also consistent with the data from the PC4 registry, which reported a range of 5% - 22% [10]. Further, the only retrospective single center study that focused on a heterogeneous population of neonates who underwent cardiac surgery published an extubation failure rate of 17.5% [11]. This variation in extubation failure occurrence rates across centers suggests an opportunity for institutional quality assurance initiatives aimed at decreasing the occurrence of this frustrating and potentially life-threatening complication.

As targets of these quality assurance initiatives, we identified two potentially modifiable risk factors, the first of which was the use of uncuffed endotracheal tubes. Uncuffed endotracheal tubes have historically been more commonly employed in pediatric patients because of the notion that the narrowest point of the airway in young children is at the level of the circumferential, non-distensible cricoid cartilage below the vocal cords [20,21]. Uncuffed endotracheal tubes, when inserted into these airways, should optimally be large enough to seal the cricoid ring but small enough to allow an air leak when airway pressures of 20 to 30 cmH₂O are applied [22]. As our understanding of the developmental changes of the upper airway has improved [22] and modern low-pressure cuffed endotracheal tubes have become readily available [23], uncuffed endotracheal tubes have fallen out of favor in some pediatric institutions. Despite this evolution, use of uncuffed endotracheal tubes is still relatively common for neonatal populations, where concern for airway damage from excessive cuff pressures is especially fervent. In fact, several of the neonates in our study were endotracheally intubated preoperatively by neonatologists with uncuffed tubes, and these tubes remained in use until the first postoperative extubation attempt. Based on our data, physicians in our study chose endotracheal tubes with significantly larger inner diameters (indexed to body surface area) when using uncuffed tubes, presumably to ensure adequate ventilation without an excessive leak. Some authors have asserted that when these larger diameter uncuffed endotracheal tubes are used, irritation of glottic and subglottic areas likely occurs, especially to the rigid cricoid ring and

vocal folds, which are particularly susceptible to damage from mucosal shear [21]. Stridor was only noted in two patients who failed extubation, but significant injury to the upper airway is not always accompanied by stridor [24]. Indeed, in neonates, small decreases in airway diameter from airway edema or inflammation may not cause overt stridor but could markedly increase airway resistance, which is proportional to radius to the fourth power [8]. In neonates with underlying cardiac disease, this increase in airway resistance could overwhelm their limited cardiopulmonary reserve, increase ventricular wall stress (i.e., afterload), and promote extubation failure. Standardized use of smaller diameter low-pressure cuffed endotracheal tubes may be a relatively simple way of decreasing the occurrence rate of extubation failure in neonates recovering from cardiac surgery.

The second potential modifiable risk factor identified herein is prolonged duration of open sternotomy. Though neonates with prolonged open sternotomy likely had greater disease burden in the early postoperative period, this variable remained significant after adjustment for many markers of disease complexity and severity, including the presence of HLHS, STAT mortality category, duration of cardiopulmonary bypass, postoperative vasoactive inotrope score, and duration of mechanical ventilation. Neuromuscular blockade has been shown to potentiate the diaphragmatic atrophy that can occur during mechanical ventilation [25]. Though there was no difference in the number of patients who received neuromuscular blockade in patients who failed extubation and patients who extubated successfully, we did not quantitate the cumulative dose or number of days that neuromuscular blockade was administered. Since nearly 90% of patients with prolonged open sternotomy received neuromuscular blockade, we speculate that cumulative exposure to neuromuscular blockade was likely greater in these neonates as compared to the rest of the cohort. If so, these patients may have had more diaphragmatic weakness at the time of extubation. Other unknown effects of prolonged open sternotomy on respiratory system function could also have played a role. Regardless of the

pathophysiology behind our finding, earlier sternal closure when possible may improve the chances of successful neonatal extubation.

Our data also suggest that the length of time mechanically-ventilated does not independently effect the likelihood of extubation success or failure in neonatal cardiac surgical patients. Likewise, in the only prior single center study to examine extubation failure in a heterogeneous group of neonates who underwent cardiac surgery and in the study recently presented from the PC4 database, no independent effect of duration of mechanical ventilation on the likelihood of extubation failure was found [7,10] In contrast, recent data from a large cohort of children of all age groups with critical cardiac disease (the majority of which underwent cardiac surgery), demonstrated duration of mechanical ventilation to be the most important risk factor for extubation failure [5]. Hence, while most clinicians commonly have heightened awareness of the risk of extubation failure in patients who have required prolonged mechanical ventilation, this increased concern for extubation failure should be applied to all neonates following cardiac surgery, whether extubation is occurring early or late in their course.

We also found extubation failure to be independently associated with worse outcome, in a multivariable model that included several additional co-morbidities and markers of disease severity. To our knowledge, our study represents the first to perform such an analysis. We do not assert that the extubation failures in and of themselves were responsible for the worse outcomes, but rather one of several possible contributors. In two patients, extubation failure was associated with cardiopulmonary arrests that resulted in death or emergent ECMO cannulation. These findings further underscore the need for institutional efforts and future clinical research aimed at reducing the occurrence of extubation failure in neonates recovering from cardiac surgery. Additional studies on promising adjuncts to traditional extubation readiness assessment protocols such as near-infrared spectroscopy monitoring [26] and dead space-to-tidal volume calculations [27] should be pursued.

We acknowledge that our study has some limitations. Though this study included centers representing a reasonable mix of small, moderate, and large volume centers in different geographic locations, only seven centers were involved and the number of extubation failures in the study was not high. A study with a greater number of extubation failures could potentially have power to identify other important risk factors. For example, unlike the review of the PC4 registry [10], underlying airway or respiratory anomaly, which was only present in 13 of our patients, could not be determined to be an independent risk factor for extubation failure in our study. Additionally, while data for an extensive list of variables were collected, there were likely some patient characteristics that could have contributed to extubation failures but could not be analyzed in this observational study. For instance, across institutions, the level of consciousness or nutritional state at the time of extubation were not be objectively measured nor was the occurrence of narcotic or sedative withdrawal consistently assessed as standard practice, preventing us from determining whether these factors could have had a role in any of the extubation failures. The assessment of extubation readiness was not protocolized, as we did not aim to determine the effectiveness or ineffectiveness of different extubation readiness strategies with this dataset. Prospective studies examining specific extubation readiness methods (e.g. trials of continuous positive airway pressure with pressure support) are needed to appropriately address this question. We were also unable to gain additional insight into the aforementioned adjuncts to extubation readiness assessment (e.g. near-infrared spectroscopy and dead space-to tidal-volume ratio), as these modalities were inconsistently implemented at the participating institutions. Further, our study was not designed to detect advantages or disadvantages to the various modalities available for respiratory support upon extubation (e.g. oxygen via nasal cannula, high-flow nasal cannula, or non-invasive positive pressure), and thus the observed differences in extubation failure rates across the three modalities should not be over-interpreted. Randomized controlled trials in this patient population would be needed to determine if there is a clear benefit or detriment to the routine use of one of these therapies and

should be pursued. Lastly, though we did not detect any center-level effects on our findings, we acknowledge that there may be some intangible or immeasurable center-specific factors that could have influenced the likelihood of extubation success or failure. Despite these limitations, this study has generated some meaningful results that can act as the impetus for both institutional quality assurance initiatives and future research aimed at this important clinical problem.

Conclusions

Our multicenter analysis has demonstrated an extubation failure rate of 12% in neonates who underwent surgery for congenital heart disease, and extubation failure was independently associated with adverse postoperative consequences. We have also identified potentially modifiable risk factors for extubation failure. Efforts to reduce the occurrence of extubation failure could therefore ultimately improve the clinical outcomes of these complex and fragile neonates.

References

1. Polito A, Patorno E, Costello JM, Salvin JW, Emani SM, Rajagopal S, et al. Perioperative factors associated with prolonged mechanical ventilation after complex congenital heart surgery. *Pediatr Crit Care Med* 2011; 12:e122-126.
2. Pagowska-Klimek L, Pychynska-Pokorska M, Krajewski W, Moll JJ. Predictors of long intensive care unit stay following cardiac surgery in children. *Eur J Cardiothorac Surg* 2011; 40:179-184.
3. Baisch SD, Wheeler WB, Kurachek SC, Cornfield DN. Extubation failure in pediatric intensive care incidence and outcomes. *Pediatr Crit Care Med* 2005; 6:312-318.
4. Harkel AD, van der Vorst MM, Hazekamp MG, Ottenkamp J. High mortality rate after extubation failure after pediatric cardiac surgery. *Pediatr Cardiol* 2005; 26:756-761.
5. Gaies M, Tabbutt S, Schwartz SM, Bird GL, Alten JA, Shekerdemian LS, et al. Clinical Epidemiology of Extubation Failure in the Pediatric Cardiac ICU: A Report from the Pediatric Cardiac Critical Care Consortium. *Pediatr Crit Care Med* 2015; 16:837-845.
6. Gupta P, McDonald R, Gossett JM, Butt W, Shinkawa T, Imamura M, et al. A single-center experience of extubation failure in infants undergoing the Norwood operation. *Ann Thorac Surg* 2012; 94:1262-1268.
7. Laudato N, Gupta P, Walters HL 3rd, Delius RE, Mastropietro CW. Risk Factors for Extubation Failure Following Neonatal Cardiac Surgery. *Pediatr Crit Care Med*. 2015; 16:859-867.
8. Newth CJ, Venkataraman S, Willson DF, Meert KL, Harrison R, Dean JM, et al. Weaning and extubation readiness in pediatric patients. *Pediatr Crit Care Med* 2009; 10:1-11.

9. Gupta P, McDonald R, Goyal S, Gossett JM, Imamura M, Agarwal A, et al. Extubation failure in infants with shunt-dependent pulmonary blood flow and univentricular physiology. *Cardiol Young* 2014; 24:64-72.
10. Mastropietro CW, Benneyworth B, Graham E, Klugman D, Costello JM, Zhang W, et al. Multi-institutional Analysis of Extubation Failure after Neonatal Cardiac Surgery. *Critical Care Med* 2016; 43:19.
11. Jacobs JP, O'Brien SM, Pasquali SK, Jacobs ML, Lacour-Gayet FG, Tchervenkov CI et al. Variation in outcomes for risk-stratified pediatric cardiac surgical operations: an analysis of the STS Congenital Heart Surgery Database. *Ann Thorac Surg* 2012; 94:564-571.
12. STS Congenital Heart Surgery Database v3.3. Available at:
<http://www.sts.org/node/42208>
13. Pasquali SK, Hall M, Li JS, Peterson ED, Jagers J, Lodge AJ, et al. Corticosteroids and outcome in children undergoing congenital heart surgery: analysis of the Pediatric Health Information Systems database. *Circulation* 2010; 122:2123-2130.
14. Butts RJ, Scheurer MA, Atz AM, Zyblewski SC, Hulse TC, Bradley SM, et al. Comparison of maximum vasoactive inotropic score and low cardiac output syndrome as markers of early postoperative outcomes after neonatal cardiac surgery. *Pediatr Cardiol* 2012; 33:633-638.
15. Gaies MG, Jeffries HE, Niebler RA, Pasquali SK, Donohue JE, Yu S, et al. Vasoactive-inotropic score is associated with outcome after infant cardiac surgery: an analysis from the Pediatric Cardiac Critical Care Consortium and Virtual PICU System Registries. *Pediatr Crit Care Med* 2014; 15:529-537.
16. Davidson J, Tong S, Hancock H, Hauck A, da Cruz E, Kaufman J. Prospective validation of the vasoactive-inotropic score and correlation to short-term outcomes in neonates and infants after cardiothoracic surgery. *Intensive Care Med* 2012; 38:1184-1190.

17. Miletic KG, Delius RE, Walters HL 3rd, Mastropietro CW. Prospective Validation of a Novel Vasoactive-Ventilation-Renal Score as a Predictor of Outcomes After Pediatric Cardiac Surgery. *Ann Thorac Surg* 2016; 101:1558-1563.
18. Paret G, Ziv T, Barzilai A, Ben-Abraham R, Vardi A, Manisterski Y, et al. Ventilation index and outcome in children with acute respiratory distress syndrome. *Pediatr Pulmonol* 1998; 26(2):125-128.
19. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int* 2007; 71:1028–1035.
20. Taylor C, Subaiya L, Corsino D. Pediatric cuffed endotracheal tubes: an evolution of care. *Ochsner J* 2011; 11:52-56.
21. Litman RS, Maxwell LG. Cuffed versus uncuffed endotracheal tubes in pediatric anesthesia: the debate should finally end. *Anesthesiology* 2013; 118:500-501.
22. Litman RS, Weissend EE, Shibata D, Westesson PL. Developmental changes of laryngeal dimensions in unparalyzed, sedated children. *Anesthesiology* 2003; 98:41-45.
23. Newth CJ, Rachman B, Patel N, Hammer J. The use of cuffed versus uncuffed endotracheal tubes in pediatric intensive care. *J Pediatr* 2004; 144:333-337.
24. Holzki J, Laschat M, Puder C. Stridor is not a scientifically valid outcome measure for assessing airway injury. *Paediatr Anaesth* 2009; 19 Suppl 1:180-197.
25. Testelmans D, Maes K, Wouters P, Gosselin N, Deruisseau K, Powers S, et al. Rocuronium exacerbates mechanical ventilation-induced diaphragm dysfunction in rats. *Crit Care Med* 2006; 34:3018–3023.
26. Foster CB, Spaeder MC, McCarter RJ, Cheng YI, Berger JT. The Use of Near-Infrared Spectroscopy During and Extubation Readiness Trial as a Predictor of Extubation Outcome. *Pediatr Crit Care Med* 2013; 14:587-592.

27. Hubble CL, Gentile MA, Tripp DS, Craig DM, Meliones JN, Cheifetz IM. Dead-space to tidal volume ratio predicts successful extubation in infants and children. *Crit Care Med* 2000; 28:2034-2040.

Figure Legends

Figure 1 - Timing of extubation failures: Most extubation failures occurred within the first 12 hours after extubation.

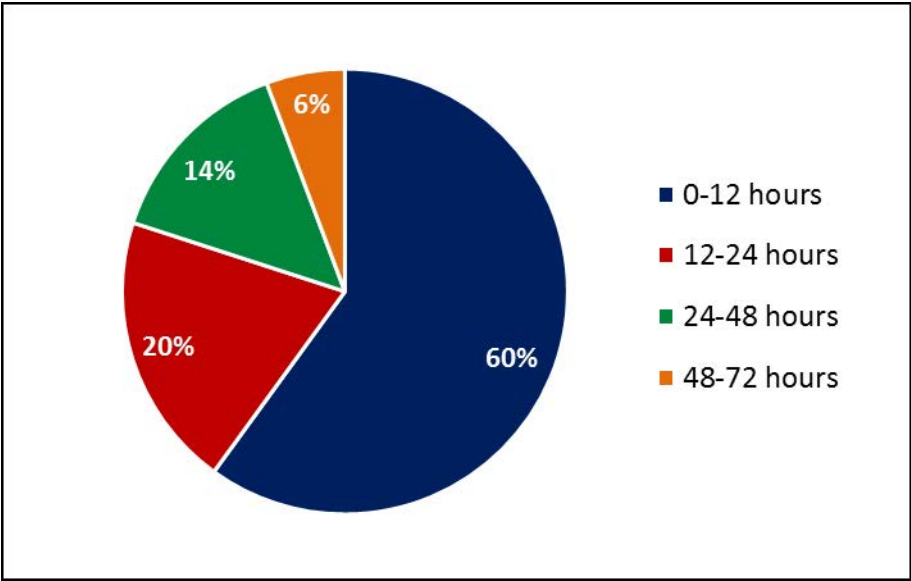


Figure 2 – Analysis of endotracheal (ET) tube size with: Mean ET tube inner diameter size was greater in neonates who failed extubation as compared to neonates who extubated successfully, P=0.014. Neonates with uncuffed tubes who failed extubation (n=12) were largely responsible for this observed difference, as the mean inner diameter of their ET tubes was substantially greater than that of the neonates with cuffed endotracheal tubes who failed extubation (n=23), P=0.008. Data represented as mean with standard error. * indicates statistical significance.

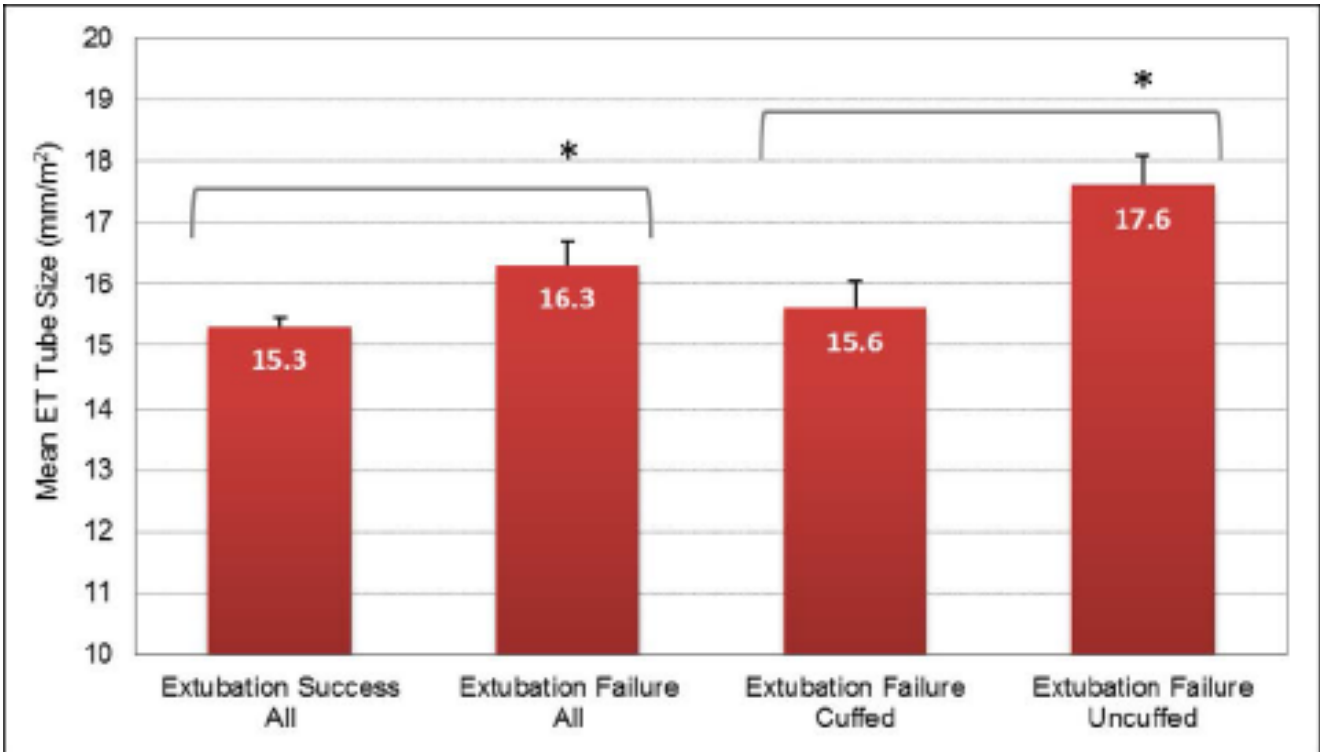


Figure 3 - Respiratory support provided upon extubation: Number of neonates extubated to room air or oxygen via nasal cannula (NC), oxygen via high-flow nasal cannula (HFNC), and non-invasive positive pressure ventilation (NIPPV). Each bar represents neonates successfully extubated (green), neonates in which support was escalated to HFNC or NIPPV but not re-intubated (yellow), and neonates who required reintubation (red).

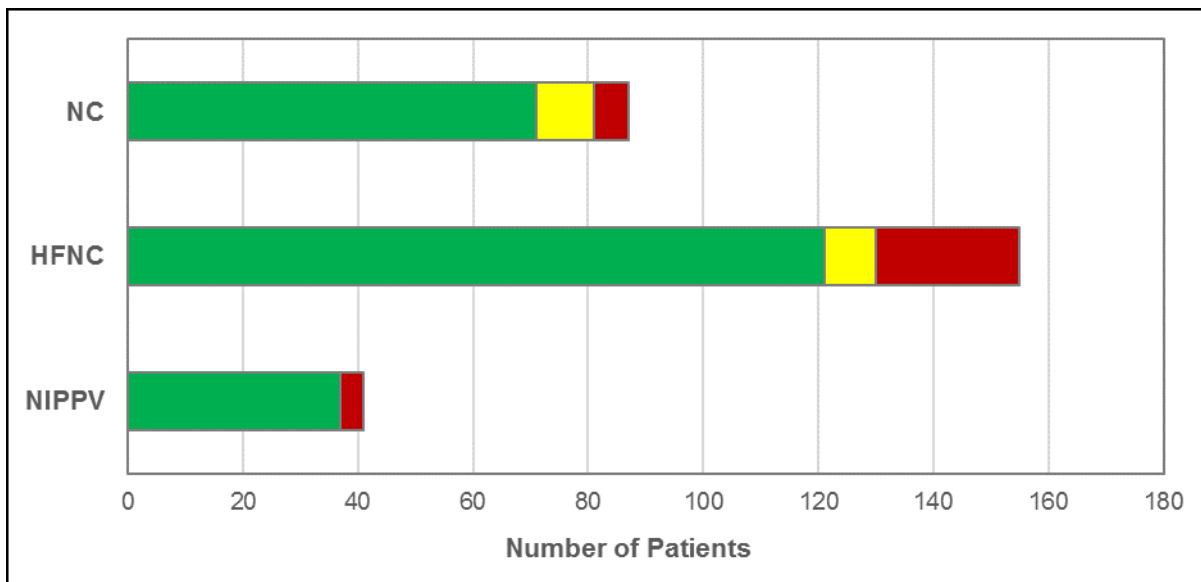


Table 1. Data Collection and Definitions

Preoperative Data

- Age
- Sex
- Anthropometric data
- Estimated gestational age at birth
- Prematurity – Less than 37 weeks gestation
- Underlying cardiovascular diagnoses
- Presence of genetic anomalies or non-cardiac anatomic anomalies
- Need for preoperative mechanical ventilation
- Preoperative shock - defined as pH less than 7.2 or lactate greater than 4 mg/dL, to be consistent with the definition used by Society of Thoracic Surgeons-Congenital Heart Surgery Database [12]
- Infection - clinically relevant positive blood, urine, respiratory, or wound cultures, or culture-negative sepsis (i.e. systemic inflammatory response syndrome with suspected infection) treated with ≥ 7 days of antimicrobial therapy [13]
- Necrotizing enterocolitis
- Stroke or seizure - patients with clinical or sub-clinical seizure activity were recorded as having seizures
- Whether patient was cared for in a dedicated cardiac ICU or multidisciplinary ICU
- Center size - centers were arbitrarily categorized as small-to-moderate volume (< 50 neonatal surgeries per year) and large volume (> 50 neonatal surgeries per year)

Perioperative Data

- Use of systemic corticosteroids
- Endotracheal tube size and presence or absence of a cuff
- Society of Thoracic Surgeons-European Association for Cardio-thoracic Surgery Society Congenital Heart Surgery Mortality Category (STAT mortality category)[11-12]

Perioperative Data

- Duration of cardiopulmonary bypass and aortic cross clamping
 - Use of deep hypothermic arrest or antegrade cerebral perfusion
-

Postoperative Data

- Admission and pre-extubation vasoactive medication requirements
 - Vasoactive medication requirements were quantified using the vasoactive-inotropic score [14-17], calculated according to following formula: $VIS = \text{dopamine } (\mu\text{g/kg/min}) + \text{dobutamine } (\mu\text{g/kg/min}) + 100 \times \text{epinephrine } (\mu\text{g/kg/min}) + 10 \times \text{milrinone } (\mu\text{g/kg/min}) + 10,000 \times \text{vasopressin } (\text{U/kg/min}) + 100 \times \text{norepinephrine } (\mu\text{g/kg/min})$
 - Admission and pre-extubation ventilator settings and arterial blood gas measurements
 - ventilation support at the time of admission was quantitated using the ventilation index [18], which was calculated according to the following formula: $VI = RR \times (PIP - PEEP) \times PaCO_2 / 1000$, where RR is respiratory rate, PIP is peak inspiratory pressure; PEEP is positive end-expiratory pressure
 - Use of extracorporeal membrane oxygenation
 - Use of inhaled nitric oxide therapy
 - Use of cardiopulmonary resuscitation
 - Presence and duration of open sternotomy
 - Maximum doses of fentanyl, morphine, midazolam, or dexmedetomidine infusions, if used
 - Narcotic doses are reported in morphine equivalents
 - Fentanyl doses were converted to morphine equivalents by multiplying the doses by 80, based on standard conversion tables
 - Use of neuromuscular blockade
 - Occurrence of postoperative arrhythmia
 - Acute kidney injury defined by pRIFLE criteria [19]
-

Postoperative Data

- Infection or necrotizing enterocolitis
 - Stroke or seizure
 - Use of systemic corticosteroids
 - Fluid balance from ICU arrival to the first extubation attempt
 - Presence of clinically important residual cardiac lesions - residual valvular regurgitation described to be trivial or mild and residual septal defects described to be small on postoperative echocardiograms were not included as clinically relevant residual cardiac lesions
 - Respiratory support provided upon extubation and whether or not the support was escalated
 - Timing and presumed reason for reintubation, if it occurred
-

Outcome Data

- Duration of mechanical ventilation prior to the first extubation attempt
 - Total duration of mechanical ventilation
 - Duration of intensive care unit
 - Hospital length-of-stay (LOS)
 - In-hospital mortality
-

Table 2. Cardiovascular Surgical Procedures Organized by STAT Categories

Primary surgical procedure	All Patients (N=283)	Extubation Success (n=248)	Extubation Failure (n=35)
STAT Category 1 or 2	50 (18%)	40 (16%)	10 (29%)
CoA, end-to-end anastomosis	38	33	5
Repair, RVOT obstruction	7	5	2
Aortic valvotomy	2	0	2
Other	2	2	1
STAT Category 3	39 (14%)	37 (15%)	2 (6%)
Arterial switch, d-TGA with IVS	34	33	1
Patch aortoplasty	4	4	0
Repair, CoA with ventricular septal defect	1	0	1
STAT Category 4	140 (49%)	127 (51%)	13 (37%)
Arterial switch, complex d-TGA*	26	25	1
Systemic-to-PA Shunt	33	29	4
Single ventricle	17	14	2
Two ventricles	16	14	2
PA banding	16	14	2
Single ventricle	13	12	1
Two ventricles	3	2	1
PA banding + arch repair	9	7	2
Repair, TAPVC	17	17	0
Aortic arch reconstruction	15	14	1
Repair, truncus arteriosus	9	9	0
Repair, interrupted aortic arch	7	5	2
Other	8	7	1
STAT Category 5	54 (19%)	44 (18%)	10 (29%)
Norwood procedure	46	37	9
Blalock-Taussig shunt	16	14	2
Sano shunt	30	23	7
Hybrid procedure, HLHS	3	3	0
Damus-Kaye-Stanzel	2	1	1
Repair, TAPVC + systemic-to-PA shunt	2	2	0
Yasui Procedure	1	1	0

CoA: coarctation of the aorta; d-TGA: d-transposition of the great arteries; HLHS: hypoplastic left heart syndrome; PA: pulmonary artery; PDA: Patent Ductus Arteriosus; RVOT: Right ventricular outflow tract obstruction; TAPVC: total anomalous pulmonary venous connections

Table 3. Demographic, Anthropometric, and Preoperative Data

Variable	All patients (N=283)	Extubation Success (n=248)	Extubation Failure (n=35)	P-value
Gestational age at birth (weeks)	38.5 ± 1.7	38.6 ± 1.7	38.1 ± 1.8	0.08
Age at surgery (days)	9 ± 6	9 ± 6	9 ± 5	0.56
Weight (kg)	3.2 ± 0.6	3.3 ± 0.6	3.1 ± 0.7	0.10
Body surface area (m ²)	0.21 ± 0.10	0.22 ± 0.10	0.2 ± 0.03	0.12
Sex (male)	179 (63%)	158 (64%)	21 (60%)	0.67
Prematurity, less than 37 weeks (n)	39 (14%)	32 (13%)	7 (20%)	0.29
Genetic anomaly (n)	41 (14%)	32 (13%)	9 (26%)	0.044
Downs syndrome	5	3	2	
Turners syndrome	3	3	0	
DiGeorge syndrome	4	3	1	
Williams syndrome	2	1	1	
Other	27	22	5	
Any non-cardiac anatomic anomalies	37 (13%)	29 (12%)	8 (23%)	0.10
Anatomic airway / respiratory anomaly	13 (5%)	9 (4%)	4 (11%)	0.06
Neurologic anomaly or insult ^a	19 (7%)	15 (6%)	4 (11%)	0.27
Mechanical ventilation (n)	130 (46%)	110 (44%)	20 (57%)	0.16
Mechanical ventilation (days)	0 (0, 2)	0 (0, 1)	1 (0, 2)	0.16
Mechanical ventilation to surgery (n) ^b	70 (25%)	57 (23%)	13 (37%)	0.07
Shock (n)	42 (15%)	36 (15%)	6 (17%)	0.68
Infection (n)	14 (5%)	13 (5%)	1 (3%)	1.00
Necrotizing enterocolitis (n)	7 (2%)	6 (2%)	1 (3%)	1.00
Single ventricle anatomy (n)	93 (33%)	76 (31%)	17 (49%)	0.035
Hypoplastic left heart (n)	59 (21%)	46 (19%)	13 (37%)	0.011
Hypoplastic right heart (n)	24 (8%)	22 (9%)	2 (6%)	0.75
Heterotaxy (n)	10 (4%)	8 (3%)	2 (6%)	0.36
Dedicated cardiac ICU (n)	214 (76%)	191 (77%)	23 (66%)	0.15
Large volume center (n) ^c	187 (66%)	166 (67%)	21 (60%)	0.42

Continuous variables represented as mean (standard deviation) or median (25th%, 75th%); categorical data represented as absolute counts (%)

^a Underlying neuroanatomic anomaly, or stroke or seizures prior to surgery

^b After endotracheal intubation, remained on mechanical ventilation until surgery

^c Greater than 50 neonatal cardiac surgeries in 2015

Table 4. Perioperative and ICU Admission Data

Variable	All Patients (N=283)	Extubation Success (n=248)	Extubation Failure (n=35)	P- value
Endotracheal tube characteristics				
Diameter (mm/m ²)	15.4 ± 2.2	15.3 ± 2.2	16.3 ± 2.2	0.014
Uncuffed (n)	49 (17%)	37 (15%)	12 (34%)	0.005
Operative Data				
STAT 4 or 5 (n)	190 (67%)	168 (68%)	22 (63%)	0.57
Cardiopulmonary bypass (n)	219 (77%)	194 (78%)	25 (71%)	0.37
Cardiopulmonary bypass (min)	132 (51, 189)	132 (60, 193)	134 (0, 170)	0.48
Aortic cross clamp (min)	52 (16, 91)	51 (18, 93)	57 (0, 78)	0.36
DHCA (n)	68 (24%)	58 (23%)	10 (29%)	0.50
ACP (n)	83 (29%)	69 (28%)	14 (40%)	0.14
DHCA and ACP (n)	36 (13%)	28 (11%)	8 (23%)	0.10
Corticosteroids (n)	211 (75%)	187 (66%)	24 (69%)	0.39
Delayed sternal closure (n)	94 (33%)	78 (31%)	16 (46%)	0.09
Delayed sternal closure (days)	0 (0, 2)	0 (0, 1)	0 (0, 4)	0.015
Delayed sternal closure ≥ 4 days (n)	31 (11%)	20 (8%)	11 (31%)	<0.001
ECMO (n)	15 (5%)	10 (4%)	5 (14%)	0.03
Clinically relevant residual lesion (n)	48 (17%)	41 (17%)	7 (20%)	0.61
Post-operative Admission data				
pH	7.35 ± 0.08	7.35 ± 0.08	7.33 ± 0.07	0.09
Lactate (mg/dL)	3.7 ± 2.6	3.6 ± 2.4	4.7 ± 3.5	0.021
Peak inspiratory pressure (mmHg)	22 ± 5	22 ± 5	23 ± 5	0.11
PEEP (mmHg)	5 ± 1	5 ± 1	6 ± 1	0.10
Dynamic compliance (mL/cmH ₂ O/kg)	0.6 ± 0.2	0.6 ± 0.2	0.5 ± 0.2	0.67
Ventilation index	19 (14, 25)	18 (14, 25)	21.1 (16, 26)	0.26
Vasoactive-inotrope score	8 (5, 11)	8 (5, 11)	8 (0, 13)	0.51

Continuous variables represented as mean (standard deviation) or median (25th%, 75th%); categorical data represented as absolute counts (%)

ACP: antegrade cerebral perfusion; DHCA: Deep hypothermic circulatory support; ECMO: extracorporeal membrane oxygenation; PEEP: positive end expiratory pressure

Table 5. Postoperative and Pre-extubation Data

Variable	All Patients (n=283)	Extubation Success (n=248)	Extubation Failure (n=35)	P-value
Postoperative Data				
Intra/postoperative CPR (n)	12 (4%)	9 (4%)	3 (9%)	0.17
Inhaled nitric oxide use (n)	64 (23%)	53 (21%)	11 (29%)	0.18
Any arrhythmia (n)	73 (26%)	60 (24%)	13 (37%)	0.10
Tachyarrhythmias (n)	54 (19%)	43 (17%)	11 (29%)	0.047
Necrotizing enterocolitis (n)	6 (2%)	4 (2%)	2 (6%)	0.16
Infection (n)	24 (8%)	21 (8%)	3 (9%)	1.00
Acute kidney injury – I or F (n) ^a	57 (20%)	48 (19%)	9 (26%)	0.38
New seizures or stroke (n)	11 (4%)	10 (4%)	1 (3%)	1.00
Fluid balance (mL/kg)	+4 (-51,+48)	+5 (-49,+46)	+1 (-63,+54)	0.85
Corticosteroid use				
Pre-cardiopulmonary bypass (n) ^b				
Hydrocortisone therapy (n) ^c	91 (31%)	78 (31%)	13 (37%)	0.50
Peri-extubation dexamethasone (n) ^d	76 (27%)	64 (26%)	12 (34%)	0.29
Pain and sedation management				
Narcotic infusion (n)	228 (81%)	202 (81%)	26 (74%)	0.32
Max narcotic dose (mcg/kg/hr) ^e	80 (25,160)	80 (25, 160)	40 (20, 160)	0.22
Midazolam infusion (n)	98 (35%)	86 (35%)	12 (34%)	0.96
Dexmedetomidine infusion (n)	116 (41%)	102 (41%)	16 (46%)	0.90
Neuromuscular blockade (n)	122 (43%)	104 (42%)	18 (54%)	0.29
Pre-extubation data				
Pressure support (cmH ₂ O)	10 (10, 10)	10 (10, 10)	10 (10, 10)	0.37
Pressure support > 10cmH ₂ O	40 (14%)	36 (15%)	4 (11%)	0.50
PEEP (cmH ₂ O)	5 ± 1	5 ± 1	5 ± 1	0.36
PEEP > 5 cmH ₂ O	37 (13%)	29 (12%)	8 (23%)	0.07
Vasoactive-inotrope score	5 (3, 6)	5 (3, 6)	5 (3, 7)	0.40
Mechanical ventilation (hrs) ^f	72 (42, 134)	70 (42, 116)	138 (57, 238)	<0.001
Respiratory Support Provided Upon Admission				
Oxygen via nasal cannula	87 (31%)	81 (33%)	6 (17%)	0.06
Oxygen via high-flow nasal cannula	156 (55%)	131 (53%)	25 (71%)	0.038
Non-invasive positive pressure	40 (14%)	36 (15%)	4 (11%)	0.80

Continuous variables represented as mean (standard deviation) or median (25th%, 75th%); categorical data represented as absolute counts (%); *CPR*: Cardiopulmonary resuscitation; *PEEP*: positive end expiratory pressure

^a Acute kidney injury categorized as “Injury” or “Failure” based on pRIFLE criteria; ^b Intravenous methylprednisolone 30mg/kg/dose or dexamethasone 10mg/kg/dose; ^c Hydrocortisone provided for postoperative hemodynamic instability, 1mg/kg/dose; ^d dexamethasone provided to peri-extubation to limit airway edema, 0.5 mg/kg/dose; ^e Provided in morphine equivalents; ^f From ICU arrival after surgery to the first extubation attempt

Table 6. Multivariate Logistic Regression Analysis for Predictors of Extubation Failure

Variable	Odds Ratio	95% Confidence Intervals	<i>P</i> -value
Hypoplastic Left Heart	1.9	0.7 – 4.7	0.19
Underlying airway anomaly	2.7	0.6 – 11.6	0.18
Uncuffed endotracheal tube	4.6	1.8 – 11.6	0.001
Prolonged open sternotomy ^a	4.8	1.3 – 17.1	0.02
PEEP greater than 5 cmH ₂ O ^b	2.7	0.99 – 7.3	0.05
Duration of mechanical ventilation ^c	1.3	0.3 – 5.9	0.23

^a Greater than or equal to 4 days; ^b at the time of extubation; ^c Variable was non-linear in the logit and was categorized into quintiles; odds ratio represents longest quintile compared to shortest quintile

Table 7. Clinical Outcomes

Outcome	All Patients (n=283)	Extubation Success (n=248)	Extubation Failure (n=35)	<i>P</i> -value
Total duration of ventilation (hrs)	83 (44, 178)	71 (42, 134)	359 (208, 749)	<0.001
ICU stay (days)	11 (5, 20)	9 (5, 17)	30 (16, 61)	<0.001
Hospital stay (days)	19 (11, 37)	17 (11, 30)	46 (26, 76)	<0.001
Mortality (n)	9 (3.2%)	1 (0.4%)	8 (22.9%)	<0.001

Continuous variables represented as median (25th%, 75th%); categorical data represented as absolute counts (percentages)

Table 8. Multivariate Logistic Regression Analysis for Predictors of Worse Clinical Outcomes ^a

Variable	Odds Ratio	95% Confidence Interval	P-value
Single ventricle anatomy	3.4	1.6 – 7	0.001
Genetic or chromosomal abnormality	2.9	1.1 – 7.5	0.03
Non-cardiac anatomic abnormality	3.7	1.7 – 9.6	0.01
Clinically-significant residual cardiac lesion	2.5	1.03 – 6.3	0.04
Infection or necrotizing enterocolitis ^b	3	1.2 – 7.6	0.02
Duration of mechanical ventilation ^c	1.01	1.005 – 1.013	<0.001
Extubation Failure	5.1	2 – 13	0.001

^a Defined as neonates with lengths of hospital stay in the upper 25% or death prior to hospital discharge

^b Preoperatively or postoperatively prior to first extubation attempt; ^c prior to first extubation attempt