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ARTICLE

Delivery room oxygen physiology and respiratory interventions for newborns with cyanotic congenital heart disease

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Abstract

Objective To characterize pulse oxygen saturation (SpO_2) trajectories and respiratory interventions after birth for newborns with cyanotic congenital heart disease (CCHD).

Study design Retrospective single-site study of newborns ≥32 weeks gestation with CCHD: single ventricle with critical aortic obstruction (SV-CAO), critical pulmonic obstruction (CPO), transposition of the great arteries (TGA). Minute-to-minute SpO_2 values and respiratory interventions were summarized and compared.

Results Two hundred infants were enrolled. SpO_2 at each minute differed across groups ($p < 0.01$), with the lowest values in TGA. All interventions were most frequent in TGA ($p < 0.01$). Continuous positive airway pressure was provided in 22% SV-CAO, 23% CPO, and 66% TGA. Positive pressure ventilation occurred in 7% SV-CAO, 14% CPO, and 33% TGA. Intubation occurred in 4% SV-CAO, 10% CPO, and 53% TGA.

Conclusion We defined SpO_2 trajectories and delivery room respiratory interventions for three CCHD phenotypes. These results inform delivery room management of these high-risk populations.

Introduction

Immediately after birth, the newborn experiences several rapid physiologic changes which result in increased arterial oxygen saturation levels, from relative hypoxemia in the fetus to normoxemia in the newborn [1–3]. Previous studies established reference oxygen saturation trajectories and respiratory interventions during this transition for term and preterm newborns without cyanotic congenital heart disease (CCHD) [4–7]. Based on these reference ranges, the neonatal resuscitation program (NRP) provides target pulse oxygen saturation (SpO_2) values based on minute after birth [8], which inform treatment during neonatal resuscitation.

Established reference SpO_2 values and NRP guidelines for newborns without CCHD may not apply to resuscitation of neonates with altered transitional oxygen physiology. Congenital heart disease is one of the most common congenital anomalies, affecting ~40,000 infants – or 1% of births – in the United States per year [9, 10]. Due to abnormal cardiac or great vessel anatomy, infants with specific forms of congenital heart disease are expected to be cyanotic after birth. The transition from fetal to neonatal physiology in these newborns likely differs from newborns without CCHD, but the extent and pattern of these differences remains relatively unexplored. As a result, there is a critical gap in evidence to help clinicians effectively manage neonates with CCHD in the delivery room.

The study objective was to characterize the SpO_2 values during neonatal transition and to identify the frequency and intensity of delivery room interventions for newborns with

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CCHD. We hypothesized that infants with CCHD have distinct SpO_2 trajectories during the transitional period immediately after birth compared to newborns without CCHD. Likewise, we anticipated that newborns with CCHD receive more delivery room respiratory interventions compared to newborns without CCHD.

Patients and methods

Study design

This retrospective single-site study was conducted at the Children's Hospital of Philadelphia, a pediatric quaternary care center with a level IV neonatal intensive care nursery. In this hospital, infants with prenatally diagnosed congenital anomalies, including congenital heart defects, are born in a dedicated delivery unit with ~450 births per year. This study was deemed exempt for review by the Children's Hospital of Philadelphia institutional review board.

Study subjects were identified from a registry of all infants with congenital heart disease born in the hospital. We enrolled infants born at ≥32 weeks gestation between March 1, 2016 and December 31, 2018 with prenatally diagnosed congenital cardiac disease expected to experience a mixing physiology of systemic and pulmonary circulation resulting in cyanosis at birth. Based on the detailed anatomy of the underlying cardiac diagnosis on the most recent fetal echocardiogram obtained before birth, we grouped eligible infants into three categories. Subjects were grouped by shared cardiovascular physiology to be inclusive of anatomic variability within common physiological patterns, which would be anticipated to have similar responses to immediate postnatal transition.

These groups were:

1. Single ventricle physiology with critical aortic obstruction (referred to in the text as SV-CAO; such as hypoplastic left heart syndrome (HLHS) or HLHS variants); a common physiology of mixing of the systemic and pulmonary venous returns in a single ventricle, with ductus arteriosus flow supporting the systemic arterial circulation.
2. Critical pulmonic obstruction with either single or two ventricle physiology (referred to in the text as CPO; such as pulmonary atresia with intact ventricular septum, tricuspid atresia, or tetralogy of Fallot with severe pulmonary stenosis or pulmonary atresia); a common physiology of either single ventricle or two-ventricle intracardiac mixing of systemic and pulmonary venous returns with ductus arteriosus flow shunting into or supporting pulmonary blood flow.
3. Transposition of the great arteries physiology (referred to in the text as TGA; including TGA or TGA-like physiology such as double outlet right ventricle with subpulmonic ventricular septal defect); a common physiology in which systemic venous return is directed or streamed to the systemic arterial circulation and pulmonary venous return is directed or streamed into the pulmonary arterial circulation with the two circulations not in series but in parallel.

We excluded infants with major non-cardiac congenital anomalies expected to alter typical cardiopulmonary transition and infants with missing resuscitation records. Infants intubated in the first 10 min after birth or without any recorded pulse oxygen saturation data in the first 10 min after birth were excluded from the pulse oximetry analysis.

Resuscitation guidelines

In our hospital, newborns are stabilized in a dedicated resuscitation suite to support respiratory transition and establish vascular access prior to transfer to the intensive care unit. The resuscitation teams use standardized care guidelines for infants with CCHD based on anticipated disease severity and hemodynamic instability at birth. These guidelines were consistent throughout the study period. The policy during this study period was to place the pulse oximetry sensor on the right hand for all neonates.

For infants with anticipated postnatal cyanosis, our site-specific guidelines indicate an ultimate desirable goal preductal (right hand) SpO_2 of 75–85%. For infants with TGA, our site-specific guidelines recommend initiating respiratory support with supplemental oxygen administration or continuous positive airway pressure (CPAP) if the SpO_2 remains below 75% at 5 min after birth. Furthermore, endotracheal intubation is recommended by 15–20 min after birth for infants below the target SpO_2 range. Providers apply the NRP algorithm for decisions around provision of additional support, such as positive pressure ventilation (PPV) for apnea or bradycardia. Delayed cord clamping was not routinely practiced during the study period.

Data sources

We abstracted all data from the maternal and infant medical records. SpO_2 values from the vital sign monitor were documented in the record by a recording nurse in real-time at the time of resuscitation. The heart rate at the first clinical assessment, as obtained via auscultation or cardiac monitoring, and the first time at which the heart rate was recorded as greater than 100 beats per minute were also abstracted from delivery room records. We collected data for the occurrence, timing, and duration of all interventions performed in the resuscitation suite after birth, including supplemental oxygen, non-invasive CPAP, PPV, intubation,

and medication administration. Study data were collected and managed using REDCap electronic data capture tools hosted at the Children's Hospital of Philadelphia [11, 12].

Statistical analysis

The infant characteristics and interventions performed were presented using standard summary statistics. Data were summarized for each diagnostic group. The timing of SpO_2 data was calculated relative to time of birth, which was defined as the point at which the infant's head and body are entirely expelled from the mother. For study purposes, time of birth was considered "time zero." Due to paucity of data points in the first 2 min after birth, we presented SpO_2 data starting from 3 min after birth.

Delivery room interventions and minute-to-minute SpO_2 values were compared across and between diagnostic groups using Chi-square test and Fisher's exact test for categorical data and Kruskal-Wallis test and Wilcoxon Rank Sum test for continuous measures. As these were exploratory analyses, no corrections were made for multiple comparisons.

Smoothed conditional curves of the 25th, 50th, and 75th percentiles for pre-ductal SpO_2 values for minutes 3–10 after birth were plotted for each diagnostic group using R version 3.6.3 [13]. The curves were generated from the discrete SpO_2 values measured at each minute after birth using local weighted regression. For comparison, the 25th, 50th, and 75th percentile values for SpO_2 at each minute reported for infants without CCHD by Dawson et al. [4]. were overlaid. In post-hoc analysis, we also generated a combined figure of the CPO and SV-CAO groups (Fig. S1).

Results

There were 208 infants ≥32 weeks gestation with eligible prenatally diagnosed cardiac lesions born during the study period. Of these, 5 were excluded due to concurrent major congenital anomalies (including congenital diaphragmatic hernia and giant omphalocele), and 3 were excluded due to missing resuscitation records, leaving 200 enrolled infants. Of these, 196 infants were included in the analyses of pulse oximetry data. Three infants were excluded from pulse oximetry analyses for absent SpO_2 data in the first 10 min after birth and 1 infant was excluded based on endotracheal intubation and need for urgent mechanical ventilation within 10 min after birth.

The mean gestational age for all groups was 38 weeks, with 50% of all infants born via Caesarean section (Table 1). Documentation regarding delayed cord clamping was inconsistent and therefore this information is not reported. There were 68 infants with diagnoses consistent with SV-CAO, 74 infants with CPO, and 58 infants with TGA physiology. Initial heart rates were greater than 100 beats per minute in 93% of SV-CAO, 93% of CPO, and 90% of infants with TGA physiology respectively.

The SpO_2 trends from minutes 3–10 after birth are presented for each diagnostic group in Fig. 1A–C. Infants with SV-CAO and infants with CPO contributed a median of 2 (IQR 2–3) SpO_2 data points, while infants with TGA physiology contributed a median of 3 data points (IQR 2–4). The TGA group had lower pulse oximetry values at each time point (Table 2). Three-way comparison of all CCHD groups showed significant differences in minute-to-minute SpO_2 values at $p < 0.01$. Comparisons of each group separately to TGA showed significant differences in SpO_2 values at each minute (all $p < 0.01$ for CPO v TGA and all $p < 0.02$ for SV-CAO v TGA). Pairwise comparison of the SV-CAO group to CPO group showed no significant differences ($p > 0.05$) in SpO_2 values at each minute after birth.

Infants with TGA physiology received supplemental oxygen and non-invasive respiratory interventions more frequently than the infants in the SV-CAO and the CPO groups (Table 3). There were no significant differences detected in the frequency of non-invasive respiratory support or supplemental oxygen provided to the SV-CAO compared to the CPO group. Significantly more infants with TGA physiology underwent endotracheal intubation in the resuscitation suite (53%) compared to infants with CPO (10%) or SV-CAO (4%) ($p < 0.01$). Intubations in the TGA group occurred at a median of 24 (IQR 18–35) minutes after birth.

Discussion

Congenital heart disease is one of the most common congenital anomalies, affecting 40,000 infants per year in the United States [9, 10]. Despite this prevalence, limited data are available to inform delivery room management of infants with congenital cardiac anomalies. Our study reports transitional SpO_2 values and respiratory interventions performed among infants with CCHD. Infants with CCHD across three different physiological categories had lower pulse oximetry values at birth and throughout the transitional period compared to previously published SpO_2 trends in infants without congenital heart disease. A significantly higher proportion of infants with TGA physiology received respiratory interventions compared with infants with SV-CAO or CPO, both during the first 10 min after birth and throughout stabilization.

The etiology of the relative hypoxemia and cyanosis in each group differs. The most severe deprivation of

Table 1 Infant characteristics.

	Single ventricle-critical aortic obstruction $N = 68$	Critical pulmonic obstruction $N = 74$	Transposition of the great arteries physiology $N = 58$
Gestational age (GA), wk, mean (SD)	38.8 (1)	38.2 (1.7)	38.8 (1)
Preterm (32–36 wk), *N* (%)	3 (4)	12 (16)	3 (5)
Birth weight, grams, mean (SD)	3228 (482)	3003 (627)	3380 (515)
Birth weight <10th percentile for GA, *N* (%)	8 (12)	10 (14)	2 (4)
Male sex, *N* (%)	46 (68)	42 (57)	42 (72)
Race, *N* (%)			
Black or African-American	8 (12)	13 (18)	4 (7)
White	42 (62)	35 (47)	35 (60)
All others	18 (27)	26 (35)	19 (33)
Hispanic ethnicity, *N* (%)	8 (12)	19 (26)	8 (14)
Singleton, *N* (%)	68 (100)	69 (93)	57 (98)
Caesarean delivery, *N* (%)	38 (56)	36 (49)	26 (45)
Maternal systemic opioid or benzodiazepine during labor, *N* (%)	2 (3)	1 (1)	1 (2)
Maternal general anesthesia, *N* (%)	3 (4)	2 (3)	0 (0)
Subjects with first recorded HR > 100 bpm, *N* (%)	63 (93)	69 (93)	52 (90)
Min from birth to first recorded HR > 100 bpm, median (IQR)	1 (1–3)	2 (0–3)	2 (1–3)
Apgar score at 1 min, median (IQR)	8 (8–8)	8 (8–8)	8 (7–8)
Apgar score at 5 min, median (IQR)	9 (8–9)	9 (8–9)	8 (8–9)

GA gestational age, *bpm* beats per minute, *IQR* interquartile range, *SD* standard deviation.

oxygenated blood delivery occurs in TGA as a result of ineffectual parallel circulation. Infants with CPO experience hypoxemia in the setting of decreased pulmonary blood flow, while infants with SV-CAO experience oxygenated blood flow deprivation due to mixing of the systemic and pulmonic circulations delivered to the systemic arterial circulation. We anticipate that these individual physiologies and their unique cardio-pulmonary patterns likely lead to the SpO_2 trends we describe during physiologic postnatal transition. To our knowledge there are no published data specifically reporting the SpO_2 values during this transitional period for any of these groups. While we found that TGA infants experience a significantly different SpO_2 trajectory compared to the other groups, the SpO_2 values did not differ significantly between the CPO and SV-CAO groups.

These SpO_2 trajectories should be interpreted in the context that many infants received supplemental oxygen and respiratory interventions during this time frame. Given the frequency of respiratory interventions performed, it would be difficult to generate an unaided or "natural" SpO_2 trajectory in these populations. However, by combining the SpO_2 trends of many infants with similar cardiac physiology, these trajectories provide context for clinicians on expected trends based on resuscitations at a high-volume center. Even with these respiratory interventions in place, the infants with CCHD were nearly uniformly hypoxemic compared to the Dawson subjects.

Other perinatal factors may influence oxygenation trends, including mode of delivery and delayed cord clamping. Previous studies have shown that infants born via Cesarean section had significantly lower SpO_2 values in the first 5 min after birth compared to infants born vaginally.[45] In our study, 50% of all subjects were born through Cesarean section, compared to 48% of infants in the Dawson study [4] and 31.9% of infants born in the US annually [14]. In a recent study, term newborns who underwent delayed cord clamping for longer than 60 s had higher SpO_2 values in the first 5 min after birth compared to the Dawson values [15]. Delayed cord clamping was not routinely performed in this unit during the study period.

Infants in all CCHD groups more frequently received delivery room respiratory interventions compared with infants without CCHD. The frequency of PPV ranged from 7 to 33% in our CCHD groups, compared with reported delivery room PPV rates of 2.3–6% among newborns without CCHD [16–18]. Likewise, 22–66% of infants in each group received CPAP in our study, compared to 2.6% of majority term newborns without CCHD in a recent study [17]. Finally, 53% of infants in our TGA

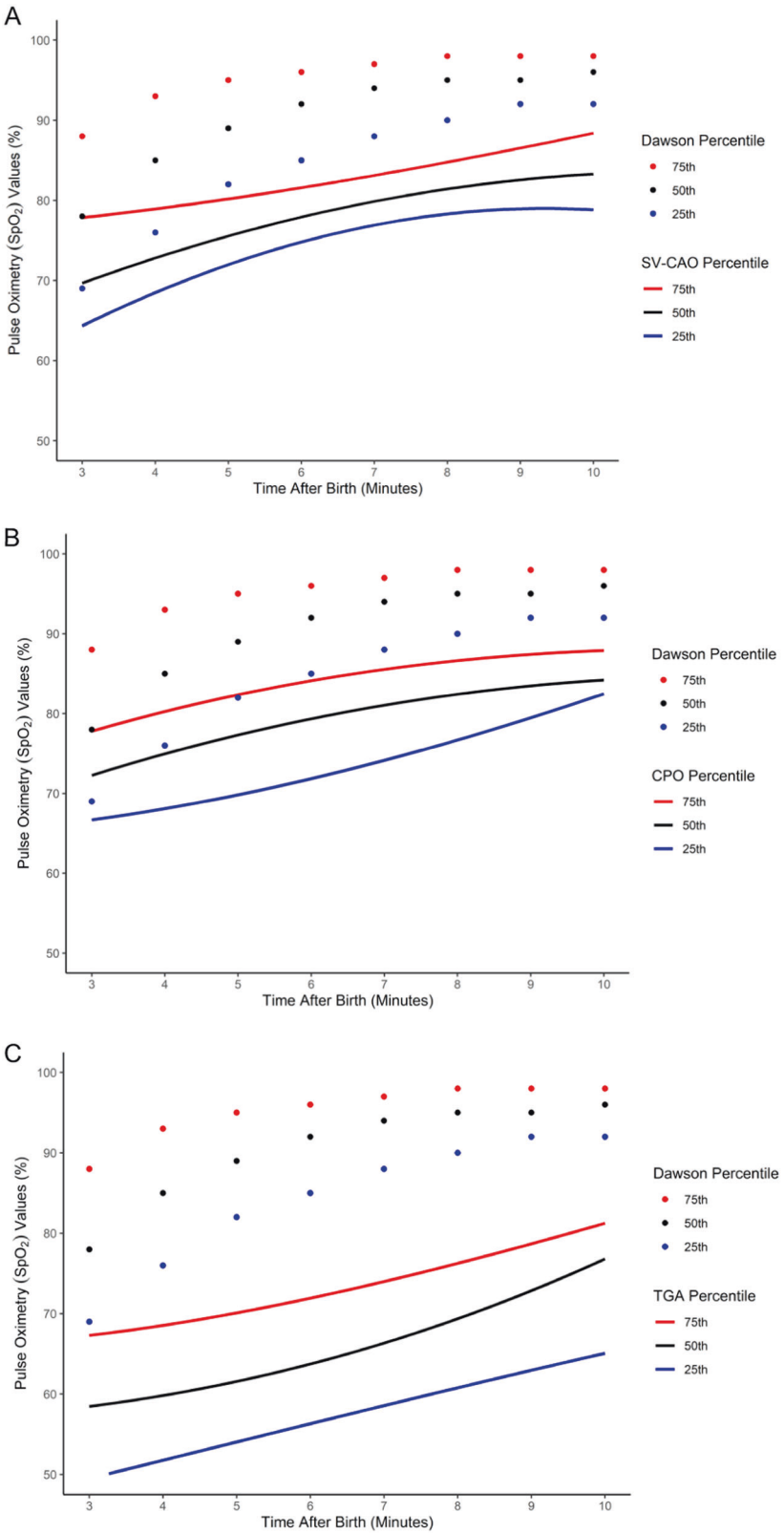

Fig. 1 The 25th, 50th, and 75th pre-ductal SpO_2 percentiles up to 10 minutes after birth for infants within each sub-group of CCHD. Data from published reference ranges reported by Dawson et al. [4] are overlaid for comparison. **A** Infants with single ventricle - critical aortic obstruction (SV-CAO; $n = 68$). **B** Infants with single or two ventricle—critical pulmonic obstruction (CPO; $n = 72$). **C** Infants with transposition of the great arteries (TGA) physiology ($n = 56$).

Table 2 SpO_2 values at 3–10 min after birth.

SpO_2 %, Median (IQR)				
Time after birth	Dawson [4] $n = 468$	Single ventricle-critical aortic obstruction $n = 68$	Critical pulmonic obstruction $n = 72$	Transposition of the great arteries physiology $n = 56$
3 min	78 (69–88)	70 (66–79) ($n = 29$)[a]	72 (68–76) ($n = 28$)	58 (51–70) ($n = 18$)
4 min	85 (76–93)	72 (67–77) ($n = 19$)	77 (67–84) ($n = 24$)	61 (51–66) ($n = 28$)
5 min	89 (82–95)	77 (72–81) ($n = 20$)	74 (72–80) ($n = 24$)	63 (53–68) ($n = 22$)
6 min	92 (85–96)	77 (74–80) ($n = 15$)	82 (67–86) ($n = 21$)	64 (58–70) ($n = 25$)
7 min	94 (88–97)	80 (78–85) ($n = 19$)	81 (77–84) ($n = 23$)	65 (59–78) ($n = 23$)
8 min	95 (90–98)	81 (79–84) ($n = 27$)	83 (78–89) ($n = 14$)	69 (60–77) ($n = 12$)
9 min	95 (92–98)	84 (82–89) ($n = 15$)	82 (81–85) ($n = 15$)	74 (65–80) ($n = 14$)
10 min	96 (92–98)	83 (77–87) ($n = 8$)	85 (81–89) ($n = 19$)	77 (64–80) ($n = 19$)

Three-way comparison of SpO_2 values across all three CCHD groups: $p < 0.01$ at all time points.

In two group comparisons: SV-CAO versus TGA: $p < 0.02$ for all time points; CPO group versus TGA: $p < 0.01$ for all time points; SV-CAO versus CPO: $p > 0.05$ for all time points.

SpO_2 pulse oxygen saturation, *IQR* interquartile range.

[a]n = number of SpO_2 values recorded at that time point.

Table 3 Respiratory support provided during stabilization.

Respiratory Intervention	Single ventricle-critical aortic obstruction $n = 68$	Critical pulmonic obstruction $n = 74$	Transposition of the great arteries physiology $n = 58$	*P
$FiO_2 > 21\%$ given in first 10 min after birth, *N* (%)	10 (15)	16/72 (22)	42/56 (75)[a]	<0.001
$FiO_2 > 21\%$ given at any time while in resuscitation suite, *N* (%)	12 (18)	22 (30)	45 (78)[a]	<0.001
Non-invasive CPAP in first 10 min after birth, *N* (%)	13 (19)	10/72 (14)	32/56 (57)[a]	<0.001
Non-invasive CPAP at any time in resuscitation suite, *N* (%)	15 (22)	17 (23)	38 (66)[a]	<0.001
Non-invasive PPV in first 10 min after birth, *N* (%)	4 (6)	8/72 (11)	12/56 (21)[b]	0.03
Non-invasive PPV at any time in resuscitation suite, *N* (%)	5 (7)	10 (14)	19 (33)[a]	<0.001
Intubated within first 10 min after birth, *N* (%)	0 (0)	1/72 (1)	0 (0)	0.42
Intubated at any time in resuscitation suite, *N* (%)	3 (4)	7 (10)	31 (53)[a]	<0.001
If intubated: minute after birth intubation was performed, median (IQR)	49 (36-54)	27 (16-58)	24 (18-35)	0.43

For all interventions, $p > 0.05$ for comparisons between SV-CAO and CPO.

FiO_2 fraction of inspired oxygen, *CPAP* continuous positive airway pressure, *PPV* positive pressure ventilation, *IQR* interquartile range.

**P* values for comparison between all three groups.

[a]$P < 0.01$ between TGA and SV-CAO *and* between TGA and CPO.

[b]$P < 0.05$ between TGA and SV-CAO only.

group were intubated following site-specific guidelines, compared to 0.4-2% of term or near-term newborns [17, 19]. The high frequency of respiratory support provided to all groups of CCHD infants, in particular newborns with TGA physiology, as reported here, might guide delivery room planning, such as the presence of individuals with airway skills.

The provision of supplemental FiO_2, non-invasive respiratory support, and frequent intubation in our study likely reflect a combination of delivery room management following NRP recommendations in addition to our site-specific guidelines, which suggest the goal of achieving pre-ductal oxygen saturation values of 75–85% for infants with expected mixing physiology. The rationale for our practice guidelines is to achieve a balanced circulation with 1:1 systemic and pulmonary flow using supplemental oxygen and respiratory supports to affect the relative resistance of the systemic and pulmonary vascular beds [20]. However, the ideal physiologic oxygen saturation values during the first 10 min after birth in infants with CCHD are unknown.

Established prenatal risk stratification protocols using sequential prenatal echocardiograms can identify infants

with CCHD at risk of hemodynamic instability during the postnatal transition [21, 22]. These protocols set the stage for delivery room planning, such as predicting how urgently an infant may need prostaglandin initiation, cardiac catheterization, or transfer to a specialized center. Once the infant with CCHD has been stratified by expected risk, continued clinical assessment after birth is required to ensure the newborn is transitioning safely. Targeted SpO_2 values for each minute after birth are included in neonatal resuscitation program guidelines and inform clinical assessments and interventions during delivery room resuscitation. Percentile values allow providers to recognize how the individual patient's clinical trends relate to the context of a large group of patients with similar physiology. Because published SpO_2 norms do not apply to infants with CCHD, we sought to describe oxygenation trends for each CCHD subpopulation. These data may guide clinicians who care for these infants in the delivery room to assess whether an infant with a particular defect is transitioning as anticipated immediately after birth. Deviations from anticipated SpO_2 trajectories may indicate impaired transition or concurrent pulmonary disease. Early recognition would allow clinicians to provide timely and effective resuscitation including further work-up and interventions as needed.

After postnatal transition, supplemental oxygen is carefully titrated to ensure adequate tissue oxygenation while avoiding pulmonary overcirculation and/or hypoxemia-mediated oxidative stress [23]. How supplemental oxygen should be titrated immediately after birth requires identification of goal SpO_2 targets relative to minute of life. The oxygen saturation trends reported in this study are a step towards establishing reference ranges for distinct phenotypes of CCHD during postnatal transition.

Further study is needed to understand the effect of physiology-specific oxygen saturation targets for newborns with CCHD. Peripheral SpO_2 and cerebral oxygenation during postnatal transition may impact infant outcomes beyond the delivery room [24]. Lower oxygen saturation levels in the first few minutes after birth are associated with neurologic injury or death in preterm infants [25, 26]. Infants with CCHD are also at high risk of cerebral injury, which has been associated with cerebral hypoxia during the pre-surgical period [27, 28]. A critical next step is to determine the role of specific targets for SpO_2 and potentially cerebral oxygen saturation during postnatal transition on neurologic outcomes in this population.

We acknowledge study limitations. Due to the retrospective study design, the number of pulse oximetry recordings is limited to what was documented in the medical record during delivery room management. Each infant contributed a median of 2–3 SpO_2 values in our study. A prospective study would allow for more frequent data collection and monitoring of the pulse oximeter waveform to ensure quality of the measurement. Likewise, we presented SpO_2 data starting from 3 min after birth, due to the paucity of data points prior to that time. This reflects the realities of clinical practice, including the time interval for transporting the newborn to the resuscitation warmer and drying/stimulating the infant prior to placing the oximeter sensor and acquiring a reliable signal. In previous studies, the mean time interval from birth to stable pulse oximeter reading was up to 79 s [29–31]. Limited documentation also precluded our ability to comment on the reasons why delivery room interventions were initiated, such as whether a patient received PPV due to apnea or due to persistent bradycardia. Although we did not trend heart rate trajectories in this study, initial bradycardia was uncommon, as ≥90% of CCHD infants had a heart rate >100 beats per minute at the time of first clinical assessment.

Our study has several strengths. First, we present delivery room data from a large cohort of infants with CCHD, an understudied setting for this population. Second, by grouping together infants with similar expected physiology, our results are more generalizable across a spectrum of cardiovascular anatomic variants encountered in practice.

This study contributes to defining the SpO_2 trajectory in newly born infants with CCHD. In an era where prenatal diagnosis of CCHD is increasing in frequency, our study contributes to the development of optimal care models for this fragile population. We also establish that newborns with TGA physiology receive more frequent and more intensive respiratory support compared to infants with other types of CCHD. These data can inform providers' ability to target pulse oxygen saturations to the expected physiological phenotype of the CCHD newborn and optimally prepare for delivery room management of each subpopulation.

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Author contributions AT conceptualized the study design, collected and analyzed the data, and drafted the manuscript. AM refined the study collection tools, collected data, and reviewed and revised the manuscript. MH and DW analyzed the data, and reviewed and revised the manuscript. AA conceptualized the study design and reviewed and revised the manuscript. JR conceptualized the study design, analyzed the data, and reviewed and revised the manuscript. EF conceptualized the study design, refined the study collection tools, analyzed the data and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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