BRIEF REPORT

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Noninvasive Respiratory Support Does Not Prevent Extubation Failure in High-Risk Norwood Patients

Adel M. Hassan, BS[1]
Sebastian Acosta, PhD[2]
Feng Zheng, MD[3]
Craig Rusin, PhD[2]
Fabio Savorgnan, MD[4]

OBJECTIVES: This study aims to determine whether bilevel positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP) effectively mitigate the risk of extubation failure in children status post-Norwood procedure.

DESIGN: Single-center, retrospective analysis. Extubation events were collected from January 2015 to July 2021. Extubation failure was defined as the need for reintubation within 48 hours of extubation. Demographics, clinical characteristics, and ventilatory settings were compared between successful and failed extubations.

SETTING: Pediatric cardiovascular ICU.

PATIENTS: Neonates following Norwood procedure.

INTERVENTIONS: Extubation following the Norwood procedure.

MEASUREMENTS AND MAIN RESULTS: The analysis included 311 extubations. Extubation failure occurred in 31 (10%) extubation attempts within the first 48 hours. On univariate analysis, higher rate of extubation failure was observed when patients were extubated to CPAP/BiPAP relative to patients who were extubated to either high-flow nasal cannula (HFNC) or nasal cannula (NC) (16% vs 7.8%; $p = 0.027$). On multivariable analysis, the presence of vocal cord anomaly (odds ratio, 3.08; $p = 0.005$) and lower pre-extubation end-tidal CO_2 (odds ratio, 0.91; $p = 0.006$) were simultaneously associated with extubation failure while also controlling for the post-extubation respiratory support (CPAP/BiPAP/HFNC vs NC).

CONCLUSIONS: Clinicians should not rely on CPAP or BiPAP as the only supportive measure for a patient at increased risk of extubation failure. CPAP or BiPAP do not mitigate the risk of extubation failure in the Norwood patients. A multisite study is needed to generalize these conclusions.

KEY WORDS: extubation failure; Norwood; parallel circulation; post-extubation respiratory support; single ventricle

The Norwood procedure has historically had very high mortality rates. In-hospital mortality has steadily decreased from 59% in 1993 to 19% in 2000 due to improved surgical techniques (1, 2). However, many post-surgical parameters can be fine-tuned to reduce morbidity and mortality. For example, 24% of Norwood patients experience extubation failure after their surgery (3, 4). Extubation failure is a significant problem associated with greater cardiac ICU (CICU) length of stay, higher risk of ventilator-associated pneumonia, and in-hospital mortality (5, 6, 7).

As a result, clinicians employ many strategies to avoid extubation failure, including intermediate respiratory support. Some of the most common respiratory support modalities include continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), high-flow nasal cannula (HFNC), and standard nasal cannula (NC). Because CPAP and BiPAP provide a greater

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KEY POINTS

- **Question:** Do bilevel positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP) effectively mitigate the risk of extubation failure in single ventricle neonates after the Norwood procedure?
- **Findings:** In this population, BiPAP and CPAP do not effectively mitigate the frequency of extubation failure imposed by risk factors including vocal cord anomalies and vulnerable pre-extubation respiratory state.
- **Meanings:** Clinicians should not rely on BiPAP or CPAP as the only supportive measure for a postoperative Norwood patient at increased risk of extubation failure.

degree of respiratory support than HFNC and NC, many clinicians prefer to use CPAP and BiPAP in patients at greater risk of extubation failure. However, it is unknown how effective this practice is clinically.

Therefore, this study aims to determine whether BiPAP and CPAP effectively mitigate the risk of extubation failure in children status post-Norwood procedure.

MATERIALS AND METHODS

This is a retrospective analysis of patients admitted to the CICU at Texas Children's Hospital from January 2015 to July 2021 with Hypoplastic Left Heart Syndrome status post-Norwood procedure. This study was performed in accordance with the standards of the Helsinki Declaration of 1975 and approved by the Institutional Review Board of Baylor College of Medicine with a waiver of written consent in March 2021 under protocol H-40811.

Patient demographics, medication use, ventilator settings, and laboratory values were extracted from the electronic medical records. Demographic data included gestational age, age, and weight at the time of surgery, gender, race, genetic, vocal cord, airway, or diaphragm anomalies. The clinical data include length of stay in the CICU, length of each intubation, delayed sternal closure, shunt type, extracorporeal membrane oxygenation support, vasoactive/inotropic support dosage (Vasoactive-Inotropic Score), cardiopulmonary bypass time, aortic cross-clamp time, circulatory arrest time, pressure support trail, laboratories before each extubation, and post-extubation respiratory support. Extubation failure was defined as the need for mechanical ventilator support or death within 48 hours following planned extubation. Protocols of extubation were constant across the period of observation. Neonates were excluded if they had tracheostomy before surgery, died before a planned extubation attempt, or were extubated to withdraw life-sustaining therapy.

The univariate associations between successful-versus-failed extubation were computed using the nonparametric Wilcoxon rank-sum test for continuous variables and Fisher exact test for categorical variables. Multivariate analysis was based on logistic regression. These tests were run using the Python StatsModels v0.12.2 library (http://www.statsmodels.org). For all tests, statistical significance was concluded at a p value of less than 0.05.

RESULTS

There were 311 extubations. Extubation failure occurred in 31 (10%) extubation attempts within the first 48 hours. The demographic and clinical characteristics of the patients are shown in **Table 1**. These univariate analyses showed that a higher rate of extubation failure was observed when patients were extubated to CPAP/BiPAP relative to patients who were extubated to either HFNC or NC (16% vs 7.8%; $p = 0.027$). Vocal cord anomalies ($p = 0.005$) and lower pre-extubation end-tidal CO_2 ($ETCO_2$) ($p = 0.010$) were also found to be associated with extubation failure. Out of the 31 extubation failures, 24 were followed by a reintubation with a successful extubation. The median intubation length for these 24 reintubations was 6.1 days. The other five extubations from the 31 failures were followed by a reintubation whose extubation failed again. The median intubation length for these five reintubations was 4.3 days. This difference is not significant ($p = 0.40$). A larger sample size may be needed to establish a difference. None of the five patients who failed the extubation twice underwent tracheostomy.

On multivariable analysis, the presence of vocal cord anomaly (odds ratio [OR], 3.08; 95% CI, 1.40–6.76; $p = 0.005$) and lower pre-extubation $ETCO_2$ (OR, 0.91; 95% CI, 0.85–0.97; $p = 0.006$) were simultaneously associated with extubation failure while also controlling for the post-extubation respiratory support (CPAP/BiPAP/HFNC vs NC). Details of the multivariable model are presented in **Table 2**.

TABLE 1.
Univariate Analyses for Association With Extubation Failure

Variables	All Extubations	Successful Extubations	Failed Extubations	*p*
Overall frequencies	311 (100%)	280 (90%)	31 (10%)	Not available
Post-extubation O_2 support				
Continuous positive airway pressure/ bilevel positive airway pressure	103 (33%)	87 (31%)	16 (52%)	0.027
High-flow nasal cannula	149 (48%)	139 (50%)	10 (32%)	0.087
Nasal cannula	59 (19%)	54 (19%)	5 (16%)	0.812
Race/ethnicity				
Hispanic	118 (38%)	108 (39%)	10 (32%)	0.562
Non-Hispanic Asian	5 (2%)	3 (1%)	2 (6%)	0.080
Non-Hispanic Black	27 (9%)	25 (9%)	2 (6%)	1.000
Non-Hispanic White	161 (52%)	144 (51%)	17 (55%)	0.850
Shunt type				
Blalock-Taussig shunt	131 (42%)	120 (43%)	11 (35%)	0.452
Right ventricular to pulmonary arterial shunt	180 (58%)	160 (57%)	20 (65%)	0.452
Genetic disorder	139 (45%)	122 (44%)	17 (55%)	0.257
Airway anomaly	35 (11%)	31 (11%)	4 (13%)	0.764
Diaphragm anomaly	16 (5%)	13 (5%)	3 (10%)	0.206
Vocal cord anomaly	108 (35%)	90 (32%)	18 (58%)	0.005
Delayed sternal closure	220 (71%)	196 (70%)	24 (77%)	0.533
Pressure support trial	77 (25%)	72 (26%)	5 (16%)	0.281
Vasoactive-Inotropic Score ≥ 4	111 (36%)	102 (36%)	9 (29%)	0.554
Demographics and clinical characteristics				
Age, d	7.0 (4.5–13.5)	7.0 (4.8–13.0)	9.0 (5.5–16.5)	0.095
Weight, kg	3.4 (3.0–3.8)	3.4 (3.0–3.8)	3.5 (2.8–4.2)	0.471
Gestational age, wk	39.0 (37.0–39.0)	39.0 (37.0–39.0)	38.0 (36.0–39.0)	0.142
Cardiopulmonary bypass time, min	201.0 (181.0–229.0)	201.0 (180.0–227.5)	202.5 (181.5–245.0)	0.286
Aortic cross-clamp time, min	107.0 (90.5–123.0)	107.0 (90.0–123.0)	102.5 (96.5–121.0)	0.373
Circulatory arrest time, min	11.0 (8.0–16.0)	11.0 (8.0–16.0)	13.0 (9.0–23.0)	0.128
Respiratory support characteristics				
Intubation length, d	3.9 (1.6–7.8)	3.9 (1.6–7.8)	3.8 (2.4–8.7)	0.492
Pressure support, mm Hg	10.0 (10.0–10.0)	10.0 (10.0–10.0)	10.0 (10.0–10.0)	0.183
FIO_2, %	30.0 (20.0–30.0)	25.0 (21.0–30.0)	25.0 (21.0–40.0)	0.142
Positive inspiratory pressure, cm H_2O	17.0 (15.0–20.0)	17.0 (15.0–19.3)	17.0 (15.0–20.0)	0.385
Positive end-expiratory pressure, cm H_2O	5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.0 (5.0–5.0)	0.358
End-tidal volume, cc	32.0 (28.0–40.0)	32.0 (28.0–40.0)	32.0 (26.0–38.0)	0.352
Respiratory rate, per min	12.0 (10.0–16.0)	12.0 (10.0–16.0)	12.0 (11.0–16.0)	0.299
End-tidal CO_2, mm Hg	35.0 (32.0–39.0)	35.0 (33.0–39.0)	34.0 (31.0–36.5)	0.010
Vital signs pre-extubation				
Heart rate, per min	133.1 (121.9–144.5)	132.6 (121.9–144.5)	137.6 (128.8–146.3)	0.185
Pulse oxygen saturation, %	83.3 (80.6–85.7)	83.3 (80.7–85.9)	83.1 (80.2–84.3)	0.210
Respiratory rate, per min	37.2 (30.3–43.0)	36.0 (30.3–42.7)	40.5 (36.2–50.2)	0.380

Categorical variables are described by frequency (%) and compared using the Fisher exact test. Continuous variables are described by median (interquartile range) and compared using Wilcoxon rank-sum test.

TABLE 2.
Multivariable Logistic Regression for the Association Between Extubation Failure and Types of Post-Extubation Noninvasive Respiratory Support, Vocal Cord Anomaly, and End-Tidal CO_2

Covariables	Coefficient	OR (95% CI)	*p*
Intercept	0.607		0.641
Post-extubation continuous positive airway pressure/ bilevel positive airway pressure (reference: NC)	0.543	1.72 (0.57–5.16)	0.332
Post-extubation high-flow nasal cannula (reference: NC)	−0.315	0.73 (0.23–2.29)	0.590
Vocal cord anomaly (reference: no anomaly)	1.124	3.08 (1.40–6.76)	0.005
Pre-extubation end-tidal CO_2 (mm Hg)	−0.099	0.91 (0.85–0.97)	0.006

NC = nasal cannula, OR = odds ratio.

DISCUSSION

In this study, we retrospectively analyzed the records of 311 extubations in neonates who underwent the Norwood procedure. A higher rate of extubation failure was observed when patients were extubated to CPAP/BiPAP relative to patients who were extubated to either HFNC or NC (16% vs 7.8%).

These results align with Herrera et al (3). They found that use of CPAP or BiPAP after extubation was associated with increased rates of extubation failure relative to HFNC. In their analysis, Herrera et al (3) interpreted this as a reflection of their hospital protocol, which recommends starting BiPAP for all patients in imminent danger of extubation failure, to avoid reintubation. Our study looked at the respiratory support provided immediately after extubation in contrast to using BiPAP "at any point" after extubation. Therefore, the explanation provided by Herrera et al (3) does not apply. Instead, it appears that the relationship between the application of post-extubation CPAP/BiPAP and the extubation failure rate is confounded by the severity of the patient's illness.

The multivariable analysis supports this hypothesis. After combining all of the variables that independently predicted extubation failure into a multivariate logistic regression model, only vocal cord anomaly and lower pre-extubation $ETCO_2$ were significantly correlated with extubation failure. This suggests that after controlling for vocal cord anomaly and $ETCO_2$, the other predictors, namely post-extubation CPAP/BiPAP and post-extubation HFNC, were not significantly correlated with extubation failure. These results also reveal that the risk introduced by a vocal cord anomaly (OR = 3.08) is much larger than that of having lower $ETCO_2$ (OR = 0.91).

Vocal cord paralysis is a known risk factor for extubation failure. In a study by Gupta et al (4), 14% of Norwood patients who failed extubation were also found to have vocal cord paralysis. Given that vocal cord paralysis is a risk factor for extubation failure, it is reasonable to understand why other vocal cord anomalies could also contribute to difficulties with airway patency and result in extubation failure. The other significant risk factor was pre-extubation $ETCO_2$. Lower $ETCO_2$ could be associated with tachypnea and/or lower pulmonary blood flow due to lower cardiac output in this patient population. We found that patients who failed extubation had lower pre-extubation $ETCO_2$ but no significant difference in respiratory rate. Hence, it is reasonable to conclude that patients who failed the extubation had compromised hemodynamics that did not tolerate the extubation. Thus, the presence of vocal cord anomaly and lower $ETCO_2$ indicate patients who are more severely ill, and such patients are more likely to be extubated to CPAP or BiPAP instead of HFNC or NC.

And yet, despite these additional precautions, these more severely ill patients continue to experience higher rates of extubation failure than their peers. This suggests that post-extubation CPAP and BiPAP cannot fully mitigate underlying risk factors such as vocal cord anomaly and lower pre-extubation $ETCO_2$. This finding highlights the importance of taking additional measures to manage these high-risk patients, such as ensuring that extubation is not undertaken prematurely. To this end, our future directions will use machine-learning-based algorithms to predict when Norwood patients are ready for extubation based on their hemodynamic data.

One of the limitations of this study is its retrospective nature. Without a randomized controlled trial, it is difficult to quantify how much risk reduction can be achieved by CPAP/BiPAP, only that it is not enough. However, since withholding CPAP/BiPAP from severely ill patients would be unethical, retrospective analyses provide the best estimate possible. Furthermore, it should be noted that this is a single-center study; thus, the risk factors identified reflect our institution's protocols and our clinicians' treatment preferences. Other institutions applying a different extubation algorithm may find different risk factors. However, considering the convergent results from Herrera et al (3) and Gupta et al (4), we believe that some aspects of our study could be generalized to other institutions in future studies. Another limitation of the retrospective nature of the study is that the precise etiology of the extubation failures was not known in every case.

CONCLUSIONS

CPAP and BiPAP are used as respiratory support for patients at high risk of extubation failure. In this single-center study, we found that Norwood patients remain at high risk after applying CPAP or BiPAP after the extubation procedure. Therefore, clinicians should not rely on CPAP or BiPAP as the only supportive measure for a Norwood patient at increased risk of extubation failure. Other factors, such as the appropriate timing for extubation, should also be considered. A multicenter prospective study is warranted to confirm or generalize these conclusions.

1 *School of Medicine, Baylor College of Medicine, Houston, TX.*

2 *Department of Pediatrics, Division of Cardiology, Texas Children's Hospital and Baylor College of Medicine, Houston, TX.*

3 *Department of Pediatrics, Division of Neonatology, Texas Children's Hospital and Baylor College of Medicine, Houston, TX.*

4 *Department of Pediatrics, Division of Critical Care Medicine, Texas Children's Hospital and Baylor College of Medicine, Houston, TX.*

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For information regarding this article, E-mail: sacosta@bcm.edu

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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