

Title: Near-Infrared Spectroscopy for Prediction of Extubation Success after Neonatal Cardiac Surgery

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Abstract

Introduction: Reliable predictors of extubation readiness are needed and may reduce morbidity related to extubation failure. We aimed to examine the relationship between changes in pre-extubation near-infrared spectroscopy measurements from baseline and extubation outcomes after neonatal cardiac surgery.

Materials and Methods: In this retrospective cross-sectional multicenter study, a secondary analysis of prospectively collected data from neonates who underwent cardiac surgery at seven tertiary-care children's hospitals in 2015 was performed. Extubation failure was defined as need for re-intubation within 72 hours of the first planned extubation attempt. Near-infrared spectroscopy measurements obtained before surgery and before extubation in patients who failed extubation were compared to those of patients who extubated successfully using t-tests.

Results: Near-infrared spectroscopy measurements were available for 159 neonates, including 52 with single ventricle physiology. Median age at surgery was 6 days (range: 1-29 days). Fifteen (9.4%) failed extubation. Baseline cerebral and renal near-infrared spectroscopy measurements were not statistically different between those who were successfully extubated and those who failed, but pre-extubation cerebral and renal values were significantly higher in neonates who extubated successfully. An increase from baseline to time of extubation values in cerebral oximetry saturation by $\geq 5\%$ had a positive predictive value for extubation success of 98.6% (95%CI: 91.1% - 99.8%).

Conclusion: Pre-extubation cerebral near-infrared spectroscopy measurements, when compared to baseline, were significantly associated with extubation outcomes. These findings demonstrate the potential of this tool as a valuable adjunct in assessing extubation readiness after pediatric cardiac surgery and warrant further evaluation in a larger prospective study.

Key Words: airway extubation; cardiac surgery; near-infrared spectroscopy; neonate

Introduction

Extubation failure is not uncommon in pediatric patients and has been shown to be a significant contributor to morbidity in children with cardiac disease.^{1,2} Children with congenital or acquired cardiac disease may be particularly vulnerable to adverse outcomes related to extubation failure, as many have a decreased ability to compensate for the alterations in cardiac loading conditions and increased cardiac output demands that occur upon extubation relative to patients without underlying heart disease. Previous studies have suggested that extubation failure in children with cardiac disease is a poor prognostic sign associated with a higher mortality.^{2,3}

Neonates in particular have a higher rate of extubation failure (12%) as compared to older children.^{3,4,5} Reported rates of extubation failure after neonatal cardiac surgery range from 5% to 23%.^{3,5,6} Common indicators utilized for assessing extubation readiness following congenital heart surgery include subjective and objective measures of neuromuscular function and oxygenation and ventilation and indirect markers of adequate cardiac output.⁴ However, extubation readiness tools that have incorporated these indicators have not yet been proven to be reliable in neonates.

Near-infrared spectroscopy is a real-time, non-invasive technology that has become ubiquitous in pediatric cardiac operating rooms and ICUs. It is utilized to assess regional oximetry as a surrogate for cardiac output.⁷⁻¹¹ In a recently published single center study, a decrease in somatic near-infrared spectroscopy values during an extubation readiness trial was associated with an increased risk of extubation failure in children and adolescents who underwent cardiac surgery.⁸ To our knowledge, multicenter studies examining the role of regional oximetry to predict extubation outcomes after neonatal cardiac surgery have not been published. We therefore aimed to use a multicenter dataset to evaluate the relationship between near-infrared spectroscopy values and extubation outcomes in neonates who underwent cardiac surgery. We

hypothesized that favorable changes in cerebral or renal regional oximetry from baseline values would be predictive of extubation success in neonates following cardiac surgery.

Materials and Methods

In this retrospective cross-sectional multicenter study, we conducted a secondary analysis of data collected during a prospective observational study of neonates (less than or equal to 30 days of age) who underwent cardiac surgery from January 1, 2015 to December 31, 2015 in seven tertiary-care children's hospitals in the United States and had at least one extubation attempt. Each site obtained institutional review board approval prior to data collection. Six out of the seven centers involved in the original study utilized near-infrared spectroscopy monitoring routinely. At those six centers, cerebral and renal near-infrared spectroscopy measurements were collected at baseline (i.e., in the operating room prior to surgical incision) and in the ICU prior to extubation using Medtronic's INVOS Cerebral/Somatic Oximeter. Baseline regional oximetry values were obtained preoperatively in order to reflect patients' steady state prior to any intervention, as opposed to the immediate post-operative period, which can be a very dynamic and often volatile time. We also recorded pre-extubation regional oximetry measurements that were entered into the patients' medical record closest to the time of the first extubation attempt. Neonates without cerebral or renal near-infrared spectroscopy values at either time point were excluded from the current study. Due to the observational nature of our study, we did not provide a protocol for extubation readiness assessment; rather, clinicians at each center made extubation decisions based on local practices and individual discretion. Extubation failure was defined as need for unplanned re-intubation within 72 hours of planned extubation. This definition was based on data obtained from local quality assurance initiatives examining extubation outcomes within the participating centers. This definition was supported by the findings in our previous work and confirmed by recent data published from the Pediatric

Cardiac Critical Care Consortium, where a notable proportion (15.5%) of the neonates who failed extubation within 72 hours did so within the 48 to 72-hour time frame.^{3,5}

Statistical Analysis

De-identified demographic, anthropometric, preoperative, operative, and postoperative data were collected for all patients. Descriptive statistics were used to represent collected data, with categorical variables expressed as absolute count with percentage and continuous variables expressed as median with 25th%, 75th%. Bivariate comparisons in patients who failed extubation and patients who were successfully extubated were performed using chi-squared tests, Fisher's exact tests, and Wilcoxon rank sum tests as appropriate for individual variables. To determine optimal cutoff points for the change from baseline to pre-extubation cerebral and renal near-infrared spectroscopy values as predictors of extubation success, receiver operating characteristic curves were generated. Sensitivity, specificity, positive predictive value, negative predictive value, and positive likelihood ratios were then determined for the identified cutoff measurements. Due to inherent differences in the normal ranges of goal oxygen saturations for the various congenital heart lesions included in the study, sensitivity, specificity, positive predictive value, negative predictive value, and positive likelihood ratios were not assessed for absolute regional oximetry values. Finally, multivariable analysis was performed to determine if near-infrared spectroscopy measurements were independently associated with extubation outcome. Statistical analyses were conducted with Stat version 14 (StataCorp, College Station, Texas). *P*-values less than 0.05 were considered statistically significant.

Results

There were 293 neonates who underwent cardiac surgery at the seven institutions during the study period. Of these patients, 159 had at least one pair of baseline and pre-extubation near-infrared spectroscopy measurements and at least one extubation attempt and were included in

this study. Of these 159 patients, 133 had both cerebral and renal regional oximetry measurements, 16 had only cerebral values, and 10 had only renal values (Figure 1). The most common operations performed in this cohort included arterial switch operation for d-transposition of the great arteries (n=37); Norwood operation for hypoplastic left heart syndrome or one of its variants (n=21); systemic-to-pulmonary shunt placement (n=20); isolated repair of coarctation of the aorta (n=17); repair of total anomalous pulmonary venous connections (n=11); pulmonary artery banding (n=9); aortic reconstruction (n=8); and repair of truncus arteriosus (n=7).

Fifteen patients (9.4%) failed their first extubation attempt: 8 were reintubated due to presumed respiratory failure and 7 were reintubated due to signs and symptoms of cardiogenic shock. None of the patients who were reintubated died during their hospitalization. There were no extubation failures after 72 hours in any of the neonates included in this analysis.

Characteristics of patients who were extubated successfully and those who were reintubated are compared in Table 1. Patients from the two cohorts were statistically similar in terms of age at surgery, weight at surgery, number of functional cardiac ventricles, duration of cardiopulmonary bypass, postoperative use of extracorporeal membrane oxygenator support, and other clinically relevant variables. Patients who failed extubation however were more likely to have delayed sternal closure ≥ 4 days ($p=0.005$). This variable was also identified in our previous analysis as an independent risk factor for extubation failure.³

Cerebral and renal regional oximetry values are summarized in Table 2. Note that 149 of the 159 patients in the study (136 extubation successes, 13 extubation failures) had cerebral measurements at both time points and 143 patients in the study (128 extubation successes, 15 failures) had renal measurements at both time points. Baseline near-infrared spectroscopy

measurements (i.e., in the operating room before the commencement of surgery) were not different between patients who were extubated successfully and those who failed. Patients who extubated successfully had significantly higher absolute pre-extubation cerebral and renal regional oximetry measurements as compared to patients who failed extubation. Additionally, the median change in cerebral regional oximetry measurements from baseline to pre-extubation was increased in patients who extubated successfully, whereas the median change in cerebral regional oximetry measurements from baseline to pre-extubation was decreased in patients who failed extubation.

Sensitivity, specificity, positive predictive values, negative predictive values, and positive likelihood ratios for identified cutoff values for change in cerebral and renal regional oximetry measurements from baseline as predictors of extubation success are provided in Table 3. Based on receiver operating characteristic curve analysis, we identified an increase in cerebral regional oximetry percentage values of 5% or more as the optimal cutoff for predicting extubation success. Specifically, in the 70 patients who had a change in cerebral regional oximetry measurements from baseline to pre-extubation of at least 5%, 69 extubated successfully, which equates to a positive predictive value of 98.6%. Moreover, in a multivariable analysis that included adjustment for prolonged sternal closure greater than 4 days, an increase in cerebral regional oximetry measurements of 5% or greater from baseline values to time of extubation was independently associated with extubation success (OR 10.9; 95% CI:1.4, 87.4; $p=0.027$).

An optimal cutoff value for the change in renal regional oximetry measurements as a predictor of extubation success was not easily identifiable. We therefore utilized an increase in renal regional oximetry value of greater than or equal to 5% as the cutoff point, to allow for comparison of our analysis of cerebral regional oximetry. In contrast to cerebral regional

oximetry measurement, an increase in renal regional oximetry greater than 5% was a poor predictor of extubation outcome (Table 3).

Discussion

Extubation failure occurs in 5%-23% of critically ill infants and children with cardiac disease.^{3,5,6,12} Several recent studies have shown that neonates, not surprisingly, are more likely to fail extubation than older children. In our multicenter investigation of extubation failure in a heterogeneous cohort of neonates who underwent surgery for congenital heart disease, 12% failed extubation, which was consistent with a recent study from the Pediatric Cardiac Critical Care Consortium (PC4) that reported an extubation failure rate of 11% in 899 neonates who had undergone cardiac surgery.^{3,5,12} By comparison, extubation failure occurred in 6% of the general cardiovascular ICU population.^{5,12} Furthermore, extubation failure has consistently been shown to be associated with increased morbidity and mortality in pediatric populations.^{1,2,12,13} For example, Baisch et al. showed that it contributes to increased mechanical ventilation days as well as longer ICU and hospital length of stay.¹ Likewise, an analysis of data from the Pediatric Cardiac Critical Care Consortium (PC4) registry found an association between extubation failure with longer cardiovascular ICU length of stay and in-hospital mortality.¹² Efforts aimed at identifying measures to predict and possibly prevent extubation failure could beneficially impact patient outcomes.

Several risk factors for extubation failure in neonates after cardiac surgery have been identified. In a single-center retrospective study of neonates who underwent cardiac surgery, Laudato and colleagues found that genetic abnormalities, hypoplastic left heart syndrome, and postoperative infection were independently associated with neonatal extubation failure.¹⁴ Gupta and colleagues found the use of inhaled nitric oxide after surgery, prolonged mechanical ventilation,

and atelectasis on chest x-ray prior to extubation to be risk factors for extubation failure in a single-center, retrospective study in neonates who had undergone the Norwood operation.¹⁵ More recently, in a multicenter cohort of neonates from the Pediatric Cardiac Critical Care Consortium (PC4) registry, Benneyworth et al. identified the presence of congenital airway anomaly as an independent risk factor for extubation failure.⁵ In our previous work, we reported use of uncuffed endotracheal tubes and delayed sternal closure of four days or greater as independently associated with extubation failure after cardiac surgery.³ In the present study, prolonged duration of delayed sternal closure was indeed significantly more common in patients who failed extubation, while use of uncuffed endotracheal tube was not. The latter discrepant finding may be attributed to the fact that only 12 of the 49 patients with uncuffed endotracheal tubes from our initial study had adequate near-infrared spectroscopy data to be included in this analysis.

While knowledge of risk factors associated with extubation failure can help guide extubation practices, objective measures to assess extubation readiness in this complex patient population are also needed to better guide extubation practices. In particular, objective measures of cardiac output during the transition off of mechanical ventilation would be most helpful since many children recovering from congenital heart surgery have reduced cardiopulmonary reserve and, consequently, have limited ability to adapt to the metabolic demands associated with respiratory distress and increased work of breathing. Several studies in the adult literature that include post-operative cardiac surgical patients have demonstrated rapid declines in mixed venous oxygen saturation during spontaneous breathing trials and immediately after extubation due to either a decrease in oxygen delivery, increase in oxygen consumption, or an increase in systemic oxygen extraction during the transition off of mechanical ventilation.^{16,17} To our knowledge, similar data in the pediatric cardiac population are lacking. Near-infrared spectroscopy, which has become ubiquitous in pediatric cardiac operating rooms and ICUs in

recent years, represents a non-invasive means of monitoring this delicate balance of oxygen delivery and demand in these patients. Recent studies have demonstrated that low cerebral regional oximetry values in both single ventricle and two ventricle children after cardiac surgery can be a reflection of inadequate oxygen economy and are predictive of worse clinical outcomes.^{9,18} In one single-center, prospective observational study, Foster et al. evaluated the use of near-infrared spectroscopy to predict extubation outcome in children after cardiac surgery.⁸ These researchers found that a 12% decline in somatic regional oxygen saturation during an extubation readiness trial was associated with an increased risk of extubation failure, suggesting that the addition of somatic regional oxygen saturation measurements to an extubation readiness trial may improve the ability to predict extubation outcome in pediatric cardiac patients.⁸

Similar to the work of Foster and colleagues, our data support the use of near-infrared spectroscopy measurements as an adjunct to extubation readiness assessment. In our study, we showed that an increase in cerebral regional oximetry greater than or equal to 5% from baseline prior to extubation was predictive of extubation success in 99% of cases. We speculate that this increase in near-infrared spectroscopy measurements may be reflective of a greater degree of cardiopulmonary reserve, which allowed these patients to better tolerate the increased metabolic demands that can occur upon extubation. Importantly, renal near-infrared spectroscopy measurements had limited ability to predict extubation success. Moreover, the interquartile ranges presented in Table 2 for the change in renal near-infrared spectroscopy measurements are visibly wider than the cerebral measurements, which is evidence of greater variation in the former measurements between patients. In one single center study of 20 children recovering from cardiac surgery, renal or splanchnic near-infrared spectroscopy measurements were not predictive of low cardiac output.¹⁹ Variations in probe placement and thickness of the abdominal wall or flank region, which were suggested as possible reasons for

their findings, could have played a role in our results as well.²⁰ We also speculate that variations in preoperative and postoperative feeding practices across patients and centers, which would result in variable mesenteric and renal oxygen extraction, could have negatively affected the predictive value of renal near-infrared spectroscopy measurements.

Importantly, we acknowledge that while the positive predictive value of the change in cerebral near-infrared spectroscopy measurements was robust, the sensitivity and negative predictive value were low. Notably, 67 neonates in whom cerebral regional oximetry values were not increased by 5% or greater at the time of extubation were extubated successfully. From these data, we can conclude that while an increase of 5% or more in cerebral regional oximetry should provide reassurance that extubation success is likely to occur, the absence of this positive change in cerebral regional oximetry should not be, in and of itself, a deterrent to extubation. Rather, our findings corroborate the potential of near-infrared spectroscopy observed in earlier studies as a valuable adjunct for the assessment of extubation readiness in cardiac neonates.

Our study has several limitations. First, there are inherent limitations of regional oximetry technology that can hinder its ability to accurately reflect the adequacy or inadequacy of systemic oxygen delivery. Examples of these limitations include variability that can result from differences in patients' body habitus or the degree of tissue edema, and the absence of published age-based normal values in children with cardiac disease. In addition, near-infrared spectroscopy monitoring was performed at the discretion of the clinicians at each center and was not standardized. Additionally, extubation readiness assessment and criteria for reintubation were not protocolized across participating institutions and were not assessed as a part of this study. The decision to extubate or reintubate was made with some combination of the results of local extubation readiness tests and the impression of the clinical team. Also, clinicians were not blinded to cerebral and renal oximetry measurements, and the extent to

which these measurements may have influenced the decision to extubate is unknown. Our data were obtained from a larger data set from a prior study that was not specifically designed to assess the effectiveness of near- infrared spectroscopy as an extubation readiness tool. Thus, cerebral and renal oximetry measurements were only recorded when available and at two time points, limiting the number of patients we could include in this sub-analysis and prohibiting us from analyzing the relationship between trends in cerebral and renal oximetry measures during ventilator weaning and extubation outcomes. Even with these limitations, our data, in conjunction with the data previously published by Foster and colleagues, highlight the promise of regional oximetry as an adjunctive tool for extubation readiness assessment in pediatric cardiac surgical patients and should stimulate further study. Further investigation, which should include additional measures of systemic oxygen delivery such as arterio-venous oxygen difference to support the notion of regional oximetry as a reflection of cardiopulmonary reserve, is warranted to specifically address the question of how to best implement this technology in extubation readiness protocols.

Conclusions

In conclusion, improvements in cerebral regional oximetry measurements from baseline to just prior to extubation were associated with extubation success in neonates recovering from cardiac surgery. More specifically, an increase in cerebral regional oximetry measurement of at least 5% from baseline to pre-extubation was robustly predictive of extubation success. Our results suggest that near-infrared spectroscopy monitoring has great potential as an aid to the bedside clinician in determining the likelihood of extubation success in neonates who have undergone congenital heart surgery.

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Conflicts of Interest: None.

Ethical Standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (United States National Institutes of Health Belmont report) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional review boards of each participating institution.

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Table 1. Bivariate Comparison of Characteristics of Patients Who Were Extubated Successfully and Patients Who Failed Extubation.

Variables^a	Extubation Success (n = 144)	Extubation Failure (n = 15)	p-value
Age, days	6.5 (5,10)	6 (3,10)	0.23
Weight, kg	3.2 (2.9-3.6)	3.1 (2.9,3.4)	0.24
Male	89 (62)	6 (40)	0.10
Prematurity (< 37 weeks gestation)	15 (10)	3 (20)	0.38
Genetic abnormality	17 (12)	4 (27)	0.12
Non-cardiac anatomic anomaly	12 (8)	3 (20)	0.15
Single ventricle physiology	45 (31)	7 (47)	0.23
STAT mortality category 4 or 5	104 (72)	10 (67)	0.76
Mechanical ventilation prior to surgery	31 (22)	5 (33)	0.33
Pre-operative shock ^b	15 (10)	2 (13)	0.66
Cardiopulmonary bypass	118 (82)	10 (67)	0.17
Cardiopulmonary bypass duration, min	137 (73-196)	120 (0-188)	0.31
Uncuffed endotracheal tube	10 (7)	2 (13)	0.32
PaO ₂ on ICU admission, mmHg	77 (48-125)	62 (42-99)	0.26
PaO ₂ prior to extubation, mmHg	70 (44-94)	63 (41-80)	0.62
Delayed sternal closure	46 (32)	7 (47)	0.25
Delayed sternal closure ≥ 4 days	9 (6)	5 (33)	0.005
Postoperative ECMO	5 (3)	2 (13)	0.13

^a ECMO: extracorporeal membrane oxygenation; STAT: Society of Thoracic Surgeons - European Association for Cardio-Thoracic Surgery congenital heart surgery mortality category; categorical data represented as absolute counts (%) and continuous variables represented as median (25%,75%)

^b As defined by the Society of Thoracic Surgeons Congenital Heart Surgery Database: Metabolic acidosis with arterial pH < 7.2 and/or lactate > 4 mmol/L

Table 2. Cerebral and Renal Near Infrared Spectroscopy (NIRS) Measurements

Cerebral NIRS Measurements^a	Extubation Success (n=136)	Extubation Failure (n=13)	p-value
Baseline	67 (57,76)	68 (64,72)	0.72
Pre-extubation	72 (61,79)	57 (56,68)	0.04
Δ NIRS	5 (-7,13)	-1 (-12,3)	0.04
Δ NIRS \geq 5%	69 (51%)	1 (8%)	0.003
Renal NIRS Measurements^a	Extubation Success (n=128)	Extubation Failure (n=15)	p-value
Baseline	62 (55,72)	58 (55,74)	0.88
Pre-extubation	77 (64,85)	68 (55,76)	0.03
Δ NIRS	10 (-1,25)	-1 (-11,17)	0.09
Δ NIRS \geq 5%	79 (62%)	7 (47%)	0.24

^a149 study patients (94%) had cerebral NIRS measurements at baseline and pre-extubation and 143 patients (90%) had renal NIRS measurements at baseline and pre-extubation; Data provided as median (25%,75%) for continuous variables and absolute counts (%) for categorical variables

Table 3. Sensitivity, Specificity, and Predictive Values for the Change (Δ) in Cerebral and Renal Near Infrared Spectroscopy (NIRS) as Predictors of Extubation Success

Tests	ΔCerebral NIRS \geq 5%	ΔRenal NIRS \geq 5%
Sensitivity	50.7% (42.1%, 59.4%)	62.2% (53.1%, 70.1%)
Specificity	92.3% (62.1%, 99.6%)	53.3% (27.4%, 77.7%)
Positive Predictive Value	98.6% (91.2%, 99.9%)	91.9% (83.4%, 96.4%)
Negative Predictive Value	15.2% (8.4%, 25.4%)	14.3% (6.8%, 26.8%)
Positive Likelihood Ratio	6.6 (1.0, 43.6)	1.4 (0.76, 2.3)

Data provided as calculated percentage or ratio with 95% confidence intervals

Figure Legends

Figure 1. Flow chart of patients included and excluded in the study analysis. 159 patients from 6 institutions involved in the original study had at least one pair of near infrared spectroscopy (NIRS) measurements (i.e. cerebral and/or renal at baseline and pre-extubation).

