**Comparison of Postoperative Respiratory Function in Neonates with Hypoplastic Left Heart
Syndrome Following First Stage Palliation**

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Abstract

Purpose

Available surgical procedures in the first stage of the palliation of hypoplastic left heart syndrome (HLHS) are currently the Norwood procedure with Blalock-Taussing (BT) shunt, Norwood with a Sano shunt (5.0 mm right ventricular-pulmonary artery conduit), or a hybrid procedure combining surgical pulmonary artery band placement and catheter-based closure of the ductus arteriosus. Following any of the three procedures, it is necessary for patients to be mechanically ventilated for a period of time; however, little is known about the differences in pulmonary function and outcome among the three groups.

Methods

We conducted a retrospective chart review of 14 neonates who underwent stage 1 palliation for HLHS, by hybrid procedure or Norwood procedure with BT or Sano shunts, at Phoenix Children's Hospital from September 2013-December 2014. Demographic, hemodynamic, and outcome information was collected. Heart rate, respiratory rate, mean arterial pressure, end tidal carbon dioxide (ETCO₂), cerebral and renal somatic oximetry, mean airway pressure, ratio of partial pressure of arterial oxygen to inspired oxygen (P_aO₂/FiO₂), partial pressure of arterial carbon dioxide (PaCO₂), dead space fraction (V_d/V_t), and dynamic compliance were measured preoperatively, postoperatively, and at multiple time points from 6 to 120 hours postoperatively. Respiratory data was collected using the NM3 monitor (Philips Respironics, Pittsburgh, PA). Outcome measures collected included maximum postoperative lactate, time to extubation, hospital length of stay, and mortality.

Results

Of the 14 patients, 7 received the Norwood with BT shunt, 5 received the Sano shunt, and 2 received the hybrid procedure. Through linear regression analysis of groups stratified by shunt size, we found that the V_d/V_t ratios of the Sano and 3.0 mm BT shunt groups were higher at earlier times points, but became indistinguishable by 48 hours postoperatively (p=0.02). Linear regression of the 3 surgical groups comparing V_d/V_t across all times points did not show any

significant differences ($p = 0.79$). Linear regression of dynamic compliance among the three groups across all time points also was not significant ($p = 0.72$). No significant difference was observed in dynamic compliance across all time points when groups were stratified by shunt size ($p = 0.33$). Examining differences between BT and Sano groups at each time point from 0-120 hours postoperatively using Mann Whitney U analysis did not reveal significance. Analysis of outcomes of length of mechanical ventilation ($p=0.61$), hospital length of stay ($p =0.99$), and mortality ($p>0.99$) also did not differ significantly among the 3 surgical groups.

Conclusion

Our study identified that the 3.0 mm BT and Sano shunt group had higher Vd/Vt ratios throughout the first 48 postoperative hours. No other differences were found in Vd/Vt or dynamic compliance when surgical groups or shunt sizes were compared. Despite the early differences noted, lack of differences in outcome measures suggests that these early differences have little influence on prognosis.

Table of Contents

Introduction and Significance	1-3
Materials and Methods.....	4-5
Results	7-15
Discussion.....	16-17
Future Directions	18
Conclusions	19
References	20

List of Figures and Tables

Table 1: Demographic information

Figure 1: Comparison of mean V_d/V_t among BT, Sano, and Hybrid Groups

Figure 2: Comparison of mean V_d/V_t among BT and Sano Groups

Figure 3: Linear regression of V_d/V_t of Groups Stratified by Shunt Size

Figure 4: Maximum Postoperative Lactate among BT, Sano, and Hybrid Groups

Figure 5: Time to Extubation among BT, Sano, and Hybrid Groups

Figure 6: Length of Hospital Stay BT, Sano, and Hybrid Groups

Figure 7: Mortality within 30 days of discharge among

Introduction

Background

Hypoplastic left heart syndrome (HLHS) is a congenital heart disorder that accounts for 1 out of every 4,344 babies born in the United States.¹ HLHS is characterized by severe underdevelopment of the left ventricle, possible dysfunction of the mitral and aortic valves, as well as a potential decrease in the size of the aorta. In the past, the expected 5-year survival rate for HLHS was as low as 50%, but changes in treatment and management of HLHS has altered current expectations of HLHS infants to reach adulthood at 70%.²

Current recommendations for management of HLHS include 3 stages of surgical management. The first stage of surgical palliation is performed in neonates, with the overarching goals being to relieve obstructions to systemic outflow, provide adequate coronary and pulmonary artery blood flow, and create a nonrestrictive atrial septal defect. Available surgical procedures for first stages palliation in HLHS include the Norwood, Sano, and hybrid procedures. The Norwood procedure with modified Blalock-Tussing (BT) shunt involves the creation of a “neo-aorta”, made through closing off the distal pulmonary artery and combining the proximal pulmonary artery with homograft material to reconstruct the aortic arch. A source of pulmonary blood flow is established by placing the BT shunt, typically a 3.0 or 3.5 mm Gore Tex tube, between the brachiocephalic and proximal right pulmonary artery. Lastly, the atrial septum is resected.³ The Sano modification involves the creation of right ventricle to pulmonary artery conduit, which establishes pulmonary blood flow in place of a BT shunt.⁴ The hybrid method of first stage palliation in HLHS is a combination of surgical and transcatheter approaches. Catheter techniques are utilized to place a stent in the ductus arteriosus, causing it to remain patent and allowing the right ventricle to support systemic circulation. Restricting bands are then placed on the branches of the pulmonary artery to restrict pulmonary blood flow. The atrial septum is either removed by an atrial balloon septostomy or a stent is placed in the interatrial septum to connect the atria.⁵ Neonates with congenital heart defects frequently suffer from poor pulmonary function primarily due to impaired pulmonary perfusion, and monitoring the respiratory function of these neonates after surgery is vital in preventing a potentially turbulent post-operative course.

Dead space measurements provide valuable clinical information about disease progression and prognostic implications. Dead space measurements and end tidal CO₂ measurements through volumetric capnography have been shown to have good agreement with identical measurements taken through conventional methods. Volumetric capnography measurements of dead space are taken through calculation of the area under the single breath test-CO₂ waveform, whereas conventional Douglas bag calculation of dead space is done through collection of mixed-expired gas. Volumetric capnography has been shown to be both an effective and accurate method of measuring physiological dead space in mechanically ventilated patients.^{6,7} Increased dead space fractions have been shown to be a feature of early phase of acute respiratory distress syndrome in mechanically ventilated patients, and elevated values are associated with increased risk of death.⁸

In a study conducted by Matthews et al, respiratory compliance was measured in infants with various forms of univentricular heart physiology following shunt placement. It was found respiratory compliance was reduced in patients with large systemic-pulmonary arterial shunts, respiratory resistance was higher with increased heart size, and there was an inverse relationship between a decreased pulmonary to systemic shunt ratio and an increased arterial to end tidal CO₂.⁹ A study performed by Shakti et al compared postoperative differences in patients who received the Norwood BT and right ventricular-pulmonary artery conduit procedures. The authors found that dead space fraction (V_d/V_t) was lower in patients with BT shunts over all time points, but maximum V_d/V_t on day 1 and 2 was not. Higher maximal V_d/V_t during the first 48 postop hours was independently associated with fewer ventilator and hospital free days in the first month after stage 1 palliation.¹⁰

Significance and Rationale

Little is known about the differences in respiratory compliance of HLHS neonates following the three types of surgical palliation: Norwood procedure with either the BT shunt or Sano modifications, or the hybrid procedure. Following any of the three first-stage palliative surgical procedures for HLHS, it is necessary for neonates with HLHS to be intubated for a period of time; however, previous studies have not investigated the differences in intubation time and

overall respiratory system compliance among the three surgical groups. In the present study, volumetric capnography was used to assess differences in pulmonary function among neonates who have undergone the Norwood procedure with BT or Sano modifications, or the hybrid procedure. Analysis of which procedure provides the best post-operative respiratory parameters and outcome measures may provide physicians with important prognostic information when choosing forms of first stage palliative surgery for HLHS neonates

Research Question/Hypothesis

The research question was to identify if there are differences in postoperative pulmonary function or outcome measures in patients who undergo first stage palliation with the hybrid procedure or Norwood procedure with BT or Sano shunts. We hypothesized that patients with BT shunts and hybrid procedures will have abnormally low respiratory system compliance, while those with Sano shunts will have normal or high compliance and higher parameters of dead space measurements.

Goals of Study

The goals of the present study were to (1) determine parameters of pulmonary function in neonates with HLHS prior to first stage palliative repair using the Respirationics NM3 noninvasive monitor, (2) compare the pulmonary function and (3) outcome measures of patients with HLHS after each type of first stage repair, as information about post-operative courses could aid providers' future decision making.

Materials and Methods

We conducted a retrospective chart review of 14 neonates who underwent stage 1 palliation for HLHS by hybrid procedure or Norwood procedure with BT or Sano shunts, at Phoenix Children's Hospital from September 2013-December 2014. Inclusion criteria were HLHS patients undergoing first-stage surgical palliation utilizing the Norwood procedure with either BT or SANO shunts, or the hybrid procedure. To homogenize the population of patients, we only enrolled HLHS and its variants, including aortic stenosis/aortic atresia, aortic stenosis/mitral stenosis, aortic atresia/mitral stenosis, and interrupted aortic arch ventricular septal defect hypoplastic left heart were included. Patients with unbalanced or malaligned atrioventricular canal and Shone's complex were excluded. In addition, patients with known pulmonary abnormalities (hypoplastic lungs, congenital cystic adenomatoid malformations, or other congenital anomalies), endotracheal tube leak >20%, tracheostomy, or significant concurrent pulmonary disease (pneumothorax, pneumonia, etc.) were excluded from the study. Respiratory data was collected using the NM3 Respironics Monitor (Phillips Respironics, Philadelphia, PA). Respiratory and hemodynamic data were collected at 0, 6, 12, 18, 24, 36, 48, 72, 96, and 120 hours postoperatively. Demographic information collected included birth weight, sex, age at time of operation, cardiac anatomy, presence of genetic syndrome, extracardiac anomalies, procedure, shunt size, bypass and cross clamp times. **Table 1** displays the demographic characteristics of the patients in the study. The hemodynamic information collected at each of the postoperative intervals were heart rate, respiratory rate, mean arterial pressure, and regional oximetry. The respiratory information collected by the NM3 monitor at each of the postoperative time points included mean airway pressure, $\text{PaO}_2/\text{FiO}_2$, EtCO_2 , V_d/V_t , and dynamic compliance. Postoperative outcomes analyzed were maximum postoperative lactate, time to extubation, hospital length of stay, and mortality within 30 days of hospital discharge. The study represented less than minimal risk to the privacy of the individuals included; only non-identifiable patient information by chart review was involved in data analysis. All study procedures were performed according to protocol and IRB-approved recruitment/consent procedures and the enrollment inclusion/exclusion criteria previously listed. Data security was ensured by performing all research at the Phoenix Children's Hospital

Cardiovascular Intensive Care Unit. Once the initial query was completed, all data was de-identified to exclude any link back to individual identity.

Table 1: Demographic information of patients included in study

Variable	Norwood BT (n=7)	Sano (n=5)	Hybrid (n=2)	P value
BSA (m²)	0.21 (0.01)	0.21 (0.01)	0.17 (0.01)	0.07
Gender (female)(%)	2 (28.5%)	2 (40%)	2 (100%)	
Genetic Syndrome (%)	0	0	1 (50%)	
Age at surgery (days)	8 (5.86)	7.2 (2.17)	8.5 (2.12)	0.61
Extracardiac (%)	2 (28.5%)	1 (20%)	1 (50%)	
Cardiac Anatomy	(3) HLHS/AA/MA (2) HLHS (1) HLHS/AS/MS/ VSD (1) HLHS w/o intrinsic valvular stenosis or atresia (Hypoplastic AV + MV + LV) (HLHC)	(1) HLHS/AS/MA (4) HLHS/AA/MA	(1) HLHS/AS/MV hypoplasia (1) HLHS/AS/MS/ IVS	
Total Pump Time	183.143 (17.69)	193 (13.95)	NA	0.34
Cross Clamp Time	55 (11.28)	51.5 (4.51)	NA	0.78
Shunt Size	3.0 mm – 3 patients 3.5 mm – 4 patients	5.0 mm – 5 patients	NA	

Data presented as n (%) of mean (Standard Deviation).

Results

Data from 14 patients were analyzed in this study. 7 patients had undergone the Norwood with BT shunt, 5 received the Sano shunt, and 2 underwent the hybrid procedure.

Respiratory Parameters

Kruskal Wallis analysis of V_d/V_t across all time points among the BT, Sano, and hybrid groups did not reveal a significant difference ($p = 0.632$) (**Figure 1**). Comparison of V_d/V_t among BT and Sano groups across all time points utilizing the Mann-Whitney U also showed no significance ($p = 0.828$) (**Figure 2**). Through linear regression analysis of groups stratified by shunt size, we found that V_d/V_t ratios of the Sano and 3.0 mm BT shunt groups were higher at earlier times points, but became indistinguishable by 48 hours postoperatively ($p = 0.02$) (**Figure 3**). Linear regression of the 3 surgical groups comparing V_d/V_t across all times points did not show any significant differences ($p = 0.79$). Linear regression of dynamic compliance among the three groups across all time points also was not significant ($p = 0.72$). No significant difference was observed in dynamic compliance across all time points when groups were stratified by shunt size ($p = 0.33$).

Figure 1: Comparison of mean Vd/Vt among BT, Sano, and hybrid groups

Figure 2: Comparison of mean V_d/V_t among BT and Sano groups

Figure 3

Outcome Measures

Analysis of outcomes of maximum postoperative lactate ($p = 0.06$), length of mechanical ventilation ($p=0.61$), hospital length of stay ($p =0.99$), and mortality ($p>0.99$) also did not differ significantly among the 3 surgical groups (**Figure 3,4,5,6**).

Figure 4: Maximum Postoperative Lactate among BT, Sano, and Hybrid Groups

Figure 5: Time to Extubation among BT, Sano, and Hybrid Groups

Figure 6: Length of Hospital Stay BT, Sano, and Hybrid Groups

Figure 7: Mortality within 30 days of discharge among BT, Sano, and Hybrid Groups

Discussion

The results from our study showed that 3.0 mm BT shunt and Sano shunt groups have higher V_d/V_t ratios within the first 48 hours postoperatively. The finding of increased V_d/V_t in the Sano group is consistent with our hypothesis and may be explained by decreased pulmonary perfusion associated with overall lower flow associated with no diastolic runoff, as compared with similarly sized BT shunts. The increased V_d/V_t seen in the 3.0 mm BT shunt group is likely due to the smaller shunt size.

Previous studies have shown increased postoperative V_d/V_t ratios in neonates with CHD to have a negative association with outcome measures. Ong et al conducted a prospective cross-sectional study of 52 intubated pediatric patients within 24 hours of congenital heart surgery. They found that pulmonary dead space fraction significantly correlated with duration of mechanical ventilation and length of hospital stay. Increased V_d/V_t (>0.5) was an independent predictor for prolonged mechanical ventilation.¹¹ Shakti et al demonstrated in a cohort of 51 patients with univentricular physiology following stage 1 palliation that patient with BT shunt had lower V_d/V_t at all time points as compared to those who had received RV-PA shunt. It was found that higher V_d/V_t was associated with prolonged mechanical ventilation and longer length of hospital stay. Large differences in arterial to end-tidal CO_2 at the time of extubation between the 2 groups suggested that differences in V_d/V_t persisted beyond mechanical ventilation.¹¹

The findings from our study are not consistent with the previous studies, as increased dead space fractions within the first 48 hours seen in the 3.0 mm BT shunt and Sano groups were not associated with prolonged time to extubation or hospital length of stay. Our study suggests that choice of surgical procedure may affect respiratory parameters within the first 48 hours of surgery, but these respiratory changes do not translate to an appreciable effect on short-term prognosis.

Several limitations of our study need to be taken into account when appreciating our findings. Perhaps the most significant was the limited power of this study given the sample size of 14. Our study was also limited by the frequency of each of the three procedures. We were only able to obtain data from one patient who underwent the hybrid procedure, which limited our ability to compare across the three groups. Another limitation of our study was the frequency with which the measurements from the NM3 Respiromics monitor were included in the electronic medical record. It is possible that some of the sparsely recorded data for a few of our patients was a result of the NM3 Respiromics monitor being incorporated as a standard of care for intubated patients fairly recently at Phoenix Children's Hospital. Regulation of data recording could have provided the opportunity to compare preoperative pulmonary function to postoperative. As with all retrospective studies, our study was subject to unknown confounders and selection bias. It is possible that our findings may be a result of confounding factors not identified in our data set.

Future Directions

As a major limitation of this study was the small pool of patients, further investigation would necessitate a power analysis to determine the appropriate size cohort needed to produce potentially significant results. Given the rarity of HLHS, it is likely that a multicenter study would be necessary to achieve a large enough sample size. More specifically, recruitment of hybrid patients in a future study would aid in further analysis, as some of the impetus behind performing this study was to analyze if there were any differences noted in the hybrid procedure group as compared to the more traditional Norwood BT and Sano shunts.

Conclusion

Our study identified that the 3.0 mm BT and Sano shunt group had higher V_d/V_t ratios throughout the first 48 postoperative hours. No other differences were found in V_d/V_t or dynamic compliance when surgical groups or shunt sizes were compared. Despite the early differences noted, lack of differences in outcome measures suggests that these early differences have little influence on prognosis.

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